A GRADUÁLIS ÉS POSZTGRADUÁLIS KÉPZÉS folyóirata
Alapítva 1911-ben

2020. XCV. évfolyam, 1. szám

2020.
XCV.
évfolyam,
1. szám

ORVOS-KÉPZÉS

ORVOSKÉPZÉS

PhD Tudományos Napok, 2020

PhD Scientific Days, 2020

Semmelweis Kiadó

ORVOSKÉPZÉS
A graduális és posztgraduális képzés folyóirata
2020; XCV. évfolyam, 1:1-148.

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Hungarian PhD Conference of Medical, Pharmaceutical and Health Sciences

PhD Scientific Days, 2020

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(H-1094 Budapest, Tűzoltó utca 37-47.)

16-18th March 2020

Országos Orvos-, Gyógyszerész- és Egészségtudományi PhD Konferencia

PhD Tudományos Napok, 2020

Semmelweis Egyetem,
Elméleti Orvostudományi Központ
(1094 Budapest, Tűzoltó utca 37-47.)

2020. március 16-18.

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ORVOSKÉPZÉS folyóirat szerzői útmutatója

A folyóirat célja: Az 1911-óta megjelenő Orvosképzés legfontosabb célja a hazai orvoskollégák folyamatos graduális és posztgraduális képzésének támogatása. A lap elsősorban olyan munkák közlését tartja feladatának, amelyek az orvostudomány egy-egy ágának újabb és leszűrt eredményeit foglalják össze magas színvonalon úgy, hogy azok a gyakorló orvoshoz, szakorvoshoz, klinikushoz és elméleti orvoshoz egyaránt szóljanak. Emellett lehetőség van eredeti közlemények és esetismertetések benyújtására, és az újság a Semmelweis Egyetem szakmai kötelező szinten tartó tanfolyamok előadási összefoglalóinak is teret ad. Az eredeti közlemények a rendszeres lapszámokban, vagy a témához kapcsolódó tematikus lapszámokban kapnak helyet. Fontos feladatunknak tartjuk, hogy rezidens kollégák tollából származó esetismertetéseket is közöljünk, melyeket mentori ajánlással kérünk benyújtani. A beadott dolgozatokat a szerkesztőbizottság előzetes bírálatra adja ki, és a kézirat közlésére a bírálat eredményének függvényében kerül sor. Tudományos dolgozat benyújtására az alábbiak szerint van lehetőség:

- Esetismertetés (case report)
- Fiatal doktorok (PhD) tudományos beszámolója, új eredményeinek összefoglalása (nem tézisek vagy doktori értekezések!)
- Klasszikus összefoglaló közlemény az elméleti és klinikai orvostudomány bármely területéről, a legújabb irodalmi eredmények felhasználásával
- „Update" jellegű közlemény, azaz nem egy téma kidolgozása, hanem adott szakterület legújabb tudományos eredményeinek összefoglalása
- Előadási összefoglaló (a tanfolyamszervezők felkérése alapján)

A kézirat: A tudományos közleményeket elektronikusan, Word dokumentum formátumban kérjük eljuttatni a szerkesztőségbe. Az illusztrációkat, ábrákat és táblázatokat külön file-ként kérjük elküldeni. Az ábrák címeit és az ábramagyarázatokat a Word dokumentumban külön oldalon kell feltüntetni, az ábra/táblázat számának egyértelmű megjelölésével. A digitális képeket minimum 300 dpi felbontásban kérjük, elfogadunk tif, eps, illetve cdr kiterjesztésű file-okat. A kézirat elfogadása esetén az ábrákat a szerkesztőség nyomtatott formában is kéri elküldeni. Az orvosi szavak helyesírásában az Akadémia állásfoglalásának megfelelően, a latinos írásmód következetes alkalmazását tekintjük elfogadottnak. Magyarosan kérjük írni a tudományágak és szakterületek, a technikai eljárások, műszerek, a kémiai vegyületek neveit. A szerkesztők fenntartják maguknak a stiláris javítás jogát. A mértékegységeket SI mértékrendszerben kérjük megadni.

A kézirat felépítése a következő: (1) címoldal, (2) magyar összefoglalás, kulcsszavakkal, (3) angol összefoglalás (angol címmel), angol kulcsszavakkal, (sorrendben): magyar cím, angol cím, (4) rövidítések jegyzéke (ha van), (5) szöveg, (6) irodalomjegyzék, (7) ábrajegyzék, (8) táblázatok, (9) ábrák. Az oldalszámozást a címoldaltól kezdve kell megadni és az egyes felsorolt tételeket külön lapon kell kezdeni.
(1) A *címoldalon* sorrendben a következők szerepeljenek: a kézirat címe, a szerzők neve, valamint a szerzők munkahelye, a kapcsolattartó szerző pontos elektronikus és postai címének megjelölésével. (2–3) Az *összefoglalást* magyar és angol nyelven kell beküldeni, külön oldalakon, a következő szerkezet szerint: „Bevezetés" („Introduction"), „Célkitűzés" („Aim"), „Módszer" („Methods"), „Eredmények" („Results") és „Következtetések" („Conclusions") lényegre törő megfogalmazása történjék. A magyar és az angol összefoglalások terjedelme – külön-külön – ne haladja meg a 200 szót (kulcsszavak nélkül). A témához kapcsolódó, maximum 5 kulcsszót az összefoglalók oldalán, azokat követően kérjük feltüntetni magyar és angol nyelven. (4) A kéziratban előforduló, nem általánosan elfogadott *rövidítésekről* külön jegyzéket kell készíteni abc-sorrendben. (5) A szövegtörzs szerkezete világos és az olvasó számára átlátható legyen. Eredeti közlemények esetén a „Bevezető"-ben röviden meg kell jelölni a problémafelvetést, és az irodalmi hivatkozásokat a legújabb eredeti közleményekre és összefoglalókra kell szűkíteni. A „Módszer" részben világosan és pontosan kell leírni azokat a módszereket, amelyek alapján a közölt eredmények születtek. Korábban közölt módszereket esetén csak a metodika alapelveit kell megjelölni, megfelelő irodalmi hivatkozással. Klinikai vizsgálatoknál a kézirathoz csatolni kell az illetékes etikai bizottság állásfoglalását. Állatkísérletek esetén a Magyar Tudományos Akadémia – Egészségügyi Tudományos Tanács – állatkísérletekre vonatkozó etikai kódexe érvényes, melyre a metodikai részben utalni kell. A statisztikai módszereket és azok irodalmát is meg kell adni. Az „Eredmények" és a „Megbeszélés" részeket világosan kell megszerkeszteni. *Referáló közlemények* benyújtása esetén a szövegtörzs altémákra osztható, melyeket alcímek vezessenek be. *Összefoglaló referátumoknál* a szövegtörzs terjedelme ne haladja meg a 30 000 karaktert (szóközzel), *eredeti közleménynél* (klinikai, vagy kísérletes) ne haladja meg a 20 000 karaktert (szóközzel), *esetismertetésnél* ne haladja meg a 10.000 karaktert (szóközzel), *előadási összefoglaló* esetén pedig ne haladja meg a 8000 karaktert (szóközzel).
Irodalom: a hivatkozásokat (maximum 50, előadási összefoglalónál maximum 10) a szövegben való megjelenés sorrendjében tüntessék fel. A szövegben a hivatkozást a sorszáma jelöli.
Hivatkozás cikkre: sorrendben: szerzők neve (6 szerző felett et al./és mtsai), cikk címe, folyóirat neve (Index Medicus szerint rövidítve), év; kötetszám:első-utolsó oldal. Példa: 1. Kelly PJ, Eisman JA, Sambrook PN. Interaction of genetic and environmental influences on peak bone density. Osteoporosis Int 1990; 1:56-60. *Hivatkozás könyvfejezetre,* sorrendben: a fejezet szerzői. A fejezet címe. In: szerkesztők (editors). A könyv címe. A kiadás helye, kiadó, megjelenés éve; fejezet első-utolsó oldala. Példa: 2. Delange FM, Ermans AM. Iodide deficiency. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's the thyroid. 7th ed. Philadelphia, Lipincott-Raven, 1996; 296 316.
Ábrajegyzék: a megjelenés sorrendjében, arab számmal sorszámozva egymás alatt tartalmazza az ábra címét és alatta rövid és lényegre törő ábramagyarázatot
Táblázatok: külön-külön lapokon kérjük, címmel ellátva és arab számmal sorszámozva. Törekedjenek arra, hogy a táblázat könnyen áttekinthető legyen, ne tartalmazzon zavaróan sok adatot.
Ábrák: külön-külön lapokon kérjük. Csak reprodukálható minőségű ábrákat, fényképek küldését kérjük (min. 300 dpi felbontásban), a korábban megjelölt file formátumokban. A kézirat elfogadása esetén a nyomtatott ábrát kérjük beküldeni a szerkesztőségbe és az ábra hátoldalán puha ceruzával kérjük jelölni a szerző nevét, arab számmal az ábra sorszámát és a vertikális irányát.

A formai hiányossággal beküldött kéziratokat nem tudjuk elfogadni. A gyors lektori és korrektúrafordulók érdekében kérjük a legbiztosabb levelezési, illetve e-mail címet, telefon- és faxszámot megadni. Elfogadás esetén külön levélben kérjük jelezni, hogy a szerzők a közleménnyel egyetértenek (és ezt aláírásukkal igazolják), valamint lemondanak a folyóirat javára a kiadási jogról. Írásbeli engedélyt kérünk mellékelni a már közölt adat/ábra felhasználása, felismerhető személy ábrázolása, szerzőnek nem minősülő személy nevének említése/feltüntetése esetén. A szerkesztőség az általa felkért szakértők személyét titkossággal kezeli. A kézirat tulajdonjoga a megjelenésig a szerzőt illeti meg, a megjelenés napján tulajdonjoga a kiadóra száll. A megjelent kéziratok megőrzésére szerkesztőségünk nem tud vállalkozni.

A kéziratok benyújtását a következő címre várjuk:
Dr. Merkely Béla egyetemi tanár, felelős szerkesztő
Semmelweis Egyetem, Kardiológiai Központ
1122 Budapest, Városmajor u. 68
Tel: (06-1) 458-6810
E-mail: orvoskepzes@kardio.sote.hu

Országos Orvos-, Gyógyszerész- és Egészségtudományi PhD Konferencia támogatói*

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Semmelweis Egyetem, Budapest

RICHTER GEDEON Nyrt.

Új Nemzeti KIválóság Program

Doktoranduszok Országos Szövetsége

*2020. február 12-i adatok / Data as of February 12, 2020

Dear PhD Students,

On behalf of the Doctoral Council of the Semmelweis University I cordially invite you to the first Hungarian PhD Conference of Medical, Pharmaceutical and Health Sciences.

Our University organizes PhD Scientific Days every year, where the students can report their research achievements and practice their presentation and discussion skills. The PhD Scientific Days are also a great opportunity to initiate scientific collaborations or even friendships between young researchers representing the next generation of the scientific community. In this academic year the Semmelweis University celebrates its 250th anniversary which gives us an excellent opportunity to extend this initiative to our partner universities in Hungary and beyond the borders of our country as well. The conference also offers the opportunity for the recently established ÚNKP Excellency Scholarship holders to give the compulsory conference presentation for a larger audience.

I hope that many of you will accept this invitation and I am looking forward to seeing you in Budapest in March 2020!

Prof. Dr. Zoltán Benyó
Head of the Doctoral Council
Semmelweis University

Kedves PhD Hallgatók!

A Semmelweis Egyetem doktori iskolái 1999 óta minden évben megrendezik a PhD Tudományos Napok konferenciát, melyen doktoranduszok és doktorjelöltek mutathatják be kutatási eredményeiket, gyakorolhatják és fejleszthetik előadói és vitakészségüket.

A rendezvény kiváló lehetőség arra, hogy az új kutatói nemzedék tagjai között olyan együttműködések, akár barátságok formálódjanak, amelyek megalapozhatnak későbbi eredményes kollaborációkat.

Az Országos Orvos-, Gyógyszerész- és Egészségtudományi PhD Konferencia 2020. március 16-18. között a közösen elnyert EFOP-3.6.3-VEKOP-16-2017-00009 pályázatban részt vevő társegyetemek közreműködésével, mind magyar, mind külföldi társegyetemek hallgatói részvételével kerül megrendezésre, lehetőséget teremtve új intézményi szintű tudományos együttműködések kezdeményezésére.

A program az Új Nemzeti Kiválósági Program egyetemi rendezvénye is, az ÚNKP pályázati támogatást elnyert PhD-hallgatók és doktorjelöltek itt mutatják be a támogatott kutatási projektjeik eredményeit.

A minden eddiginél nagyobb számú, izgalmas, új kutatásokat bemutató konferenciával Egyetemünk 250 éves évfordulójának méltó megünnepléséhez is szeretnénk hozzájárulni.

Prof. Dr. Benyó Zoltán
a Semmelweis Egyetem Doktori Tanács
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250 ÉVE AZ EGÉSZSÉG SZOLGÁLATÁBAN

A **Semmelweis Egyetem** története 250 évvel ezelőtt, 1769-ben kezdődött, amikor Mária Terézia orvosi karral egészítette ki a Nagyszombati Egyetemet. Magyarország legrégebbi, ma is működő orvosképző intézménye. Mára a hat karral működő szakegyetemként egyedülálló helyet foglal el a magyar egészségtudományi felsőoktatásban. Három fő tevékenysége az **oktatás**, **kutatás** és **gyógyítás**, és e hármas egység teszi nemzetközileg is elismert tudásközponttá.

A 250. jubileumi évfordulóra kiadott exkluzív ajándéktárgyak megvásárolhatók.

Legendus és EOK könyvesbolti átvételkor az ajándéktárgyak feltüntetett árából a Semmelweis Egyetem polgárainak **20% kedvezmény** jár.

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A könyvek megvásárolhatók a Legendus és az EOK Könyvesboltban, illetve megrendelhetők honlapunkról.

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Doktori képzés a Semmelweis Egyetemen

PhD Studies at Semmelweis University

Dr. Benyó Zoltán[1,2] és Dr. Ivanics Tamás[2]

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ÖSSZEFOGLALÁS Az orvos-, gyógyszerész- és egészségtudományi doktori képzésnek egyszerre kell komoly minőségi és mennyiségi kihívásoknak eleget tennie napjainkban. A képzés minőségének a javítása a hatékonyság fokozásával érhető el, ugyanis a képzési idő megnyújtása finanszírozási problémákat és a hallgatói érdeklődés csökkenését vonná maga után. A mennyiségi fejlesztés feltétele a kutatás iránti érdeklődésnek a felkeltése már a graduális képzés alatt, illetve azt megelőzően már a közoktatásban. Hasonlóan hangsúlyos szempont a hallgatók tudományos munkájának anyagi és erkölcsi megbecsülése, támogatása. Munkánkban azokat a fejlesztéseket foglaljuk össze, amelyeket a Semmelweis Egyetem az utóbbi években e célok elérése céljából valósított meg.

KULCSSZAVAK doktori képzés, PhD, orvostudományok, gyógyszerészeti tudományok, egészségtudományok, kutatás

SUMMARY At present, PhD training in medical, pharmaceutical and health sciences must meet intense challenges from both qualitative and quantitative point of view. Qualitative improvement of training should be achieved by enhancement of its efficiency, since extension of the training period would be accompanied by financial difficulties and waning interest from the part of the students. Conditions of quantitative development of training are based on raising the interest for research in the gradual training period and on the quality of public education prior to that. Equally important aspects are the support and appreciation of the students' research activities both in financial and ethical terms. This paper has been designed to summarize all those developments which have been implemented to achieve these goals at Semmelweis University for the past years.

KEY WORDS PhD studies, medical sciences, pharmaceutical sciences, health sciences, research

Bevezetés

A hazai kutatás, fejlesztés és innováció (K+F+I) mennyiségi és minőségi mutatói elmaradnak az európai átlagtól, aminek egyik fő oka a magasan képzett szakemberek hiánya. Magyarország nemzetközi egyezményekben és hazai stratégiai programokban egyaránt megfogalmazott célkitűzése a kutatói létszám jelentős, közel 50%-os növelése. E cél elérését segíti a felsőoktatási hallgatók tudományos műhelyeinek támogatására 2016-ban kiírt EFOP-3.6.3-VEKOP program, valamint az államilag finanszírozott PhD-ösztöndíjak számának 2019-ben bevezetett másfélszeres növelése. A fentiek tükrében szükségessé vált a doktori képzés folyamatainak áttekintése és fejlesztése.

A doktori képzés kihívásai

Az orvos, fogorvos és gyógyszerész diplomával rendelkezők körében az utóbbi években sajnálatos módon csökkent az érdeklődés a doktori képzés iránt, aminek okait döntően a következőkben kell keresnünk:

1. A pályakezdő diplomások javuló anyagi megbecsülése: a közszférában és még inkább a gazdasági szférában a fizetéseknek, a szakképzésben az ösztöndíjaknak és kiegészítő juttatásoknak a PhD-ösztöndíjaknál jelentősebb mértékű emelkedése.
2. A doktori képzés megnyúlása 3-ról 4 évre főleg azok körében hátrányos, akik utána szeretnének szakképzésbe is bekapcsolódni, ugyanis az 5–6

év alapképzés, 4 év doktori képzés, majd 3–6 év szakképzés sokak számára nehezen vállalható anyagi/egzisztenciális szempontból. Különösen igaz ez a nők körében, akik ebben az életszakaszban szeretnének gyermeket is vállalni.

3. A külföld elszívó hatása, ami a legtehetségesebb hallgatók esetében érvényesül rendkívül erőteljesen. Több éves tapasztalat, hogy a PhD felvételi vizsgán legtöbb pontot szerző hallgatók közül néhányan végül nem iratkoznak be a képzésbe, hanem jobb anyagi és munkakörülmények reményében külföldre mennek doktoranduszoknak vagy MD fokozatuk birtokában akár posztdoktornak.

A doktori képzés fejlesztése a Semmelweis Egyetemen

A doktori képzés iránti érdeklődés csökkenése hosszú távon a PhD témavezetői utánpótlás csökkenésén keresztül a folyamat további felerősödésének veszélyét vetíti előre. E kedvezőtlen folyamatok megállítására és visszafordítására az utóbbi években a Semmelweis Egyetemen több fejlesztés valósult meg a doktori képzésben. Ezek célja a doktori képzés vonzóbbá tétele **az oktatási program színesítésével és színvonalának emelésével,** valamint a **teljesítményt ösztönző kiválósági programok** bevezetésével. A fejlesztések jelentős mértékben a Semmelweis Egyetem, a Debreceni Egyetem, a Pécsi Tudományegyetem és a Szegedi Tudományegyetem az **„Az orvos-, egészségtudományi- és gyógyszerészképzés tudományos műhelyeinek fejlesztése”** című, **EFOP-3.6.3-VEKOP-16-2017-00009** azonosítószámú projektjének finanszírozásával valósultak meg. Ezt kiegészítendő, az Egyetem további támogatást biztosított pályázati forrásokból és saját bevételből. A reformokhoz szükséges szabályozási változások a **Doktori Szabályzat átalakítását, modernizálását** is szükségessé tették.

Az EFOP/VEKOP pályázat és ehhez kapcsolódóan a Semmelweis Egyetem alapvető célja, hogy olyan képzési, kutatási és ösztönző rendszert/rendszereket alakítson ki, amelyek növelik a kutatói utánpótlásban résztvevő tehetséges hallgatók számát, fokozzák a kutatói utánpótlás és képzés hatékonyságát, meghonosítanak olyan kutatási programokat, amelyek a legmodernebb nemzetközi kutatási irányvonalaknak felelnek meg, segítik a tudományos eredmények közreadását, és így összességében emelik a PhD fokozatot szerzők számát. A Semmelweis Egyetem által tervezett tevékenységek mind a kutatás és képzés megvalósítását, mind azoknak a fejlesztését (hatékonyságnövelését) célozzák, és egyben támogatják az innovációt is. A programelemek megvalósításához az Egyetemi Doktori Tanács, a Doktori Iskolák, az Egyetemi Tudományos Tanács, a Tudományos Diákköri Tanács, a Kerpel-Fronius Tehetséggondozó Program, a Korányi Frigyes Szakkollégium és az Innovációs Igazgatóság együttesen alakította ki a cselekvési tervet, és a feladatokat a graduális és posztgraduális oktatás keretein belül együttesen valósítják meg.

A minőségi kutatói utánpótlás biztosítása érdekében számos új képzési forma és kutatási támogatási, ösztönző rendszer került bevezetésre a Semmelweis Egyetemen, ezeket ismertetjük az alábbiakban.

A doktori képzés kutatási programjainak bővítése új kutatási témák indításával

A nemzetközi kutatások homlokterébe került legújabb tudományos szakterületeken (pl. biotechnológiai módszerek alkalmazása gyógyszerészeti kutatásokban, onkológiai kutatások meghirdetése experimentális és klinikai eljárások ötvözésével, valamint nanotechnológiai metodikák alkalmazása a molekuláris medicina egyes területein) összesen közel 30 új kutatási téma indult. Az új témák indítását a témára felvett első hallgató kutatómunkájának jelentős anyagi támogatásával ösztönöztük.

Új metodikai és interdiszciplináris PhD-kurzusok szervezése és a gyakorlati képzés erősítése

Az új kurzusok, melyek indításához és a tananyagfejlesztéshez személyi és dologi támogatást lehetett elnyerni a pályázati forrásból, bővítik a PhD-hallgatók metodikai ismereteit, valamint segítséget nyújtanak a felmerülő módszertani kérdések és problémák megoldásában. A program elősegíti a doktorandusz kutatások tervezését, valamint eredményes kivitelezését. Az új kurzusokat a gyakorlatorientáltság jellemzi készségfejlesztés céljából, és a támogatás feltétele volt a kurzusok magyar és angol nyelven való meghirdetése.

Kiemelt terület volt a biostatisztikai képzés fejlesztése, illetve ezzel összefüggésben a klinikai kutatási módszertan oktatása. Ez a statisztikai ismereteken túl magában foglalja kutatástervezési, epidemiológiai, etikai, jogi, illetve kutatás menedzsmenttel kapcsolatos ismeretek átadását. A program keretén belül négy, a kutatásban is aktív oktató elvégzett egy nemzetközileg elismert képzést (Global Clinical Scholars Research Training Program, Harvard Medical School), majd ez alapján kidolgozta a **Klinikai Vizsgálatok Módszertana I. és II.** képzés programját, és elindította a képzést magyar és angol nyelven.

Az előbbieken kívül minden évben egy blokkosított nyári PhD kurzust tartunk **Summer School** néven, részben külföldi előadók részvételével. Általuk új módszereket, probléma felvetéseket és megoldásokat ismerhetnek meg a hallgatók, ami hozzájárul a kutatói látásmódjuk bővítéséhez.

Kiválósági PhD Ösztöndíj

Az ebbe a programba bekerülő tudományos diákkörös hallgató már a graduális képzése utolsó 2 évében megkezdi felkészülését a doktori képzésre, melynek során kiegészítő ösztöndíjat és kutatási támogatást kap. Ez alatt az időszak alatt szemeszterenként 4 kreditnek megfelelő PhD-kurzust is el kell végeznie, és a 2. év végére egy közlésre elfogadott publikációval kell rendelkeznie. E feltételek teljesülése esetén az egyetemi diploma megszerzése után egyéni felkészülőként jelentkezik doktori képzésre, és sikeres komplex vizsga letételét követően két éven keresztül fokozatszerzési ösztöndíjat és kutatási támogatást kap. Ez alatt teljesítenie kell a PhD fokozatszerzés publikációs és egyéb követelményeit, és a doktori értekezését be kell nyújtania. Ez a rendszer a rezidensek esetében is bevezetésre került, és alapvető célja a teljes képzési idő rövidebbé tétele.

Nemzetközileg kiemelkedő publikációs aktivitás, valamint nemzetközi konferencián vagy kurzuson való részvétel támogatása

A PhD-hallgatók tudományos előre lépése érdekében elengedhetetlen, hogy nemzetközileg elismert folyóiratokban tudják közölni kutatási eredményeiket. A publikációs tevékenységet azonban megnehezíti a publikációs költségek növekedése, mely jelentős anyagi terhet jelent a témavezetők számára. A publikációs tevékenység közvetlen támogatásának formájában, a legjobb nemzetközi folyóiratokban közlésre kerülő D1 kategóriájú elsőszerzős közlemény megjelenésével kapcsolatos publikációs költséget támogatjuk a PhD- és TDK-hallgatóknak a publikációs aktivitás segítése céljából.

A fiatal kutatók bekapcsolása a nemzetközi tudományos életbe szintén rendkívül fontos, mivel így nyílik lehetőségük szemléletük bővítésére, jövőbeli kutatási együttműködések, munkakapcsolatok kiépítésére, tanulmányutak tervezésére. Az utazási támogatás közvetlenül szolgálja a TDK- és PhD-hallgatók nemzetközi kutató életbe történő bekapcsolását. A tudományos eredmények konferenciákon való prezentálását jó eséllyel követi publikáció, amely alapvető feltétele a PhD-fokozat szerzésének.

Tudományos diákkörös hallgatók motiválása és felkészítése doktori képzésre

A doktori képzés utánpótlását legnagyobb mértékben a tudományos diákkör jelenti. Ennek erősítésére számos olyan programot szervezünk, amelyen TDK- és PhD-hallgatók együtt vesznek részt, megismerkednek egymással és egymás kutatásaival. A Tudományos Diákköri Tanács és az Egyetemi Doktori Tanács egyaránt igen fontosnak tartja a doktoranduszok és predoktorok bevonását a fiatalabb hallgatók oktatásába, TDK témavezetésébe. A TDK-témavezetés lehetőséget teremt a PhD-hallgatók számára, hogy tapasztalatot szerezzenek az oktatásban, a fiatalabb hallgatókkal való együttműködésben. Ennek támogatására szolgál a legkiválóbb **TDK-témavezető PhD-hallgatók díjazása** minden évben az egyetemi TDK-konferenciákon.

A **Kerpel-Fronius Tehetséggondozó Program** szervezésében szemeszterenként több alkalommal a fiatal TDK- és PhD-hallgatók bemutatják legújabb tudományos eredményeiket egy kötetlenebb közegben történő vita fórum keretében. Ez a fórum a fiatal kutatók előadókészségének, vitakészségének fejlesztésére is kiváló lehetőséget nyújt.

A **Semmelweis Tehetségkonferenciát** a Semmelweis Egyetem Korányi Frigyes szakkollégiumának egy-egy szakmaspecifikus platformját alkotó és egyben TDK-munkát végző hallgatói szervezik abból a célból, hogy más tudományterületen kutató TDK-hallgatók kapjanak betekintést az adott platform által jelentősnek tartott, legújabb szakmaspecifikus kutatásokba. Moderátorokként kutatókat és PhD-hallgatókat hívnak meg, ezáltal három egymást követő kutató generáció láthat bele egymás munkájába. A konferenciának természetes következménye lehet a kutatócsoportok hálózatban való gondolkodása, későbbi kooperációk elősegítése.

A TDK és PhD kutatások közötti további kapcsolódási pont, hogy az Egyetem Innovációs Igazgatóságával együttműködésben, a **Semmelweis Innovációs Nap**-hoz kapcsolódóan minden évben díjazzuk a leginnovatívabb kutatómunkát felmutató 2–2 TDK- és PhD-hallgatót.

Összefoglalás

Az orvos-, gyógyszerész- és egészségtudományok XXI. századi rohamos fejlődése új feladatok elé állítja a doktori képzést, melynek egyszerre kell minőségi és mennyiségi kihívásoknak eleget tennie. A képzés minőségének a javítása a hatékonyság fokozásával érhető el, ugyanis a képzési idő megnyújtása finanszírozási problémákat és a hallgatói érdeklődés csökkenését vonná maga után. A mennyiségi fejlesztés feltétele a kutatás iránti érdeklődésnek a felkeltése már a graduális képzés alatt, illetve azt megelőzően már a közoktatásban. Hasonlóan hangsúlyos szempont kell legyen a hallgatók tudományos munkájának anyagi és erkölcsi megbecsülése, támogatása.

MD/PhD kiválósági program indul nemzetközi hallgatóknak a Semmelweis Egyetemen

MD/PhD Excellence Program for International Students at Semmelweis University

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ÖSSZEFOGLALÁS Az idei 250. jubileumi tanévhez kapcsolódó orvosképzési reform bevezetésével párhuzamosan, a Semmelweis Egyetem Doktori Iskolája meghirdette az MD/PhD kiválósági programot a nemzetközi hallgatók számára. A program lehetőséget teremt a legkiválóbb nemzetközi hallgatóknak, hogy már egyetemi tanulmányaik során bekapcsolódhassanak a magas szintű kutató munkába és a diploma megszerzését követően, valamint a komplex vizsga letétele után PhD-hallgatókká váljanak. Ez azt jelenti, hogy a programban részt vevő hallgatók az egyetem elvégzését követő két éven belül PhD-fokozatot szerezhetnek. A program bevezetésétől azt várjuk, hogy az egyetem graduális és posztgraduális képzései egyre népszerűbbek lesznek a nemzetközi hallgatók körében. Ez nagymértékben hozzájárulhat mind az oktatás, mind a kutatás színvonalának emelkedéséhez egyetemünkön.

KULCSSZAVAK Doktori Iskola, angol nyelv, egyetemi hallgató, posztgraduális képzés, kutatás

SUMMARY In this 250th jubilee year, parallel with the introduction of a new curriculum for medical training, the Doctoral School of Semmelweis University announced the MD/PhD Excellence Program for international students. The program offers an excellent opportunity for international students to get involved in high quality research during their gradual training and right after graduation. Having taken the complex exam they are to become PhD candidates. Thus, students enrolled in this program could get the PhD degree within two years after graduation. We hope that the introduction of this MD/PhD Excellence Program at Semmelweis University will further promote both the gradual and post-gradual training programs among the international students. This could significantly increase the quality of both teaching and research activities at our university.

KEY WORDS Doctoral School, English language, undergraduate student, postgraduate training, research

A 2019/20-as tanév kiemelt fontosságú a Semmelweis Egyetemen, mivel most ünnepeljük a szervezett orvosképzés magyarországi kezdetének a 250. évfordulóját. A jubileumi év rangját egy tíz hónapon át tartó rendezvénysorozat emeli, amely a tudományos konferenciák szervezésétől, emlékérme-kibocsátáson keresztül, a Semmelweis 250 mozdony bemutatásáig tart. Egyetemünk jövője szempontjából még fontosabb, hogy ebben a tanévben elindult az orvosképzés mélyreható curriculum reformja, amely az elméleti oktatás magas színvonalának megtartása mellett a gyakorlati képzés előtérbe helyezését és erősítését célozza. A megújított orvosképzési program garanciát jelent arra, hogy a Semmelweis Egyetem megőrizze népszerűségét a jelenlegi és a jövőben nálunk tanulni szándékozó külföldi hallgatók körében. Végső soron a rendszerszintű átalakítás célja az, hogy olyan korszerű elméleti és gyakorlati tudást adjunk minden magyar és külföldi hallgató számára, amely segíti őket, hogy minél előbb képesek legyenek az önálló munkára. Ehhez a reformfolyamathoz szervesen illeszkedik az egyetem Doktori Iskolájának azon törekvése, hogy az idegen nyelvű PhD-képzését fejlessze. Ezt a fejlesztést két lépésben valósítjuk meg. Első lépésben a már nálunk tanuló nemzetközi hallgatókat szólítjuk meg, hogy az egyetemi diplomájuk megszerzését követően, a PhD-fokozatukat is az Semmelweis Egyetemen szerezzék meg. Ezt követően a második lépésben olyan nemzetközi hallgatók jelentkezését várjuk, akik diplomájukat nem a Semmelweis Egyetemen szerezték, de olyan tudományterületeken szeretnének dolgozni és kutatni, amelyeken egyetemünk magas szintű PhD-képzési kapacitással rendelkezik.

Az új Doktori Szabályzat, amely rövidesen az egyetem Szenátusa elé kerül, már tartalmazza azokat a sa-

rokpontokat, amelyek alapján biztosítjuk külföldi hallgatóinknak az idegen nyelvű MD/PhD kiválósági programhoz való csatlakozás lehetőségét. A program olyan külföldi hallgatóinknak szól, akik tudományos diákkörösként bizonyítják a kutató munkára való rátermettségüket. A jelentkezők, a témavezető írásbeli támogatásával, legfeljebb négy szemeszterrel a várható diplomaszerzés előtt még egyetemi hallgatóként csatlakozhatnak a programhoz és kapcsolódhatnak be a kutató munkába. Ebben az időszakban a hallgatók kedvezményes képzési díjat (a teljes díj 50%-a) fizetnek, amely részben fedezi a kutatás költségeit, részben pedig a képzésben részt vevő oktatók/kutatók bérét egészíti ki.

A programban részt vevő hallgatók az egyetemi diploma megszerzését és a komplex vizsga abszolválását követően válhatnak a fokozatszerzésre egyénileg felkészülő PhD-hallgatóvá. A komplex vizsga feltétele a kutató munkában eltöltött négy aktív szemeszter teljesítése és ezen idő alatt legalább 16 tanulmányi kreditpont megszerzése. A komplex vizsga során a hallgató:

- rövid szóbeli beszámolót tart az addig elért tudományos eredményeiről a Doktori Iskola által kijelölt vizsgabizottság előtt,
- elméleti vizsgát tesz, melynek témáit (főtéma + melléktéma) a Doktori Iskola állítja össze.

Az idegen nyelvű képzésre való jelentkezés feltételei megegyeznek a magyar nyelven zajló képzésre való felvétel szabályaival, azzal az eltéréssel, hogy a Doktori Iskola vezetője és a leendő témavezető felelősek a megkívánt felkészültség, a nyelvi képességek és a kutatói munkára való alkalmasság megítélésének elbírálásáért. A sikeres felvételi vizsga után a PhD-hallgató a kutatási és disszertációs szakaszba lép, amely legalább egy, de legfeljebb négy szemeszter lehet. Fontos megjegyezni, hogy a hallgatók ebben az időszakban is jogosultak a kedvezményes képzési díj fizetésére. Az a Doktori Iskola, amelyben idegen nyelven folyik a doktoranduszok képzése köteles gondoskodni a megfelelő színvonalú és kreditpont-értékű angol nyelvű kurzus megszervezéséről. Természetesen ez maga után vonja az angol nyelvű űrlapok biztosítását, a kötelezően választható kurzusok meghirdetését, a hallgatók tájékoztatását és az eljárások angol nyelven történő lebonyolítását.

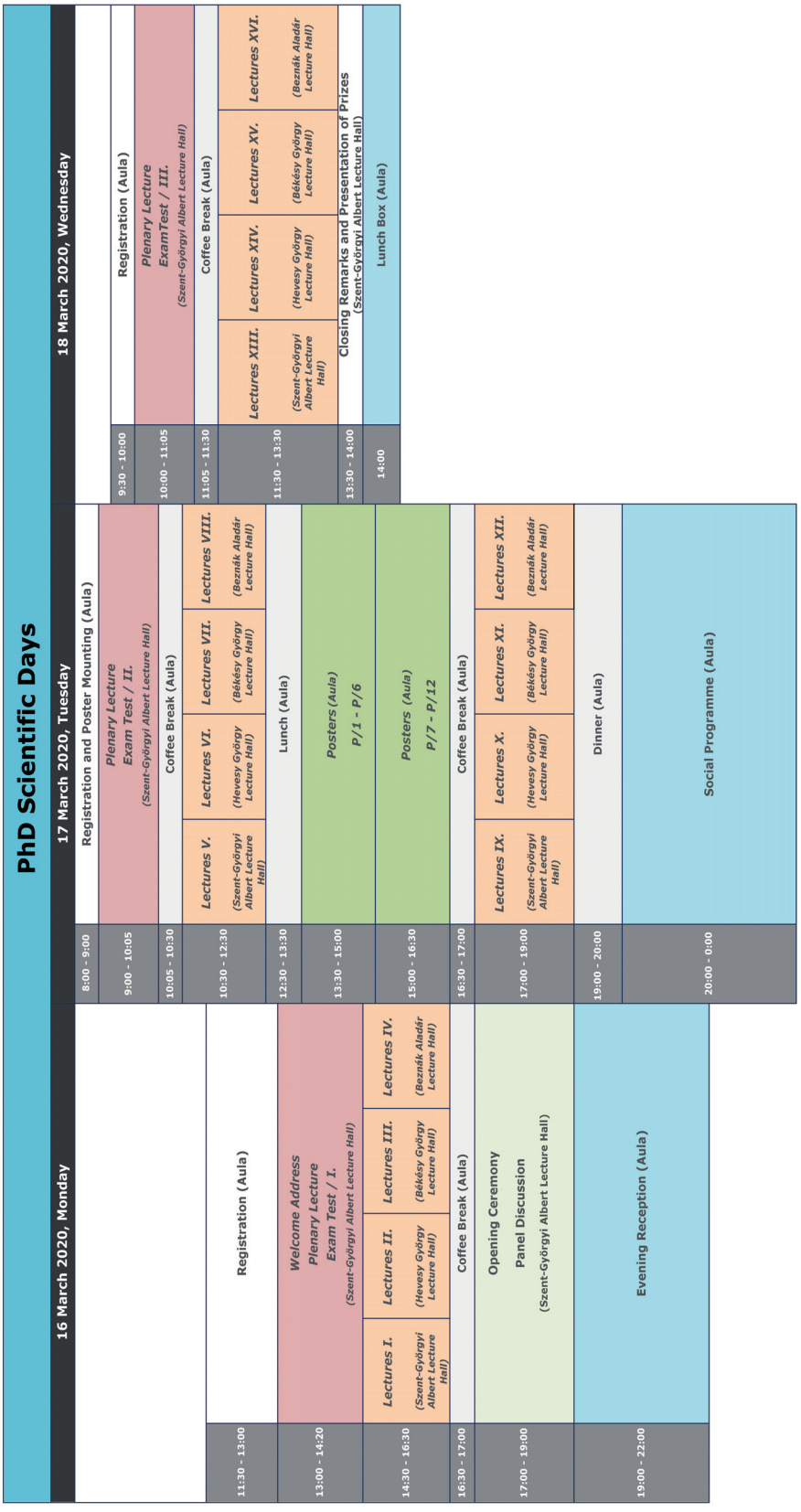
Az egyetem jelenleg a következő tudományterületeken kínál képzési lehetőséget az MD/PhD kiválósági programhoz csatlakozni szándékozó nemzetközi hallgatóinak:

- elméleti orvostudományok,
- klinikai orvostudományok,
- gyógyszertudományok,
- egészségtudományok,
- biológiai tudományok,
- szociológia.

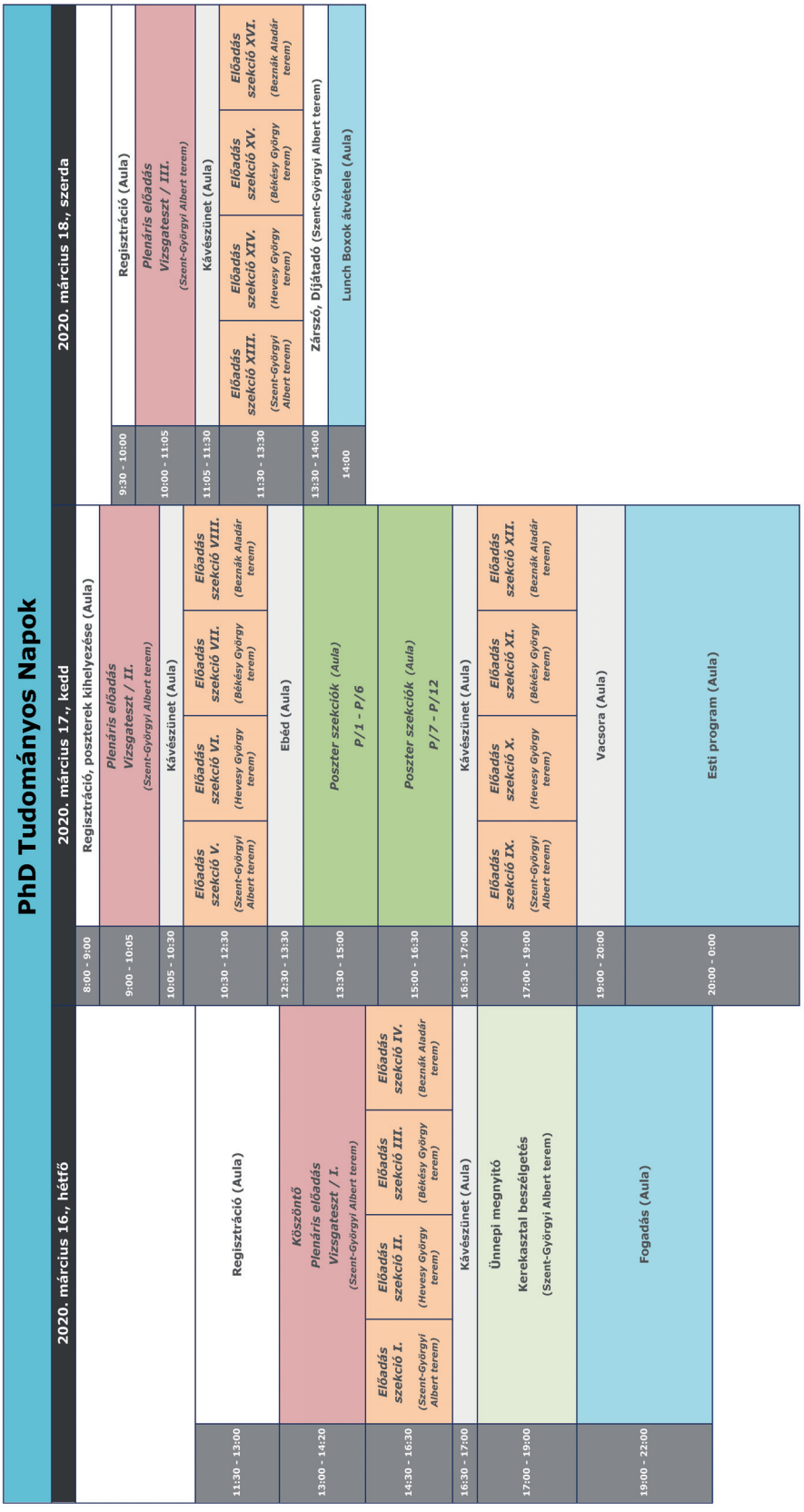
A fokozatszerzéshez az MD/PhD kiválósági programban részt vevő hallgatóknak ugyanazokat a publikációs követelményeket kell teljesíteniük, mint a doktori fokozatszerzésre egyénileg felkészülő hallgatóknak. Ez azt jelenti, hogy a hallgatóknak legalább két tudományos közleményt kell publikálniuk, amelyek összesített impakt faktora el kell, hogy érje a képzést abszolutóriummal teljesítőkre vonatkozó minimum követelmény 150%-át. További feltétel, hogy a hallgató a két közlemény közül legalább az egyiknek első szerzője legyen. A disszertációt a komplex vizsgát követő három éven belül be kell nyújtani a Doktori Iskolához.

Az MD/PhD kiválósági program bevezetésétől azt várjuk, hogy a Semmelweis Egyetem népszerűsége tovább emelkedik a nemzetközi hallgatók körében. Ezen túlmenően a kiváló nemzetközi hallgatók bevonása a PhD-képzésbe emeli mind az oktatás, mind a kutatás színvonalát egyetemünkön.

Program of the Hungarian PhD Conference of Medical, Pharmaceutical and Health Sciences, 2020



Országos Orvos-, Gyógyszerész- és Egészségtudományi PhD Konferencia, 2020 programja



Abstracts of the Hungarian PhD Conference of Medical, Pharmaceutical and Health Sciences

Országos Orvos-, Gyógyszerész- és Egészségtudományi PhD Konferencia absztraktjai

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Retrospective Analysis of Genetic Markers with Prognostic Significance in Chronic Lymphocytic Leukemia

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Introduction: Previous studies of chronic lymphocytic leukemia (CLL) suggested that genetic biomarkers such as chromosome abnormalities, TP53 mutations and mutational status of the immunoglobulin heavy-chain variable (IGHV) gene are associated with prognosis and can stratify patients for standard chemo-immunotherapy or for novel targeted therapies.

Aims: To investigate the distribution and prognostic significance of recurrent genetic alterations in a large cohort of Hungarian CLL patients.

Methods: Diagnostic peripheral blood samples from 1509 patients were collected in the 1st Department of Pathology and Experimental Cancer Research, Semmelweis University. Trisomy of chromosome 12 as well as deletions of the chromosome regions 11q (ATM), 13q (DLEU) and 17p (TP53) were screened by fluorescence in situ hybridization. Coding region of the TP53 gene was interrogated by Sanger and/or next-generation sequencing (NGS). IGHV mutational status was analyzed by Sanger sequencing, with the results being interpreted according to the recommendations of the European Research Initiative on CLL (ERIC).

Results: Trisomy 12 proved to be most common cytogenetic abnormality (28%), while deletions including del(11q), del(13q) and del(17p) were observed in 22.0%, 18.5% and 6.8% of the patients, respectively. Del(13q) was associated with the longest median time-to-first treatment period, while del(11q) and del(17p) were associated with more advanced disease stage. TP53 mutations were identified in 11% of the cases; these patients are typically resistant to standard chemo-immunotherapy but can greatly benefit from novel targeted therapies. Forty percent of all analyzed cases showed a mutated IGHV pattern usually associated with longer survival, while unmutated IGHV status typically being correlated with more adverse clinical outcome was observed in 54% of the patients. In 10% of the cases, prognostic IGHV receptor stereotypes were detected, from which 2.4% belonged to the so called group #2, associated with very poor prognosis.

Conclusions: In our cohort, distribution of recurrent genetic markers showed high concordance with data previously reported by large international studies. The results confirm that molecular cytogenetic and molecular genetic alterations can serve as reliable biomarkers for prognosis assessment and treatment response prediction in CLL.

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Maternal-related factors in the origin of isolated cleft palate

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Introduction: Isolated cleft palate (CPO) is the rarest form of oral clefting affecting 1 to 25 per 10,000 newborns worldwide. There is increasing evidence for the different pathogenetic backgrounds of CPO and cleft lip with or without cleft palate. The role of environmental factors in the origin of nonsyndromic and syndromic CPO is unclear in most patients.

Aims: The aim of this study was to estimate possible maternal risk factors in the origin of CPO.

Methods: The Hungarian Case-Control Surveillance of Congenital Abnormalities contains data of 32,345 birth defect cases and 57,231 control newborns. The study samples included 751 cases with isolated CPO, 1,196 matched controls and 57,231 population controls. Maternal diseases during pregnancy in cases and population controls were compared and adjusted ORs with 95% CI were calculated in a multivariable unconditional logistic regression model.

Results: Beyond the well-known robust female excess (58.9%) – maternal smoking (OR with 95% CI: 2.34, 1.94-2.81) medically recorded maternal anaemia (OR: 1.8, 1.3-2.7), threatened abortion (OR: 4.9, 3.1-7.9) and excessive vomiting in pregnancy (OR: 3.2, 2.6-4.0) were associated with a higher risk for CPO in the offspring. An elevated risk was found in Graves-disease (OR: 4.30, 1.74-10.62), epilepsy (OR: 4.64, 2.44-8.82), migraine (OR: 2.82, 1.18-6.76) and essential hypertension (OR: 2.33, 1.32-4.10). Among acute diseases common cold (OR: 4.94, 3.48-7.03), acute respiratory infections (OR: 4.20, 1.49-11.82), influenza (OR: 2.95, 1.75-4.95), pulpitis (OR: 7.85, 2.80-22.03), cholecystitis (OR: 3.15, 1.16-8.60), acute urinary tract infections (OR: 4.08, 2.22-7.49) and pelvic inflammatory diseases (OR: 3.93, 1.62-9.53) during pregnancy also were associated with an increased risk for developing CPO.

Conclusions: The findings of this study suggest that maternal diseases and lifestyle factors during the first trimester play a significant role in the development of isolated cleft palate.

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Revealing genetic variants as possible predictors of the risk of severe aortic manifestations in Marfan syndrome by genome wide association study

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Introduction: Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder caused by the mutation of the fibrillin-1 (FBN1) gene. Manifestations of the syndrome, including the possibly life threatening aortic involvement, occur in greatly diverse combinations and with varying severity. For precise cardiovascular risk stratification and thus for choosing the appropriate therapeutic strategy it is indispensable to reveal factors that are responsible for the varying expressivity.

Aims: By utilizing an unbiased approach here we aimed to reveal single nucleotide polymorphisms (SNPs) that are related to severe forms of aortic involvement.

Methods: 125 MFS and 250 age and gender matched control patients were enrolled into a genome wide association study (GWAS). MFS patients were classified based on the severity of the aortic involvement, and after the quality control of the GWAS results assessed by the Axiom Precison Medicine Research Array platform, with the use of the PLINK software we searched for SNPs significantly associated to the above defined phenotypes.

Results: Out of the 20 SNPs showing the highest association with aortic involvement 3 variants were identified that were related to the transforming growth factor ß (TGF-ß) pathway. These genes are the following: TGIF1 ($p = 9.756e-06$), HLF ($p = 2.438e-05$) and TNC ($p = 6.299e-05$).

Conclusions: By utilizing an unbiased target identification approach significant association with severe aortic manifestations was identified in case of three genes participating in the TGF-ß signal transduction pathway. Based on the well-known central role of TGF-ß in the development of aortic involvement, after validation, assessment of the above variants in MFS and in related disorders could facilitate the prediction of severe aortic involvement and consequently the selection of the optimal therapeutic approach.

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The mammalian target of rapamycin regulates the RIG-I-like receptor-mediated immune functions in human dendritic cells

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Introduction: As professional antigen-presenting cells, dendritic cells (DC) provide an essential link between innate and adaptive immunity. The unique feature allows DCs to deliver antigens into the lymphoid tissues where they interact with naive T cells and initiate their activation, expansion and differentiation. DC functions are tightly regulated by the mammalian target of rapamycin (mTOR) that controls numerous cellular processes of DCs including metabolism, transcriptional responses, development, maturation, cytokine production, and T cell stimulatory activity. Previously mTOR was identified as a critical regulator of Toll-like receptor-dependent DC activation, however the role of mTOR in the regulation of RIG-I-like receptor (RLR)-mediated DC functions has not been explored yet.

Aims: Our goal is to study the possible modulatory effects of mTOR on the outcomes of RLR-mediated immune responses in human DCs.

Methods: Human monocyte-derived DCs were pre-treated with mTORC1 inhibitor, rapamycin at therapeutically achievable concentrations then activated with specific RLR ligands. Changes in RLR-mediated responses of DCs were monitored by Q-PCR, flow cytometry, ELISA, lactate-assay and western blotting, whereas their T-cell activating capacity was examined by CFSE assay and intracellular flow cytometry after co-culturing with naive CD8+T cells.

Results: We found that mTOR inhibition did not induce remarkable changes in RLR-mediated expression of cell surface molecules, however significantly decreased the RLR-induced pro-inflammatory and polarizing cytokine secretion of DCs. Furthermore, mTOR blockade impaired the activation-induced glycolytic transition in the cells and diminished the ability of RLR-stimulated DCs to promote the proliferation of IFN-γ producing CD8+T cells.

Conclusions: Our results demonstrate that the regulatory function of mTOR is also essential to elicit RLR-induced activation, cytokine production and T cell stimulation of human DCs providing additional insight into the complexity of mTOR-mediated DC functions.

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Effect of Podocin Variants on the Podocin-Nephrin and Nephrin-Nephrin Interaction

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Introduction: Podocin is a major component of the glomerular slit diaphragm. It is encoded by NPHS2, the most frequently mutated gene in nephrotic syndrome. We formerly showed that its most frequent non-silent variant, R229Q makes podocin prone to form abnormal oligomers. Podocin binds nephrin, the major, transmembranous component of the slit diaphragm. The shortest dimension of the glomerular pore (3,5-4 nm) is determined by the distance between nephrin molecules in cis position. We hypothesized that podocin oligomerization regulates the distance between the nephrin molecules.

Aims: We aimed to explore the effect of podocin variants on the podocin-nephrin and the nephrin-nephrin interaction.

Methods: To assess the effect of podocin variants on the nephrin-nephrin distance, wild type nephrin tagged C-terminally with YPet or with mRuby3 and HA-tagged podocin variants were coexpressed in HEK293 cells. In a second set of experiments the fluorescent tags were inserted in the extracellular, juxtamembranous part of nephrin.

To investigate the effect of R229Q podocin on the nephrin-podocin interaction, C-terminal YPet-tagged nephrin was coexpressed with mRuby3-tagged wild type (wt) podocin and either HA-tagged wt or R229Q podocin in HEK293 cells. The mRuby3-tagged and the HA-tagged podocin were encoded by the same vector (pKK-BI16) allowing the equal expression of the two forms.

Förster resonance energy transfer (FRET) was measured between the fluorescently labelled nephrin or podocin and nephrin molecules in living cells. The fluorescence decay curves measured by time-correlated single photon counting (Chronos BH, ISS Inc.) were decomposed into lifetime components, and the longest lifetime population was used for further calculations.

Results: The FRET efficiency between the nephrin molecules increased when wt podocin was coexpressed ($p<0.0005$), but remained unaltered in the presence of pathogenic podocin variants (R286Tfs*17, R138Q, A284V, F344Lfs*4). Similar results were obtained with the extracellular nephrin tags.

R229Q podocin reduced the FRET efficiency between nephrin and podocin as compared to the wt podocin ($p<0.05$).

Conclusions: Podocin regulates the distance between the nephrin molecules: the shortest dimension of the glomerular pore. R229Q podocin induces a change in the conformation or the binding capacity of the nephrin-podocin complex.

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Lymphatics modulate the development of contact hypersensitivity

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Introduction: Contact hypersensitivity (CHS) reaction, the mouse model of human allergic contact dermatitis, is inducible by repeated exposure to contact allergens. In the sensitization phase immune cells are activated by allergens, while in the elicitation phase activated immune cells induce inflammation and tissue destruction following the second antigen exposure. Lymphatics play an important role in the regulation of the immune response in infectious diseases of the skin but the function of lymphatics in the development of allergic contact dermatitis remains unclear.

Aims: We aimed to characterize the role of the lymphatics in sensitization and elicitation phases of contact hypersensitivity.

Methods: In this study Vegfr3kd/+ mice, which lack lymphatics in the entire skin, and a conditional lymphatic loss of function mouse model, in which local deletion of the lymphatic vessels can be induced by diphtheria toxin (DT) injection were used. CHS was initiated by the exposure of the skin to TNCB followed by a second treatment. Disease progression was assessed by ear thickness measurements, hematoxylin and eosin histology, and immunostaining of lymphatic and immune cell markers. The infiltrated immune cells were monitored by flow cytometry.

Results: Our results revealed reduced inflammation with reduced immune cell infiltration was detected in Vegfr3kd/+ mice lacking lymphatics both in the sensitization and the elicitation phases compared to the control. In contrast, DT-injected mice lacking lymphatics only in the elicitation phase showed robust inflammation. In the adaptive CHS model sensitized immune cells from wild type mice were transferred into Vegfr3kd/mice lacking lymphatics in the skin, and increased inflammation with more infiltrating immune cells was detected compared to the control.

Conclusions: We conclude that skin lymphatics play an important role in the sensitization and elicitation phases of CHS, however their function is different in the two phases. Lymphatics contribute to the sensitization process of the immune cells in the sensitization phase, while they moderate the inflammatory response and immune cell infiltration in the elicitation phase.

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Comparison of Ion Channel Inhibitor Effects in Human and Rat Cardiac Ventricular Action Potentials Preparations

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Introduction: Rodent models, such as rats and mice, are commonly used as model organisms in health sciences, due to their higher accessibility compared to larger animals (dog, pig, goat) and the availability of the toolset for their genetic manipulation. However, the translatability of data gathered from rodents is unclear in the field of electrophysiology.

Aims: The aim of this study was to compare the effect of variuos channel blocking agents in human and rat cardiac preparations.

Methods: Ventricular preparations (papillary muscles and trabecules) were studied from human (n=58) and rat (n=36), using the conventional microelectrode technique at basic cycle length of 1000 ms. We assessed the effect of ion channel blockers HMR-1556 (500 nM; IKs), chromanol 293B (100 uM; IKs>Ito), dofetilide (50 nM; IKr); 4-aminopyridine (50-100 uM; IKur>>Ito), XEN-D101 (1-3 uM; IKur), and barium chloride (10 uM, IK1).

Results: Action potential duration (APD90) of human ventricular preparations was 285-± 6.7 ms (mean ± SEM), in rat it was 54 ± 3.5 ms. HMR-1556 caused no significant change in either of the preparation types. Subsequent administration of chromanol caused no change either in human preparations, but in rat it induced significant prolongation. Dofetilide significantly prolonged repolarization in human, but caused no changes in rat. In human preparations 4-aminopyridine induced a slight prolongation, but no such effect was detectable in rat. XEN-D101 did not affect human repolarization, but significantly prolonged that of rat preparations. Barium chloride significantly prolonged action potential duration both in human and rat preparations.

Conclusions: Rodent action potential is characterized by rapid repolarization and no plateau phase, which is a distinctive difference compared to large animals. Our findings suggest that the cardiac ion channel composition of rodents also differs from that of human. Thus, utililization of rodents instead of large animals may not be advisable in cardiac electrophyisiological research.

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Study of the course of hole healing in rats during tooth extraction

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Introduction: Despite significant progress in surgical dentistry, it is still relevant to address issues related to the prevention and treatment of complications in the post-operative period, in particular with complex tooth extractions.

Aims: Study of the effect of hydrogen water and saline solution ionized with silver on the course of the wound process during complex tooth extraction in laboratory rats.

Methods: The experiments were conducted on the basis of the EBM research Institute of VSMU. N. N. Burdenko on 30 white male rats of the Wistar line.

In 10 rats (control group), a physiodispenser and saline irrigation were used for cutting the tooth with boron around the circumference and extraction.

In 10 rats (the main group 1), a physiodispenser and irrigation with saline solution ionized with silver were used when cutting the tooth with boron around the circumference and extraction. In 10 rats (main group 2), a physiodispenser and 8ppm hydrogen water irrigation were used for cutting the tooth with boron around the circumference and extraction.

Results: In the group of control rats after tooth extraction lethargic, not active for 2 or 3 days the hole is covered with a dirty gray patina with an unpleasant odor, the gums around the extracted tooth is brightly hyperemic, on the 7th day remains the flushing of the hole, vanish coating on the 14 and 30 day signs of redness there, the hole is filled in the epithelial layer.

In the main group 1 animals after tooth extraction 2 days active in the mouth there is no unpleasant smell, the hole is filled with clot for a 3 day over the clot is formed and granulation tissue, no swelling at 14 days the hole is fully covered by the epithelial layer.

In the main group 2, the rats after removal were active, took regular food within a few hours, on day 3 there was no hyperemia around the removed tooth, there was no edema, on day 7 the hole was partially covered with epithelial tissue, on day 14 it was completely covered with an epithelial layer.

Conclusions:

1. Using white rats for biomodeling allows you to reproduce the conditions of the wound process.
2. Experimental modeling helps in-depth study of regeneration processes, which can increase the clinical effectiveness of prevention of complications.
3. Further improvement of treatment methods will help to avoid undesirable complications in surgical practice.

7062

Occurrence of bacteria producing extended spectrum β-lactamases in food animals

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Introduction: Multidrug resistance due to production of extended-spectrum beta-lactamases (ESBLs) is a major problem in human as well as veterinary medicine. These strains appear in animal and human microbiome and can be the source of infection both in animal and human healthcare, in accordance with the One Health theorem.

Aims: In this study we examined the prevalence of ESBL producing bacteria in food animals.

Methods: We examined 100 porcine and 114 poultry faecal samples. The samples were cultured on eosine-methylene-blue agar supplemented with 2 mg/L cefotaxime, recovered isolates were identified by MALDI-TOF-MS. Susceptibility testing was performed by Kirby-Bauer disk-diffusion test based on EUCAST guidelines; ESBL phenotype was examined using the double-disk method.

Results: In the porcine and poultry samples 72 and 39 ESBL-producing isolates were found, respectively. All poultry and 43 porcine isolates were Escherichia coli; 21 Proteus spp., 7 Myroides odoratimimus, 5 Citrobacter freundii, 2 Morganella morganii and 1 Providencia rettgeri were also found in porcine isolates. We compared further E. coli of poultry and porcine origin.

The phenotypic resistance was similar among the porcine and poultry E. coli isolates: amoxicillin/clavulanic acid (79,1% vs. 74,1%), cefotaxime (100,0% vs. 99,0%), cefepime (97,7% vs. 97,5%), colistin (0,0% vs. 2,6%), amikacin (39,5% vs. 35,9%) and tobramycin (39,5% vs. 35,9%). In case of gentamicin and sulfamethoxazole/trimethoprim (SXT) the resistance was higher within porcine isolates (79,1% vs. 12,8% and 81,4% vs. 35,9%, respectively). All isolates were susceptible to carbapenems.

The prevalence of ESBL gene families were different among the two type of isolates. The most common was group CTX-M-1, its prevalence was higher in porcine isolates (90,7% vs. 69,7%). The CTX-M-2 gene family found only in porcine isolates (4,7%), while the CTX-M-9 have been found in case of poultry E. coli (7,7%). CTX-M-8 family was totally absent.

Conclusions: The ESBL producing bacteria are prevalent in the faecal samples of the examined food animals, with a dominance of the CTX-M-1 group enzymes.

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Lymph Flow Induces the Postnatal Formation of Mature and Functional Meningeal Lymphatic Vessels

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Introduction: Recently, the presence of lymphatics has been demonstrated and characterized in the dura mater, which is in contrast to the well-accepted view indicating the lack of a classical lymphatic drainage system of the central nervous system. Moreover, the role of meningeal lymphatics in the pathogenesis of Alzheimer's disease and multiple sclerosis was suggested. However, the possible regulators of the developmental program and function of meningeal lymphatics remain unclear.

Aims: We aimed at characterizing the lymph flow dependence of the developmental program and function of the meningeal lymphatic vessels.

Methods: C57BL/6 wild type and lymphatic reporter mice Prox1GFP and Flt4YFP from different ages were used to investigate the developmental program of the meningeal lymphatics. Lymphatic vessels were visualized by whole-mount immunostaining. Lymphatic function was assessed by injection of fluorescently labelled macromolecules and lipids. Flow dependence of the developmental program and function of the meningeal lymphatic vessels was studied in PLCγ2-deficient mice.

Results: First, we demonstrated that lymphatics present in the dura mater are involved in the uptake and transport of macromolecules from the CNS. Meningeal lymphatics develop during the postnatal period which process involves the maturation and structural remodeling of the vessels. The formation of mature meningeal lymphatics coincides with the increase of the drainage of macromolecules from the CNS to the deep cervical lymph nodes. Importantly, the structural remodeling and maturation of meningeal lymphatics is impaired in Plcγ2-/- mice with reduced lymph flow. Furthermore, macromolecule uptake and transport by the meningeal lymphatics are also affected in Plcγ2-/- mice.

Conclusions: Collectively, our results indicate that the meningeal lymphatics are involved in the uptake and transport of macromolecules from the CNS. A postnatal structural remodeling of meningeal lymphatics induces the uptake and drainage of macromolecules from CNS. Lymph flow-induced mechanical forces are required for the postnatal formation of mature and functional meningeal lymphatic vessels. Defining lymph flow-dependence of the development and function of meningeal lymphatics may lead to better understanding of the pathogenesis of neurological diseases including Alzheimer's disease and multiple sclerosis.

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A Novel Potential of SGLT2 Inhibition: Antifibrotic Effect in Diabetes

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Introduction and aims: Clinical data suggest that improved renal outcomes by sodium-glucose cotransporter 2 inhibitors (SGLT2i) are partly beyond their glucose lowering effects; however, mechanisms are still elusive. Enhanced glucose reabsorption in diabetes leads to tubular hypoxia playing part in fibrogenesis. Hyperglycemia is in strong association with increased protein O-GlcNAcylation contributing to renal fibrosis. Considering the proximal tubular involvement in renal pathogenesis and the key role of SGLT2 in glucose metabolism, here we investigated the effects of SGLT2i on tubular hypoxia and O-GlcNAcylation.

Methods: Diabetes (D) was induced by streptozotocin (65 mg/bwkg, ip.) in adult, male Wistar rats. Following the onset of D rats were treated for six weeks with dapagliflozin (D+DAPA, 1 mg/bwkg/day, po.). Metabolic parameters and renal function were evaluated. Novel urinary biomarkers of extracellular matrix remodeling and profibrotic growth factors were determined. Histological evaluation of renal damage were performed. The effect of hyperglycemia was tested in human proximal tubular epithelial cells (HK-2) kept under normal glucose (5.5 mM), high glucose (35 mM) or high mannitol (osmotic control, 35 mM) conditions for 24 hours. HG cells were treated with 10 μM DAPA. To test the effect of hypoxia cells were treated with 10 μM DAPA and were placed in a hypoxic chamber (1% O_2) for 2 hours. Hypoxia markers were measured.

Results: DAPA decreased blood glucose levels and improved renal function. Subsequently novel fibrosis biomarkers, profibrotic growth factor expressions and renal fibrotic tissue accumulation were reduced. DAPA minimized hyperglycemia-induced total protein O-GlcNAcylation in HK-2 cells. Hypoxia-induced HIF-1á elevation was suspended by DAPA treatment. EPO, VEGFA and profibrotic factor levels were also increased in hypoxia and DAPA prevented EPO, TGF-β and PDGF elevation.

Conclusions: These data highlight the role of ameliorated O-GlcNAcylation and diminished tubular hypoxia as important benefits of SGLT2i treatment. Our results support the link between glucose toxicity, tubular hypoxia and fibrosis, a vicious trio that may be targeted by SGLT2i. All these mechanisms are important parts in the puzzle of the complex system behind the protective effect of SGLT2i.

