LÉKAŘSKÁ FAKULTA UK V HRADCI KRÁLOVÉ

A

FAKULTNÍ NEMOCNICE HRADEC KRÁLOVÉ

XX. VĚDECKÁ KONFERENCE

P R O G R A M

20. ledna 2016

Velká posluchárna budovy Teoretických ústavů Lékařské fakulty
v Hradci Králové

Vydavatel: Univerzita Karlova v Praze, Lékařská fakulta v Hradci Králové
ISBN: 978-80-906155-5-7

T e c h n i c k é p o k y n y

V programu jsou uvedeny názvy řešených projektů a jména odpovědných řešitelů.

Věcná část publikovaných abstrakt dodaných řešiteli nebyla editována.

Ústní sdělení

1. Doba sdělení 10 minut, diskuse 5 minut.
2. K dispozici je dataprojekce.

Plakátová sdělení

Postery budou vyvěšeny po celou dobu konání konference. Prohlídka plakátových sdělení je možná v průběhu přestávek.

XX. vědecká konference Lékařské fakulty Univerzity Karlovy v Hradci Králové a Fakultní nemocnice Hradec Králové 20. ledna 2016

09.00 - 09.15 Z a h á j e n í k o n f e r e n c e
prof. MUDr. RNDr. Miroslav Červinka, CSc. děkan lékařské fakulty
prof. MUDr. Roman Prymula, CSc., Ph.D. ředitel fakultní nemocnice

Sekce I Předsedající: **doc. Ing. Josef Hanuš, CSc.**

09.15 - 09.30 Vliv konzervačních látek na složení mikrobiomu a vznik Crohnovy nemoci u geneticky predisponovaného hostitele
MUDr. Lucia Hrnčířová
GA UK 906613 (LF)

09.30 - 09.45 Role miRNA 302/367 v buněčném reprogramování
Rishikaysh Pisal, M.Sc. (přednášející: prof. MUDr. Jaroslav Mokrý, Ph.D.)
GA UK 1854214 (LF)

09.45 - 10.00 Zavedení nových praktických cvičení z biochemie se zaměřením na preanalytické vlivy
Mgr. Eva Peterová
MŠMT IP 2015 (LF)

10.00 - 10.15 Výuka vlastností a odolností mechanických struktur umělých kostních náhrad - (Inovace ve výuce - praktické ukázky)
Ing. Martin Kopeček, MEng
MŠMT IP 2015 (LF)

10.15 - 10.30 Diagnostika a léčba chrapotu – současné metody diagnostiky a léčby
MUDr. Katarína Smatanová
MŠMT IP 2015 (LF)

10.30 - 10.45 Léčba percepční ztráty sluchu reohemaferézou
MUDr. Jakub Držata, Ph.D.
IGA MZ ČR NT/13475-4/2012 (LF)

10.45 - 11.00 *Přestávka – občerstvení*

Sekce II Předsedající: **prof. MUDr. Zuzana Červinková, CSc.**

11.00 - 11.15 Vztah mezi množstvím bakterií v plodové vodě a intenzitou intraamniální zánětlivé odpovědi u pacientek s předčasným odtokem plodové vody
doc. MUDr. Marian Kacerovský, Ph.D.
IGA MZ ČR NT/13461-4/2012 (LF)

11.15 - 11.30 Cervikální tekutina - neinvazivní detekce histologické chorioamnionitidy a funisitidy u pacientek s předčasným odtokem plodové vody
doc. MUDr. Marian Kacerovský, Ph.D.
IGA MZ ČR NT/14104-3/2013 (FN)

11.30 - 11.45 Antracyklinová kardiotoxicita – nové možnosti farmakologické protekce a rizika kombinace s biologicky cílenou protinádorovou léčbou
doc. PharmDr. Martin Štěrba, Ph.D.
IGA MZ ČR NT/13457-4/2012 (LF)

11.45 - 12.00 Farmakokinetika a gastrointestinální motorické účinky nových acetylcholinesterasových modulátorů u experimentálních prasat
prof. MUDr. Jan Bureš, CSc.
IGA MZ ČR NT/14270-3/2013 (FN)

12.00 - 12.15 Stanovení apoptózy v biopticky odebraných vzorcích z tlustého střeva
MUDr. Darina Kohoutová, Ph.D.
IGA MZ ČR NT/13413-4/2012 (FN)

12.15 - 12.30 Kineticky řízené odstranění plazmatického pegylovaného liposomálního doxorubicinu ke zvýšení benefitu cytostatické léčby karcinomu ovarií
prof. MUDr. Stanislav Filip, Ph.D.
IGA MZ ČR NT/14035-3/2013 (LF)

12.30 - 14.00 *Přestávka na oběd*

Sekce III Předsedající: **doc. MUDr. RNDr. Milan Kaška, Ph.D.**

14.00 - 14.15 Význam insulinové resistence v patogenezi kardiometabolického rizika u diabetes mellitus
prof. MUDr. Vladimír Bláha, CSc.
IGA MZ ČR NT/12287-5/2011 (LF)

14.15 - 14.30 Cílená proteomická analýza u hypertrofické kardiomyopatie
prof. MUDr. Radek Pudil, Ph.D.
IGA MZ ČR NT/13721-4/2012 (LF)

14.30 - 14.45 Užití syntetických biomateriálů k léčení rozsáhlých defektů skeletu při reimplantaci totální endoprotézy kyčelního kloubu
doc. MUDr. Pavel Šponer, Ph.D.
IGA MZ ČR NT/13477-4/2012 (LF)

14.45 - 15.00 Predikce odpovědi na léčbu u pacientek s karcinomem ovaria
MUDr. Iva Sedláková, Ph.D.
IGA MZ ČR NT/14107-3/2013 (FN)

15.00 - 15.15 Komplexní hodnocení vlivu mikroprostředí na klinický průběh chronické lymfocytární leukémie
doc. MUDr. Lukáš Smolej, Ph.D.
IGA MZ ČR NT/13412-4/2012 (FN)

15.15 - 15.30 Optimalizace léčby suché formy věkem podmíněné makulární degenerace rheohemaferézou
prof. MUDr. Hana Langrová, Ph.D.
IGA MZ ČR NT/14037-3/2013 (LF)

15.30 - 15.45 *Přestávka - občerstvení*

Sekce IV Předsedající: **prof. MUDr. Radek Pudil, Ph.D.**

15.45 - 16.00 Rizikové faktory vzniku akutní pankreatitidy jako komplikace dvojbalonové enteroskopie
prof. MUDr. Marcela Kopáčová, Ph.D.
IGA MZ ČR NT/13414-4/2012 (FN)

16.00 - 16.15 Diagnostika poškození tenkého střeva nesteroidními antiflogistiky pomocí kapslové endoskopie
MUDr. Ilja Tachecí, Ph.D.
IGA MZ ČR NT/13532-4/2012 (FN)

16.15 - 16.30 Vývoj diagnostického panelu pro monitorování perioperačního poškození tenkého střeva
MUDr. Radomír Hyšpler, Ph.D.
IGA MZ ČR NT/13536-4/2012 (FN)

16.30 - 16.45 Management diagnostiky a terapie poruch polykání
MUDr. Michal Černý, Ph.D.
IGA MZ ČR NT/13725-4/2012 (FN)

16.45 - 17.00 Ovlivnění kolorektálního karcinomu biologickou léčbou - in vitro studie
prof. MUDr. Aleš Ryška, Ph.D. (přednášející: MUDr. Stanislav John)
IGA MZ ČR NT/14150-3/2013 (FN)

17.00 - 17.15 Využití ultra vysokoúčinné kapalinové chromatografie s hmotnostní detekcí pro stanovení vitaminu D a jeho metabolitů pro klinickou praxi
RNDr. Lenka Kujovská Krčmová, Ph.D.
IGA MZ ČR NT/14265-3/2013 (FN)

17.15 - 17.30 Personalizace antibiotické léčby u chirurgických nemocných se závažnou bakteriální infekcí a významnou sekvestrací tekutin
doc. MUDr. RNDr. Milan Kaška, Ph.D.
IGA MZ ČR NT/14089-3/2013 (LF)

17.30 - 17.45 U k o n č e n í k o n f e r e n c e
prof. MUDr. Roman Prymula, CSc., Ph.D. ředitel fakultní nemocnice
prof. MUDr. RNDr. Miroslav Červinka, CSc. děkan lékařské fakulty

Projekty prezentované formou plakátových sdělení

Vulnerabilita a možnosti reparace peroperačního iatrogenního poškození chámovodu v experimentu
R. Štichhauer, J. Koudelka, A. Ryška, K. Petkov, M. Kaška
GA UK 160315 **(LF)**

Vascular endothelial growth factor is associated with the morphologic and functional parameters in patients with hypertrophic cardiomyopathy
R. Pudil, M. Vašatová, A. Fučíková, H. Řehulková, P. Řehulka, V. Palička, J. Stulík
IGA MZ ČR NT/13721-4/2012 **(LF)**

Changes in glycocalyx thickness after hip/knee surgery
D. Astapenko, V. Černý
AZV MZ ČR 15-31881A **(FN)**

NA LF UK V HRADCI KRÁLOVÉ A VE FN HRADEC KRÁLOVÉ SE V ROCE 2015 DÁLE ŘEŠILY NÁSLEDUJÍCÍ PROJEKTY

(abecedně podle jmen řešitelů)

V tomto přehledu jsou uvedeny ostatní smluvně podložené projekty a spolupráce na projektech.