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7004

Test method to investigate the reliability of wall-mounted handrub dispensers

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Hand hygiene with alcohol-based handrub is one of the most efficient tools in fighting healthcare-associated infections. The applied volume of handrub is critical for efficacy. In clinical settings, handrub is usually provided by the means of wall-mounted dispensers. Our previous study found that the dispensed amount can decrease dramatically if dispensers are not in use for a few hours.

The aim of this study was to describe a short, simple protocol for testing wall-mounted dispensers in hospitals.

In the first part of the study, dispensers in regular, daily clinical use were tested. Dispensed amount of handrub was collected after 10 minutes resting, and volume was measured. A total of 21 dispensers were tested, representing 5 different models from various manufacturers. In the second part, dispensers were investigated in laboratory environment. Samples were collected after 2, 3, 5, 10, 30 and 60 minutes. Every time point was measured in triplicates.

We found that even the same type of dispensers can perform differently. From one particular type of dispenser, 5 pieces were tested; in the worst case, after 10 minutes resting idle the dispensed amount decreased to 58% of the original volume, while other pieces of the same type did not lose volume (0% and 2%). During the second part, dispensers were defined as defective if dispensed volume decreased by more than 40% during an hour. In the case of defective dispensers, a significant decrease is detectable even after 3 minutes.

Results suggest that all dispensers should be quality checked regularly, as even the same type dispensers can perform fundamentally different in their critical function of dispensing the proper amount. In the case of defective dispensers, there is no need for time-consuming long-term assessment measurements, as the decrease can be detected in minutes.

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7013

Oral screening of children living with diabetes-orthodontic perspectives

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Aims: Our aim was to provide orthodontic screening, analysis, and treatment for children living with type 1 diabetes as part of the diabetes-dental working group at Semmelweis University.

Methods: We participated in the Budapest Diabetes Day event in 2018 and 2019 with our diabetes- dental working group to provide free oral screening and dental consultation. Before every examination, the patients needed to fill a questionnaire, in order to the ethical approval of the Semmelweis University Ethical Board (SE RKEB:204/2018). The participation in this screening was voluntary based. All the patients under the age of 18 who needed orthodontic treatment got a referral to the Department of Paediatric Dentistry and Orthodontics Semmelweis University, where panoramic radiography, lateral cephalogram, impressions, and photographic documentation were performed. In January and October of 2019, we also took part in the Children Diabetes Day. We collected the data of more than 400 children altogether.

Results: Approximately 120 children were guided to the Semmelweis University for further orthodontic treatment. In 47 cases the orthodontic treatment has already been started. Compared to the control group we expect better oral hygiene and cooperation in the type 1 diabetes group.

Conclusions: There is a need for interdisciplinary cooperation with the help of an orthodontist. Diabetic patients have a higher risk for oral health problems (caries, infections) especially in the cases of dental crowding or different type of malocclusions. Orthodontic treatment may help them to have better metabolic results.

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6900

Visually-guided in vivo juxtacellular recording from CCK/CB1+ basket cells and axo-axonic cells in the mouse M2 premotor cortex

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Introduction: Perisomatic region-targeting inhibitory neurons (PTIs) in the brain are in a key position to control the activity of their postsynaptic partners. In cortical structures one of the main inhibitory inputs onto the soma and proximal dendrites of pyramidal cells originates from cholecystokinin and type 1 cannabinoid receptor-expressing basket cells (CCK/CB1+ BCs), while the axon initial segment (AIS) of pyramidal neurons is innervated exclusively by axo-axonic cells (AACs). In spite of the importance of the PTIs, the in vivo spiking activity of these two interneuron types is largely unknown in higher order associative cortices.

Aims: Here, we aimed to reveal the firing characteristics of these interneurons in M2 premotor cortex in response to noxious stimuli.

Methods: We made visually-guided in vivo juxtacellular recordings to detect the firing of CCK/CB1+ BCs and AACs and their responses to noxious stimuli in urethane-anesthetized mice and compared these results to the activity of the neighboring pyramidal cells. Our results show that the spiking of CCK/CB1+ BCs is elevated upon noxious stimuli. This increase in their firing is most likely caused by the pain-triggered overall network activity, since their spiking response followed pyramidal cell firing with a slight delay. In contrast, AACs were also modulated by noxious stimuli, but their spiking activity varied from short- and long-term suppression even to massive increase in their firing rate.

Conclusions: These observations suggest that CCK/CB1+ BCs might inhibit pyramidal cells in a feedback manner upon noxious stimulation, whereas the activity of AACs is more diverse under these circumstances.

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7015

Developing spheroid models for mutant KRAS targeting strategies

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Introduction: KRAS is a driver oncogene in a variety of cancer types including adenocarcinomas of the lung, colon and pancreas. However, development of successful targeting strategies is still urgently needed and it requires proper preclinical model systems. One critical aspect is that impact of KRAS mutation seems to be more prominent in 3D enviroments than in 2D cultures.

Aims: We are developing complex tissue like spheroid models containing non-transformed stromal cells that can be used for investigations of KRAS biology and drug development. Additionally, we aim to increase the number of KRAS mutant cell models with spheroid formation capacity by optimizing culture conditions.

Methods: Literature based optimization of sphere formation media supplements were performed on SW48 colon cells and isogeneic derivatives transfected with mutant KRAS. Protocol for spheroid processing and embedding was also developed in order to perform histological analysis and immunohistochemistry. Co-cultures of tumor cells with normal fibroblasts and endothelial (HUVEC) cells were treated with a specific covalent inhibitor of KRAS G12C protein.

Results: Sphere formation was successful in all cell lines tested. Immunohistochemical identification of the individual components of the spheroid provide a unique feature to assess specific antitumoral- and bystander drug effects. Based on spheroid size and cell type staining we demonstrated the effective and selective inhibition of tumor cell growth without affecting the stromal cells.

Conclusions: Spheroid cultures of tumor and stromal cells are useful tools for drug development, especially for mutant KRAS targeting. Following optimization, it can be as reproducible and robust as conventional 2D methods.

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Examination of the Relation between Red Blood Cell Aggregation and Hematocrit in Various Species

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Introduction: Red blood cell (RBC) aggregation is a reversible clumping of cells at low shear-rate or in stasis. In addition to cellular and plasmatic factors, hematocrit (Hct) also determines this process, since the number of cells involved has an effect on the degree of aggregation and the dynamics of cell-cell interactions.

Aims: We hypothesized that the RBC aggregation – hematocrit relation differs in species.

Methods: Blood samples were taken from 7 healthy male volunteers (DE-RKEB-3189-2010), 6 male Crl:WI rats, 6 male Beagle dogs, and 7 female Hungahib pigs (24/2016/UDCAW, 7/2014/UDCAW, 13/2014/UDCAW). From the samples 20, 40 and 60 % Hct RBC - autologous plasma suspensions were prepared. We measured hematological parameters (Sysmex F-800 or Sysmex K-4500 microcell counter), RBC aggregation by the light-transmission (Myrenne MA-1 aggregometer) and light-reflectance method (LoRRca Maxsis Osmoscan ektacytometer). For statistical analysis, ANOVA test was used.

Results: Using the light-transmission method, the M5s aggregation index parameter significantly differed between the species. At 20% hematocrit human values were significantly higher than pigs' values, at 40% Hct the rat blood samples showed a significantly lower results compared to all other species. In the LoRRca aggregation index for human, dog and pig samples there was a decrease with the risen of Hct values. At 60% human specimens were significantly lower and rat samples were significantly higher than the other samples. In the aggregation amplitude (Amp) the lowest values were measured in rat, followed by pig, human and dog blood samples. At 20% human samples differed from all other species. At 60% the rat samples showed lower Amp values to the other. In the syllectogram half-life (t1/2) parameter, in the native samples the dog blood showed the highest values. In human, dog and pig samples, there was a continuous increase in t1/2. The highest increase was observed in human. At 60% Hct the human and the dog specimens showed a difference to the other samples, both were higher than the others.

Conclusions: The relationship between RBC aggregation and hematocrit varies between species. Results suggest that the ability of human blood to aggregate is the most sensitive to hematocrit's changes. These data can be useful for extrapolating results of animal experiments.

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Nanoparticle-reinforced fibrous meshes with antibacterial properties

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Introduction: In the recent decades, nanoparticles with antibacterial properties (e.g. silver nanoparticles) have emerged to be promising candidates in the replacement of antibiotics in the fight against multidrug resistant bacteria strains.

Nanoparticles can be easily incorporated into fibrous polymer meshes utilizing a versatile polymer processing method, namely electrospinning. Electrospinning is an efficient and low-cost method for polymer processing that allows the formation of non-woven fibrous meshes. The structure of these meshes is highly similar to the natural extracellular matrix therefore, they might be able to mimic the environment of skin tissues. Due to this structural similarity fibrous meshes could be used as wound dressings. Incorporation of silver nanoparticles (AgNP) could provide antibacterial properties to the fibrous system. Minimizing pain could also be achieved by encapsulation of small-molecule drugs such as paracetamol.

Aims: The aim of our research was developing a one-pot method for the synthesis of AgNPs in the presence of a biocompatible poly(amino acid) derivative, polysuccinimide (PSI), then creating a novel antibacterial wound dressing system and finally investigating its antimicrobial properties and mechanical characteristics.

In addition, a small drug molecule (paracetamol) was also encapsulated in the meshes. Release profile was examined, as well as the mechanical strength as the function of drug-content.

AgNPs were synthesised by chemical reduction method in the presence of PSI then the resulting nanoparticles were characterized with DLS. Fibrous meshes were prepared using an electrospinning device and the surface structure was examined by SEM. For the evaluation of antibacterial properties disc diffusion tests were carried out. Release kinetics of paracetamol was studied using UV-Vis spectroscopy.

Methods: By changing the synthesis and electrospinning parameters, an optimization procedure was carried out and drug-loaded electrospun PSI fibers containing AgNPs were successfully prepared. Antibacterial studies confirmed that silver-content can hinder the colonisation of the meshes by E. coli, S. epidermidis and other bacteria strains, but the antibacterial properties are highly dependent on the paracetamol content as well.

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Assessment of health related quality of life among early-treated Hungarian adult PKU patients

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Intruduction: The implementation of neonatal screening and the early initiation of lifelong therapy helped to prevent severe complications and enabled a much more favorable outcome for early-treated PKU (ETPKU) patients. However, PKU patients tend to develop subtle cognitive and psychosocial abnormalities whereas the strict dietary therapy also presents financial and social burden. Thus, PKU is expected to affect the quality of life of these patients. There is insufficient evidence regarding the relation between metabolic control and Health Related Quality of Life (HRQoL).

Aims: We aimed to assess the short and long term therapy effect on quality of life of Hungarian adult PKU population using the standardised PKU specific PKU-QoL questionnaire.

Methods: We conducted a single centre, cross sectional, observational study in Hungary. We included adult PKU patients treated with diet and aminoacid supplements only. Patients reported HRQoL with the standardized adult PKU-QoL questionnaire whereas average blood Phe concentration was assessed in three different time periods: previous 10 years, previous year and actual metabolic status. Correlation between patients' QoL scores and their Phe levels was investigated. Classical PKU group was further divided into "good" and "suboptimal" adherent group based on the individual mean Phe levels in the examined time period. We evaluated differences in quality of life among the two subgroups of classical PKU patients.

Results: Data from 88 adult patients were analysed (66 of them classical PKU). No median score reached mayor or severe impact/frequent symptoms in any domain. Highest scores (meaning larger burden) are mostly related to emotional impact of PKU and disease management. When performing correlation analysis between Phe levels and QoL scores by all patients we found weak to fair positive correlation in several domains either short or long term. Good therapy adherent Classical PKU patients tend to report better scores than patients with suboptimal adherence.

Conclusions: We conclude that patients showed good HRQoL using the PKU specific questionnaire. Our study demonstrates that suboptimal metabolic control is negatively associated with patients health related quality of life.

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7077

TNMplot: transcriptome based database for the comparison of gene expression profiles of normal, malignant and metastatic tissues.

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Introduction: Over the past two decades robust amount of cancer related data have became available online, including both RNA sequencing (GDC) and gene-chip based data (NCBI-GEO). Currently, there is a lack of user-friendly web-tool, that allows the comparison of normal, tumor and metastatic data within and across these databases.

Aims: To create a database which enables the comparison of normal, tumor and metastatic data across all genes and multiple databases.

Methods: Our database is built on two platforms, gene chip and RNA-seq. The gene chip data were processed from the NCBI-GEO database using a total of 3180 assays, from which we manually selected the appropriate samples, followed by the normalization process using the MAS5 algorithm. RNA sequencing data was downloaded from TCGA, TARGET and GTEx databases. TCGA and TARGET contain mainly tumor and metastatic data from adult and pediatric patients, while data found in GTEx are from healthy tissues. A total of 23.418 sample sequences from the three databases were used, which were normalized using the DESeq2 algorithm.

Results: A total of 33.520 samples were included from 3180 gene chip-based assays, comprising of 453 metastatic, 29.376 tumorous and 3691 normal samples, across 38 tissue types. From the TCGA database, we used 11010 samples (394 metastatic, 9886 tumorous and 730 normal) representing 33 tissue types, from TARGET we used 1193 samples (1 metastatic, 1180 tumor, 12 normal) in 7 tissue types, based on GTEx data we withdrew 11.215 normal samples over 53 tissue types.

Conclusions: In this study, we created a transcriptome-based database containing 56.938 samples. This database serves as a base for the establishment of an online application to track the development and progression of tumors.

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Cell type-specific Examination of Tonic Cannabinoid Signaling

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Retrograde endocannabinoid (eCB) signaling via presynaptic cannabinoid (CB1) receptors play an essential part in the calibration of neurotransmitter release probability in both phasic and tonic manner. Tonic eCB signaling plays considerable role in fine-tuning synaptic strength and thus adjusting network oscillations in interneuron type-specific and activity-dependent manner. Specific disruption of this pathway is associated with many neurological disorders, such as autism, epileptic seizures and Huntington's disease indicating its significant importance. However, despite the fact, that the most common endocannabinoid messenger 2-arachidonoylglycerol (2-AG) and its predominant synthesizing enzyme diacylglycerol lipase-α (DGLα) are essential elements of phasic eCB signaling, they role in persistent eCB signaling has remained elusive. Therefore, we aimed to study specific features of this molecular pathway in cell-type specific manner using paired patch-clamp electrophysiology with the combination of Stochastic Optical Reconstruction Microscopy (STORM), and liquid chromatography/tandem mass spectrometry. We found that presynaptic CB1 receptors on hippocampal perisomatic interneuron axon terminals specifically mediate tonic eCB signaling and AM251 is a specific antagonist/invers-agonist of the CB1 receptors. Furthermore, we have shown the presence of a persistently active 2-AG production in the slice preparations mediated by DGLα enzyme. The continuously generated 2-AG is kept under the tight control of the main 2-AG hydrolyzing enzyme monoacylglycerol lipase (MGL), although surprisingly, the lack of tonic 2-AG production does not alter basic synaptic transmission. Moreover, despite the significant role of DGLα in neural pathfinding and synaptogenesis, no morphological alterations were observed at perisomatic interneurons in mice lacking DGLα. Our findings uncovered a previously undescribed, DGLα – 2-AG independent form of tonic eCB signaling at these synapses. This signaling pathway is able to maintain synaptic function on homeostatic levels even in the absence of DGLα.

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The Application of 3D Printing in the Formulation of Personalized Drug Delivery Systems

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Introduction: The interest toward additive manufacturing is growing considering the formulation of personalized medicines. 3D printing is commonly an additive process, which results in layer-by-layer built objects. The most common types are Photopolymerization, Selective Laser Sintering (SLS), Fused Deposition Modelling (FDM). The first 3D printed orodispersible tablet was approved by the FDA in 2015.

Aims: The objective of our study was to design and print biodegradable drug delivery systems.

Methods: Commercially available filament materials were screened as well as the print settings were optimized. In addition, the influence of design parameters (e.g. wall thickness, morphology, pores) on drug delivery in case of model drugs was investigated. Moreover, the applicability of matrix polymers and gelling agents in the process of 3D printing was studied. There were some formulations aiming the study of dose proportionality, in order to expand the opportunities of personalized medication.

The designed polygon models were sliced(Ultimaker Cura 3.6, Netherlands) and an FDM printer (Creality Ender 3, China) was used to print the objects with polylactic acid (PLA) and polyvinyl alcohol (PVA) based filaments. The investigated printing parameters were the following: temperature of the extruder: 170-250 °C; bed temperature: 50-110 °C; printing speed: 5-40 mm/s; cooling fan performance: 30-100% and infill: 0.1-0.4 mm. The dissolution profile of the model drug was examined in different pH media (1.2; 4.5; 6.8) recording also the particle size distribution of solid filaments.

Resuts: As a result of this study, the morphology of PLA and PVA based carriers were optimalized via the proper print settings. According to the biorelevant dissolution studies, the PVA based printlets form colloidal dispersion in aqueous media without reference to H^+ concentration (Z-avg Aquapur: 235.13±2.12 nm; Z-avg pH=1.2: 245.85±11.67 nm; Z-avg pH=6.8:249.57±11.67 nm). The drug release was significantly influenced by the morphology and layer characteristics of the carriers, the presence and number of pores and excipients. The released API contents of equally increased dose samples showed great linearity with high R2 values (ranging from 0.983 to 0.992) which confirms the dose proportionality.

Conclusions: These adjustable properties lead to wide range of opportunities to precisely tailor the release profile of the 3D printed drug delivery systems.

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The Concept of an Integrated Central Blood Pressure-Aortic Stiffness Score, a Potential New Tool for Cardiovascular Risk Stratification: Further Results in Chronic Kidney Disease

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Introduction: Arterial vascular stiffness and central blood pressure are potential tools in cardiovascular risk assessment. Different values resulting from many available methods, however, make the emergence of an international consensus difficult.

Aims: Our aim was to study the predictive power of Integrated Central Blood Pressure- Aortic Stiffness (ICPS) risk categories on cardiovascular (CV) mortality in end-stage renal disease (ESRD) patients on hemodialysis therapy.

Methods: In our retrospective cohort study 91 patients were involved from two dialysis centers. Pulse wave velocity (PWV), central systolic blood pressure (cSBP) and central pulse pressure (cPP) were measured with tonometric method, patients were followed for a median of 29.5 months and CV mortality was registered. Patients were classified into tertiles based on their PWV, cSBP and cPP values. After the analysis of the predictive values of the tertiles of the identical parameters, patients were scored. One score was given, when a patient had a third tertile value of cSBP or a second or third tertile value of PWV or cPP. Then the CV outcome was analyzed with Cox regression analysis of the groups of patients with different ICPS scores and three ICPS risk categories were defined: average (0-1 point), high (2 points) and very high (3 points).

Results: During follow-up 31 events occurred. After adjustment for multiple factors, compared with the average ICPS risk category group (n=35; 38%), those, who were in the high risk group (n=33; 30%) showed a tendency for significantly higher hazard ratio (HR) of CV mortality (HR=2.62, 95% confidence interval (CI):0.82-8.43), while patients in the very high ICPS risk category (n=23; 21%) had a markedly increased risk (HR=10.03, CI:1.67-60.42).

Conclusions: The ICPS risk categories can help in the identification of ESRD patients with high CV risk.

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7010

Improving molecular diagnostics in pediatric Acute Lymphoblastic Leukemia with comprehensive biostatistical analysis of RNA based panel sequencing

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Introduction: Acute Lymphoblastic Leukemia (ALL) is the most frequent malignancy during childhood. It affects 60-70 children in Hungary annually. Although the overall survival increased dramatically during the last century, novel diagnostic-, and personalized therapeutic methods could increase the survival rate even more. Additionally, these methods could reduce the side-effects caused by the usually applied chemotherapy.

Aims: Our long term aim is to develop an integrated next-generation sequencing (NGS) and bioinformatic analysis pipeline, in order to provide clinically relevant diagnostic information based on transcriptome panel sequencing. Using this information, personalized therapy can be administered to patients. The aim of this study was to analyze NGS results from a bioinformatical and statistical point of view and provide initial recommendations in interpreting them for medical reports and clinical diagnosis.

Methods: We performed RNA-based QuiaSeq PanCancer panel sequencing on 77 ALL patients and 11 control samples, using an Illumina MiSeq device. We analyzed raw sequencing data using the FusionCatcher, STAR Fusion, and Pizzly tools, besides integrating the data with the FusionHub database. Fusion transcript results were further analyzed with R and R-Studio. We evaluated the distribution of fusion transcript spanning and paired reads, besides their expression, in order to optimize sensitivity and specificity of medical diagnosis presented in reports.

Results: We detected numerous well-known fusion transcripts occurring in pediatric ALL including: ETV6-RUNX1 fusion transcripts in 9 patients, P2RY8-CRLF2 in 4 patients, and KMT2A-AFDN, DDX5-LEF1, NFATC1-RNPS1 each of them in 2 patients. Moreover, we found several hundred fusion transcripts with a known pathogenicity in other diseases, or unknown clinical significance.

Conclusions: Here we present a comprehensive bioinformatics and biostatistics analysis of 11 RNA-based QiaSeq PanCancer NGS runs. This dataset may serve as the basis of optimization for the downstream bioinformatic analysis of NGS data of the Hungarian pediatric ALL patient population in order to improve the quality of the personalized molecular diagnosis.

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Lateral Left Ventricular Lead Position is Superior to Posterior Position in Long-term Outcome of Patients Underwent Cardiac Resynchronization Therapy

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Introduction: Preferring side branch of coronary sinus during cardiac resynchronization therapy (CRT) implantation is empirical due to the limited data on the association of LV lead position and long-term clinical outcome.

Aims: We evaluated the long-term all-cause mortality by left ventricular (LV) lead non-apical positions and further characterized them by interlead electrical delay (IED).

Methods: In our retrospective database 2087 patients were registered between 2000 and 2018. Those with non-apical LV lead locations were classified into anterior (n=108), posterior (n=643), and lateral (n=1336) groups. All-cause mortality was assessed by Kaplan-Meier and Cox analyses. Echocardiographic response was measured 6 months after CRT implantation.

Results: During the median follow-up time of 3.7 years, 1150 (55.1%) patients died, 710 (53.1%) with lateral, 78 (72.2%) with anterior and 362 (56.3%) with posterior positions. Patients with lateral position had significantly better outcome in all-cause mortality compared to others (HR 0.80; 95% CI: 0.71-0.90; $p<0.0001$), which was also confirmed by multivariate analysis after adjusting for relevant clinical covariates (HR 0.81; 95% CI: 0.72-0.91; $p<0.0001$). When echocardiographic response was evaluated in the lateral group, patients with an IED longer than 110 ms (ROC AUC 0.63; 95% CI: 0.53-0.73; $p=0.012$) showed 2.1 times higher odds of improvement in echocardiographic response 6 months after the implantation.

Conclusions: In this study we proved that after CRT implantation only the lateral LV lead location was associated with long-term mortality benefit. Moreover, patients with this position showed the greatest echocardiographic response over 110 ms IED.

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Functional Characterization of NLRP3 Inflammasomes in Human Plasmacytoid Dendritic Cells

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Introduction: Plasmacytoid dendritic cells (pDCs) are referred to as the most powerful innate immune cells of antiviral responses due to their selective expression of viral nucleic acid sensing endosomal TLRs and their unique capability to produce high amounts of type I IFNs. Furthermore the cytosolic receptors including RIG-I-like helicases evolved for detecting virus replication are also functional in pDCs. However the activity of inflammasome-forming cytosolic receptors such as NLRP3 or their IL-1β producing capacity that can be involved in the antibacterial defense of the cells has not been explored yet.

Aims: In this study we aimed at characterizing the NLRP3 activity in pDCs which could influence the outcome of pDC-mediated immune responses.

Methods: Human pDCs were stimulated with various cell surface or endosomal TLR ligands, NLRP3 activators or live pathogenic and non-pathogenic bacteria then the expression and activity of NLRP3 pathway components were detected by Q-PCR at the mRNA level, and western blotting or ELISA at the protein level.

Results: We found that pDCs express the essential components of the NLRP3 pathway and produce pro-IL-1β upon challenges with TLR ligands or live bacteria. Interestingly, pDCs are able to release the mature form of IL-1β in response to the potassium ionophore nigericin but not to ATP that might be explained by the poor expression of P2X7 purinergic ATP receptors in pDCs. We also observed that pathogenic bacteria have greater capacity to induce NLRP3 activation in these cells in contrast to the commensal ones. Moreover specific inhibition of NLRP3 abolished IL-1β secretion indicating that IL-1β is produced in an NLRP3-dependent manner in pDCs.

Conclusions: Here we demonstrated for the first time that beside their strong antiviral properties pDCs can form active NLRP3 inflammasomes and can be involved in the IL-1-mediated pro-inflammatory responses as well.

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7126

Coagulation profile of kidney transplanted children, using Rotational Thromboelastometry (ROTEM)

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Introduction: ROTEM is a worldwide accepted and used procedure in terms of acute blood loss and chronic illnesses which affect coagulation factor production.

Coagulation problems are frequent in chronic kidney disease. On one hand, bleeding occurs in about 50% of patients with end-stage renal disease (ESRD). On the other hand, the risk of venous thromboembolism is also increased in patients with ESRD and following kidney transplantation (KT).

Aims: Our goal was to describe the coagulation status in paediatric KT children. Correlation analysis between ROTEM and classic coagulation parameters and evaluating ROTEM parameter differences in normal and kidney transplanted children population.

Methods: All patients were randomly selected from the KT patients, treated at the I. Dep. of Paediatrics, Semmelweis University.

Standard laboratory values, classic coagulation parameters (PT-INR, aPTT, TT, fibrinogen, AT) and an extended evaluation of haemostasis by means of ROTEM were measured, which included EXTEM (extrinsic pathway activated), INTEM (intrinsic pathway activated), FIBTEM (fibrin polymerisation) and APTEM (extrinsic activated, with fibrinolysis inhibition) measurements.

Results: 18 patients (7 female), with an average age of 14,05 years were included. None of the patients were on antithrombotic therapy. In terms of EXTEM parameters, we have found significantly longer clotting time (CG) 67s/57s (p 0,002), thicker maximum clot firmness 68 mm/60 mm (p 0,006), and decreased cloth lysis 97,5%/87% (p 0,002) in the 11 to 16 years KT group compared to the age specific control group. However, only the Clotting time (CT) was significantly prolonged 184s/171s (p 0,008) in this age group, concerning INTEM parameters.

Correlation analysis showed moderate correlation (r 0,5–0,7) between INTEM CT, clot formation time, maximal clot firmness (MCF) and APTI, platelets, fibrinogen parameters. Strong correlation (r 0,58–0,75) was found between FIBTEM MCF and APTI, fibrinogen. APTEM MCF correlation was more prominent with fibrinogen, compared to the EXTEM MCF (r 0,65 vs. 0,54), but a moderate correlation was found between EXTEM MCF and platelets (r 0,63).

Conclusions: ROTEM parameters are showing good correlation with the classic coagulation parameters. Clot formation via extrinsic or intrinsic pathway activation tends to be slower, but extrinsic activated clot was relatively stronger, compared to the control group.

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Importance of iron deficiency in athletes

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Introduction: Iron metabolism determines the oxygen transport of the blood, thereby affecting the exercise capacity and performance. In patients with heart failure iron deficiency (ID) is a major risk factor that predicts and influences patient's quality of life.

Aims: In athletes diagnosing ID is also extremely important as it determines sport performance. Our aim is to study the correlation of iron metabolism parameters with exercise capacity in athletes.

Methods: Cardiopulmonary exercise test (CPET) was performed as part of detailed sports cardiology screening. We studied in athletes the changes of iron metabolism parameters (serum iron, transferrin, total iron-binding capacity (TIBC), ferritin) and its correlation with the exercise physiology parameters.

Results: Our measurements were performed on 105 top athletes: swimmers (n=58,55%; male=29; junior=30; 20,4 ± 4,6 y), football players (n=47, 45%; junior=6; 23,2 ± 5,4 y). Laboratory test verified hemoglobin (male=153,8 ± 9,4; female=141,2 ± 7,7 g/L; p<0,001) and hematocrit (male=0,45 ± 0,03; female=0,42 ± 0,02 L/L; p<0,001) value in a normal range for all. In women, significantly lower ferritin (67,8 ± 76,2 vs. 98,9 ± 48 ug/L; p<0,05) and higher TIBC (78,1 ± 14,3 vs. 66,5 ± 9,3 umol/L; p<0,001) were observed. Young male athletes had significantly lower serum iron (16,1 ± 6 vs. 21,2 ± 7,5 umol/L; p<0,05), ferritin (68 ± 42,7 vs. 109,1 ± 45,5; p<0,01) and higher TIBC (76,1 ± 11,0 vs. 64,3 ± 7,4 umol/L; p<0,001) compared to adults. During CPET male athletes had higher maximal aerobic capacity (52.2 ± 4.4 vs. 55.9 ± 5.5 mL/kg/min; p<0.001) and ventilation (115.8 ± 16.1 vs. 153.2 ± 26 L/min; p<0.001) compared to females. VO2 max and ventilation showed positive correlation with ferritin (p<0,0001). Iron supplementation was required in almost half of the athletes (n=49, 47%).

Conclusions: Diagnosing ID in athletes, complete iron panel containing ferritin is required. According to our results iron status determines performance, therefore ID screening and iron supplementation is extremely important.

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Intracellular Signaling Pathways of Bradykinin-induced Detrusor Contraction in Murine and Human Urinary Bladder

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Introduction: Overactive Bladder (OAB) affects more than a hundred million people's quality of life. Currently, antimuscarinic drugs are the first-line medical therapy for the management of OAB. However, their application is limited due to the severe side-effects. Bradykinin (BK) is a peptide mediator that evokes contraction in several smooth muscle tissues and its potential role in OAB has been proposed in the literature. We investigated the role of BK in the regulation of mouse and human detrusor contraction as well as the signaling pathways involved.

Aims: Our aim was to identify novel, more specific potential therapeutic targets for the treatment of OAB.

Methods: Experiments on murine bladders were performed on adult, male, wild-type (WT) and Gαq/11 or Gα12/13 knockout (KO) mice. Human detrusor tissues were gained from urinary bladders surgically removed during radical cystectomy, from a macroscopically tumor-free area, approved by a uropathologist. Urothelium-free smooth muscle strips were mounted on a myograph system, the force and time course of their contractile responses were registered under isometric conditions. Changes in the muscle tone were normalized on the contractions induced by124 mM K^+.

Results: BK evoked dose-dependent contractions in both murine and human detrusor muscle. The muscarinic acetylcholine receptor antagonist atropine had no influence on BK-induced contractions. The B2 receptor antagonist HOE-140 significantly reduced the effect of BK in bladder strips of both species and its simultaneous application with the B1 antagonist R715 abolished the detrusor contractions. The contractile responses to BK were significantly lower in the Gαq/11 and Gα12/13 KO murine detrusor strips. The selective inhibitor (Y27632) of ROCK enzyme also diminished the effect of BK in WT mice and in Gαq/11 KO bladder strips it blocked the contractions completely.

Conclusions: Our results demonstrate that BK evokes contraction directly on the bladder smooth muscle, independently of cholinergic signaling pathways in both human and murine detrusor. The effect of BK is mediated predominantly by B2 receptors in both species. In mice the Gq/11-coupled and the G12/13-Rho-ROCK pathways mediate simultaneously the effect of BK on the detrusor. The B2 receptor as well as the ROCK enzyme offer potentially more selective therapeutic targets for the management of OAB.

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Predictors and characteristics of coronary artery plaque progression using serial CT imaging.

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Introduction: The progression of coronary atherosclerosis is a dynamic process with significant changes in metabolism and morphology. Several studies have demonstrated that plaque progression can be seen as a prognostic factor of adverse events, regardless of the severity of the stenosis. In order to refine risk prediction better understanding of the predictors of plaque progression is of utmost importance.

Aims: Our study evaluates the extent of coronary artery disease (CAD) and the degree of the stenosis by serial coronary CT angiography (CCTA) with the aim to further elucidate the predictors of coronary plaque progression in patients with suspected CAD.

Methods: In our retrospective study 115 patients were enrolled (mean age was 60.98±9.89; 74.5% male) who underwent serial CCTA. In order to analyze changes in plaque burden CCTA images were assessed by a single reader. Segment involvement score (SIS) and segment stenosis score (SSS) were assessed in 1577 segments. Using multivariate linear mixed models the effect of cardiovascular risk factors and statin therapy were also evaluated on SSS, SIS and the progression rate of coronary artery disease.

Results: In multivariate analysis age, male gender and statin therapy had direct effect on SSS. Regarding SIS, older age, male gender, diabetes mellitus and statin therapy were associated with higher scores. Annualized progression of SIS and SSS was increased by smoking: β=0.35 (CI: 0.09-0.6, p=0.007) and β=0.20 (CI: 0.04-0.37, p=0.017).

Conclusions: Our study results showed that CCTA accurately detects coronary plaque progression. SSS increased by gender, age and statin therapy, whilst total plaque burden was also associated with diabetes. Smoking is a significant factor of progression rate of coronary artery disease.

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Application of a RGB autofluorescence based techniques for the non-invasive screening of pigmented skin lesions

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Introduction: In the recent years more and more non-invasive imaging methods are available to assess different skin diseases in all over the world. From the countless indications of these methods the differential diagnosis of benign pigmented skin lesions and melanoma is one of the most relevant topics in the field of dermato-oncology.

Aims: We utilized a handheld device operating based on the principles of RGB autofluorescence using LED (light emitting diode) light to detect various skin lesions.

Methods: We performed the study in two different centres, in the Department of Dermatology, Venerology and Dermatooncology of Semmelweis University, and in the Oncology Centre of Latvia in Riga. We examined 1600 pigmented lesions with this method and documented these cases with clinical and dermoscopic photographs. We used LED light four different wavelengths of 405 nm, 526 nm, 663 nm and 964 nm, which excite different components in the skin a based on their distinct excitation spectra. The 526 nm is absorbed mainly by the hemoglobin, the 663 nm is by the melanin, while 964 nm grants deeper penetration depth . The light at the wavelength of 405 nm induces certain endogenous fluorophores in the skin including keratin, flavins and elastin. From these data a Matlab based software (MathWorks Inc., Natick, MA, USA) counts a p parameter to estimate the risk of melanoma. We analyzed the p parameters using Student's two-sample t-test.

Results: The device proved to be suitable to differentiate melanoma from other benign pigmented skin lesions using the parameter p. The value of the parameter p refers to the risk of the lesions, and the range between 0,5 and 1 means the high risk group. Among the melanoma cases the p parameter had an average value of 1,407 (n=21) while it was 0,17 among the benign lesions.

Conclusions: The present device is a potential screening tool in the field of to differentiate benign pigmented skin lesions from melanoma. In addition to its low cost and safe application, the exposition time of 40 seconds is short enough to use it in the everyday clinical practice. Also, p parameter is calculated within one minute following the image exposition. Thus, this device could be applied as a potential screening tool for the assessment of skin lesions at the offices of general practitioners.

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Frontal cortical control of an extrathalamic inhibitory pathway projecting to the intralaminar nuclei of thalamus

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The intralaminar nuclei of thalamus (IL) is a thalamic node with links to the prefrontal cortex, the cerebellum and the basal ganglia as well. As a consequence the IL has been implicated in higher order motor as well as cognitive functions. Our research group discovered an extrathalamic inhibitory pathway from the pontine reticular formation (PRF) which selectively innervated IL. Photoactivation of PRF-IL fibers evoked complete behavioral arrest and the appearance of a slow cortical oscillation in the frontal LFP for the duration of the stimulation supporting the complex function of IL in organizing behavior.

Aims: We aimed to examine the cortical inputs of the PRF inhibitory cells in order to assess whether frontal cortex is able to inhibit and/or pattern IL activity via a PRF inhibitory interface.

Methods and results: Injections of AAV-ChR2 into the frontal cortex (M2 and Cg) of RBP4-Cre/Glyt2-eGFP double transgenic mice revealed that GlyT2+ neurons of the PRF receives L5 inputs. Juxtacellular recording and labelling in the PRF demonstrated that photoactivation of M2 L5 cells evoked short latency action potentials with high probability in the GlyT2+ cells of the PRF. Spontaneous rhythmic activity of Glyt2+ cells was tightly linked to the slow cortical oscillation and was disrupted upon cortical desynchronization. These data together indicated strong frontal cortical control over the PRF-GlyT2 cells.

Conclusions: Our results indicate that frontal cortical regions conveying a behavioral signal and can reliably activate inhibitory neurons of the PRF. PRF GlyT2 cells in turn transfer this to the IL as an inhibitory signal strongly affecting thalamocortical and thalamostriatal activity.

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Impaired Skeletal Muscle Regeneration and Altered Inflammatory Cytokine and Gdf3 Production in Transglutaminase 2 Knock Out Mouse

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Introduction: Skeletal muscle regeneration is initiated by local inflammation and is accompanied by the removal of dead cells from the injured area. Apoptotic cell phagocytosis regulates the inflammatory program in macrophages by converting the inflammatory phenotype into a healing one. Therefore, abnormal phagocytosis or deregulated inflammation can lead to impaired muscle regeneration.

Aims: Tissue transglutaminase (TG2) is a versatile enzyme playing a role in both the phagocytosis and regulation of inflammation in macrophages; therefore, we aimed to characterize skeletal muscle regeneration in mice in the absence of TG2.

Methods: Muscle injury was induced by cardiotoxin injection into the tibialis anterior of TG2+/+ and -/- mice. Laminin immunohistochemistry and DAPI staining were performed on frozen histological sections of isolated muscles to determine the cross-sectional area of myofibers and the number of multinucleated myofibers. We examined the proportion of immune cells invading the regenerating muscle by flow cytometry. Leukocytes (CD45+ cells) were isolated from injured muscles to examine the expression of inflammatory cytokines and growth factors they produce.

Results: We found smaller average myofiber cross-sectional area and higher frequency of smaller fibers in control and regenerating TG2-/- muscles than in the wild type ones. We also observed a lower number of multinucleated myofibers in TG2 KO muscles that may refer to the impaired fusion of myogenic cells. Although the number of infiltrating neutrophils and macrophages is similar during regeneration in wild type and TG2 deficient muscles, the gene expression of TNFα, IL1β, and IL6 pro-inflammatory cytokines at day 2, and the expression of TGFβ1 anti-inflammatory cytokine at day 4 were lower in leukocytes isolated from TG2-/- muscles. Compared to wild type leukocytes the Gdf3 expression was also lower in the absence of TG2.

Conclusions: These results indicate that TG2 affects cytokine and growth factor expression in regenerating skeletal muscle which results in disturbed skeletal muscle development and regeneration.

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Pharmacogenetic Study of the Central Nervous System in Pediatric Acute Lymphoblastic Leukemia

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Introduction: Pediatric acute lymphoblastic leukemia (ALL) has a favorable prognosis thanks to the combined chemotherapy, however, relapsed disease and serious adverse effects caused by the treatment still need to take into consideration. We focused on the central nervous system (CNS) in pediatric ALL investigating ALL first relapse recurring in the CNS and the adverse effect, acute toxic encephalopathy (ATE). Interindividual differences regarding the diversity of symptoms connecting to CNS- relapse (REL) or neurotoxicity could be explained by the patients' genetic background. We hypothesized single nucleotide polymorphisms (SNPs) can influence these events by modifying the function of enzymes and transporters which are located in the blood-brain-barrier and have a role in the metabolism of chemotherapeutic drugs.

Methods: Clinical data were collected from the patients' medical records retrospectively. ATE symptoms were graded according to the Common Terminology Criteria for Adverse Events v3.0. DNA was isolated from peripheral blood collected in remission (QIAmp® Blood DNA Maxi Kit, Qiagen). Genotyping was performed using TaqMan® OpenArray™ Genotyping System (Thermo Fisher Scientific). We studied the association between 62 SNPs and the incidence of CNS- REL or ATE. Logistic regression adjusted for potential confounders was performed using SPSS v25.

Results: Study population consisted of pediatric patients with ALL (0-18 years), 670 patients for ATE (cases= 86) and 842 for CNS- REL (cases= 30) projects, respectively. For the relapse project cases were isolated CNS- RELs or combined CNS and bone marrow RELs. We have found that the GSTP1 rs1695 G allele protected against ATE (p=0.002; OR=0.239; CI95%=0.096-0.597). Evaluating the association between these 62 SNPs and CNS- REL is still running. One GSTP1 variant associated with a reduced incidence of ATE.

Conclusions: This result might contribute to personalized medicine in pediatric ALL: it could be a possible genetic marker for the risk of ATE after further investigations.

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Characterization of the Lymphatic Vasculature in Atherosclerosis

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Introduction: Atherosclerosis is a chronic inflammatory disease of medium and large-sized arteries. It is characterized by a plaque formation in the arterial wall due to lipid and cholesterol accumulation. Excess cholesterol is transported from the periphery back to the liver for excretion by reverse cholesterol transport which has been linked to the development of atherosclerosis. Recently it has been shown that lymphatic vessels participate in reverse cholesterol transport. Lymphatic vessels are known to be present in the adventitia of the arterial wall, suggesting a possible role in the development of atherosclerosis.

Aims: Characterization of the morphology and growth of the lymphatic vasculature in atherosclerosis and investigation of the role of lymphatics in the pathogenesis of atherosclerosis.

Methods: Lymphatic reporter mice were used to visualize lymphatic vessels in the arterial wall. Ldlr-/- and ApoE-/- mice on control or high-fat diet were used to characterize the lymphatic vasculature in the development of atherosclerosis. Isolation of the aortae was followed by paraffin-based histology and H/E-stainings as well as stainings against lymphatic and blood vessel markers. Whole aortae were stained with Alizarin Red S and Oil-Red-O. To visualize lymphatic vasculature in whole aortae a tissue clearing method was used, followed by immunostaining against lymphatic marker.

Results: We could show the presence of lymphatic vessels in the adventitia of blood vessels. We demonstrated the different density of the lymphatic vasculature in different parts of the aorta, finding no lymphatic vessels in the aortic arch and more lymphatic vessels in the lower parts of the aorta. Both Ldlr-/- and ApoE-/- mice developed severe atherosclerosis on a high-fat diet, indicating the largest atherosclerotic plaques in the aortic arch. Atherosclerotic mice showed an increased density of lymphatic vessels in the adventitia of the arterial wall.

Conclusions: Our results suggest the possible role of the lymphatic vasculature in atherosclerosis. In current experiments we are using genetic loss-of-function and gain-of-function approaches to block and stimulate lymphatic growth in atherosclerotic mice. Defining the role of the lymphatic system in the pathogenesis of atherosclerosis may lead to the development of novel therapeutic approaches in the future.

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Lacking ARHGAP25 RacGAP mitigates The symptoms of contact hypersensitivity in mice

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Introduction: Contact hypersensitivity is a complex inflammatory dermal disease mediated by T cells. First contact of the allergen initiates the sensitization phase, which leads to the activation of innate immune cells e.g. neutrophilic granulocytes. Our group previously demonstrated, that the leukocyte specific ARHGAP25 regulates phagocyte functions and has an important role in the effector phase of complex inflammatory diseases.

The aim of this study is to reveal the influence of ARHGAP25 on the pathogenesis of contact hypersensitivity.

Methods: In our experiments either full wild type (WT) and knock out (KO), or bone marrow chimeric mice were used, which either had wild type bone marrow (WT chimeras), or they lacked ARHGAP25 only in the hematopoietic compartment (KO chimeras). For sensitization, the belly of the mice was coated with 3% TNCB (2-chloro-1,3,5-trinitrobenzene), or acetone in the control group. After 5 days, for elicitation, ears were coated with 1% TNCB. Severity of inflammation was investigated by measuring ear thickness, possible tissue damage by examining histological sections, the ratio of different leukocytes was determined by flow cytometry and the composition of cytokine environment by mouse cytokine array.

Results: We observed significantly reduced ear thickening in full KO compered to full WT mice. This difference was also significant between chimeric mice. Neutrophil and cytotoxic T cell count was decreased in the KO ears compared to WT. There was a markable difference in cytokine environment between KO and WT ears. In the control group, no difference was observed, between KO and WT.

Discussion: Our results indicate, that ARHGAP25 expressed in the hematopoietic cells is required for contact hypersensitivity. In its absence the severity of inflammation is significantly lower. This can be the result of the difference in leukocyte and/or cytokine composition between KO and WT ears.

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Examination of plasma cell subpopulations in plasma cell myeloma

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Introduction: Plasma cell myeloma is an incurable type of cancer. Flow cytometry analysis of bone marrow aspirations plays an important role in its diagnosis and monitoring. A challenge of this method is that immunophenotype of cancer cells can change as a consequence of treatments and antibodies used in immunotherapy can cover epitopes. Thus, new types of plasma cell markers are needed. VS38c is a monoclonal antibody which binds to the CLIMP-63 (Cytoskeleton-Linking Membrane Protein 63) in the endoplasmic reticulum. CLIMP-63 is much more expressed in plasma cells than in other bone marrow cells, thus VS38c could be suitable to separate them.

Aims: We wanted to examine the VS38c staining of normal and neoplastic plasma cells, and whether the preparation of the sample or the time between taking the sample and its processing influence the results. We were also interested in the usability of CLIMP-63 in prognosis.

Methods: We examined the bone marrow of 134 myeloma patients with flow cytometry, staining the typical plasma cell surface markers and CLIMP-63. During intracellular staining we used different types and concentrations of permeabilization agents (IntraStain kit, Triton X-100).

Results: We observed two subpopulations of plasma cells while staining with VS38c, a dim and a bright (VS38dim and VS38br). Their ratio depended on the concentration of the permeabilization agent and on how much time passed between taking the sample and its processing. Higher concentration and longer time differences both caused the VS38cdim population to decrease/disappear while VS38cbr increased with the same amount. Washing the sample also led to a loss of the dim population. Furthermore, the VS38cdim population's ratio increased with the progression of the disease.

Conclusions: VS38c (combined with other markers) is suitable to detect plasma cells. The difference between the populations is probably not caused by difference in expression, but likely by structural differences in the ER membrane. The VS38cdim population is more vulnerable and can be lost during preparation more easily. The change in the ratio of the populations draws attention to that the feasibility of staining the sample also changes during its storage. Furthermore, labeling with VS38c antibody could uncover a myeloma subpopulation which might play an important role in the progression of the disease.

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Von Willebrand multimer structure and extensibility analyzed by single-molecule AFM

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Introduction: Von Willebrand factor (VWF) is a multimeric glycoprotein of 1-24 homodimer molecules. The extended multimers are cofactors of platelet adhesion at high shear in a size-dependent manner. The size of the multimers is tightly regulated to prevent bleeding or thrombotic events. Based on electron microscopic analyses, dimers within the multimer consist of two large globules and a small one which correspond to the N- and C- termini, respectively. The globules are connected via flexible, rod-like structures. The distance between of the two large globules is 120 nm uniformly. Based on atomic force microscopic (AFM) analyses these distances are 80-100 nm and the relative extension of multimers depends on the number of the component dimers.

Aims: In order to uncover whether the extension of a VWF multimer depends only on the number of the component dimers, or the dimers might also become extended, we analysed the axial structure of the multimers by employing high-resolution single-molecule techniques.

Methods: We purified plasma-derived VWF multimers with heparin affinity chromatography and investigated their topographical structure with AFM. Samples were diluted to 1 ng/µl in PBS pH7.4 containing 50% glycerol and dropped on mica either incubated for 1 min or immediately extended by molecular combing with receding meniscus (13000 rpm for 10s), washed and dried. Igor Pro 6/AR14 was used to analyse images.

Results: The contour length of the elongated multimeric molecules varied between 126 and 2650 nm. As expected, the contour length increased with the number of dimers in the chain. However, it was longer than calculated by the known length of dimers. The median length of dimers also increased, from 13 nm to 294 nm, and correlated with the contour length ($r=0.73$ ($p<0.0001$, $n=68$). The number of small globules between the dimers varied from 0 to 3 depending on the extension.

Conclusions: We conclude that the variation in the extension and structure of the dimers within the multimer explain the size-dependent function of VWF multimers. The large number of component dimers and their extended state, which appear to be a hallmarks of multimeric VWF, provide large local binding-site concentration and conformational accessibility, respectively, for platelet adhesion. The single-molecule approach employed here thus sheds light on the size-dependent diversity in the haemostatic role of VWF.

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Culture Conditions Determine the Long Term Persistence and Phenotype of HER2 Specific CAR T Cells

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Introduction: Genetically modifying T cells to express synthetic chimeric antigen receptors (CARs) is one of the most promising strategies for the immunotheraphy of cancer. CARs constructed from a monoclonal antibody and effector domains of the T cell receptor complex allow T cells to recognise and kill tumor cells in a HLA unrestricted manner. The proliferative ability and the phenotype define the qualities of the produced CAR T cell population, which are largely determined by the method of T cell activation and expansion.

Aims: With a view to optimize the activation and expansion of CAR T cells produced in our lab, we aimed to explore and compare the persistence and phenotype of second generation HER2 specific CAR T cells using a conventional and a novel medium, as well as a conventional and a novel stimulation method.

Methods: We used HER2 targeting CAR constructs containing the CD3z effector, and one of the CD28 or 41BB costimulatory domains. The constructs were retrovirally transduced into human T cells. Mock-transduced cells were used as negative controls. We cultured T cells from two donors in RPMI or Medium X, combined with either of two stimulation methods: anti CD3 + anti CD28 or anti CD3 + Reagent Y. For assessing in vitro persistence, a re-challenge assay was implemented, where CAR T cells were removed from the HER2-FC target antigen after an optimized killing time period (3 days), counted in flow cytometry and added to new targets to measure proliferation again, continued until anergy was reached. The phenotype of the CAR T cells was determined by immunostaining using antiCD4–A488 and antiCD8-A647 to measure cytotoxic/helper ratio, and antiCCR7-FITC with antiCD45RA-APC to determine naive/effector differentiation by flow cytometry.

Results: Among the applied methods the antiCD3 + antiCD28 stimulation combined with Medium X proved to be the most effective in terms of in vitro endurance. Anti-CD3 + Reagent Y significantly raised the ratio of CD8+ cytotoxic CAR T cells combined with both media, but lowered proliferation rates. The percentage of the naive phenotype showed no significant difference in either of the applied methods.

Conclusions: Among the tested methods for CAR T cell activation and expansion Medium X yielded promising results, thus we are going to test it further, adding more donors to the experiment.

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7003

Depression, anxiety, affective temperaments in patients with sleep apnea syndrome (Presentation of ongoing research)

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Introduction: Obstructive Sleep Apnea Syndrome (OSAS) is the most common respiratory distress during sleep, a prevalence of 2-4% in the general population. OSAS is an independent cardiovascular risk factor, including hypertension twice, frequency of myocardial infarction three times higher, and risk of diabetes five times higher than in the general population. The relationship between mood disorders and cardiovascular risk is known, but no study has been conducted to investigate the relationship between OSAS and mood disorders and affective temperaments.

Aims: Investigation of the relationship between OSAS and anxiety, depression and affective temperaments in cooperation with the Sleep Lab of the Hungarian Defense Forces Health Center.

Methods: During the surveys, we record laboratory parameters, social and anthropometric characteristics, use the self-reported TEMPS-A (Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire) temperament questionnaire, the Short Beck Depression Questionnaire, the HADS-A Anxiety Questionnaire, the Promis-57 questionnaire. Diagnosis is made by polysomnography. For statistical analysis we used SPSS Statistics 23.

Results: Until now 68 patients with sleeping disorders were involved in our study. The mean age of the patients was 55,3±12,9 (years±SD), 72% was male. 82% of the patients have OSAS. The prevalence of medium/severe depression symptoms were extremely high 49%.

We found anxiety in 22,4% of the cases. Among female patients with OSAS we found significantly higher prevalence of medium/severe depression symptoms (63% vs. 45%, p=0,023) and anxiety (30,7% vs. 19,4%, p=0,31). The most prevalent dominant temperaments were the cyclotime and irritable temperaments (4,25% and 4,4%).

Conclusions: The depression and anxiety are very common among OSAS patients. A routine screening for depression and anxiety symptoms among them would be an important part of the effective patient care. Timely treatment of anxiety and depression may also improve the compliance of the patients with OSAS. According to our preliminary hypothesis, the cyclotime and irritable dominant affective temperaments were the most common temperaments among OSAS patients.

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7081

EuvisionTab©: new screening system for examination of stereovision

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Amblyopia is a neurodevelopmental disease occurring with 3-6% prevalence resulting in irreversibly impaired vision of one eye. It is mostly evoked by strabismus, anisometropia or hypermetropia. Since a major consequence is the lack of stereopsis, stereotests could be appropriate to detect amblyopia and even preamblyopic conditions. We are developing an innovative mobile screening tool to examine stereovision (EuvisionTab©), using random dot stereogram (RDS) stimuli. In the present study, the sensitivity and specificity of RDS was evaluated.

Children (n=130) between 4-13 years were involved, including 23 amblyopic. Following an ophthalmological examination, the EuvisionTab© test was performed on a tablet. We used static and dynamic stimuli with different densities of random dots composing the stimulus to set different levels of difficulty: Low density dynamic (1%) with noise (LDD), very low density dynamic (0.7%) without noise (VLDD), and a higher density (8%) static test (HDS). In comparison, Lang II, TNO, Stereofly and Frisby stereotests were also performed, then predictive values and ROC analysis were computed for each stereotests.

With refractive correction, RDS LDD, VLDD and HDS had a sensitivity of 91%, 87% and 87% for amblyopia, while the specificity was 71%, 74% and 88%. The sensitivity and specificity of the other stereotests were as follows: Lang II 78% and 94%, TNO 87% and 71%, Stereofly 74% and 91%, and Frisby 61% and 89%. When RDS was performed without refractive correction to mimick a real screening situation the sensitivity was 91% for LDD, 100% for VLDD and 87% for HDS, while the specificity was 63%, 70% and 88%. In the ROC analysis area under the curve (AUC) values are over 0.8 for RDS, and there is no significantly difference between RDS and other stereotests. The performance of the RDS test was significantly better in case of preamblyopic conditions, such as hyperopia, anisometropia, and strabismus.

RDS test is slightly more effective for the detection of amblyopia and preamblyopic factors compared to other stereotests. LDD has the greatest sensitivity while HDS has the best specificity. In a real screening situation VLDD showed the best sensitivity. With the randomized order of image sequences, cloud-based data storage, and flexible settings, RDS may serve as an essential part of the state-of-the-art vision screening.

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7076

Comparative proteome analysis identified ALCAM as a potential serum biomarker for enzalutamide resistance in castration-resistant prostate cancer

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Introduction: Enzalutamide (ENZA) is a second-generation androgen receptor inhibitor, which has been approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Despite of clinical benefits, many of patients have baseline or acquired resistance to ENZA, however the molecular mechanisms of resistance are not completely understood.

Aims: We aimed to identify potential serum biomarkers, which are involved in ENZA resistance of mCRPC.

Methods: ENZA-resistant (LNCaPabl-ER, DUCaP-ER, LAPC4-ER) and sensitive (LNCaPabl, DUCaP, LAPC4) prostate cancer cell lines were comparatively analysed by applying the liquid chromatography tandem mass spectrometry (LC-MS/MS) technique. The most promising biomarker candidates were identified by using three different bioinformatic approaches. Six selected proteins (ALCAM*, AGR2, NDRG1, RRM2, GR, IDH1) were analysed in baseline serum samples of 72 ENZA-treated patients by using the ELISA method. Serum biomarker concentrations were correlated with clinicopathological and follow-up data.

Results: Our comparative proteome analysis identified 278 at least two-fold, significantly upregulated proteins in ENZA-resistant cell lines. Five of the six examined proteins were detectable in patients' serum samples. High ALCAM serum levels were significantly associated with shorter overall survival. Multivariable analyses revealed the presence of bone metastases, high PSA and ALCAM levels as independent predictors of poor patients' survival in ENZA-treated CRPC patients (p=0.021, p=0.021 and p=0.012, respectively).

Conclusions: Our results imply that ALCAM serum levels may help to select patients who less benefit from ENZA-treatment and may therefore help to improve therapeutic decision-making in CRPC. Currently, we are working on functional knock-down analyses of ALCAM protein in cell culture in order to assess its role in ENZA resistance. Additionally, further upregulated proteins will be selected and analysed as candidate predictive serum markers.

*activated leukocyte cell adhesion molecule

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Well-Being and Well-Doing in Health Goals of Emerging Adults: The Role of Goal Context and Approach and Avoidance Orientation

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Introduction: Goals, more specifically goals concerning our health are vital for our health behaviour. Approach and avoidance health goals can be differentiated by moving toward or away from an outcome (Elliot and Friedman, 2007). A critical period affecting different life domains including health is emerging adulthood, as lifestyle changes and habits evolving in that age can be persistent through adulthood (Helgeson et al, 2014).

Aims: The aim of the present study was to examine which aspect of the context (i.e. health status and health behaviour) might be related to goal choice and the extent of well-being and well-doing while pursuing these goals.

Methods: We run a questionnaire study on a sample of 212 Hungarian undergraduate students. For assessing health goals Personal Project Assessment was used. After goal-elicitation, respondents rated their most important health goal along several aspects concerning perceived social support, average level of positive and negative emotions, self-efficacy and self-concordance. Then health goals were classified into approach/avoidance categories. Respondents were also asked about their current health status (e.g. self-rated health, Body Mass Index (BMI), existence of a chronic illness) and lifestyle (e.g. physical activity, diet, smoking and alcohol consumption). For identifying possible determinants of goal orientation we applied binary logistic regression analysis and Independent-Sample t-tests for addressing differences between those who chose an approach and an avoidance goal.

Results: Results showed that smoking (B = -0.250, p = 0.001) and higher BMI (B = -0.132, p = 0.005) predicted lower odds of choosing an approach goal. Those who chose an approach goal rated this goal more self-concordant, experienced more positive feelings and self-efficacy and perceived more support for their goals compared with those who followed an avoidance health goal.

Conclusions: The results imply that approach goal orientation is usually embedded in a context of advantageous health behaviour and health status, which is also interrelated with well-doing in these goals, thus these can be prosperous for mental and physical health during the lifespan.

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7159

Role of music activities in psychiatric rehabilitation

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In Hungary, the use of music in rehabilitation is a scarcely researched area. In this study we aimed to examine the structure, purpose, and role of music activities in the rehabilitation process of psychiatric patients, as well as its effect on the healing and reintegration. All of this has been compared to the structure, timing and effectiveness of music therapy methods used worldwide.

The 10-person sample consisted of patients participating in the rehabilitation program of the Psychiatric Clinic of the University of Szeged, who agreed to attend music sessions there 10-15 times over a two-week interval. During the first and last interventions, we measured patient satisfaction with life, perceived social support, and levels of depression and trait anxiety. In addition, we measured changes in anxiety during a single music session, and a short structured interview was completed with each patient at the time of the last session.

Our results show that patients' perceived social support increased during the intervention period - especially regarding the family dimension. The level of anxiety decreased and the level of depression also showed a marginally significant decrease. No significant differences were found in the changes of life satisfaction and the immediate anxiety-relieving effect of music practice. The content of the interviews however confirmed that there is indeed an immediate anxiety-relieving effect of a single music session.

To summarise the quantitative and qualitative data, it can be stated that the music activities of the Clinic are several points in line with the international practice, and operate with low risk and high efficiency. The work done here has confirmed that music activities can be an effective method along with the clinical treatments and play an important role in the rehabilitation process.

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Modulated Electro-hyperthermia Suppresses H19, a Tumor Promoting Long Non-coding RNA, in a Triple Negative Breast Cancer Model

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Modulated electro-hyperthermia (mEHT) is a complementary antitumor therapy, based on selective tumor cell killing by a 13.56 MHz radiofrequency induced electric field. H19 long non coding RNA (lncRNA) is involved in tumor progression and metastasis. It's overexpression is associated with poor prognosis in breast cancer. We observed previously significant tumor inhibitory effects of mEHT.

Our aim was to investigate mEHT related inhibition of H19 lncRNA in triple negative breast cancer (TNBC) spheroids and in TNBC bearing mouse models.

4T1 spheroids were embedded in Matrigel® and treated with mEHT for 30 minutes. Samples were collected 24 hours after treatment and processed for Real-Time PCR (RT-PCR). TNBC cells (4T1, 4T07) were inoculated orthotopically in female BALB/c mice. Tumor growth was monitored in vivo by digital caliper and ultrasound, mice were randomized into groups based on tumor size. Mice were treated with mEHT in monotherapy or in combination with methotrexate (MTX) 2 or 3 times for 30 minutes with 0.7±0.3W power. The tumors were dissected and processed for molecular biologic techniques. H19 expression was measured with RT-PCR, results were normalized to GAPDH.

Single mEHT treatment of 4T1 spheroids reduced significantly H19 expression compared to normothermic control (Ctr: 0.004±0.0004, mEHT: 0.0006±0.0002, $p<0.0001$) There was a significant decrease in H19 expression of 4T1 tumors after two (sham: 0.068±0.044, mEHT: 0.033±0.024, $p<0.05$) and three mEHT treatments (sham: 0.097±0.059 vs mEHT:0.050±0.030, $p<0.05$) compared to the sham group. In case of combination treatments H19 expression was significantly lower in the mEHT+MTX group compared to MTX only (MTX: 0.104±0,038 vs mEHT+MTX: 0.056±0.025, $p<0.01$). The basic expression of H19 was significantly lower in 4T07 tumors compared to the more aggressive 4T1 tumors (4T07:0.006±0.004 vs 4T1:0.399±0.071, $p<0.0001$). In 4T07 tumors H19 expression didn't change after 3 mEHT treatments (sham: 0.404±0.334 vs mEHT: 1.391±1.840, $p>0.10$) compared to the sham group.

Our results demonstrate, that mEHT can reduce the expression of tumor promoting H19 lncRNA in vitro and in vivo both in monotherapy and in combination with chemotherapy. Our findings suggest, that mEHT as an alternative complementary treatment could promote antitumor therapy by inhibiting the tumor progression mediating H19 lncRNA expression.

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6978

Metabolic Plasticity Alters the Aggressiveness and Drug Response of Human Breast Cancer Cells in Different Cell Culturing Systems

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Introduction: 2D cell culturing – as one of the first line drug screening tests – has several limitations which could increase the miss-selection failures of drug development. In vitro models could not completely resemble to the tumorous microenvironment and consequently could alter cellular response. 3D and in vivo conditions induce metabolic changes and the development of tumor heterogeneity which could be considered in the experimental tests.

Aims: For comparing the culturing conditions and their effects on metabolic profiles/characteristics, we studied different cell maintaining methods using breast cancer cell lines in vitro (2D, 3D – hanging drop – and spheroids selected/subcloned as new cell cultures) and in vivo.

Methods: Different culturing conditions and their effects on metabolic characteristics and drug (mTOR and other metabolic inhibitors e.g. GLS, mitochondrial inhibitors) sensitivity were studied using breast cancer cell lines (MDA-MB-231, ZR75.1) in in vitro and in vivo tests. The tumor growth was followed using in vitro cell counting, Alamar Blue, SRB tests, and established xenografts. LC-MS and WES Simple techniques were used for studying the metabolic activity and the expression of metabolic enzymes.

Results: According to our findings, 3D state can modify the metabolic features – alters both intra- and extracellular concentrations of glycolytic and OXPHOS metabolites (e.g. lactate, pyruvate, malate) and bioenergetics related enzyme activities (e.g. mTOR complexes, CPT1A, HK2). It was also observed that the spheroid-derived tumor cells have a more rapid proliferation rate both in vitro and in explanted xenografts compared to traditionally cultured cells. The 3D conditions could initiate metabolic rewiring and more aggressive phenotype of the studied cells.

Conclusions: The maintaining conditions altered the drug sensitivity and the metabolic characteristics of the studied cells. Based on these, it is advisable to apply new techniques which both mimic the living state more accurately to understand the background of adaptation processes and are more comparable to tumor microenvironment to achieve a better model system for early drug development. These can contribute to select and find new feasible agents, metabolic targets for cancer therapy.

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Effects of Modulation of NMDA Receptors in Ischemia/Reoxygenation Injury of Cardiac Cells

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Introduction: Ischemic heart diseases are the leading cause of death among cardiovascular diseases, therefore the attenuation of ischemia/reoxygenation injury is a relevant and timely research area. In the central nervous system, activation of the non-selective ionotropic N-methyl-D-aspartate (NMDA) receptors has been shown to worsen I/R injury in stroke. The receptor is expressed in cardiac cells, however, their role in the heart is unclear.

Aims: We aimed to examine the effects of the modulation of NMDA receptors in ischemia/reoxygenation injury of cardiac cells.

Methods: We used a rat cardiomyoblast-derived cell line (H9c2 cells) in our experiments. Cells were treated with an NMDA receptor activator (NMDA, 25-400 μM), an NMDA receptor inhibitor (MK-801, 0.47-960 μM), and the combination of these agents both in normal, stress-free conditions and in a model of simulated ischemia/reoxygenation injury. Calcein staining was used to determine viability of the cells at the end of the experiments.

Results: Under stress-free conditions, neither NMDA nor MK-801 treatment influenced the viability of H9c2 cells. In simulated ischemia/reoxygenation experiments, the NMDA treatment increased cell death in a dose-dependent manner, where 200 and 400 μM NMDA increased cell death significantly. The NMDA antagonist MK-801 improved cell viability at a concentration of 7.5 μM (105±2 vs. 100±1%, $p<0.05$). Furthermore, the MK-801 treatment significantly attenuated the cell death caused by 400 μM NMDA treatment.

Conclusions: According to our results, the activation of NMDA receptors may be involved in the development of ischemia/reoxygenation injury in the heart.

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The Role of TRPM4 Ion Channels in Pancreatic Acinar Cell Function

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Introduction: We are interested in the role of ion channels in the primary fluid secretion mechanism of pancreatic acinar cells. As intracellular [Ca^{2+}] play a crucial role in this process, we aim to identify new effectors of Ca2+ among ion channels.

Aims: Our QPCR study, have shown that TRPM4 is highly expressed in the gland, therefore, our aim is to investigate the role of this ion channel in the function of mouse pancreatic acinar cells. As TRPM4 channels are Ca^{2+}-activated monovalent cation channels, we hypothesize that TRPM4 is activated by Ca^{2+} during secretagogue stimulus and causes the depolarization of the plasma membrane, which diminishes the driving force of Ca^{2+} entry.

Methods: Patch-clamp technique (voltage-clamp, current-clamp) and calcium imaging using fura-8-AM ratiometric dye.

Results: Accordingly, our patch-clamp experiments demonstrated Na^{+} current activation during elevated intracellular Ca^{2+} levels, which were inhibited by TRPM4 inhibitors 9-phenanthrol and CBA. We also observed a CBA-sensitive, Ca^{2+}-dependent depolarization of the resting membrane potential. To further test our theory, intracellular Ca^{2+}-imaging experiments were performed, which demonstrated that the rate of elevation of [Ca^{2+}]i during Ca^{2+} entry was much higher in the presence of CBA and in TRPM4 KO pancreatic acinar cells compared to control, which verify our hypothesis about the role of TRPM4 in pancreatic acinar cells.

Conclusions: Based on these results we suggest that depolarization caused by the activation of TRPM4 diminishes the driving force of Ca^{2+} entry through the plasma membrane.

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Periodontal plastic surgical approach to correct localized gingival enlargements /A retrospective case series/

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Introduction: Localized gingival enlargements are frequently encountered challenges in the daily practice. Postoperative complications following surgical removal, such as recurrence and subsequent gingival recessions as well as loss of keratinized tissues are commonly observed. Nevertheless, a state of the art comprehensive treatment approach has not been reported yet to overcome the above mentioned sequels.

Aims: The aim of this retrospective case series was to present a periodontal plastic surgical approach to definitively remove localized gingiva enlargements and to simultaneously correct consecutive esthetic disturbances.

Methods: 5 patients were treated presenting localized gingival enlargements in various locations. Patients underwent initial periodontal treatment including subgingival root planning, after 2 months of healing, open flap debridement (OFD) was performed simultaneously with in toto surgical excision. Consecutive gingival recessions occurred in all cases, which were immediately treated within the same surgical sessions. All cases were treated by a coronally advanced flaps (CAF) with individual modifications for root coverage.

Results: No recurrence was experienced during 12 months follow-up. 12 months postoperatively percentage of root coverage averaged 63,2%. Mean gingival recession depth decreased from 3,8±0,8 mm to 1,4±0,6 mm. Differences were significant compared to baseline. Mean keratinized tissue width decreased/increased from 4,2±2,2 mm to 2,4±0,5 mm. Differences were not significant compared to baseline.

Conclusions: Before removal of localized gingival enlargements, individual circumstances should always be considered. Reduction of bacterial inflammation through the completion of initial periodontal treatment is a prerequisite for optimal treatment outcomes. Adjacent teeth and soft tissue dimensions as well as consistency of the lesions should be taken into account when choosing an individually tailored surgical approach. The presented treatment strategies based on periodontal plastic surgery principles represent a predictable solution to successfully remove localized gingival enlargements with esthetically acceptable results and no recurrence.

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Electrocardiographic Predictors of Myocardial Fibrosis and Hypertrophy in Hypertrophic Cardiomyopathy

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Structural myocardial changes in hypertrophic cardiomyopathy (HCM) are associated with different abnormalities on electrocardiographs (ECGs). The diagnostic value of the ECG voltage criteria used to screen for left ventricular hypertrophy (LVH) may depend on the presence and degree of myocardial fibrosis. Fibrosis can cause other changes in ECG parameters, such as pathological Q waves, fragmented QRS (fQRS) or repolarization abnormalities.

The aim of our study was to investigate the diagnostic accuracy of ECG hypertrophy criteria using CMR to diagnose LVH and the impact of myocardial fibrosis on these criteria and to define ECG predictors of LVH and myocardial fibrosis in patients with HCM.

We investigated 85 patients with HCM who underwent cardiac magnetic resonance imaging with late gadolinium enhancement (LGE) and standard 12-lead ECG. On the ECG, depolarization and repolarization abnormalities, the Sokolow-Lyon index, the Cornell index and the Romhilt-Estes score were evaluated. The left ventricular ejection fraction, volumes, myocardial mass (LVM) and maximal end-diastolic wall thickness were quantified. LVM was evaluated with the exclusion (conventional method) and inclusion (threshold-based method) of the trabeculae and papillary muscles. Myocardial fibrosis was quantified on LGE images.

The Romhilt-Estes score was positive in 74% of the cases and had the strongest correlation with the LVM index (LVMi) ($p<0.001$; $r=0.39$). Weak correlation was found both between LVMi and the Cornell index ($p<0.01$; $r=0.28$), and LVMi and the Sokolow-Lyon index ($p<0.05$; $r=0.22$). The Cornell index correlated negatively with the amount of fibrosis ($p<0.05$; $r=-0.22$), the Romhilt-Estes score was independent of fibrosis ($p=0.604$; $r=0.06$). The presence of fQRS or strain pattern associated independently with an increased amount of myocardial fibrosis, they predicted additional 5.6% and 5.2% fibrosis of LVM, respectively ($p<0.01$). Our results were independent of the method of LVM measurement and the observer's experience.

The Romhilt-Estes score is the most sensitive ECG criterion to detect LVH in HCM patients, as myocardial fibrosis has no effect on this criterion. The presence of fQRS and strain pattern predicts myocardial fibrosis.

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6999

Review of mortality prediction algorithms for STEMI patients undergoing primary percutaneous coronary intervention

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Mortality risk of ST-segment elevation myocardial infarction (STEMI) patients shows high variability. In order to assess individual risk, several scoring systems have been developed and validated. Yet, as treatment approaches evolve with improving outcomes and as even older patients with complex disease patterns are treated invasively, new or updated risk prediction algorithms are needed to maintain or increase prognostic accuracy. One of the most relevant improvements of therapy is primary percutaneous coronary intervention (PCI), since, compared with fibrinolysis, it further reduces mortality. Prediction algorithms may provide useful information for patients and relatives, as well as help physicians to allocate hospital resources. In addition, they may contribute to an improved quality of care as they can be used for risk adjustment in inter-organizational comparisons of health care providers with different case mixes. Furthermore, risk models may be helpful in clinical trial design identifying patients with the needed risk profile thereby increasing statistical power and reducing sample size and costs.

In the present work, we overview the general and individual characteristics and discriminative performance of the most studied and some recently constructed mortality risk models that were validated in patients with STEMI who underwent primary percutaneous coronary intervention.

We found that though the extensively validated "Global Registry of Acute Coronary Events" (GRACE) model was not particularly derived from data of invasively treated STEMI patients, it also performs well in the era of transradial primary PCI. Similarly, the Zwolle, "Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications"(CADILLAC), "Assessment of Pexelizumab in Acute Myocardial Infarction" (APEX-AMI), and "Age, Life support, Pressure, Heart rate, Access site" (ALPHA) models, that were constructed using primary PCI data, all seem to have comparable discriminative abilities. In contrast, the admission model "Thrombolysis in Myocardial Infarction" (TIMI), which was developed in the fibrinolysis era, might have less predictive power. Finally, the primary PCI admission model "Primary Angioplasty in Myocardial Infarction" (PAMI) is likely the weakest among the comparatively studied risk models concerning discriminatory ability.

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EEG-Based Connectivity in Patients with Partial Seizures with and without Generalization

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Introduction: Partial epileptic seizures are generated within circumscribed cortical areas. Some epilepsy patients have focal seizures exclusively (simple or complex partial seizure). Other patients display partial and secondarily generalized seizures or secondarily generalized exclusively. Neurophysiological basis of this diversity has not been investigated in human epilepsy as yet.

Aims: To investigate cortico-cortical electrical connectivity, the presumed neurophysiological basis of secondary generalization in interictal state.

Patients and methods: 131 unmedicated and medicated focal epileptic patients were sorted into five groups: patients with simple partial seizures exclusively (sp, n=22); patients with simple partial and secondarily generalized seizures (spsg, n=16); patients with complex partial seizures exclusively (cp, n=27); patients with complex partial and secondarily generalized seizures (cpsg, n=35). The sg group (n=31) was composed of patients with secondarily generalized seizures exclusively. The sp and cp groups were collapsed into the spcp group (n=49). Resting state EEG functional connectivity (EEGfC) was computed in the source space, among 23 cortical areas in the left and right hemispheres. EEGfC was computed for 25 narrow frequency bands from 1 to 25 Hz (LORETA Source Correlation software, www. appliedneuroscience.com). Statistical analyses (two-tailed t-tests with Bonferroni correction) were carried out between the sp-sg and sp groups; between the cp-sg and cp groups and between sg and sp-cp groups. Bonferroni-corrected $p<0.05$ values were accepted as statistically significant.

Results: EEGfC differences emerged at specific frequencies (spsg > sp at 15-21 Hz; cpsg > cp at 20 Hz and sg > spcp at several frequencies. The findings indicated increased coupling between motor cortices and several non-motor areas in patients with partial and sg seizures as compared to patients with partial seizures and no sg seizures.

Conclusions: Tendency towards secondary generalization of partial seizures is presumably related to abnormally facilitated cortico-cortical electrical connectivity in partial epilepsy.

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7030

Morphological changes in lungs and liver and phagocytic activity of peripheral blood cells in tolerant and susceptible to hypoxia wistar rats with LPS-induced systemic inflammatory response

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Introduction: In the mechanisms of a systemic inflammatory reaction, one of the key factors is oxygen deficiency due to microcirculatory disorders. Probably, individual resistance to hypoxia can determine the severity of inflammatory reactions.

Aims: To characterize the morphological changes in the lungs and liver, and the phagocytic activity of peripheral blood cells during the systemic inflammatory response, induced by lipopolysaccharide (LPS) in animals with different resistance to hypoxia.

Methods: Male Wistar rats (n=40) were exposed to hypobaric hypoxia, equal to 11500 m elevation. Hypoxic tolerance was determined by measuring the time taken for the onset of gasping (GT). The tolerant animals had GT more 240 sec (n=15), the susceptible – less 80 sec (n=13). After a month, a systemic inflammatory response was induced by intraperitoneal administration of E.coli LPS at a dose of 1.5 mg/kg. 24 hours after LPS injection, a morphological and morphometric study of the lungs and liver was performed, as well as the measuring of corticosterone and C-reactive protein level, the activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes in blood serum. In the peripheral blood, the granulocyte number and phagocytic activity were examined.

Results: In comparison to the tolerant to hypoxia animals, the systemic inflammatory response in susceptible rats was more pronounced: was noticed a significant infiltration of the lungs interalveolar septa with neutrophils, a large area of necrosis in the liver, increased levels of AST and ALT activity, the content of C-reactive protein and corticosterone in the blood serum. More severe effects of a systemic inflammatory reaction in susceptible to hypoxia rats were accompanied by activation of peripheral blood phagocytes, while in tolerant to hypoxia ones, an increase in the relative number of granulocytes in peripheral blood was detected without changes in the phagocytosis activity.

Conclusions: Thus, more severe effects of a systemic inflammatory response in susceptible to hypoxia rats were accompanied by activation of peripheral blood phagocytes. The data obtained could be useful in the development of new approaches to the treatment of infectious and inflammatory diseases, taking into account individual sensitivity to the oxygen level.

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Measurement of personality change using PID-5 after short-term inpatient group schema therapy and group cognitive behavior therapy - a pilot study

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Introduction: Group schema therapy (GST) is proven to be effective in the treatment of various personality disorders, social anxiety disorder, eating disorders or depression. The majority of these studies have compared GST to waiting list, treatment as usual or other less complex therapeutic approaches. However, to date, comparison to group cognitive behavior therapy (GCBT) has been understudied.

Aims: Comparison of the effectiveness of GST to GCBT in a 4-week-long inpatient setting on mixed population.

Methods: The study was conducted at the Psychotherapeutic Rehabilitation Unit of Semmelweis University, Department of Psychiatry and Psychotherapy in Budapest, Hungary. A total of 267 patients (37,97±13,269) were enrolled in the study, comprising of 81 male and 186 female participants, with primary diagnosis of personality disorder. 90 patients have received GCBT, 177 patients have received GST. Our main outcome measure was the Personality Inventory for Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (PID-5), a 220-item self-report inventory designed to assess personality characteristics on 5 main factors and 25 traits, which was assessed at the beginning and at the end of our 4-week-long inpatient treatment program. A dependent t-test was performed and effect size was calculated (Cohen's d). Data analysis was performed using IBM SPSS Statistics 21.

Results: Patients receiving GCBT have shown medium effect size (d>0.5) on Depressivity and Withdrawal traits. Patients receiving GST have demonstrated strong effect sizes (d>0.8) on Distractibility and Perseveration traits, medium effect sizes (d>0.5) on Callousness, Depressivity, Eccentricity, Emotional Lability, Irresponsibility and Risk taking traits, and on the main factors of Disinhibition and Psychoticism, and small effect sizes (d>0.2) on the Unusual beliefs and experiences trait and on the Negative affectivity main factor.

Conclusions: While GCBT is an effective treatment method for anxiety disorders and depression, it does not seem to induce personality change. GST, on the other hand, may induce change on various personality traits. This finding implies that for the treatment of personality disorders experiential techniques added to cognitive techniques render psychotherapy more effective, compared to methods using cognitive techniques solely.

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Role of Aquaporin 4 in Lacrimal Gland Ductal Fluid Secretion in Mice

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Introduction: Aquaporins (AQPs) are transcellular water channels that can be essential in the physiology of various secretory epithelia. Although earlier reports demonstrated presence of AQP4 in the duct cells from rabbit lacrimal glands (LG) and substantial alterations of AQP4 mRNA levels were also demonstrated in experimental dry eye and during pregnancy.

Aims: The functional relevance of AQP4 in LG duct secretion has to be clarified, therefore in this present study ductal fluid secretion was investigated using AQP4 knock out (KO) mouse strain.

Methods: Immunofluorescence was used to localize AQP4 protein in LGs. Duct segments were isolated from wild type (WT) and KO mice as we previously described. After the ends of the ducts were sealed, ductal fluid secretions evoked by cell-permeable cAMP analogue (8-bromo cAMP, 100 μM); carbachol (100 μM); vasoactive intestinal peptide (VIP, 200 nM); and phenylephrine (PHE, 10 μM) were measured by video-microscopy. Statistical significance was calculated with one-way ANOVA. Data were presented as means ± SEM. A p value of <0.05 was regarded as significant.

Results: Immunofluorescence demonstrated the predominant presence of AQP4 protein in the basolateral membranes from WT mice. The secretory rates (Jv, pl/min/mm2) were calculated for the first 10 minutes of stimulation. Carbachol (WT: 215.7±73.9; KO: 216.2±37.3; p=0,242), and PHE (WT: 248.5±91.3; KO: 195.3±51.01; p=0,183) caused similar secretory responses in ducts from WT and KO animals. In contrast, 8-bromo cAMP (WT: 190.5±22.4; KO: 57.6±23.8; p=0.026), and VIP (WT: 256.3±51.02; KO: 141.07±34.26; p=0.01) stimulation resulted in significantly reduced secretory rates in ducts from KO LGs compared to WT LG ducts.

Conclusions: Our results demonstrate that AQP4 plays functional relevance in the fluid secretion of mouse LG ducts. Role of AQP4 seems to be different in fluid secretions stimulated by various secretagogues and its activity may be related to the intracellular mechanisms induced by the stimulatory agents. These assumptions need further investigations.

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7005

Disadvantaged Populations' Mental Health in Segregated Settlement Areas

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Introduction: The disadvantaged populations' bad health-state is owing to the negative effects of the economic drawback and geographical isolation of poverty (Forray 2013). This is especially conspicuous in North-East of Hungary, which is the most obscurantist region among people living in segregated neighbourhoods (Kósa 2006). Social support, as an important health-factor, basically determines peoples' mental health and psychical well-being. Those with strong social support show depressive symptoms seldom, but 55% of those who have only got a low level of social support, show some kind of depressive symptoms as well (ELEF 2014).

Aims: The main goal of this study is to reveal the relation between social network characteristics and mental health status among disadvantaged people living in an impoverished area, where the rate of multiple deprivation is one of the highest in the country.

Methods: Data is based on a research carried out in two, geographically segregated areas of a county town, in the North-East of Hungary. Sample size is 271, the average age is 43,50. The rate of self-reported roma is 41%. SF-36 Quality of Life questionnaire was applied to measure mental health status (Huszti-Ember 2019).

Results: The number of friends and confidants of people living in the two segregated areas (ie. blocks of flats) are far lower than that of the national sample. Rate of people with no friends and confidants are also remarkably high. The studied population's situation is worse in terms of the level of vitality and the state of mind than it is the case with the average population of the same city. There is a significant relationship between the number of friends and the mental health status of the studied population: more friends contribute to better mental health. In terms of getting social support, differences can be observed between the two examined neighbourhoods (Huszti-Ember, 2019).

Conclusions: The location of the segregated areas and the dysfunctional contact networks are additional risk factors to mental health status. More secluded neighbourhood coincides with a worse state of mind.

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Hormonal and metabolic disorders as a risk factor of endometrial, ovarian and breast cancer

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Introduction: The increased attention to the issue is explained by the steady growth of female genital organs cancer incidence all over the world, including Russia. The main reason of such ill-being is late diagnosis of malignant neoplasms in outpatient clinics and an increase of neglected forms. The oncofertility is also a main cornerstone of the problem, because we need more organ-preserving surgeries that require the integration of the efforts of an obstetrician-gynecologist, fertility specialist and oncologist. The understanding of the key molecular mechanisms included into endometrial cancer pathogenesis promotes the formation of the criteria to create an effective predictive model for endometrial oncopathology and to reveal the targets for targeted pharmacological effects on pathologically altered cells in order to prevent the recurrence of hyperplasia and oncotransformation.

Aims: further specification of the meaning and genetic factors in the pathogenesis of endometrial, ovarian and breast cancer.

Nowadays there are more information about endometrial cancer pathogenesis, then about other hormone-dependent tumors. However, this fact stipulates not only theoretical interest of further studies, but also their perspectivity.

All these allow to optimize and to improve the scientific and practical recommendations on the application in clinical practice of the most effective methods for detecting and treating patients with endometrial cancer.

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The Role of Hemoglobin Oxidation Products in Triggering Inflammatory Response upon Intraventricular Hemorrhage in Premature Infants

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Introduction: Intraventricular hemorrhage (IVH) is a frequent complication of prematurity that is associated with high neonatal mortality and morbidity. IVH is accompanied by red blood cell (RBC) lysis, hemoglobin (Hb) oxidation, and sterile inflammation. Recent studies showed extracellular Hb, methemoglobin (metHb) and heme to be involved in inflammation following IVH. They also highlighted the role of Hb oxidation and heme release in inflammation after the onset of IVH.

Aims: Our goal was to perform a qualitative and quantitative analysis of Hb content of human cerebrospinal fluid (CSF) collected from premature infants after the onset of IVH. We also wanted to investigate the pro-oxidant and pro-inflammatory effects of Hb forms on human brain microvascular endothelial cells.

Methods: We collected cerebrospinal fluid (N=20) from premature infants with grade III IVH at different time points after the onset of IVH. Levels of Hb, metHb, and ferrylHb were determined by analysis of the visible spectra of CSF samples. Oxidative Hb crosslinking was assessed by Western blot. Concentrations of soluble adhesion molecules VCAM-1, and ICAM-1 and the pro-inflammatory cytokine IL-8 in CSF were determined by ELISA. Our in vitro experiments were performed on human brain microvascular endothelial cells (HBECs).

Results: Levels of Hb, metHb, total heme and free heme were the highest in CSF samples obtained between days 0-20 after the onset of IVH and were mostly non-detectable in CSF collected between days 41-60 of post-IVH. Besides Hb monomers, we detected crosslinked Hb dimers and tetramers in post-IVH CSF samples obtained in days 0-20 and 21-40, but only Hb tetramers were detected in CSF samples obtained after 41-60 days. VCAM-1 and IL-8 levels were higher in CSF samples obtained between days 0-20 than in CSF samples collected between days 41-60 of post-IVH. Applying free heme and oxidized Hb forms on human brain microvascular endothelial cells revealed, that free heme induces cell death whereas oxidized Hb forms in particularly ferrylHb triggers an inflammatory response.

Conclusions: We concluded that RBC lysis, Hb oxidation and heme release play important roles in the inflammatory response following IVH. However, the pathogenic role of covalently crosslinked Hb multimers need to be further investigated.

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7008

Microbial composition and diversity of mice colonized with a carbapenemase-producing Klebsiella pneumoniae strain

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Emergence and spread of multidrug-resistant bacteria represent a serious problem worldwide. The extended-spectrum β-lactamase (ESBL) and carbapenemase-producing Enterobacteriaceas (CPE) are in the critical category on the WHO antimicrobial resistance priority list. These bacteria are responsible for a large proportion of hospital-acquired infections. The therapeutic options for CPE are limited, therefore controlling the spread of these bacteria is important. Intestinal colonization plays a crucial role in the spread of CPE.

In this study our goal was to investigate the effect of different per os antibiotic treatments on the microbial composition and diversity of C57BL/6 mice colonized with K. pneumoniae (KP5825). This strain expressed a carbapenemase gene, a PMQR gene and an ESBL gene. We also examined the colonization rate and the resistance gene copy number changes in the colonized mice.

All experiments were carried out using 6–8 weeks-old C57BL/6 male mice. For colonization, 5x10^6 CFU of KP5825 was administered orally on the 14th and 15th days of ampicillin pretreatment. After the colonization mice were divided into 6 groups. These groups received the following antibiotic treatments for 15 days: 0.5g/L ampicillin (AMP), 0.1g/L ceftazidime (CAZ), 0.5g/L ceftazidime, 0.1g/L ciprofloxacin (CIP) and 0.5g/L ciprofloxacin was administered in the drinking water (6th group: control). Fresh fecal pellets were collected from the animals every 3 days throughout the 15 days period. From the fecal samples microbial DNA was extracted.

In the second phase of our experiments we used qPCR technique to determine the KP5825 DNA quantities and assess the resistance gene copy numbers. The V3-V4 region of the 16S rRNA gene was amplified and sequenced with the Illumina MiSeq platform to determine the microbiota composition and diversity in the intestines of colonized mice.

Our results show that AMP and CAZ increased the colonization KP5825 and reduced the gut microbiome diversity originally characterized by Bacteroides dominance. In contrast, CIP did not increase the colonization rate. We also observed strong negative correlation between the presence of Lachnospiraceae NK4A136 group 11319, Roseburia, Anaerostipes, Lachnoclostridium 11308, Lachnospiraceae UCG-004, Tyzzerella, Agathobacter, Lachnospiraceae NK3A20 group 11318 genera and the colonization rate with KP5825.

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Macrophage heme oxygenase-1 in the clearance of apoptotic cells

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Every day billions of cells die in our body to eliminate those that are harmful, useless or senescent. Uncleared apoptotic corpses can promote inflammation, so their rapid and non-immunogenic removal is essential for maintaining tissue homeostasis. Heme is important for all aerobic cells, although it can be poisonous in a non-protein-bound form. Disposal of heme is important for preventing heme and iron-mediated cellular toxicity. Heme oxygenase-1 (HO-1) is an inducible microsomal enzyme that catalyzes the first and rate-limiting step in heme degradation.

A previous research in our laboratory has shown that HO-1 mRNA level was increased in wild type bone marrow-derived macrophages (BMDMs) after incubation with apoptotic thymocytes (aT). Thus we decided to investigate the role of HO-1 in the engulfment program.

In our experiments, we measured HO-1 induction in wild type BMDMs that were incubated with aTs, apoptotic red blood cells (aRBCs) or with their supernatant alone, in the presence of HO-1 inhibitor or an engulfment inhibitor. We were curious wether inhibition of HO-1 activity, thus lack of heme degradation affects phagocytosis. Percentage of engulfing BMDMs was determined after 30 minutes, 7 or 25 hours incubation with apoptotic cells. Finally, we studied the effect of HO-1 inhibition on the cytokine profile of resting and apoptotic cell treated BMDMs.

The uptake of both apoptotic cell types induce HO-1 expression in macrophages. Even if phagocytosis is inhibited, the HO-1 mRNA level is increased in the presence of aTs, but not in case of aRBCs, indicating that aTs mainly use extracellular signals regulate HO-1 expression. No difference was found during short-term or mid-term phagocytosis of apoptotic cells in the absence of HO-1 activity. However, when the time of phagocytosis was increased, less aRBCs were engulfed by macrophages in the presence of HO-1 inhibitor. Normally clearance of apoptotic cells is an immunologically silent process. However, when BMDMs were exposed to aRBCs in the presence of HO-1 inhibitor, we found that the expression of some pro-inflammatory cytokines were increased.

Our data indicate that different dead cells might use different mechanisms for inducing HO-1: low heme-containing apoptotic thymocytes mainly use extracellular pathway, while high heme-containing aRBCs mainly use intracellular HO-1 induction pathway.

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EEG functional connectivity and network structure mark hub overload and vulnerable brain networks in Mild Cognitive Impairment during memory maintenance

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Introduction: Changes in the functional interaction between brain regions have been reported in Alzheimer's disease, especially in the alpha frequency band. Furthermore, beta-amyloid deposition primarily affects highly connected cortical hub regions that are essential for normal cognition but also constitute vulnerable spots of brain networks. From a network perspective, hub overload and failure might explain the pathological process of neurodegenerative diseases. However, it is not yet entirely known whether changes in functional connectivity (FC) and network structure are able to mark cognitive decline in the early stages of the disease.

Aims: Our study aimed to analyze EEG FC and network differences in the alpha band during memory maintenance between Mild Cognitive Impairment (MCI) patients and healthy elderly with subjective memory complaints.

Methods: FC and network analysis of 17 MCI patients and 20 control participants were studied with 128-channel EEG during the Paired Associates Learning task. FC between EEG channels was estimated with the envelope correlation with leakage correction (AEC-c), a reliable measure of genuine connectivity. To examine network topology we applied the Minimum Spanning Tree (MST) approach that provides an unbiased reconstruction of the critical backbone of the original network and captures changes in topology while it addresses several methodological limitations.

Result: We did not find group differences in the mean FC in the alpha frequency band, however, memory load had a different modulatory effect in the two study groups: while increasing task difficulty enhanced connectivity in the control group, the MCI group showed significantly ($p<0.05$) diminished FC in the highest memory load condition, which might indicate the impairment of memory maintenance. Network analysis revealed increased maximum degree, betweenness centrality and degree divergence, and decreased diameter in the MCI group compared to the control group. This indicates a rerouted network in MCI with a more centralized topology and a more unequal traffic load distribution, where central hubs might become vulnerable to overload and failure.

Conclusions: FC sensitively reflects memory load-related modulation and impairment of memory retention in MCI, while changes in the network topology point to the increased vulnerability of brain networks of MCI patients.

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Studying the proteinase complex of micromycete Tolypocladium inflatum as a new approach for thrombotherapy

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Introduction: The problem of fibrin clots and thrombosis prevention during the severe cardio-vascular disorders such as infarctions, ischemic strokes and blood diseases remains extremely relevant for vascular medicine. Along with already known methods of treatment, new approaches are emerging that involve the use of micromycete proteinases to prevent thrombosis.

Aims: To examine the biochemical properties, defining the possible therapeutic application of micromycete T.inflatum.

Methods: The preparation of proteinases was obtained by culture fluid proteins precipitation with acetone, followed by drying stage on the sixth day of cultivation, performed with thermostatically controlled shaker in a deep culture conditions on a selected medium. The protein fractions separation of the drug was conducted by the method of liquid isoelectric focusing with the activity control by caseinolysis. Proteolytic and plasminogen activator activity was measured by fibrin plates method. Thrombolytic potential was examined in a fibrin thrombus lysis model (evaluation the weight loss of fibrin clot after 30 min, 1hr and 3 hrs exposition with the preparation of proteinases).

Results: After isoelectrofocusing were obtained 3 peak fractions with the caseinolysis activities 77,4; 111,9 and 179,8 mkM Tyr/ml×min. The fibrinolytic activities were 333; 255 and 934 u/ml respectively and the plasminogen activator activities were 169,3; 163,5 and 328 respectively, which is comparable to well-known plasminogen activators (e.g. urokinase) or preparations, obtained from investigated plasminogen activators, such as Sarocladium strictum.In experiments with the fibrin clot lysis model the preparation of T. inflatum proteinases (fractions all together) demonstrated high efficiency of fibrin clot thrombolysis (29,6 % of fibrin clot weight elimination after 30 min; 70,1 % after 1 hr; 90,0% after 3hrs).

Conclusions: The obtained data indicate that the proteinases preparation, obtained from the culture fluid of the micromycete Tolypociadium inflatum, demonstrates the pronounced thrombolytic, fibrinolytic and plasminogen activator activities, which allows to suggest the therapeutical potential in thrombosis treatment in vascular medicine and, what is more, the biotechnological potential for the development of diagnostic kit for hemostasis system disorders monitoring.

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Novel magnetic Prussian Blue nanoparticles for in vivo T1 MR-imaging

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Introduction: Iron-oxide nanoparticles have long been researched for their superparamagnetic properties. These T2 MRI contrast agents (CAs), which are also called negative CAs, cause a hypointense change of the MR image. This property makes it difficult for the human eyes to detect and diagnose most small tumor details. Currently, Gd and Mn-containing substances are commercially available for this purpose, however, they are known to have toxic effects.

Aims: The aim of my work was to develop a Prussian Blue nanoparticle (PBNP) based MRI contrast agent and to investigate its properties in vitro and in vivo, in a mouse model.

Methods: For the synthesis, PBNP-AC (citrate coated; biocompatible) and PBNP-HCl (non-biocompatible) PBNPs were used in different ratios. The degree of dispersion (PDI) and stability of the system was checked by Dynamic light scattering (DLS). During in vitro MRI measurements T1 and T2 relaxivity of my samples was compared with the CAs widely used in the clinical practice. An authorized radiopharmaceutical, Gadovist (T1 CA) and with Salsol (T2 CA) were the contoll probes. Subsequently, in my in vivo experiment I used only the sample with best relaxation time, compared to the T1 controll. The stability of the prepared system was examined for 6 weeks. In vitro MRI scans clearly show the change in signal intensity caused by different compositions of samples. Evaluating the resulting T1 and T2 weighted signal intensity curves, the signal intensity of the PBNP-AC: PBNP-HCl 1:2 sample was the most appropriate for further in vivo measurement.

After intravenous administration of the CA, the biodistribution of NPs was investigated, which resulted in hyperintense changes on T1-weighted images, while on T2-weighted images hypointense changes were observed e.g. in the vascular system compared to the surrounding tissues.

Conclusions: As a conclusion, I successfully developed and tested a Prussian Blue based nanosystem that proved to be a CA for in vivo MRI imaging, also as a T1 CA. Considering the previously developed fluorescence labeling and pegylation protocol of the nanosystem, the present compound has a huge potential for innovation in imaging diagnostics.

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6990

Apoptosis and DNA damage caused by modulated electro-hyperthermia in preirradiated pancreas adenocarcinoma cell line

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Aims: Malignant tumors of the pancreas respond very poorly to classical oncotherapy. The survival of patients with inoperable pancreas adenocarcinomas is poor despite the sophisticated guidelines of using newest chemotherapy drugs. The high resistance of tumor cells is attributed mostly to the upregulation of the survival mechanisms.

Modulated electro-hyperthermia (mEHT) is a complementary non-invasive cancer treatment using impedance-coupled radiofrequency to generate selective heat of <42°C. We have tested the effect of mEHT after irradiation on a radioresistant pancreatic adenocarcinoma cell line Panc1.

Methods: Panc1 pancreas adenocarcinoma cells grown on coverslips were treated in monotherapy using either mEHT (1 hour mEHT at 42°C) or radiotherapy (2 Gy using 137Cs) and by combining these treatments: irradiation followed by mEHT. The results were compared to each other and to untreated controls concerning viable cell number, cell stress, apoptotic ratio, DNA double-strand breaks and DAMP protein levels and localization. Detection and quantification of changes in various protein expression was done using flow cytometry , digital microscopy.

Results: 24 hours post-mEHT treatment the viable cell number decreased significantly in all treated groups. Hematoxylin-eosin morphology revealed apoptosis specific changes including nuclear shrinkage, chromatin condensation and apoptotic bodies especially in groups treated with mEHT only or in combination therapy. The apoptotic ratio was the highest in groups receiving both mEHT and irradiation and significant increase was measured also after mEHT monotherapy. Also, cleaved/activated caspase 3 positive nuclei increased significantly in these two treatment groups. Furthermore, significantly higher number of H2AX nuclear positive tumor cells were detected indicating DNA double-strand breaks after mEHT treatment after irradiation.

Conclusions: The molecular changes showed efficient tumor destruction of mEHT monotherapy or combined with irradiation. The detected apoptosis was mainly caspase 3 dependent. Though irradiation alone had no major effect on Panc1 cells, its combination with mEHT resolved the irradiation resistance and thus improved the efficiency of radiotherapy.

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Parents' Perspective on Medical Communication During the Transition to Palliative Care in Pediatric Oncology

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Introduction: The treatment of pediatric malignant diseases with poor prognosis affects the whole family. Several models have been developed that address the timing of curative and palliative elements in the treatment process. Literature suggests that in instances of poor prognosis, communication about the integration of palliative care should begin early, yet everyday practice and experiences of doctors and parents may differ.

Aims: To explore the parents' perspective on features and circumstances of medical communication during the transition to palliative care, in order to develop recommendations for more effective doctor-parent communication.

Methods: Semi-structured interviews comprised of 18 questions were conducted with parents who had lost their child to cancer within the past 1-5 years. Questions explored parents' experiences and the circumstances of the transition to palliative care; demographic data of each participant was also recorded. Recruitment occurred by phone via main centers of Hungarian pediatric oncology care; a clinical psychologist conducted all interviews. Transcribed and narratives were scrutinized with Interpretative Phenomenological Analysis.

Results: As of now, preliminary analysis has been performed on 23 interviews. Free (inductive) coding, the first step in our analytical process, yielded the following codes that will be used to develop the final code tree: Participants of the conversation (subcodes: psychologist, spouse/partner, other), Language (subcodes: positive/negative appraisal of communication, use of word "death"), Institutional support in grief (subcodes: needed, not needed, needed from other resources) and Behavior towards child (subcodes: changed, not changed). Coding suggests that the presence of a psychologist during conversations about palliative care and institutional support in grief are favored by parents, appraisal of direct communication and use of the word "death" is varied.

Conclusions: According to our preliminary results, ensuring psychological support throughout the treatment process would be beneficial to doctor-parent communication. The salience and reasons behind preference for direct and indirect communication need to be explored further to formulate recommendations.

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Clinical Effectiveness and Cost-Effectiveness of Oral-Health Promotion in Dental Caries Prevention among Children: Systematic Review and Meta-Analysis

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Introduction: The objective of this study was to evaluate the clinical effectiveness and cost-effectiveness of oral-health promotion programs (OHPPs) aiming to improve children's knowledge of favorable oral health behavior to lower decayed/-missing/-filled teeth (DMFT) while reducing the financial cost on health institutions.

Methods: An electronic search was performed in seven databases. Studies were restricted to human interventions published in English. The search study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, and the risk of bias was assessed based on the Drummonds Checklist. A total of 1072 references were found. Among these, 19 full texts were included. Most studies had a strong quality.

Results: The overall pooled impact of OHPPs estimates children suffering from DMFT /S to have 81% lower odds of participating in OHPP (95% CI 61–90%, I2: 98.3%,p=0). Furthermore, the program was shown to be effective at lowering the cost in 97 out of 100 OHPPs (95% CI 89–99%, I2: 99%,p=0). Three subgroups analyses (age groups, study countries,studies of the last five years) were performed to evaluate the influence modification on the pooled effect.

Conclusions: A comprehensive analysis of the OHPPs confirmed a reduction effect on child DMFT, hence,lowering the financial burden of dental-care treatment on health institutions.

Keywords: Oral Health Promotion Programs (OHPP); Decayed Missing Filled Teeth (DMFT); cost-effectiveness analysis (CEA); Incremental Cost Effectiveness Ratio (ICER)

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Dissection of Subclonal Evolution by Temporal Mutation Profiling in Chronic Lymphocytic Leukemia Patients Treated with Ibrutinib

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Introduction: The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib is changing the therapeutic landscape of chronic lymphocytic leukemia (CLL), especially in patients with refractory/relapsed disease or with TP53 defect. Due to ibrutinib therapy, secondary resistance mutations leading to therapy failure may occur in the BTK and PLCG2 genes besides other genomic changes in the subclonal architecture of CLL cells.

Aims: We aimed to delineate the ibrutinib-driven clonal evolution affecting all relevant mutation targets in CLL, and to develop a method for early and sensitive detection of resistance mutations.

Methods: Matched peripheral blood samples of 20 CLL patients were collected before and during ibrutinib therapy (median follow-up time: 22.5 months, range: 3-34 months). After DNA isolation we performed a targeted ultra-deep analysis using a custom 30-gene-panel and HiSeq/MiSeq sequencing with an average allelic depth of 7500x. Variant annotation was carried out using different bioinformatic pipelines including Illumina VariantStudio and JSI SeqNext softwares. Droplet digital PCR was used in order to detect resistance mutations sensitively.

Results: The ultra-deep next-generation sequencing revealed a total of 211 somatic variants in the 20 paired samples. Majority (157/211) of the variants represented subclonal alterations with variant allelic frequency of <10%. A remarkable subclonal heterogeneity was detected across the cases with an average of 5 mutations (range: 0-19) detected in individual patients, affecting an average of 4 genes (range: 0-18). NOTCH1 (70%, 14/20), ATM (70%, 14/20), TP53 (65%, 13/20) and BCOR (55%, 11/20) represented the most frequently mutated target genes. With an extended median follow-up time of 36.5 months, 35% (7/20) patients relapsed with BTK or PLCG2 mutations. The BTK/PLCG2 mutations emerged on average 10.5 months (range: 7-15 months) before the clinical relapse.

Conclusions: Our time-resolved ultra-deep genomic scrutiny of mutation target genes revealed unique patterns of highly dynamic clonal variegation associated with BTK inhibition and identified novel resistance-associated BTK mutations in individual patients. In addition, evidence is provided that sensitive molecular monitoring of treatment response can facilitate the early detection of impending relapse.

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NMR-based Quantification of 2′-fucosyllactose in Infant Formulas and Other Commercially Available Products

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Introduction: Human milk oligosaccharides (HMOs) can be found in breastmilk and those are the third most abundant solid component in human milk. HMOs possess prebiotic, antiadhesive and immune modulator functions, and they also play significant role in brain development [1]. Among the 150 distinct HMO structures the trisaccharide 2'-fucosyallactose (2'-FL) is the most abundant and it has been accepted recently as novel food. Therefore, it is commercially available in infant formulas and also in various dietary supplements and cosmetic products [2].

Aims: Our aim was to develop an NMR-based method for the identification and determination of 2'-FL in various matrices, to provide a fast and reliable analytical method for the screening of 2'-FL.

Methods: Each sample required unique sample preparation steps, such as liquid-liquid extraction, solid phase extraction, pH adjustment and sample enrichment. One of the main challenges in method development was to find the appropriate resonance frequency for the quantitation of 2'-FL by NMR. The doublet resonance of the fucose moiety around 1 ppm was chosen for quantitation purposes. The samples were recorded in H_2O/D_2O and maleic acid was applied as the quantitative NMR (qNMR) standard using a 600 MHz spectrometer. Solvent suppression was also applied.

Results: The 2'-FL content of two new generation infant formulas and one protein powder was measured by 1H NMR while the 2'-FL content of an infant spray was assessed by using solvent suppression technique. qNMR was also conducted on a cosmetic product containing both fucose and 2'-FL.

Conclusions: We have developed an NMR-based technique to quantify 2'-FL in infant formulas, dietary supplements and cosmetic products. This new analytical method provides an opportunity for the quantitative characterization of the most abundant HMO in complex matrices with a single NMR measurement following a short sample preparation process. Our results clearly indicate the shortcomings of quantitative data provided for 2'-FL in various commercially available products.

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7002

The Long-term Risk of Suicide in Children and Adolescents with Attention Deficit and Hyperactivity Disorder – a Systematic Review

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Introduction: The attention deficit and hyperactivity disorder (ADHD) is one of the most common mental disorder in childhood. Recently several studies showed the high suicide risk of patients with ADHD, however most of these researches, including our group's previous study had cross-sectional design.

Aims: The aim of my PhD research is to investigate the suicide risk of ADHD patients in a follow-up study. As a first step we completed a systematic review of the available data of the already published studies with longitudinal design.

Methods: The systematic search was made on OVID Medline, PsycInfo, PubMed, Scopus and Web of Science. The search terms were (ADHD OR attention deficit hyperactivity disorder) AND (suicide OR suicidal OR suicidality) AND (follow-up OR longitudinal study OR prospective study). Inclusion criteria were: written in English; participants under 18 years at the baseline; longitudinal, prospective studies; ADHD population at the baseline and at the follow-up; suicide behavior as primer outcome. Exclusion criteria were: the study did not contain empirical data, reviews/metaanalyses and studies which aimed to investigate the drug treatment efficacy of ADHD.

Results: After the screening process finally 17 papers were included in the systematic review. Altogether 11 articles were published in the last 5 years, the range of the follow-up periods varied between 3.9 and 20.0 years. Several different assessment tools were used to investigate the symptoms and/or the diagnosis of ADHD and the suicidal risk. Eight studies enrolled children aged under 12 at baseline, six studies birth cohort data and there were no strict age-based inclusion criteria. 16 studies found a positive association between ADHD diagnosis at baseline and the presence of suicidal behavior and/or attempts at the follow-up visits.

Limitations: From the 17 studies only 2 included into the data analyses if patents with ADHD were under treatment or not.

Conclusions: The results highlight the importance of screening suicidality in long term in patents with ADHD, however further studies are needed, which compare in long-term the suicidal risk of treated and untreated groups of ADHD patents.

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Effect of intracerebroventricularly injected streptozotocin on the cognitive performance of Long-Evans rats

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Brain insulin resistance is one of the molecular symptoms of Alzheimer's disease (AD). In rats, intracerebroventricularly injected streptozotocin causes insulin resistance and produces many symptoms of the human disease (cognitive decline, amyloid deposits, increase in phospho-tau). Our aim was to establish the model, which has exclusively been used with Wistar rats in the literature, in Long-Evans rats as well. Three months old male animals were treated with 2x1.5 mg/kg STZ or citrate buffer vehicle injected bilaterally into the lateral ventricles on days 1 and 3. Learning and memory capabilities of the rats were then tested in the following paradigms: five choice serial reaction time test (daily training, started from week 2 post surgery and lasting until the end of the experiment), novel object recognition test (at week 8), passive avoidance (at week 11) and Morris water-maze (at week 14). Besides, open-field activity (at 1 month) and elevated plus maze performance (at week 6) were also investigated. 15 weeks after the STZ treatment the animals were sacrificed and the brain phospho tau/tau protein ratio were determined by Western Blot technique. We couldn't find any significant difference between the treated and the control groups in any of the assays, however, due to the low number of data (n=9 and n=8, respectively), no far-reaching conclusion can be drawn. Nevertheless, our findings suggest that the Long-Evans strain may be more resistant to the STZ treatment than the Wistar rats and higher doses may be needed to trigger pathological changes in these animals.

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Structural differences between Gelsolin and Flightless-I proteins and their behavior in the presence and absence of Ca^{2+}-ion

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Gelsolin homology (GH) domain proteins are central to the control of the actin cytoskeleton. Its eponymous member; the six-GH-domain gelsolin (GSN) is a calcium-activated multifunctional actin regulator. Recently, a unique member; Flightless I (Fli-I) was identified by the six-GH-segment structure alloying a leucine-rich repeat. Both GSN and Fli-I are implicated in pathologies, including sepsis and tissue regeneration, respectively. Albeit, the structural-functional relation in GSN upon Ca^{2+}-dependent activation has been well described the role of Ca^{2+} in the actin activities of Fli-I is unraveled. Our functional analyses indicate that GSN and the GH16 domains of Fli-I respond to Ca^{2+} differently implying different conformational characteristics of the GH domains in the two proteins. We aimed to investigate the structural behavior of GSN and Fli-I in the presence and absence of calcium-ion by using fluorescence spectroscopy and biochemical approaches.

The change in the fluorescence parameters (emission and maximum wavelength) of Trp in GSN upon quenching by acrylamide or guanidine-hydrochloride induced chemical denaturation are consistent with marked conformational rearrangements in response to Ca^{2+}. This is in agreement with the high-resolution structural model of GSN activation. In contrast, our data suggest that the microenvironment of Trp residues in Fli-I GH16 is different from that of GSN even in Ca^{2+}-free conditions and not markedly affected by the presence of the divalent cation. The hydrophobic properties of GSN and Fli-I GH16 were also found to be different based on the spectral emission changes of 1-anilinonaphthalene-8-sulfonic acid (ANS). Fluorescence spectroscopy data is supported by the different kinetics of limited proteolysis observed for GSN and Fli-I GH16. Our experimental findings are supported by bioinformatics analysis predicting that the sequence elements responsible for Ca^{2+}-activation of GSN are not conserved in Fli-I GH16. Altogether, our work reveals different Ca^{2+}-response and predicts distinct modes of activation of GSN and Fli-I.

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Left Ventricular Hypertrabeculation – An Unanswered Question

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Left ventricular (LV) hypertrabeculation (H-TRAB) is a morphological description when the LV is highly trabeculated, but it remains below the diagnostic criterion of noncompaction cardiomyopathy (NCMP). Although, it is a frequent finding on cardiac MRI scans its diagnostic and prognostic relevance remains controversial.

In this cardiac MR study, we aimed to describe the LV functional and feature-tracking strain values of healthy subjects with LV H-TRAB to decide whether it is a normal variant or an NCMP-like pattern.

We included 63 adult subjects with LV H-TRAB, with good ejection fraction, and without co-morbidities; an age- and sex-matched NCMP and a healthy control group.

MR examinations were performed with 1,5T Philips Achieva and Siemens Aera devices. The Medis Suite software was used for post-processing analysis, the MedCalc software for statistics, ($p<0.05$).

No significant differences were found between the functional parameters of the H-TRAB and NCMP groups. However, in comparison to controls, the EF was decreased, the end-diastolic (EDVi), and end-systolic volume (ESVi), the myocardial mass (LV-massi), and trabeculated muscle mass (LV-trabi) values were increased in both groups (H-TRAB vs. control: EF: 66.4±5.4 vs. 69.0±5.0%, EDVi: 74.4±14.3 vs. 69.7±12.8 ml/m^2, ESVi: 25.1±6.7 vs. 21.7±5.8 ml/m^2, LV-massi: 77.0±15.1 vs. 71.2±12.3 g/m^2, LV-trabi: 25.0±5.1 vs. 20.1±4.0 g/m^2; NCMP vs. control: EF: 65.8±5.5 vs. 69.0±5.0%, EDVi: 77.8±15.0 vs. 69.7±12.8 ml/m^2, ESVi: 26.7±7.9 vs. 21.7±5.8 ml/m2, LV-massi: 76.8±18.0 vs. 71.2±12.3 g/m^2, LV-trabi: 25.9±7.5 vs. 20.1±4.0 g/m^2; $p\leq0.05$). The global circumferential strain (GCS) differed significantly between these groups: its absolute value was the lowest in the NCMP and the highest in the control group (NCMP vs. H-TRAB vs. control: -30.2% vs. -34.3% vs. -35.9%; $p<0.05$). Regarding the segmental circumferential strains the average apical-, mid- and basal-part strain values showed similar distribution. These absolute values were the lowest in the NCMP patients, followed by the H-TRAB, and were the highest in the control group.

These results suggest that the LV functional and strain values of the H-TRAB population are more similar in NCMP patients compared with healthy controls. Further studies are necessary to determine the pathological implications and consequences of this morphology.

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Multidimensional ROI-level combination of micro- and macrostructural measures for epileptic lesion detection

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Introduction: In a recent publication (Gyebnar et al. 2019) we showed that the voxel-wise Mahalanobis-distance is a suitable metric of dissimilarity for the detection of malformations of cortical development (MCD), using the three dimensional distribution of diffusion tensor (DTI) eigenvalues. While the method proved sensitive to the abnormal tissue microstructure related to MCDs, specificity was constrained by the inaccuracies of spatial coregistration when comparing to control subjects. In the current work, the method was amended in two ways: a) by including cortical volumetry and morphology measures, and b) by performing the statistical analysis on the ROI-level.

Aims: The aim of the current study was to test the multidimensional approach, using the extended parameter space and ROI-level-statistics on healthy controls and individuals with MCDs; and to find the optimal parameter set to maximize the efficiency of lesion detection.

Methods: Diffusion and T1-weighted imaging data of 45 healthy subjects and 13 individuals with MCDs (16 lesions) were processed with ExploreDTI and the Freesurfer software suite. Using the 360 labels of the multi-modal cortical atlas of the Human Connectome Project (HCP-MMP, Glasser et al. (2016)), ROI-level average DTI-eigenvalues, volumetry, and morphology measures were exported. The multidimensional Mahalanobis-distance was used to identify regions of abnormal tissue micro- and macrostructure using in-house software with all possible combinations of measures.

Results: MCD-related lesions were identified in 14 out of 16 cases, detection performance was improved using measures of cortical morphology (average cortical thickness, rectified mean curvature, and folding index) with reduced number of false positives. DTI-derived measures resulted in more false positives in regions usually affected by susceptibility and EPI-related distortions.

Conclusions: The surface-based approach was efficient in registering the cortical labels to each individuals' image space, and the combination of DTI, volumetry, and morphology measures improved the detection of MCDs in the multidimensional framework.

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Examination of Acoustic Features in Depression, Developing an Automatic Decision System for Discriminating Speech Pathology

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Introduction: WHO studies show that the prevalence of major depression increased 18,4% in the last ten years. The early diagnose and adequate treatment of depression decrease suicidal risk and mortality, which shows a great need for new and fast diagnostical methods. The effects of depression in speech are studied with computer sciences in the past decades. Before that era physicians could only tell about the qualitative features of speech like speed, intensity, pauses. In the past few years, machine learning was introduced in diagnostical studies, with the ability to find regularities in big data. In our study, we developed a support vector regression-based machine learning system for discriminating the speech of patients with depression.

Aims: Our purpose is to develop an automatic decision system, that can be used to separate speech samples of patients with depression from healthy speakers and give a probability of the severity of depression.

Methods: Speech samples were collected from patients diagnosed with depression. The severity of depression was assessed by Beck Depression Inventory-II (BDI) and Hamilton Depression Scale (HAM-D). Patients on antipsychotic medication were left out of the study, because it's probable effect on the acoustical features of speech. The samples contained a read text called "The North Wind and the Sun", each speech was segmented on phonema level and support vector regression was used in the automatic decision system.

Results: In this phase of the study we introduced the HAM-D to objectify the diagnose of depression and improve the accuracy of the automatic decision system, which was previously built with 158 speech samples of patients with depression. With the use of HAM-D, in a current database of 22 patients, we could increase the accuracy (91%) and sensitivity (95%) in speech analysis.

Conclusions: The results of our study show that the acoustic biomarkers of depression can be a viable diagnostical tool in the early recognition of depression. With machine learning, an automatic decision system in speech analysis can be helpful in general medical practice as a screening process for depression. In psychiatry, this system can speed up the initiation of proper treatment and can be used as an objective indicator to measure the effectiveness of variable form of therapies and keep track of the change during treatment.

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The Role of Neutrophil Granulocytes in Skeletal Muscle Regeneration

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Introduction: The skeletal muscle is permanently exposed to physical damage but in normal condition the tissue is able to repair itself in a very efficient way. However, we know several degenerative muscle diseases with inflammation and impaired tissue regeneration. Neutrophils enter traumatized, stressed tissues firstly and act as professional phagocytic cells. Like macrophages, neutrophils also form a heterogeneous population, they can contribute to inflammation and to repair as well. The myeloid-specific deletion of the Mcl-1 antiapoptotic protein in mice leads to dramatic reduction of circulating and tissue neutrophil counts without obvious changes in other immune cell numbers. In these Mcl-1 deficient mice we observed a delayed skeletal muscle regeneration which may indicate the role of neutrophils in the repair mechanisms.

Aims: Our aim is to investigate the role of neutrophils during a sterile muscle injury model. We would like to identify the neutrophil subtypes in the tissue regeneration in order to understand the molecular mechanisms and immunological pathways better.

Methods: The muscle injury is induced by cardiotoxin injection in tibialis anterior muscle, both in Mcl-1 KO and wild-type mice. The muscle isolation and processing is performed at day 1, 2, 4 and 8 post injury. The muscle regeneration is followed by analysing the satellite cells and infiltrating immune cells with flow cytometry. We would like to restore the delayed repair with transferring Ly6G+ neutrophils from MHC-compatible, WT mice by adoptive cell transfer.

Results: The migration of macrophages into the damaged muscle was delayed in the absence of neutrophils. The number of Ly6ChighF4/80med and Ly6CmedF4/80high macrophages differed in Mcl-1 KO mice compared to the control mice. We optimized the appropriate neutrophil cell number for the adoptive cell transfer and showed that the transferred Ly6G+ CD45.1 neutrophils entered the damaged muscle tissue after 24 hours.

Conclusions: These preliminary results show that the neutrophils have a pivotal role in normal muscle regeneration. The identification and investigation of neutrophil subtypes during a sterile muscle injury might be useful in the discovery of new therapeutic targets in muscle degenerative disorders and injuries.

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Possible therapeutic effects of organic and inorganic content of Szigetvár medicinal water. A double blind, randomized, controlled trial in Szigetvár Spa, Hungary

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One objective of the trial was to investigate the therapeutic effect of the medicinal water of Szigetvár in patients suffering from osteoarthritis of the hips and the knees; and the other was to identify if this effect is attributed to the organic or inorganic matter of water. During the treatment period patients received a 30-minute underwater jet-massage in a bath tub, 5 times a week. The first patient group received jet-massage in a bathtub containing medicinal water, the second group received the same treatment in tap water, the third group in water containing the organic fraction and the fourth group in water containing the inorganic fraction. 94 patients were enrolled in the study. After randomisation patients were divided into four groups. Primary outcomes were measured by range of movement of the involved joints and Western Ontario and McMaster University Osteoarthritis Index. Visual analogue scale was applied to measure current severity of pain. Furthermore, quality of life was assessed using the Short Form 36 questionnaire. Our results have proved the therapeutic effect of Szigetvár medicinal water and that it can be replaced by the organic fraction itself.

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Investigation of the osmoregulatory role of TRPV4 ion channels in human podocytes

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The transient receptor potential ion channels (TRP channels), with a few exceptions, have a non-selective permeability to cations, including calcium. These are multimodal cellular sensors that are sensitive to various stimuli in the cell's physicochemical environment, such as temperature, pH, osmotic pressure, volume, stretch, and vibration. They are expressed in the epithelial cells of the kidney tubules, and our research group discovered thermosensitive TRPV (mainly TRPV4) channels in podocytes, which have an important role in the formation of a glomerular filtration barrier.

In this project we are looking for the role of functionally expressed TRPV4 channels in regulating certain biological processes in podocytes and how they can contribute to the physiological functions of these cells and to the formation of a filtration barrier.

For our experiments we used an immortalized human podocyte cell line. We tested the function of TRPV4 with pharmacological methods by using specific agonist (GSK1016790A) and antagonist (HC067047). We investigated the response of podocytes to hypotonic solutions and the role of TRPV4 susceptible to hypo-osmotic stimuli by using Fluo-4 fluorescent Ca^{2+} indicator to assess intracellular Ca^{2+} concentration.

Based on our research, TRPV4 may play an important role in hypotonic stress induced responses, because the intracellular Ca^{2+} signals evoked by hypo-osmotic challenges were diminished in the presence of the TRPV4 antagonist.

These results suggest that TRPV4 channels in human podocytes could play a role in the regulation of the filtration barrier.

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Investigation of somatostatin receptor expression in renal tumors

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Kidney cancer is the 10th most common malignancy worldwide and around 2,000 new cases are reported each year. The disease is poorly predicted and difficult to treat, can spread asymptomatically, is resistant to chemotherapy, and is very common in metastatic cases. The hormonal neuropeptide receptors for somatostatin are SSTR 1-5, with subtypes 2 and 5 showing the highest affinity for the hormone and its synthetic analogues. In the literature, SST receptors are expressed at high levels in certain tumors and in blood vessels formed by tumors, compared to normal tissues. Following the expression of the characteristic somatostatin receptor (SSTR) in kidney tumors and the ligand binding, the internalization of SSTR may serve as a basis for future treatment.

Our aim was to investigate the presence of SSTR (1-5) in human kidney tumor tissue samples and cell lines. In vitro studies aim to investigate the presence of somatostatin on the expression of somatostatin receptors on human kidney tumor cell lines (A-498 and CAKI-2).

In our examinations, we had tumor and norml kidney tissue samples from 20 patients with surgically removed kidney tumors from the University of Debrecen. Total RNA was isolated from the samples and following reverse transcription, the expression of SSTR -1, -2, -3, -4, -5 was analyzed by specific oligonucleotide primers by real-time qRT-PCR (CFX-96, BIORAD). The human kidney tumor cell lines A-498 and CAKI-2 were used for in vitro studies.

According to our results, a significant proportion (~90%) of the tested kidney samples express SSTR-2 and SSTR-5 receptors to a greater extent than SSTR-1,3,4. The age group and gender distribution of the examined cases did not show any correlation with the somatostatin receptor expression. The presence of SSTR-2 and SSTR-5 was confirmed in both A-498 and CAKI-2 cell lines, and the receptor expression on the cell line showed a similar pattern to that observed in tissue samples.

A significant proportion of tissue samples express subtypes of various somatostatin receptors at the mRNA level. Our findings will hopefully contribute to a better understanding of the disease, help in the early detection of metastasis, the use of synthetic analogues of somatostatin, their radionuclide or cytotoxic derivatives in diagnostic and/or targeted tumor therapy, and provide new knowledge in the use of somatostatin peptide.

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Examining The Role Of The Subthalamic Nucleus In a Stop Signal Reaction Time Task In Patients With Parkinson's Disease

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Parkinson's disease (PD) is one of the most common neurodegenerative disorders. While the symptoms are initially dominated by motor impairment, the overwhelming majority of PD patients develop cognitive impairment with the progression of the disease.

The subthalamic nucleus (STN) is modulated by frontal cortex and thought to mediate motor responses during decision making. Therefore, during decision conflict, the precise timing of STN activation may be crucial for response inhibition.

In our study, we investigated the role of STN neural activity in decision making, focusing on its proposed role on inhibitory control. PD patients performed a stop-signal reaction time task, in which two numbers were presented on a screen and the patients had to press the corresponding buttons on a button box as fast as possible. After a subset of the cues, a stop instruction was presented, indicating that the patient had to withhold the motor response. The patients performed this task before, during and after DBS implantation surgery. During surgery, extracellular unit recording from the STN and frontal EEG was co-registered. A subpopulation of STN neurons were suppressed during button presses, consistent with their role in the indirect basal ganglia pathway. Importantly, a subset of STN neurons showed differential activity upon cue presentation before successful and unsuccessful stops, thus predictive of successful inhibition. This activation pattern is consistent with the proposed role of the STN in inhibitory control during decision making. Simultaneous EEG recordings may reveal how STN coherence with frontal cortical population activity mediates successful and unsuccessful response inhibition.

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Fine-tuning of AMPK-ULK1-mTOR Regulatory Triangle Is Crucial for Periodic Activation of Autophagy

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Introduction: The autophagy-dependent self-eating is tightly regulated by mTOR and AMPK kinases. AMPK promotes autophagy by phosphorylating ULK1, the key inducer of autophagosome formation, meanwhile mTOR down-regulates it under nutrient rich condition. However, the active ULK1 can inhibit both AMPK and mTOR. Interestingly, a periodic activation of ULK1 was also observed during prolonged stress.

Aims: We claim that the negative and double negative feedback loops of AMPK-mTOR-ULK1 regulatory triangle determine an accurate dynamical characteristic of autophagic process to cellular stress (such as starvation or rapamycin-induced mTOR inhibition).

Methods: We approach our scientific analysis from a systems biological perspective by using both theoretical and molecular biological techniques. For molecular biological experiments HEK293T cell line is used, meanwhile the dynamical characteristic of the regulatory network is described by mathematical modelling.

Results: In our study we suppose that a delayed negative feedback loop between AMPK and ULK1 is essential to manage a proper cellular answer upon autophagy induction. By using both molecular and theoretical biological techniques, we suggest that AMPK kinase gets induced followed by ULK1 activation during prolonged starvation or rapamycin treatment, whereas active ULK1 kinase quickly down-regulates AMPK resulting in a delayed decrease in ULK1 activity. This periodic repeat of AMPK-ULK1 activation/inactivation due to the negative feedback between them generates an oscillatory activation of autophagy, as well. We demonstrate that this periodic induction of autophagy is essential to guaranty the suitable dynamical features of the control network when mTOR is down-regulated.

Conclusions: Understanding how the regulation of the cell survival with precise molecular balance of mTOR-AMPK in autophagy occurs, is highly relevant in several cellular stress related diseases (such as neurodegenerative diseases) and might help to promote advanced therapies in the near future, too.

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Neuroimmune Communication in the Epidermal Compartment of Human Skin

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The immune system is strongly linked to the nervous system within the human organism, to the point that in many diseases they cannot be fragmented to separate entities. Specifically, some inflammatory skin diseases such as atopic dermatitis and psoriasis have been reported to be intensified by stress, and, interestingly the skin lesions in these diseases sometimes resolve after nerve injury. The putative cause underlying this empirical observation is that sensory nerves secrete neuropeptides and other mediators that are important members of neuro-immune communication. Neuropeptides play a key role in skin immunity, the inflammation process, and wound healing. Inside the epidermis, the only dedicated resident immune cells under steady-state are the antigen-presenting cells called Langerhans cells (LC). LCs are anatomically associated with neurons that produce, Calcitonin Gene-Related Peptide (CGRP) possibly playing a role in the cutaneous inflammation.

Previous reports have shown that CGRP reduces LC antigen-presentation to a Th1 clone however, the exposure of the CGRP in LCs enhances the antigen-presentation for Th2 clones. The cytokine secretion after chicken ovalbumin (cOVA) challenge was shifted toward a Th2 profile, since IL-4 was increased while IFNγ production was decreased. While these results are interesting, they were carried out in mouse models, therefore we decided to test all the results on human monocyte-derived LCs.

In this project, the aim is to discover the communication between LCs and neurons located in the skin.

As a first, exploratory step we utilized RNA sequencing from monocyte-derived LCs samples from five donors and we detected the expression of neuropeptide receptor genes. We found a high expression of CGRP receptor and its coreceptor RAMP1 and also one of the neurotensin receptors (SORT1, also known as NTR3) and the Brain Natriuretic peptide receptor(NPR1). These results will be validated with q-PCR and western-blot in monocyte-derived LCs. We would like to analyze the effect of these peptides in the differentiation of monocyte-derived LCs and dendritic cells with flow cytometry. Furthermore, we are also curious about the signal transduction pathways initiated by these peptides.

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Different imaging modalities for the follow up of patients with noncompaction cardiomyopathy: which one to use?

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The measurement of left ventricular (LV) volumetric and strain parameters in patients with noncompaction cardiomyopathy (NCMP) with 2D and 3D speckle tracking echocardiographic (2D-STE, 3D-STE) is more challenging than the same with cardiac MRI (CMR).

The agreement of these imaging modalities has been already studied in different cohorts but not in patients with NCMP.

Our aim was to assess the correlation and agreement between CMR, 2D-STE, and 3D-STE by comparing the volumetric and strain values of NCMP and healthy control participants.

We studied 21 NCMP patients who had no co-morbidities and 21 control participants (NCMP: age: 37±15 years EF: 67.5±3.9%; Control: age: 17±3years, EF: 58.8±4.4%) with Philips Achieva 1.5 T scanner, and GE Vivid E95 echocardiography equipment. Medis Suite, TOMTEC 4D LV-Analysis 3, and TOMTEC Cardiac Performance Analysis software were used for post-processing. Data were analyzed with Pearson's correlation and Bland-Altman plots with percentage error (PE). $P < 0.05$ was considered as significant. Volumetric data were indexed to body surface area.

Volumetric measurements correlated well between the studied modalities in both group (NCMP and control groups: end-diastolic volume: r between 0.7 and 0.9, end-systolic volume: r between 0.7 and 0.8, stroke volume: r=0. 7) while the strain parameters showed poor correlation.

We found better agreement between CMR and 2D and 3D echocardiography in the healthy group than in patients ($p = 0.01$). However, only the healthy subjects' global strain values showed good agreement between the modalities (GLS MR-2D: $p<0.014$ PE=23.4%; MR-3D: $p<0.01$ PE=24.7%; GCS MR-2D: $p<0.01$ PE=20,7 %; MR-3D: $p<0.01$ PE=23.7%).

Our pilot study suggests that LV hypertrabeculation may cause difficulties in measuring STE strain parameters. Further studies are needed to find the optimal follow-up modality for this patient population.

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Relevance of Nitric Oxide and Prostanoid Mediators in the Autoregulation of Cerebrocortical Blood Flow in Mice

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Introduction: The understanding of cerebral autoregulation mechanisms has become of notable importance due to the increased incidence of carotid artery stenosis worldwide. Many debates exist in the scientific literature including the role of endothelial and neuronal nitric oxide (NO) synthases (eNOS and nNOS) and prostanoid mediators (PMs). According to our previous observations, eNOS does not seem to play an important role in the autoregulation of the cerebrocortical blood flow (CoBF) to unilateral common carotid artery occlusion (CAO) (1).