Difúzní velkobuněčný a folikulární lymfom – analýza vlivu prognostických faktorů a léčebných postupů na osud nemocných; lymfomový projekt České republiky
MUDr. David Belada, Ph.D.
(odp. řešitel: prof. MUDr. Marek Trněný, CSc. - VFN Praha)
IGA MZ ČR NT/12193-5/2011 **(FN)**

Observační studie pro nově diagnostikované pacienty s lymfomem z plášťových buněk (mantle cell lymphoma, MCL) nevhodné k vysokodávkované podle protokolu alternujícího R-CHOP a R-AraC (3+3 cykly)
MUDr. David Belada, Ph.D.
(odp. řešitel: prof. MUDr. Marek Trněný, CSc. – VFN Praha)
IGA MZ ČR NT/13072-4/2012 **(FN)**

Testování a porovnání prokrvení anastomózy tračníku konstruované tkáňovým lepidlem ve vztahu k tradičně používaným technikám vytváření anastomóz
MUDr. Slavomír Blažej
GA UK 187515 **(LF)**

Design a enzymové cílení nových antibakteriálně účinných sloučenin vůči multilékově rezistentním kmenům
doc. RNDr. Vladimír Buchta, CSc.
(odp. řešitel: prof. RNDr. Jarmila Vinšová, CSc.- UK FaF HK)
IGA MZ ČR NT/13346-4/2012 **(FN)**

Studium vaginální mikrobioty ve vztahu k rekurentnímu vulvovaginílnímu dyskomfortu
doc. RNDr. Vladimír Buchta, CSc.
AZV MZ ČR 15-29225A **(FN)**

Cílený screening kolorektálního karcinomu u diabetiků 2.typu a osob s vysokým kardiovaskulárním rizikem: multicentrická prospektivní studie
prof. MUDr. Jan Bureš, CSc.
(odp. řešitel: MUDr. Štěpán Suchánek – ÚVN VoFN Praha)
IGA MZ ČR NT/13673-4/2012 **(FN)**

Využití volné nádorové DNA jako nového cíle pro minimálně-invazivní diagnostiku a zpřesnění molekulární klasifikace kolorektálních nádorů
prof. MUDr. Jan Bureš, CSc.
(odp. řešitel: MUDr. Petra Mináriková, Ph.D. – ÚVN VFN Praha)
IGA MZ ČR NT/14383-3/2013 **(FN)**

Význam nových metodických přístupů pro klinickou praxi vnitřních chorob
prof. MUDr. Jan Bureš, CSc.
SVV 260178 **(LF)**

IMPACT - Inovace, metodika a kvalita jazykového vzdělávání a odborného vzdělávání v cizích jazycích v terciární sféře v ČR
PhDr. Jan Comorek, Ph.D.
(odp. řešitel: PaedDr. Hana Reichová, Ph.D. – MU Brno)
MŠMT OP VK CZ.1.07/2.2.00/28.0233 **(LF)**

Alterace glykokalyx v kritických stavech a během velkých operačních výkonů a možnosti její protekce
prof. MUDr. Vladimír Černý, Ph.D., FCCM
AZV MZ ČR 15-31881A **(FN)**

International conferences in medical sciences 2015/12th International medical Postgraduate conference
prof. MUDr. RNDr. Miroslav Červinka, CSc.
SVV 260182 **(LF)**

Nové postupy v diagnostice a terapii civilizačních chorob a onemocnění spojených se stárnutím populace
prof. MUDr. RNDr. Miroslav Červinka, CSc.
PRVOUK P37 **(LF)**

Studium nového mechanismu hepatotoxicity acetaminofenu a možností terapie po předávkování.
prof. MUDr. Zuzana Červinková, CSc.
(odp. řešitel: RNDr. Tomáš Roušar, Ph.D. – UPCE)
IGA MZ ČR NT/14320-3/2013 **(LF)**

Výzkum a vývoj pokročilých tenkovrstvých elementů pro přímé sledování časové proměnné pomocí přesně kalibrovatelné barevné změny
doc. MUDr. Karel Ettler, CSc.
(odp. řešitel: MVDr. Tomáš Obr – INVOS, spol. s. r. o.)
TA ČR TA03010548 **(LF)**

Hodnocení kvality multimodální péče u nemocných s jaterními metastázami kolorektálního karcinomu v rámci komplexních onkologických center ČR Multicentrická studie
prof. MUDr. Alexander Ferko, CSc.
(odp. řešitel: prof. MUDr. Miroslav Ryska, CSc. – ÚVN – VoFN Praha)
IGA MZ ČR NT/13660-4/2012 **(FN)** – abstrakt nebyl dodán

Neurovědy - Lidské zdroje pro neurovědní výzkum v Královéhradeckém a Ústeckém kraji
prof. MUDr. Stanislav Filip, Ph.D.
(odp. řešitel: prof. Eva Syková, DrSc., FCMA – ÚEM Praha)
MŠMT OP VK CZ.1.07/2.3.00/20.0274 **(LF)**

Remodelace svalu na podkladě extracelulární matrix osázené funkčně charakterizovanými buňkami
prof. MUDr. Stanislav Filip, Ph.D.
GA ČR 15-09161S **(LF)**

Centrum pro výzkum toxických a protektivních účinků léčiv na kardiovaskulární systém
doc. PharmDr. Martin Štěrba, Ph.D. (prof. MUDr. Vladimír Geršl, CSc.)
(odp. řešitel: doc. PharmDr. Tomáš Šimůnek, Ph.D. – UK FaF UK)
UNCE 204019/304019 **(LF)**

Rizikové faktory vzniku zubního kazu a parodontopatií u dětí narozených s velmi nízkou porodní hmotností.
doc. MUDr. Romana Ivančaková Koberová, CSc.
(odp. řešitel: doc. MUDr. Vlasta Merglová, CSc. – LF UK Plzeň)
IGA MZ ČR NT/14336-3/2013 **(FN)**

Kvalita života a její vliv na celkové přežití nemocných po trasplantaci krvetvorných buněk v ČR
prof. MUDr. Ladislav Jebavý, CSc.
(odp. řešitel: prof. MUDr. Marek Trněný, CSc. – VFN Praha)
IGA MZ ČR NT/11299-6/2010 **(FN) –** abstrakt nebyl dodán

Charakterizace diagnostického potenciálu nativních polypeptidů plodové vody
doc. MUDr. Marian Kacerovský, Ph.D.
(odp. řešitel: Mgr. Juraj Lenčo, Ph.D. – UO FVZ HK)
IGA MZ ČR NT/13599-4/2012 **(FN)**

Optimalizací kolemoperační chirurgické terapie pro její úspěšnější výsledky
doc. MUDr. RNDr. Milan Kaška, Ph.D.
SVV 260180 **(LF)**

Koncept nekvarterních reaktivátorů AChE jakožto antidot otrav organofosfáty – nová naděje či slepá cesta?
prof. Ing. Kamil Kuča, Ph.D.
GA ČR 15-16701S **(FN)**

Vývoj multifunkčního léčiva na Alzheimerovu nemoc: kombinace inhibitoru AChE a derivátu melatoninu
prof. Ing. Kamil Kuča, Ph.D.
AZV MZ ČR 15-30954A **(FN)**

Biomedicínská fotonická zařízení pro pokročilou lékařskou diagnostiku a terapii
RNDr. Martin Kuneš, Ph.D.
AZV MZ ČR 15-33459A **(FN)**

OPtimization of Treatment and Management of Schizophrenia in Europe
prof. MUDr. Jan Libiger, CSc.
(odp. řešitel: prof. dr. René S. Kahn - University Medical Center Utrecht)
FP7 OpTiMiSE **(LF)**

Studium patofyziologických mechanizmů vnitřních onemocnění, možností prevence a nových diagnostických a terapeutických intervencí - pokračování 2015
prof. MUDr. Stanislav Mičuda, Ph.D.
SVV 260179 **(LF)**

Modulátory mitochondriálních enzymů k léčbě neurodegenerativních onemocnění
doc. PharmDr. Kamil Musílek, Ph.D.
AZV MZ ČR 15-28967A **(FN)**

Příprava lékové formy s řízeným uvolňováním glukosy k prevenci hypoglykemických stavů.
MUDr. David Neumann, Ph.D.
(odp. řešitel: PharmDr. Aleš Franc, Ph.D. – VFU Brno)\
IGA MZ ČR NT/14479-3/2013 **(FN)**

Parametrické sledování kvality TME jako nástroj k omezení lokálních recidiv po operacích pro karcinom rekta
MUDr. Július Örhalmi
(odp. řešitel: prof. MUDr. Jiří Hoch, CSc. - FN Motol)
IGA MZ ČR NT/13726-4/2012 **(FN)**

Prediktivní imunologické markery u pacientů s infekcí virem hepatitidy C
doc. MUDr. Stanislav Plíšek, Ph.D.
(odp. řešitel: prof. MUDr. Pavel Chalupa, CSc. – Nemocnice Na Bulovce)
IGA MZ ČR NT/14072-3/2013 **(FN)**

Racionální design nových immunomodulátorů – potenciální adjuvans pro vakcíny – na bázi ligandů TLR4
prof. MUDr. Roman Prymula, CSc., Ph.D.
GA ČR 15-11776S **(FN)**

POSTDOCI II UK - Zvýšení kapacity vědecko-výzkumných týmů Univerzity Karlovy prostřednictvím nových pozic pro absolventy doktorandských studií
prof. MUDr. Radek Pudil, Ph.D.
MŠMT OP VK CZ.1.07/2.3.00/30.0061 **(LF)**

Nové metody a postupy v diagnostice a hledání prediktivních a prognostických markerů nádorových onemocnění
prof. MUDr. Aleš Ryška, Ph.D.
SVV 260181 **(LF)**

BBMRI
prof. MUDr. Aleš Ryška, Ph.D.
(odp. řešitel: prof. MUDr. Dalibor Valík, Ph.D. – MOÚ Brno)
MŠMT BBMRI_CZ **(LF)**

Analýza klonální heterogenity chronické lymfocytární leukemie pomocí sekvenování nové generace genu B-buněčný receptor. Národní studie.
doc. MUDr. Lukáš Smolej, Ph.D.
(odp. řešitel: prof. MUDr. Michael Doubek, Ph.D. – FN Brno)
AZV MZ ČR 15-30015A **(FN)**

Prediktivní faktory patologické odpovědi na neoadjuvantní chemoterapii u nemocných s karcinomem prsu a HER-2 pozitivním nebo triple negativním fenotypem
doc. RNDr. Dagmar Solichová, Ph.D.
(odp. řešitel: prof. MUDr. Bohuslav Melichar, Ph.D. – UP Olomouc)
IGA MZ ČR NT/13564-4/2012 **(FN)**

Tkáňové trauma a pooperační stres u pacientek s chirurgicky léčenými časnými stádii karcinomu endometria
doc. RNDr. Dagmar Solichová, Ph.D.
(odp. řešitel: prof. MUDr. Radovan Pilka, Ph.D. – UP Olomouc)
IGA MZ ČR NT/13566-4/2012 **(FN)**

Vývoj nových dezinfekčních činidel proti patogenům vyskytujících se v nemocničním prostředí
PharmDr. Ondřej Soukup, Ph.D.
AZV MZ ČR 15-31847A **(FN)**

Vulnerabilita a možnosti reparace peroperačního iatrogenního poškození chámovodu v experimentu
MUDr. Radek Štichhauer
GA UK 160315 **(LF)**