Aims and Methods: We aimed to analyze the combined lack of eNOS and nNOS and the role of PMs in cerebrovascular autoregulation by analyzing the changes of CoBF with laser-speckle imaging after reducing the cerebral perfusion pressure by unilateral (left) CAO in wild-type (WT), as well as in eNOS/nNOS double knock-out (KO) male mice. The role of PMs was tested by indomethacin administration (1 mg/kg, i.p.) and in thromboxane receptor knock-out (TPR-KO) male mice.

Results: In WT animals CoBF reduction in the left temporal cortex started immediately after CAO, reaching its maximum (-27%) at 6-9 s. Thereafter, CoBF recovered close to the pre-occlusion level within 30 s indicating the activation of regulatory pathway(s). Surprisingly, in eNOS/nNOS double KO animals the acute CoBF reduction after CAO was unaltered in all cerebrocortical regions, but the recovery of CoBF was worsened as compared to controls. Indomethacin treatment resulted in a faster recovery in the temporal region, specifically 9-21 s after the occlusion. In TPR-KO animals, however, the recovery of the CoBF was slightly diminished.

Conclusions: These results indicate that (1) the combined lack of eNOS and nNOS impairs only the subacute phase of the recovery after unilateral CAO and (2) indomethacin treatment results in a faster recovery, probably by inhibiting the release of a vasoconstrictor prostanoid, which is not thromboxane A2.

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Modulation of Excitatory Neurotransmission by P2X7Rs in Mouse Dentate Gyrus

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P2X7 receptors (P2rx7) are ligand gated ion channels and impact on several pathological processes in the brain, including neuroinflammation, cell death, hyperexcitability, changes in neurotransmitter release etc. However, the involvement of P2X7Rs in excitatory neurotransmission in dentate gyrus granule cells keeps unclear. To investigate this question, we utilized P2X7 KO mice to record NMDA-mediated miniature EPSC in granule cells. Surprisingly, we found that the amplitude and frequency significantly decreased in P2X7 KO mice compared to WT counterparts. Meanwhile, the application of selective antagonist of P2X7R (JNJ-47965567) could partly mimic the results. To summarize, P2X7Rs participate in excitatory neurotransmission via both pre-and postsynaptic sides partly through action potential-independent mechanism in adult dentate gyrus granule cells.

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Saccharomyces cerevisiae var. 'boulardii' Infections: Diagnosis and Investigation of Pathogenicity

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Nowadays the use of probiotics is widespread due to their concieved beneficial effects on health. However, the rising popularity of probiotic products lacked a concomitant increase in scientific risk assesment and awareness of side effects. An increasing number of infections originating from probiotic use are reported worldwide, with the majority of such cases caused by the yeast Saccharomyces 'boulardii', a subtype of S. cerevisiae. Because of their frequent use, they pose a significant health risk, especially to severely ill or infant patients, and patients with prolonged hospitalization. Nonetheless, techniques that reliably link infectious cases to probiotic products are often time-consuming and difficult to implement in routine diagnostics.

Our aim was to optimize a quick and reliable multiplex PCR method for the identification of the S. cerevisiae 'boulardii' subtype. Additionally, we wanted to find out the reasons behind the pathogenic behaviour of the yeast.

In our work we propose a multiplex PCR protocol for the identification of S. 'boulardii' based on a combined analysis of interdelta fingerprinting and microsatellite typing. To facilitate probiotic risk assessment, we investigated the genetic basis of phenotypic adaptations in clinical isolates of the probiotic yeast and conducted in vivo microevolutionary experiments in mice. These were followed by stress-phenotyping in order to reveal the traits under selection during pathogenic lifestyle.

We show that probiotic origin is common among clinical Saccharomyces, and that the new multiplex method enables rapid and unequivocal identification of probiotic yeast infections. This method can be applied for the identification of yeast infection sources, helping decisions on probiotic use.

Our data suggests that the clinical isolates and subclones derived from the experimental infection show adaptations to higher osmotic stress and altered cell wall composition compared to the commercial probiotics, resulting in increased survival in our mammalian model. Based on these results we investigated the application of genetic engineering tools to create probiotic yeasts unable to adapt to the host environment outside the gut. Such a strain would be unable to cause systemic infections, in contrast to currently marketed products with questionable safety.

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Malignant Potential of Verrucous Leukoplakia

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Introduction: proliferative verrucous leukoplakia (PVL) is a special and aggressive form of leukoplakia, which is now considered by the WHO classification as a potentially malignant disease of the oral mucosa. Neoplasia can develop in 40%-100% of cases, after 4.4–11.6 years. For this reason, PVL should be detected as early as possible. PVL exhibits varied clinical features in four clinical stages: focal flat white keratosis, diffuse and multifocal white patches, slowly progressive horizontal and exophytic growth resulting in a warty surface with focal erythematous areas and development of verrucous or squamous cell carcinoma. The most controversial issue is the presence of dysplasia in PVL. In the WHO classification of the 2017 year is indicated that dysplasia develops only during the late stages of PVL, before progressing into carcinoma. However, not every PVL goes through these clinical stages and development of carcinoma has been noted in PVL clinically presenting as multifocal flat patches. Therefore, the urgent task is to search for new diagnostic criteria, allowing to assess the malignant potential of PVL in the early stages of the disease.

Aims: An investigation of dysplastic changes in the epithelial cells of the oral mucosa with verrucous hyperorthokeratosis (VH), verrucous carcinoma (VC) and oral squamous cell carcinoma (OSCC).

Methods: Oral mucous membrane biopsies of 33 patients with a clinical diagnosis of PVL were investigated. Histologically in 19 cases (57.6%) was revealed VH, in 8 cases (24.2%) – VC and in 6 cases (18.2%) – OSCC. Tissue antigens were determined using mouse monoclonal antibodies to Ki-67 and mouse monoclonal antibodies to cytokeratin 15.

Results: In comparison with the proliferative activity of epithelial cells in the malpighian layer in VH (17.2±8.1%) was detected an increase of cell proliferation in epithelial growth zone in VC (33.8±8.1%) and in the peripheral zone of solid areas in OSCC (51.2±35.7%). A significant decrease in the expression of cytokeratin 15 in the cytoplasm of tumor cells was noted in VC and OSCC in comparison with VH.

Conclusions: The obtained results proclaim that there is no stage of epithelial dysplasia during tumor transformation of PVL into VC and OSCC. Malignization of PVL by the nature of the proliferative activity, cell atypia and expression of cytokeratin 15 corresponds to carcinoma in situ.

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Diagnostic Performance of Coronary Computed Tomography Angiography-Derived Fractional Flow Reserve in Patients with Acute Myocardial Infarction and Moderate Non-Culprit Coronary Stenosis

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Introduction: Revascularisation of significant non-culprit coronary lesions (NCL) may improve clinical outcome in patients with myocardial infarction and multi vessel disease, however management of moderate NCLs is still controversial. Dobutamine stress echocardiography (DSE) and invasive fractional flow reserve (FFR) are accepted methods to detect myocardial ischemia, nevertheless coronary CT angiography-derived fractional flow reserve (CT-FFR) is a new modality, which has not been widely investigated to date in patients with NCLs.

Aims: Our aim was to determine the diagnostic performance of CT-FFR compared to DSE and invasive FFR.

Methods: In this prospective trial, DSE, FFR and CT-FFR were performed in every patient with MI and at least one moderate NCL (30-70% diameter stenosis by visual assessment). New or worsening wall motion abnormality in at least two contiguous myocardial segments on DSE, and FFR value<0.8 in invasive FFR and CT-FFR as well were determined as abnormal. In comparison, DSE and FFR were regarded as reference standard methods.

Results: Between March of 2017 and December of 2018, 51 patients (58.2±10.4 years, 74.5% male) were enrolled and 71 NCLs (40 LAD, 13 LCx, 18 RCA) were investigated. Dobutamine stress echocardiography, FFR and CT-FFR were positive in 30.9%, 32.3% and 22.5% of all lesions, respectively. FFR values were higher with CT-FFR compared to invasive FFR (0.85±0.11 vs. 0.83±0.08, $p<0.05$). Compared to DSE, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of CT-FFR were 40.9%, 85.7%, 56.2%, 76.3% and 71.8%, respectively. The same values were 39.1%, 85.4%, 56.2%, 74.5% and 70.4% compared to invasive FFR, respectively. Correspondence of CT-FFR with DSE (k=0.29) and with FFR (k=0.27) was weak.

Conclusions: Our results demonstrated moderate diagnostic accuracy, excellent specificity, poor sensitivity and PPV and acceptable NPV of CT-FFR compared to DSE and FFR. At this stage, CT-FFR is probably not accurate enough to determine revascularisation strategy of moderate NCLs as a single non-invasive method.

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Implementation of Hot-melt Extrusion as a Tool for 3D Printing: Design and Evaluation of Baicalin-loaded Thermoplastic Filaments

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Introduction: 3D printing is a process that creates a three-dimensional object layer-by-layer based on a 3D digital model. One of the most widely used 3D technology is fused deposition modelling (FDM), which utilizes a thermoplastic filament for the creation of different prototypes. Hot-melt extrusion (HME) is a process that can be applied for the production of filaments. The active molecule is blended with a thermoplastic polymer and then extruded as filaments that are used in 3D printing. Baicalin, the model drug used in this study, is a flavone glycoside, extracted from the root of Scutellaria baicalensis Georgi. It has numerous pharmacological effects (antioxidant, antimicrobial and anti-tumor), but the poor biopharmaceutical properties hamper its oral bioavailability. Furthermore, it has a thermolabile property.

Aims: The aim of this study was the development, analysis and preparation of baicalin-loaded filaments by hot-melt extrusion, which has suitable properties for 3D printing (flexibility, drug-loading, thermoplasticity, tensile strength). The focus was put on the evaluation of critical process-, and filament attributes. Other important goal was the characterization of crystalline-amorphous phase transition by powder x-ray diffraction.

Methods: Preparation of drug-loaded filaments was carried out by hot-melt extrusion using different process parameters (temperature, rotation speed) and pharmaceutical excipients. Morphological characterization of filaments was fulfilled by digital microscopy using high-resolution imaging. The tool for the study of phase transitions was powder x-ray diffraction.

Results: PEG 6000 as thermoplastic polymer was successfully used for the creation of filaments. The optimized process parameter in case of HME was 60 °C and 3 rpm. From 1 g of powder approx. 50 cm of filament can be generated. The filament disintegrates in pH 1.2 dissolution medium within 15 minutes. Baicalin was added and blended with the polymer before extrusion and acceptable content uniformity was measured. Unfortunately, these kind of filaments were rigid and brittle. Therefore, triethyl citrate was added to the blend as a plasticizer, which gave filaments with suitable physical properties.

Conclusions: HME is a suitable method for the preparation of drug-loaded filaments. By optimizing the excipient system, 3D printed tablets can be generated.

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7059

Examination of Serum miRNAs as Possible Biomarkers for the Diagnosis of Acute Rejection after Kidney Transplantation

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Introduction: Because of the lack of non-invasive, specific biomarkers, early detection of acute rejection after kidney transplantation represents a challenge. microRNAs (miRNAs) belong to a class of small, noncoding RNAs and they were found to be involved in pathological processes that occur following kidney transplantation.

Aims: We analyzed the association of serum expression levels of miR-15b, miR-16, miR-24, miR-103a and miR-107 with acute rejection episodes that occur during the early phase after transplantation. We also investigated the capability of these miRNAs to differentiate between acute rejection episodes and other pathological processes.

Patients and Methods: Prospectively collected serum samples of kidney allograft recipients with stable graft function (n=10), urinary tract infection (UTI) (n=9), borderline rejection (n=9), acute tubular necrosis (ATN) (n=9) or biopsyproven acute rejection (n=9), who were transplanted between 2015 and 2017 were analyzed. In addition, serum samples of 7 patients with an acute rejection episode were also investigated at different time points after kidney transplantation. miRNA expression levels were determined by real-time quantitative reverse-transcription-polymerase chain reaction (RT-PCR). Spiked-in cel-miR-39 was used as a normalization control.

Results and Discussion: As compared to patients with stable graft function, decreased serum levels of miR-15b, miR-16 and miR-24 were observed on post-Tx day 8 in kidney transplant patients with borderline rejection, ATN or acute rejection. miR-15b and miR-24 levels were lower in patients with ATN than in patients with UTI. miR-103a level was also lower in patients with ATN or acute rejection than in patients with stable function. Longitudinal analysis of individual patients showed that miR-107 is increased during acute rejection and decreases with the improvement of the kidney function. One patient with ABMR showed extremely decreased levels at all timepoints.

Conclusions: The determination of serum miR-15b, miR-16, miR-24 and miR-103a levels may allow the detection of allograft damage after kidney transplantation; however, these miRNAs do not seem to distinguish acute rejection from other transplant pathologies. In contrast, the quantification of serum miR-107 appears to be useful for monitoring the therapy success in patients with an acute rejection episode.

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Cell type specific inhibition of calretinin-positive neurons in the dorsomedial thalamus reduces arousal

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Stress-related sleep disorders affect many people worldwide, however neuronal links between sleep and stress are presently unclear. Dorsomedial thalamus (DMT) can potentially connect these two phenomena since the involvement of DMT in stress and wakefulness is well established. The aim of our present research is to investigate the role of DMT in stress-related sleep disorders. Earlier experiments by our research group have shown that graded optogenetic stimulation of DMT calretinin positive cells (DMT/CR+) can generate arousal (Mátyás et al., 2018). Based on these results, we investigated the effect of photoinhibition of DMT/CR+ on normal sleep and on sleep following a stressful situation.

Prolonged inhibition of DMT/CR+ at the beginning of the mice' inactive phase led to a significant decrease in the EMG activity and movements of the mice and a concomitant increase in the power of sleep related delta activity in the EEG. Reduced arousal was maintained after terminating the inhibition. Prolonged inhibition of DMT/CR+ cells led to a 50% decrease in sleep onset. In the next step we used the same protocol following the exposure of mice to predator (fox) odor in a novel environment and studied the effect of poststress inhibition of DMT/CR+ cells on the development of stress induced sleep disturbances.

Our experiments demonstrated that photoinhibition of the DMT/CR+ cells results in decreased vigilance, consistent with the proposal that these neurons are involved in the regulation of forebrain arousal level. The involvement of DMT/CR+ cells in altered, stress related elevation of arousal level remains to be established.

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Comparison of the previous and current trauma-related shock classifications – The more the better? – A retrospective cohort study from a level I trauma center

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Introduction: According to the previous Advanced Trauma Life Support (ATLS) guidance, the early assessment and classification of trauma patients with haemorrhage were based upon the vital signs (heart rate (HR), systolic blood pressure (SBP), Glasgow Coma Scale (GCS)). Recently, national trauma registry analyses suggested to extend the assessment criteria with the base deficit (BD), referring to the metabolic status. Although commonly used, the relevance of BD is still controversial.

Aims: The study aim was to compare the predictive performance of the previous, vital sign based (VS) and the current, extended (VS+BD) criteria of classification with respect to the outcomes of mortality. We also studied the predictive values of the individual parameters (HR, SBP, GCS, BD) respectively.

Methods: Retrospective analysis from a level I trauma center. Data were collected on trauma patients that met the inclusion criteria (trauma team activation, age ≥ 12, 30-day follow up, complete dataset of VS and BD). They were assigned into shock classes (I-IV) based on their worst parameter from VS and VS+BD criteria, respectively. Chi-square tests and a two-proportion Z-test were performed to calculate and compare the predictive performance of VS and VS+BD classifications. Receiver operating characteristic (ROC) curve was calculated for each variable.

Results: A total of 156 patients met the inclusion criteria. 34 patients died within the first 30 days, resulting a mortality rate of 21.79%. Both classifications have shown strong relation with mortality (p=0,000021 vs. p=0,000009). There was no significant difference in their performance predicting mortality (p=0.981). According to our ROC-analysis, GCS, BD and SBP had significant predictive values (AUROC curves [95% CI]: GCS: 0.799, [0.722,0.875]; BD: 0.683, [0.576,0.790]; SBP: 0.633, [0.521,0.744]). HR was found ineffective in predicting mortality. (AUROC: 0.595, [0.480,0.710]).

Conclusions: According to our study, the current ATLS classification of hypovolaemic shock does not appear to be superior to the previous, vital sign based one in predicting mortality in a setting where only the worst parameter of patients determines their shock class. The analysis of the individual parameters showed that GCS, BD and SBP have a significant predictive potential. HR does not seem to reflect the clinical condition accurately.

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3D reconstruction and analysis of chronic lower extremity wounds

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Introduction: Difficulties of the management of chronic lower-extremity wounds (LEW) put a major burden on patients and healthcare systems. The most common etiology of LEW is chronic venous insufficiency, followed by peripheral arterial disease and diabetes mellitus. Unusual causes, such as vasculitis, autoimmune disorders, or tumors, are responsible for 5% of LEW. The prevalence of chronic LEW is 1.2-2, showing an increase with the aging of the population. The cost of treatment of LEW represents 1% of the healthcare budget in the EU.

Aims: The objective of this multicenter study, led by MedInnoScan Ltd., was to develop a mobile application capable of high-resolution 3D reconstruction of LEWs. We aimed to create a 3D imaging method to provide fast and structured standardized assessment of LEWs. A further goal is to establish an artificial neural network based on deep learning to determine the etiology of LEW and recommend appropriate dressing types based on data collected with the application.

Methods: 1,400 cases of LEW have been involved in the study, out of which 250 cases were collected at the Dept. of Dermatology, Semmelweis University. 40 images of each LEW were taken from different viewing angles using the mobile application, along with a questionnaire collecting data of ECOG status, obesity, and other medical conditions; LEW status and administered smart dressings. Once the images and questionnaire are uploaded the main server executes photogrammetric reconstruction to prepare a 3D model of the LEW.

Results: We have achieved a high-resolution reconstruction of 3D models of examined LEWs with accuracy within 1mm compared to the results of laser scanning performed on selected test LEWs. Most mobile phones (8MP+ camera required) can be utilized to achieve this accuracy. With this technology we could measure the depth of LEW, presence and the extent of the necrosis and reepithelialization.

Conclusions: This mobile application is a novel, fast, accessible, and cost-effective technology to create 3D reconstructed models of a LEW. These models could be useful to record and to follow-up the healing process of a LEW in a structured standardized way. This technique could be appropriate to assess the current status of a LEW. Furthermore, it could be capable to specify the etiology and to choose the optimal therapy for each LEW.

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Evaluation of the expression of Serpin E1/PAI-1 in biological samples of inflammatory bowel disease patients

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Introduction: Inflammatory bowel diseases are chronic disabling gastrointestinal disorders. Anti-TNF therapies are primary treatment options in IBD, but in 40-60% of the cases the patients do not respond to the initial treatment or lose response over time. Imbalance of pro-, and anti-inflammatory cytokines alter inflammatory response and determine response to therapy. Thus, patient-specific determination of individual cytokine profiles could improve the prediction of therapeutic response.

Aims: Our aim was to determine the cytokine profile of the IBD patients. In the next step, we wanted to further characterize the expression of promising cytokines.

Methods: Biopsies were obtained from the inflamed and non-inflamed part of the colon of IBD patients and controls undergoing colonoscopy. Total protein and mRNA were isolated from the biopsy samples. We used Cytokine Array to analyse the cytokine pattern. Gene expression and localization of the selected cytokines were assessed by qRT-PCR and immunostaining.

Results: We defined the cytokine profile of 36 biopsy samples. As expected, in the control samples no cytokines were detected, which potentially play a role in the inflammatory process. In samples from IBD patients remarkable discrimination between the inflamed, or non-inflamed areas was possible. MIP1-α/β, IL-1β, IL-8, IL-18 and Serpin E1 were detected in the majority of inflamed samples. Serpin E1/PAI-1 is an inhibitor cytokine inhibiting the tissue plasminogen activator (tPA) resulting in inhibited fibrinolysis and activation of coagulation. As the risk to develop deep venous thrombosis is 6 times higher in the IBD patients than the healthy people, we analysed Serpin E1 further. We compared the expression of Serpin E1 in patients received or not received treatment. Our results suggest that biological therapy decreases the expression of Serpin E1 both at mRNA and protein level.

Conclusions: Our results showed remarkable difference in the cytokine profile of biopsy samples captured from inflamed area compared to controls, or non-inflamed samples. The gene expression of Serpin E1 was the highest in the inflamed sample and the lowest in the control. As a result of biological therapy the expression of SerpinE1 decreased. In the next steps we will increase the sample numbers and analyze the correlation between SerpinE1 expression and clinical response.

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Genetic versus Environmental Background on the Relationship of Telomere Length and Bone Mineral Density

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Introduction: Environmental and genetical factors determine the development of diseases, although the amount of impact made by these components may vary significantly in different disorders. Telomere length (TL), as a hallmark of cellular aging, may be involved in the development of several diseases associated with aging by modulating oxidative stress. Bone mineral density (BMD) is an indicator of osteoporosis that has been associated with oxidative stress suggesting a possible connection with TL.

Aims: To investigate the genetic and environmental influences on telomere length and to examine the possible relationship with BMD in a twin study.

Methods: 56 twin pairs (37 monozygotic and 19 dizygotic pairs, 63% female, mean age: 51.8±14.1 ys) underwent central (lumbal spine L1-L4, femoral neck and hip) and peripheral (radius) bone DEXA scans (Hologic Horizon WI, Hologic Sahara) and blood test. TL was measured from peripheral blood samples by calculating the number of telomere repeats compared to a single-copy gene (albumin) using qPCR. ACE model was used to decompose the variance into additive genetic, common and unique environmental factors and log-linear regression was used between TL and BMD.

Results: The estimate correlations in monozygotic (0.796, confidence interval [CI] 0.686 to 0.871) and dizygotic (0.770, CI 0.576 to 0.881) pairs indicated no additive genetic effect on TL. In the CE model, the impact of shared environmental factors explained 78% (95% CI, 69% to 85%), while the unique environmental factors explained 22% (95% CI, 15% to 31%) of the variance in TL. In the regression test we found significant linear relationship between the logarithm of TL and mineral density of bones (estimate: 0.091, $p<0.05$, R^2: 0.115), which combined with the results of the ACE model, are attributed to environmental factors.

Conclusions: In our study TL was mainly influenced by environmental factors. Our results showed a non-genetic relationship between TL and BMD suggesting a possible link between oxidative stress and osteoporosis. Our preliminary study might stimulate further investigations to specifically target the possible link between TL and osteoporosis markers, with the aim to develop additional early predictive markers for osteoporosis.

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Salt induced three dimensional electrospun fibrous matrices

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Electrospinning is a widely investigated and used technique for creating nano and microfibres which has a wide range of medical and pharmaceutical applications. For cell culturing and tissue engineering it is a greatly investigated method because it resembles the extracellular matrix. Changing the electrospinning parametres we affect the properties of these systems to fine tune it for our needs. To create a high porosity fibrous mesh for culturing different cells in a suitable three dimensional way, we need to step forward from conventional electrospinning. My aim was to find a reproducible way of creating three dimensional fluffy structures from polysuccinimide, which is a biocompatible and biodegradable polymer, in the presence of different concentrations of LiCl, $MgCl_2$ and $CalCl_2$ in the solution.

Ion-ion and ion-solvent (dimethylformamide) interactions were characterised using vibration spectroscopy and quantum calculations. Also, structural changes of the fibrous mesh by macroscopic and SEM (Scanning Electron Microscopy) images were recorded.

$CaCl_2$, $MgCl_2$ and LiCl were identified as salts that promote fluffy structure upon mixing in polysuccinimide-dimethylformamide solutions used for electrospinning. FTIR and computational investigation showed that there is a strong interaction between their respective ionic components and the solvent. Furthermore, according to our data the most important thing is the quality of the salt and through that its interaction with the solvent used for electrospinning.

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Simultaneous investigation of behavioral synchronization of two individuals during social interaction

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Introduction: Interpersonally synchronized behaviors play a fundamental role in social interactions. An important component for the development of behavioral synchronization is the "Theory of Mind", i.e., mentalization ability of the people who are involved in the interaction. The "Reading the Mind in the Eyes" (RMET) test is widely used to measure mentalization, including social cognition and empathy. However, previous research using the RMET examined individuals in isolation, without being involved in actual social interaction with another person. Thus, it is not known whether the performance measured by the RMET test correlates with the actual behavioral synchronization processes.

Aims: To investigate the relationship between the synchronous behavior of two interacting individuals during a social interaction (joint action) task and the "Theory of Mind" performance, as measured by the RMET test.

Methods: 48 healthy subjects (24 pairs) were included in the study. We examined shared neural mechanisms during cooperation (joint action) in an EEG hyperscanning experiment, and investigated the behavioral data for the purpose of this project. We used the images of the International Affective Picture System as a stimuli, using the Presentation software. We applied the RMET test to describe empathy/social cognition. Participants' synchronous behavior was characterized by the synchronization of responses to stimuli in terms of reaction times (indexed by the correlation of the pairs of responses by the two participants). In order to characterize the performance with respect to social cognition and empathy, we used the proportion of correct answers from the RMET test.

Results: There was a significant positive correlation between the synchronization of the behavioral responses (reaction times) of the pairs tested and the performance measured by the RMET test ($p < 0.05$). With better social cognitive performance (85% recognition rate,i.e., 1 SD above the mean), the correlation coefficient for behavioral response synchronization was significantly higher ($r = 0.45$) than with lower social cognitive performance (60% recognition rate, i.e., 1 SD below the mean) ($r = 0.22$).

Conclusions: The mentalization ability, as measured by the RMET test, is closely related to the level of behavioral synchronization between the individuals who participate in actual social interactions.

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Supervisor: Pál Czobor

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Novel Cyclodextrin-based Drug Carriers to Target the Blood-brain Barrier: Synthesis, Analytical- and In Vitro Characterisation

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Introduction: In the development of new drugs for neurological diseases, the main limiting factor is the presence of the blood-brain barrier (BBB), inhibiting the delivery of therapeutics into the brain. Glucose transporters provide ideal targets for new carrier systems aiming the central nervous system (CNS), as they are overexpressed on the surface of the BBB.[1] Another approach is the use of positively charged carriers to achieve high affinity for the negatively charged endothelial cells of the brain capillaries. It is evidenced, that organizing monomeric compounds to macromolecular systems enhances their transport across the cell membranes.[2]

Aims: As cyclodextrins (CDs) are known as ideal drug carriers, our aim was to develop new CD-based drug delivery systems, capable to cross the BBB. Based on the aforementioned considerations, we have synthetized two sets of CD derivatives: (1) glucose appended beta-CD (BCD) and hydroxypropyl-BCD (HPBCD) scaffolds using click-chemistry, (2) positively charged polymer by crosslinking (2-hydroxy-3-N,N,N-trimethylamino)propyl-BCD (QA-BCD) with epichlorohydrin.

Methods: For the in vitro investigation of the compounds, their fluorescent labeling was necessary. As fluorescent tags, 7-alkylamino-4-nitrobenzofurazan (NBF) and fluorescein-isothiocyanate (FITC) were used. The labelled glucose-modified CDs were synthetized by the simultaneous attachment of the fluorophore and a targeting unit via click-reaction and characterized by NMR and MALDI-TOF-MS. The FITC-labelled polymers were synthetized through a copolymerization of the QA-BCD and 1% FITC-BCD monomer and characterized using NMR and dynamic and static light scattering.

Results: Cellular internalization properties of the conjugates are under investigation using isolated human brain microvascular endothelial cells (HBEC-5i). The HBEC-5i monolayer serves as a barrier model. Confocal fluorescence microscopy is used to determine the internalization process and flow-cytometry is used to quantify the cell-penetration.

Conclusions: Various new CD-based drug carriers targeting the CNS have been synthetized and characterized by NMR, MS and microscopy.

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Pharmacological Characterization of Somatostatin 4 Receptor Agonists, as Novel Analgesic Candidates

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Introduction: Our group has previously provided several lines of evidence that somatostatin released from the capsaicin-sensitive peptidergic nociceptors mediates analgesic and anti-inflammatory effects via its sst4 receptor without influencing endocrine functions. Therefore, sst4 is suggested to be a novel target for drug development, especially in chronic neuropathic pain, which is a huge unmet medical need.

Aims: We investigated the binding, receptor activation abilities, and the effects of our four novel small molecule sst4 receptor agonists in mouse models of chronic neuropathic pain and acute neurogenic inflammatory hyperalgesia.

Methods: We examined the in silico binding and sst4-linked G protein activation of our novel small molecule pyrrolo-pyrimidine compounds on stable sst4 expressing CHO cells (1 nM-10 μM). The effects of the two most potent ligands were tested on thermal and mechanical hyperalgesia in the resiniferatoxin-induced acute neurogenic inflammation (500 μg/kg p.o.) and mechanical hyperalgesia in the partial sciatic nerve ligation-induced traumatic mononeuropathy (20, 100, 500, 1000, 2000 μg/kg p.o.) models in mice.

Results: All our four tested compounds bind to the same high affinity binding site of sst4 as the reference compound J-2156 and are able to activate the sst4-linked G protein. The 500 μg/kg dose of one compound significantly reduces neurogenic inflammatory thermal and mechanical hyperalgesia, and two of them exert significant, 60-70% maximal anti-hyperalgesic effects in the neuropathy model after a single administration on the 7th postoperative day.

Conclusions: Our novel, orally active small molecule sst4 agonists can open promising analgesic drug developmental perspectives for inflammatory and neuropathic pain.

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Mechanisms of cerebrovascular autoregulatory adaptation to preeclampsia - review of the literature

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Aims: Preeclampsia is a serious disease, complicating 2%-8% of pregnancies and imposing great hemodynamic load on the cerebral circulation of the mother, but it is very dangerous for fetus, as well (Chen, 2014). A constant blood flow to the brain is provided by cerebrovascular autoregulation - within wide range of systemic blood pressure (Jeyabalan, 2013). Impairment of this regulation can have serious consequences on the brain.

Methods: The available literature (PubMed) has been reviewed and critically analyzed regarding the importance of cerebrovascular vasomotor responses and the efficacy of cerebral autoregulation in preeclampsia.

Results: According to the international research results, in preeclampsia there are more frequent strokes and cerebral events (Chandra, 2017). The placental ischemia/hypoxia is one of the initiatory mechanisms of preeclampsia, which induces oxidative stress, immunological dysfunction and imbalance between pro- and anti-angiogenic factors (Hod, 2015). It has been demonstrated by animal studies, that placental insufficiency is an important step in the manifestation of preeclampsia (Granger, 2006). Through maternal vascular endothelial dysfunction, placental insufficiency leads to the reduction of vasoactive mediators (changes of the arachidonic acid mechanism) and increased generation of vasoconstrictor molecules, thus reduce the blood supply to multiple organs (Gilbert, 2008). Studies have shown, that myogenic responses of middle cerebral artery importantly involved in the autoregulation are impaired in preeclampsia (Ryan, 2011).

Conclusions: The main mechanisms regulating the diameter of the small cerebral arteries are the pressure- and flow-induced diameter changes, which provide constant cerebral blood flow, however further studies are needed to characterize the myogenic response and the flow mediated constriction in brain vessels during preeclampsia. Through the identification and pharmacological modulation of the arachidonic acid related signalling pathways better prevention and treatment can be developed for hypertension during pregnancy.

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The male factor – impact of semen quality on the insemination result in women with endometriosis

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Little is known about the effect of endometriosis on the outcome of insemination (IUI). In the first 6 month after surgery women with minimum to mild endometriosis have the same chance to get pregnant with IUI as couples with unknown infertility. The ESHRE guideline recommend insemination as treatment for infertility with minimum to mild endometriosis, but this statement is not linked to any study with male fertility factors.

This is a retrospective study performed between 2010 January and 2019 May at university settings. Patients treated with endometriosis and infertility were selected from our institute database such as diagnosis of endometriosis, date of previous surgeries, date of insemination and total motile sperm count (M/ml). Data of IUI treatments were analyzed in two groups.Endometriosis group: cycles with the diagnosis of previously surgically proven endometriosis. Control group: cycles with "unknown infertility".

Endometriosis group was further divided into two subgroups according to the time elapsed between surgery and IUI. Subgroup A: IUI ≤6 months after surgery; Subgroup B: IUI in 7-18 months after surgery. Total motile sperm count and pregnancy rates were compared in Endometriosis and Control groups.

The pregnancy rate of insemination cycles of women with endometriosis (23/341; 6,7%) was similar to the Control group (9/171; 5,2%) (P=0,513). Subgroup analysis of endometriosis patients showed similar pregnancy rates in Subgroup A (4/69; 5,8%) and Subgroup B (10/129; 7,7%) (P=0,609). The progressive motile sperm count in the pregnant IUI cycles was 34,9±18,4 M/ml, in the Endometriosis group, while 25,8±14,6 M/ml in the Control group. The difference was not significant (P=0,304). The mean of 22,5 ±9,2 M/ml of progressive sperm count was found in pregnancy in Subgroup A. That is similar to the Control group's result. However, that of Subgroup B higher sperm number was found in pregnancy cycles (37,3±11,3 M/ml), but the difference was not significant (P=0,327).

It seems that within 6 months following the endometriosis surgery patients need comparable amount of motile sperm to get pregnant by insemination as the patients with unknown infertility. After this half year period, patients need higher sperm count to get pregnant. These differences can be explained with the recurrent appear of endometriosis changing the pelvic environment.

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Complex morphological characterization of core-shell fibers

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During the last decade, the formulation of nanofibrous materials loaded with different drugs for biomedical applications has evoked considerable interest. The core-shell fibers with their complex, unique structure can provide improved compatibility with target tissue and can further control of the drug release.

This study aimed to prepare polylactic acid (PLA) - poly(vinylpyrrolidone) (PVP) bicomponent core-shell fibrous sheets and examine the electrospinnability of the precursor combinations.

A full factorial experimental design (of two factors in three levels) was used to determine the best combination of the core (PLA)-and shell (PVP) viscous solutions for coaxial electrospinning. The morphology structure of the prepared sample was studied by scanning electron microscopy (SEM), transmission electron microscopy (TEM) and X-ray photoelectron spectroscopy (XPS) and Raman spectroscopy.

The SEM photos showed that fibrous structures were obtained, without any beads and film-like areas in case of the preliminary study prepared with single-needle electrospinning and also in case of the coaxial electrospun samples. As the core and shell materials have different electron transmission abilities, the TEM method was suitable to detect the core-shell structure and their homogeneity as well. In the case of each composition, the desired structure was obtained with different homogeneity. The best sample was achieved with 15% (w/w) shell concentration combined with 8 % (w/w) PLA solution concentration. The XPS spectra of the nanofiber surfaces indicated that there is good interfacial stability between the inner and outer solution. Thus the developed coaxial electrospinning method with the examined solution concentration is an effective process for core-shell fiber formation. Raman spectroscopy also confirmed the core-shell structure and pointed out that amorphous solid dispersion was formed and homogenous drug distribution was obtained in the case of both samples.

Core-shell fibers of different compositions were successfully prepared. A novel Raman microspectrometry method was developed, which besides capable of verifying a core-shell structure, also can provide information of the drug distribution and the physical state of the active pharmaceutical ingredients incorporated to the polymer-based solid dispersions.

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Differentiation between Pancreatic Cystic Lesions Using Image Processing Software (FIJI) by Analyzing Endoscopic-Ultrasonographic (EUS) Images

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EUS is the most accurate imaging modality for evaluation of different types of pancreatic cystic lesions; however, distinguishing between malignant and benign lesions remains challenging.

Our aim was to analyze EUS images of pancreatic cystic lesions using an image processing software (FIJI).

We specified echogenicity of the lesions by measuring the gray value of pixels inside the selected areas. Besides the entire lesion, its cystic and solid parts were also separately selected for assessment. Following the software analyzing process images were divided into groups (serous cystic neoplasm /SCN/, non-SCN and pseudocyst) according to the cytology results of the lesions. Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) were classified as non-SCN category.

EUS images of 33 patients (21 females, 12 males; mean age of 60.9±10.1 and 66.3±11.6 years, respectively) were assessed. Overall 73 images were processed by the software: 36 in non-SCN, 13 in SCN and 24 in the pseudocyst group. The mean gray value of the entire lesion in non-SCN group was significantly higher than in SCN group (31.7 vs 25.5; p=0.022). The area ratio (area of cystic part/entire lesion) in non-SCN, SCN and pseudocyst group was 42%, 55% and 70%, respectively; significantly lower in non-SCN group than in SCN and pseudocyst group (p=0.0058 and p< 0.0005, respectively). The lesion density (sum of the gray values/area of the lesion) was also significantly higher in non-SCN group compared to the SCN- and pseudocyst group (4802.48/mm^2 vs 3865.87/mm^2 vs 3192.27/mm^2; p=0.022 and p=0.004, respectively). No correlation was found between the intracystic CEA levels and the analyzed cystic gray values.

The computer-aided diagnosis decision is being used increasingly due to the rapid development of the information technology. The EUS image analysis process may have a potential to be a diagnostic tool for the evaluation and differentiation of pancreatic cystic lesions.

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Intratumoral cellular heterogeneity critically influences the uptake of extracellular vesicles, a potential tool for targeted therapies

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Colorectal cancer (CRC) is one of the most abundant cancer types in the developed countries. With the exception of some cases, the role of intratumoral heterogeneity of cancer cells is not yet well known. Patient-derived 3D organoids represent one of the most modern methods to study this heterogeneity. Extracellular vesicles (EVs) are membrane-surrounded structures participating in the intercellular communication and they hold a great promise for targeted therapies. IFITM1 plays a critical role in membrane-enclosed virus uptake, raising the possibility that this molecule regulates the effects of EVs as well. Furthermore, there is a strong negative correlation between the amount of cancer-associated fibroblasts (CAF) and the time to disease relapse in CRC. Thus, we aimed at i) determining the heterogeneity in the expression level of IFITM1 and ii) its role in fibroblast EV uptake in CRC.

The Medical Research Council of Hungary approved our experiments and informed consent was obtained from patients. We prepared single cells from organoids and sorted different cell subpopulations. We analyzed proliferating cells, organoid diameter, protein and RNA level in patient-derived normal colon, adenoma and CRC organoids. We detected EVs by antibody-coated beads and by Nanoparticle Tracking Analysis (NTA). The uptake of labelled large EVs was visualized by confocal microscopy and the functional importance of the uptake was detected by immunocytochemistry.

We observed a higher expression of IFITM1 in adenomas and CRCs than in the normal colon. IFITM1high CRC cell-derived organoids were larger and they contained more Ki67+ proliferating cells compared to IFITM1low organoids, however, we found no difference in the percentage of apoptotic cells. Whereas the two cell populations did not differ in their EV release, IFITM1low CRC cells took up more EVs. Furthermore, adding fibroblast-derived EVs to IFITM1low organoids resulted in a more pronounced increase in Ki67+ cell number compared to IFITM1high cells, leading to the disappearance of the difference in organoid size.

Our results indicate that the intra-tumoral heterogeneity results in tumor cell subpopulations with different EV uptake ability, leading to different proliferation potential. Thus, this intra-tumoral heterogeneity may be a critical factor when designing EV-based targeted therapy in CRC.

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7021

Photoinitiated Thiol-Ene Additions on Various Unsaturated Carbohydrates with Carbohydrate Thiols

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Introduction: Carbohydrates bearing α-glycosidic bonds are abundant in the nature, from the tiny procaryotes to the developed organisms. The O-glycosidic bond is, however, inherently susceptible to enzymatic degradation, so we focused our attention on synthesizing the S-glycosidic analogues of biologically relevant carbohydrates. Thioglycosides are more stable in biological environments, therefore they are better suited for glycobiological and drug development studies than the natural O-glycosides. However, forming the critically important 1,2-cis-α-thioglycosidic bond is an extremely difficult task, there is no known method that can be applied generally.

Methods: Photoinitiated thiol-ene addition reaction was applied to form tiodisaccharide mimetics with outstanding regio- and stereoselectivity via reacting exoglycals and carbohydrate thiols [1]. This method was also used on 2-substituted glycals, and we found that it is an outstanding method for the formation of the challenging 1,2-cis-α-glycosidic bond [2]. An unusual phenomenon has also been observed: cooling promotes while heating hinders the completion of the addition reaction [3].

Results and conclusions: In this study, the synthesis of numerous biologically relevant and potentially antibiotic thioglycosides is described in detail. The reaction was extended to numerous thiols and unsaturated carbohydrates while the effects of the various conditions (temperature, solvent, initiation time) on the conversion and isolated yield were also examined thoroughly.

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Involvement of a Novel Thalamo-Preoptic Neuronal Pathway in Social Interaction Using Double Viral Chemogenetics in the Rat

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We previously identified the posterior intralaminar thalamic nucleus (PIL) as a relay station of socially relevant sensory information activating oxytocin-secreting neurons upon social encounter. Here, we addressed to characterize the exact role of the PIL in the regulation of the social behavior, especially its neurons projecting to the preoptic area of the hypothalamus.

Projections from the PIL were analyzed using anterograde tract-tracing. We determined the effect of chemogenetic stimulation of the PIL neurons on the social interactions between familiar adult female rats using the designer receptor exclusively activated by designer drugs (DREADD) technique. The brain activation patterns were determined following direct social interaction, and also with the exclusion of physical interaction using the c-Fos technique. The selective chemogenetic stimulation of the preoptic area-projecting PIL neurons was performed using double viral injections. A retrogradely spreading adeno-associated virus (AAV) encoding Cre-recombinase was injected into the preoptic area, and labeled the PIL. Another AAV, which expressed Cre-dependent DREADD was injected into the PIL.

PIL projects to several socially implicated brain regions, such as the lateral septal nucleus, the medial amygdala, the medial preoptic area, the paraventricular and dorsomedial hypothalamic nuclei and the infralimbic cortex. Chemogenetic stimulation of the PIL resulted in the activation of the previously anatomically identified target areas and also increased the duration of direct interactions during social behavior. Direct contact during social interaction caused the largest increase in the activity in the medial preoptic area. Specific chemogenetic stimulation of the PIL-preoptic pathway led to elevated direct social contact.

The results suggest that posterior thalamic PIL neurons convey socially relevant information to a variety of different forebrain centers, among which the preoptic area is involved in the processing of physical contact. Thus, we identified an important novel component of the social brain network, which may increase the motivation for positive direct interactions.

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Alterations In Titin Expression In Athlete's Heart Using A Rat Model

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Introduction: The giant elastic protein titin provides passive stiffness to striated muscles. The adult cardiac muscle contains two titin isoforms: the more compliant N2BA and the stiffer N2B isoforms. Titin reduces passive stiffness in cardiac muscle by increased expression of the more compliant N2BA isoform (elevated N2BA:N2B ratio). Moreover, decreased passive stiffness is associated with increased exercise tolerance. Long-term, chronic exercise induces physiological adaptation of the heart, termed athlete's heart. Currently, there is limited data of titin's role in the athlete's heart.

Aims: Our aim is to evaluate exercise-induced morphological and functional changes of the heart. Furthermore, to determine the N2BA:N2B ratio in the rat model of athlete's heart.

Methods: Rats were divided into exercised (n=12) and control (n=12) groups. Athlete's heart was induced by a 12-week-long swim training (200 min/day). The control group swam 5 min/day. Following the training period cardiac changes were assessed by echocardiography. Left ventricular (LV) pressure-volume (P-V) analysis was performed to examine in vivo cardiac function. Titin isoform expressions were detected by sodium-dodecyl-sulfate (SDS)-agarose gel electrophoresis.

Results: Echocardiography and post-mortem measured cardiomyocyte diameters confirmed LV hypertrophy in exercised rats. P-V analysis showed improved contractility, active relaxation and mechanoenergetics in the exercised group. The N2BA:N2B titin ratio was significantly increased in exercised rats compared to controls.

Conclusions: Our results confirm the morphological and functional changes of the athlete's heart. The increased ratio of N2BA:N2B titin corresponds to a more compliant heart in the exercised rats.

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7019

NAMPT and CD44 as possible serum biomarkers in docetaxel-resistance of castration resistant prostate cancer

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Introduction: Docetaxel (DOC) chemotherapy is still one of the standard first-line therapies in metastatic castration-resistant prostate cancer (CRPC) but most of the patients have baseline or will acquire resistance to this treatment. At the same time, novel therapeutic agents provide reasonable alternatives for DOC-resistant patients. Therefore, prediction of DOC-resistance has become clinically important in order to optimize therapy decisions.

Aims: Our aim is to identify serum-biomarkers which are able to select patients who will not benefit from DOC treatment.

Methods: DOC-sensitive (PC3; DU145) and resistant (PC3-DR; DU145-DR) prostate cancer cell lines were comparatively analysed by the liquid chromatography tandem mass spectrometry (LC-MS/MS) technique. Results were processed using bioinformatic methods in order to identify promising biomarker candidates. Serum levels of six selected proteins (NAMPT, CD44, HGFR, LNPEP, GSN, IL13RA2) were measured in pretreatment and follow-up serum samples of DOC-treated CRPC patients by ELISA. Serum levels were correlated with clinicopathological and follow-up data.

Results: Proteome analysis identified 177 at least two-fold, significantly overexpressed proteins in DOC-resistant cell lines. Applying our bionformatic approach, six serum proteins were selected for further investigations. Higher NAMPT and CD44 serum levels showed significant correlations with poor patients' survival (p=0.012 and p=0.021, respectively). The multivariate model revealed the presence of metastases, higher pretreatment PSA, CD44 and NAMPT serum levels as independent predictors of poor survival in DOC-treated CRPC patients. Furthermore, NAMPT serum levels were significantly higher before (median= 2.87 ng/ml) and at radiograpic diesease progression (3.27 ng/ml) compared to baseline values (1.62 ng/ml).

Conclusions: Our results imply that serum NAMPT and CD44 levels might be used as biomarkers for the identification of DOC-resistant patients and may therefore help to optimize future clinical decision-making regarding the type and timing of other treatments for CRPC patients. Functional experiments using cell culture techniques with gene silencing are currently ongoing in order to assess the possible functional involvement of NAMPT and CD44 in DOC-resistance.

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Thromboxane A2 mediates C3a-induced vasoconstriction in mouse and human coronary arteries

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Introduction: Several recent reports indicate a marked crosstalk between innate immunity and vasoregulation. Anaphylatoxins C3a and C5a have been reported to induce vasoactive effects, but the mechanism of their actions is obscure. Earlier studies reported increased plasma levels of C3a in cadiovascular diseases, especially pulmonary hypertension. Therefore, complement activation may contribute to changes of the vascular tone and reactivity under pathophysiological conditions.

Aims: In our present study we investigated the effects of C3a, the cleavage product of C3, the most abundant complement protein of the human circulation, on the arterial tone and blood pressure as well as the signaling pathways involved.

Materials and methods: Thoracic aortic segments were isolated from adult male C57Bl/6 wild type (WT) and knockout (KO) mice deficient in either thromboxane prostanoid receptor (TP KO) or cyclooxygenase 1 (COX1 KO). Human coronary arteries were obtained from the recipient hearts of patients undergoing transplantation for ischemic heart disease and/or dilated cardiomyopathy. Isometric tension changes of vascular segments were measured via myography and quantitated as percent of reference contraction induced by 124 mM K^+.

Results: C3a (63-77), a specific C3a receptor agonist, evoked a pronounced vasoconstriction in WT vessels, which effect remained unaltered in the absence of endothelium. The vessels of COX1 KO mice showed a decreased response, and the C3a fragment caused a similarly reduced constriction in TP KO vessels. The vasoconstrictor effect of the peptide was remarkable in human coronary arteries, and was abolished by the pharmacological inhibition of COX1 and TP.

Conclusions: Our experiments indicate that C3a causes vasoconstriction in a non-endothelium-dependent manner, and this effect is mediated by COX1 and TP. These results propose that C3a-mediated vasoconstriction is mediated by smooth muscle derived thromboxane A2. These results altogether indicate that C3a is involved in the regulation of vascular tone and/or reactivity via stimulating thromboxane A2 release.

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Molecular and Histopathological Characterisation of Richter Transformation in Ibrutinib Treated CLL

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Richter's syndrome (RS) is a life-threatening complication of chronic lymphocytic leukemia (CLL), despite the emergence of novel targeted therapies including ibrutinib and venetoclax. Although these drugs generated remarkable responses in CLL, the frequency of RS remains unchanged at 5-16%, representing an adverse clinical event associated with poor outcomes. Therefore, better understanding of this phenomenon represents a significant unmet need.

The aim of our study was to characterize the histopathological and molecular features of 7 patients who developed RS while treated with ibrutinib or venetoclax. Pre- and post-transformation peripheral blood, bone marrow, lymph node and other solid tissue biopsy samples were analyzed depending on availability. The histopathological characterization of samples was carried out by an expert hematopathologist. To decipher the molecular alterations underlying the development of RS in these cases, the following molecular assays were performed: IGHV and TP53 mutation analysis, quantitative monitoring of BTK, PLCG2 and BCL2 mutations, SF3B1c.2098A>G, MYD88c.794T>C and NOTCH1p.P2514*fs mutation analysis and copy number aberration (CNA) assessment.

The high-grade lymphoma diagnosed as RS was DLBCL in 5 cases (patients 1-5). Patients 6 and 7 were diagnosed with plasmablastic lymphoma and null phenotype high-grade lymphoma with Hodgkin-like morphology, respectively. In our patient cohort the IGHV mutation status was unmutated in all cases apart from Patient 7. The transformation was frequently associated with TP53 aberrations, in three cases with NOTCH1p.P2514*fs and/or SF3B1c.2098A>G mutations, and in two cases with a BTK mutation. A BCL2 mutation was also found in case of a patient receiving venetoclax therapy consequential to ibrutinib. The CNA profiles of the diagnostic and transformed samples revealed three distinct patterns: identical CNAs; clonal evolution; and a combination of conserved and dynamic CNAs at the time of relapse.

The molecular alterations described in the presented set of cases are associated with suboptimal response to different treatment modalities such as chemotherapy, monoclonal antibodies and novel agents. Therefore, the integrated histopathologic and molecular genetic profiling for RS risk stratification could be the basis of an optimized treatment strategy.

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Microscopic Gastrointestinal Stromal Tumors next to Gastric Adenocarcinoma – Coincidence or Common Molecular Pathomechanism?

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Introduction: Gastrointestinal stromal tumors (GISTs) are the most common tumors in the digestive tract arising from the mesenchymal components of the tissue. Small subtype of GISTs (micro-GIST, MG) are usually asymptomatic and most frequently found in gastric surgical specimens of patients suffering from gastric cancer. Background of the frequently occurred coincidence is still an open question.

Aims: Our aim was to investigate molecular pathomechanisms of both tumors to find similarities in their development at the mutational level.

Methods: Nine cases including both gastric adenocarcinoma and MG were selected between 2002 and 2018 from the register of the 2nd Department of Pathology. Direct sequencing of KIT (exons 9, 11, 13, 14, 17) and PDGFRA (exons 18, 10, 12, 14), Epstein-Barr virus PCR and mismatch repair (MMR) immune panel, CD117, CD34 and DOG1 immunohistochemical analyses were performed on both tumors. Gastric cancers were classified according to TCGA subgroups.

Results: Prevalence of synchronous MG in gastric cancer specimens was 1.5% (10/665). All of the MGs were of spindle cell variant and immunohistochemically positive with CD117, CD34 and DOG1. All adenocarcinomas were negative for CD117 and CD34 while positive DOG1 immunostain was detected in four cases. Four GISTs carried mutations in KIT (exon 9, exon 13 and two cases in exon 11) while two further cases in PDGFRA (both of them in exon 18). None of the synchronous adenocarcinomas carried mutations in KIT or PDGFRA. Regarding the MSI status of the synchronous tumors, MMR immune panel identified the gastric cancer component of one case as microsatellite unstable tumor. Neither the adenocarcinomas nor the MGs were positive with EBV PCR. Considering the TCGA classification of gastric cancer, one case is in the MSI group, three cases are in the genomically stable group since five cases showed chromosomal instability.

Conclusions: This study comprehensively characterized 9 MGs and gastric cancers present in the same surgical specimen analyzing the markers of GISTs, the KIT/PDGFRA status and EBV/MSI status on both tumor types. Incidence of MGs in gastrectomy specimens was lower in our cohort than in other studies. Although a common carcinogenic effect cannot be ruled out, our data suggest that distinct mechanisms play role in the development of synchronous MGs and gastric cancers.

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Reduced Isolated Red Signal Pattern of ALK FISH in Lung Cancer Patients

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Introduction: Fluorescence in situ hybridization (FISH) is widely used for detection of anaplastic lymphoma kinase (ALK) gene rearrangement. Rare atypical signal pattern with reduced isolated red (RIR) ALK 3' FISH signals was described in ALK positive non-small cell lung cancer (NSCLC).

Aims: Our aim was to examine the incidence and diagnostic significance of this unusual finding among the diagnostic samples of two routine FISH laboratories.

Methods: FISH analysis with dual color ALK break apart probe and/or triple color break apart/fusion ALK-EML4 FISH test was re-examined in 996 NSCLC cases. ALK rearrangement of cases with atypical RIR signals was confirmed by next generation sequencing and ALK immunohistochemistry. The signal pattern was analyzed with ImageJ software on red channel of composite z-stack FISH images by measuring the peak and total fluorescence intensity of both the attenuated and normal red signals in 50 tumor cells of each case with RIR signals.

Results: Extraordinary RIR signals were found in three out of 59 ALK positive cases. Sequencing and positive ALK immunohistochemistry verified an existing ALK rearrangement in each of RIR signal cases. Both peak and total intensity of RIR signals was significantly decreased; in comparison with means of the non-rearranged signals the peak/total intensity means of RIR signals were reduced to 50/34%, 55/55% and 58/67% in case 1-2-3, respectively ($p<0.001$ for each pairwise comparison).

Conclusions: RIR is a rare and challenging signal pattern among ALK positive cases. Thus, risk of misinterpreting these true FISH positive cases is high, especially by using manual analogue fluorescent microscope without z-stacking.

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Psycho-social and Clinical Characteristics of Complementary and Alternative Medicine Use in Hungarian Women with Breast Cancer

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Introduction: The use of complementary and alternative medicine (CAM) in average population has increased in the US from 10% to 52%, and may reach 86% in the EU. 40% of cancer patients and 45% of women with breast cancer use CAM in Europe. CAM can affect oncological treatment. The high utilization rates draw attention to unmet needs regarding to healthcare system.

Aims: There are few systematic researches on this theme, especially in Hungary. Our aim was to examine CAM use preferences of Hungarian breast cancer patients and to examine related psychological, social and clinical factors in women undergoing surgery.

Methods: In a cross-sectional survey a self-administered questionnaire was used. The questionnaire included demographic and anamnestic questions, as well as validated questionnaires on social support, distress, anxiety, depression, coping with illness, health-related control beliefs, beliefs about CAM, use of CAM, and paranoid ideation. Clinical variables were collected from the healthcare documentation. Data were collected from 145 patients.

Results: The most commonly used CAM were vitamins (57%), herbs (33%) and self-help practices (meditation 33%, relaxation 21%, yoga 20%). It is remarkable that the mean values of depression and anxiety are also increased.

Conclusions and clinical implications: Since the use of CAM is widespread in breast cancer patients, it would be important to include this theme into the conventional oncological consultations to educate patients about CAM practices. Data on paranoid ideation and psychological factors indicate a greater need for well designed psycho-social interventions for women undergoing oncological treatment.

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Study on Attitudes of Hungarian Medical Oncologists Toward Hospice and Palliative Care, and the Effect on End of Life Therapy for Patients with Advanced Cancer

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Introduction: Palliative care is an approach that improves the quality of life of patients and their families through holistic treatment of pain, physical, psychosocial and spiritual problems. Integration of active oncological and palliative care is currently one of the biggest challenges in caring for patients with advanced cancer. The ideal solution would be if patients receiving oncotherapy would also receive matching hospice-palliative care at least in the last six months of their life.

Aims: Hospice palliative care is fully reimbursed by social security in Hungary, but only just a small part of the patients gets palliative care with adequate timing during their disease.

Methods: Our study analyses the knowledge and prevalence of ordering hospice-palliative care amongst doctors caring for advanced cancer patients in Hungary, using an internationally validated questionnaire: ESMO Survey of Medical Oncologist Attitudes to the Management of Patients with Advanced Cancer 2003. The survey tool addressed demographics (5 items), the palliative care units in the hospital, collaboration with supportive/palliative care clinicians (8 items), direct involvement in palliative and supportive care (7 items), and attitudes (24 items). There are also questions about the training in palliative care during and after the medical university. We ask about how many service providers do they know and how often do they refer their patients for hospice-palliative care. We are going to get all the professions dealing with end-stage cancer patients, the oncologists, the surgeons, the radiotherapists, and the primary care doctors. We are planning to get 800 surveys completed. We aim to study how increased knowledge about hospice and palliative care (training) and the accessibility of the caregivers (palliative mobile units, hospice units within the institute, etc.) affect the end of life therapies used for patients with advanced cancer. The ethics approval number is 45994-5/2019EKU.

Results: We can present the results of the pilot study. It will be completed by March 2020.

Conclusions: We would like to demonstrate, that if the doctors providing care for oncology patients were better trained in palliative care, fewer patients would be cured with aggressive chemotherapies in the last months and, more could receive palliative care in an earlier stage of their treatment.

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Progression of Experimental Melanoma B16 Depends on Resistance to Hypoxia

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Introduction: Local hypoxia activated by hypoxia factors (HIF) increased metastasis and tumor growth. Features of melanoma progression in animals with high and low resistance to hypoxia is poorly studied. We assumed the progression of melanoma in animals with low resistance to hypoxia and high expression of HIF, will be more pronounced than in resistant to hypoxia ones.

Aims: To determinate features of B16 melanoma progression in male C57Bl/6 mice with initially high and low resistance to hypoxia.

Methods: Mice were divided by resistance to hypoxia in a pressure chamber at the altitude of 10,000 m. Based on their gasping time C57Bl/6 male mice were divided into two groups - High Resistance (>10 min, n=8) and Low Resistance (<3 min, n=10) to hypoxia. One month after testing, B16 melanoma was inoculated to high- and low-resistant animals. We estimated weight of primary tumor node, area of necrosis, number of Ki-67+ proliferation cells and caspase-3+ dying cells by apoptosis in primary tumor node, number of metastasis cases in the lung. Expression of mRNA Hif-1α, VEGF in the liver of control groups and animals with melanoma were estimated by RT-PCR.

Results: Tumor growth progression was more pronounced in low-resistant mice, which was seen from high weight of the primary tumor node, relative necrosis area, proliferation rates (mitotic index and number of Ki-67+ cells), and expression of vegf-a gene in the liver. In high-resistant to hypoxia animals, the number of caspase-3+ cells dying by apoptosis was higher.

Conclusions: The data on more rapid melanoma progression in mice with low resistance to hypoxia should be considered during the search of new prognostic markers and methods for therapy of malignant neoplasms.

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Nutrition therapy for dysphagia with special emphasis on stroke patients

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Introduction: Stroke and its immediate complications are the third most common cause of death in our country. The increasing number of stroke diseases implies the need to treat the associated dysfunction, including swallowing. 30-50% of acute stroke patients (ASPs) suffer from dysphagia. These patients have a high risk of dehydration, malnutrition, aspiration pneumonia, and cough due to reduced nutrient and fluid intake due to dysphagia. Their poor prognosis is higher mortality.

Aims: My goal is to draw attention to the negative consequences of dysphagia, its complications, and effective solutions to help patients with dysphagia avoid time-consuming and consistently malnutrition. Supporting their quality of life, effective healing, and rehabilitation.

Methods: A questionnaire design designed at designated stroke department to examine the characteristics of applying a texture-modified (dysphagia diet)will help provide adequate, elaboration of an educational method for dietitians, based on the professional protocols of nutrition therapy, to facilitate the practical implementation of the nutritional therapy of dysphagia.

Result: The educational program consists of two important elements. One is the dysphagia chef program, which has already been tried and successfully operated for three years, on which we can build the first, unified educational method for dietitians. They will master the technology recommendations based on practical elements and have been tested in advance and will then be taught the circumstances, conditions, needs and process of preparing foods of changed consistency.

Conclusions: The method first handles and develops educational materials designed for dietitians to enrich the nutrition team with scientifically sound knowledge and practical.

I successfully presented this topic at the 2019 National Stroke Conference.

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Stability Tracking of pH Modifier- or Solubilizer-Containing Furosemide-Loaded Electrospun Nanofibrous Systems

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Introduction: Electrospun nanofibrous drug delivery systems are promising alternatives for enhanced solubility formulations of drugs belonging to BCS (Biopharmaceutical Classification System) IV class, like furosemide, by keeping the drug in an amorphous state.

Aims: This study aimed to compare solubiliser (triethanolamine, TEA) or pH modifier (sodium hydroxide)-containing furosemide-loaded electrospun nanofibers from the point of their macro- and microstructural properties during storage.

Methods: Two hydroxypropyl cellulose and poly(vinylpyrrolidone)-based formulations were prepared. Triethanolamine or sodium hydroxide was used for solubility improvement of furosemide. Accelerated stability test (T=40°C, RH=70%, 4 weeks) was performed. Morphological characterisation was carried out by scanning electron microscopy (SEM). X-ray diffraction spectroscopy (XRD) and Fourier-transform infrared spectroscopy (FTIR) were applied to investigate the amorphous or crystalline nature of furosemide in the electrospun samples. Small-volume dissolution test (pH 6.8, 37 °C) was worked out to distinguish any difference in the drug release between the two formulations. The furosemide content was determined with UV-vis spectrophotometry at 277 nm wavelength.

Results: The SEM measurements showed similar morphology and fiber diameter distribution in case of the unstored samples. In TEA-containing electrospun samples widened and merged individual fibers appeared from the first week of storage, and along with the time it has become even more dominant. In contrast, the NaOH-containing samples remained the fibrous structure with some slight changes. The microstructural studies confirmed that the formulations contained furosemide in amorphous salt form, and it was preserved during the one-month storage in each case. The dissolution test showed rapid and complete drug release from the fibrous samples.

Conclusions: Amorphous furosemide salt-containing nanofibrous formulations were successfully prepared, which preserved the drug in its amorphous state during the one-month storage. Since the SEM measurements revealed significant differences, the NaOH-containing formulation can be more promising.

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Adaptive responses of biological networks during the evolution of cancer and drug resistance

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Despite enormous research efforts, cancer is still among the main causes of mortality worldwide. There is an increasing need for new scientific methods for a better understanding of the disease, and to improve the efficiency of drug development. Network science is an emerging tool in systems biology and oncology, with which cells can be modelled as protein-protein interaction networks. In my work I collaborate with the Urology Clinic of Semmelweis University to study the oncogenesis of prostate cancer as well as the development of drug resistance to docetaxel, enzalutamide and abiraterone with comparative network topological analysis.

My aim is to create a new method to identify the structural changes and find those otherwise unseen, cardinally important nodes that have an organizing role in the evolution of cancer and therefore can be new therapeutic targets.

In the network models used nodes represent proteins, and the edges display the interactions of proteins. Edge weights represent the probability of the interaction calculated as the product of the protein abundance in the proteomic data. Based on our data, three different phenotypic networks can be created: a) normal healthy cells, b) drug sensitive cancer cells and c) drug resistant cancer cells. My main topological interests are the modular structure, especially the inter-modular bridge nodes that have a crucial role regarding the information transfer, hubs, and the core-periphery structure of the network. I use Cytoscape and its two plugins, ModuLand and EntOpt, which both were developed by our research group, as well as Metascape, a recently published online tool and Gene Ontology for functional annotation and statistical enrichment analysis. NetworkX, a package for Python provides additional topological parameters.

The data has been examined on several signalling and protein-protein interaction networks, such as the Human Cancer Signalling Network, the ComPPI database, the Pathway Commons resource, OmniPath database, the Reactome, and the STRING database. The best fitting networks have been chosen for analysis, based on the method of my former work on colorectal carcinoma.

The initial results correlate well with the recently published literature findings and provide additional information about the characteristics of enzalutamide sensitive and resistant prostate cancer at the systems level.

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Comparative Evaluation of Approach to Cardiovascular Care in Asphyxiated Infants with Hemodynamic Instability between a Large Canadian vs Hungarian Referral Center

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Introduction: Patients with hypoxic-ischemic encephalopathy (HIE) may present with hemodynamic instability. Therapeutic hypothermia (TH) improves neurodevelopmental outcome in asphyxiated newborns, but may worsen hemodynamic instability.

Aims: Our primary aim was to compare the approach to management of hemodynamic instability and short term outcomes in asphyxiated infants at two high volume centers.

Methods: In this retrospective cohort study, we studied 176 term infants with HIE, who were admitted to the NICU of the Hospital for Sick Children, Toronto, Canada (Center A, n=86) or the 1st Department of Pediatrics, Semmelweis University, Budapest, Hungary (Center B, n=90) for TH between 2015 and 2017, and developed systemic hypotension (mean arterial pressure less than gestational age). Baseline neonatal demographics, indices of hemodynamic stability and details of hemodynamic interventions were compared. Short term outcome was evaluated based on MRI examinations. Adverse outcome was defined as perinatal death or brain injury in the basal ganglia and/or in the watershed area.

Results: Baseline illness severity and HIE staging were comparable between groups. The average lowest systolic and diastolic blood pressure were similar (44/25 (32) vs 43/24 (31) mmHg). Interestingly 49% of the patients in Center A did not receive any cardiovascular support during TH, whereas only 3% remained untreated in Center B ($p<0.001$). The first line cardiovascular therapy was dobutamine (66%) in Center A vs dopamine in Center B (94%). The rate of hypertension after the initiation of cardiovascular support was 47% in Center A, while 69% in Center B ($p=0.003$). Other clinical outcomes (diuresis, convulsions, length of antibiotic treatment and invasive ventilation) were comparable. Adverse outcome was similar in the two centers (49% in Center A and 53% in Center B; $p=0.45$); however, the pattern of brain injury differed between centers and there was a trend towards increased injury in center A.