Katetrizační uzávěr ouška levé síně versus terapie novými orálními antikoagulancii u rizikových pacientů s fibrilací síní (studie PRAGUE-17)
doc. MUDr. Josef Šťásek, Ph.D.
(odp. řešitel: doc. MUDr. Pavel Osmančík, Ph.D. – 3. LF UK Praha)
AZV MZ ČR 15-29565A **(FN)**

Modernizace výuky klinického rozhodování napříč pediatrickými obory lékařských fakult v síti MEFANET - MEFANET klinické rozhodování
MUDr. Ilja Tachecí, Ph.D.
(odp. řešitel: Ing. Daniel Schwarz, Ph.D. – MU Brno)
MŠMT OP VK CZ.1.07/2.2.00/28.0038 **(LF)**

Role oxidačního stresu ve vztahu mezi buněčnou senescence a apoptózou
Mgr. Vojtěch Tambor, Ph.D.
(odp. řešitel: MUDr. Zdeněk Hodný, CSc. – ÚMG AV Praha)
GA ČR 15-03379S **(FN)**

Identifikace původců časných a pozdních nozokomiálních pneumonií u pacientů v intenzivní péči prostřednictvím genetické analýzy bakteriální DNA a určení jejich šíření.
MUDr. Zdeněk Turek, Ph.D.
(odp. řešitel: doc. MUDr. Milan Adamus, Ph.D. – FN Olomouc)
IGA MZ ČR NT/14263-3/2013 **(FN)**

Nové analytické metody pro efektivní stanovování biologických markerů.
prof. MUDr. Zdeněk Zadák, CSc.
(odp. řešitel: Ing. Michal Bartoš – Výzkumný ústav organických syntéz, a.s.)
TA ČR TA04010954 **(FN)**

Rizikové faktory vzniku rezistence CMV vůči virostatikům u pacientů po alogenní transplantaci hematopoetických kmenových buněk
doc. MUDr. Pavel Žák, Ph.D.
(odp. řešitel: MUDr. Petr Hubáček, Ph.D. – 2. LF UK Praha)
IGA MZ ČR NT/13691-4/2012 **(FN)**

Národní program studia mutací a klonality leukemických buněk u pacientů s akutní myeloidní leukémií
doc. MUDr. Pavel Žák, Ph.D.
(odp. řešitel: doc. MUDr. Zdeněk Ráčil, Ph.D. - FN Brno)
AZV MZ ČR 15-25809A **(FN)**

SOUHRNY VÝZKUMNÝCH ÚKOLŮ

ŘEŠENÝCH NA LF UK A VE FN V HRADCI KRÁLOVÉ

(ABECEDNĚ)

Title of the project: Diffuse large B cell lymphoma and follicular lymphoma - analysis of prognostic factors and treatment guideliness to patient´s outcome; lymphoma project of Czech Republic

Grant Agency: Ministry of Health ***Project Number:*** NT/12193-5

Principal Investigator: M. Trněný

Co-investigators: D. Belada, L. Boudová, A. Janíková, M. Jankovská, T. Papajik, K. Kubáčková, M. Matuška, M. Lysý

Starting date: 1.6.2011 ***Duration (years):*** 5

Total funds allocated for project - Kč (thousands): 7026

Summary of 2015 results

Title of the presentation: Diffuse large B cell lymphoma and follicular lymphoma - analysis of prognostic factors and treatment guidelines to patient´s outcome; lymphoma project of Czech Republic

Authors: D. Belada L. Boudová, A. Janíková, M. Jankovská, T. Papajik, K. Kubáčková, M. Matuska, M. Lysý

Czech Lymphoma Study Group (CLSG) consist of the majority of University Hospitals in Czech Republic (CR) which are focused on lymphoma diagnosis and management as well as of the number of regional hematology and oncology centers. The proposed multicentric project is based on the current level of collaboration in this field in CR and is focused on analysis of selected subgroups of Non-Hodgkin´s lymphomas - two most common types - diffuse large B cell lymphoma and follicular lymphoma - registered in CLSG registry and to describe the situation in Czech republic - clinical features, therapy, outcomes. The number of patients in our databasis is now about 12 000. The importance of proposed project is seen in the addressing of unanswered question of description of "real-life" situation in lymphoma field in CR and the analysis of different lymphoma subgroups and the description of clinical features, therapeutic approaches and the outcome of patients in CR. During 2015 we analysed the role of rituximab maintenance treatment schedule (every 2 months or every 3 months) and this data was published by Janikova et al.in Leukemia Lymphoma. Ahother project was focused on the position of rituximab and radiotherapy in localised stage follicular lymphoma (published by Janikova et al.). We started new project on CNS prophylaxis in patients with diffuse large B-cell lymphoma (project organised by Heidi Mocikova). New diagnostic and therapeutic guidelines by authors David Belada and Marek Trneny were proposed (publication is expected on early 2016). In our clinic about 70 newly diagnosed patients with diffuse large B cell lymphoma has been diagnosed and about 25 newly diagnosed patients with follicular lymphoma. All these patients were included into databasis and analysis. Results has been presented and discussed on local meetings in Czech Republic as well as on international meeting of European Haematology Association and American Society of Haematology in December 2015 in Orlando Project was supported by Internal Grant Agency of Ministry of Health NT/12193-5.

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Title of the project: Observational study for the newly diagnosed patients with mantle cell lymphoma unfit for high dose therapy with stem cell support based on the treatment with R-CHOP chemotherapy alternating with R-Ara-C (3+3 cycles)

Grant Agency: Ministry of Health ***Project Number:*** NT/13072-4

Principal Investigator: M. Trněný

Co-investigators: P. Klener, J. Trka, D. Belada, M. Šimkovič, D. Šálek, A. Janíková, V. Procházka, Z. Kapitánová

Starting date: 1.6.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 8686

Summary of 2015 results

Title of the presentation: Observational study for the newly diagnosed patients with mantle cell lymphoma unfit for high dose therapy with stem cell support based on the treatment with R-CHOP chemotherapy alternating with R-Ara

Authors: D. Belada, P. Klener, M. Trněný, J. Trka, M. Šimkovič, D. Šálek, A. Janíková, V. Procházka, Z. Kapitánová

The aim of this observational study for the newly diagnosed patients with mantle cell lymphoma unfit for high dose therapy with stem cell support based on the treatment with R-CHOP chemotherapy alternating with R-Ara-C (3+3 cycles) is to assess efficacy and treatment outcomes of this therapy to the cohort of older patients with unfavourable type of non-Hodgkin´s lymphoma. Altogether 61 pts (38 men and 23 women, ratio 1.7:1) were enrolled into the study between 2011-2014. Median age was 70 years. 91.5%, and 80% pts presented with stage 3/4 disease. According to the MIPI, 55.7%, 39.4%, and 4.9% pts had high, intermediate and low risk disease, resp. B-symptoms were recorded in 33.3% of pts. 76.8% and 24.2% pts were diagnosed from the lymph node, and trephine biopsy, resp. 62.8%, 27.9%, and 9.3% pts presented with classical, pleomorphic and blastoid variant MCL, resp. Ki67/MIB1 $\geq$ 30% was observed in 38% of pts. R-CHOP was used in 88% pts (12% pts received R-COEP), 86% pts received 2g / m2 cytarabine (14% pts 1g / m2). 86.3% pts with response were treated with R maintenace. Only one patient was excluded from the study due to unacceptable toxicity. 57.7% pts developed grade 3/4 hematologic toxicity (neutropenia, anemia or thrombocytopenia). Grade 3/4 non-hematologic toxicity occurred in 27.3% pts. All pts had PET-CT restaging after completion of induction. Overall response rate (CR+PR) reached 91.7%. CR and PR rate by PET was 76.7%, and 15%, resp. SD, and progression on therapy was noticed in 3.3%, and 5.0%, resp. Samples for MRD assessment were collected from 41 out of 54 pts, who completed induction and achieved response (CR or PR). At the time of abstract submission 21, 7, and 7 (out of 36 so far evaluated pts) were MRD negative, MRD positive-not quantifiable, and MRD positive-quantifiable, resp. With the median follow-up 19.1 month, there were 7 progressions and 6 deaths. 2-year PFS and OS probability were 83.9% and 88.1%. Conclusion: Alternation of R-CHOP and R-HDAC in newly diagnosed elderly or co-morbid MCL pts represents a promising, very effective and well-tolerated treatment approach that induces high ORR, and MRD negativity.

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Title of the project: Testing and comparison of microcirculation in tissue by glue constructed colon anastomosis in relation to commonly used techniques for colon anastomosis construction

Grant Agency: Charles University ***Project Number:*** 187515

Principal Investigator: S. Blažej

Co-investigators: J. Páral, Z. Turek, A. Ryška, M. Pavlík, V. Radochová, B. Jegorov, M. Kaška

Starting date: 1.5.2015 ***Duration (years):*** 2

Total funds allocated for project - Kč (thousands): 243

Summary of 2015 results

Title of the presentation: Segmental microcirculation in a site of various types of bowel anastomosis in experiment

Authors: S. Blažej et al. (above mentioned)

Background: Contemporary abdominal surgery is facing an increasing number of malignant diseases of the large bowel. Its surgical therapy is based on resection and reconstruction using common methods such as suture and stapling. A potentially usable method seems to be the application of a special glue. A microcirculation level is one of the limiting factors of anastomotic healing.

Methods: The pilot study included 12 female pigs from the controlled breed of average weight 40 kgs. Two microcirculation detection probes (Laser Doppler Flowmetry - LDF) were placed to the anastomotic site and a basic microcirculation status was measured. The bowel was transected and anastomosis was performed using an absorbable knitted thread for standard sewing technique or a stapler or the glue (Glubran2). Microcirculation intensity was measured 60 and 120 min after the construction of anastomosis. After 7 days relaparotomy in general anesthesia was performed. The biopsy was examined by HE-staining microscopically focusing on the status of healing anastomosis. Measured values of blood microcirculation were statistically processed using the software SigmaPlot 13.0.

Results: 12 animals were enrolled in 3 subgroups counting 4 animals each. It was found out that the gentlest method of all from the actual microcirculation level impact point of view is suture. The drop in microcirculation intensity at the anastomotic site was to 59.7% maximum to the original values during 120 min after anastomosis construction. A more significant drop in microcirculation from the original values was in stapling and gluing to 39.6% and 34.5%, respectively. An increase in microcirculation intensity in glued anastomosis to 46.7% from the original values was observed. Macroscopically there was no disorder in healing in any animal recorded and microscopic examination showed satisfactory healing in all cases.