Conclusions: A more aggressive approach to cardiovascular care did not lead to better MRI outcomes, but was associated with increased rate of hypertension. Use of early comprehensive echocardiography may provide enhanced diagnostic precision enabling investigation of the relationship of heart function and systemic hemodynamics to brain injury.

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Essential role of the avian ceca for formation of the hindgut enteric nervous system

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The enteric nervous system (ENS), which is derived from neural crest cells (NCC) during gut development, represents the neuronal innervation of the gastrointestinal tract and is critical for regulating normal intestinal function. Compromised NCC migration can lead to Hirschsprung Disease, which is characterized by an aganglionic distal bowel. We find that removal of the ceca, a paired structure present at the midgut-hindgut junction in avian intestine, leads to incomplete NCC colonization of the hindgut, suggesting that the ceca are required for ENS development. To test this, we replaced the ceca of embryonic day 6 (E6) wild-type chicks with ceca from transgenic GFP chicks. Interestingly, the entire hindgut ENS arises from the GFP+ ceca-derived NCC population. Comparative transcriptome profiling of the cecal buds compared to the inter-ceca gut shows that the non-canonical Wnt signaling pathway is preferentially expressed in the cecal buds. Specifically, Wnt11, a non-canonical Wnt protein, is highly expressed in the ceca, as confirmed by RNA in situ hybridization, leading us to hypothesize that cecal expression of Wnt11 is important for normal NCC colonization of the hindgut. We used avian intestinal organ cultures at E5, when NCC have not yet reached the ceca, and at E6, when NCC are entering the proximal hindgut, to test this hypothesis. Cultures were treated with soluble antagonists of the canonical (XAV939) and non-canonical (Y-27632) Wnt pathways. Treatment with XAV939 had no effect, while Y-27632 arrested NCC migration in E5 explants and led to hindgut aganglionosis. While removal of the ceca leads to failure of NCC colonization of the hindgut, placement of Wnt11 protein-coated beads at the base of the resected ceca rescues this phenotype. These results confirm an important role for Wnt11 signaling in the ceca in promoting normal migration of enteric NCC and complete formation of the hindgut ENS.

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Effect of ethanol exposure on longevity and chemotaxis on Caenorhabditis elegans

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Alcohol is one of the most frequently abused addictive substances in humans, which has a wide range of effects on the central nervous system. About 70% of C. elegans genes are homologous to those of humans and a resemblance between the nervous systems of the two species can clearly be pointed out: Dopaminergic as well as serotonergic neurons are present in their central nervous systems, which play a role in the reward system and are indispensable when discussing addiction. Both dopamine and serotonin affect movement and behavior of the animals. The fully mapped out neuronal network and the precise knowledge of the functionality of its synapses makes C. elegans a valuable model for addiction research.

In the longevity paradigm C. elegans was treated with 400mM and 200 mM ethanol from day one adult age onwards. In the diacetyl race paradigm animals were conditioned to 400 mM and 200 mM ethanol for 24 hours during late L4-young adult state, and after 1 hour withdrawal period transferred to a race plate (infused with or without ethanol) and subjected to an attractive odorant stimulus (diacetyl).

High dose ethanol reduces lifespan by almost 50%, whereas low dose has either no, or considerably effect on longevity. Upon alcohol treatment, the worm's characteristic movements are also altered. In diacetyl race after high dose treatment (400mM), the worms may lose the ability to coordinate their movement, orientation or their interest towards the attractant diacetyl. Upon lower dosage, these responses were less prevalent. Wild type (N2) animals were compared to serotonin deficient (tryptophane-hydroxylase) tph-1-, and dopamine receptor deficient dop-2 (ortholog of human DRD2) null mutants.

Our results have shown that alcohol induces changes in C. elegans longevity as well as behavior in a dose dependent manner. High concentration ethanol exposure decreases life span dramatically and hinders locomotor performance that can be at least partially rescued by low dose exposure during the race. Neurotransmitter deficient mutants also showed alterations in motility patterns. A further advantage of the worm model is the possibility of examining transgenerational and epigenetical effects.

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Potential purine biomarkers in plasma, in mental disorders

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The aim of our study is to identify potential biomarkers in the plasma, which are associated with the purinergic signaling. P2X7 is an ATP-gated cation channel localized in different cell types in the central nervous system. P2X7 receptor activity, by regulating the release of proinflammatory cytokines, may be involved in the pathophysiology of different mental disorders, including schizophrenia.

In this study, we are measuring the ATP and adenosine levels of 120 schizophrenic patients and 40 healthy controls from a small amount of blood; and we administer the PANSS interview. After signing the official informed consent form, a nurse is taking 150-200 µL blood from the patient's fingertip, which sample is analysed immediately with a SMARTChip biosensor. Besides, we are also collecting 3.5 ml blood, from which the P2X7 concentration is measured with the use of an ELISA kit.

Our two main questions are: 1.) Is there any difference in the level of adenosine between healthy controls and schizophrenic patients? And 2.) Is there any correlation between the level of purines and the PANSS scores?

The preliminary results suggest that there is no significant difference in the level of purines between healthy controls and schizophrenic patients. However, a certain pattern in the correlations can be observed: the correlation between the level of adenosine and the PANSS scores is slightly positive in every case, while these correlations with the ATP levels are slightly negative.

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Comprehensive mutation screening by targeted next-generation sequencing in pediatric acute myeloid leukemia at diagnosis

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Introduction: Recent medical advances dramatically improved the outcome of pediatric cancers, still the prognosis of childhood AML remains unfavorable due to primary therapy resistance and frequent relapses. AML represents the leading cause of childhood leukemia mortality, with a 5-year overall survival (OS) of 60-70%.

Aims: To establish the mutational profiles of 60 Hungarian pediatric AML patients diagnosed in our institute between 2005 and 2019 using next-generation sequencing (NGS).

Methods: Diagnostic samples were obtained from bone marrow (n=44), peripheral blood (n=14), skin (n=1) and lymph node biopsy (n=1), with three sequential samples collected at diagnosis and two subsequent relapses from a single patient. Median follow up time was 55 months (range 0.2-179.0 months) with a 5-year OS of 55% representing a relatively low survival rate owing to the high proportion of patients with poor prognosis in this cohort. Targeted NGS analysis of 54 genes recurrently altered in myeloid malignancies was performed using the TruSight Myeloid Gene Panel with the libraries sequenced on a NextSeq500 instrument.

Results: NGS revealed a total of 101 somatic variants in 60 diagnostic samples with an average allelic depth of 7400x across the 54 genes analyzed. On average, 1.7 mutations (range: 0-5) were detected per sample, with an average variant allele frequency of 32.3% (range: 2.0-83.1%), and with ten patients presenting with wild-type genotype for all 54 genes analyzed. The most frequently mutated genes included FLT3 (30%), NRAS (18%) and WT1 (17%). Patients with normal karyotype carried a slightly higher number of variants compared to patients with chromosomal abnormalities (2.5 vs 1.7 variants on average per sample). Interestingly, 53% of patients harbored mutations in genes encoding actionable proteins including FLT3, NRAS and IDH1. Active clonal evolution was documented in one patient carrying NPM1 and FLT3-ITD mutations at diagnosis. At first relapse, elimination of FLT3-ITD was accompanied by the emergence of an ASXL1 mutation, with acquisition of a novel FLT3-TKD mutation by the time of the second relapse.

Conclusions: Targeted NGS using the TruSight Myeloid Sequencing Gene Panel seems to be an efficient, high-throughput assay for the genomic characterization of pediatric AML, with potentially actionable mutations detected in 53% of patients in our cohort.

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Development and characterization of 3 dimensional in vitro model of neuroendocrine tumors

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Introduction: In vitro two dimensional cell cultures are widely applied in cancer biology. However, there is a considerable difference among tumour cell behaviour of existing models and solid tumours because monolayer cell cultures do not represent the heterogeneity of human tumours reliably. Treatment options of endocrine tumours are limited and do not respond to radiation therapy either. Until now the information about 3D culturing of endocrine tumours is minimal.

Aims: Establishment of three-dimensional in vitro models of endocrine tumours and their comparison with monolayer cell cultures in order to identify novel pathomechanisms and potential new therapeutic targets.

Materials and methods: Induction of spheroid formation of pituitary tumours (GH3, RC-4B/C), adrenal carcinoma (H295R) and phaeochromocytoma (PC12) cell lines was performed by different methods: using serum-free defined medium, ultra-low attachment plate and matrigel. AlamarBlue assay was used to examine cell viability and proliferation. Live and dead cell ratios were determined by trypan blue exclusion assay. The effect mitotane treatment was assessed on H295R adrenocortical cells. Steroid hormone production was monitored by liquid chromatography coupled with tandem mass spectrometry. Inhibition of the SDHB enzyme in PC12 cells was done by itaconate and the glutaminase enzyme was inhibited by a selective inhibitor compound .

Results: While pituitary tumour cells were not able to form spheroids, H295R cells were capable of producing 3D structure using several conditions. Regarding PC12 cells spheroid induction was successful using SFDM. In 3D cultures H295R and PC12 cells further proliferated and kept their viability up to 10 days. H295R spheroid cell culture showed a higher tendency for cortisol production compared to monolayer cell culture. Significantly reduced hormone production capacity was identified after anti-proliferative effect of mitotane in spheroids. Regarding PC12 cells, the proliferation and viability upon itaconate and BPTES treatment of 3D and monolayer cultures showed difference.

Conclusions: Cell viability, growth characteristics and hormone production differed in 3D and 2D cultures and they showed different response to therapy as well. In vitro 3D models could be a useful model for neuroendocrine tumours mimicking solid tumour cell behaviour more reliably.

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Multi-organ damage following perinatal asphyxia in rat model

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Introduction: Perinatal asphyxia (PA) leads to death of more than half million mature newborns yearly. PA is associated with several serious complications including hypoxic encephalopathy, renal- hepatic- and cardiovascular injury, as well as respiratory distress. Basic research and clinical trials mainly focus on mitigating central nervous system damage by selective head or whole-body cooling. However, the extent of PA-associated multi-organ damage is not clarified yet and effective therapies are lacking.

Aims: The aim of the present study was to determine acute renal, hepatic and cardiac damage after PA and to identify pathways involved in the pathomechanism.

Methods: Postnatal 7 day-old male Wistar rat pups (n=5-10/group) were randomly grouped as follows: (i) Baseline: sacrificed immediately (ii) Control: pups were separated from the dam and incubated in normal air; (iii) PA: pups were separated and incubated in 4% O2; 20% CO2 in N2 gas mixture for 15 minutes. Samples were collected after 4 (T4) and 24 (T24) hours. Serum levels of electrolytes, kidney and liver functional parameters and Troponin I were determined. Sensitive tubular injury markers Kim1 and Ngal were measured. Expressions of hypoxic (Hif1a, Hif2a), inflammatory (Il1α, Il1β, Il6, Tnfα), apoptotic (Bax, Bcl-2) and angiogenic genes (Vegf, Epo) and heat shock proteins (Hsp27, Hsp72) were investigated. Periodic-Acid Schiff and anti-CD45 staining on kidney, and Hematoxylin&Eosin staining on liver sections were performed.

Results: Blood urea nitrogen (BUN) and serum GPT were elevated at T4 following PA. Kim1, Ngal and heat shock protein expressions were increased, inflammatory and angiogenic pathways were activated in the kidney after PA. Vacuolisation, cytoplasmic degradation, and the onset of necrosis were observed in the liver following PA. In the liver hypoxic and apoptotic pathways were activated at T24 in the PA and in the control group. Serum Troponin I was elevated after PA indicating myocardial damage. Inflammatory cytokine and heat shock protein expression increased in the heart as well.

Conclusions: Acute renal, hepatic and myocardial damage was observed after PA. These results may justify the need for clinical follow-up and novel treatment strategies for possible multi-organ damage. The molecular pathways described here are potential targets for therapeutic intervention.

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The role of PARK7 in peritoneal dialysis associated fibrosis

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Introduction: During peritoneal dialysis (PD) complications as peritoneal mesothelial cell loss, progressive submesothelial fibrosis or vasculopathy are caused by the toxicity of dialysis solutions. Despite the unmet medical need there is no effective therapy for inhibiting peritoneal fibrosis. Recently, the role of PARK7 was demonstrated in the regulation of tissue fibrosis in various organs including the kidney and liver.

Aims: We aimed to prove the yet unknown presence, localisation and role of PARK7 in the peritoneum's physiological and pathophysiological processes.

Methods: Peritoneal dialysis effluents (PDE) of children receiving PD at the 1st Dept. of Pediatrics were collected. PARK7 level was measured in the PDEs by Western blot (Wb). In vitro experiments were carried out on human paerietal mesothelial cells (HPMC) and primary peritoneal fibroblasts (pPF) isolated from the peritoneum of children enrolled in our study. The effect of PDE on the viability of the different cells was assessed by MTT and LDH proliferation assays. Similarly, the effect of PDE on the mRNA expression of PARK7 was investigated by real-time RT-PCR. By implementing the chlorhexidine digluconate (CG)-induced mouse model of peritoneal fibrosis, we studied the localisation and amount of PARK7 by immunofluroescent staining (IF), Wb and RT-PCR respectively.

Results: The PARK7 level of PDEs differed among the individuals. PARK7 was present in the HPMCs and pPFs. HPMCs and pPFs proliferated and PARK7 expression increased following PDE-treatment. PARK7 immuno-reactivity was present in the mesothelial layer and also submesothelially in the resident fibroblasts. While PARK7 expression decreased, the level of fibronectin increased in the parietal peritoneum of CG treated mice.

Conclusions: Regarding our results PARK7 have a potential role in the pathomechanism of PD induced peritoneal fibrosis. The decreased level of PARK7 might explain at least in part the progression of peritoneal fibrosis in the CG treated mice. Therefore it represents a promising therapeutic target to be able to lengthen the effective application of PD.

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The Relationship between Social Value Orientation and Pathologic Personality Traits

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Introduction: The concept of social value orientation (SVO) summarizes our preferences in interdependent social scenarios. Previous research showed that Big-5 and HEXACO domains show connection with SVO. We examined whether DSM-5's pathologic personality traits have similar connections with SVO and with subjects' expectations regarding the SVO of other people.

Aims: We hypothesized that individualists and competitives think that the other person would behave as they do, and prosocials can anticipate all kinds of SVO categories. We aimed to create subgroups within the SVO categories based on the participants assumptions about the other's SVO. We presumed that these subgroups would show significant differences regarding their pathologic personality traits.

Methods: 75 healthy subjects completed the Slider Measure, a social dilemma developed by Murphy et al. (2011).The test categorizes people into four SVO groups -altruists, prosocials, individualists and competitives. Participants filled out the reversed version of the test: they had to imagine themselves into the place of another person and tell us their expectations of the other's behaviour. They completed the SCID II Screen Questionnaire and the Personality Inventory for DSM-5 (PID-5). Data was analyzed using SPSS.

Results: 14 subjects were individualists and all of them expected individualistic behaviour from the other, whereas the 61 prosocials anticipated all SVOs (÷(3,N=75)=15.061, p=.002). We created two subgroups within the prosocials: the ones who think the other would be prosocial (PP, N=33) and prosocials who think the other would be individualistic (PI, N=26). We compared the two prosocial groups and the individualists. The prosocials scored higher in Disinhibition (F(2,70)=3.784, p=0.028) and Distractibility (F(2,70) =3.233, p = 0.045). The PI group scored higher in Negative Affect (F(2,70) =3.401, p=0.039) and Emotional Lability (F(2,70) =4.307, p = 0.017). The PI and the individualist group scored higher on Suspiciousness (F(2,70) =3.315 , p = 0.042).

Conclusions: Individualists and prosocials differed significantly in their expectations. We were able to distinguish subgroups amongst the prosocials and found significant differences in the three examined groups regarding their pathologic personality traits.

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Organizational method influencing the effectiveness of postoperative pain management is the Acute Pain Service

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Introduction: The issue of postoperative pain relief means a major challenge for the health care personnel as the patient satisfaction is not always adequate. The not well controlled postoperative pain can lead to complications. There is a great risk of developing of chronic postoperative pain, which burdens the other level of health care system. Establishing of Acute Pain Service (APS) teams is a major step forward to improving the effectiveness of postoperative pain relief besides the drug interventions.

Aims: The aims are to describe the definition of Acute Pain Service, its organizational and functional structure, quality criteria of it, and the advantages of adverse events prevention based on publications.

Methods: A systematic literature review with the help of the PICO technique was used. Processing of results to determine whether they contain information for the definition structure, operating procedures, and activities of the APS and their role in the avoidance of adverse events.

Results: 263 articles were found in total. Following the evaluation of the above-mentioned criteria, 42 papers were processed, most in English, 3 in German and 4 in Hungarian. Our results show that APSs were developed in many countries around the world. There are several models of operation and cost. The quality criteria of APS are the definition of staff for postoperative pain management, organization of patient care at night and weekends, written protocols for postoperative pain management, regular assessment and documentation of pain scores. These quality criteria were defined, which contribute to the postoperative condition improvement, reducing side effects, increasing patient satisfaction and the improvement of patient safety.

Conclusions: The APS modell is worldwide spread in the field of postoperative pain relief. In Hungary, we know little about the situation and operation of the teams. Further investigations are needed to assess, how many pain teams work in our country and how many components of criteria appear in the Hungarian postoperative pain care. In this direction, steps are taken during research.

Supervisors: Judit Lám, Péter Gaál

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Parallel connections in the frontal thalamo-cortical system of mouse

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The frontal thalamo-cortical system plays important roles in many cognitive processes. Any damage or dysfunction in this network can lead to neurological disorders like anxiety and schizophrenia. Although the large dataset regarding this system found in the literate, the precise anatomical organization between the involved medial thalamic and frontal cortical regions is missing. As the presence or absence of a calcium binding protein, the calretinin (CR) characterizes distinct medial thalamic populations (CR+, CR-negative), we used cell type- and target-specific approaches in Calb2(CR)-Cre mice to anatomically dissect the frontal thalamo-cortical system. CR+ and CR- thalamic neurons gave rise to a rather nonoverlapping axon arborizations in the cortex: while CR+ cells preferentially innervated prelimbic, infralimbic, orbital and insular cortices, CR- neurons sent axons to the cingulate and secondary cortical areas. The layer-specific distribution of their axonal inputs was also different in those cortical areas which were targeted by both populations. In addition, their subcortical projections were also distinct. While CR+ cells targeted limbic structures like ventral striatum, amygdala and ventral hippocampus/ subiculum, CR- neurons avoided these regions. Besides that, distinct CR+ populations also showed some level of heterogeneity in their cortical and subcortical connectivity. For example, the amygdala- and the nucleus accumbens projecting medial thalamic cells innervated distinct domains of the bed nucleus stria terminalis and different layers of the frontal cortical regions, revealed by a retroanterograde viral approach. Altogether these findings indicate that the frontal thalamo-cortical system is organized in a complex manner by several parallel thalamic routes.

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Noxious Stimulation Excites Neurons in the Basolateral Amygdala with a Short Latency

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The basolateral amygdala complex (BLA) plays an essential role in Pavlovian fear conditioning, when mice learn to associate a neutral cue (CS) with an aversive, unconditioned stimulus (US), like a mild electrical shock. The BLA consists of distinct nuclei, including the lateral (LA), and basal nuclei (BA), however our knowledge is limited how the information gets processed within these structures during fear conditioning. The current 'serial' model states that the pairing of the CS and US occurs in the LA followed by the information transfer into the BA. Here, we examined how electrical shocks excite neurons in both the LA and BA to get insights into the information flow within the BLA upon US delivery.

In our experiments, we used silicon probes in awake, head-fixed mice to simultaneously record single-units from both the LA and BA during US delivery. We observed that a portion of neurons discharged action potentials upon shock delivery with a short (<30 ms) latency. Surprisingly, these neurons could be found both in the LA and BA. To validate our results, we repeated the US presentation in anesthetised mice, while spiking activity was detected by juxtacellular recordings followed by intracellular labelling. The results of these experiments confirmed that some neurons located both in the LA and BA were indeed excited by the US with a short latency.

These findings indicate that the noxious signal is processed by BLA circuits not in a serial, but in a parallel manner.

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Ménière's disease and Intratympanic steroid administration. Gait system correlation pre- and post-administration

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Introduction: Attacks of rotatory vertigo, progressive hearing loss, fluctuating tinnitus, along with vegetative symptoms and postural instability are the characteristics of Ménič̆re's disease (MD). Intratympanic steroid (dexamethasone) injection (ITS) in part, it can treat the hearing loss.

Aims: To estimate whether ITS treatment has a significant effect on the stability of patients.

Methods: ITS treatment was given to 38 patients (13 male and 25 female patients, mean age 56.3 years ± 10.2 SD) along with 82 patients with unilateral MD that did not receive ITS treatment (37 males and 45 female patients, mean age 60.8 years ± 10.6 SD) were enrolled. Comparison of the results of the vestibular function tests, using ultrasound computerized craniocorpography (US-COMP-CCG) before and after administration of ITS injection were made. Statistical analysis was performed by using the IBM SPSS V24 software.

Results: MD patients who received ITS injection, showed no deterioration based on the values of US-COMP-CCG. Occurrence of aberration after ITS treatment was not frequent. According to log rank test there is no statistically significant difference between the before and after treatment groups [p = 0.445; Odds ratio: 0.605 (95% CI: 0.166-0.197)]. There was also no significant difference between the control and ITS treatment parameters.

Conclusions: ITS treatment of dexamethasone does not affect patient stability, which is supported by the unchanged US-COMP-CCG parameters after treatment administration.

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Role of the LPC-ATX-LPA Pathway in the Development of Endothelial Dysfunction

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Introduction: Lysophosphatidylcholine (LPC) is a component of the oxidized low-density lipoprotein that plays a major role in the development of atherosclerosis. LPC impairs endothelium-dependent vasorelaxation through decreasing the bioavailability of NO. Although LPC can be hydrolyzed into lysophosphatidic acid (LPA) by the lysophospholipase autotaxin (ATX), the involvement of this pathway in the development of LPC-elicited endothelial dysfunction has not been evaluated yet.

Methods: Myographic experiments were performed on thoracic aorta segments isolated from adult male C57Bl6 and LPA1, LPA2, LPA4, LPA5 receptor knock out (KO) mice. The effect of LPC (10 μM) or LPA (10 μM) on the NO-dependent vasorelaxation was measured after a 20 min incubation. The vessels were pre-contracted using phenylephrine (PE) prior to exposure to increasing concentrations of acetylcholine (ACh) to evoke vasorelaxation. In some experiments, the ATX inhibitor GLPG1690 (10 μM) was added to the baths, 10 min prior to the administration of LPC. To evaluate the expression of ATX in the aortic tissue, we used immunohistochemical staining .

Results: We confirmed the presence of ATX in the aortic endothelium. LPC significantly attenuated the ACh-induced vasorelaxation, in addition LPA treatment was also able to evoke endothelial dysfunction. The ATX inhibitor GLPG1690 diminished the effect of LPC and interestingly, it was more pronounced in the aortic arch as compared to the distal aorta. In addition, the effect of LPC developed in the LPA1, LPA2, and LPA4 KO mice, but was decreased in the LPA5 KO mice.

Conclusions: Our study shows that ATX and LPA play an important role in the development of LPC-elicited endothelial dysfunction and the involvement of this pathway is more pronounced in the aortic arch. Furthermore, LPA appears to mediate this effect via LPA5 receptors. Clinical evidence indicates that the development of atherosclerotic lesions is more pronounced and progressive in the aortic arch, thus the LPC-ATX-LPA5 axis might contribute to the progression of this disease.

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The killing effect of modulated electro-hyperthermia on B16F10 melanoma cells

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Introduction and aims: Modulated electro-hyperthermia (mEHT) is a novel adjuvant, non-invasive form of tumor treatment which induces tumor-selective heat shock at 42 °C. The objective of the present study was to examine the effect of mEHT on B16F10 mouse melanoma cell line in vitro. Our aim was to detect the effect of mEHT on cell viability and to examine if hyperthermia can augment the cell killing effect of various chemotherapeutic agents.

Methods: B16F10 melanoma cells were grown on coverslips, treated with mEHT using LabEHY 100 (Oncotherm Ltd.) at 42 °C. To define the optimal dose of hyperthermia the cells were treated for 30, 60, 90 or 120 minutes. Cell viability was measured by cell titer blue and apoptosis by Annexin-V/ 7-AAD staining using flow cytometry 24 hours post-treatment. For analyzing gene expression cells were harvested 1, 3, 9, 24 hours after 60 minutes mEHT. In combined protocols, after 60 minutes mEHT cells were treated with dacarbazine (40 μM), paclitaxel (40 nM) or nutlin-3a (10 μM). Cell viability as well as cleaved caspase-3 as an indicator of apoptosis were detected by flow cytometry 48 hours after mEHT.

Results: Three hours after the treatment the peak levels of HSPA2 expression were 3 times higher as compared to the untreated control in a time-matched experiment. Next, we showed that in parallel to the upregulation of pro-apoptotic genes Puma, Bak-1, Bax, and downregulation of pro-survival genes XIAP, Bcl-2, Bcl-XL were induced by mEHT. In combination with chemotherapy, mEHT augmented the cell killing effect of dacarbazine or nutlin-3a but it had no effect on paclitaxel- induced cell death 48 hours post-treatment.

Conclusions: mEHT induced nuclear translocation of p53 which in turn regulates pro- and anti-apoptotic gene expression accounting for the upregulation of apoptotic genes and decreased cell viability.The sensitizing effect on chemotherapeutics demonstrate the efficiency as an adjuvant modality in cancer treatment.

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Network approach to identify molecular targets of cardiac ProtectomiRs

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Background: Protection of ischemic heart is an unmet need. We have previously found that cardiac non-coding microRNA expression fingerprint is significantly changed in the ischemic heart with or without ischemic pre- and postconditioning and identified miRNAs that are involved in cardioprotection. We termed these microRNAs ProtectomiRs. Common downstream molecular targets of ProtectomiRs may reveal potential new targets in cardioprotection.

Aims: We aimed to identify targets modulated by ProtectomiRs based on an unbiased network theoretic approach and experimentally validate the predicted downstream targets.

Methods: Target genes regulated with high probability by ProtectomiRs were collected with miRNAtarget.com software. MicroRNA-target network was constructed and visualized based on miRNA-target interactions. After the target prediction, the microRNA target with the highest degree (RICTOR) was chosen for validation. Myocardium samples for validation were originated from a translational pig model of pre- and postconditioning in ischemia/reperfusion injury. Validation of RICTOR was performed with qRT-PCR and Western blot analysis.

Results: MicroRNA-target network analysis resulted in 882 genes ranked by interaction degree. RICTOR had degree 5, other 14 genes had degree 3, and others less than 3 degrees. Expression of RICTOR mRNA tended to decrease in ischemic postconditioning (1.000±0.151 vs. 0.618±0.134 AU; p=0.19, one-way ANOVA), and remained unchanged in ischemic preconditioning (1.000±0.151 vs. 1.369±0.381; one-way ANOVA). RICTOR protein was significantly decreased in ischemic postconditioning (0.642±0.171 vs. 0.222±0.012 AU; one-way ANOVA), and not influenced in ischemic preconditioning (0.642±0.171 vs. 0.601±0.066 AU; one-way ANOVA) with western blot analysis.

Conclusions: Unbiased analysis of cardioprotective microRNAs and their target network revealed the common regulated protein RICTOR in ischemic conditioning. Therefore, RICTOR could be a potential target in cardioprotection

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Cross sectional twin study shows significant heritability in the background of bone mineral density

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Purpose: Previous studies have demonstrated that risk of hip fracture is heritable. The aim of this study was to determine the genetic component of bone mineral density (BMD), using both X-ray and ultrasound assessment at multiple sites.

Methods and Materials: 160 adult, healthy Hungarian twins (97 monozygotic, MZ, 62 dizygotic, DZ; mean age 50.6±14.7 years), recruited from the Hungarian Twin Registry with no history of oncologic disease underwent cross sectional BMD studies in 2019. We measured X-ray BMD at multiple sites (lumbar spine, femur, hip and radius), whileas broadband ultrasound attenuation of the calcaneus was also determined. Heritability was calculated using univariate ACE model.

Results: Bone density had a strong genetic component at all sites with estimates of heritability ranging from 0.619 to 0.829. Lumbar and calcaneus BMD had major genetic components with estimates of 0.828 and 0.829 respectively, and least heritable (0.619) at femur. Broadband ultrasound attenuation at calcaneus had also a strong genetic component with an estimate of 0.816. No common environmental effect was found. The remaining variance was influenced by unique environment (0.171 to 0.381).

Conclusions: Bone mineral density is strongly heritable at all sights which may explain the importance of family history as a risk factor for bone fractures. Our results might stimulate further studies in family risk based osteoporosis screening.

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The local ethical committee approved the study (approval number: 189-4/2014). All participants gave informed consent.

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The Effect of Disturbed Sleep, Circadian Rhythm and Chronotype on Glycemic Control in T2DM

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Introducion: Sleep quality and circadian rhythm have a profound effect on metabolism. The disturbed sleep and circadian dysruption have a pivotal role in the pathogenesis of T2DM, but the effect of sleep improvement and circadian rhythm normalisation on metabolic control are understudied and not supported with sufficient evidence.

Aims: to perform a cross sectional survey of sleep disorders and disturbed circadian rhythm and to conduct a randomised controlled trial of sleep intervention (I-CBT) in T2DM patients.

Methods: Patients with T2DM are recruited from the outpatients of the 2nd Department of Internal Medicine, Semmelweis University. Sleep quality, circadian rhythm, chronotype, health behaviour and diabetes management are assessed with questionnaires. Metabolic parameters are collected during the examination period. Our patients are followed and two groups are formed from those who are suffering from sleep disorder to assess the effectiveness of sleep improvement on glycemic control. The control group get sleep hygiene and diabetes management counseling. In the interventional group we carry out cognitive behavioural therapy for insomnia. After the intervention we monitorize metabolic parameters for one year, performing statistical analysis and interpreting our results.

Results: Collecting and assessing data are in progress. We present the current results of our cross-sectional survey.

Conclusions: Our future results can call attention to the importance of sleep and circadian rhythm on the therapy of T2DM and give new ways for behavioural medicine in diabetes care.

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Resting state fMRI correlates of mental fatigue and reward-induced improvement in task performance

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Instruction: Sustaining attention for prolonged periods of time can lead to a decay in performance and an increase in subjective fatigue, labelled in the literature as Time-on-Task effect (ToT) or mental fatigue. However, previous studies showed that the ToT effect is reversible by increasing task rewards.

Aims: In this study, we explored the link between reward-induced changes in task performance after prolonged performance of the psychomotor vigilance task and resting state functional connectivity (FC) obtained by fMRI.

Methods: Thirty-nine healthy participants underwent resting state functional magnetic resonance imaging, while they were instructed to fixate on a cross with eyes open. Then, participants performed the 15-min version of the psychomotor vigilance task out of scanner (ToT-period) followed by a 5-min rewarded run of the same task.

Results: Participants showed robust ToT effects indicated by slower reaction times and higher subjective fatigue. On the other hand, a significant improvement in performance was found in the rewarded run possibly due to reward-induced increase in motivation. At the neural level, we found that the magnitude of the ToT effect was negatively related to FC of the bilateral putamen and the cerebellum. In addition, graph theoretical analyses showed that the ToT effect was negatively correlated with global efficiency but positively correlated with clustering coefficient, both indicating that higher functional integrity predicts lower sensitivity to the detrimental effects of ToT. Critically, reward-induced improvements in performance were positively associated with the FC of the right lateral sensorimotor region with the right anterior insula, left anterior supramarginal gyrus, left intraparietal sulcus and left insular cortex.

Discussions: Our results suggest that the positive effects of reward manipulation on restoring one's performance are associated with increased FC between brain areas involved in visual attention, perceptual-motor coordination and the processing of costs and punishments.

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Behavioral Effect of GABA Release from Forebrain Cholinergic Neurons

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Introduction: The basal forebrain cholinergic system comprises several nuclei that provide innervation to cortical areas. It contributes to the regulation of arousal, attention and memory, including fear and extinction learning, and it is implicated in anxiety and post-traumatic stress disorder. We have recently shown that cholinergic terminals synaptically release not only acetylcholine, but GABA as well, the release of which can be modulated independently.

Aims: Although previous studies demonstrated that the alteration of GABAergic cotransmission is possible and has functional consequences in other non-cholinergic brain regions, the role of GABA release from forebrain cholinergic cells is unknown.

Methods: We created a conditional knockout mouse strain (ChAT-vGAT-cKO) showing decreased GABA release from cholinergic neurons.

Results: Preliminary results from behavioral phenotyping of this strain revealed that decreased GABA release from cholinergic neurons led to increased hippocampal theta activity during sleep and increased cognitive performance in an operant learning task, possibly due to a relatively more efficient cholinergic effect. However, ChAT-vGAT-cKO mice showed significant deficits in fear extinction learning after cued fear conditioning.

Conclusions: These results suggest that inefficient GABA release from cholinergic cells may explain certain fear-related pathological conditions.

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Elevated PD-L1 Protein Expression Predicts Poor Survival Outcomes in Patients with Malignant Pleural Mesothelioma: An International Multicenter Study

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Introduction: The PD-1/PD-L1 immune-checkpoint blockade is a promising new therapeutic strategy in cancer patients, yet the expression pattern and prognostic significance of both PD-L1 and PD-1 are still partly controversial in human malignant pleural mesothelioma (MPM).

Aims: Our study aimed to investigate the expression of PD-L1/PD-1 in the tumor samples of MPM patients and to analyze potential correlations with clinicopathological parameters.

Methods: Diagnostic biopsies of 203 MPM patients were collected from five Central European centers. The formalin-fixed paraffin-embedded samples were evaluated for PD-L1 and PD-1 expression on tumor cells and tumor-infiltrating lymphocytes by immunohistochemistry, and their prognostic significance was examined. To assess the PD-L1 and PD-1 expression pattern threshold value of 10% was used regardless of intensity.

Results: High (>10%) tumor cell PD-L1 expression was found in 8% of samples and high (>10%) tumor-infiltrating lymphocyte PD-1 expression in 24%. No significant associations were found between PD-L1/PD-1 expression and clinicopathological variables (patients' age, gender, histological subtype, stage and treatment modality). As for their prognostic relevance, the median overall survival time of patients with high (>10%) PD-L1 expression on tumor cells was significantly shorter compared to those with lower PD-L1 expression (6.2 vs. 15.1 months, respectively; $p<0.001$). Notably, high PD-L1 expression (>10%) proved to be an independent prognostic factor in the multivariate Cox regression analysis as well regardless of histology (hazard ratio HR] 2.711; 95% confidence interval [CI] 1.201 to 6.118; $p=0.016$). No significant difference was found in overall survival regarding PD-1 expression ($p=0.481$).

Conclusions: The results of this multicenter study demonstrate that high (>10%) PD-L1 expression on tumor

cells is an independent prognostic factor for worse survival outcomes in MPM. Furthermore, this is the first report comprehensively evaluating the expression and prognostic value of PD-1 on tumor-infiltrating lymphocytes.

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Molecular Subtypes of Small Cell Lung Cancer: Proteomic Characterization and Potential Clinical Implications

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Introduction: Until recently, small cell lung cancer (SCLC) was defined as a homogenous entity and thus SCLC patients have been treated similarly with no relevant changes in the standard of care chemotherapy for over three decades. Nevertheless, recent results suggest that there are significant differences within the SCLC category with regards to the expression of four different lineage-specific transcription regulators.

Aims: Our aim was to investigate the four molecular subtypes of SCLC at the proteome level and to explore their clinical relevance.

Methods: In total, 19 SCLC cell lines were subjected to in-depth proteomic analysis, qPCR and Western Blot techniques. We investigated the mechanisms and molecular background underlying the differences between subtypes utilizing integrative bioinformatic analyses. In order to investigate the clinicopathological relevance of the molecular subtypes, immunohistochemical analyses will be performed on 153 surgically resected SCLC tissue specimens.

Results: Comprehensively, 9228 proteins were quantified in the 19 SCLC cell lines (>8000 proteins per sample). Unsupervised hierarchical cluster analysis of the protein expression levels clearly distinguished the SCLC molecular subtypes of the cell lines. The results of the cluster analyses were confirmed by qPCR and Western Blot techniques. In regard to the protein expression heterogeneity between different subtypes, a significant difference was found in case of 1650 proteins [17% ($p<0.001$)]. Furthermore, we identified 126 unique proteins, that were expressed only in one particular subtype. The immunohistochemical classification of the surgically resected tumor tissue specimens are in progress and will be presented at the conference.

Conclusions: This study is the first differentiating SCLC molecular subtypes based on in-depth proteomic analysis. Accordingly, our results might help to gain a deeper understanding of the oncogenesis of SCLC, the resistance mechanisms and, moreover, to identify markers that may guide treatment decisions with regard to the molecular subtypes.

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Translocatome: a novel resource for the analysis of protein translocation between cellular organelles

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Subcellular localization of proteins is essential in the spatial and temporal organisation of biological processes. Translocating proteins play a key role in the reconfiguration of cellular functions after environmental changes, as well as in embryonic or disease development. Protein translocation as a systems biology phenomenon, refers to the regulated movement of a protein between subcellular compartments. Translocation changes the interaction partners and leads to altered function(s) of translocating proteins. Though several protein translocations are well characterized, the systematic analysis of this phenomenon was still missing.

The Translocatome database (translocatome.linkgroup.hu) contains 213 manually curated human translocating proteins. The database contains information about the details of the translocating proteins' structure, localization, regulation and interacting partners. Based on the manually curated proteins we implemented a machine learning algorithm using the XGBoost learning algorithm. To predict the translocation probabilities of 13 066 human proteins we used 139 human non-translocating proteins as a negative learning set and annotated each protein in our database with functional (Gene Ontology) and network parameters. With this method, we identified 1133 high-confidence and 3268 low-confidence translocating proteins.

The Translocatome database enables a systematic analysis of protein translocation. Thus, we'll be able to better understand the role translocating proteins play in cellular behaviour and certain cellular disfunctions. As translocating proteins play a key role in cancer progression the better understanding of this phenomenon may lead to the recognition of new therapeutic targets.

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Benefit of implanting an ICD in diabetic CRT patients

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Introduction: Heart failure (HF) patients with diabetes (DM) have a higher risk for all-cause mortality and also for sudden cardiac death. We lack data on the effect of adding a cardioverter defibrillator (ICD) to cardiac resynchronization therapy (CRT) on all-cause mortality in diabetic patients.

Aims: We aimed to investigate the risk of DM on all-cause mortality in CRT patients, and to examine the beneficial effect of adding an ICD in this patient population.

Methods: We examined retrospectively 2524 patients who underwent CRT implantation based on the current guidelines between 2000 and 2018, of which 927 (36%) had DM. The primary endpoint was all-cause mortality. Time to event data was investigated by Kaplan Meier and Cox regression analysis.

Results: During our mean follow-up time of 4.6 years, 1432 (56%) patients reached the primary endpoint, of which 552 (38%) had DM. Diabetic CRT patients were more obese (non-DM group BMI 26 vs. DM group BMI 28; $p < 0.01$). Hypertension (66% vs. 82%; $p<0.01$), ischemic aetiology (44% vs. 56%; $p<0.01$) and myocardial infarction (36% vs. 43%; $p<0.01$) were more frequent in the DM group, respectively. DM was associated with a 24% higher risk for all-cause mortality (HR 1.24; 95% CI 1.11-1.38; $p<0.01$), also observable with Cox regression analysis (HR 1.17; 95% CI 1.06-1.31; $p<0.01$). Addition of an ICD reduced the risk of all-cause mortality significantly by 32% (HR 0.68; CI 0.57-0.8; $p<0.01$) during the first six years, diminished at long-term (HR 0.94; CI 0.79-1.11; $p=0.46$). Regarding antidiabetic treatment, insulin (HR 1.82; CI 1.43-2.33; $p<0.01$) and sulfonylureas (HR 0.67; CI 0.52-0.87; $p<0.01$) could be associated with a higher all-cause mortality compared to metformin. Patients on metformin with a CRT-D had a significantly better survival up to 5 years (HR 0.56; CI 0.33-0.94; $p=0.02$), unseen in insulin or sulfonylurea treated patients.

Conclusions: Diabetes was found as an independent predictor of all-cause mortality in CRT patients.

In diabetic CRT patients the addition of an ICD reduced the risk of all-cause mortality mostly seen in the first six years. The type of antidiabetic treatment also altered the outcome, the benefit of implanting an ICD was the most dominant with metformin use. These findings might implicate the relevance of adding an ICD to CRT in those with severe comorbidities such as diabetes.

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Early-Life Social Isolation is Linked to Abnormal Social Behaviour in Adulthood and Disrupted Network Organization in the Prefrontal Cortex

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Introduction: Brain regions modulating social behaviour undergo dynamic changes in early life, rendering them vulnerable to social adversities experienced during this period. Aims: We aimed to characterize social behavioural changes induced by post-weaning social isolation (a model of childhood neglect) in mice and investigate underlying network disturbances in the prefrontal cortex (PFC), a key modulator of social behaviour. We focused on parvalbumin (PV) interneurons, a neuronal population closely tied to critical period closure.

Methods: Mice were weaned at postnatal day 21 and were housed either socially (4 mice/cage) or were isolated (alone) until adulthood. In adulthood, we used the resident-intruder (RI) test to investigate social behaviour and aggression. Mice were perfused either under resting conditions (no RI) or 90 minutes following social encounter (RI). Using immunohistochemistry and confocal imaging, we investigated (1) general c-Fos activation and co-activation patterns of PFC subregions, (2) activation of PV-containing (PV+) and perineuronal net-surrounded (PNN+) neurons in each subregion under resting conditions or following social encounter (RI) and (3) changes in general and excitatory inputs to the soma of parvalbumin interneurons in social and isolated animals via Bassoon and vGlut1 staining.

Results: Isolated mice display social disturbances in adulthood, manifested as increased defensive and abnormal aggressive behavior disregarding species-specific rules. Correlation matrices reveal that social encounter exerts differential c-Fos activation patterns in the PFC of isolated animals. In dorsal PFC regions RI increased the activity of PV+PNN+ neurons in both social and isolated animals. Conversely, in the infralimbic cortex social encounter decreased the activity of PV+PNN+ neurons in socially-reared mice, an effect absent in isolated animals. Isolation also lead to a decrease in Bassoon+ and vGlut1+ puncta surrounding parvalbumin interneurons. In conclusion, social isolation leads to social behavioural abnormalities and impaired activity of PV+PNN+ neurons following social encounter. Changes in inputs to parvalbumin interneurons could contribute to their abnormal activity. Our results aid us in understanding how early-life adversities disrupt developmental processes, leading to social abnormalities in adulthood.

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The possible role of animal-assisted therapies in clinical recovery and improving quality of life

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Introduction: Any musculoskeletal or mental illness means a significant burden for the patient, including the deterioration in quality of life. Animal assisted therapy may be helpful in the rehabilitation process and in the treatment of patients to alleviate the phenomenon. Nevertheless, this solution has been widely acknowledged internationally, its pivotal role in patient recovery requires further recognition and reinforcement in Hungary.

Aims and methods: In the framework of a prospective, multicentric randomized, controlled trial among a prospective number of 250 patients of the South Pest Central Hospital and the patients brought in by the Institute of Behavioural Science of Semmelweis University have been participating in a 45-minute long dog therapy session a week, throughout a minimum of a 3-week period, since October 2018.

Experiences to date and expected results: Significantly favourable statistical results are expected in the psychological markers (mood, state anxiety, subjective and chronic stress levels) of participants, as well as in some of their physiological parameters (motor function improvement, pain reduction) for the impact of the intervention. The subjective perception of life quality and coping with illness by patients become easier with the aids provided by dog-therapy, while their motivation to complete the program is further strengthened. According to experiences to date, sessions with the therapeutic dog truly alleviates patient state anxiety, reduces pain, and exerts a positive influence in their daily lives. Additionally, according to our observations animal assisted therapies may be adequately included in the rehabilitation program of patients enhancing the impact of other treatments.

Conclusions: Animal assisted therapy as complementary therapy certainly has its place in the rehabilitation process and it is proposed that consideration should be given to the application of the method on a larger scale in health care. The statistical proof of the above mentioned is the major target for the continuation of our research work.

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Prognostic Importance of Brain-Derived Neurotrophic Factor (BDNF) in Renal Transplantation

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Introduction: The prevalence of end-stage renal disease (ESRD) has increased ten times higher in the past twenty years, where renal replacement therapy (dialysis or kidney transplantation, KTx) is the sole treatment. KTx is the preferred option as it is associated with improved survival and quality of life as well. Delayed graft function (DGF) is one of the main problem affecting long-term kidney survival. Brain-derived neurotrophic factor (BDNF) signalling pathways play pivotal role in mitigating cerebral ischemia/ reperfusion injury (IRI), however the relation of BDNF and IRI in KTx is unknown.

Aims: The aim of our human clinical study was to explore the relationship between serum BDNF concentration, BDNF gene polymorphism and renal graft function after KTx.

Methods: Study characteristics: 59 ESRD patients (57% male) with average age of 54.8±12 years received KTx. Average cold ischemic time: 927±310 min, warm ischemic time: 54.5±39 min. DGF: 5 cases. Baseline triple immunosuppression therapy: tacrolimus, mycophenolate or everolimus, and prednisolone. Until now, 44 patients completed the 2 years follow-up. For a comparable control group, we collected blood samples from 79 healthy volunteers with average age of 53.9±16 years and with male gender proportion of 52%. Serum BDNF, creatinine, blood urea nitrogen, haemoglobin, blood glucose level and thrombocyte numbers were measured, before KTx, and 1 week, 1-, 3-, 6 months, and 1-, 2 years after, as well as in controls. GFR was estimated based on CKD-EPI formula. BDNF Val66Met polymorphism was determined by PCR-RFLP.

Results: There was no difference in genotype or allele distribution between any of the groups, and no correlation could be observed between serum BDNF and different genotypes either. Serum BDNF level was lower in ESRD patients than healthy controls (p=0.03). There was a weak correlation and marginal significance (p=0.056) between eGFR and serum BDNF level in controls, while in KTx recipients this correlation reached higher significance (p=0.01). Above median BDNF values at 1 month after KTx were predictive for better graft function during the 2 observed years.

Conclusions: Our preliminary human study proposes that BDNF could be a novel biomarker of posttransplant graft function, however further clinical studies with significantly larger population are definitely needed to confirm these results.

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Intratympanic Gentamicin for Ménière's Disease. Is there a Selective Vestibulotoxic Effect?

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Introduction: Ménière's disease is a disorder characterized by vertigo, hearing loss, tinnitus, and vegetative symptoms. For intractable cases, intratympanic gentamicin could be used in clinical practice.

Aims: The aim of our study is to investigate the effectiveness and safety of the treatment, based on vertigo diaries and pure tone audiograms.

Methods: The complete medical documentation of 105 definite patients (31 males, 74 females, mean age ± SD, 57.38 years ± 11.07) suffering from Ménière's disease was analyzed. In the studied group, 9 patients were treated with intratympanic gentamicin. The application of gentamicin was carried out under a microscope, through the anteroinferior part of the tympanic membrane, using local anesthetization. 8 mg gentamicin sulphate was used, on alternate days, 2 to 4 times until acute unilateral vestibular hypofunction with typical clinical signs appeared. Long-term follow-up of the patients was carried out, using vertigo diaries, medical letters, anamnestic data, and pure tone audiograms. Audiometric results and vertigo complaints before and after treatment were contrasted using IBM SPSS V24 software, based on Mann-Whitney U test, logistic regression and survivorship curves.

Results: Based on our analysis, vertigo attacks appeared significantly less often after gentamicin treatment [$p < 0.001$; Odds ratio: 0.003 (95% CI: 0.001-0.012)], which confirms the efficacy of the therapy. Pure tone stages before and after the application of gentamicin were contrasted using the Mann-Whitney U test. When comparing the audiometric results of long-term follow-ups by using the logistic regression, a statistically significant difference was observed between the treated and not treated groups [p=0.001; Odds ratio: 0.141 (95% CI 0.064 – 0.313)], and based on the survivorship curve hearing impairment was more common in the not treated group, which also supports our results. Based on the non-parametric test, there was no significant difference (p= 0.84) between the pure-tone stages of the control group and of those treated with gentamicin, nor was when the lower (p= 0.49) and higher (p= 0.1) frequencies were contrasted.

Conclusions: Our results indicate that intratympanic gentamicin is effective in controlling vertigo attacks, and there is no higher risk for hearing loss than in case of spontaneous progression of the disorder.

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6876

Examining the Functioning of Multidisciplinary Teams in Hungary

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Introduction: The psychiatric teams in Hungary are characterised by diversity with regard to their composition, methods and patient care.

Aims: The aim of the research is to examine the leadership, communication, competencies, and role expectations within the team.

Methods: One part of the research, beside the review of related literature, consisted of conducting focus groups at the annual conference of the Hungarian Psychiatric Society in 2017, 2018, 2019 and 2020. These four groups focused on the issues of leadership, communication within the team, competencies and role expectations. The groups of an average of 17 people formed spontaneously with the participation of various professionals (2017. N = 18, 2018. N = 16, 2019. N = 16, 2020. N = 15). In the quantitative part of our research we conducted a questionnaire survey among the professionals working in the psychiatric care in Hungary. The questionnaire used is the Hungarian version of COPSOQ II. (Nistor et al, 2015), which was complemented with questions derived from the results of our focus groups.

Results: The main results of our focus groups were as follows: 1. There is a hierarchy within the team as well. The task of the leader is to set the goals, define the tasks, distribute the roles and responsibilities (St Pierre, 2011), and put an end to destruction. 2. Informal channels are present in the teams. 3. The competencies are often unclear and there is a generational gap as well. These both result in tension within the team. 4. Interpersonal factors have an impact on medical decisions. Data collection via questionnaires is in process.

Conclusions: Based on foregoing results it seems necessary to clearly define and reconsider the professional competencies in the psychiatric training and integrate these in the education; to enhance the development of 'psychiatric specialist list of competencies' in Hungary for the legislators; providing 'team supervision'; involving external supervisors, and including supervision in the job description. Our further goal is to obtain a clearer and refined picture about the possible intervention areas with the help of COPSOQ II questionnaire, and make recommendations in order to increase the quality of the psychiatric care.

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Signal transduction pathways of detrusor smooth muscle contraction evoked by prostanoids and isoprostanes in murine and human urinary bladder

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Overactive bladder (OAB) is a clinical condition with a prevalence of 16% and affects the patients' quality of life significantly. The current pharmacological treatment is limited due to the adverse effects of anticholingergics. The arachidonic acid derivate prostaglandins (PGs) and the isoprotanes (isoPs), the latter produced non-enzymatically during oxidative stress, might act directly on the detrusor smooth muscle leading to detrusor overactivity.

Our aim was to examine the effects and the signal transduction pathways of PGs and isoPs in murine and human urinary bladder smooth muscle (UBSM), and potentially provide theoretical basis for the development of more specific medication of OAB with less adverse effects.

Urinary bladder tissues were obtained from mice with various genetic background and from human patients underwent radical cystectomy. UBSM strips were prepared without urothelium under microscope. Contraction force was measured by myograph under isometric conditions and normalized to reference contractions evoked by 124 mM K^+.

PGE2 and PGF2α, as well as 8-epi-PGE2 and 8-iso-PGF2α evoked contraction in the murine UBSM strips. The effect of the PGs was decreased, and the effect of the isoPs was abolished in the strips of thromboxane receptor (TP) KO mice. The TP agonist U-46619 evoked dose-dependent contraction in both murine and human UBSM samples. The responses were abolished in the presence of TP receptor antagonist SQ29548, but were not altered in the presence of cholinergic antagonist atropine or the purinergic P2X-antagonist pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS), indicating that the TP agonist has a direct effect on the detrusor muscle. The contraction responses were decreased in the strips of Gα12/13-KO mice. Correspondingly, the responses evoked by the PGs and isoPs were reduced by the Rho-kinase (ROCK) inhibitor Y-27632. In the strips of Gα/11-KO mice, the responses were also decreased, and in the presence of Y-27632 abolished completely.

The examined PGs and isoPs evoke contraction acting directly on the detrusor muscle. These responses are mediated mainly by the TP receptor and are linked to the Gαq/11 and to the Gα12/13-Rho-ROCK intracellular signaling pathways in the murine urinary bladder. The Rho-ROCK signaling pathway may provide a novel, more specific target in the treatment of OAB.

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Dendritic Outgrowth Alterations During the Pathogenesis of Schizophrenia in Genetic Mouse Models of P2X7R

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Introduction: P2x7 receptors (P2X7Rs) are potential therapeutic targets in schizophrenia (SCZ). Genetic deficiency and pharmacological blockade of P2X7Rs shown to attenuate schizophrenia-like behaviour in rodents (Koványi et al., 2016).

Aims: Neurons in some regions of the brain affected in SCZ show reduced dendritic length suggesting an abnormal dendritic outgrowth in schizophrenic patients. Our objective is to determine the regulation of neuronal outgrowth by P2X7Rs and the morphological correlates of P2X7R in primary cultures of murine hippocampal neurons derived from conventional wild-type (WT, P2rx7+/+) and P2X7 receptor knockout (KO, P2rx7-/-) offspring in an animal model of SCZ.

Methods: Primary hippocampal neurons from P2X7R WT and KO mice obtained from E17.5–E18.5 embryos would be dissected and processed. Likewise, morphology will be analysed in the WT and KO offspring subjected to the immunostimulant Poly(I:C), which causes an inflammatory reaction at gestational day 12.5. For each condition, at day in vitro 10, transfection with GFP plasmid will allow a clear visualization of the morphology of individual neurons in order to perform Neurolucida Software. Immunocytochemistry for the strengthening of the transfection will be performed. One and Two-way ANOVA were used to determine statistically significant differences in the Sholl analyses, depending on the needs. All data are presented as mean ± SEM.

Results: Deficits in dendritic outgrowth have been reported in P2X7R deficient mice and WT subjected to the Poly (I:C) treatment, but also, in primary hippocampal neurons from wild-type animals co-cultured with P2X7R antagonist in a dose dependent manner.

Conclusions: P2X7R depletion led to abnormal dendritic arborisation in primary hippocampal neurons, demonstrating that P2X7R is needed for normal dendritic outgrowth during neuronal development, proliferation and maturation. The dendritic deficits observed also in the disease model could constitute good correlates of the cognitive deficits in the schizophrenia.

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Neurochemical and electrophysiological features of extended amygdala projecting neurons located in the periaqueductal grey and dorsal raphe nucleus

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Periaqueductal grey (PAG) and dorsal raphe nucleus (DRN) are brainstem structures, which are involved in defensive responses, nociception or social interaction. The vPAG/DRN dopaminergic neurons project to the extended amygdala, particularly to the lateral part of the central amygdala (CeL) and to the bed nucleus of stria terminalis (BNST). Vasoactive intestinal polypeptide (VIP) and cholecystokinin (CCK) containing cells, which can be found in this region, also innervate both CeL and BNST.

Given the confounding and partially overlapping information available on the cytoarchitecture and projections of the vPAG/DRN nuclei, we aimed to explore the neurochemical content of vPAG/DRN neurons, focusing on those ones, which project to CeL and/or BNST.

To this end, we intracranially injected retrograde tracers into the BNST and CeL of transgenic mice, to visualize the projecting cells and identify their neurochemical content using immunocytochemistry.

Our results indicate a wider distribution of CCK+ neurons within the whole PAG. In contrast, VIP+ neurons are confined to the lateral and ventral parts adjacent to the 4th ventricle. We found that 39% of VIP+ neurons co-expressed CCK. In tracing experiments using CCK-DsRed mice (n=2) we revealed that more than 60% of projecting cells in vPAG/DRN contained only CCK, 2% contain only VIP and 25% express both neuropeptides. We found 13.3% of cells projecting to both nuclei. Using in vitro whole-cell patch clamp technique in vPAG/DRN containing sections of VIP-ZsGreen1 mice, we recorded the firing pattern of VIP+ neurons and analyzed their intrinsic properties, which where compared to those data obtained from inhibitory neurons sampled in VGAT-ZsGreen1 mice. Our data show that vPAG/DRN VIP+ neurons have similar features than those described for dopaminergic neurons, as well as clearly different membrane properties than local inhibitory neurons.

In summary, we provide a map for the distribution of CCK and VIP containing neurons, as well as the overlap in their neurochemical content in vPAG/DRN. Based on the electrophysiological features of these VIP+ cells likely glutamatergic. We demonstrate that both CCK+ and VIP+ neurons project to the CeL and BNST, and interestingly that some projecting cells send collaterals to both regions, providing the structural basis for the simultaneous control of the CeL and BNST function.

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Tumor associated prognostic biomarkers in different types of tumors

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Introduction & Aims: Cancer hallmark genes are responsible for the most essential phenotypic characteristics of malignant transformation and progression. In this study, our aim was to estimate the prognostic effect of the established cancer hallmark genes in multiple distinct cancer types.

Methods: Raw RNA-seq HTSeq counts and survival data from 26 different tumor types were acquired from the TCGA repository. DESeq was used for normalization. Correlations between gene expression and survival were computed using the Cox proportional hazards regression and by plotting Kaplan-Meier survival plots. The false discovery rate was calculated to correct for multiple hypothesis testing.

Results: Signatures based on genes involved in genome instability and invasion reached significance in most individual cancer types. Thyroid and glioblastoma were independent of hallmark genes (61 and 54 genes significant, respectively), while renal clear cell cancer and low grade gliomas harbored the most prognostic changes (403 and 419 genes significant, respectively). The eight genes with the highest significance included BRCA1 (genome instability, HR=4.26, p<1E-16), RUNX1 (sustaining proliferative signaling, HR=2.96, p=3.1E-10) and SERPINE1 (inducing angiogenesis, HR=3.36, p=1.5E-12) in low grade glioma, CDK1 (cell death resistance, HR=5.67, p=2.1E-10) in kidney papillary carcinoma, E2F1 (tumor suppressor, HR=0.38, p=2.4E-05) and EREG (enabling replicative immortality, HR=3.23, p=2.1E-07) in cervical cancer, FBP1 (deregulation of cellular energetics, HR=0.45, p=2.8E-07) in kidney renal clear cell carcinoma and MYC (invasion and metastasis, HR=1.81, p=5.8E-05) in bladder cancer.

Conclusions: We observed unexpected heterogeneity and tissue specificity when correlating cancer hallmark genes and survival. These results will help to prioritize future targeted therapy development in different types of solid tumors.

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Liquid Biopsy-Based Monitoring of Ezh2 Mutations in Follicular Lymphoma: Implications for Non-Invasive Disease Monitoring and Targeted Therapy

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Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin lymphomas, with an average overall survival rate of 15 years. The majority of FL patients experience disease progression or high grade transformation to a more aggressive lymphoma, raising the need for effective treatment response monitoring, which however is hampered by the limited specificity and sensitivity of the most widely used, imaging based PET-CT method. Molecular analysis of tumor derived circulating DNA (ctDNA), frequently referred as liquid biopsy, is a promising minimally invasive, radiation-free disease monitoring tool for patients suffering from a wide range of different tumor types. Recent studies interrogating the genomic background of FL have revealed activating mutations in the epigenetic regulator EZH2 gene in 25% of patients at diagnosis.

In this feasibility study, we tested the power of detection and time-resolved monitoring of EZH2 mutations in ctDNA of FL patients receiving immunochemotherapy (ICT).

Thirty-five blood plasma samples have been collected from 19 EZH2 mutant FL patients treated with ICT. After ctDNA isolation, EZH2 mutations were screened in each sample using digital droplet PCR (Bio-Rad Laboratories, USA). The acquired genetic results were compared with PET-CT based imaging data where available.

EZH2 mutations were detected in plasma samples of four patients suffering from active or transformed FL. All patients with EZH2 wild type plasma samples were in complete or partial remission. In patients with EZH2 mutation positive ctDNA, allele frequencies of the mutations correlated with the amount of metabolically active tumor sites observed on PET-CT scan images. Variant allele frequencies of EZH2 mutations rapidly declined or dropped below the detection limit upon successful treatment, while in one patient, treatment failure was associated with high EZH2 variant allele frequency. We also demonstrated spatial heterogeneity of EZH2 mutations in another case where different EZH2 mutations deriving from distinct anatomical sites could simultaneously be detected in the plasma.

Our results suggest that liquid biopsy based EZH2 mutation analysis with sensitive digital droplet PCR method offers a real-time, radiation free, sensitive treatment response monitoring tool for patients with active EZH2 mutant FL.

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Stable, Multi-day, Functional Measurement to Study Cellular Level Plasticity in Mouse Primary Visual Cortex by Fast 3D Imaging

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We investigated how 3D representation of the visual information, which is perceived and understood by the behaving animals in the primary visual cortex (V1), is changed while the animal engaged in a visual task.

To reach this goal we use in vivo two-photon acusto-optic microscopy (with AAV-Syn-GCaMP6s or AAV-Syn-jRGECO1a) to record cellular responses (through different cortical layers) to visual stimuli in V1 before (baseline) and after (effect) visual training. During training period, the mice learn to discriminate visual landmarks in a virtual reality.

To study cellular plasticity in time we had to measure the same neuronal ensembles (up to 200 cells) during the baseline and effect period which can be apart in time (10-20 days). As neuronal responses are very sensitive to the spatial inconsistency of recording coordinates, therefore, orientation tuning and other properties of the recorded visually evoked responses could be contaminated with recording artifacts. To resolve this critical issue, we used 3D AO drift scanning microscopy, which can extend each scanning point to small 3D line-, surface- or volume-elements. Furthermore, we are able to scan small volumes (40x40x40 μm) around each cell bodies in 3D, and use these mini-volume information to carefully and precisely realign all individual scanning regions at each measurement day, significantly reducing the chance of mismatching the recording coordinates. AO scanning of hundreds of cells at cortical depths up to 1 mm makes it feasible to examine the effect of learning in behavior experiments both at single-cell and at network scales.

We found that, in contrast to previous theories, adult mice brain is plastic as the temporal dynamics of the visual representation can change at multiple temporal scales following visual learning in individual neurons.

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Prevalence of multiresistant Enterobacterales in black-headed gulls (Chroicocephalus ridibundus) and a comparison with contemporary human isolates

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Introduction: During winter, large number of black-headed gulls (Croicocephalus ridibundus) flocks at the docks of Budapest. These birds frequently use anthropogenic food sources such as landfills.

Aims: This study investigates the prevalence of third generation cephalosporin resistant Enterobacterales in gulls and compare ESBL-producing Escherichia coli isolates to contemporary human-derived strains.

Methods: In the winter 2018-2019, 123 fecal samples were obtained from gulls captured at the docks of Budapest. Isolates were recovered from eosin-methylene blue media supplemented with 2 mg/l cefotaxime. ESBL-production was determined by double-disc synergy test, carbapenemase production using MASTDISCS Combi Carba test. We also collected 136 contemporary ESBL-producing E. coli from inpatients of the Semmelweis University. ESBL-producing isolates were screened for the following resistance genes: blaSHV, blaTEM, blaCTX-M-1,2,8,9 groups. E. coli phylotypes and members of sequence type (ST) 131 clonal lineage were identified by PCR.

Results: Enterobacterales resistant to cefotaxime were carried by 59% (73/123) of the sampled gulls, 123 isolates were recovered (82 ESBL-producers, 31 AmpC-producers and 10 carbapenem resistant isolates). Dominant ESBL genes were blaCTX-M-1 group (68% and 68%) and blaCTX-M-9 group (22% and 27%) in both gull and human isolates. Most gull E. coli isolates (70%) belonged to commensal phylogroups (A, B1, C, and E) while B2 was predominant among human isolates (74%), which is associated with extraintestinal infections. Of the gull isolates 26% (18/68) belonged to the B2 phylotype and 15 of them were pandemic ST131, seven of C2 and eight of C1-M27 clades. Of human isolates 63% (86/136) belonged to ST131, one, one, two, 31 and 51 were members of A, B, C1, C1-M27 and C2 clades, respectively. Of carbapenem resistant isolates, four E. coli showed metallo beta-lactamase (MBL) producer and one OXA-48-producer phenotype, two MBL-producing and one OXA-48-producing Klebsiella pneumoniae, one MBL and one porin deficient Enterobacter spp were found.

Conclusions: Gulls may play a role in the dissemination of these agents because of their vagrant behavior, highlighting the importance of One Health in case of antibiotic resistance.

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7075

Combination of molecular genetic analysis with decision-supporting database in order to identify potentially effective drugs for rare adenocarcinomas of the urinary bladder

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Introduction: Primary bladder adenocarcinoma (PBAC) and urachal carcinoma (UrC) are rare, accounting for less than 2% of all bladder cancers. UrC and PBAC are histopathologically similar yet different entities with no clinically proven standard therapies. In lack of prospective clinical studies, targeted therapies represent a promising option for patients with rare tumors. For this, a better understanding of the molecular background and pathogenesis of PBAC and UrC is needed.

Aims: We aimed to collect a large number of UrC and PBAC tissue samples with clinicopathological and follow-up data in order to identify genetic alterations of clinical and therapeutic significance.

Methods: We conducted a sample and data collection by using a National Cancer Registry-based and an international multicenter approach. UrC samples have been sequenced on an Oncomine Comprehensive Assay panel by using the ionTorrent technology. This sequencing panel detects SNVs, CNVs, gene fusions and indels of 161 cancer driver genes. The annotations of genetic variants based on Ion Reporter 5.6 and open access databases (VEP, COSMIC, ClinVar, VarSome). Identified pathogenic alterations were interpreted by using the Qiagen Clinical Insight (QCI) evidence-based decision support software.