Conclusions: Partial ischemia of the large bowel tissues in the first 120 min after anastomosis construction is significantly higher in stapling and gluing. Function and biopsy results do not show significant differences in healing of the bowel whether the reconnection was performed by stapling, suture or glue.

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Title of the project: The role of insulin resistance in the pathogenesis of cardiometabolic risk in diabetes mellitus

Grant Agency: Ministry of Health ***Project Number:*** NT/12287-5

Principal Investigator: V. Bláha

Co-investigators: L. Sobotka, J. Lesná, F. Musil, A. Šmahelová, R. Hyšpler, M. Bláha, J. Víšek

Starting date: 1.7.2011 ***Duration (years):*** 5

Total funds allocated for project - Kč (thousands): 6907

Summary of 2015 results

Title of the presentation: Omentin-1 plasma levels and cholesterol metabolism in obese patients with diabetes mellitus type 1: impact of weight reduction.

Authors: J. Lesná, F. Musil, A. Šmahelová, V. Bláha, R. Hyšpler, A. Tichá, Z. Zadák, L. Sobotka. Fac. Med., Charles Univ., Hr.Králové, IIIrd Dept Metabolism and Gerontology, University Hospital, Hradec Králové; Charles University, Prague, Czech Republic

Background**:** Omentin-1 is an anti-inflammatory adipokine produced preferentially by visceral adipose tissue. Plasma levels of omentin-1 are decreased in obesity and other insulin-resistant states. Insulin resistance contributes to the changes of cholesterol synthesis and absorption as well. The aim of this study was to characterise omentin-1 plasma levels in obese patients with diabetes mellitus type 1 during weight reduction, and to elucidate the relationship between cholesterol metabolism and omentin-1.

Methods**:** Plasma levels of omentin-1 were measured in obese type 1 diabetics (n = 14, body mass index 43.0 kg/m^2, age 29–62 years) by enzyme-linked immunosorbent assay (BioVendor). Gas chromatography with flame ionisation detector (Fisons Plc.,) was used to measure squalene and non-cholesterol sterols—markers of cholesterol synthesis and absorption (phase I). Measurements were repeated after 1 month (phase II; 1 week of fasting in the hospital setting and 3 weeks on a diet containing 150 g saccharides per day) and after 1 year (phase III) on a diet with 225 g saccharides per day.

Results**:** Omentin-1 plasma levels were stable during phases I and II, but significantly increased ($P<0.001$) during phase III. Omentin-1 plasma dynamics were significantly associated with plasma levels of high-density lipoprotein ($P = 0.005$) and triacylglycerols ($P = 0.01$), as well as with lathosterol ($P = 0.03$).

Conclusion**:** Omentin-1 plasma levels significantly increased during the weight reduction programme. Omentin-1 plasma dynamics suggest a close relationship with cholesterol metabolism.

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Title of the project: Design and enzyme targeting of antibacterial active compounds against multidrug resistant strains

Grant Agency: Ministry of Health ***Project Number:*** NT/13346-4

Principal Investigator: J. Vinšová

Co-investigators: V. Buchta, P. Paterová, M. Vejsová

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 6624

Summary of 2015 results

Title of the presentation: *In vitro* antimycobacterial and antimicrobial activity of new synthetic substances.

Authors: V. Buchta (1), P. Paterová (1), M. Vejsová (1)
Fac. Med., Charles Univ., Hr. Králové: Dept. of Clinical Microbiology (1)

Tuberculosis remains one of the most important priority of the WHO due to a significant mortality and morbidity over the world population. The infections caused by MDR and XDR strains of Mycobacterium tuberculosis refractory to treatment represent main problem and challenge to clinical practice and pharmaceutical research. The project focused on pyrazine derivatives and their in vitro efficacy against human pathogenic mycobacteria (including atypical), and selected bacteria and fungi using broth microdilution standards. Minimal inhibitory concentration (MIC) and its relationship to in vitro antimicrobial effect were evaluated. In sum, in vitro susceptibility (MIC, minimum inhibitory concentraion) of Mycobacterium tuberculosis H37Rv, M. avium 152, and M. kansasii My 235/80 to a series of pyrazinamide derivatives (n=118) was determined by modified broth dilution method using Middlebrook medium. Of the group 6-alkylamino-N–phenylpyrazine-2-carboxamides the derivatives with prolongation of simple alkyl chain and with heptylamino substituti displayed the most promising activity (MIC = 5–10 μM) against M. tuberculosis H37Rv. Derivatives of 5-alkylamino-N-phenylpyrazine-2-carboxamides (propylamino to octylamino derivatives) also showed similar or increased activity (2.5 to 12.2 μM) against M. tuberculosis H37Rv, 5-butylamino to 5-heptylamino derivatives exerted similar activity also against M. kansasii. No of above mentioned compounds inhibited M. avium. Most of those compouds had no effect on bacterial and fungal strains tested with exception of the latter series of which some compounds inhibited Gram-positive bacteria.

Literature: •Zitko, J.; Servusova-Vanaskova, B.; Paterova, P.; et al. Chem. Pap., 2015. [ISSN (Online) 1336-9075]•Servusova-Vanaskova, B.; Jandourek, O.; Paterova, P.; et al. MedChemComm, 2015, 6, p. 1311–1317.•Semelkova, L.; Konecna, K.; Paterova, P.; et al. Molecules, 2015, 20, p. 8687–8711.•Zitko, J.; Franco, F.; Paterová, P. Čes. Slov. Farm., 2015, 64, p.19–24.•Servusová-Vaňásková, B.; Paterová P.; et al. Synthesis and antimicrobial evaluation of 6-alkylamino-N-phenyl-pyrazine-2-carboxamides. Chem. Biol. Drug Des. 2015, 86, p.674–681.•Kucerova-Chlupacova, M.; Kunes, J.; Buchta, V.; Vejsova, M.; Opletalova, V. Molecules, 2015, vol. 20, p. 1104–1117.•Zitko, J.; Servusová, B.; Janoutová, A.; Paterová, P.; Mandíková, J.; Garaj, V.; Vejsová, M.; et al. Bioorg. Med. Chem. 2015, 23, p.174–183.

Project was supported by the Internal Grant Agency of Ministry of Health, No NT/13346-4

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Title of the project: Study of vaginal microbiota and its relationship to recurrent vulvovaginal discomforts

Grant Agency: Ministry of Health ***Project Number:*** 15-29225A

Principal Investigator: V. Buchta

Co-investigators: M. Kacerovský, J. Nekvindová, M. Drahošová, J. Vávrová

Starting date: 1.5.2015 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 12754

Summary of 2015 results

Title of the presentation: Study of vaginal microbiota.

Authors: V. Buchta (1), L. Nováková (2), J. Kestřánek (3), D. Leško (3), A. Drbohlavová (1), R. Kutová (4), V. Pilařová (2), J. Nekvindová (4)
University Hospital., Hradec Králové, Dept. of Clinical Microbiology (1)
Fac. Pharm., Charles Univ. in Prague, Dept. of Analytical Chemistry (2)
University Hospital., Hradec Králové, Dept. of Obstetrics and Gynecology (3)
University Hospital., Hradec Králové, Dept. of Clinical Biochemistry and Diagnostics (4)

Vaginal microbiota is a unique part of human microbiome, which represents finely balanced ecosystem with specific microbe-microbe relationships. Composition and structure of vaginal microbiota are influenced by hormonal millieu and interactions with immune system and have a substantional impact on the vaginal health and disease. The most frequent reasons for visiting of gynecology practitioners are different forms of dysbiosis, mainly bacterial vaginosis, and vulvovaginal candidasis. The project is focused on the patients with vaginal discomfort, including that of Candida origin. Factors affecting the composition of vaginal microbiota such as sexual hormones (beta-estradiol, progesterone), physiology of the vagina (acidity), humoral factors of immunity (interleukins), and specific properties of some relevant vagina microbes will be studied. Special attention will be paid to Candida albicans (spectrum, biofilm formation, production of quorum sensing) and its role in natural vaginal microbiota. In addition, anamnestic and social-economic data (questionnaire) of the patients plus control group will be gathered and evaluated in the context of microbiological and other laboratory data. The aim is to characterize the factors which influence structure of the vaginal microbiome and its impact on a delicate balance of the health and disease of the vagina. First year was focused on elaboration of methodology, in particular, on analysis of vaginal microbiota by next generation sequencing, and detection and quantification of Candida species and Saccharomyces cerevisiae. Further, the methods of detection of quorum sensing (farnesol, tyrosol) and production of microbial biofilm were prepared for study of yeasts and some bacteria. Biological specimen (vaginal secretion, blood) were collected and stored for analysis of vaginal microbiota, level of sexual hormones, humoral compounds of immunity, and Candida quorum sensing. ***Literature:*** Buchta V. Novinky ve studiu vaginální mikrobioty: Je čas na změnu paradigmatu? KMINE, 23. - 25. 9. 2015, Bedřichov- Špindlerův Mlýn. Abstrakt (přednáška)
Drbohlavová A., Buchta V. Hodnocení tvorby biofilmu a in vitro citlivost k antimykotikům u vaginálních izolátů Candida albicans. KMINE, 23. - 25. 9. 2015, Bedřichov- Špindlerův Mlýn. Abstrakt (poster)
Project was supported by Ministry of Health of the Czech Republic, grant nr. 15-29225A

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Title of the project: Pharmacokinetics and gastrointestinal motor effects of novel acetylcholinesterase modulators in experimental pigs

Grant Agency: Ministry of Health ***Project Number:*** NT/14270-3

Principal Investigator: J. Bureš

Co-investigators: K. Kuča, I. Tachecí, K. Musílek, J. Květina, M. Kuneš, M. Kopáčová, J. Žďárová Karasová, S. Rejchrt, D. Jun

Starting date: 1.5.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 8391

Summary of 2015 results

Title of the presentation: IMPACT OF TACRINE AND 7-METHOXYTACRINE ON GASTRIC MYOELECTRICAL ACTIVITY ASSESSED USING ELECTROGASTROGRAPHY IN EXPERIMENTAL PIGS

Authors: J. Bureš (1), D. Jun (2,3), M. Hrabinová (2), I. Tachecí (1), J. Květina (1), M. Pavlík (2), S. Rejchrt (1), T. Douda (1), M. Kuneš (3), K. Kuča (2,3), M. Kopáčová (1)

)1) 2nd Dept. Int. Med. - Gastroenterol., Charles Univ. Fac. Med. & Univ. Hosp., Hradec Králové; (2) Dept. Toxicol, Univ. Defence, Fac. Milit. Health Sci., Hradec Králové; (3) Biomed. Res. Ctr, Univ. Hosp., Hradec Králové; Czech Republic.

Objective of the study: Tacrine was the first acetylcholinesterase inhibitor approved for therapy of Alzheimer's disease. Tacrine has dose limiting side effects, including diarrhoea, nausea, vomiting and abdominal discomfort. The aim of this study was to assess the impact of these two compounds on gastric myoelectrical activity by means of surface cutaneous electrogastrography (EGG) in 12 experimental pigs. Methods: A single dose of tacrine (200 mg i.m., n=6) or 7-MEOTA (7-methoxytacrine; 200 mg i.m., n=6) was administrated. All EGG recordings were performed under general anaesthesia. Running spectral analysis was used.

Results: Maximal inhibition of blood cholinesterase activity was recorded after 10 minutes, being significantly stronger after administration of tacrine (20.5±19.2%) compared to 7-MEOTA (72.8±14.4%), $p<0.001$. Tacrine decreased EGG dominant frequency 10 minutes after its administration (from basal 3.1±0.6 to 2.8±0.6 cycles per minute; $p=0.014$). Tacrine induced a 60-minute but not significant increase of the power (with maximal value 493±533 μV^2 at 20 minutes; $p=0.300$) and power ratio (with maximal value 2.04±3.4 at 10 minutes; $p=0.330$). Tacrine caused significant gastric arrhythmia. 7-MEOTA did not influence dominant frequency of gastric slow waves significantly. 7-MEOTA caused a short-term late increase of the power (from basal 618.3±747.3 to 2540.2±6130.3 μV^2 at 90 minutes; $p=0.079$) and power ratio at 60 minutes (6.3±11.2; $p=0.003$). Blood cholinesterase activity did not correlate with any EGG parameter either after tacrine or 7-MEOTA at any time. Conclusions: Tacrine and 7-MEOTA have different impacts on EGG. Tacrine decreased dominant frequency and induced long-lasting gastric arrhythmia. 7-MEOTA caused a short-term late increase of the EGG power in experimental pigs.

Publications: Bureš J et al. J Appl Biomed 2015; 13(4): 273-277

Bureš J et al. Neuroendocrinol Lett 2015; 36, Suppl 1, in press

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Title of the project: Targeted colorectal cancer screening in type 2 diabetes patients and high cardiovascular risk patients - a prospective multicentre study

Grant Agency: Ministry of Health ***Project Number:*** NT/13673-4

Principal Investigator: Š. Suchánek

Co-investigators: J. Bureš and 10 centres of the Czech Republic involving gastroenterologists, diabetologists, general practitioners and biomedical statisticians

Starting date: 2.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 15143

Summary of 2015 results

Title of the presentation: Targeted colorectal cancer screening in patients with metabolic syndrome: a multicenter prospective study

Authors: J. Bureš, J. Cyrany, D. Kohoutová (1), A. Šmahelová (2), M. Plíšková (2), A. Kašková (3), M. Středová (3), L. Pázlerová (3), P. Hlúbik (3)

(1) 2nd Dept. Int. Med. - Gastroenterol., Charles Univ. Fac. Med. & Univ. Hosp., Hradec Králové;

(2) 3rd Dept. Int. Med. - Metabol. Care Gerontol., Charles Univ. Fac. Med. & Univ. Hosp., Hradec Králové;

(3) general practitioners of the Hradec Králové Region

Colorectal cancer screening programes does not take into account an individual metabolic risk factors, although there is an epidemiological evidence of higher risk of CRC in individuals with metabolic syndrome.

This study compares prevalence of colorectal neoplasia in the target group (diabetes mellitus type 2 and cardiovascular risk - defined as SCORE > 10% or presence of IHD) and control group. All participants underwent biochemical testing, lifestyle questionnaire, faecal occult blood testing and colonoscopy.

Results of this year interim analysis of 1416 individuals (807 men, mean age 60 years, 700 in the target group) showed higher prevalence of adenomas and advanced adenomas in the target group in comparison to the control group (49% versus 36%; OR 1,2; p=0,165 and 19% versus 9%; OR 1,7; p=0,005; respectively). Prevalence of cancer was not different between both groups. We can conclude, that metabolic risk factors (cardiovascular and type 2 diabetes mellitus) are associated with higher prevalence of advanced colorectal neoplasia in the Czech republic and can thus modify the screening program strategy in the future.

Reference:

(1) Š. Suchánek et al. Targeted colorectal cancer screening in patients with metabolic syndrome: a multicenter prospective study. Submitted for Digestive Disease Week San Diego 2016.

Address for correspondence: J. Bureš, 2nd Dept. Int. Med. - Gastroenterol., Charles University in Prague, Faculty of Medicine in Hradec Králové, University Hospital, Sokolská 581, 500 05 Hradec Králové, Czech Republic. E-mail: bures@lfhk.cuni.cz

Title of the project: Use of cell-free tumour DNA as a new target for minimally invasive diagnostics and specification of molecular classification of colorectal tumours

Grant Agency: Ministry of Health ***Project Number:*** NT/14383-3

Principal Investigator: P. Mináriková

Co-investigators: M. Minárik, L. Benešová, T. Hálková, Š. Suchánek, J. Bureš, J. Cyrany

Starting date: 1.5.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 1484

Summary of 2015 results

Title of the presentation: Molecular characterization of colorectal tumours based on CIMP/MSI/BRAF/KRAS classification

Authors: J. Bureš, J. Cyrany, 2nd Dept. Int. Med. - Gastroenterol., Charles Univ. Fac. Med. & Univ. Hosp., Hradec Králové

Patients with different molecular subtypes of colorectal cancer have different prognosis and this can be used for personalisation and optimalisation of management of the disease. This study compares molecular subtypes of proximal, distal colonic and rectal neoplasia of various stages (AA - advanced adenoma [adenoma larger than 10mm and/or with high grade dysplasia], EC - early carcinoma [stage I or II], LC - late carcinoma [stage II or IV]). This subanalysis was performed within the frame of project aimed on cell-free DNA.

297 tissue specimens were obtained by an endoscopic biopsy, polypectomy, mucosal resection or submucosal dissection of colorectal neoplasia (159 AA, 74 EC, 64 LC). DNA was extracted and MSI (microsatellite instability), CIMP (CpG-island mutator phenotype), BRAF, KRAS, APC (adenomatous polyposis coli) and TP53 were evaluated. MSI was detected only in proximal carcinomas (20% EC, 24% LC) - this correlates with supposed serrated (methylation) pathway of carcinogenesis in this part of the colon. CIMP+/BRAF+ type increased with stage of proximal neoplasia (5,3% in AA, 13% in EC and 26% in LC). TP53 frequency increased with neoplasma stage throughout the colon (5,1% AA, 38% EC, 41.3% LC) - this confirms roles of these mutations in carcinoma development.

Reference:

(1) P. Mináriková et al. Prospective longitudinal molecular characterization of colorectal tumors based on CIMP/MSI/BRAF/KRAS classification: comparion of advanced adenomas to early and late carcinomas. Submitted for Digestive Disease Week San Diego 2016.

Address for correspondence: J. Bureš, 2nd Dept. Int. Med. - Gastroenterol., Charles University in Prague, Faculty of Medicine in Hradec Králové, University Hospital, Sokolská 581, 500 05 Hradec Králové, Czech Republic. E-mail: bures@lfhk.cuni.cz

Title of the project: Significance of new systematic approach for clinical praxis in internal medicine

Grant Agency: Ministry of Education ***Project Number:*** 260178

Principal Investigator: J. Bureš

Co-investigators: J. Horáček, V. Bláha, R. Pudil, M. Kopáčová, J. Čáp, J. Vojáček, L. Sobotka, P. Žák, J. Petera, S. Filip, M. Bayer, L. Hosák and 15 students of doctoral studies

Starting date: 1.1.2015 ***Duration (years):*** 1

Total funds allocated for project - Kč (thousands): 1300

Summary of 2015 results

Title of the presentation: Significance of new systematic approach for clinical praxis in internal medicine.

Authors: J. Bureš (1), J. Horáček (2), V. Bláha (3), R. Pudil (4), M. Kopáčová (1), J. Čáp (2), J. Vojáček (4), L. Sobotka (3), P. Žák (2), J. Petera (5), S. Filip (5), M. Bayer (6), L. Hosák (7) and 15 students of doctoral studies

Charles Univ Fac Med, 2nd Dept Med (1), 4th Dept Med (2), 3rd Dept Med (3), 1st Dept Med (4), Dept Oncol Radiother (5), Dept Paediat (6), Dept Psychiatry (7)

Specific university research programme supports research, experimental development and innovations of students of doctoral studies. In total, 15 students and their doctoral projects were supported in 2015 coming from internal medicine, paediatric, oncology and radiotherapy and psychiatry. They included pericarditis in rheumatoid arthritis (related to other extraarticular involvement), apoptosis in colorectal neoplasia and inflammatory bowel disease, sarcopenia as a prognostic survival factor in transjugular intrahepatic portosystemic shunt, cholesterol metabolism in obese patients with type 1 diabetes mellitus, assessment of microcirculatory status in critically ill patients (using a LASER Doppler imaging), efficacy and safety of rituximab with dexamethason in chronic lymphocytic leukaemia, inhaled furosemid in chronic obstructive pulmonary disease, extracorporeal elimination of circulating pegylated liposomal doxorubicin in platinum-resistant ovarian cancer patients, flow cytometry in the assessment of residual disease, analysis of oncogenes in aspiration biopsy of the thyroid gland, anti-TNF-treatment in paediatric inflammatory bowel disease, humoral immune response to ischaemia and re-perfusion in acute myocardial infarction, compliance of patients with chronic heart failure and others. Specific university research programme helps doctoral students to facilitate their theses and to obtain their own original results. New systematic research, diagnostic and therapeutic approach significantly improves clinical praxis in internal medicine.