Results: We collected 64 UrC and 20 PBAC formalin-fixed paraffin embedded (FFPE) samples. So far, thirty-two UrC samples have been sequenced and 26 of them met the quality criteria. We observed pathogenic alterations in 38 of 161 assessed genes. TP53 was altered in 84% of cases (21/26), followed by KRAS (40%; 10/26) and MYC (20%; 5/26). The MAPK and DNA-repair were the most often affected patways. Fifteen of 38 altered genes found to be potentially druggable. QCI interpretation predicted 41 targeted therapeutic drugs and 13 chemotherapy agents to be effective, providing at least one potentially effective treatment for 24 of 26 UrC patients.

Conclusions: Based on these results, we conclude that targeted sequencing in combination with decision-support databases identify potentially effective systemic treatments (chemo- or targeted therapies) for most of the UrC patients. Further prospective testing is needed in order to objectively evaluate the benefit of this approach. Our results confirm the involvement of MAPK and suggest the importance of the DNA repair pathway in the pathogenesis of UrC.

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Examination of possible causes of ineffective radiosynoviorthesis

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Introduction: Synovitis is the inflammation of the synovial membrane which can develop due to various causes. It is usually associated with pain and swelling of the joint. This is followed by the production of inflammatory cytokines as the synovial membrane attaches to the joint surface causing cartilage damage, leading to pain, reduced range of motion, and osteoarthritis in the long-term. For these reasons, it is important to treat the synovitis. Radiosynoviorthesis is suitable for eliminating synovitis in the treated joints with a 73%±17% success rate according to the international literature.

Aims: 773 radiosynoviortheses were performed at the Orthopaedic-Trauma Department of Uzsoki Hospital since 2003. The follow-up examinations proved 81% success rate. The goal of our study was to analyse the possible reasons of ineffective procedures. We assumed that the cause of ineffectiveness is that the injected colloid wasn't phagocytised by „A" type macrophages and that synovitis is still persisted.

Patients and methods: We performed 38 arthroscopic synovectomies in different joints (4 hips, 28 knees and 6 ankles) in 38 patients an average 10 month (7-16) after the ineffective radiosynoviortheses. According to the therapeutic protocol this procedure was the second step. There were 25 female and 13 male patients. The average age was 52 years (26-64). Histological and electronmicroscopic examinations were carried out on 76 segments from the surgically removed synovial membranes. The electronmicroscopic examinations were performed in the Institute of Experimental Medicine of the Hungarian Academy of Sciences. The histological examinations were performed at the Pathology Department of Uzsoki Hospital.

Results: The histological examinations revealed that, all of the synovial samples were inflamed, meaning that synovitis is still persisted in all of the treated joints after ineffective radiosynoviorthesis. In case of the electron-microscopic examinations we couldn't detect stable isotope in the lysosomes of „A" type macrophages.

Conclusions: Radiosynoviorthesis can be a good alternative in the treatment of synovitis. In case of ineffective procedures synovitis persisted. We concluded that the main cause of ineffectiveness is that the macrophages didn't phagocytise the injected isotope.

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Investigation of LCR activity and E2 viral protein of human papillomavirus 11 intratypic variants

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Our former results showed that different severity of recurrent respiratory papillomatosis may be associated with given nucleotide polymorphisms identified in the ORF encoding replication and transcription regulatory protein E2 and in the long control region (LCR) of human papilloma-virus virus (HPV) 11.

Our aim was to determine the interaction of LCR and E2 viral protein by transient co-transfection experiments to analyse how the polymorphisms in LCR and E2 influence LCR activity.

Six E2 variants (V1-V6) and six LCR patterns (P1-P6) were identified by comparison with HPV11 reference sequence (M14119). The P1 LCR pattern and the V1 E2 variant were present in nine HPV11 sequences of our samples. The other five HPV11 sequence carried unique LCR pattern and E2 variant. The identified unique LCRs were cloned into pALuc reporter vector and the E2 ORFs were cloned into pCDNA3.1+ expression vector, then transformed into Escherichia coli XL-1 bacterial strain. Plasmids transfected into HEP-2 cells with Lipofectamine 2000. Luciferase activities were compared by ANOVA with Tukey's post-test. In variant E2 and reference LCR co-transfection experiments, the highest luciferase activity was measured for reference LCR and E2 combination and in case of an identical HPV11 genome originated from cervical atypia. In case of five E2 variants (V1; V2; V3; V4; V5), the LCR activity was increased significantly lower level than in case of the reference E2. For three unique combinations (V4 + P4, V1 + P2, V2 + P1) the transactivating effect of LCR was significantly lower than the reference. Analysing the effect of E2 variants on the own LCR patterns, highest activity was also observed for the combination of the reference LCR and the reference E2. In case of co-transfection of unique LCR patterns and reference E2, the highest activity was found to be the combination of P6 LCR+ reference E2. The activity of P1 LCR+ reference E2 and P2 LCR + reference E2 was significantly lower than all other combinations. The 58 bp deletion in V2 E2 variant significantly reduces the E2 activity in both reference LCR and unique LCR assays.

Our data suggest that individual HPV11 E2 variants influence the transactivation activity of HPV11 LCR sequences and seem to confirm our hypothesis, that intratypic variantion of HPV11 genome may influence the disease outcome.

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Laminar Specificity of Perisomatic Inhibition in the Mouse Prefrontal Cortex

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Perisomatic inhibition provided by local GABAergic interneurons is critical for cortical functions, but the details of these inhibitory circuits, especially in associative cortices, are still unknown.

Here, we examined the laminar specificity of two types of basket cells (BC) expressing parvalbumin (PV) or cholecystokinin (CCK) in the mouse prefrontal cortex (PFC).

Using whole-cell patch clamp technique, we performed recordings in acute slices containing the PFC. The recordings were accompanied by intracellular labeling that allowed us to identify the interneuron types post hoc.

We observed that BCs located in distinct layers differed in their morphological features. Examining the distribution of axons and dendrites of PVBCs, we found layer preferences in both types of processes. In contrast, CCKBCs displayed layer-specific differences only in their dendritic arborization. In addition, we examined the inputs from extra-PFC afferents onto PV-expressing interneurons using trans-synaptic viral approach. We observed that afferents from the thalamus and basal amygdala preferentially innervate PV-expressing cells in the layer 5a and 5b, respectively. Moreover, using retrograde tracing and single cell labeling, we examined the innervation of pyramidal cells by PVBCs. The analyses uncovered that single PVBCs contacted pyramidal cells with distinct projections.

These results suggest that morphologically different BCs are present in the PFC microcircuits. Furthermore, PVBCs in different layers are preferentially contacted by distinct extra-PFC afferents and innervate pyramidal cells in their vicinity irrespective where they project. Thus, BCs innervating all pyramidal cells in their neighborhood may control PFC function in a layer-specific manner.

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Beneficial effects of tricetin flavonoid in cerulein induced acute pancreatitis in mice

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Introduction: Acute (AP) and the chronic pancreatitis (CP) are one of the most common gastrointestinal diseases of the developed societies, with 30-40% mortality. The reason of the high mortality is the lack of specific therapy, wich could reduce the progression of the diseases. In physiological condition the digestive enzymes are synthetized in zymogen granules in pancreatic acinar cells. Due to some insults, the enzymes are prematurely activated in the cells, from where they harm the tissues of the organ. In case of long term AP evolves the chronic form with multiorgan failure and diabetes mellitus because of a severe pancreatic injury.

Aims: Our aim was to examine the possible beneficial effect of an antioxidant flavonoid (tricetin) in the severity of the cerulein induced AP.

Methods: In vitro the effect of the flavonoid was investigated in cerulein treated (in 100nM concentracion) isolated acinar cells. Calcein, LDH, PI assays, cellomics, and qPCR were used in the examination.

After that we investigated the effect of tricetin in vivo by intraperitoneal injection (10 mg/kgBW) 1 hour before the AP was induced by intraperitoneal injections of cerulein (50 μg/kgBW) eight times at 1 hour intervals. The mice were sacrificed 10 hours after the fist cerulein injection. We exemined α-amylase and lipase level of the serum, and MPO level from the pancreas. We made HE staining sections and qPCR from the pancreatic tissues.

Results: In vitro the flavonoid significantly (α=0,05) decreased the harmful effect of the cerulein treatment. In vivo it significantly (α=0,05) derceased the level of the digestive enzymes and the MPO and also decreased the expression of inflammatory genes.

Conclusions: Our results show that used tricetin successfully decreased the harmful effect of the cerulein in isolated acinar cells, and derceased the severity of the cerulein induced acute pancreatitis in mice.

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First steps of dysphagia screening

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Dysphagia means a sort of swallowing disorder, which can lead complications, such as malnutrition, dehydration, aspiration pneumonia or choking. In addition to that, the above mentioned complications can lead longer length of stay in rehabilitation unit with unnecessary costs. There can be several hidden causes related to dysphagia. The incidence rate is 93% in severe traumatic brain injury (TBI) population, and approximately 29–64% after stroke.

The main activity of the Brain Injury Rehabilitation Unit in the National Institute for Medical Rehabilitation is giving comprehensive rehabilitation program for patients suffered TBI or stroke.

The patients require complex rehabilitation program which involves diagnostic process and treatment in related with dysphagia. The first step in diagnosing dysphagia is the appropriate screening. The dysphagia screening can only be performed by qualified speech and language pathologist or trained health care professional. Dysphagia screening test has developed in our unit which can be applied during the daily routine.

The aim of screening test is to explore the various risk factors which might show swallowing disorders and for taking a prediction for duration of dysphagia. A positive result based on this screener leads to further investigation with instrumental evaluation which is essential in order to choose the most effective therapy method.

In this long-term (10 months) study, 20 patients have been screened with swallowing disorders with respect of liquids according to the medical history. In regards to the existence of the swallowing difficulties, we found positive results in case of 5 patients (out of the 20 cases). All of these patients were sent to endoscopic swallowing assessment and have been diagnosed with dysphagia. The remainders with negative test results had no complications during oral fluid intake.

In conclusion, the screening test has predictive value for the existence and duration of dysphagia. It is a notable progress in regards to the patients' quality of life and can facilitate the different type of rehabilitation interventions. Our study has some limitations and further examinations are needed.

7025

Oxidized hemoglobin forms contribute to NLRP3 inflammasome-driven IL-1β production upon intravascular hemolysis

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Introduction: Damage associated molecular patterns (DAMPs) are released from red blood cells (RBCs) during intravascular hemolysis (IVH). Extracellular heme, with its pro-oxidant, pro-inflammatory and cytotoxic effects, is sensed by innate immune cells through pattern recognition receptors such as toll-like receptor 4 and nucleotide-binding domain and leucine-rich repeat-containing family, pyrin domain containing 3 (NLRP3), while the availability of free heme is strictly controlled.

Aims: To establish the formation of oxidized Hb forms in vivo upon sterile intravascular hemolysis and to investigate the involvement of different Hb forms in the hemolysis-associated inflammatory response.

Methods: We used C57BL/6 (WT) and NLRP3-/- mice and induced IVH by injecting phenylhydrazine into the peritoneal cavity of mice. The levels of Hb redox forms were determined spectrophotometrically in plasma, heme was determined by a heme assay kit, IL-1β was measured by ELISA. Expressions (mRNA and protein) of NLRP3, caspase-1, and IL-1β were determined by quantitative RT-PCR and western blot. Peritoneal infiltration of monocytes and neutrophils was assessed by flow cytometry. In vitro study was performed on murine macrophages.

Results: We found that after IVH most of the extracellular heme molecules are localized in oxidized Hb forms. IVH was associated with caspase-1 activation and formation of mature IL-1β in plasma and in the liver of C57BL/6 mice. We showed that ferrylHb (FHb) induces active IL-1β production in LPS-primed macrophages in vitro and triggered intraperitoneal recruitment of neutrophils and monocytes, caspase-1 activation and active IL-1β formation in the liver of C57BL/6 mice. NLRP3 deficiency provided a survival advantage upon IVH, without influencing the extent of RBC lysis or the accumulation of oxidized Hb forms. However, both hemolysis-induced and FHb-induced pro-inflammatory responses were largely attenuated in Nlrp3-/- mice.

Conclusions: We concluded that besides heme, FHb is a potent trigger of NLRP3 activation and production of IL-1β in vitro and in vivo, suggesting that FHb may contribute to hemolysis-induced inflammation. Identification of RBC-derived DAMPs might allow us to develop new therapeutic approaches for hemolytic diseases.

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Characterization of the mechanisms leading to age-related changes of meningeal lymphatics

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Background: Recent studies have described the presence of the meningeal lymphatic vessels in the dura mater, and suggested their role in Alzheimer's disease and multiple sclerosis. In our former study we described that lymph flow induces the postnatal maturation of the meningeal lymphatic structures. It has also been suggested that the VEGFR3 signaling plays an important role in the development and maintenance of meningeal lymphatic vessels.

Aims: We aimed at characterizing the age-related structural changes of the meningeal lymphatics and investigating the role of lymphangiogenic factors in the development and maintenance of the meningeal lymphatics.

Materials and methods: For characterization of the meningeal lymphatic structures, lymphatic endothelial cell-specific immunostainings were used in wild-type mice and mice with lymphangiogenic factor deficiency at different ages including young and old animals. Lymphatic function was monitored by injection of labeled macromolecules into the CNS followed by assessment of uptake and drainage to the cervical lymph nodes.

Results: We have characterized the structural changes in the meningeal lymphatic structures in young animals and during aging. Our results showed that the structural integrity and density of meningeal lymphatic vessels gradually decrease over time. Moreover, lymphangiogenic factor deletion impaired the postnatal development of the meningeal lymphatics, and enhanced the degradation of the meningeal lymphatic structures in aged mice.

Conclusions: We revealed that a structural degradation of the meningeal lymphatics occurs during aging. Our results also indicate the importance of lymphangiogenic mechanisms not only in the development, but also in the prevention of the age-related degradation of meningeal lymphatics. The degradation of meningeal lymphatic structures in aging may play an important role in the pathophysiology of Alzheimer's disease.

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NLRP3-independent inflammasome activation in heart failure

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Introduction: Inflammation and cytokine release is considered an important feature of progressive heart failure. Canakinumab, a monoclonal antibody against interleukin-1β (IL-1β), has been shown to provide benefit against cardiovascular events, suggesting that blockade of IL-1β secretion and signaling might be a promising new therapeutic target. Therefore, we aimed to assess inflammasome activation in end-stage failing human hearts to identify the exact source of IL-1β in the failing heart.

Methods: Inflammasomes were analyzed by immunoblot and immunohistochemistry in end-stage failing human hearts. To investigate the molecular background of inflammasome activation in cardiac tissues, cell culture experiments were performed on AC16 human cardiac and THP-1 human monocytic cell lines.

Results: Expression of the inflammasome protein absent in melanoma 2 (AIM2) and NLR family CARD domain-containing protein 4 (NLRC4) increased in heart failure regardless of the etiology. There was a robust infiltration of monocytes/macrophages in all groups of failing hearts, in which cells AIM2 expression was confirmed. In vitro AIM2 inflammasome activation in THP-1 cells, as well as vesicular transfer of the inflammasome adaptor protein ASC, was reduced significantly by the pharmacological blockade of pannexin-1 channels, with the clinically used uricosuric drug probenecid.

Conclusions: This is the first demonstration that AIM2 and NLRC4 inflammasome activation contribute to chronic inflammation in heart failure. Our findings suggest that repurposing probenecid is a promising strategy to reduce inflammasome activation in chronic heart failure.

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7040

Characterization of Neutrophil Granulocytes Generated In Vitro From HoxB8-Transduced Myeloid Progenitor Cells

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Neutrophils play a critical role in the innate immunity. However, deeply understanding their biology has been challenging, as they are short-lived, terminally differentiated cells.

Our aim is to overcome this obstacle using the HoxB8-driven, immortalized myeloid progenitor cell line. This allows us to generate unlimited amounts of neutrophils, followed by detailed analysis of various cell functions.

HoxB8 progenitors were cultured in medium containing β-estrogen. Neutrophils were grown in estrogen free medium supplemented with G-CSF. Reactive oxygen species (ROS) production was monitored via cytochrome-c reduction. In vitro phagocytosis was measured using green fluorescent Staphylococcus aureus (USA300). HoxB8 chimeras were generated with the adoptive transfer of HoxB8 progenitors. Migration and phagocytosis assays were performed in vivo. KBxN serum transfer arthritis model was used to monitor HoxB8 neutrophils' role in autoantibody-induced inflammation.

Hoxb8 progenitors differentiated into neutrophils in 5 days, in vitro. These HoxB8 neutrophils could produce ROS upon various stimuli comparable to WT bone marrow-derived neutrophils. They could carry out phagocytosis of opsonized bacteria in vitro. Upon adoptive transfer of HoxB8 progenitors, HoxB8 neutrophils soon appeared in the circulation of the recipients'. These neutrophils were able to migrate into the inflamed peripheral tissues, where they carried out phagocytosis of heat inactivated Candida albicans particles. However, in 2 days HoxB8 neutrophils dissappeared from the recipients, possibly because the progenitors were unable to colonize their bone marrow permanently. Upon arthritogenic serum treatment, chimeras having only WT Hoxb8 neutrophils developed a systemic joint inflammation, comparable to the WT animals. Meanwhile Syk (Spleen Tyrosine Kinase) KO HoxB8 chimeras seemed to be completely protected in the same circumstance.

The HoxB8 progenitor cell line is a robust tool to generate neutrophils in vitro. HoxB8 neutrophils, both in vitro and in vivo, are quite similar to their BM derived counterparts as far as their effector functions are concerned. Their role in acute inflammation further proves the cell line's utility in wide-ranging studies of neutrophils. Moreover, the in vitro cultured HoxB8 progenitors can act as good targets for genetic modifications, manifesting on the neutrophil level.

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Extracellular vesicles transmit epithelial growth factor activity in the intestinal stem cell niche

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The intestinal epithelium is continuously renewing by a proliferating stem cell population, residing at the bottom of the intestinal crypts. Intestinal stem cells (ISC) critically depend on niche factors, such as R-Spondin1, noggin and EGF, secreted into the surrounding microenvironment by intestinal fibroblasts or Paneth cells. Three-dimensional organoid culture technology has emerged as a novel, cutting edge tool to study ISCs. Stem cell containing intestinal crypts form self-organizing organoids called „miniguts" after embedded into 3D matrix. Extracellular vesicles (EV) are membrane-enclosed vesicles secreted by virtually all cell types. Although understanding factors critically contributing to the ISC niche is central for regenerative medicine, the effect of EVs on this process is unknown.

To investigate the role of fibroblast-derived EVs in the normal ISC niche.

EVs were isolated by differential ultracentrifugation from fibroblast culture supernatants and they were added to murine small intestinal, colon or to human colon organoids. Organoid survival ratios were quantified by microscopy. Surviving stem cell ratios were determined by confocal microscopy. EV surface proteins were detected by capillary-based Western blot or bead based flow cytometric assays.

Here we provide evidence that both mouse and human intestinal fibroblasts secrete EVs. Fibroblast-derived EVs do not increase the number of ISCs when all niche factors are present. We observed a massive organoid death when niche factors were removed from the culture medium one-by-one. Fibroblast-derived EVs could rescue organoid death in the absence of EGF, but they had no effect when either R-Spondin1 or noggin lacked both in mouse and human intestinal organoids. EVs mediated their rescue effect through the EGF-receptor, which became phosphorylated when EGF was replaced by EVs. Importantly, fibroblasts express a wide range of EGF family members and we found that at least one of them, amphiregulin is transported via EVs. Neutralizing EV-bound amphiregulin blocked the rescue effect of EVs. Furthermore, EVs had no additional effect when EGF was dispensasble, such as after the tumour initiating APC mutations.

We provide evidence that fibroblast-derived EVs are key players in forming the ISC niche by transmitting EGF activity both in mice and in human.

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Symptoms and mechanisms of nanoparticulate-induced pseudoallergy in mice

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Introduction: A new promising direction in medicine is the use of nanoparticulate vehicles for controlled, targeted drug delivery. However, an unsolved problem is that nanomedicines can cause IgE-independent side effects known as infusion reaction, pseudoallergy or anaphylactic reaction.

Aims: We aimed to characterize the symptoms and basic mechanisms of pseudoallergy caused by intravenous injection of amphotericin B containing liposomes (AmBisome, 300 mg/kg; Abelcet, 30 mg/kg), polystyrene nanoparticles (NP, 500 nm, 26 mg/kg), as well as direct complement (C) activators, zymosan (ZY, 30 mg/kg) and cobra venom factor (CVF, 100 U/kg) in mice.

Methods: The carotid artery and jugular vein were cannulated in anesthetized (pentobarbital, 90 mg/kg i.p.) male NMRI mice (n=5-7/group), and also in wild type (WT), thromboxane prostanoid receptor deficient (TP KO) mice on C57Bl/6 background, and blood pressure (BP) was recorded. Blood was collected from other groups of NMRI mice at 3-5 min after treatments, and plasma C3a and thromboxane B2 (TXB2) concentrations were assayed using ELISA. Blood count was carried out in Abacus vet5 hematology analyzer.

Results: All treatments caused an initial hypertension lasting for 3-5 min, while BP returned to baseline after administration of liposomes and NP but progressed to hypotensive shock after treatment with direct C activators. All treatments decreased leukocyte and platelet counts, increased hematocrit and plasma C3a and TXB2 concentrations. However, direct C activators caused much greater changes in plasma C3a concentrations than nanoparticles. Pretreatment with SB290157 (10 mg/kg, i.v.), a C3a receptor antagonist, attenuated the hypertensive response to Abelcet and led to delayed hypotension, while DF2593A (1 mg/kg, i.v.), a C5a receptor antagonist, considerably lengthened the hypertensive effect of Abelcet. Abelcet caused hypotension only in TP KO mice.

Conclusions: Blood pressure and hematological changes are the main symptoms of nanoparticulate-induced pseudoallergy in mice, which seemed to be caused at least in part by complement activation and consecutive thromboxane secretion leading to hypertension. The detailed mechanisms of hypotensive effect remain to be elucidated.

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New therapeutic opportunity in the treatment of ischemia-reperfusion induced acute renal failure

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Introduction: Acute renal failure (ARF) has a high risk of morbidity and mortality without reliable therapeutic intervention. The most common cause of ARF is renal ischemia reperfusion (I/R) injury, which may associated with various clinical situations including major surgery, cardiac arrest or organ transplantation.

Aims: Our aim was to better understand the patho-mechanism of renal I/R injury find new biomarkers or therapeutic targets.

Methods: Two-dimensional gel electrophoresis and proteomic evaluation was carried out on rat kidneys following I/R injury. The significantly changed proteins were analyzed by bioinformatics approaches. The role of Parkinson's diseases 7 (PARK7) in oxidative stress (H_2O_2) induced cell death was investigeted by its overexpression or pharmacological modulation in the HEK-293 kidney epithelial cells. We also examined the effect of the modulation of PARK7 in I/R induced mice models of ARF in vivo.

Results: PARK7 was identified as central factor related to I/R induced oxidative stress in the kidney. PARK7 overexpression and its pharmacological modulation decreased H_2O_2 induced apoptosis of HEK-293 cells. Accordingly, pharmacological modulation of PARK7 improved renal function in mice following I/R induced ARF.

Conclusions: Our data suggest that PARK7 plays a role in the reduction of renal I/R injury associated oxidative damage probably through activation of antioxidant or anti-apoptotic mechanisms. Therefore, PARK7 may serve as therapeutic target in the treatment of I/R injury induced ARF.

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The effect of high-NaCl intake on skin tissue remodeling

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Introduction: Wound healing is a complex, inflammation and extracellular matrix (ECM) remodeling associated process in which dermal fibroblasts play a central role. Based on literature data, high-NaCl intake induces inflammatory response and causes or often worsens several pathological conditions. However, the effect of high-NaCl diet on the process of skin ECM remodeling and fibroblast activity is not fully understood.

Methods: To investigate the effect of high-NaCl consumption on skin tissue remodeling we kept the mice on high NaCl diet and than we performed the imiquimod (IMQ) induced mouse model of dermatitis. Dermal mRNA level of ECM component collagen-1, fibronectin and the fibroblast marker alpha smooth muscle actin (α-SMA) was measured by real-time RT-PCR. The effect of increased NaCl concentration on ECM production and cellular motility was investigated on human primary dermal fibroblasts in vitro.

Results: The effect of high-NaCl diet on the IMQ treated group resulted in lower skin mRNA levels of fibronectin, collagen1 and α-SMA compared to the IMQ treated mice on normal salt diet. Increased NaCl concentration reduced the fibronectin and collagen-1 mRNA expression, as well as the TGF-β induced fibroblast motility in human dermal fibroblast cell line.

Conclusions: Taken together, our results reveal that high salt intake reduces the expression of ECM markers and motility of dermal fibroblasts. Therefore high dietary NaCl intake may be responsible for hindered wound healing.

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Vitamin D Receptor Deficiency Compromises the Cerebrovascular Adaptation to Carotid Artery Occlusion due to Impaired Pial Collateral Development in Mice

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Introduction: Vitamin D deficiency is a global health problem, which can increase the risk of cerebrovascular diseases including ischaemic stroke. However, the pathophysiological mechanism underlying this association is not well understood yet.

Aims: The goal of the present work was to analyze the impact of vitamin D receptor signaling on the anatomical and functional aspects of cerebrovascular adaptation to unilateral carotid artery occlusion (CAO).

Methods: Acute cerebrocortical blood flow (CoBF) changes after CAO were measured in anesthetized, adult male mice carrying a functionally inactive vitamin D receptor (VDRΔ/Δ) and in their wild-type littermates (WT) using laser speckle imaging. The compensatory blood flow increase in the contralateral carotid artery was determined using transit-time ultrasonic flow meter. The morphology of the leptomeningeal collaterals and the distance of the anastomotic line (half distance between the nearest branching points of the anterior cerebral artery (ACA) and the middle cerebral artery (MCA)) from the midline were evaluated after staining of the cerebral vasculature.

Results: CoBF showed a significantly increased drop after CAO in VDRΔ/Δ mice as compared to WT animals in the parietal region and in the zone of pial anastomoses ipsilateral to CAO, and the difference between the groups was even more sustained in the temporal region. Vitamin D receptor deficiency had no significant influence on the carotid arterial blood flow, however, it decreased the number of leptomeningeal collaterals between the ACA and MCA, whereas the tortuosity of the collaterals was enhanced. The anastomotic line measured at 4 mm caudally from the frontal pole was located cc. 400 μm closer to the midline in VDRÄ/Ä than in WT mice, therefore the territory supplied by the MCA increased.

Conclusions: Vitamin D receptor deficiency leads to impaired development of leptomeningeal collaterals resulting in more pronounced CoBF reductions after CAO. These alterations can potentially compromise the cerebral circulation therefore it may worsen the outcome of stroke, especially in the cortical regions supplied by the MCA.

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Applications of Virtual, Three-Dimensional Planning and Surgical Simulation in Reconstructive Periodontal Surgery (Proof of Concept)

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Introduction: In advanced cases of periodontal tissue breakdown, it is difficult to determine the true defect morphology and extent of complex defects on two-dimensional (2D) intraoral radiographs, consequently the surgical intervention and regenerative strategy is also difficult to plan. Various surgical fields, such as: orthopedic surgery, cardiac surgery and cranio-maxillofacial surgery, utilize three-dimensional (3D) planning and virtual simulation on digital and 3D printed anatomical models for the planning of surgical interventions. Anatomically accurate 3D models are created from DICOM (Digital Imaging and Communications in Medicine) datasets of MRI (Magnetic Resonance Imaging) and CT (Computed Tomography) images.

Aims: To implement radiographic image processing techniques used in cardiovascular surgical planning, to create anatomically accurate 3D models of teeth and periodontal defects, for planning and digital simulation of the procedure.

Materials and Methods: 4 patient were included in this examination. High definition Cone-beam CT (CBCT) is taken preoperatively. In order to get the best image quality, cotton rolls are placed in the vestibule to retract the buccal mucosa, and metal artifact reduction algorithms are used if necessary. Semi-automatic and manual segmentation tools are used to select the regions of interest (ROI), in this case teeth and bone. 3D polygon model is generated from the ROIs. Further refinement and preparation for 3D printing is done in CAD (Computer Aided Design) based software. Models are manufactured with selective laser sintering (SLS). Measurements were taken both intraoperatively and, on the 3D printed models at decisive anatomical landmarks.

Results: Models were used in the planning of the surgical procedure. Better understanding of the defect morphology allowed for a less invasive and faster surgical procedure. Knowing the exact 3D defect morphology, the extension of the flap could be kept minimal compared to the extension of the defect.

Conclusions: Digital three-dimensional modelling of teeth and alveolar bone in periodontally involved patients is a new method, that can be utilized in periodontal diagnostics, treatment planning and surgical simulation. However, to validate the accuracy of this method, preliminary methodological studies have to be conducted first.

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Sphingomyelinase-induced enhanced vasorelaxation in db/db mice

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Introduction: Our group investigate the vascular effects of enhanced sphingomyelinase (SMase) activity in a mouse model of type 2 diabetes mellitus (T2DM) and to gain understanding of the secondary signaling pathways involved.

Aims: We aimed to examine the vasoactive effects of of sphingomyelinase (nSMase) on vascular tone in wild-type (WT) and diabetic (db/db) mice.

Methods: Our experiments were performed on the thoracic aorta prepared from adult male WT and db/db mice with wire myograph. In experiments, nSMase (0.2 U /ml), eNOS inhibitor L-NAME (100 μM), selective TP receptor antagonist SQ 29,548 (SQ) (1 μM) and for the examination of NO sensitivity of smooth muscle nitroprusside sodium (SNP) (0.1 nmol / l - 10 μmol / l) was used.

Results: Application of nSMase evoked a complex vascular effect both WT and db/db group. Following precontraction with phenylephrine (PE), nSMase resulted in further contraction in WT vessels. In contrast, after the initial vasorelaxation by nSMase the vascular tone showed a slight increase in db/db vessels. Thus, in db/db vessels, in addition to relaxation, there was a delayed and transient vasoconstriction response too. The vasoconstrictive response in time was similar to that observed in WT vessels but it was less. We aimed to isolate the constrictor and the relaxant components of nSMase-induced changes in vascular tone. The TP receptor antagonist SQ was administered 30 minutes before treatment with nSMase. Blocking the TP receptor not only eliminated vasoconstriction, but the subsequent nSMase treatment induced vasorelaxation in both db/db and WT vessels. This vasorelaxation was significantly higher in db/db group. Finally, we investigated the mechanism of nSMase-induced enhanced vasorelaxation in db/db vessels. This may be due to an eNOS-mediated vasorelaxation or a NO-independent mechanism. Co-administration of the nitric oxide synthase (NOS) inhibitor L-NAME abolished the vasorelaxation in both groups.

Conclusions: These results show that the same pathways - namely the TP-mediated vasoconstriction and the a NO-mediated vasorelaxation - mediate the vasoactive effects of nSMase both under physiological conditions (control group) and in pathophysiological conditions (T2DM).

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Sleep changes and epileptiform discharges in Parkinson's and Alzheimer's disease: 24-hour EEG study

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Background: Sleep changes are common in ND diseases but their pathophysiological significance is uncertain. The occurrence of epilepsy and epileptiform discharges is not known in Parkinson's disease (PD),while increasing amount of data suggests that Alzheimer's disease (AD) may be associated with higher risk of epileptic seizures.

Aims: We aimed to investigate the sleep structure, cognitive dysfunction, prevalence of epileptiform discharges and their relationship in PD and AD patients.

Methods: We included 25 PD (age:68,2+/-7,7y), 14 AD (age: 68,5+/-9,2y) patients and 17 controls (C) (age: 66,1+/-3,97y). All subjects underwent 24-hour EEG recording and neuropsychological tests. We analysed 8-hour recordings registered during the night. The sleep and EEG data were processed by Fercio's EEG Plus and SystemPLUS EVOLUTION. SPSS Statistics was applied for statistical analysis.

Results: We found decreased total sleep time in PD and AD group (PDvsC p<0,001; ADvsC p<0,001), increased N1 stage of sleep in PD (PDvsC p=0,03), increased N2 stage in AD (ADvsC p= 0,042); decreased N3 stage in both PD and AD (PDvsC p<0,001, ADvsC p<0,001) and decreased REM sleep in PD (PDvsC p=0,003).Neuropsychology showed significant reduction in verbal fluency scores in the PD group (PDvsC p<0,001) particularly in semantic verbal fluency (SVF) (PDvsC p<0,001) and in all modalities in AD group. The frequency of epileptiform discharges was significantly higher in patients than in controls (80% in PD, 71% in AD, 23,5% in C; PDvsC p<0,001, ADvsC p=0,003). We found significantly lower semantic verbal fluency scores in the PD group having epileptiform discharges compared to PD patients with negative EEG (p= 0,010).

Conclusions: Since both AD and PD patients suffered from poor night sleep with loss of slow wave sleep and REM sleep reduction was specifically associated with PD, sleep characteristics might help in the differential diagnosis of various forms of neurocognitive disorders. More than half of our patients showed epileptiform discharges.The higher incidence of them in PD and the correlation with reduced performance in semantic verbal fluency may indicate the early involvement of temporal lobe in PD as well. Epileptiform discharges might have a negative effect on the cognitive function of dementia patients representing an important direction for further studies.

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Examination of the Reorganisation of Parvalbumin Positive Perisomatic Innervation in Different Cortical Areas of Dysgenetic Samples of Human Epileptic Patients

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Introduction: Drug resistant epilepsy is often associated with focal cortical dysplasia (FCD). FCD is a neuro-developmental disorder with diverse pathological changes, such as the appearance of abnormal cell types and impaired cortical lamination. Type II FCDs are characterized by the presence of morphologically abnormal cells, including cytomegalic dysmorphic neurons or balloon cells and abnormal glial cells besides the different degrees of disruption of the cortical lamination. In TLE enhanced perisomatic inhibition was found which may increase synchronous firing of principal cells and seizure probability.Therefore, we wanted to investigate, whether changes of perisomatic inhibitory inputs can be found in epilepsy with FCD background, suggesting the possibility of similar patomechanism in different types of epilepsies.

Methods: Surgical samples from FCD patients (FCDIIb, 6 cases: 4 frontal, 1 parietal, and 1 occipital cortex) were compared to control samples of the same cortical regions with short post mortem interval (2-5 h, perfusion fixation) (6 control subjects: 4 samples from frontal, 1 from parietal, and 1 from occipital area). The perisomatic inhibitory terminals contacting principal cells were examined with PV-immunostaining and quantified by PV-NeuN double immunostaining in confocal fluorescent microscope.

Results: The pathological pattern of epileptic patients with FCD was heterogeneous from mostly control-like tissue to disorganized cortical layers and abnormal cells. The current study was performed on samples with control-like layers.Despite the individual variations, comparison of pooled data of PV-immunopositive synaptic coverage of principal cells from control and epileptic subjects showed that the number of PV-immunostained terminals/unit of perimeter is significantly larger in FCD cases.

Conclusions: It is unclear that the amount of PV or PV-stained inhibitory elements are changing due to the adaptive mechanism balancing the excessive electrical discharges, or is a prior pathological alteration that is further increasing by the effects of seizures. However, the change of the perisomatic inhibitory system in both cases could further increase the probability of seizure activity. Therefore, the alteration of perisomatic inhibition of principal cells may be a general mechanism of abnormal network activity, because it was observed in TLE as well.

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The Role of Phytocannabinoids on Monocyte-derived Dendritic Cells Differentiation and Maturation

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Introduction: Dendritic cells (DCs) act as a major link between the innate and adaptive immune systems. Their main function is to capture antigens in the periphery (e.g. the skin) and to present them to T cells, and to thereby act as messengers between the innate and the adaptive immune systems. Nowadays, as the use of herbal active ingredients from the cannabis plant (Cannabis sativa) is gaining in popularity, the use of these products has shown an exponential increase, even in topical formulations that can directly influence the main function of DCs. Up to now more than 100 different cannabinoids have been isolated from the Cannabis plant, which are called phytocannabinoids (PCs). PCs, especially the non-psychoactive compounds, have been shown to have beneficial effects in multiple inflammatory disease models; nevertheless, they were mostly investigated in mouse models and not on human cells.

Methods: In our current work, we investigated the effect of non-psychoactive PCs (Cannabidiol (CBD), Cannabinol (CBN), Cannabigerol (CBG), Tetrahydrocannabivarin (THCV), in regulating responses of monocyte-derived dendritic cells (moDCs) by monitoring changes in their maturation markers.

Results: First, to exclude the possibility of the onset of early apoptotic or necrotic processes, we performed viability tests (PrestoBlue and G6PDH release assay), which demonstrated that our phytocannabinoids did not cause any cell death of moDC. Moreover, we found that our PCs generally induced cell maturation at high concentrations on moDC, whereas LPS-induced maturation was not affected. To support our functional data we showed that Cannabinoid receptor 1 is expressed on the protein level with the help of western blots. Furthermore, we also found that CBG and THCV lead to an increase in the pinocytotic capability of iDCs. We also investigated the effect of PCs on TRPV channels by monitoring changes in the intracellular Ca^{2+} concentration. To explore the secondary messenger systems activated by PC treatment we determined the relative levels of human protein kinase phosphorylation with the help of Proteome Profiler Human Phospho-Kinase Array Kit.

Conclusions: Taken together, our data suggest that PCs may play varied roles on the immunological function of moDCs, and their use as potent anti-inflammatory treatments must be tested extensively.

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Modified oligonucleotide library production for RSV selective aptamer generation

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The respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infection during infancy and late elderhood that often leads to hospitalization. The current treatment for RSV is based on a monoclonal antibody vaccination that is accessible for only a small portion of the patients. Therefore, an affordable and safe RSV treatment is desperately needed.

Aptamers are single stranded DNA or RNA oligonucleotides that rival antibodies in target selectivity and binding affinity, and excel in terms of robustness and cost of synthesis. Aptamers are selected from a randomized oligonucleotide library by the utilization of an iterative, in vitro method. So far, only a tiny fraction of selected aptamers made their way into therapeutics due to various limiting factors including their short half-life in vivo. This shortcoming can be salvaged by application of non-natural nucleotides to increase the nuclease resistance of aptamers. Furthermore, modified nucleotides can also expand the physico-chemical properties of aptamers by introducing hydrophobic side chains.

Our long term aim is to provide hydrophobic side chain possessing aptamers with therapeutic potential of RSV infection.

Here, we present a novel method for creating a DNA aptamer library consisting of hydrophobic side chain carrying oligonucleotides. First, we studied the incorporation efficiency of a tryptamino-uracil analogue (TAdUTP) by several DNA polymerases to identify the most suitable one for modified aptamer library production. To determine if TAdUTP was successfully inserted during PCR, NGS analysis was performed. Using the most promising enzyme, the aptamer library was successfully amplified using emulsion PCR to minimize by-product formation. Melting curve analysis was also applied as a proof of incorporation of TAdUTP nucleotides. In further experimental work, this library will be used to generate RSV selective modified aptamers.

Our protocol yielded a generally applicable method for creating an aptamer library bearing tryptophan-like side chains that can further expand the possibilities of aptamer-target interactions and are also expected to increase the aptamers' in vivo durability.

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Artificial Intelligence Based Colorectal Cancer Screening Decision Support

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Introduction: Hungary leads the colorectal cancer morbidity and mortality statistics worldwide. To reduce the prevalence of this disease a nationwide screening program has been started in 2018. Patients are checked by colonoscopy after producing positive stool test. The elevated number of colorectal biopsies might be prefiltered by an Artificial Intelligence (AI) algorithm.

Aims: The aim is to help pathologists speed up the process of the true negative cases filtration, and AI make diagnostic annotations on the positive slides. As a result the pathologists have more time to devote on the complex cases, and to form improved diagnoses.

Methods: 712 HE stained colorectal biopsy slides were gathered from the archive of the 2nd Department of Pathology Semmelweis University. The slides were scanned via P1000 digital slide scanner (3DHistech Ltd.). Compressed, lossy and lossless datasets were formed after the scanning process. A Convolutional Neural Network (CNN) was trained on 612 slides and 100 slides were used as a testing dataset. The pictures have been pre-processed by dropping the background and cutting the images into 512×512 pixel image patches.

All whole slides were annotated by resident doctors and every single annotation was supervised and validated by board certified pathologists. The annotation process involved: 1) global, textual annotation for general diagnosis, 2) local, textual annotation for tagging specific tissue parts, 3) graphical, pixel level annotation for denoting the area of locally annotated tissue parts.

Results: The performance of the CNN was measured with the Area Under receiver operating characteristic Curve (AUC) score for the local labels. The CNN was least successful for the „suspicious invasion" category with 83% AUC while the best result was achieved for the „tumour necrosis" where the learner reached higher than 99% AUC score. Note, that this is an ongoing project, hence we expect further improvement.

Conclusions: Nowadays the legal environment does not allow to produce only algorithm based medical report without human supervision, signature and accountability. However, the workload on the pathologists might be reduced by a built-in decision support module into the digital pathology software infrastructure, resulting doctors to focus on the complicated cases, and supervise the AI.

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Metabolic adaptation as potential therapeutic targets in therapy resistance

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Introduction: Despite early detection and increased efficacy of treatments of human breast cancer cases, the number of patients and mortality rates are still increasing. Beside developing genetic characterization of the human tumours we have to find new targets to decrease the incidence of tumour recurrence and therapy resistance of gliomas and breast cancers. Furthermore, the intra-tumoural heterogeneity can also support the metabolic adaptation of tumours.

Aims: Metabolic characteristics of human glioma and breast cancer cases and in vitro inhibitor sensitivity of related cell lines were studied to find new options to treat patients with worse prognosis.

Methods: Anti-proliferative effects of several metabolic (mTOR, glycolytic, glutaminolytic, lipid metabolic inhibitors and antibiotics inhibiting mitochondrial functions) drugs were tested using Alamar blue and SRB assays in vitro in glioma and ER+/HER2+/TN breast cancer cell lines. The mTOR signalling and cellular metabolic activity related protein expression patterns were analysed applying Western blot/WES Simple and immunohistochemistry.

Results: mTORC1, mTORC2 complex activity distribution and metabolic enzyme expressions showed individual differences in the studied cell lines. The mTOR inhibitor sensitivity was in correlation with mTOR activity. However, rapamycin/dual inhibitors and BPTES have only moderate anti-proliferative effects in monotherapy. The glycolysis inhibitor (3BP) was the most effective in the majority of breast cancer cell lines correlated to their in vitro glucose dependent growth. Although only the combinations of used drugs have significant growth inhibitory effect both in glioma and breast cancer cells. Additional interesting observations from in situ multiplex metabolic characterisation of human biopsies showed correlations to clinicopathological features, survival data, as well. The multiplex profile analysis (mTOR and metabolic activity) showed that metabolic plasticity might influence tumour prognosis.

Conclusions: mTORC1/C2 activity and in correlation metabolic adaptation potential have to be characterised to understand resistance mechanisms and find new targets for therapy in highly malignant cases including gliomas and breast cancers.

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Actual issues of etiopathogenesis and treatment of inflammatory periodontal diseases

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Introduction: Among all periodontal diseases, 90% are inflammatory periodontal diseases-gingivitis and periodontitis. Inflammatory and destructive periodontal diseases are one of the most common causes that lead to tooth loss in adults and young people, as well as lead to morphofunctional changes in the chewing apparatus, as well as to disruption of the function of the temporomandibular joint, negatively affect the functioning of the digestive organs, affect the aesthetics of the face and speech.

Aims: The search for new methods of complex treatment of patients with inflammatory periodontal diseases remains relevant.

Methods of diagnosis and treatment: The effectiveness of early diagnosis and a comprehensive approach to treatment is reduced due to the lack of timely treatment of patients for routine examinations and sanitation of the oral cavity, asymptomatic course of the inflammatory process and the Erasure of the clinical picture.

According to modern standards, complex treatment should be aimed at the pathogenesis and elimination of individual manifestations, which implies the use of such drugs and their combinations, which have different purposes, to eliminate the inflammatory process, restore the structural and functional properties of the periodontium, increase local and General protection factors.

A comprehensive approach to treatment includes symptomatic treatment (for example, keratolytics), enzymes (trypsin, chymotrypsin), keratoplasty, as an etiotropic treatment, antibacterial drugs are used: ointments, gels, rinses, and pathogenetic treatment, including vitamin therapy, immunostimulants.

The appointment of antibacterial therapy should be appropriate and should be prescribed strictly taking into account the sensitivity of the microflora, in order to achieve the desired result.

In inflammatory periodontal diseases, steroid and non-steroidal anti-inflammatory drugs are often prescribed as pathogenetic therapy.

The use of physical therapy, laser therapy, magnetic and electromagnetic fields also has a positive effect in the treatment of inflammatory periodontal diseases. However, there are both General and local contraindications.

Conclusions: Treatment of inflammatory periodontal diseases should be carried out comprehensively and be as individual as possible for each patient.

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Complications of iliosacral screw fixation

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Introduction: Currently, the most common way to fix the back of the pelvic ring is to use the cannulated screws Gire, J. D. (2018). However, there are risks of damage to the superior gluteal artery, internal iliac artery and nerve branches of the lumbosacral plexus, which is associated with a narrow corridor for installing screws, as well as encountered pelvic dysmorphisms, which requires its identification at the preoperative stage.

Aims: Evaluate rate of complications of iliosacral screw fixation.

Methods: We conducted a retrospective analysis of 43 patients treated on the basis of the Clinical Hospital named after A.K. Eramishantseva from 2017 to 2018 with damage to the pelvic ring, which was performed fixing the sacrum with cannulated screws.

Results: Excellent and good quality of reposition according to the criteria of Tornetta – Matta (1989) was achieved in 38 (88.3%) cases. Satisfactory quality of reposition was achieved in 5 (11.7%) cases. Long-term results 6 months after surgery were monitored in 38 patients and evaluated on a Majeed S.A. scale (1989). Excellent and good results were observed in 35 (92.1%) patients and in 3 (7.9%) patients satisfactory. Among the complications, superficial soft tissue infection was noted in 3 (7%), and neurological complications in 4 (9.3%) cases in the form of sensory and motor disorders that appeared at the stage of outpatient follow-up treatment within 40.6 ± 6.5 days after surgery. In three cases, regression of symptoms was observed against the background of conservative treatment. In one case, in connection with a pronounced, non-stopping pain syndrome, it was necessary to remove the screw, which led to the restoration of sensitivity, but motor disorders remained in the form of the absence of dorsal flexion of the fingers and foot on the ipsilateral side. We used screws with full thread in 25 (58.1%) cases and with partial thread in 18 (41.8%) cases. At the same time, we did not observe a correlation between the occurrence of neurological complications and the use of partially threaded screws.

Conclusions: Despite prolonged using, iliosacral screw fixation are accompanied by various complications. Thorough preoperative assessment and different types of intraoperative navigation should be use. Require further study of the possibilities and results of this technique.

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Value Added Medicines: Potential Benefits and Challenges of Incremental Innovation

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Introduction: Due to the high costs of pharmaceutical research and development (R&D) only a minority of patients can access innovative medicines worldwide. Affordability constraints are becoming an ever-growing problem even for high-income countries. Incremental innovation resulting in value added medicines (VAMs) may offer potential benefits at significantly lower R&D costs.

Aims: The objective of this exploratory research was to identify potential benefits, main barriers and relevant stakeholders of VAM development in the pharmaceutical arena.

Methods: A targeted literature review was conducted to identify the value attributes of VAMs and to recognize current obstacles in their R&D, registration and reimbursement processes.

Results: VAMs may address a wide range of health care needs and problems in an affordable and patient-centric manner. Using established products in new indications (repositioning) could address off-label use of medicines and polypharmacy, whilst the reformulation of existing medicines can improve patient adherence and meet the needs for home and/or personalized health services. However, several barriers prevent society from utilizing the maximum benefits of VAM-related incremental innovation. Generic manufacturers have limited budget and experience to demonstrate the value of new VAMs. Current market exclusivity options do not efficiently exclude free-ridership and do not guarantee return on investment for VAM innovators. Value propositions of VAMs are limitedly consistent with current health technology assessment (HTA) frameworks. Consequently, incremental innovation is neither acknowledged, nor rewarded with differential pricing by payers. As a result, VAMs are often perceived solely as generic medicines by prescribers and high co-payment potentially make them unaffordable for patients.

Conclusions: Within the context of incremental innovation, current HTA and reimbursement practices need to be revised in order to exploit the full societal benefits of VAMs. The introduction of more efficient policies has become essential to guarantee market exclusivity for incremental innovators, to acknowledge a fair price premium based on specific value domains and to ensure the acceptance of low-cost evidence generation methods.

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Anatomical mapping of cariprazine binding sites in the brain

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Cariprazine is a new third generation antipsychotic drug, used in the treatment of scizophrenia, major depression and bipolar disorder. Despite of its clinical success, the underlying mechanism of its action remains elusive. The exploration of the exact anatomical localization of cariprazine binding sites in the brain can improve our understanding of effects of cariprazine, and it may aid the development of new drugs acting in the central nervous system.

We aimed to generate a map of high affinity cariprazine binding sites in the brain. The application of immuno-histochemical markers allows the identification of specific brain regions, cell types and cellular profiles, that are occupied by the drug. To reveal the nanoscale distribution of the drug, we also aimed to perform super-resolution imaging.

To investigate the large-scale three-dimensional distribution of the drug, we registered and reconstructed epifluorescent image sequences of histological slices. For more detailed examination, we generated confocal microscopic and stochastic optical reconstruction microscopy (STORM) super-resolution images. Brain samples from wild type and D3 dopamine receptor knock-out animals were investigated. We found a unique distribution of cariprazine binding sites in the forebrain, which is due to its preference towards D3 dopamine receptor.

In summary, our results reveal new insights into the molecular and anatomical basis of cariprazine actions.

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The Association between Reinforcement Sensitivity and Substance Use is Mediated by Individual Differences in Temperamental Affectivity in Adolescents

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Individual differences in reinforcement sensitivity are associated with substance use, with this link particularly relevant in adolescence; a developmental phase characterized by heightened reward sensitivity and that marks the onset of substance use experimentation. Despite data on pairwise associations among these variables, no comprehensive, systematic investigation of reinforcement sensitivity and adolescent substance use is available and mechanisms through which heightened reinforcement sensitivity predisposes youth to substance use remain unknown.

Aims were to examine whether (1) reinforcement sensitivity, indexed by behavioral approach (BAS) and behavioral inhibition (BIS) system sensitivity, is associated with substance use and (2) associations are mediated by positive (PA) and negative (NA) affectivity.

Participants were N=71 adolescents (Mage=15.01 years, SD=.80; 44% boys).

Findings evince bivariate associations across variables, with greater reinforcement sensitivity associated with greater substance use and greater BAS and BIS associated with greater PA and NA, respectively (all rs>.3 and/or ps<.05). Results further show that the association between BAS and nicotine use (point estimate=-.28; SE=.12; 95%CIs [-.52;-.05]) and BAS and marijuana use (point estimate=-.02; SE=.01; 95%CIs [-.05;-.01]) was mediated by PA but no mediational effect of temperament on the BAS-alcohol use association was observed. The association between BIS and alcohol use was mediated by NA (point estimate=.06; SE=.02; 95%CIs [.02;.12]) but no mediational effect of temperament on the BIS-nicotine or the BIS-marijuana use association was observed. With data collection ongoing, findings will be presented on a larger sample, and clinical (e.g., for personalized prevention) and conceptual implications will be discussed at the conference.

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6870

Integrating transpersonal methods into clinical psychology

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Introduction: Transpersonal psychology is a field or approach of psychology that integrates the spiritual and scientific aspects of the human experience with the framework of psychology. It exceeds the former interpersonal concepts by transpersonal qualities and emphasizes the significance of peak-experiences. In this interactive lecture I will share my experiences about how can a psychologist work with transpersonal approach.

Aims: I will highlight the three phases of transpersonal psychological work in my view. I. Psychodiagnostics II. Peak-experience that fits the client III. Integrating the experiences.

Methods: I will show this process through a qualitative case study.

Results & Conclusions: In some cases transpersonal methods can activate the "inner radar" of the clients and through a peak-experience they can move on from "feeling stucked" more effectively compared to the classical (psychodinamic, cognitive-behavioral, etc.) approaches.

Other therapists' comments and questions are especially welcomed that let us think together in order to integrate the transpersonal approach into clinical psychology.

6986

Horizontal inhibition of the RAS/RAF and RAS/PI3K pathways in BRAF mutant cancer cell lines

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Introduction: Oncogenic mutations in the RAS/RAF and RAS/PI3K pathways play an important role in carcinogenesis and maintenance of tumors. The direct targeting of mutant BRAF as monotherapy has limited efficacy due to acquired resistance, therefore combination is inevitable in targeted therapy. Often additional pathways are affected by mutations, however, it is not clear whether these mutations predict the impact of the combined inhibition of the corresponding pathways.

Aims: In our study, we aimed to determine the effectiveness of the horizontal combined inhibition of the RAS/RAF and the RAS/PI3K pathways in BRAF mutant cells with or without oncogenic mutations in the PI3K pathway.

Methods: Selumetinib and BEZ235 were tested alone and in combination on eight BRAF mutant human cancer cell lines (melanoma, lung and colon) including five with mutations in the PI3K pathway. To assess the effect of these inhibitors on cell lines, short term cell viability, long term colony formation and protein expression examination were performed via SRB assay, clonogenic assay and western blot, respectively.

Results: Selumetinib was more effective on BRAF mutant cell lines compared to cells with BRAF and concomitant mutations from the PI3K/Akt pathway, especially in short term examinations. In contrast, BEZ did not show strong mutation-specific effect on the cells. Combinations of these inhibitors had synergistic effect in a few cell lines based on combination index. BEZ and selumentinib decreased p-S6 and p-Erk levels upon treatment, respectively. Combination treatment either resulted in similar effect or increased the phosphorylation of these proteins. Interestingly, p-Akt level decreased upon treatment with BEZ and especially with selumetinib plus BEZ only in the cell line with highest sensitivity against combination therapy.

Conclusions: These results show that combination therapy can be more effective than single treatment in certain cases. Furthermore, decrease of Akt activation upon combination treatment in the most sensitive cell line suggests that Akt activation may have a key role in the sensitivity for this combinational treatment. However, further investigations are warranted to find predictive markers for effective treatment combinations.

Supervisor: Balázs Hegedűs

7047

The acute phase response is a prominent renal proteome change in sepsis in mice

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Introduction: Septic acute kidney injury (AKI) is the most common form of AKI with poor outcomes. Intraperitoneal (i.p.) injection of bacterial lipopolysaccharide (LPS) is used to model systemic inflammation during sepsis.

Aims: Our aim was to study the temporal profile of the renal proteome changes in LPS-induced AKI.

Methods: Male mice were injected i.p. with LPS or saline (control). AKI was assessed by measuring plasma urea concentration and renal mRNA expression of TNFα, IL-6 and neutrophil gelatinase-associated lipocalin (Lcn-2). Renal proteome was studied by LC-MS/MS (ProteomeXchange: PXD014664) at the early phase (EP, 1.5 and 6 h after 40 mg/kg LPS) and the late phase (LP, 24 and 48 h after 10 mg/kg LPS) of LPS-induced AKI. Renal mRNA expression of acute phase proteins (APP) was assessed by qPCR.

Results: AKI was indicated by increased renal TNFα, IL-6 and Lcn-2 mRNA expression from 1.5 h after LPS administration. Plasma urea concentration was elevated from 6 h and started to decline at 48 h. Renal proteome change was milder in EP than in LP. APPs dominated the proteome changes in LP. The ratio of APPs among all the proteins upregulated at least 4-fold were as follows (APPs/all): EP, 1.5h: 0/10, 6h: 1/10; LP, 24h: 22/47, 48h: 17/44. Lipocalin-2, complement C3, fibrinogen, haptoglobin and hemopexin were the most upregulated APPs. Renal mRNA expression preceded the APP concentration changes with peak effects at 24 h. LPS upregulated renal ceruloplasmin and haptoglobin mRNA expression from 1.5 h, and fibrinogen-α, -β, -γ, serum amyloid A, hemopexin, ferritin heavy chain and inter alpha-trypsin inhibitor 4 mRNA from 6 h. Complement C3 and transferrin mRNA were upregulated only in LP. Albumin mRNA was downregulated in LP.

Conclusions: Gene expression analysis revealed local production of the majority of APPs that commenced a few hours post injection and peaked at 24 h. This is the first demonstration of a massive, complex and coordinated acute phase response of the kidney involving several proteins not identified previously.

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Two Phase Spike Detection using Deep Learning

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Introduction: Automatic identification of the single unit activities is a major part in the analysis of the electrophysiological data recorded from within the central nervous system. Despite multiple unsupervised methods were proposed to detect and sort neural activity, they require hyperparameter tuning for every individual recording.

Aims: The goal was to build a robust, reliable detector which is unaffected by any parameters of the recording site. Our proposal is a new detection system, which utilizes deep learning tools to induce generalization.

Methods: The proposed detection system consists of a pre-detector and a main detector. The electrophysiological data is filtered with the pre-detector, ensuring that the information arriving to the main detector has a higher probability being a positive sample. The pre-detector system is built with low computational cost and high operating frequency in mind, while the main detector with moderate computational cost and operating frequency, keeping the option of a future real-time detector open.

To evaluate the performance of our model we used 5 different recordings and cross-validated them having at every step training and validation samples from 4 datasets, while the remaining one serving as the test dataset.

Results: For evaluating the performance we used the recall, precision and accuracy metrics. We cross-validated our model on small epoch size and selected the best performing configuration which was trained for a longer time, with the following results: 89.59%, 61,40% recall, 88,77%, 50,32% precision and 95%, 81% accuracy for validation and test datasets respectively.

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Intracardiac levels of soluble P selectin is associated with ischemic stroke risk in patients with atrial fibrillation

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Introduction: Atrial fibrillation (AF) is the most prevalent sustained arrhythmia that associates with an increased risk of stroke. Although in AF local, intracardiac hemostasis changes are thought to occur, limited data exists on soluble markers of platelet and endothel activation reflecting the local environment of the left atrium and their association with the risk of ischemic stroke.

Aims: Here we aimed to test whether levels of soluble P selectin (sPsel) and soluble E selectin (sEsel) differ in intracardiac blood samples of patients with AF as compared to a peripheral site. Also, we aimed to determine the association of intracardiac sPsel and sEsel levels with ischemic stroke risk.

Methods: Patient group consisted of 90 patients with paroxismal/persistent AF undergoing elective transcatheter ablation procedure. All medications influencing platelet activity were discontinued at least 10 days prior to procedure. Blood samples were drawn from the femoral vein and the left atrium before the initiation of ablation. Levels of sPsel and sEsel were determined from platelet-free plasma using ELISA method. Patients were grouped according to their estimated stroke risk based on their CHA2DS2-VASc score (0-1 points: "low-risk": group A, n=49 and 2-6 points: "high-risk": group B, n=41). All patients provided written informed consent.

Results: In the whole cohort, elevated levels of sPsel was found in intracardiac and peripheral samples as well. Levels of sEsel showed slight, but significant increase in intracardiac vs. peripheral samples in the whole cohort (mean±SD: 28.0±12.1 ng/mL vs. 26.3±11.5 ng/mL; $p<0.001$). As compared to the group with low-risk, intracardiac sPsel was significantly elevated in the high-risk stroke group (group A: median: 35.6; IQR: 26.6-46.7 ng/mL vs group B: 44.6; IQR: 32.3-60.1 ng/mL; $p=0.01$). Intracardiac levels of sEsel did not differ between groups.

Conclusions: Intracardiac levels of sPsel is associated with the estimated ischemic stroke risk in patients with AF.

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6871

Investigation of the Direct Cardiovascular Protective Effects of a Novel Group of Antidiabetic Agents

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Introduction: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are novel antidiabetic agents that have shown superior efficacy in preventing hospitalization for heart failure (HF) in diabetic, as well as non-diabetic patients. The latter suggests that SGLT2 inhibitors exert direct cardio-protection independently of antidiabetic action, the mechanism of which is incompletely understood but has been proposed to be partially mediated by unspecific inhibition of SGLT1.

Aims: We sought to characterize left ventricular (LV) mRNA expressions of SGLT1 and SGLT2, as well as those of the other two major glucose transporters (GLUT1 and GLUT4) in control and end-stage HF patients with various aetiologies.

Methods: Control LV papillary muscles were harvested from patients undergoing mitral valve repair with otherwise no evidence of myocardial disease or LV functional alteration (Control, n=9). An overall of 44 LV myocardial samples from patients with end-stage HF undergoing heart transplantation were obtained, with the following subgroups: idiopathic dilated cardiomyopathy (DCM, n=12), ischemic heart disease with or without type 2 diabetes (IHD+T2DM, n=11; IHD, n=14) and hypertrophic cardiomyopathy (HCM, n=7). mRNA expressions were evaluated by quantitative real-time polymerase chain reaction (qRT-PCR). Echocardiography-derived LV end-diastolic diameter (LVEDD) and LV ejection fraction (LVEF) were registered prior to surgery.

Results: We found no expression of SGLT2 in the myocardium. Compared to controls, patients with DCM, IHD and IHD+T2DM had a two-fold increase in LV SGLT1 mRNA expression, while in HCM patients SGLT1 expression was unchanged. LV SGLT1 expression significantly correlated with LVEDD ($r=0.493$, $P<0.001$) and LVEF ($r=-0.477$, $P<0.001$). GLUT1 was also significantly upregulated in HF patients (except in HCM) but correlated significantly only with LVEF ($r=-0.326$, $P=0.021$). GLUT4 expression was unchanged.

Conclusions: Left ventricular SGLT1 mRNA expression shows aetiology-dependent alterations in end-stage HF patients and correlates strongly with LVEDD and LVEF, indicating a possible involvement in adverse cardiac remodelling. HF patients with higher LV SGLT1 expression might derive more benefit from SGLT2 inhibitor therapy.

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Effects of modulated electro-hyperthermia on triple negative mouse breast cancer with differential metastatic potential

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Introduction: Breast cancer is the most common malignancy among women. In triple negative breast cancer (TNBC) lack of receptors excludes hormone- and HER2-targeted-therapies. Modulated electro-hyperthermia (mEHT) is a possible complementary treatment. We investigated two distinctly progressing isogenic mouse TNBC clones.

Aims: Our aim was to investigate the effects of modulated electro-hyperthermia in non-metastatic and highly metastatic triple-negative mammary carcinoma bearing mouse models.

Methods: 4T1 (more aggressive) and 4T07 (less aggressive) cells were inoculated orthotopically into female BALB/c mice. Tumor growth was monitored by caliper and ultrasound (Phillips Sonos 5500). Animals were randomized into sham (n=10) and mEHT (n=11) treated groups 6 days after inoculation. Animals received mEHT treatment 3 times in every 48 hours with Labehy 200 (Oncotherm Ltd.). On day 12, animals were euthanized, tumors were dissected, weighed and processed. Histology slides were digitalized and evaluated with HistoQuant of Caseviewer (3DHistech Ltd.) Tumor Destruction Ratio (TDR) was evaluated on cleaved caspase 3 and H&E stained slides. Heat-shock protein (HSP70) and Ki67 proliferation marker were evaluated (relative mask area). Immune-related markers (T-lymphocyte: CD4, CD8) and immune-checkpoint molecules (PD-1, PD-L1) were measured by quantitative PCR normalized to GAPDH.

Results: mEHT treatment reduced the size and weight (sham: 199.7± 17.35 mg vs mEHT: 139.6 ± 12.07 mg, $p<0.001$) of 4T1 but not 4T07 tumors (sham: 91 .40± 33.14 mg vs mEHT: 102.3± 39.77 mg, ns). mEHT increased TDR and HSP70 in all treated mice. Ki67 strong positive nuclei were not different from sham mice in either model. Markers of immune infiltration and immune checkpoint inhibitor molecules had an order of magnitude lower expression in the 4T1 model. 24 hours after the last treatment mEHT reduced both tumor cell- and infiltrating lymphocyte-count. However, both infiltrating immune cells and checkpoint molecules increased compared to sham, if tumors were removed 96 hours after the last treatment suggesting a possible immune-stimulatory role of mEHT.

Conclusions: 4T07 tumors grew slower supporting that they have a less aggressive phenotype. The effect of mEHT treatment on TNBC was related to heat-shock response and was more effective against the more aggressive 4T1 type TNBC.

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Supervisor: Péter Hamar

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Long-term all-cause mortality of patients after De novo vs. Upgrade Cardiac Resynchronization Therapy

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Introduction: However, patients with a conventional pacemaker (PM) or implantable cardioverter defibrillator (ICD) can develop heart failure due to the right ventricular pacing, recent guidelines do not provide a comprehensive recommendation for cardiac resynchronization therapy (CRT) upgrade.

Aims: To assess long-term clinical outcomes of patients who were upgraded to CRT from a PM or ICD and compared to those with De novo CRT implantation.

Methods: Patients, who underwent CRT implantation based on the current guidelines at our clinic between 2000-2018 were registered. Primary endpoint was all-cause mortality, secondary endpoint was echocardiographic response 1 year after the implantation.

Results: Overall 2525 patients were included in our registry of which 1977 (78%) were De novo and 548 Upgrade (22%) patents. Regarding the baseline clinical characteristics of upgrade vs de novo groups, upgrade CRT patients were older, had higher percentage of prior myocardial infarction (MI), atrial fibrillation (AF), higher creatinine level, wider QRS and they were more frequently males. From 2525 patients 1085 (55%) de novo, and 346 (62%) upgrade patients reached the primary endpoint during the mean follow up time of 4 years. By univariate analysis all-cause mortality was 41% higher in the upgrade group compared to de novo group (HR 1.41; 95% CI 1.23-1.61; $p<0.001$). After adjusting for relevant clinical parameters multivariate Cox regression analysis showed similar outcome in the two groups (HR 1.22; 95% CI 0.92–1.41; $p=0.37$). When echocardiographic response was investigated, favourable improvement was found in the de novo CRT group 1 year after the procedure (ΔLVEF De novo 9% vs Upgrade 5%; $p=0.02$; LVEF response de novo 63% vs Upgrade 54%; $p=0.03$). Regarding peri-procedural complications, pneumothorax occurred more frequently in de novo group, while lead disfunction and pocket infection occurred more frequently in after CRT upgrade.