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Title of the project: IMPACT – Innovation, Methodology and Quality of Language Teaching and Language for Specific Purposes Teaching in Tertiary Sphere in the Czech Republic

Grant Agency: Ministry of Education ***Project Number:*** CZ.1.07/2.2.00/28.0233

Principal Investigator: H. Reichlová

Co-investigators: J. Comorek, L. Koláčková, Z. Kůs

Starting date: 1.5.2012 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 3200

Summary of 2015 results

Title of the presentation: Innovation, Methodology and Quality of Language Teaching and Language for Specific Purposes Teaching in Tertiary Sphere in the Czech Republic

Authors: PhDr. Jan Comorek, Ph.D., PhDr. Pavel Nečes, Ph.D., Mgr. Dagmar Vrběcká, Mgr. Eva Schánělová, Mgr. Klára Čebišová, Matthew Shane Renfro B.A.

The project (which finished in spring 2015) was focused on tertiary language education (graduate and undergraduate programmes) where languages are not the major subject. The goal of the team of teachers involved in the project at the Faculty of Medicine in Hradec Králové was: a) to improve existing language curricula b) in co-operation with other partners of the project to improve the system for testing LSP and c) to improve teaching materials.

The achieved results for individual languages (Latin and English) are:

LATIN - a) A new teaching materials have been introduced. They are based on large database of diagnoses which was founded in cooperation with other project partners. New teaching materials are at the moment in print and will serve as a teaching material in several other faculties of medicine in Czech republic. The materials are accompanied by new tests.

ENGLISH - a) English curricula have been significantly altered. The chosen core medical topics cover general medical knowledge corresponding with other theoretical subjects the students have in their third year and all topics are linked and supported online on Moodle (texts, exercises, links). Corresponding new types of medical English tests have been introduced. A significant change in oral testing represented by a structured diagnose should show how well and active is the language of the students. This type of evaluation fits better the requirements of real medical practice and helps to set up at least some objectives for EMP (English for Medical Purposes) within CEFR (Common European Framework of Reference).

Though the framework works well for general English it does not for LSP as each field has very different characteristics. The project attempted to unify standardisation of language performance in medicine (and other branches) but with regard to massive differences of the input teaching conditions (number of students in a teaching group, number of allocated teaching time, year of the study, student´s profile and so on) it was not possible to create a universal system going across all branches.

The project has also helped to improved qualifications of individual teachers who took part in various seminars and international conferences. Our department of languages organized one such international conference on testing in tertiary education. We also published a collective monograph on testing. The project helped to deepen a cooperation with similar departments in the Czech republic and attempted the cooperation with university of Hull.

All project´s administrative requirements have been fulfilled, the final report has been approved by the Ministry of Education and Youth. The project has met all the monitored data and has been approved as successful.

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Title of the project: Management of diagnostics and therapy of swallowing disorders

Grant Agency: Ministry of Health ***Project Number:*** NT/13725-4

Principal Investigator: M. Černý

Co-investigators: P. Mandysová, K. Zeleník

Starting date: 1.8.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 4005

Summary of 2015 results

Title of the presentation: Validation of the Czech version of the SWAL-QOL-CZ questionnaire

Authors: Michal Cerny[1], Jana Satankova[1], Lucia Stanikova[2], Karol Zelenik[2], Petra Mandysova[3], Viktor Chrobok[1]

[1] Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital, Faculty of Medicine in Hradec Kralove, Charles University in Prague

[2] Department of Otorhinolaryngology, University Hospital Ostrava

[3] Faculty of Health Studies, University of Pardubice

Introduction and Aims: Quality of life (QoL) monitoring has become an indispensable part of the diagnostics and treatment evaluation. For patients with dysphagia, various general as well as disease-specific QoL assessment tools have been introduced (MDADI, UW-QOL, DHI, SWAL-QOL and SWAL-CARE). The Swallowing Quality of Life (SWAL-QOL) questionnaire by McHorney et al. is an excellent tool that has been translated and validated in many other languages and has been widely used in patients with dysphagia. The purpose of the study was to develop and validate the Czech version of the questionnaire (SWAL-QOL-CZ).

Material and Methods: Patients with primary diagnoses linked to a risk of dysphagia, including diagnoses due to both structural and neurogenic causes were assessed by the SWAL-QOL-CZ and the WHOQOL questionnaires. As a control group, patients with extraoesophageal reflux and a dysphagia-free status, as shown by Flexible Endoscopic Evaluation of Swallowing (FEES), were used. Intra-class correlations and Cronbach's alpha coefficient and confirmatory factor analysis (Varimax rotation) were computed.

Results: The study enrolled a total of 337 patients (209 males, 128 females) with various diagnoses that were linked to dysphagia (head and neck cancer surgery and/or chemoradiotherapy, stroke, neurodegenerative diseases, trauma and so forth). Except for the Eating Desire domain, which had weak yet still usable reliability (Cronbach's alpha 0.54), all groups had good (Cronbach’s alpha > 0.7) to excellent (Cronbach’s alpha > 0.9) reliability (Burden 0.84, Symptoms 0.91, Fatigue 0.87, Sleep 0.81, Food Selection 0.83, Eating Duration 0.86, Communication 0.93, Fear 0.84, Mental Health 0.94 and Social Functioning 0.93).

Conclusion: The analysis showed that that the Czech version of the SWAL-QOL questionnaire is a valid tool that can be used for assessment of patients with dysphagia using the Czech language.

Address for correspondence: M. Černý, Department of Otolaryngology, University Hospital Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic.

Title of the project: Alterations of glycocalyx in critical illness and during major surgery and approaches for glycocalyx protection

Grant Agency: Ministry of Health ***Project Number:*** 15-31881A

Principal Investigator: V. Černý

Co-investigators: D. Astapenko, R. Černá Pařízková, P. Dostál, Z. Turek, I. Saleh Abdo, R. Škulec, R. Hyšpler, A. Tichá, Z. Zadák, J. Martínková, J. Beneš, J. Pouska, Ch. Lehmann

Starting date: 1.1.2015 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 8340

Summary of 2015 results

Title of the presentation: Changes in glycocalyx thickness after hip/knee surgery

Authors: D. Astapenko (1) and V. Černý (1, 2)
(1) Dept. of Anaesthesiology and Intensive Care, University Hospital Hradec Kralove, Charles University in Prague, Faculty of Medicine in Hradec Kralove, Hradec Kralove, Czech Republic
(2) Dept. of Research and Development, University Hospital University Hospital Hradec Kralove, Czech Republic

Endothelial glycocalyx (EG) represents a sugar-based gel-like structure coating vascular endothelium. It plays key role in maintaining vascular integrity, however, due to its fragile structure, EG can be affected by various noxious stimuli. Clear evidence of changes of glycocalyx during surgery and/or anaesthesia does not exist. Non-invasive method of evaluating EG thickness by using Perfused Boundary Region (PBR) has been introduced just recently. The aim of the study was to evaluate changes in PBR in patients after hip/knee replacement.
After obtaining informed consent, 30 consecutive patients were prospectively investigated. Selected demographic, clinical and physiological data were recorded. Images of sublingual microcirculation were recorded before and 24 hours after surgery. Recordings were analysed automatically for PBR (in μm) with specialized software (GlycoCheck, Maastricht, Netherlands). Data are presented as a mean +/- standard deviation, statistical analysis was done by using GraphPad Prism, $p \leq 0.05$ was considered as statistically significant.
Fourteen women and 16 men were evaluated (age 46-84 years, ASA status 2-3). Values of PBR (in μm) changed significantly from baseline to 24 hours after surgery (1,95 +/- 0,24 resp. 2,10 +/- 0,19, $p = 0,0005$).
We conclude that hip/knee surgery led to significant increase of PBR, which may suggest that surgery and/or anaesthesia contribute to glycocalyx damage. Further studies to explore this finding and its possible impact on clinical practice are definitely needed.

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Title of the project: International conferences in medical sciences 2015/12th International Medical Postgraduate Conference

Grant Agency: Ministry of Education ***Project Number:*** 260182

Principal Investigator: M. Červinka

Co-investigators: V. Palička

Starting date: 1.1.2015 ***Duration (years):*** 1

Total funds allocated for project - Kč (thousands): 800

Summary of 2015 results

Title of the presentation: New Frontiers in the Research of PhD Students

Authors: M. Červinka, V. Palička

The 12th International Medical Postgraduate Conference took place in Hradec Kralove on November 26-27, 2015 under the auspices of Rector of the Charles University in Prague.
Medical schools across the Europe nominated 33 students of medical doctoral study programmes from 11 European countries (Austria, Croatia, Georgia, Germany, Great Britain, Hungary, Poland, Portugal, The Netherlands, Slovak and Czech Republics). The members of International Evaluation Committee were the experts from 8 countries inclusive the President of Association of Medical Schools in Europe.
All presentations were published in the conference proceedings.
We consider this particular meeting of postgraduate students in biomedicine very important from the point of international harmonisation of PhD studies in Europe and for its multidisciplinary focus. The participants often find that other fields of medicine are interesting and beneficial for them and how knowledge of other areas of medicine may be valuable.
The other conference aims were also fulfilled, namely comparing achieved results and levels of PhD programmes at medical schools, presentation of the scientific works, meeting the students and experts from European countries and the opportunity to discuss common problems.
The best three participants received a financial award and the invitation to the ORPHEUS conference in Cologne in 2016.

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Title of the project: New procedures in diagnostics and therapy of lifestyle diseases and diseases connected with population ageing

Grant Agency: Charles University ***Project Number:*** P 37

Principal Investigator: M. Červinka

Co-investigators: Z. Červinková, Z. Fiala, M. Kaška, J. Krejsek, M. Kuba, J. Malý, S. Mičuda, J. Mokrý, A. Ryška, E. Rudolf, R. Pudil, L. Sobotka, R. Slezák

Starting date: 1.7.2012 ***Duration (years):*** 5

Total funds allocated for project - Kč (thousands): 37876

Summary of 2015 results

Title of the presentation: New procedures in diagnostics and therapy of lifestyle diseases and diseases connected with ageing of population

Authors: M. Červinka, Z. Červinková, Z. Fiala, M. Kaška, J. Krejsek, M. Kuba, J. Malý, S. Mičuda, J. Mokrý, A. Ryška, E. Rudolf, R. Pudil, L. Sobotka, R. Slezák

This complex research project is focused on main problems of European medicine. The leading idea of the project is the fact that populations in the Czech Republic is ageing. The main health problem associated with this demographic facts is an increasing number of people suffering from lifestyle diseases. Therefore we need intensive, effective and complex research in these areas.

1. Research in the sphere of lifestyle diseases affecting cardiovascular system is focused on problems of ischemic heart disease, sudden heart death and specification of risks, but also on a non-pharmacological and pharmacological prevention of such events. Other spheres of the research are the conditions for regeneration of myocardium in experiment and in clinical practice and diseases affecting gastrointestinal system (functional disorders, usage of the latest diagnostic methods, possibilities for prevention and so on.
2. The area of oncology and haemato-oncology: The study of prediction of the impact and toxicity of the treatment, importance of individual dosage regulation of medicaments and prediction of the response to these medical procedures. A significant attention is paid to oncological problems of digestive tract. The reason is occurrence of tumours, namely tumours of the large intestine and also probable impact of today´s diet and other lifestyle factors.
3. The problem of ageing and related health problems including the study of regeneration on all levels. The research will be aimed at basic metabolic and molecular manifestation of ageing and on reparation and regeneration processes. An accompanying sphere of interest is the study of damage and reparation on the level of DNA, cell and organ level, including possibilities to influence such processes.

The research work in all three mentioned interconnected areas has been fulfilled by 13 working groups. The results of the fourth year of the project are 92 original research papers and publications, from these 66 published in journals with impact factor.

Address for correspondence: M. Červinka, Charles University in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 50038 Hradec Králové, Czech Republic

Title of the project: Study of a new mechanism of acetaminophen toxicity in liver and possibilities of therapy

Grant Agency: Ministry of Health ***Project Number:*** NT/14320-3

Principal Investigator: T. Roušar

Co-investigators: Z. Červinková, O. Kučera

Starting date: 1.1.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 1751

Summary of 2015 results

Title of the presentation: Study of hepatoprotective action of N-acetyl cytestine on acetaminophen toxicity in vitro and in vivo

Authors: O. Kučera, Z. Červinková
Fac. Med., Charles Univ., Hr. Králové: Dept. of Physiology

Acetaminophen (APAP) poisoning is the most common cause of acute drug-induced liver failure in humans. N-acetyl cysteine (NAC) is the only drug used to treat acetaminophen overdose in clinical practice. NAC may prevent depletion of reduced glutathione (GSH) and thus formation of APAP-protein adducts.

The aim of our project in 2015 was to study time dependence of NAC administration to primary cultures of rat and mouse hepatocytes exposed to APAP. Furthermore in accordance with the project plan, we studied also hepatoprotective effect of NAC on APAP hepatotoxicity in mouse.

Rat and mouse hepatocytes in primary cultures were treated with APAP at concentrations of 5 and 1.5 mmol/L for 24 hours, respectively. NAC (5 and 1.5 mmol/L) was added to culture media of rat and mouse hepatocytes together with APAP or 2, 4 and 8 hours after APAP exposure.

Although mouse hepatocytes were more sensitive to the toxic effect of APAP than rat hepatocytes (earlier damage to the plasma membrane and more steep decrease in intracellular GSH level), NAC was more efficient in treatment of injury induced by APAP in mouse hepatocytes. Damage to the plasma membrane (measured by LDH activity in culture medium) was partially prevented when NAC was added to culture medium up to 4 ($p<0.001$) and 8 hours ($p<0.001$) after exposure to APAP in rat and mouse hepatocytes, respectively. Furthermore the effect of NAC on a decrease in LDH activity was more expressed in mouse hepatocytes. In both rat and mouse hepatocyte cultures, NAC (up to 8 hours after APAP administration) was able to prevent partially depletion of intracellular content of GSH ($p<0.001$). NAC was more effective in prevention of GSH lost in mouse hepatocytes (65% vs 91% of control values of rat and mouse hepatocytes, resp.).

Despite the fact that mouse hepatocytes are more sensitive to the toxic action of APAP, NAC treatment of APAP-induced injury is more effective in mouse hepatocytes than in rat hepatocytes.

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Title of the project: Treatment of sudden sensorineural hearing loss with rheohaemapheresis

Grant Agency: Ministry of Health ***Project Number:*** NT/13475-4

Principal Investigator: J. Dršata

Co-investigators: V. Chrobok, V. Bláha, M. Bláha, M. Lánská

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 6374

Summary of 2015 results

Title of the presentation: Treatment of sensorineural hearing loss - final results

Authors: J. Dršata (1), M. Bláha (2), V. Chrobok (1), M. Lánská (2). Dpt. of ORL HNS (1), 2nd Dpt. of Internal Medicine (2); University Hospital Hradec Kralove, Charles University in Prague, Faculty of Medicine in Hradec Kralove.

The salvage therapy in Sudden Idiopathic Sensorineural Hearing Loss (SISHL) is a treatment option after a failure of conventional steroid therapy. The project aim was to compare efficacy and safety of salvage therapy by means of Rheohaemapheresis (group R) with an alternative wing of salvage therapy by means of MicroWick system (group M) and outcome of alone standard corticotherapy (group S).

Patients and Methods: the groups of patients (group S, n = 54; group R, n = 33; group M, n = 19) were characterized by age, sex, side of lesion, time to treatment initiation. Furthermore, anamnestic and anthropometric data were evaluated. Neuro-otological methods used for evaluation in all observation groups (S, R, M) were pure tone, impedance and speech audiometry, BERA, posturography and Tinnitus Severity Index (TSI) QOL query. Besides, biochemical, hematological and immunological characteristics were studied. Adverse events were recorded.

Results: in pure tone audiometry, the improvement was achieved by 12 – 20,7 dB in average in the group S, 18 – 25 dB in the group R and no improvement in the group M. Speech reception threshold and speech discrimination score improved in the group S and group R, while remained unchanged in the group M. Results of other neurootological methods are a subject of further evaluations. The preliminary results appear the treatment in the group S and group R achieved improvement of tinnitus both in tinnitometry and TSI. The results of BERA, impedance audiometry and posturography seem to be not significant as markers of SISHL improvement. Immunologic observations indicate, the complement (especially an alternative pathway) plays an important role in microcirculation disorders, presumably in SISHL too. The role of platalet volume in SISHL was not changed and the entire problem seems to remain unclear.

Conclusion: the salvage therapy with rheohaemapheresis seems to be an effective and safe treatment option for patients who fail in hearing improvement after standard corticotherapy. The MicroWick system does not seem to provide additional benefit in comparison with the rheohaemapheresis and corticotherapy.

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Title of the project: Research and development of advanced thin film sensors for direct monitoring of the time variable by means of preciously calibrated colour change

Grant Agency: Czech Republic ***Project Number:*** TA03010548

Principal Investigator: K. Ettler

Co-investigators: V. Wertzová, O. Sitařová

Starting date: 1.1.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 657

Summary of 2015 results

Title of the presentation: Development of personal UV and visible light dosimeter

Authors: K. Ettler, V. Wertzová

The aim of the project comprises design and development of special advanced sensors for independent monitoring of the time variable by means of visually well detectable colour change. The sensing elements will be completed on the basis of photochemical and photocatalytic principles with additional parts. Thin films, which reveal the time dependent and calibrated colour change are specifically well suited as efficient tools for simple visual evaluation of the time variable. The main promissible stains for UV and visible light detections seem to be Acid Red 1, Acid Orange 7 and Thymol Blue.

The project comprises the scale testing of the designed and developed sensors for dermatology (especially for UV phototherapy and photodynamic therapy). Personal UV dosimetry is very usefull during summer season to avoid sunburning and other sun infury of the skin.

Functional prototypes of dosimeters have been tested during phototherapeutical courses under halid mercury lamp (main colour change after 2 minutes of irradiation), narrow band UV-B 311 nm (minimal dose for blanching was 0,6 J/cm2) and broad band UV-A (reaction after 5 J/cm2), also under solar simulator (Q sun). These dosimetric bands reactions were in concordance with minimal erythemal doses of mentioned kinds of phototherapy.

Two patent applications for functional prototypes of dosimeters were registered at Patent Authority of the Czech Republic. Two prototypes of personal strip solar dosimeters were prepared for commercial use and tested by consumers during “Night of Science” (23SEP2015) in Brno.

Literature:

K. Ettler, V. Wertzová: Problematika osobní UV dozimetrie. Abstracts of X. Congress of Slovak and Czech Dermatologists, Štrbské Pleso, 12. - 14. 6. 2014

K. Ettler, V. Wertzová: Měření UV záření – proč, kdy a jak? Abstracts of 21st National Dermatological Congress, Brno, 13. - 14. 11. 2015

Address for correspondence: K. Ettler, Dept. of Dermatology, Charles University in Prague, Faculty of Medicine in Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic, e-mail: ettler@lfhk.cuni.cz

Title of the project: Kinetically guided removal of plazma pegylated liposomal doxorubicin to enhance the benefit of cytostatic therapy of patients with ovarian cancer

Grant Agency: Ministry of Health ***Project Number:*** NT/14035-3

Principal Investigator: S. Filip

Co-investigators: M. Bláha, J. Martínková, J. Špaček, O. Kubeček, J. Maláková, V. Bláha

Starting date: 1.5.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 4996

Summary of 2015 results

Title of the presentation: Plasma filtration as a possible contributor to kinetic targeting of pegylated liposomal doxorubicin (PLD) in order to prevent organ toxicity and immunosuppression.

Authors: S. Filip (1), M. Bláha (2), J.Martínková (3), J. Špaček (4), O. Kubeček (1), J. Maláková (5), V. Bláha (6)

Dept. Oncology and Radiotherapy (1), 4th Dept. of Internal Medicine (2), Dept. of Surgery (3), Dept. of Gynecology (4), Dept. of Medical Biochemistry (5), Dept. Gerontology and Methabolic (6).

Purpose

To examine the removal of pegylated liposomal doxorubicin (PLD) during plasmafiltration (PF); determine whether the drug could be withheld prior to its organ distribution responsible for mucocutaneous toxicity.

Methods

Six patients suffering from platinum-resistant ovarian cancer were treated with a one-hour IV infusion 50 mg/m2 of PLD/cycle I-III q4w. From h 44 postinfusion, five patients underwent a one-volume 2–3 hour plasmafiltration using separator (Cobe-Spectra or Optia, Terumo, Likewood, OA). A series of blood samples was taken until h 116 postinfusion. Doxorubicin pharmacokinetic parameters and the fraction of the administered dose eliminated both in vivo and removed extracorporeally were calculated. Toxicity was evaluated using CTCAE v4.0.