Conclusions: CRT upgrade patients show higher risk of all-cause mortality compared to de novo CRT group, which is derived from co-morbidities. After adjusting for relevant clinical parameters, patients after CRT upgrade or de novo implantation showed comparable outcome. Furthermore, we found higher echocardiographic response rate in de novo CRT group. However, higher complication rate was associated with the CRT upgrade procedures.

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Penetrance of the CFTR 5T allele in congenital bilateral absence of the vas deferens

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Introduction: Congenital bilateral absence of the vas deferens (CBAVD) is responsible for 2% of male infertility. One third (25-40%) of patients with CBAVD are compound heterozygous for the CFTR 5T (c.1210-7_1210-6delTT) variant and another variant in trans. The 5T allele, with a MAF of 3% in the general European population, causes the loss of exon 10 in 95% of mRNA.

Aims: Using a formerly developed population-genetic algorithm we aimed to assign the penetrance of the 5T variant.

Methods: We collected phenotype and genotype data from 3279 patients with biallelic CFTR mutations from PubMed. The penetrance (P) of the 5T variant was calculated by comparing its allele count (AC) to the AC of the loss-of-function (LOF) variants in the European non-Finnish patient population and in the gnomAD as P=(AC5T/ACLOF)patient/(AC5T/ACLOF)gnomAD, tested by Fisher's exact test.

Results: We found the 5T allele in 339/3279 (10.34%) patients, trans-associated to LOF mutations in 187/635 (29.3%) of the patients with CBAVD. None of the compound heterozygous patients with the 5T allele (without other variant in cis) developed CF. We found the penetrance of the 5T variant to be 4.3% (p=5x10-389).

Conclusions: According to our penetrance estimation, for a couple with heterozygous CFTR 5T allele in one parent and a LOF variant in another, the risk of a son being affected by CBAVD is 1% (25% x 4.3%).

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The Role of Neuropeptide Y in Obese Patients with Bronchial Asthma

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Introduction: The obesity-asthma phenotype is particularly difficult to treat, while its prevalence is increasing. In recent years, attempts have been made to analyze the presence and nature of the relationship between neuropeptide Y (NPY) and asthma. Several studies have reported that certain NPY genotypes are associated with asthma, and Y1 receptors of NPY play an important role in allergic airway inflammation.

Aims: to analyze the role of serum levels of NPY in obese asthmatic patients during periods with no exacerbations.

Materials and methods. 113 patients (23.89% men and 76.11% women) participated in the study. Spirometric data, body mass indexes, results of an asthma control test (ACT) were analyzed. Three groups of patients were formed according to their weight. The levels of leptin, adiponectin, neuropeptide Y (NPY), and general oxidative damage were measured in all patients.

Results: Obese asthmatic patients had lower asthma control than overweight and normal body weight patients. Levels of leptin and NPY were significantly higher in the group of patients with obesity ($p<0.05$). The NPY levels had an inverse correlation with such spirometry parameters as VC index ($r=-0.75$; $p<0.05$), FEV1 ($r=-0.57$; $p<0.05$), FEF 25%, ($r=-0.53$; $p<0.05$); FVC ($r=-0.45$; $p<0.05$), Tiffno index ($r=-0.32$; $p<0.05$), FEF 50% ($r=-0.41$; $p<0.05$), PEF ($r=-0.38$; $p<0.05$). At the same time, NPY levels inversely correlated with ACT ($p<0.05$). The positive correlation with the level of total oxidative damage was noted ($p<0.05$).

Conclusions: In patients with asthma and obesity, a higher level of NPY is observed, having an inverse correlation with spirometric parameters, asthma control (according to ACT) and a positive correlation with the level of general oxidative damage, which indicates a possible pro-inflammatory effect of neuropeptide Y, contributing to an unfavorable course of bronchial asthma. Thus, further studies are required to establish the nature of the relationship between NPY and BA exacerbations, as well as the mechanism of NPY influence on BA pathogenesis.

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7124

The effects of sleep duration on atrial fibrillation and coronary artery disease

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Aims: Previous studies have evaluated that short and long sleep duration (<5 hours and >9 hours) is associated with increased risk of cardiovascular diseases including hypertension, coronary artery disease (CAD), heart failure, stroke, and all-cause mortality. Therefore, we aimed to determine the effect of sleep duration on the presence of atrial fibrillation (AFib) and CAD in patients who underwent cardiac CT angiography.

Methods: We retrospectively included patients from 2013 until 2019 who arrived for left atrial CT angiography before catheter ablation due to AFib and patients with suspected CAD who underwent coronary CTA. We registered the duration of average sleeping hours as part of our self-reported anamnestic questionnaire. We divided the patient population into groups based on the presence of Afib and CAD.

Results: We had a patient population of 2937 patients. Since 335 prefered not to answer questions regarding sleeping hours, therefore we analyzed the data of 2602 participants. Mean age of the patients were 59.2±12.5 years; 37.6% were female. Average sleep duration was 7.0±1.4 hours. We did not find any significant difference in sleep duration between those with and without AFib (6.9±1.6 versus 7.0±1.3 hours; $p=0.33$). When analyzing the effect of sleep duration on the presence of CAD, we did not find difference in sleeping hours between those with and without CAD (7.0±1.3 versus 6.9±1.1; $p=0.61$).

Conclusions: In our analysis, self-reported sleep duration did not differ significantly between those with or without Afib or CAD.

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Characteristic load-elongation behavior of weak electrospun fiber texture

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Electrospun nano- and micro-fiber networks have attracted an intensive research area over the past decades, due to their high mechanical performances and low weight. However the electrospinning technology is well developed, little is known on the deformation mechanism of electrospun fiber networks. For biomedical applications damage accumulation, fraction and nonlinear mechanical behavior are important characteristics of the fibrous materials.

The main purpose of this research is to establish the characteristic load-displacement behavior of weak, planar, randomly oriented fiber bundles.

The fundamental mechanical properties were studied by unidirectional strain-controlled stretching on fibrous electrospun networks prepared from polysuccinimide, which is the anhydrous form of poly(aspartic acid), so the networks are biocompatible and biodegradable, ideal for several biomedical applications like scaffold for cell proliferation and artificial extracellular matrix. 2D randomly oriented fibre mats were prepared using a home-made electrospinning instrument.

The experimental loading curve shows a symmetrical parabolic type dependence at large scale and saw tooth-like force-extension behavior at small scale. The damage formation was quantified by determining the number and the magnitude of abrupt force drops. The experiments evidenced that damage evolution is a consequence of strain induced random events, which may caused by failure and rupture of fibers. Based on the Fiber Bundle Model, the loading force can be directly related to the cumulative probability distribution function of failures, appearing on the loading curve as abrupt force drops during extension. We estimated the cumulative empirical distribution function of rupture force and analyzed them on the basis of Weibull distribution. The shape parameter of distribution proves that, the rupture force of electrospun fiber bundles follows the exponential distribution function.

This experimental technique can provide the initial stiffness as well as to explain load bearing capacity of several synthetic and biological textures that are composed of fibers. It also suggests improved probabilistic approaches to the development of more sophisticated statistical models.

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Spirituality at the End of Life

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Introduction: The possible health benefits of spirituality at end of life care became in focus in the last decades. Studies pay special attention to the relation between well-being, quality of life, coping, anxiety, depression, fear of death, suicide and spirituality.

Spirituality has multidimensional nature and has been defined in different ways. The central of most definitions are ultimate meaning of life and relationship to self, others, nature and the scared. Spirituality is often used interchangeably with phrase such as religion in many scientific studies. Despite this other researcher make strict difference of the define of these terms, most scholars agree that spirituality and religion are related constructs.

Aims: Explore the relevancy of spirituality and changing of spirituality to end of life care and the uniqueness of the Hungarian cultural approach to spirituality.

Methods: A semi-structured interview -based qualitative research study will be conducted by terminal patient in hospice care. I will interview 30 hospice patients in Budapest Hospice House, interviews will last from 30 minutes to 1 hours depends on patient's condition. Interviews would focus on two topics of discussion: 1. their spiritual lives and experiences now; 2. how they experienced their spirituality in earlier life.

Results: The examination is still in progress, the study might demonstrate evidence that confrontation with their own vulnerability raises in some patients the opening to spirituality or change his/her belief.

Conclusions: The knowledge of studies about spirituality is essential in ensuring that hospice team members are aware and able to recognize and respond to spiritual needs of patient.

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6980

The prognostic significance of the early ventricular fibrillation in acute myocardial infarction presenting with and without ST-segment elevation

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Introduction: The prognostic significance of an early ventricular fibrillation (EVF) due to acute coronary syndrome needs further investigation in both STEMI and NSTEMI populations. In our pilot study we found that EVF increases the 30-day mortality. Between 30 days and 1 year an additional worsening of mortality rate can be observed among NSTEMI patients.

Aims: The aim of our study was to extend our previous investigation about the factors influencing the prognosis of patients presenting with STEMI/NSTEMI after EVF and to compare the clinical characteristics of the VF and non-VF population.

Methods: In our retrospective study 12270 consecutive patients were investigated, among whom 547 were VF positive. 30-day and 1-year survival data were examined in patients who were admitted due to NSTEMI (n=6840) and STEMI (n=5430).

Results: Three-vessel coronary artery disease including LM involvement and PCI of more than one main vessel was associated with worse prognosis in STEMI patients only. Significant differences in 30-days and 1-year mortality could be demonstrated in patients with vs. without EVF ($p<0.0001$). A higher ratio of STEMI cases, diabetes, reduced ejection fraction and kidney function were found after EVF ($p<0.0001$). Among EVF positive cases the severity of the acute event (heart- and kidney failure, on-site CPR, cardiogenic shock, respiratory treatment) had a significant impact on the 30-day and 1-year mortality in patients with STEMI. The one-year mortality of cardiogenic shock patients proved to be extremely high in both STEMI and NSTEMI populations with EVF. In terms of survival NSTEMI compared to STEMI showed worse outcome after an EVF.

Conclusions: The presence of EVF worsens prognosis in patients initially surviving STEMI and NSTEMI. The present guidelines do not offer appropriate rules to select and treat these subjects. Further risk stratification may change the current guidelines regarding a better patient selection, among others who may benefit from early ICD implantations.

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Intratumoral Cisplatin Measurement by LA-ICP-MS: an Innovative Technique to Assess the Clinical Impact of Chemotherapeutic Drug Distribution in Malignant Pleural Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM) is a devastating malignancy with dismal prognosis. In MPM the systemic chemotherapy is based on cisplatin. Although platinum agents have been applied for decades to treat solid tumors, there is limited information about the concentration and spatial distribution of platinum (Pt) in human MPM.

Aims: We aimed to analyze the spatial distribution of Pt by Laser Ablation-Inductively Coupled Plasma-Mass Spectrometry (LA-ICP-MS) in MPM tissues and in paired serum samples. The study attempts to clarify if insufficient drug penetration in the tumor tissue is a major component of platinum resistance in MPM.

Methods: We analyzed the spatial distribution of Pt in the surgically removed tumor samples (n=27) after induction chemotherapy (CHT) with LA-ICP-MS, which enables 2D imaging. These results were compared with clinico-pathological features. In addition, microvessel density (MVD) and ratio of apoptotic cells have also been investigated. With the 2D imaging we examined the heterogeneity of the tumor tissue in correlation with drug distribution. We used collagen staining to label the fibrotic tissue compartments. Additionally, we also measured the blood Pt levels and sought for potential correlations with the tissue concentrations and with the above-mentioned parameters as well.

Results: We found that the spatial distribution of Pt was heterogenous in the tissue samples. Large collagen-rich fibrotic areas had high Pt levels while the tumorous compartment contained relatively low concentrations. There was no correlation between serum and tissue Pt concentrations, but the circulating drug concentrations negatively correlated with the time between the last CHT cycle and sample collection. We could not observe any correlation between tissue/serum Pt concentrations and age and number of CHT cycles received, neither between tissue MVD and Pt concentration. The Pt content of tumor tissue had no prognostic significance.

Conclusions: By using an innovative technique (LA-ICP-MS) for lateral trace element distribution analysis, we are the first to demonstrate heterogenous Pt levels in human MPM tissue samples.

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Investigation of Fatty Acid Desaturation and the Associated Electron Transfer Chain

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Introduction: Lipotoxicity has received a growing attention in the past decade, and it became evident that elevated free fatty acid (FFA) levels are deleterious to a wide variety of cells and tissues. Recent publications show, that the accumulation of triglycerides might have a protective role. However, during the synthesis of triglycerides, normally, a saturated fatty acyl group is attached to the first position of glycerol and an unsaturated fatty acyl group occupies the second position. Thus, the surplus of saturated or trans fatty acids (FAs) may block the triglyceride synthesis. Increased levels of saturation of membrane lipids can induce ER stress and hence it may cause severe malfunction of cells or even apoptosis. During the metabolism of FAs, FA-CoA molecules can be elongated or desaturated by ER-associated enzymes. In humans, one of the key enzymes of desaturation is the stearoyl-CoA desaturase 1 (SCD1), which inserts a cis double bond at the Δ9 position into saturated FAs. SCD1 receives electrons from NAD(P)H via cytochrome b5 reductase and cytochrome b5. Ncb5or is an oxidoreductase, which has a cytochrome b5 reductase like and cytochrome b5 like domain as well, thus it may also play a role in FA desaturation. In case of an oversupply of saturated FAs, expression of SCD1 or/and the associated electron transfer proteins may be induced to alleviate the toxic effects. Because of the presence of an alternative electron transfer chain, and the protective role of Ncb5or against palmitate toxicity, one may assume that there is a need for an enhancement of the chain.

Aims: In this work, we aimed to investigate the influence of the expression level of each protein involved in the desaturation process on the desaturating activity.

Methods: We overexpressed SCD1, CYB5R, CYB5, NCB5OR, or their combinations in human HEK293T cells and analyzed the FA profile with our own developed and validated gas chromatography-flame ionization detection method with special attention on the alterations in the unsaturated/saturated ratio.

Conclusions: Our results reveal that the level of the desaturase enzyme defines the cells' capacity to desaturate FAs in our model, and the expression levels of the associated electron transfer chain components do not have any obvious impact on FA desaturation in a wide range. The physiological and pathological role of an alternative electron transfer still remains to be elucidated.

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Investigation of the cognitive perfomance in adult Attention Deficit/Hyperactivity Disorder and Borderline Personality Disorder using the CANTAB neuropsychological software

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Introduction: In our reserach we study the cognitive performance and the phenomenon of impulsivity, which are hypothetised potential endophenotypes in psychiatric disorders. We investigated patients with Adult Attention Deficit/Hyperactivity Disorder (aADHD) and Borderline Personality Disorder (BPD), because impulsivity is a main symptom for both diagnoses, however the etiology is different.

Aims: The aim of our presentation is to summarize two studies, with the aim to identify potential endophenotypes and their genetic associations. The first study compared the cognitive performance and the level of impulsivity in aADHD, BPD and control groups (CG). The second study focus on the genetic association of impulsivity, using a dimensional approach in an aADHD sample. The gene that we investigated, was the norepinephrine-transporter-gene (NET/SCL6A2).

Methods: Three groups were included in the first study: aADHD (31 patients), BPD (24 patients) and control groups (39 participants). The diagnosis in the patient groups were set up according to DSM-5 criteria. To characterise the cognitive performance the CANTAB (Cambridge Neurocognitive Test Automated Battery) software was used. Participants were recruited from the Department of Psychiatry and Psychotherapy, Semmelweis University. The genetic associtation study included 148 aADHD patients. The three investigated single-nucleotide polymorphisms (SNP) of SCL6A2 were the following: in the promoter region rs28386840, and rs2242446, and the intronic rs3785143. For clinical phenotype a subjective measurement was used: the Conners' Adult ADHD Rating Scale (CAARS). To investigate data, GLM analyses were performed.

Results: We found several differences in cognitive performance between patients and the CG. In working memory, working memory capacity, and response inhibition domains BPD and aADHD groups performed poorer than the CG. In the second study we found significant associations of impulsivity and all of the examined NET polimorphysms. The rs3785143 showed a relationship not only with impulsivity but also the severity of other ADHD symptoms.

Conclusions: Based on our results, we found that CANTAB is able to give accurate phenotypic data which can be used as potential endophenotypes. Our further plans is to increase the number of samples, and begin to describe the genetic basis of CANTAB-based cognitive differences.

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Bivariate Focus-Based Multifractal Formalism: A Novel Method for Estimating the Multifractal Dynamics of the Resting State Functional Connectivity

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Introduction: Lately, examining resting-state (rs) brain network dynamics – via functional connectivity (FC) of interacting regions – has been a growing field of neuroscience. Such investigations can be also carried out by electroencephalography (EEG) that captures the underlying rapid neuronal dynamics from functionally coupled cortical areas. As a result of previous developments, the interplay between resting-state FC and scale-free brain dynamics could be characterized with the aid of bivariate multifractal (MF) analytical tools. However, a robust characterization of the scale-free nature of the coupled EEG-fluctuations is still lacking. This scarcity gave birth to the bivariate focus-based multifractal formalism (BFMF).

Aims: The purpose of this work was to demonstrate the valuable features of this novel method by investigating the presence of MF dynamics as well as their spatial organization in the rs EEG.

Methods: EEG of 12 subjects was recorded during 5 minutes of eyes closed in rs using a 62-channel BrainAmp. Based on the covariance between each pair of EEG signals, calculated for a set of time scales, BFMF estimated the scale-free exponent function H(q) for various order parameters ($-15 \leq q \leq 15$). From H(q), a measure of long-term memory (H(2)) and a non-linearity parameter ($\Delta H15$) were obtained for every time series pair. Diverse tests were realized for the verification of the true multifractality in each pair. Having the EEG channels grouped into 6 resting state networks (RSNs), the MF measures captured connectivity within and between RSNs. Kendall's W examined the subject concordance while individual t-tests examined the variability of within and between RSNs connections. Finally, the MF functional networks were compared with networks constructed using Pearson correlation and mutual information (MI) as FC estimators.

Results: Most of coupled EEG-dynamics showed true MF character. Regional variability of connections as well as subject agreement was found to be significant. When compared to the Pearson and MI constructed networks the MF networks differed in their architecture.

Conclusions: This study provides insight into the spatial organization of brain networks by utilizing BFMF, a method capable of capturing the scale-free coupling between EEG time series. BFMF could provide the clinical neuropsychiatric studies with new, much needed, biomarkers.

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Protective role of Sigma-1 receptor in corneal fibrosis

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Introduction: Corneal scarring is a pivotal cause of visual impairment, which accounts for over 4% of blindness worldwide with 2 million cases each year. Scarring of the corneal tissue, also known as fibrosis, commonly occurs after infection, postsurgical complications, and response to injury or metabolic disease. Corneal fibrosis is characterized by the presence of myofibroblasts and deposition of extracellular matrix components. Currently, treatment options for cornea scarring are limited and the only effective treatment is corneal transplantation.

Our research group proved that activation of Sigma-1 receptor (S1R) by fluvoxamine (Flu) has antifibrotic effect in the kidney and lung, therefore we hypothesize that Flu could have a protective role in the prevention of fibrosis in the cornea as well.

Aims: To optimize the methods and culturing techniques of primary fibroblast cells from the cornea. To detect the presence of S1R in primary corneal fibroblasts and to measure the effect of Flu on platelet-derived growth factor (PDGF-BB) or transforming growth factor-beta1 (TGF-β1) -induced proliferation and migration of corneal fibroblast cells.

Methods: Cells were treated with PDGF-BB or TGF-β1 to induce fibrotic process. S1R (localization), F-actin and α-SMA (for morphological changes/cytoskeleton rearrangements) were detected by immunofluorescence staining. Cell proliferation was evaluated by thiazolyl blue tetrazolium bromide (MTT) method. Cell migration were followed by wound healing assay.

Results: Primary corneal fibroblast cell culturing method was optimized in three species (human, rat and mouse). S1R is localized in the cytosol of corneal fibroblast cells. PDGF-BB and TGF-β1 increased the proliferation and migration of corneal fibroblast cells and promoted the transformation of fibroblasts to myofibroblasts. These effects were inhibited by Flu.

Conclusions: Flu reduces cytoskeletal rearrangement, myofibroblast transformation and migration, indicating its antifibrotic properties. Our preliminary results propose that Flu could be a potential candidate for development of a novel drug reducing fibrosis in the cornea. However, further molecular experiments (such as investigating inflammatory and apoptotic pathways) and in vivo animal models are needed to reinforce these results.

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New perspectives on non-culture based diagnostics of community-acquired sepsis: a pilot study from bedside to benchmark

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Introduction: Community-acquired sepsis (CAS) is a potentially fatal systemic reaction to infection starting ≤72 hours after hospital admittance. Clinical and microbiological data concerning CAS, especially among Hungarian patients are sparse. Furthermore, the causing agents of CAS are not identifiable by routine microbiological methods in some patients.

Aims: Our aim was 1) to identify adult CAS patients from a large cohort who did not have any causative agents indentified during hospital stay by routine microbiological methods (culturing, PCR, serology), 2) measure the rate of this phenomenon and 3) assess the usefulness of 16S rRNA metagenomic sequencing analysis in the identification of CAS etiologies.

Methods: This pilot study had 2 phases. In the first phase, a retrospective cohort study was done among a cohort of adult CAS patients admitted to a national referral center during 2016. In the second phase, whole blood samples were taken from randomly selected CAS patients for 16S rRNA metagenomic sequencing analysis. Patients with possible healthcare associations were excluded, sepsis definitions and severity were given according to ACCP/SCCM SIRS-criteria.

Results: In the first phase, 206 patients were included (mean age 58.4±20.4 years, 56.7% female). Estimated incidence of CAS was 285 / 10.000 admittances per year. 66/206 (32.0%) cases were severe sepsis, and 59/206 (28.6%) were septic shock. The identified causative organisms were mainly E. coli (56/216, 25.9%), S. aureus (14/216, 6.5%) and S. pneumoniae (15/216, 6.9%), and in quarter of all cases, no organism could be identified (54/216, 25.0%). Bacteraemia was proven in half of cases (104/206, 50.5%). In the second phase, blood samples of 15 patients are being analysed at the moment. 5 patients did not have any causative organisms identified.

Conclusions: A relevant number of CAS patients do not have a causative agent identified by routine microbiological methods. We hope that 16S rRNA metagenomic sequencing analysis might have a role in the identification of these infections.

The first author is a granted PhD student of the New Excellency Scolarship.

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The reason of altered methylation pattern in pituitary adenoma

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Introduction: DNA methylation is one of the widest studied epigenetic motifs, which assign the chromatin structure and gene activity. DNA methylation is a reversible process, methylation drived by DNA methyl transferases (DNMTs) and active demethylation by TET enzymes. The two process cofactors are UHRFs. In cancerous cells the altered methylation level is general, and the interdependence between proliferation and methylation status is known for a long time.

Aims: We were intrested to clear the background of the proliferation dependent methylation status both in vitro and human Pituitary Neuroendocrine tumour samples.

Materials and Methods: We growed two rodent pituitary adenoma cell lines: GH3 and Rc-4B/C (according to ATCC instructions), and treated them with decitabin (dissolved in DMSO). We analyzed the cell viability and the methylation- demethylation status with HPLC-MS/MS. To analyze some epigenetical key enzymes, we isolated total RNA from 44 pituitary adenoma samples (29 gonadotroph, 12 somatotroph and 3 corticotroph – according to 2017 WHO classification), and these gene expression were measured with Real-Time qPCR. Data were analyzed with Statistica software 12.0.

Results: The agent inhibits the cell proliferation (GH3 $p<0.0001$; Rc-4B/C $p<0.0001$). We examined decreased DNA methylation level (GH3 $p<0.0001$; Rc-4B/C p:0.077), and increased demethylation level (GH3 $p<0.0001$; Rc-4B/C p:0.019).

In human RNA sampels we estabilished stronger TET (1,2 and 3), and UHRF1 expression in high proliferating tissues, but we did not observe any tendency in UHRF2 or DNMT1 gene activity.

Conclusions: The inhibition of DNA methylation led to decreased cell proliferation in vitro. In human samples next to high proliferation and low demethylation level (as we previously presented) we detected increased TET (1-3) and UHRF1gene activity. These results suggested that there is a feedback mechanism between DNA methylation–demethylation status and the regulator protein expression.

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Role of the Proton/Water Channel in the Physiological and Reactive Oxygen Species Generating Activities of the Human Dihydrolipoamide Dehydrogenase

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Introduction: Human dihydrolipoamide dehydrogenase (hLADH, hE3) deficiency is an often lethal genetic disease caused by inactive or partially inactive hE3 variants. In order to reveal the molecular pathomechanisms of hE3-deficiency, recently we determined the crystal structures of the wild type hE3 and seven of its pathogenic variants. The Glu332 and Arg460 residues were found to possess two alternative conformations in the wild type hE3 and therefore were suggested modulating the geometry and polarity of the so-called H^+/H_2O channel. Altered properties of the H^+/H_2O channel, including loss of conformational flexibilities of the above-mentioned residues, were associated with the pathomechanisms of the D444V-, I445M-, R447G- and R460G-hE3 variants.

Aims: Specifically designed hE3 variants were aimed to be subjected to functional studies to clarify the potential roles in catalysis of the Glu332 and Arg460 amino acids.

Methods: The LADH and superoxide-generating activities of the Glu332 or Arg460 substituted hE3 variants were determined by monitoring the NADH concentration or cytochrome c reduction via spectrophotometry. Results were evaluated taking into account structural and functional data on various pathogenic hE3 variants.

Results: The E332A substitution lowered the LADH activity by 43 and 39% in the forward and reverse catalytic directions, respectively. The enzymatic activity was even more compromised by E332D in both catalytic directions, but was more retained in E332Q-hE3. The R460A, R460E, and R460K substitutions affected the LADH activity dissimilarly in the reverse direction (68, 51, and 161%, respectively), but in a more similar fashion and only modestly in the forward direction (89%, 81%, and 72%, respectively). From all the investigated variants, only E332Q-hE3 exhibited enhanced superoxide generation.

Conclusions: Glu332 likely contributes to the stabilization of the substrate or a reaction intermediate in the active site and/or H^+/H_3O^+ translocation in the course of the catalytic cycle; altered conformation of the Glu332 residue could therefore be associated with the molecular pathomechanisms of the D444V-, I445M-, and R460G-hE3 variants. The side chain of Arg460 is likely important for maintaining the integrity of the active site and/or modulating the redox potential of the FAD prosthetic group by stabilizing two α-helices.

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Association between gut microbial diversity and various cardiovascular imaging phenotypes

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Introduction: The importance of the gut microbiome is growing, because the composition of the gastrointestinal microbiome greatly influences the development, process and therapy of diseases. The role of lifestyle in this process is unclear, as well as how it modifies the heritability of the diseases studied.

Aims: To find the associations between intestinal microbiome diversity, environmental factors and various cardiovascular imaging phenotypes.

Methods: 114 twins (mean age 53.4±14.4 years, 59% female, 55 monozygotic, MZ and 2 same-sex dizygotic, DZ pairs) recruited from the Hungarian Twin Registry were involved who met at least one of the following criteria: (1) carotid and femoral ultrasound examination revealed increased intima-media thickness (IMT) or plaque; (2) twins discordant for obstructive sleep apnea (OSA), osteoporosis, fatty liver, thyroid nodule, cervical or lumbar discus bulging or hernia; (3) MZ twins diagnosed with Hashimoto thyreoiditis or OSA. A special stool sampling container was mailed and received from each participant. After DNA extraction, library construction was performed specifically for the V3-V4 hypervariable region of microbial 16S rDNA. Next, the microbiome composition of the samples was determined using the QIIME software. In addition, questionnaires were completed to assess health status, dietary habits and physical activity. After getting all the data a comparison with the various cardiovascular imaging phenotypes, including local arterial stiffness, IMT and plaque burden will be possible.

Results: Until the end of January 2020, 100 participants returned their stool samples from 34 cities throughout the country, mainly (56 subjects) from Budapest. The youngest twin pair was 25 and the oldest was 76 years old. BMI of the participants proved to be variable (mean 26±4.5 kg/m2). 13% of the twins smoked, 46% have been diagnosed with hypertension and 6% with diabetes. All the twins with OSA (48 subjects) and 93% of twins having increased IMT or plaque burden returned their samples.

Conclusions: This is the first Hungarian twin study to assess gut microbiome in twins. By mapping the gastrointestinal microbiome, we can gain a more accurate picture how the composition and interactions of the microbiome can influence the atherosclerotic imaging phenotypes. Besides, more effective prevention strategies and treatments can be developed.

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The diagnostic and prognostic value of cardiac magnetic resonance imaging in survivors of malignant ventricular arrhythmias

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Background: The primary cause of malignant ventricular arrhythmias (VA) is coronary artery disease, however in patients with normal coronary angiography (CA) the differential diagnosis of the underlying disease is still challenging. Cardiac magnetic resonance (CMR) provides functional, morphological and tissue specific information, including necrotic and scar tissue.

Aims: We aimed to assess the diagnostic and prognostic implications of CMR in patients after ventricular fibrillation (VF) or sustained ventricular tachycardia (SVT) but with normal coronary angiography.

Methods: Ninety-nine patients (42 ±17 years, 54 male) presenting with malignant VA but with normal CA, who underwent CMR before secondary prevention Implantable Cardioverter Defibrillator (ICD) implantation were included in our study. Cine movie images and late gadolinium enhanced (LGE) images were performed. Feature-tracking strain analysis and left ventricular (LV) scar quantification was carried out. Patients were followed for the endpoint of all-cause-mortality and appropriate ICD therapy.

Results: Overall, CMR proved structural myocardial abnormality in 72%: dilated (n=20), arrhythmogenic (n=11), hypertrophic cardiomyopathy (n=6) and other cardiomyopathies (n=3). We found LGE pattern showing chronic myocardial infarction (n=4) and in 27 cases nonspecific structural alterations were detected. The CMR examination changed the clinical diagnosis in 55% of the patients. Scar was present in 52%, with an average extent of 12 ± 8% of the LV myocardium. During a median follow-up at 2 years, 6 patients died and 41 experienced appropriate ICD therapy. We found strong association between mortality and the presence of scar (logrank: 6.985, $p < 0.01$). Among all CMR parameters LV ejection fraction, structural myocardial abnormality, myocardial scar, global LV strain parameters including longitudinal and circumferential strain were univariate predictors of cardiac events ($p<0.05$). On multivariate analysis only the extent of myocardial scar was independent predictor of adverse clinical outcome was ($p<0.01$).

Conclusions: Our study demonstrates the diagnostic yield of CMR in survivors malignant VA but with normal CA. Our findings suggest that patients with structural myocardial disease, especially if myocardial scar is present, have higher risk of death and appropriate ICD therapy.

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Evolution of the usage of end-of-life care within public health expenditure

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Introduction: It is well-know that health expenditures are significantly concentreted and some health care services are used more common at the end of the life. However, only a few data are available on the relationship between the two known facts and the extentent of the role of health care form – outpatient, inpatient, drug subsidies, hemodialysis - in the expenditure concentration and end-of-life care.

Aims: Examining the financing of end-of-life healthcare and determining the concentraction of health care service with special regard to end-of-life care.

Methods: In our study we examined the expenses of inpatient treatment, outpatient care, drug subsidies, hemodialysis based on aggregate and full national data from National Health Insurance Fund of Hungary (NEAK). We form groups of 1000 people based on the total value of total health care by the certain individual. The first group is consist the 1000 people with the highest funding, the next group is consist of 1000 people with the second highest funding, etc. To each group were assigned the total value of outpatient treatment, inpatient care, drug subsidies, hemodialysis. In each group were determined the value of health care in certain year in deceased. We examined the value of health care in each group and in all group aggregately. The results were compared in two different years (2015, 2018).

Results: All examined care were used to a greater extent by the deceased in the reference year - per capita – within the total number of persons receiving health care. The deceased in the reference year were received inpatient treatment and hemodialysis compared to survivors. The top 2% of survivors used more than 45% the health care cost. The top 2% of the deceased in the reference year only used about the 1/6 of the total health care cost. The number of deceased in reference year were not the highest in the greatest-cost group. The main correlation and characteristic of health care usage were similar in two examined year.

Conclusions: The deceased received higher proportion of each treatment, but this was most typical for inpatient treatment. The concentrating of care-usage cost on the deceased was lower compared to survivor. In the greatest cost group the survivor used drug subsidies, which was higher proportion than the drug subsidies of deceased.

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Validation of two-step centrifugation based isolation protocol of neutrophilic granulocyte derived extracellular vesicles by size exclusion chromatography

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Introduction: Our group previously described three distinct populations of extracellular vesicles (EV) derived from neutrophilic granulocytes (PMNs): EVs formed spontaneously (sEV), upon activation by opsonized particles (aEV) and apoptotic EVs (apoEV). Activation induced EV differs in protein cargo and their ability to inhibit bacterial growth.

Aims: We aimed to validate our EV isolation protocol in order to control the purity of our EV samples and ensure that neither DNA, nor granule protein aggregates cause the observed antibacterial property.

Methods: PMN were isolated from the peripheral blood of healthy volunteers. In the case of aEV, we applied opsonized Zymosan activation. We isolated EVs either by a two-step centrifugation and filtration or by size exclusion chromatography (Sepharose CL-2B) following the principles of MISEV2018. We evaluated the EV release based on their count determined by flow cytometry, their protein amount determined by Bradford assay, their size measured by dynamic light scattering, and their actin and lactoferrin content examined by western blotting. We determined the bacterial survival of GFP-expressing S. aureus by a flow cytometry based antibacterial assay.

Results: The size of the EVs in the SEC fractions (8-13) was similar to our medium-sized EVs isolated by the two-step centrifugation. However, the cumulative number of the EVs and the protein content of these fractions were significantly lower by SEC isolation. Compared to the non-vesicular fractions, the SEC EV fractions possessed the antibacterial property. On the other hand, when we performed protein precipitation to examine soluble protein content of the fractions, we could observe small amount LTF, but no actin in the non-vesicular fractions.

Conclusions: The SEC preparation resulted lower EV yield. The previously observed antibacterial effect is associated with EV, neither soluble, nor non-vesicular structures showed the same property. There is small amount of granule protein in the non-EV fractions that shows no antibacterial effect.

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Autophagy Process in relation to Mitochondria in Cholangiocarcinoma

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Introduction: Autophagy eliminates damaged cellular organelles, including mitochondria, and macromolecules for recycling of bioenergetics components and it may act as a pro-survival mechanism to protect cancer cells from cellular stress. Furthermore, modulation of autophagy may sensitize cancer cells to chemotherapeutic agents.

Aims: Our aim was to explore autophagy in cholangiocarcinoma (CC), as it is less frequently studied in CC as compared to hepatocellular carcinoma (HCC).

Methods: Tissue microarrays were prepared from 70 CC [28 intrahepatic (iCC), 19 perihilar (pCC) and 23 distal (dCC)], 31 adjacent non-tumorous and 9 HCC tissues. TOMM20 and COX-4 was monitored by immunohistochemistry to characterize the mitochondria, beclin1, LC3, and p62 for demonstration of autophagy. Mann-Whitney test, Wilcoxon rank and Spearson's rank test were applied along with Kaplan-Meier method for generating survival curves. In Huh28, TFK1 and HepG2 cells, mitochondrial morphology was detected by fluorescent dyes. Induction of autophagy was investigated by rapamycin, chemotherapy (5-FU, Cisplatin, Sorafenib) and/or autophagy inhibitor (chloroquin, CQ) treatments followed by Western blot.

Results: TOMM20, LC3 and p62 were elevated in iCC compared with surrounding tissues, whereas TOMM20 was more increased in eCC (pCC+dCC) as compared to iCC and HCC. Beclin1 showed higher levels in HCC than in iCC, and elevated p62 was found in iCC as compared with eCC. TOMM20 and COX4 showed a strong correlation in HCC ($r=0.89$), while LC3 had an association with grade in pCC ($r=0.51$). Higher TOMM20 was associated with a better survival in pCC, while higher beclin1 correlated with better prognosis in dCC. Mitochondrial staining revealed tubular distribution in HepG2, but HuH28, TFK1 showed disintegration of the mitochondrial network. LC3II/I was increased while p62 was decreased in HepG2 and Huh28 upon rapamycin and chemotherapy treatment compared with the controls. In TFK1, in contrast, neither LC3II/I was increased nor proliferation was different upon treatments.

Conclusions: Increased mitochondria volume and impaired autophagy was characteristic of iCC, whereas TOMM20 in pCC and beclin1 in dCC may be prognostic factors. Autophagy in intrahepatic tumor cells was rather inducible by rapamycin and chemotherapy, suggesting autophagy to be one of the strategies of chemotherapy resistance in these tumors.

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Examination of Interleukin 1A and 1B polimorphism in medication-related osteonecrosis of the jaw

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Introduction: The medication-related osteonecrosis of the jaw (MRONJ) is the side effect of antiresorptive and antiangiogenic therapy, that used in treatment of oncologic disease and osteoporosis. The prognosis of the disease is very unfavorable.

Aims: We examine the single nucleotid polimorphism of interleukin 1A and 1B in development and prognosis of MRONJ.

Methods: In our study we apply DentiGen Parodontitis Test for collecting samples. This test is suitable for sampling oral mucosa cells to ascertain interleukin 1A and 1B single nucleotid polymorphism (IL-1A-889, IL-1B+3953). The genetic samples were evaluated in the Istenhegyi Genediagnostic Center with DNA-hybridization technic.

In our investigation we made examination in patient group and control group. The role of gene polymorphism in development of the disease is examined by comparing the genetic results of patient group and control group. The investigation of gene polymorphism in the prognosis of the disease is based on treatment-induced stage improvement, recovery and the relapses following the treatment.

Results: During our investigation 150 genetic examination were performed. 91 patients were suffering from MRONJ and 59 patients were in the control group. In the patient group 51 (56,04%) patients carry unfavorable allelic variant, in the control group 22 (37,28%) patients had unfavorable allelic variant. We did not find any association (p=0,498) between the unfavorable polimorphism and the development of the MRONJ. In the patient group surgical therapy was used in 79 cases. In this group stage improvement was detected in 78 (98,73%) of the cases, recovery in 67 (88,15%) and relapses in 33 (49,25%). We did not find stage improvement in 1 (1,26%) case, recovery in 9 (11,8%) cases and relapses in 34 (50,74%) cases. 49 from 79 patients treated with surgical therapy had unfavorable allelic variant. We have not found any connection between the examined polymorphism and the stage improvement (p=0,382) or recovery (p=0,561). Significant association (p=0,022) was detected between the relapses and the carrying of unfavorable allelic variant.

Conclusions: We found significant association between relapses of MRONJ and the carrying of interleukin 1A and 1B polimorphism. Based on our study we did not find any association between interleukin 1 polimorphism and the development of MRONJ.

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The Effect of the Mind/Body Program for Fertility on Psychological Well-Being and Assisted Reproduction Technology (ART) Outcomes: A Randomized Controlled Trial

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Introduction: Involuntary childlessness imposes significant psychological burden on those affected, particularly those involved in assisted reproductive technology (ART). The reduction of psychological distress has been shown to improve the quality of life of those affected, and to possibly increase chances of pregnancy. So far, efficacy studies of psychological interventions have been conducted mostly in developed countries, and with no differentiation between patients' level of mental health impairment. (Preregistered at ClinicalTrials.gov ID: NCT04151485)

Aims: The effects of the Hungarian version of the Mind/Body Program for Fertility (Domar et al., 2011), will be compared to those of a fertility support group on the mental well-being and ART outcomes of psychologically affected women in reproductive treatment, in a randomized controlled pre-post design.

Methods: Women in ART treatment will fill in screening questionnaires, and moderate to high scorers will be randomized into an intervention (Mind/Body) group (N=70) and a comparison intervention (Fertility Support) group (N=70), lasting for 10 weeks each, before and/or during an ART cycle. Both interventions will be delivered by the same clinical psychologist. A smartphone application for rating subjective stress levels twice a day, from the start of the stimulation to the day of the pregnancy test, will also be administered. Optionally, whole-night sleep EEGs will be recorded. Medical data (such as diagnosis, hormone levels, previous treatment cycles, etc.) and sociodemographic (such as age, education, etc.) and psychological variables (such as personality traits, chronotype etc.) as potential moderators, as well as ART outcomes, will be reported.

Results: In this presentation, results on the mental health status of infertile women in comparison with normative Hungarian data, as well as the exact outline of the planned RCT protocol, will be presented.

Conclusions: The planned study will allow conclusions to be drawn on whether the Mind/Body Program for Fertility is more efficacious than a Fertility Support group in terms of psychological and pregnancy outcomes in distressed Hungarian infertile women. A novel contribution to the research in the field will stand in analysing the relationship between sleep parameters and IVF success rates.

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Global DNA hypomethylation can be caused by decreased methyl-donor content in tissue and liquid biopsy samples in colorectal cancer progression

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Backgrounds: Global DNA hypomethylation is characteristic in various cancer types including colorectal cancer. Alterations of DNA methylation related enzymes expression and decreased level of methyl-donor molecules (folic acid (FA), S-adenosylmethionine (SAM)) can lead to aberrant DNA methylation pattern.

Aims: Our aim was to examine global DNA methylation during aging and colorectal normal-adenoma-carcinoma sequence and in inflammatory bowel disease. Moreover, we aimed to explore the reasons of global hypomethylation on gene expression level and methyl-donor molecule content.

Methods: Bisulfite treatment was performed on DNA isolated from 30 normal (N), 10 adenoma (Ad), 10 colorectal carcinoma (CRC), 10 colitis ulcerosa (UC) tissue samples and on 11 N, 10 Ad, 15 CRC, 12 UC plasma specimens. LINE-1 PCR amplicons were generated and pyrosequenced. Whole genome mRNA expression level of 60 biopsy samples were evaluated by HTA 2.0 RNA microarraychip (Affymetrix). In situ tissue appearance of 5-methylcytosine, FA, SAM, homocysteine, and expression of DNA methyltransferases (DNMTs) were analyzed by immunohistochemistry staining (IHC).

Results: According to LINE-1 bisulfite sequencing results, significant decrease of DNA methylation was found in CRC (62.9±8.7%), Ad (66.7±5.1%) tissue samples in comparison with N samples (72±1.4%) ($p<0.001$). Significant global DNA hypomethylation was observed in CRC (78.8±1.7%), and Ad (80.1±1.7%) plasma samples compared to N specimens (82.2±1.8%) ($p<0.02$). Global DNA methylation changes were not detected in UC samples. Significantly elevated RNA expression of enzymes connected to nucleotide synthesis was noticed in Ad and CRC samples compared to N ($p<0.05$), while no changes were detected in the RNA levels of DNA methylation-related proteins. The intensity of 5-mC staining of CRC and Ad samples was lower than in N tissue specimens. Decreased FA, SAM levels were observed in CRC compared to N samples; however, no expression changes of DNMT enzymes were found.

Conclusions: Significant decrease in DNA methylation level was detected in tissue and liquid biopsy specimens of colorectal normal-adenoma-carcinoma sequence, but not in UC samples. Our results suggest that global DNA hypomethylation could have prognostic and diagnostic value as well, and reduction of DNA methylation level could be linked to decreased FA and SAM availability.

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The Hydroxylamine Derivative, BGP-15 Has Retinoprotective Effect in Animal Model of Type 2 Diabetes

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Introduction: Diabetic retinopathy is one of the most common causes of blindness in Hungary. Because of the ever-increasing incidence of diabetes mellitus, this microangiopathic complication has become more and more prevalent. Treatment of diabetic retinopathy includes good blood sugar control, intraocular anti-VEGF therapy and surgical treatments, such as vitrectomy and photocoagulation.

Aims: The hydroxylamine derivative, BGP-15 is a relatively new drug candidate, which has been tested in systemic administration in ischaemic-reperfusion injury of the heart, nephrotoxicity, neuropathy, myopathy and especially insulin resistency. However, it has not been investigated in diabetic retinopathy yet, although its effects make it a potential candidate in the treatment and prevention of the disease.

Methods: In the present study, taking into consideration all the beneficial effects of BGP-15 in the many different pathological conditions, impact of this agent was tested in a diabetic animal model, Goto-Kakizaki rats. Moreover, an attempt was made to compare the effects of well-known standard antidiabetics with this promising drug candidate.

Results: Based on our results (blood sugar, electroretinography, western blot) it can be concluded, that BGP-15 is able to induce positive changes in hyperglycemic animals comparable to the effects of metformin and pioglitazone. Electroretinographical (ERG) measurements showed, that the amplitudes of 'a' and 'b' waves, which qualify the function of the retina, were the most significantly restored in BGP-15 treated animals. Not only the decreased blood glucose level might be responsible for this result but also the changes in several proteins' expression. We demonstrated that BGP-15-treatment increased the expression of sirtuin-1 (SIRT-1) and decreased the level of matrix-metalloproteinase 9 (MMP9) therefore it could protect the retinal cells against mitochondrial injury.

Conclusions: In conclusion, BGP-15 seems to be protective in diabetic retinopathy, therefore this drug candidate may be appropriate to prevent the disease and protect against ischemic-reperfusion injury.

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Development of health literacy-promoting communication in Hungarian community pharmacies

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Introduction: Health literacy is „the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decision." More than half of patients entering Hungarian community pharmacies have low levels of health literacy which can have many adverse effects on the patient's life. Community pharmacists have a key role in providing patients with adequate and reliable information about their illness and medicines, but it is crucial that the information and education are consistent with the level of the patient's health literacy.

Aims: The aim of our research was to develop an environment that supports health literacy by improving the communication skills of the a drug dispensing staff, and to prove the feasibility of the above objectives by statistical methods.

Methods: The research was conducted by pharmacists and pharmacy assistants in Hungarian community pharmacies. The study involved a general patient group. At the beginning of the project, we conducted a self-made questionnaire survey of patients' and staff's opinion about the health literacy-friendly environment of the pharmacy, then the employees received health literacy communication training. Three months later, we repeated the questionnaire. We conducted a descriptive and deep statistical analysis of the questionnaires.

Results: The study included 333 professionals from 69 pharmacies, 890 (at the beginning) and 847 (at the end) patients. The mean score of the patinet's input questionnaire was 64.19%, which increased to 72.78% by the end of the project ($p<0.001$). For workers, the mean of the initial questionnaires was 74.68% which increased significantly to 85.20% ($p<0,001$).

Conclusions: All in all, it can be stated that the targeted communication training of the pharmacy staff, and thus the improvement of patients' health literacy has a positive effect on all patients entering the pharmacy. Based on these results, there is a particular need for the widespread implementation of these developments in Hungarian community pharmacies.

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Genetic versus environmental link between obstructive sleep apnea and lumbar degeneration

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Keywords: sleep apnea, spine, Magnetic Resonance Imaging, back pain, heritability

Introduction: The lumbar degeneration often inflects lower back pain, one of the most inportant chronic pain syndrome and cause poor sleep quality and difficulties in falling asleep. Obstructive Sleep Apnea (OSA) is one of the most common sleep disorders and causes cognitive dysfunction, excessive daily sleepiness. Previous studies advocated a connection between poor sleep quality and low back pain (LBP), but no objective genetic study was conducted to understand the common pathway.

Methods: 71 Hungarian twin pairs involved from the Hungarian Twin Registry (42 monozygotic, MZ and 29 dizygotic, DZ pairs, mean age 51±16 years) underwent overnight polysomnography (Somnoscreen Plus Tele PSG, Somnomedics GMBH, Germany) and lumbar spine MRI (Siemens Magnetom Veria and Philips Ingenia 1.5T). The presence and number of disc bulging, Pfirmann score and total endplate score (TEPS) were recorded on T1 and T2 weighted MRI sequences and summarized. Apnea hypopnea index (AHI), respiratory disturbance index (RDI) and oxygen desaturation index (ODI) were registered. Daytime sleepiness was measured by Epworth Sleepiness Scale and LBP was assessed by a validated questionnaire. ACE model was applied, and negative binomial regression was used to assess the connection between OSA and disc degeneration.

Results: Prevalence of OSA and disc bulging was 39% and 68%. Parameters of sleep quality and sleepiness showed a substantial additive genetic background (AHI, ODI, RDI between 39% and 94%, $p<0.05$, Epworth scale: 27%, $p<0.2$). The lumbar annular high intensity was heritable and showed a strong link to ODI, contrarily to the disc bulging and the Epworth sleepiness scale which was determined by environmental factors. The lumbar disc bulging showed significant relationship with AHI and ODI in the binomial models (AHI: 0.06, $p=0.021$, ODI: 0.06, $p<0.024$, respectively). Disc bulging showed no genetic background, which suggested that the connection between disc bulging and OSA parameters are attributed to environmental factors.

Conclusions: The link between the OSA and the disc degeneration is divisive. The disk bulging and OSA parameters showed a strong environmental relationship, whileas the lumbar annular high intensity and ODI was determined by genetic factors. Further research is stimulated

to understand the therapeutic role of these results in OSA patients.

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Ethical Committee Approval: Semmelweis University TUKEB 189/2014.

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Investigation of the Interaction Between Nutrient Supply and Circadian Rhythm in the Model Organism Neurospora crassa

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Introduction: Increasing experimental and clinical data suggest the significance of the interplay between metabolism and circadian timekeeping. Metabolic compensation allows the circadian oscillator to keep a nearly constant period in an environment with changing substrate levels. On the other hand, nutrient availability and coupled metabolic conditions are important Zeitgebers affecting the circadian phase of various physiological processes.

Aims: In a previous study we examined the role of the RAS2 protein in the metabolic compensation of the circadian rhythm in the model organism Neurospora crassa. As RasGEFs are upstream regulators of RAS-mediated pathways, in our next study we aimed to characterize the circadian phenotype of a strain deficient in the expression of a putative rasgef under various nutrient levels.

Methods: The conidiation rhythm was analysed in race tube assay under various conditions. The promoter activity was detected in luciferase assay. The expression levels of the investigated genes were determined by real-time PCR measurements following RNA isolation.

Results: The conidiation rhythm of the rasgef deficient strain shows pronounced metabolic sensitivity. In race tube assays the phase of conidiation is significantly delayed both in light-dark and temperature cycles. Under constant conditions the period is slightly affected by the mutation. When a luciferase reporter was expressed under the control of the rasgef promoter, rhythmic activity was detected suggesting that rasgef is a clock-controlled gene (ccg). In addition, expression levels of rasgef were sensitive to the glucose content of the medium.

Conclusions: In summary, we suggest that rasgef is a novel glucose repressible clock-controlled gene (ccg) which may play an important role in the metabolic regulation of the circadian clock of Neurospora crassa.

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VEGFC mRNA-LNP Induces Organ-Specific Lymphatic Growth and Reverses Experimental Lymphedema

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Introduction: Lack or dysfunction of the lymphatics leads to secondary lymphedema formation that seriously reduces the function of the affected organs and results in degradation of quality of life. Currently, there is no definitive treatment option for lymphedema.

Aims: Our main goal is to show wether VEGFC mRNA-LNP induces lymphatic growth and could treat lymphedema effectively in a mouse model.

Methods: Ears and other organs of Prox1-GFP transgenic mice were injected with Poly(C) – control – and VEGFC mRNA-LNPs. The organs were harvested at various time points and examined by immunfluorescent techniques. Lymphedema was induced in limbs of a Diphtheria Toxin based transgenic mouse model system. 8 days after the induction of lymphedema Poly(C) – control and VEGFC mRNA-LNPs were injected into contralateral limbs of the animals. Thickness of the limbs were measured and scored by two blinded investigators. The tissues were harvested at 30 and 75 days after the treatment and examined by immunfluorescent techniques.

Results: We utilized nucleoside-modified mRNA encapsulated in lipid nanoparticles (LNPs) encoding murine Vascular Endothelial Growth Factor C (VEGFC) to stimulate lymphatic growth and function and reduce lymphedema in mouse models. We demonstrated that administration of a single low dose of VEGFC mRNA-LNPs induced durable, organ-specific lymphatic growth and formation of a functional lymphatic network. Importantly, VEGFC mRNA-LNP treatment reversed experimental lymphedema by restoring lymphatic function without inducing any obvious adverse events.

Conclusions: Collectively, we present a novel application of the nucleoside-modified mRNA-LNP platform, describe a model for identifying the organ-specific physiological and pathophysiological roles of the lymphatics, and propose an efficient and safe treatment option that may serve as a novel therapeutic tool to reduce lymphedema.

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TGF-β, a main activator of stromal cells, increases extracellular vesicle production of normal colon and colorectal cancer fibroblasts

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Introduction: Colorectal cancer (CRC) is one of the most frequent causes of cancer-related death. The tumor microenvironment contains not only cancer cells, but other cell types, such as cancer associated fibroblasts (CAF) as well. TGFβ is a critical factor that activate stromal fibroblasts and induces invasion and metastasis in CRC. Importantly, peritumoral fibroblasts (PTF) are often used as normal colon fibroblasts. The high amount of CAFs in CRC is strongly correlated with a poor clinical outcome. Extracellular vesicles (EVs) are membrane-surrounded structures that represent a novel way of intercellular communication by delivering biologically important molecules from the releasing to the target cells. Since EVs carry their cargo in a protected and concentrated form, furthermore, their secretion is generally increased in tumorigenesis, EVs hold a great potential for early cancer diagnosis.

Aims: Here we study factors influencing stromal fibroblast-derived EV production intensity and cargo composition as a transmitting tool in CRC.

Methods: We used patient-derived organoids and fibroblasts, furthermore, commercial available normal colon fibroblasts (NCF). The Medical Research Council of Hungary approved our experiments and informed consent was obtained from patients. EVs were detected by antibody-coated beads and flow cytometry and by Nanoparticle Tracking Analysis. Gene expression was followed by RT-qPCR and immunocytochemistry. For miRNA detection we used the TaqMan system.

Results: We provide evidence that EVs can be detected in patient-derived normal colon fibroblast (PTF) and cancer associated fibroblast (CAF) cultures by a simple semi-quantitative flow cytometry-based method. We show that TGF-β, an important activator of fibroblasts, enhances EV secretion of NCFs, PTFs and CAFs. In addition, TGFβ modifies the miRNA cargo of EVs in fibroblasts. Interestingly, TGF-β treatment lead to the emergence of IL6+ fibroblast subpopulations both in PTF and CAF, but not in NCF cultures.

Conclusions: Collectively, our results show that TGF-β, a critical factor modifying fibroblast functions, has a major effect on EV release and cargo.

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Alpha-lipoic acid alters the antitumor effect of bortezomib in melanoma cells in vitro

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Introduction: Bortezomib (BOZ) is a proteasome inhibitor chemotherapeutic agent utilized to treat multiple myeloma and recently offered to cure melanoma. Bortezomib-induced peripheral neuropathy is one of the most significant and dose-limiting side-effects, which can be treated with antioxidants (e.g. alpha-lipoic acid - ALA and vitamin B1 - vit B1) as a part of cancer supportive care. We hypothesized that these antioxidants may counteract the antitumor activity of BOZ.

Aims: The objectives of our experiments were: (i) to verify the cytotoxicity of BOZ; (ii) to test and compare the influence of the antioxidants on the antitumor effect of BOZ in melanoma (A2058) and myeloma (U266) cells as clinically relevant target cells.

Methods: The cell viability was determined by xCELLigence® RTCA SP instrument and by a cell based CellTiter-Glo® Luminescent Cell Viability Assay. Then the possible molecular pattern was characterized by the analysis of phospho-p53 (S15) by flow cytometry and the cell cycle by NucleoCounter® NC-250™. Cell-based assays were also assessed on the proteasome activity and on the ROS generation. To further evaluate the apoptotic mechanism at the molecular level, proteomic profiling was conducted. The current presentation was supported by the ÚNKP-19-3-I-SE-49 New National Excellence Program of the Ministry for Innovation and Technology.

Results: At first, the cytotoxicity inhibiting effect of alpha-lipoic acid was proved in melanoma cells. Analysis of p53 phosphorylation and the cell cycle progression revealed that ALA failed to counteract the effects of BOZ on these processes. Nevertheless, a good correlation was found between the inhibition of the cytotoxicity, the anti-proteasome activity and the oxidative stress level after the co-treatment with 20 ng/mL BOZ + 100 μg/mL ALA. Downregulation of apoptotic proteins such as HO-1 and Claspin along with the inhibition of the cleavage of Caspase-3 indicated the proteomic background of the altered responsiveness of the melanoma cells exposed to BOZ + ALA.

Conclusions: The antagonizing effect of ALA on the antineoplastic activity of BOZ in melanoma cells draw the attention to the proper application of cancer supportive care.

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Phenotypic changes in CLL cells in a patient acquiring venetoclax resistance

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Introduction: Chronic lymphoid leukemia (CLL) is the most common adult leukemia in the western world, CLL is an indolent and biologically heterogeneous disease. New targeted therapies including the selective Bcl-2 inhibitor venetoclax were introduced in recent years. Although venetoclax is a highly effective drug but acquired drug resistance may make the long-term treatment challenging.

Aims: Our aim was to investigate the signal transduction and immunophenotypic changes in a patient who developed acquiring venetoclax resistance. Furthermore, we compared the phenotype of resistant CLL cells in bone marrow and peripheral blood.

Methods: We collected peripheral blood (PB) samples at the time of initiation of venetoclax therapy and on 180th, 270th, 360th, and 450th day of treatment. Furthermore, PB and bone marrow (BM) samples were available at the time of overt clinical resistance (450th day). Cell surface molecules CD49d, CD38, ROR1, CD69, CD86, CD27, CD184 and CD185 were measured by flow cytometry. We also investigated the most common Bcl-2 resistance mutation (G101V) by digital droplet PCR. Protein and apoptosis arrays were performed from PB samples on the day 0 and the day 360 of venetoclax therapy, and from PB and BM samples at the onset of resistance.

Results: We observed that the expression of surface markers CD184, CD185 and CD86 decreased during venetoclax therapy until the onset of the resistance. CD69 and ROR1 showed bimodal distribution. Higher CD69 expression was in BM and CD185 expression was higher in PB. The G101V Bcl-2 resistance mutation was not detected in any of the samples analysed. Levels of BAD, BAX, XIAP, Bcl-XL and, p-CREB proteins were elevated during therapy and decreased at the time of venetoclax resistance. Expression levels of Bcl-2 decreased during the therapy, however in the resistance sample the Bcl-2 expression was higher compared to the initial presentation. In the BM sample XIAP, Bcl-XL, and p-CREB expression levels were higher compared to the PB sample at the time of resistance.

Conclusions: Based on our results, development of venetoclax resistance is associated with changes in expression of surface proteins and phospho-proteins in CLL cells. Monitoring of these markers (CD185, Bcl-2, XIAP and p-CREB) by flow cytometry during the disease course may be helpful in the early detection of acquired venetoclax resistance.

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Novel integrative methods to identify therapeutic targets and compounds for treating kidney fibrosis

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Aims: Chronic kidney diseases (CKD) characterised by renal fibrosis leading to gradual decline of renal function. Despite the urgent medical need there is still no effective therapy to inhibit or reverse the diseases. However, so far only a few therapeutic targets and compounds have been identified in the preclinical and clinical studies for the treatment of kidney fibrosis. Our aim was to develop an integrative framework to improve the identification possible target molecules and compounds which may have anti-fibrotic effects.

Methods: Comprehensive literature research was performed to identify those genes that have a role in renal fibrosis based on gene knockout (KO) animal studies. Moreover, genes of an extensive human microarray study that correlated with the severity of chronic kidney diseases were listed. Finally, the overlapping set of the two lists were generated and coupled with known compounds altering the function of the investigated genes in anti-fibrotic manner.

Results: Based on KO animal studies we found 91 pro-fibrotic and 73 anti-fibrotic genes which influenced the amount of extracellular matrix (ECM) depositions in the fibrotic kidney. Among them the expression of 54 gene were altered in the human kidney biopsies from patients with CKD as well. More than 300 compounds were identified that affecting these genes may exert anti-fibrotic effect.

Conclusions: We established an effective method to identify new drug targets and possible compounds that can be repurposed for the treatment of renal fibrosis.

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Role of common CASR variants in chronic pancreatitis

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Introduction: The calcium sensing receptor (CASR) plays an essential role in maintaining mineral ion homeostasis and is also expressed in human pancreatic acinar and ductal cells. Over the past years, the possible involvement of common CASR variants in chronic pancreatitis (CP) has emerged, however, their role in the pathogenesis of CP remains controversial due to the lack of large case-control studies.

Aims: To analyze the clinically frequent CASR variants in an ethnically homogenous group of Hungarian CP patients and healthy controls.

Methods: In our discovery cohort 257 CP patients (cases) and 183 controls with no pancreatic disease from the Hungarian National Pancreas Registry were enrolled. As the most common CASR variants are located in exon 7, we PCR amplified and sequenced this exon with its flanking intronic regions. To further investigate the role of the p.A986S polymorphism, we will expand our cohort and use the TaqMan™ SNP Genotyping Method.

Results: In our discovery cohort we identified three common exon 7 variants: c.2956G>T (p.A986S), c.2968A>G (p.R990G) and c.3031C>G (p.Q1011E). No significant differences were found in allele frequencies of these variants in cases compared to the control group: p.A986S (19.26% vs 18.58%, OR=1.05, p=0.8), p.R990G (7.8% vs 6.3%, OR=1.26, p=0.4) and p.Q1011E (3.7% vs 4.1%, OR=0.9, p=0.8). However, genotype distribution analysis revealed, that the p.A986S variant in homozygous state was overrepresented in patients relative to controls (3.5% vs 1.1%, OR=3.3, p=0.13). Although this difference was not statistically significant, there is a clear trend which warrants extension of the studies to a larger cohort in the future.

Conclusions: The homozygous c.2956G>T (p.A986S) variant is overrepresented in the Hungarian cohort of chronic pancreatitis patients relative to the control group. Our results strengthen the previous findings in a French cohort (Masson E, 2015) and support the possible pathogenic role of the homozygous p.A986S variant in chronic pancreatitis.

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Whole genome analysis of the first feline adenovirus isolate shows relationships to human adenovirus 1

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Introduction: Adenoviruses transactivate HIV resulting in faster progression of AIDS eliciting opportunistic infections. The feline AIDS model is suitable to study retrovirus-adenovirus interaction, but no adenovirus has been obtained from Felidae. Besides, adenoviruses are used in gene therapy.

Aims: Our aim was to isolate an adenovirus from cats. After epidemiological studies in European and American cats, the feces of seropositive animals was screened for adenovirus nucleic acid by polymerase chain reaction (PCR) and cultivated on human and animal tissue cultures. We isolated an infectious agent. Its biological and molecular characterization, whole genome and phylogenetic analysis were used for identification and establishment its taxonomical order. Its sensitivity to basic environmental effects and antiviral drugs has been tested.

Methods: The cytopathic agent was verified by electron microscopy, immunofluorescence, PCR. Next generation sequencing and phylogenetic analysis using neighbour joining method were carried out. Immunochemistry was used to quantitate infectivity following in vitro treatments.

Results: The infectious agent proved to be an adenovirus and named feline adenovirus (FeAdV). Unusually, it replicates in several human and animal cell lines. Next generation sequencing identified its genome consisting of 35898 nucleotides. Phylogenetic analysis showed that FeAdV is related to human adenovirus (HAdV)-1 containing 36001 nucleotides. One nucleotide difference was demonstrated between FeAdV and HAdV-1 at position of 15081 affecting the central region of L3 gene (penton) without amino acid change. As compared to adenoviruses, FeAdV shows similar sensitivity to UV, higher sensitivity to heat, detergents and antiviral drugs, but more resistant to chlorine.

Conclusions: Relatedness of FeAdV to HAdV-1 raises the possibility of a zoonotic infection, although the human and feline pathogenesis has not been revealed. Deletion of the first and last 6 nucleotides in FeAdV might explain different biological properties and wide host range contrary to species specificity of adenoviruses. This might be based on the altered surface structure of viral polypeptides binding to cell receptors. Recombinant human and animal adenovirus are used as vectors, but due to biological incongruences new adenoviruses as FeAdV would be ideal candidates for new vectors.

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Relationship Between Autoimmunity and Vaccines: An Experimental Study of the Fluart Flu Vaccine and Chronic Rheumathoid Arthritis Association

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Introduction: Rheumatoid arthritis (RA) is the most common form of non-infectious inflammatory disorders, which mainly affects the synovial joints. RA can appear at any age and it affects nearly 1% of the population worldwide. Several studies confirm the fact, that vaccines may be responsible for the exacerbation of autoimmun diseases, including RA as well.

Aims: Hence, the main aim of our trial was to examine the effects of 3FluArt suspension influenza vaccine on CFA-induced rheumatoid arthritis rodent model depending on the day of vaccination.

Methods: 24 male Lewis rats were divided into 6 groups. As a VI: Baseline group we considered rats, which did not get any treatment. Rats with CFA pre-treatment: I: CFA flu early (vaccinated on the first day); II: CFA flu late (vaccinated on the seventh day); III: CFA control (only CFA was administered); rats without CFA pre-treatment: IV: Flu early (early vaccinated); V: Flu late (lately vaccinated).

To evaluate the severity of inflammation paw volume was measured by a plethysmometer, and the mechano-nociception of the animals was assessed by dinamic plantar aesthesiometer. Besides these methods the activity of the neutrophil myeloperoxidase (MPO) and the value of vascular leakage was evaluated as well. The study was terminated on the 21st day of the experiment. Changes in bodyweight were followed by weighing the animals on the 0., 2., 9., 21. day.

Results: The flu vaccination did not have an influence on the bodyweight neither of the animals treated with CFA nor on those which were not treated with it. The value of paw oedema or the threshold of mechanonociception was not affected by the vaccination, however there was a significant difference on the 9th day of the experiment in point of the activity of the neutrophil MPO in both vaccinated groups compared to the CFA control group, where it was elevated from the beginning of the study.

Conclusions: Our main aim was to choose the most suitable time period for the administration of the flu vaccine. To confirm our results, to enlarge the number of animals, to clarify the differences detected further investigations are required.

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Toxicity of Carboplatin Increased to Granulopoiesis in OLETF Rats with CCK-1 Cholecystokinin Receptor Deficiency

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Introduction: Damage of granulopoiesis resulting neutropenia is the most frequent dose-limiting toxicity of cancer chemotherapy. Obesity is associated with lower phagocytic activity by macrophages and decreased resistance to some infections, which may be based on an affected granulopoiesis.

Aims: Our aim was to study whether obesity-associated changes of granulopoiesis can influence toxicity of anticancer drugs, namely carboplatin.

Methods: Granulopoiesis was studied in an obese animal model in OLETF rats with CCK1 receptor deficiency in comparison to their non-obese counterparts, LETO rats. Frequency of CFU-GM and total CFU-GM content of the femoral bone marrow characterize granulopoiesis. Special soft gel colony assay was used and bone marrow cells were cultured in the presence of carboplatin in vitro. Proglumide was iv. administered in vivo using 3 mg/kg dose.

Results: Cholecystokinin, a gut-derived cytokine has a great role in control of appetite. The CCK receptor deficient OLETF rats became obese due to an excessive food intake. At first sight granulopoiesis was not differ in obese OLETF rats from the non-obese control LETO rats. However, testing vulnerability of granulocyte-macrophage progenitors (CFU-GM) by culturing them in the presence of carboplatin, we detected an increased toxicity to the CFU-GM progenitors obtained from OLETF rats dose-dependently compared to those from LETO rats. To evaluate whether the CCK receptor deficiency has a role we used pre-treatment in vivo for non-obese LETO rats by proglumide. Proglumide, a CCK antagonist resulted in similar increased sensitivity of the progenitor cells to toxic effects of carboplatin used in vitro.

Conclusions: Pharmacokinetic properties of anticancer drugs are often changed in obese patients however our results showed functional disorders of the target cells which responsible for production of mature macrophages. Increased toxicity of carboplatin to these progenitors results in more serious neutropenia with increased risk for life-threatening infections. As the CCK antagonist proglumide pre-treatment had similar effect on toxicity of carboplatin in non-obese LETO rats than the obese CCK deficient OLETF rats showed that cholecystokinin receptors are found on CFU-GM cells and they may have a role at least partly in increased myelotoxicity of anticancer drugs in obesity.

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Exploring the pathomechanism of thiopurnie-induced acute pancreatitis: Azathioprine impairs pancreatic ductal exocrine functions in mice

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Introduction: Thiopurine-induced pancreatitis (TIP) is a major difficulty in the treatment of Inflammatory Bowel Diseases, the exact pathomechanism of TIP is, however, currently unknown. It was shown recently, that other risk factors, such as ethanol, can impair the ductal HCO3- secretion, which can ultimately lead to pancreatic injury and acute pancreatitis (AP). Therefore, we wanted to investigate what effects do thiopurines have on pancreatic ductal functions and HCO3- secretion.

Methods: C57BL6 mice were selected to receive daily 1.5 and 15 mg/kg azathioprine (AZA), 6-mercaptopurine (6-MP) and 6-thioguanin (6-TG) or physiologic saline (PS) for one and for four weeks. After the oral treatment mice were either euthanized and used for further measurements or selected for in vivo fluid-secretion measurements as previously descried. For ex vivo experiments, pancreatic ductal segments (PD) were isolated from euthanized mice and PDs were transferred to perfusion chambers and were loaded with a pH-sensitive fluorescent dye (BCECF-AM). Intracellular pH and rate of HCO_3^- secretion was determined using ratio microfluorimetry. To assess the in vitro effects of thiopurines, the above mentioned microfluorimetric measurements were also conducted on ex vivo PDs from non-treated animals perfused with solutions containing different concentrations of AZA, 6-MP, and 6-TG.

Results: Acute exposition in vitro to 1, 10 or 100 ug/ml AZA significantly decreased the luminal HCO_3^- secretion rates in a dose-dependent manner. Per os treatment with AZA for one and four weeks impaired the ductal HCO_3^- secretion rate and in vivo fluid-secretion was decreased after four weeks of 1.5 mg/kg AZA treatment. Animals treated with 15 mg/kg AZA didn't survive the ketamine-sedation. Preliminary results showed that one week of 1.5 mg/kg 6-MP and 6-TG treatment didn't alter the ductal HCO_3^- secretion rates. Further in vitro and in vivo measurements with 6-MP and 6-TG are running currently.

Conclusions: AZA can impair ductal HCO_3^- secretion both in vitro and in vivo, in a dose-dependent manner. These results suggest that in TIP, beside immune-mediated mechanisms, inhibitory effects on ductal exocrine functions might also play an important role. In order to fully understand the pathomechanism of TIP, further experiments, including both pancreatic ducts and acini, are needed.

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Sex-Specific Patterns of Mortality Predictors among Patients undergoing Cardiac Resynchronization Therapy: A Machine Learning Approach

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Introduction: The relative importance of variables explaining sex differences in outcomes is scarcely explored in patients undergoing cardiac resynchronization therapy (CRT).

Aims: We sought to implement and evaluate machine learning (ML) algorithms for the prediction of 1- and 3-year all-cause mortality in CRT patients. We also aimed to assess the sex-specific differences in predictors of mortality using ML.

Methods: Using a retrospective registry of 2191 CRT patients, ML models were implemented in 6 partially overlapping patient subsets (all patients, females, or males with 1- or 3-year follow-up). Each cohort was randomly split into training (80%) and test sets (20%). After hyperparameter tuning in the training set, the best performing algorithm was evaluated in the test set. Model discrimination was quantified using the area under the receiver-operating characteristic curves (AUC). The most important predictors were identified using the permutation feature importances method.

Results: Conditional inference random forest exhibited the best performance with AUCs of 0.728 [0.645–0.802] and 0.732 [0.681–0.784] for the prediction of 1- and 3-year mortality, respectively. Etiology of heart failure, NYHA class, left ventricular ejection fraction, and QRS morphology had higher predictive power, whereas hemoglobin was less important in females compared to males. The importance of atrial fibrillation and age increased, while serum creatinine decreased from 1- to 3-year follow-up in both sexes.

Conclusions: Using ML techniques in combination with easily obtainable clinical features, our models effectively predicted 1- and 3-year all-cause mortality in CRT patients. Gender-specific patterns of predictors were identified, showing dynamic variation over time.

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Inflammatory profile characterization and 90-day mortality prediction in a randomized clinical trial of severe alcoholic hepatitis

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Introduction: Acute alcoholic hepatitis (AH) has a high short-term mortality rate. Yet, therapeutic options and clinical scores to manage this disease are limited. The Model for End-Stage Liver Disease (MELD) is generally used to evaluate severity and mortality in different liver diseases. However, new biomarkers may provide more specific tools to assesses AH.

Aims: Our goal was to explore inflammatory landscape of severe AH at the day of hospitalization to build a predictive model for 90-day mortality in a multicentric clinical trial.

Methods: Plasma samples were collected from 85 sever AH patients (MELD≥20) and 27 healthy controls. Patients were randomly assigned to treatment with anakinra (IL-1 receptor antagonist [IL-1Ra]) + pentoxifylline + zinc (n=43) or methylprednisolone (n=42). Plasma samples were analyzed for 43 biomarkers and predictive value of the molecules was assessed for 90-day mortality.

Results: 38 of the 43 biomarkers showed altered levels at baseline compared to healthy controls. 31 patients died during the 90-day follow-up, 18 in the steroid and 13 in the anakinra treatment group. In subgroup analysis of anakinra treated patients, increased IL-6, IL-22 and osteopontin as well as decreased IL-1β, IL-13 and IP-10 levels showed significant association with mortality. In steroid treated patients, high plasma lipocalin-2, MMP-2, low IL-1Ra and MCP-1 levels were found in non-survivors. In the whole cohort including both treatment groups only endotoxin and IL-6 showed significantly increased while IL-13 decreased levels in non-survivors compared to survivors. In Kaplan-Maier analysis, high IL-6 (>25.82 pg/ml) and low IL-13 (≤0.61 pg/ml) levels were significantly associated with mortality. In multivariate Cox regression model including significant clinical factors, high IL-6, low IL-13 and age were independent predictors of mortality. The combination of these 3 factors by binary logistic regression had a superior AUROC compared to MELD. In multivariate Cox regression, MELD lost its significance against the new score. Importantly, our novel score sustained its mortality predicting capacity in each treatment group.

Conclusions: Our data indicate that our new composite score using IL-6, IL-13 and age predicts 90-day mortality regardless of the type of treatment in severe AH with higher performance than the commonly used MELD score.

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Long-term effects of perinatal asphyxia on multi-organ injury

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Introduction: Detrimental effects of perinatal asphyxia (PA) are mainly associated with the complications of hypoxic encephalopathy. In a parallel experiment we showed signs of acute renal- hepatic- and cardiovascular injury following PA, however, long-term outcome of multi-organ damage is poorly investigated, clinical follow-up data is lacking. PA adults may be more vulnerable in conditions where ischemia/reperfusion (IR) injury occurs, such as transplantation, major surgeries, infarction or sepsis.

Aims: The aim of the present study was to investigate long-term effects of PA on permanent organ damage and susceptibility to IR injury in adulthood.

Methods: 35 min bilateral renal IR insult was performed on male Wistar rats at 6 months of age (n=6-7/group). The groups were the following: (i) Control; (ii) PA (postnatal day 7; 4% O_2; 20% CO_2 in N2 gas mixture; 15 mins; 37 °C) + SHAM; (iii) IR; (iv) PA+IR. Serum and tissue samples were collected 24 hours after reperfusion. Serum levels of electrolytes, kidney and liver functional parameters were determined. Highly selective tubular injury markers (Kim1, Ngal) were measured. Expressions of hypoxic (Hif1α, Hif2α), inflammatory (Il1α, Il1β, Il6), apoptotic (Bax, Bcl-2), angiogenic genes (Vegf, Epo) and profibrotic (Tgfβ, Pdgf, Ctgf) were investigated. Periodic-Acid Schiff staining on kidney tissue sections, and Hematoxylin & Eosin staining on liver tissue sections were performed.

Results: In PA rats BUN levels were elevated at the age of 6 months, suggesting a long-term impact of PA. In addition, adult PA rats were more sensitive to renal ischemic insult, confirmed by higher serum creatinine, as well as increased renal expressions of Ngal, Hif1α, Epo, Il6 and Bcl-2 in PA+IR vs. IR. No long-term effect of PA was observed in the liver. However, serum GPT levels and liver Il1β expression were higher in the PA+IR than in the IR group.

Conclusions: Long-term detrimental effects of PA on kidney and liver function were observed. In addition, birth asphyxia may increase sensitivity to renal- and hepatic injury even in adulthood, which may be worth considering in clinical situations with potential renal impairment such as major surgeries. Multiple activated pathways may be potential targets of novel therapeutic drug development, which may offer substantial benefits over current first-line therapy.

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Daprodustat accelerates phosphate-induced osteochondrogenic trans-differentiation of vascular smooth muscle cells

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Introduction: Chronic kidney disease (CKD) is frequently associated with anemia, partially due to the insufficient production of erythropoietin. Currently this condition is treated with recombinant human erythropoietin, however its application increased the risk of cardiovascular events. This initiated search for new treatment options including drugs that target the hypoxia inducible factor 1 (HIF1) pathway. One candidate is Daprodustat, a prolyl hydroxylase inhibitor which is currently tested in a Phase3 clinical trial for safety and efficacy to treat anemia in CKD patients.

Aims: Recent studies revealed that hypoxia contributes to vascular calcification via the activation of HIF1 pathway, therefore we addressed the effect of Daprodustat on osteochondrogenic trans-differentiation of vascular smooth muscle cells (VSMC).

Methods: We induced calcification of human aortic smooth muscle cells (HAoSMCs) with inorganic phosphate (Pi, 1.5-2.5 mmol/L) in the presence or absence of Daprodustat (10-1000 nmol/L). Protein expressions of HIF-1á, Glut-1, ALP and VEGF and were evaluated by Western blot and ELISA. Extracellular matrix mineralization was assessed by Alizarin red staining and Ca measurement. Quantitative RT-PCR was used to measure mRNA expressions of osteoblast-specific markers Runx2, Sox9 and ALP.

Results: Daprodustat increased HIF-1α, VEGF and Glut-1 protein expressions in a dose-dependent manner. Daprodustat induced mRNA expressions of osteochondrogenic markers Runx2, Sox9 and ALP, and potentiated the effect of Pi on extracellular matrix calcification in HAoSMCs.

Conclusions: We concluded that Daprodustat increase Pi-mediated osteochondrogenic transdifferentiation and extracellular matrix mineralization of HAoSMCs. We found that Daprodustat increased the ER stress in HAoSMCs. Further studies are warranted to address whether Daprodustat increases the risk of vascular calcification in CKD patients.

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Comprehensive characterisation of phenolic profile and antioxidant activity of Carpinus betulus

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Introduction: Plants of the Betulaceae family are considered as potential sources of new drugs, however, hornbeam species are rarely explored in this regard. Although phenolic compounds and total antioxidant effect of European hornbeam (Carpinus betulus) leaf methanol extract have been previously evaluated, analysis of other extracts of the plant has not been performed. Additionally, diarylheptanoids bearing remarkable anticancer and antioxidant activity and described in further hornbeam species, have not been identified in C. betulus.

Aims: Our aim was to comprehensively characterise the phenolic profile of C. betulus by analysing extracts prepared from distinct plant parts with various solvents. We devoted particular attention to the possible presence of diarylheptanoids. In addition, we aimed to reveal the contribution of individual constituents to the total antioxidant capacity of the extracts.

Methods: Dried and powdered bark, leaf, male and female flower samples of C. betulus were extracted successively with solvents of increasing polarity (chloroform, ethyl acetate, methanol) in ultrasonic bath. For the phytochemical analyses an LC-ESI-MS/MS method was applied. Diarylheptanoids were isolated by combinations of flash chromatographic and semi-preparative HPLC techniques and identified by HR-MS and NMR methods. We analysed the total antioxidant activity of the extracts with the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay and the contribution of each compound to the antioxidant effect using an off-line HPLC-DPPH method.

Results: Non-polar compounds in the chloroform extracts were not evaluated. Hydroxycinnamic acids, flavonol-glycosides and diarylheptanoids were representative of ethyl acetate extracts, while methanol extracts were dominated by the presence of gallic acid derivatives and ellagitannins. Five diarylheptanoids were isolated from the bark for the first time. The methanol extract of the leaves showed the highest antioxidant effect, due to its high tannin content. Galloyl-hexahydroxydiphenyl glycosides and other galloyl esters contributed the most to the total antioxidant activity.

Conclusions: Phenolic fingerprints of C. betulus extracts were compared and cyclic diarylheptanoids were identified for the first time. Gallotannins were described as constituents being responsible for the antioxidant activity of hornbeam.

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Surface Protein Interactome of Extracellular Vesicles in Blood Plasma

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Introduction: Extracellular vesicles (EVs) are the endogenous nanoparticles produced by the cells. Artificial nanoparticles have been found to develop a protein corona altering their biodistribution and bioavailability in biological media.

Aims: Here we set the aim to study if a similar protein corona is formed at the surface of EVs in biofluids and if inflammation had an effect on the protein corona formation. Also, we tested, whether the protein corona alters the biological function of EVs.

Methods: Blood plasma depleted in both platelets and EVs was generated from blood samples of healthy subjects (n=18) and rheumatoid arthritis patients (n=16). Nascent EVs of THP1 cells and platelets were isolated and incubated in different plasma samples for 30 minutes. EVs were then re-isolated by differential centrifugation, size exclusion choramatography (SEC), or density gradient ultracentrifugation (DGUC), and were studied by mass spectrometry (MS/MS), electron microscopy (EM) and flow cytometry. Controls included i) plasma without the addition of EVs and ii) EVs incubated in buffer. The effect of the protein corona was studied by exposing dendritic cells to EVs, after which flow cytometric analysis of activation markers and ELISA of the supernatant were performed.

Results: After subtracting the proteins found by MS/MS in pure (nascent) EV samples from the list of proteins of EV samples incubated in plasma for 30 minutes (coated EVs), a high number of proteins were found, out of which several were more characteristic of rheumatoid arthritis than of healthy samples. DGUC combined with a flow cytometry revealed a significantly higher density of coated vesicles compared to the nascent ones. Interactions between several blood plasma proteins and EVs were also confirmed by flow cytometry and immune EM. Functional assays showed that coated vesicles induce a more pronounced activation response (eg. surface CD83, TNFα production) of dendritic cells.

Conclusions: Our data suggest the formation of a protein corona on EVs of blood plasma. The differences in protein coronas formed in healthy and rheumatoid arthritis plasma samples, suggest that EV surface-associated proteins may play a role in disease pathology and may serve as biomarkers.

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Herpes simplex virus prevalence in 2230 explanted corneal buttons of 1860 patients

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Introduction: Herpetic keratitis is one of the leading causes of corneal blindness worldwide.

Aims: To determine herpes simplex virus (HSV) prevalence in corneal buttons of penetrating keratoplasties (PK) at the Department of Ophthalmology of Saarland University Medical Center and to analyse correlation of HSV prevalence and previous clinical signs of herpetic keratitis (HK) in these eyes.

Methods: Between March 2010 and September 2018, 2230 explanted corneal buttons (1986 eyes of 1860 patients, age at the time of surgery 57.3±19.2 years) were analyzed by real-time polymerase chain reaction (PCR) for the presence of HSV. Two- hundred eighty-one (12.6%) eyes had a positive and 1949 (87.4%) a negative previous clinical history of HK.

Results: HSV PCR was positive in 137 (6.1%) corneal samples, with a 30.57±6.01 mean cycle threshold (Ct) value. In patients with a positive clinical history of HK 108 (38.4%) were PCR positive and 173 (61.6%) negative. In patients with a negative clinical history of HK 29 (1.3%) were PCR positive and 2201 (98.7%) negative.

Conclusions: Our data show that a positive clinical history of HK is related to PCR positivity in about every 2nd to 3rd patient. In addition, about every hundreth explanted corneal tissue is HSV PCR positive, without a previous clinical HK history. These patients may need additional local/systemic antiviral treatment following penetrating keratoplasty.

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Population snapshot of the CTX-M-producing Escherichia coli isolated from haemoculture in a Hungarian hospital

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Introduction: The ST131 high risk clone, especially C2/H30Rx subclade with blaCTX-M-15 and C1-M27 subclade with blaCTX-M-27, are the predominant lineages among third-generation cephalosporin-resistant Escherichia coli. In 2018 44.6% (75/168) of invasive ESBL-producing E. coli isolates investigated at the National Public Health Center belonged to the ST131 clone, where the ratio of C2/H30Rx and C1-M27 was 1 to 0.8.

Aims: The aim of our study was determine the prevalence of invasive extended-spectrum β-lactamase (ESBL)-producing ST131 E. coli collected from a Hungarian hospital in a short time period in order to compare their genetic backgrounds.

Methods: Between October-November 2018, all invasive ESBL-producing E. coli isolates were collected from Central Hospital of Southern Pest. The antimicrobial susceptibility testing was performed according to the EUCAST guidelines. The possible clonal relationships were investigated by core genome (cg)MLST (SeqSphere+) using whole-genome sequencing (WGS) data of isolates obtained from Illumina 251-bp paired-end sequencing. From WGS data acquired antimicrobial resistance and virulence genes were retrieved using ResFinder3.1 and VirulenceFinder2.0 online tools.

Results: From total of six ESBL-producing E.coli isolates five belonged to ST131 clone (two C1-M27 and three C2/H30Rx). The remained one belonged to the ST1193 emerging clone with blaCTX-M-27. Acording to cgMLST all C2/H30Rx isolates showed relatively close clustering (≤6 allele differences), suggested an undetected nosocomial outbreak. The blaCTX-M-27-producing ST1193 isolate and C1-M27 isolates differed at least 35 alleles from each other. All the isolates proved resistant to ceftriaxone and ciprofloxacin, but susceptible to ceftazidim/avibactam, tigecyclin, fosfomycin and carbapenems. C2/H30Rx isolates showed resistance only to ceftazidime, tobramycin and gentamicin. All isolates harboured almost identical virulence gene armament like the adhesion genes (sfa, mat), siderophores (irp, esp) and high invasion associated gene ibe.

Conclusions: This population snapshot analysis highlighted the dominance of the two major CTX-M-producing E. coli subclades regarding invasive infections in Hungary: a currently rising ST131 C1-M27 subclade and the dominant C2/H30Rx one. Only the C2/H30Rx isolates showed close genetic relationship.

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Novel Aspects of the Complex Cannabinoid Signaling in Human Sebocytes

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Introduction: Sebaceous glands (SGs) are key contributors to cutaneous homeostasis. Although our understanding of their biology has grown, several aspects of human SG (patho)physiology are still unknown. Considering that SG dysfunction-associated diseases and skin conditions, such as acne, are highly prevalent disorders, there is an unmet need to explore unknown regulators of the SG physiology. We have previously shown that the "classical" endocannabinoid signaling was a positive regulator of the sebaceous lipogenesis, whereas (-)-cannabidiol (the most important non-psychotropic phytocannabinoid) exerted complex cellular anti-acne effects. Of great importance, some of its effects were mediated via the activation of non-classical cannabinoid targets (e.g. adenosine A2A receptors), highlighting that certain members of the purinergic signaling system may contribute to the regulation of SG biology.

Aims: Within the confines of the current project, we aimed to explore the role of the purinergic branch of the non-classical cannabinoid signaling in controlling sebocyte functions.

Methods: Viability, proliferation, lipid synthesis, and gene expression of human immortalized SZ95 sebocytes were monitored by MTT-assay, CyQUANT-assay, Nile Red labeling, and Q-PCR, respectively.

Results: First, we assessed the adenosine receptor expression profile of human sebocytes. Importantly, we showed that, besides A2A, A1, and A2B adenosine receptors are also expressed, whereas expression of A3 was around the detection limit. Next, we assessed the effects of a wide concentration range (1 nM–1 mM) of adenosine. We found that it had no effect on the viability and the basal, homeostatic sebaceous lipid synthesis (24-48-hr treatments), but it significantly suppressed the arachidonic acid-induced, acne-mimicking, excessive lipogenesis (1-10 nM; 24-48 hrs), and exerted anti-proliferative effects (1 mM; 24-72 hrs).

Conclusions: Our current findings strongly argue that purinergic signaling may be involved in the regulation of SG biology. Moreover, our data highlight the possibility that certain adenosine receptors may be promising anti-acne targets.

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Application of amino acid based polymers for drug delivery

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Introduction: Biopolymers such as poly(aspartamide) with high degree of polymerization are suitable materials for preparing drug delivery systems. Poly(succinimide), which is the anhydrous form of poly(aspartid acid), is chemically similar to the natural proteins, therefore it possess excellent degradation property at physiological condition. Moreover, it could provide reduced side effects and protect the drug from early deactivation. Applying electrospinning technique, fibrous polymer meshes can be produced with a diameter in the nano- or micrometer range. Due to the large specific surface, they can increase the dissolution and absorption of the conjugated drug. As a consequence of these favorable properties, better pharmaceutical theraphy can be achieved.

Aims: The aim of this study was to fabricate biocompatible and biodegradable, nanofibrous polymer-drug conjugates using dopamine-conjugated poly(aspartamid) and to investigate the incidental citotoxic effect of these systems.

Metods: In order to prepare polymer-drug conjugates, poly(succinimide) was conjugated with dopamine and formulated by electrospinning. The electrospun meshes were characterized both chemically (FT-IR) and physically (scanning electon microscopy, atomic force and two-photon microscopy). The kinetics of dopamine release and the solubility were monitored by UV-VIS spectroscopy. The biocompatibility was assessed by culturing of human dental stem cells and the SH-SY5Y human neuroblastoma cell line in the presence of these polymer-dopamine conjugates. The cell viability was determined using the WST-1 proliferation reagent and cell morphology was observed under phase-contrast, two-photon as well as confocal microscopy. The presence of dopamine receptors on both cell types were investigated by immunocytochemical analysis.

Nanofibrous meshes were successfully prepared from dopamine-conjugated poly(aspartamide) and prolonged drug release was revealed. According to the cell viability results, these conjugates are biocompatible. The cells tolerate the dopamine-polymer conjugates until a higher concentration than free dopamine.

Conclusions: Applying these biocompatible poly(aspartamide) based drug delivery systems, the side-effects can be reduced, which is a promising feature regarding the future therapy.

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In vitro and in vivo efficacy of amphotericin B against Candida auris isolates

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Introduction: C. auris is a recently emerged fungal pathogen associated with hospital outbreaks and high mortality. Similarly to other pathogenic fungi, therapeutic options are very limited and antifungal resistance commonly found for C. auris further aggravates treatment. While amphotericin B is not the drug of choice for invasive Candida infections, it may be the last resort antifungal against echinocandin resistant C. auris isolates or in cases of central nervous or urinary tract involvement.

Aims: Aim of our study was to examine the pharmacodynamic activity of amphotericin B against different C. auris lineages.

Methods: In our experiments the in vitro activity of amphotericin B was assessed with time-kill methodology on clinically relevant concentrations (0,25, 0,5, 1, 2 mg/l) against nine C. auris isolates belonging to three different lineages (South-Asian, South-African, South American). In vivo efficacy was determined in tissue fungal burden experiments, performed in a neutropenic C. auris bloodstream infection mouse model against six isolates. Daily amphotericin B treatment (1 mg/kg) of the animals was started one day postinfection and continued for five days. Residual fungal cells in the kidneys of treated and control animals were compared using Mann-Whitney test at day six postinfection.

Results: According to our results, amphotericin B exerted fungistatic activity against most of the isolates at concentrations between 0,25-1 mg/l while was fungicidal at 2 mg/l in vitro against six out of nine isolates tested. A high degree of variance in activity was observed against South-Asian isolates, while was comparable for the other two clades. Daily administration of 1 mg/kg resulted in significantly decreased kidney fungal burden compared to control at day six, however the activity was only fungistatic and while difference was significant, never exceeded two orders of magnitude. The better the in vitro activity was, the higher decrease in fungal burden was observed during in vivo experiments.

Conclusions: Based on our results in vitro activity of amphotericin B at 1 mg/l correlates best with the in vivo efficacy. While a significant decrease in fungal burden was observed, the slow elimination of fungal cells may necessitate a longer than standard course of amphotericin B treatment.

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Sigma-1 Receptor Agonist Protects Human Trabecular Meshwork Cells from Fibrotic Factors

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Introduction: Lowering intraocular pressure (IOP) is currently the only strategy to slow the progression of glaucoma. IOP can be reduced by decreasing the aqueous humor production or increasing its outflow. The fibrotic-like remodeling of the actin cytoskeleton in trabecular meshwork (TM) cells decreases outflow, thus cytoskeletal disrupting drugs could be a novel therapeutic approach to lower IOP.

We showed that fluvoxamine (Flu), the sigma-1 receptor (S1R) agonist, is anti-fibrotic in the kidney, therefore we hypothesize its efficiency in the prevention of fibrotic remodeling in the eye.

Aims: To investigate the expression of S1R in TM cells and to measure the effect of Flu on (i) proliferation and (ii) on actin cytoskeleton rearrangement of control human TM cells (HTM5).

Methods: Immunocytochemistry and Western blot were used to detect S1R on HTM5 cells. To investigate the effect of Flu on proliferation, cells were treated for 24h either with 20 ng/mL platelet-derived growth factor (PDGF) or 10 ng/mL transforming growth factor-beta 2 (TGF-β2) combined with 10 or 15 μM of Flu. Cell proliferation was determined by the thiazolyl blue tetrazolium bromide assay. Morphological changes and cytoskeleton rearrangements were visualized by immunostaining of F-actin and were detected with an inverted fluorescent microscope.

Results: S1R is present in HTM5 cells and localized in the cytosol. Cell proliferation induced by PDGF or TGF-β2 was prevented by Flu. Phalloidin staining of HTM5 cells showed a diffuse actin network of thin actin filaments in controls. A change of cytoskeleton morphology was observed upon PDGF or TGF-β2 treatment caused by the reorganization of stress fibers along a longitudinal axis, with the formation of F-actin bundles and actin-clumps. All of these phenomena were largely blocked by Flu.

Conclusions: Flu can reduce the profibrotic factors-induced cytoskeletal rearrangement that may lead to lower outflow resistance thus, enhancing outflow facility. Our preliminary results propose that Flu could be a potential candidate for the development of a novel IOP-lowering drug. However, further experiments with other treatments that alter TM functionality (CTGF or Dexamethasone) are needed to corroborate these results, as well as studies in in vivo animal models.

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Histophysiology changes of rat prostate gland after injection of sulpiride

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Introduction: Benign prostatic hyperplasia (BPH) is a progressive neoplastic disease of men, which prevalence correlates with age. It is important to elucidate the mechanism of BPH pathogenesis to develop novel therapeutic approaches, which require a detailed characteristic of experimental models, used for preclinical studies. The model of BPH is based upon the recreation of hormonal disbalance. The course administration of high doses of testosterone in rats leads to hyperplasia of epithelium of the prostate ventral lobes which is similar to morphological changes in BPH in humans. Sulpiride – a blocker of D2 dopamine receptors is utilized, it stimulates prolactin secretion by hypophysis, which in turn leads to hyperplasia of prostatic acinar epithelium. We studied the morphological changes of the prostate, proliferative activity of epithelium in prostate acini, levels of prolactin, testosterone and prostate-specific antigen (PSA) in the blood serum of Sprague-Dawley rats.

Aims: To compare the morphological hyperplastic changes of the prostate gland, the prolactin and PSA, testosterone level in the serum plasma during course administration after repeated injections of sulpiride in a dose of 40 mg/kg for 30 and 60 days and following withdrawal of injections for 10 and 30 days.

Methods: We evaluated morphological and morphometrical changes of the prostate ventral lobe and the Ki-67+ epithelial cells in the acini. ELISA was used to analyze the dynamics of serum hormones concentrations.

Results: In the group with 30 or 60 days of sulpiride injection and subsequent withdrawal for 10 days, there is hyperplasia of prostate ventral lobe epithelium, but the serum level of PSA shows no difference to the control group. In the group with 60 days of sulpiride injection and subsequent withdrawal for 30 days the pronounced hyperplastic changes of prostate remain and there is an increase of the PSA serum level, but no changes of prolactin and testosterone level.

Conclusions: The injection of 40 mg/kg of sulpiride to Sprague-Dawley rats for 60 days by morphological criteria, is a model of stable hyperplastic changes of the prostate, which are similar to benign prostatic hyperplasia in humans.

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Efficacy of Mindfulness-based cognitive therapy on stroke rehabilitation

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Introduction: Stroke often causes life-long consequences for stroke survivors, it may produce deficits in motor, perceptual, emotional and/or cognitive functioning. It is important to understand which strategies could help for patients to support successful recovery. Adjustment to living with stroke is complex, influenced by the severity of functional limitation, degree of emotional disturbance, the meaning attached to stroke, disability and rehabilitation. The efficacy of Mindfulness-based cognitive therapy (MBCT) on stroke rehabilitation has not been entirely established.

Aims: The aim of this study is to evaluate the efficacy of group-based MBCT in comparison treatment-as-usual (TAU) with MBCT+TAU in stroke survivors during inpatient stroke rehabilitation.

Methods: Clinical participants are randomly assigned either to group-based MBCT+TAU or to a TAU control group. The MBCT intervention consist of six weekly 1,5-hr didactic group sessions. Clinical symptoms are assessed by self-report symptom maesures (BDI, STAI, FFMQ, MSPSS) and by examining changes in physical condition (FM, FIM) and neurocognitive functioning (Pieron). Measures are completed at pre-treatment, post-treatment, and 3-month follow-up.

Results: Patient inclusion is ongoing. Poster presentation demonstrates only cross-sectional analysis of patients' baseline data at the onset of treatment. According to the plan the research is going to be conducted for minimum two more years. The questionnaire-based research in MBCT group too will be supplemented with qualitative tools and interviews. We hypothesize that more participants will reach clinically significant change of measured parameters (for example depression) in the MBCT intervention in comparison with the TAU control group and the findings will suggest group-based MBCT may have promising utility and could offer a suitable psychological intervention for stroke survivors.

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Integrin modulation by DARPins

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Integrins are a major family of cell adhesion molecules that mediate cell adhesion to the extracellular matrix. Integrins exist in different conformations and an activation step is required to allow for ligand binding and subsequent signaling. Integrin-mediated adhesion induces various signaling pathways and regulates cell migration and proliferation. Therefore, control over integrin activation is crucial for cell physiology.

The aim of this project was to modulate cell adhesion with designed ankyrin repeat proteins (DARPins).

These small-sized (12-18 kDa) synthetic proteins are able to mediate functions through protein-protein interactions. We selected DARPins based on their ability to bind the cytoplasmic Beta3 subunit of integrins (collaboration with group of Prof. Plückthun, University of Zurich). We focused on AlphaIIbBeta3 integrin, which is required for platelet aggregation. Platelets express these integrins to adhere to ECM proteins like fibrinogen (FNG), collagen, fibronectin and laminin. The development of materials that show compatibility with blood in medical applications is still a major challenge in the field of designing surfaces for cardiovascular use. It is widely recognized, that the adsorbed proteins of the blood (especially FNG) can be recognized by receptors of the platelets and encourage them to adhere.

Cell adhesion was examined through genetically modified CHO A5 cells producing DARPins. This cell line variant was stably transformed to express high levels of human integrin AlphaIIbBeta3; therefore, these cells are often used as platelet models.

Before cell adhesion measurements on FNG, it was necessary to establish the amount of protein adsorbed from different solution concentrations, and to assess at which concentration FNG forms a monolayer. Previous studies have shown that platelet adhesion is correlated with the degree of the adsorption-induced unfolding of the FNG, thus the conformation of the immobilized FNG.

Cell adhesion measurements were carried out on FNG-coated surfaces with DARPin-transfected, and non-transfected cells. As a positive control, Mn2+ as an external integrin activator was used. Our results showed that the expression of DARPins did not enhance cell adhesion, and thus appear unable to activate integrins. Further studies are required to elucidate the modulating process of DARPins in living cells.

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Species-Specific Glucose-6-Phosphatase Activity in the Small Intestine – Studies in Three Different Mammalian Models

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The liver is a well-known gluconeogenic organ responsible for the maintenance of blood glucose level in all post-absorptive situations. However, kidneys and intestines can also produce glucose in blood, particularly during fasting and under protein feeding. The major enzyme involved is the glucose-6-phosphatase, which catalyzes the common terminal reaction of gluconeogenesis and glycogenolysis, i.e., the hydrolysis of glucose-6-phosphate to glucose and inorganic phosphate. Observations gained in different experimental animals have given ambiguous results concerning the activity and presence of the glucose-6-phosphatase system in the small intestine.

Aims: The aim of this study was to better define the species-related differences of this putative gluconeogenic organ in glucose homeostasis.

Methods: The components of the glucose-6-phosphatase system (i.e., glucose-6-phosphate transporter and glucose-6-phosphatase itself) were analyzed at mRNA and protein level in the small intestine mucosae and liver of rats, guinea pigs, and humans. Glucose-6-phosphatase activities were also detected.

Results: The results showed that the glucose-6-phosphatase system is poorly represented in the small intestine of rats; on the other hand, significant expressions of glucose-6-phosphate transporter and of the glucose-6-phosphatase were found in the small intestine of guinea pigs and humans. The activity of the recently described fructose-6-phosphate transporter– intraluminal hexose isomerase pathway was also present in intestinal microsomes from these two species.

Conclusions: The results demonstrate that the gluconeogenic role of the small intestine is highly species-specific and presumably dependent on feeding behaviour (e.g., fructose consumption) and the actual state of metabolism.

Keywords: glucose-6-phosphatase; glucose-6-phosphate transporter; small intestine; endoplasmic reticulum; fructose

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Trait or state anxiety: refined sampling methods of emotion-related behavior in rodent models

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Mental disorders, particularly those associated with anxiety represent a serious burden on both the individual and the society. Preclinical animal models are the predominant approaches to devise therapy, however, available tests more successfully describe populational features than traits of specific subjects, as indicated by their low inter-test correlations and intra-test predictions at the individual level. Thus, current indirect approaches to measure trait anxiety may be strongly biased by the permanently changing internal states of individuals.

Here, we present a novel approach, based on serial sampling of behavior, to reduce state-dependent variance and to refine the characterization of individual traits.

We conducted a four-time sampling series, applying the three most widely used anxiety tests for rodents, the elevated plus-maze, light-dark box and open-field, in a semi-random design, under neutral and highly aversive conditions and constructed summary measures (SuM) from the spatio-temporal and ethological readouts of the tests.

Principal component analysis revealed that SuMs, such as averages and slopes of avoidance behavior, explain greater proportion of the total variance of the data than single measures (SiM). In addition, SuMs, contrary to SiMs, show consistently higher, significant inter-test correlation and stronger predictive potential to the behavioral output of same type, as well as novel anxiety tests under aversive conditions.

We suggest that the appearance of such associations between SuMs of different test types and conditions support the idea of an emotional trait as a common drive of behavior in rodent anxiety tests that is measurable by the refined sampling method presented here.

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Virtual Reality based targeted Theory of Mind Intervention for clinically stable outpatients with schizophrenia: preliminary results

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Introduction: based on the throughout literature review on the functional significance of Theory of Mind (ToM) deficits in schizophrenia, on the efficacy of the existing ToM interventions and on the feasibility of VR based interventions in schizophrenia, a new Virtual Reality (VR) based intervention has been developed by our research team at the Semmelweis University's VR-Laboratory. The current lecture aims to present the preliminary results of the ongoing feasibility study of the mentioned intervention called VR-ToMIS (VR based ToM Intervention in Schizophrenia).

Aims: Evaluate the effects of VR-ToMIS on ToM- and communicative-pragmatic skills, symptomatology and social functioning.

Methods: We conduct a randomized, controlled, single-blind trial with a three-month follow-up period to evaluate the effects of VR-ToMIS. 17 clinically stable outpatients with schizophrenia have been randomized to the VR-ToMIS program (n: 9) for 9 weeks (1 session/week) or to the passive VR group (n: 8). All patients completed pre- and post-treatment assessments of neurocognitive functions, ToM, communicative-pragmatic skills and social functioning, and some of them have already completed the follow-up assessment as well. To avoid any side-effects safety measures were also administered after each session.

Results: VR-ToMIS group demonstrated a significant improvement on ToM assessment. Additionally, patients found the intervention useful, interesting and engaging. According to their relatives' feedback reduced suspiciousness and increased willingness to participate in conversations,were also observed after the treatment.

Conclusions: Despite the obvious limitations (e.g. small sample size), our results encourage the utilization of modern technology in psychotherapies even in the case of psychotic disorders.

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All breast milk designed equally?

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Introduction: After birth breastfeeding is the only direct biological connection between the mother and newborn infant. Preterm birth disrupts intrauterine development, therefore preterm infants are deprived of transplacental hormonal exposure. Our investigation focused on the presence of pituitary hormones, like folliculus stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), and thyroxin in breast milk during the first 6 month of lactation.

Methods: Mothers of term (n=15) and preterm (n=10) infants donated samples monthly from a midday breastfeeding during the first 6 months of lactation. Donors were recruited at the Department of Gynecology, University of Pécs, Hungary.

Results: Total protein levels (10.139±0.364 g/l vs 9.542±0.297 g/l; p=0.207) and TSH concentrations (0.018±0.001 vs 0.024±0.002 mU/l; p=0.096) were similar in the two groups. LH concentrations were significantly higher in the preterm samples (0.04±0.009 vs 0.015±0.004 U/l; p=0.041), respectively. In contrast, the FSH level was significantly higher in breast milk produced for term infants (0.179±0.014 vs 0.122±0.008 ng/ml; p=0.001). Thyroxin concentration was significantly higher in the preterm samples (0.671±0.061 vs 1.124±0.073 ng/ml; p<0.001). We did not detect significant monthly changes in the distribution of the investigated hormones during the study period.

Discussion: Breast milk contains hormones produced by the pituitary gland and thyroxin as well, and we detected the presence of these hormones in both groups during the examination period. Differences between the hormonal composition of term and preterm breast milk were found. The immature gastrointestinal tract and the reduced enzyme production may facilitate the absorption of these hormones or they may influence the development of the gastrointestinal tract directly.

Ethical Committee: PTE KK RIKEB 2018/7271.

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The Evaluation of Strain Parameters Using Functional CT Angiography

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Introduction: Longitudinal strain measured by speckle tracking echocardiography (STE) has emerged as an early sensitive marker of left ventricular (LV) dysfunction. Cardiac CT angiography, due to its high spatial resolution, allows for reliable evaluation of the LV morphology. Moreover, the assessment of myocardial strain became feasible based on functional CT datasets. However, data on myocardial deformation imaging using CT angiography are limited.

Aims: To compare STE and CT derived LV and left atrial (LA) global longitudinal strain (GLS) parameters obtained by using a feature tracking algorithm in patients who underwent transcatheter aortic valve implantation (TAVI).

Methods: We enrolled 28 post-TAVI patients (mean age: 78.2 ± 9.4 years, women: 60.7%) who underwent retrospectively gated cardiac CT angiography and echocardiography on the same day. We reconstructed CT datasets in 10% increments throughout the entire cardiac cycle. LV functional parameters including ejection fraction (EF) and GLS were measured on 2- and 4-chamber views on both CT and echocardiography. In case of global peak reservoir strain (LAGS) measurements were carried out using 2-chamber images with both modalities.

Results: Median LV EF was 58.1 [47.6 - 65.2] % on CT vs. 62.5 [50.3 - 68.3] % on STE. Median LV GLS was 19.9 [14.8-22.4] on CT vs. 19.9 [16.8-24.7] on STE. Our results showed strong correlation between CT and STE for the measurement of LV GLS with a mean bias of -1.6. Between the two imaging modalities correlation coefficients were ρ=0.78 and ρ=0.70 for LV GLS and EF, respectively, $p<0.05$ in both cases. The median LAGS was 19.0 [13.5-27.3] for CT vs. 28.0 [17.5-32.6] for STE. We detected good correlation for LAGS measures with a mean bias of -5.6, inter-modality correlation coefficient was ń=0.87, $p<0.001$.

Conclusions: We demonstrated good correlation in quantifying global LV GLS and EF using CT angiography as compared with echocardiography. Moreover, the evaluation atrial strain using CT is feasible and demonstrated good correlation with STE.

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The efficiency of therapeutic antiseptic oral liquid application

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Introduction: Comprehensive daily oral hygiene is considered a key factor for periodontal diseases prevention. It is based on the use of main and auxiliary oral hygiene products. Even in the event that today's most popular antiseptic dental solutions are used, there seems to be a dilemma: antibacterial effects are not the same as anti-inflammatory ones.

Keywords: periodontal diseases, prevention, oral rinses.

Aims: to evaluate the clinical efficiency of antiseptic oral liquid application.

Research methods: As a therapeutic dental rinse for the oral cavity the antiseptic liquid Dentaseptin (OOO Tselit, Voronezh) was used and studied at the Propedeutic Dentistry Department of Voronezh State Medical University. The study involved 65 patients at the age of 20 to 60 complaining of inflammatory periodontal disorders. The patients were recommended to rinse the oral cavity with Dentaseptin for one minute twice a day after tooth brushing, before and after check-up examinations, during 3 weeks.

Results: The patients experienced an improvement in the state of the oral mucosa, which included the elimination of tension, itching and burning. The objective data is that the gums became thicker, the swelling disappeared, the bleeding and tension of soft tissues reduced. The initial examination showed that 68 % of patients had an unsatisfactory level of oral hygiene. However, three-week regular application of Dentaseptin resulted in a true ($p<0,001$) reduction in the mean value of the oral hygiene index. According to the survey data, Dentaseptin possesses good organoleptic and cleansing properties, has a permanent refreshing effect; it is easy to use. Over the research period, the check-up examinations did not reveal any cases of Dentaseptin locally irritative and allergizing effects on the oral mucosa.

Conclusions: The implementation of the complex of preventive measures with the use of antiseptic dental liquid Dentaseptin contributed to a decrease in the clinical signs of inflammatory periodontal diseases.

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Comparison of Venous and Capillary Sampling Methods by Bedside Testing

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Introduction: Analyzing venous samples by point of care testing allows faster turnaround-times and therefore faster descision-making in an emergency department setting. The newer bedside hematology analyzers are able to analyze capillary blood samples. This has additional advantages, due to the less invasive and faster sampling method. However the accuracy of capillary blood sampling does not only depend on the measurement method, but on the sampling technique as well.

Aims: We aimed to compare the capillary and venous sampling techniques in regard of accuracy and precision and to identify their clinical advantages.

Methods: We tested the analytical prescision in the first part of our study. Venous and capillary samples were obtained from 26 children, and were analyzed on the Norma Icon 5 part point of care hematology analyser, and the Orion QuikRead go® CRP test. Control measurements were made in the laboratory on a Siemens Bayer Advia 120. In the second part 25 children were divided to randomized groups to have blood tests taken from capillary or venous sampling and to have blood tests processed by point of care or laboratory. We compared the time parameters, the painfulness of blood sampling and patient satisfaction between the groups.

Results: There was no significant difference between the point of care and the laboratory results in the most commonly used parameters (e.g.: RBC, WBC, LYM, GRAN, HGB, HTC, CRP). We also found a good correlation between capillary and venous samples in these parameters. Capillary sampling took 2 minutes less on average. The point of care results were significantly earlier available. (point of care capillary vs. laboratory: $p=0,0005$, point of care venous vs. laboratory). The pain levels of capillary sampling, measured on different pain scales, suitable for the patient's age-group, were significantly lower ($p=0,028$). There was no difference on the self/parent reported measures. The survey we used for measuring patient satisfaction showed high scores in all the questions, but there was no significant difference between the groups.

Conclusions: The point of care testing provides reliable results for most parameters. Further research is needed to investigate whether the differences between capillary and venous results have a definable pattern and to indentify clinical factors that affect the precision of capillary sampling.

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Investigating the effect of antifibrotic drug candidate in the experimental model of lung fibrosis

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Introduction: Accumulation of connective tissue in the respiratory system is a serious complication of chronic inflammation leading to decreased respiratory function and increased propensity for infections. Despite the unmet medical need, there is no effective treatment against fibrotic processes of the lung.

Aims: Previously, as a part of antifibrotic drug screening using in vitro and in vivo systems, our research group identified a compound MTS004 decreasing renal fibrosis. In this study we aimed to investigate the antifibrotic effect of the compound in the experimental model of lung fibrosis.

Methods: Primary lung fibroblasts were isolated from fibrotic lung tissue of C57BL/6J mice and characterised by immunofluorescence staining of α smooth muscle actin (αSMA) and platelet-derived growth factor receptor beta (PDGFR-B). Cells were stimulated with recombinant platelet-derived growth factor B (PDGF-B), and the antiproliferative effect of MTS004 was investigated by MTT assay. Extent of bleomycin-induced pulmonary scarring in MTS004 treated mice was examined by histological staining and Western blot analysis.

Results: We optimized an in vitro system using áSMA and PDGFR-B positive primary lung fibroblast cells for the screening the antiproliferative effect of the investigated compound. Treatment with MTS004 decreased the PDGF-B-induced proliferation of primary lung fibroblast in dose-dependent manner. In our in vivo experiment MTS004 improved the survival of the bleomycin treated mice and inhibited the bleomycin-induced deposition of connective tissue.

Discussion: Our in vitro and in vivo data revealed the antifibrotic effect of MTS004 in the experimental models of kidney and lung fibrosis. These results may serve as a basis for further preclinical development of drug candidates.

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Metabolic characteristics of clear cell and papillary renal cell carcinomas

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Introduction: Metabolic reprogramming plays an important role in formation and development of kidney cancer. The bioenergetic need of tumor cells could be supported by various metabolic pathways, therefore, clarifying the presence and activity of metabolism-related proteins may provide an opportunity to identify new therapeutic targets.

Aims: Our aim was to characterize the metabolic features of clear renal cell carcinomas (CCRCCs) and papillary renal cell carcinomas (PRCCs) in details using immunohistochemical and in vitro analyses.

Methods: Human tissue samples were collected from patients with CCRCC or PRCC. To assess the expression of mTOR signaling and metabolic markers in CCRCCs and PRCCs, immunohistochemistry was performed using tissue microarray sections. Renal cell carcinoma cell lines (786-O, A498, ACHN) and human kidney proximal tubular epithelial cell line (HK2) were used to analyze the effect of different metabolic inhibitors (rapamycin, BPTES, ACSS2 inhibitor, etomoxir) on tumor growth. The expression of mTOR-related and metabolic enzymes was analyzed by WES Simple technique.

Results: The expressions of GLS, ACSS2, CPT1A (markers for alternative bioenergetic pathways) and ATPB (a marker for oxidative phosphorylation) were significantly higher in PRCCs than in CCRCCs. In contrast, expression of p-S6 (mTORC1 activity marker), GLUT1, and PFKP (glycolytic markers) was higher in CCRCCs. In our in vitro studies, all markers were expressed at a lower level in the HK2 cells as compared to the renal cell carcinoma cell lines. Rapamycin had the highest antiproliferative effect on 786-O cells that had the highest p-S6 expression. 786-O was also sensitive to glutaminase inhibitor, however, those cell lines which express both isoforms of GLS were resistant. ACSS2 inhibitor and etomoxir had a modest effect, however, glutaminase and ACSS2 inhibitors enhanced the antiproliferative effect of rapamycin in some of the cell lines.

Conclusions: In contrast to CCRCCs mTORC1 hyperactivity and high glycolytic marker expressions, PRCCs could use alternative bioenergetic pathways (glutaminolysis, acetate utilization, fatty acid â-oxidation) to fulfill bioenergetic demands. Moreover, our in vitro results suggest potential roles of metabolic inhibitors in renal cell carcinoma treatment.

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Modern aspects of postoperative pain during endodontic interventions

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Introduction: Endodontic treatment, is a section of practical dentistry, including the study, diagnosis, treatment and prevention of diseases of the pulp, root canals and periapical tissues. Modern technologies for the treatment of complicated forms of caries are at a fairly high level and are well studied. At the same time, measures to reduce post-pain syndrome have practically not been studied.

Purpose of the study: Optimization of anti-stress support for endodontic interventions using multimodal and proactive analgesia technology.

Diagnostic and treatment methods: Complicated forms of carious lesions of hard tooth tissues occupy leading positions in the structure of modern dental pathology. At the same time, endodontic interventions remain a priority in the treatment of this group of conditions.

At present, the technologies of endodontic treatment proper have been developed at a fairly high level. The technologies of their anti-stress support, on the contrary, have not been practically studied and implemented. In particular, the traditional approach used in this regard, which is the use of only local anesthesia, does not solve the problems of neurovegetative stabilization, psycho-emotional protection, post-manipulation pain syndrome.

In modern medicine, there are concepts that allow you to expand and enhance the capabilities of local anesthesia to a qualitatively different level of antinociceptive and anti-stress support. In particular, the principles of multimodal and proactive analgesia have received well-deserved attention of clinicians. However, programs providing for their use in a format adapted to the conditions of therapeutic dentistry, as well as completely "covering" the stress-limiting needs of the intra- and post-manipulation period, have not been developed to date.

Conclusions: In the course of this work, we must prevent unwanted neurovegetative and psychoemotional reactions that occur during and after endodontic treatment. To improve the quality of analgesia and prevent the appearance of pain in the post-manipulation period.

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Investigation of the inotropic and chronotropic effect of newly synthetized hypoxanthine-tricyclano on ex vivo rat atrial preparations

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Introduction: The myocardial adenosinergic mechanisms participated in exerting several protective and reparative effects. Accordingly, the adenosinergic system is a promising target of drug development to treat cardiovascular maladies including ischemic heart disease and arrhythmias. Recently in the Department of Pharmaceutical Chemistry, University of Debrecen, hypoxanthine-tricyclano, a new adenosine analogue has been synthetized. Comparing the structure of adenosine and hypoxanthine-tricyclano, adenine and ribose are substituted with hypoxanthine and a tricyclic moiety derived from morpholino, respectively. In a previous study, we have found that the inotropic effect of hypoxanthine- tricyclano can be inhibited by 8-(p-sulfophenyl)theophylline, an A1 and A2 adenosine receptor antagonist, so this effect appears to be mediated, at least in part, by the A1 adenosine receptor.

Aims: In the present work, we aimed to examine the inotropic and chronotropic effects of hypoxanthine-tricyclano in rat left and right atria, in comparison with those of adenosine.

Metods: The left auricula atrii and the right atrium (keeping the interatrial septum) were isolated from male Wistar rats and mounted at 10 mN resting tension in 10 mL vertical organ chambers containing Krebs solution, oxygenated with 95% O_2 and 5% CO_2 (36 °C; pH=7.4). Left atria were paced (3 Hz, 1 ms, 1-2 V), while right atria worked spontaneously. Concentration-effect (E/c) curves were constructed with adenosine and, after wash-out, with hypoxanthine-tricyclano on all atria. Finally, another E/c curve with adenosine was generated without washing out the hypoxanthine-tricyclano doses administered previously. The atrial contractile force and the right atrial rate were measured.

Results: As it is well-established, adenosine exerted strong negative inotropic effect that was similar on the left and right atria. In contrast, hypoxanthine-tricyclano produced a moderate positive inotropic effect (to a similar degree on the left and right atria) that was surmountable with adenosine. Consistent with their inotropic effects, adenosine caused a considerable negative chronotropic effect (as expected), while hypoxanthine-tricyclano exerted a slight positive chronotropic effect that was surmountable with adenosine.

Convlusions: These findings suggest that hypoxanthine-tricyclano is a reversible, orthosteric, partial and inverse agonist for the A1 adenosine receptor.

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Co-electrospun Poly(vinyl alcohol)/Poly(succinimide) Composite Scaffolds for Tissue Engineering

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Introduction: One of the most focused-on point in biomedical research is the fabrication of complex tissue engineering scaffolds, with the ultimate objective being a functional, biocompatible and biodegradable implant that could facilitate and enhance tissue regeneration. Creating such implants is a highly challenging and difficult task. Physical and chemical characteristics have to be optimised and the balance between biodegradability, mechanical strength and overall practicality cannot be easily obtained. In this regard, composite materials have been regularly used in numerous areas of science and engineering as they incorporate advantages from two or more component materials.

Aims: Our objective was to fabricate a composite, fibrous mesh composed of both degradable and non-degradable elements, that could be applicable as an implant with competent mechanical properties without hindering in vivo tissue integration.

Methods: Electrospinning is a technique to manufacture meshes composed of micro or even nano sized fibres that is frequently used in biomedical research due to its versatility and numerous possible modifications. Fabricated scaffolds were produced by co-electrospinning, scilicet, by concurrently electrospinning poly(vinyl alcohol) and poly(succinimide) solutions resulting in scaffolds of 1:1 mass ratios. Post-electrospinning processing including mechanical and chemical treatments were performed to reinforce the scaffolds and induce cross-linkage. Scaffolds were chemically examined with Attenuated Total Reflection–Fourier Transform Infra-Red spectroscopy to confirm the presence of both polymers while investigation of scaffold microstructure was performed with Scanning Electron Microscopy and Two-Photon Excitation Microscopy imaging. Water contact angle assessments were conducted to determine scaffold wettability and uni-axial pulling measurements were carried out to evaluate mechanical properties. Finally, cell viability examinations were executed on two different cell lines (A2058 and MeWo) to investigate possible cytotoxic effects.

Results: Results confirmed the presence and random interpenetrating distribution of both PSI and PVA fibres in the fabricated scaffolds. Mechanical studies indicate that meshes are indeed competent for implantation while cell viability study revealed no cytotoxic effects, thus in vivo investigation of biocompatibility and biodegradability can commence.

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Large-scale analysis of transcriptome changes between patients with myelodysplastic syndrome and healthy individuals

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Introduction: Our project is focusing on understanding the effect of genetic alterations in myelodysplastic syndrome (MDS) and characterizing the transcriptomic differences between healthy and MDS patients. Myelodysplastic syndromes are a group of hematological disorders, often associated with an abnormal number of blood cells, and an abundance of myeloblasts in the bone marrow and peripheral blood as well. In the early stages of MDS, there are no symptoms, therefore diagnosis has to wait until symptoms appear, and only then treatment can begin. If patients with no symptoms could be distinguishable from healthy patients by transcriptome isoform changes, treatment could start in the early stages of the disease. This would be very important as MDS transforms to acute myeloid leukemia (AML) in 30% of cases.

Aims: There are several somatic mutations which can lead to MDS. The most frequently mutated genes are splicing factors, therefore we aimed to look for changes in the splicing isoforms of various gene sets with bioinformatic methods.

Methods: We used three datasets from public sources, that contain 123 MDS and 19 controll samples derived from bone marrow. The samples were all CD34+ cells and experiments used total, stranded and paired-end RNA-Seq with the same read length. The analysis was performed with the iso-kTSP program, developed to detect consistent isoform changes between conditions.

Results: However, initially we could not distinguish healthy and MDS groups in an unambiguous manner. Here we show, that a small, but consistent and biological relevant difference exists in isoforms, that we could use in the future to make diagnosis before the development of MDS.

Conclusions: Transcriptomic alterations could be useful biological markers, and they can accelerate diagnosis and treatment by providing invaluable information about the status of patients. Low-cost detection methods, like RT-RCR or similar might be useful, when carried out on blood samples of high-risk patients admitted to the hospital for an independent reason. Detecting transcriptomic alterations in healthy and MDS patients with or without symptoms, would be a further step to personalized medicine, where every patient could get appopriate treatment based on their molecular profile. Moreover, they can also contribute to a better treatment of these diseases as well.

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Dual effect of S1P3 receptors on myocardial functions

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Introduction: In acute coronary syndrome (ACS) activated platelets release numerous bioactive mediators, such as sphingosine-1-phosphate (S1P) during the thrombotic occlusion of coronaries. These may influence the severity of ischemia/reperfusion (I/R) injury. S1P is a lysophospholipid mediator which regulates diverse biological processes through its specific receptors (S1P1-5). Among others, S1P has been shown to be protective against I/R injury in the heart. On the other hand, some studies highlighted its potential constrictive effects in the coronaries.

Aims: When S1P is released in ACS in large amounts, its favorable and potentially deleterious effects may be conflicted. We aimed to delineate how these conflicting S1P actions indeed affect postischemic cardiac injury.

Methods: Experiments were conducted on isolated Langendorff-perfused murine hearts. Left ventricular pressure and coronary flow (CF) were continously monitored. After equilibration, S1P (10-6 M) or its vehicle was infused to the perfusion line for 5 minutes. Then either wash-out or a 20-minute global ischaemia/2-hour reperfusion protocol was applied. Size of the infarcted myocardium was determined through TTC staining. Experiments were carried out in WT, S1P2 and S1P3 gene-deficient C57/Bl6 mice strains.

Results: Administration of S1P reduced CF by 1.95±0.33 ml/min and compromised left ventricular contractile performance in WT hearts. These effects in S1P2 KO mice were similar. However, in S1P3 KO hearts the S1P induced CF reduction (0.93±0.10 ml/min), and decline in contractile function were diminished. In the I/R experiments, postischemic functional recovery was weaker and infarct size was larger in S1P3 KO hearts. Preischemic S1P treatment worsened the recovery of CF and contractile function both in WT and S1P3 KO hearts.

Conclusions: In this study we observed a massive CF reducing effect of S1P that resulted in the drop of the contractile function mediated via S1P3 receptor. We verified the role of S1P3 receptor in cardioprotection, but not the S1P pretreatment that just further exacerbated I/R-induced myocardial damage. These results may suggest that S1P derived from the myocardium acts on different sites compared to S1P derived from vessels. The latter scenario can occur during ACS when a large amount of S1P is released due to platelet activation.

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Characterization of Direct Cyclodextrin Effects on Voltage-gated Potassium Channels

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Introduction: Cyclodextrins (CDs) are cyclic oligosaccharides consisting of six, seven or eight alpha-D-glucopyranoside units. Due to their truncated cone structure they can form complexes with various drugs and lipid molecules. CDs are widely used as inert carriers and in research to selectively deplete cholesterol levels in biological membranes. The direct effects of CDs on ion channels have not been studied yet. Since voltage-gated potassium (Kv) channels regulate a great variety of biological processes, direct effects of CDs on these channels can contribute to the known side effects (such as immunosuppression via Kv1.3) of numerous drugs.

Aims: Our aim was to characterize direct, ligand-like effects of CDs with different sizes and side chain substitutions on various Kv channels and to demonstrate that these are independent from their effects on membrane cholesterol depletion.

Methods and Results: We carried out patch-clamp measurements to characterize the direct effects of CDs on Kv channels. Most of the tested CDs at concentrations of 1 and 5 mM partially reversibly inhibited Kv1.3 currents within 15 seconds, while some of them had no such effect. To examine the potential membrane biophysical and cholesterol depleting effects of CDs, after 1 hour incubation we measured membrane fluidity, hydration, lipid order and the extent of cholesterol depletion. We also performed a cell viability assay on Jurkat cells using flow cytometry, where in parallel with direct inhibitory effects on Kv1.3 and independent from cholesterol depletion we detected cell death after 24-hour-long CD treatments.

Conclusions: Based on our results we can conclude that CDs exert previously unknown direct inhibitory effects on Kv ion channels independent from cholesterol depletion, which can play an important role in side effects of drugs containing CDs.

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Developmental, Maturational, and Psychopathological Differences in Perceptual Sensitivity, Variability, and Stickiness Measured through Binocular Rivalry

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Introduction: Sensory signals provide ambiguous information about the state of objects in the environment. Thus, our brain has to make perceptual decisions about the environment's most likely state. Such perceptual decisions are reflected in binocular rivalry, a perceptual phenomenon known to change during development and maturation, and to differ in certain psychopathologies, compared to neurotypicals.

Aims: We aimed to explore how some aspects of perceptual decision making change during development, maturation, and how they differ in certain psychopathologies, using binocular rivalry as a proxy measure.

Methods: We measured how children, adolescents, young adults, mature adults, and two psychopathological cohorts - adults with autism spectrum disorder, and with borderline personality disorder - behave in a binocular rivalry task. We then employed a computational model to explore the dynamics underlying binocular rivalry. Using the results of this modeling procedure, we performed simulations to predict each group's perceptual behaviour in more general conditions.

Results: We find that the observed rivalry statistics differ between groups. In terms of our model, this implies that each group (on average) operates in a particular regime of model parameter space. Functionally, these operating regimes predict different degrees of perceptual sensitivity, variability, and 'stickiness' for each group. Our results show a developmental trend from childhood to young adulthood, which regresses in late adulthood; and that each adult clinical group differs from neurotypical adults in specific ways.

Conclusions: We conclude that the dynamics underlying binocular rivalry reflect the development of the visual system that is still active in adolescence, extends to young adulthood, regresses in old age, and shows marked changes in clinical populations. Furthermore, these dynamics predict differences in perceptual decision making between the observed groups.

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Alterations of DNA methylation, DNA repair, and epithelial-mesenchymal transition in colorectal cancer cell lines by S-adenosylmethionine treatment

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Introduction: S-adenosylmethionine (SAM) is a universal methyl donor molecule, used as a dietary supplement. SAM is involved in DNA methylation processes, thereby it may have a favorable effect on gene expression of cancer-associated genes through epigenetic modifications, but may also influence DNA folding during repair processes.

Aims: We aimed to analyze the effect of SAM treatment on global and promoter-specific DNA methylation levels, gene expression, DNA integrity, cell cycle, and the proliferation of two different colorectal cancer cell lines (HT-29, SW480).

Methods: HT-29 and SW480 cells were treated with SAM in different concentrations (0, 0.5, 1 mmol/l) for 48 hours. Global DNA methylation status was analyzed by bisulfite pyrosequencing of long interspersed nuclear element-1 (LINE-1) retrotransposons. Promoter specific DNA methylation alterations were determined by Reduced Representation Bisulfite Sequencing (RRBS) method. Gene expression changes were detected using Human Transcriptome Array 2.0 (HTA 2.0). DNA integrity analysis was performed with γH2AX ELISA, immunostaining, and comet assay. Flow cytometry measurement and Sulforhodamine B (SRB) assay were assessed for cell cycle and proliferation determination.

Results: Global and promoter-specific DNA methylation alterations, as well as decreased expression ($p < 0.05$) of genes that are involved in epithelial-mesenchymal transition, were observed after SAM treatment. Increased phosphorylation of H2AX (74.9, 166.5, 200.6 pM) and decreased micronucleus number (1.47, 0.76, 0.45% of cells) were referred to the activation of reparative processes, that was supported by the changes of comet tale lengths. Treatment with SAM decreased the proportion of the cells in the G0/G1 phase (48.4, 28.5, 20.4%), while increased in the S (45.7, 61.7, 67.0%) and G2/M phases (6.0, 10.7, 12.5%). Significant ($p < 0.05$) reduction of cell proliferation (99.5, 77.97, 70.55%) was also detected with SRB assay.

Conclusions: SAM is able to alter the DNA methylation pattern of tumor cells and can induce DNA repair. Activation of these processes can lead to cell cycle arrest, decreased proliferation, and inhibition of epithelial-mesenchymal transition. Tumor cells could be targeted by SAM through different pathways; therefore, it may enhance the effect of chemotherapeutic agents.

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