Results

A single one-volume plasmafiltration removed 16–64 % of PLD dose from the systemic circulation. Drug extracorporeal clearance was 11–25 times higher than that depending on patients' eliminating capacity. Over the postfiltration period, redistribution of doxorubicin was observed with consequent prolongation of half-life of elimination (T1/2).

Conclusions

A single one-volume plasmafiltration does remove a clinically important amount of doxorubicin in a kinetic targeting approach. A redistribution phenomenon in doxorubicin plasma concentration seems to exist after plasmafiltration. Kinetically guided therapy with pegylated liposomal doxorubicin combined with plasmafiltration may be a useful tool.

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Title of the project: Human Resources for Neurosciences in the Hradec Králové and Ústí Regions

Grant Agency: Ministry of Education ***Project Number:*** CZ.1.07/2.3.00/20.0274

Principal Investigator: E. Syková

Co-investigators: S. Filip, J. Mokrý, E. Rudolf, Y. Mazurová, J. Petera, S. Řehák, P. Smolová, Z. Špuláková

Starting date: 1.11.2012 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 18728

Summary of 2015 results

Title of the presentation: Human Resources for Neuroscience – teaching program for medical students.

Authors: S. Filip, Dept. of Oncology and Radiotherapy, Charles University in Prague, Faculty of Medicine and Faculty Hospital in Hradec Králové, Czech Republic.

Introduction: At present, the global issues of biotechnology addressed the introduction of new technologies and procedures in the diagnosis and treatment of disease. Request of an interdisciplinary approach leads to a demand for closer cooperation of clinical and research centers. IEM AS CZ in Prague (Intitute of Experimental Medicine, Academy of Science), expanded considerably issues of neuroscience, cell therapy and regenerative medicine, and its activity excels in the scientific field and the training of young scientists. Medical Faculty of Charles University in Hradec Kralove has priority status in the education of future physicians in the Czech Republic as well as in clinical medicine, both in diagnosis and therapy. Linking these complementary activities enable to establish new research teams that communicate with each other to create new information and methodological approaches in the diagnosis and treatment of serious diseases. The former cooperation between Medical Faculty in Hradec Kralove and IEM has previously been created by one working group of experts aimed at the regeneration of supporting tissues (cell biology, genetics, orthopedics, neurosurgery, oncology and tissue banks) and developed a new treatment method focused on the treatment of degenerative and traumatic damage to the musculoskeletal system using cellular therapy. The main purpose of the project is to tranfer the theoretical and methodological experience of experiemental scientific teams of IEM to the training of future doctors at the Medical Faculty in particular in the field of neuroscience, and additional current Neurooncology directions with high research and social potential.

Conclusion: Undergraduate teaching of medical students was launched as planned - the teaching in the subject neurooncology and neurobiology. The projected number of students has been met. The interest in these subjects among our students is large and continues teaching. Furthermore, are according to the plan continue training events such as - Summer School, lectures and courses, scientific cooperation and other key activities in accordance with plan of project. Key project activities were fulfilled according to plan.

Acknowledgements: This project was supported by the grant Ministry of Education CZ, CZ.1.07/2.3.00/20.0274

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Title of the project: Muscle remodelling on the basis of extracellular matrix seeded with functionally characterized cells

Grant Agency: Czech Republic ***Project Number:*** 15-09161S

Principal Investigator: S. Filip

Co-investigators: J. Mokrý, G. Dayanithi, O. Forostyak, H. Hrebíková, R. Pisal, J. Chvátalová, D. Čížková

Starting date: 1.1.2015 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 5794

Summary of 2015 results

Title of the presentation: Muscle remodelling on the basis of extracellular matrix seeded with functionally characterized cells.

Authors: S. Filip (1), J. Mokrý (2), G. Dayanithi (2), O. Forostyak (2), H. Hrebíková (2), R. Pisal (2), J. Chvátalová (2), D. Čížková (2).

Department of Oncology and Radiotherapy (1); Department of Histology and Embryology (2).

In the proposed project, we suggest a novel approach to muscle organ reconstruction based on colonization of decellularized extracellular matrix (ECM) isolated from the skeletal muscle with muscle-derived cells. Optimalized cell types for recellularization are selected on the basis of their phenotypical and electrophysiological properties. Analysis of bioscaffolds alone and recellularized scaffolds implanted to animals performed at defined survival intervals includes a spectrum of morphological and molecular biological methods aimed at assessment of changes in ECM remodelling inside the graft, examination of cell activity and evaluation of function of reconstructed muscles. The results could be exploited for skeletal muscle reconstruction as well as repair of other organs.

Preliminary results show that muscle derived cells respond to caffeine, ryanodine, CPA, high K+ and glutamate but the responses to ATP were highly pronounced, observed in the absence of external Ca2+, inhibited by P2Y2 inhibitor suggesting the important involvement of P2Y signalling. Mitochondrial and ER Ca2+ uptake seem to play a major role in Ca2+ homeostasis. Our results demonstrate that Ca2+ entry induced by high K+ can be activated by specific L-type Ca2+ voltage-operated calcium channels. Histological examination of decellularized muscle scaffolds confirmed absent nuclei and sarcoplasmic components, presence of glycosaminoglycans and preservation of collagen fibres. Hydroxyproline assay proved preservation of collagen. Preservation of basal lamina was determined with immunostaining of collagen IV. DNA content was significantly reduced under 50 ng of DNA per mg of tissue. Adhesion and viability of the scaffold was confirmed by re-seeding with C2C12 murine myoblasts. Histological examination of scaffolds implanted into the murine tibial anterior muscle confirmed its good integration with the muscle and rich colonization by recipient cells.

We succeeded in producing decellularized skeletal muscle tissue with well-preserved major components (basal lamina, collagen fibres and glycosaminoglycans) that fulfilled requirement for successful decellularization (elimination of cell and nuclear components, reduction of DNA content and preservation of 3D architecture of ECM). Cytocompatibility of scaffold was proved with a successful in vitro recellularization technique and implantation of decelularized scaffold into the mouse muscle, which resulted in rich scaffold recellularization.

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Title of the project: Anthracycline cardiotoxicity – new possibilities of pharmacological cardioprotection and risks of combination with biological targeted anticancer treatment

Grant Agency: Ministry of Health ***Project Number:*** NT/13457-4

Principal Investigator: M. Štěrba

Co-investigators: O. Lenčová, E. Jirkovský, V. Geršl, Y. Mazurová, M. Adamcová, T. Šimůnek, A. Jirkovská

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 6372

Summary of 2015 results

Title of the presentation: Are cardioprotective effects of NO-releasing drug molsidomine translatable to chronic anthracycline cardiotoxicity settings?

Authors: O. Lenčová (1), H. Jansová (2), E. Jirkovský (1), J. Bureš (3), Y. Mazurová (4), A. Jirkovská (2), M. Adamcová (5), Z. Pokorná (1), P. Kovaříková (3) T. Šimůnek (2), V. Geršl (1), M. Štěrba (1)

Fac. Med., Charles Univ., Hr. Králové: Dept. of Pharmacology (1), Dept. of Histol. Embryol. (4), Dept. of Physiol. (5), Fac. Pharm., Charles Univ., Hr. Králové: Dept. of Biochem. Sci. (2) and (3) Dept. of Pharm. Chemistry and Drug Anal.

Chronic anthracycline (ANT) cardiotoxicity is a serious complication of cancer chemotherapy. NO-mediated cardioprotection has shown promises in myocardial I/R injury, but applicability to clinically relevant forms of ANT cardiotoxicity remains unknown. Molsidomine, a NO-releasing drug, has been found cardioprotective in different models of I/R injury and recently also in acute high-dose ANT cardiotoxicity. Thus, we sought whether its cardioprotective effects are translatable to chronic ANT cardiotoxicity settings without induction of nitrosative stress as well as interference with antiproliferative action of ANTs. Effects of molsidomine (0.025 and 0.5 mg/kg, i.v.) were studied on the well-established model of chronic ANT cardiotoxicity in rabbits (daunorubicin /DAU/ 3 mg/kg/week for 10 weeks). The results showed that neither of molsidomine doses was able to significantly attenuate mortality, development of heart failure and morphological damage induced by DAU. Molsidomine did not alter DAU-induced myocardial lipoperoxidation, MnSOD down-regulation, and up-regulation of HO1, IL6 and molecular markers of cardiac remodeling. Using H9c2 myoblasts and isolated cardiomyocytes, it was found that SIN-1 (an active metabolite of molsidomine) induces significant protection against ANT toxicity, but only at high concentrations that are close to the cytotoxicity of SIN-1-itself. In leukemic HL-60 cells, SIN-1 initially augmented ANT cytotoxicity in very low (clinically achievable) concentrations, but it protected these cells in the high concentrations similarly as in cardiomyocytes. HPLC-MS investigation demonstrated that the cytoprotective effects of the high concentrations of SIN-1 are caused by unexpected chemical depletion of DAU molecule. The present study conclusively demonstrates that cardioprotective effects of molsidomine are not translatable to clinically important chronic form of ANT cardiotoxicity. Supported by the grant IGA MZ No. NT13457-4/2012.

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Title of the project: Research Center for the Study of Toxic and Protective Effects of Drugs on Cardiovascular System

Grant Agency: Ministry of Education ***Project Number:*** UNCE 204019/304019

Principal Investigator: T. Šimůnek

Co-investigators: V. Geršl, M. Štěrba, O. Lenčová, E. Jirkovský, K. Vávrová, P. Nachtigal, P. Zimčík, P. Kovaříková, A. Jirkovská, R. Kučera, J. Lenčo, I. Němečková, J. Roh, P. Mladěnka, V. Nováková, P. Hašková

Starting date: 1.1.2012 ***Duration (years):*** 6

Total funds allocated for project - Kč (thousands): 18152

Summary of 2015 results

Title of the presentation: Cardioprotective effects of ADR-925 - a putative active metabolite of dexrazoxane - against anthracycline cardiotoxicity in vivo and in vitro.

Authors: E. Jirkovský (1), O. Lenčová (1), Z. Pokorná (1), A. Jirkovská (2), H. Jansová (2), J. Bureš (3), J. Roh (4), K. Vávrová (4), T. Šimůnek (2), P. Kovaříková (3), V. Geršl (1), M. Štěrba (1). Fac. Med., Charles Univ., Hr. Králové: Dept. of Pharmacology (1); Fac. Pharm., Charles Univ., Hr. Králové: Dept. of Biochem. Sci. (2), Dept. of Pharm. Chem. and Pharm. Anal. (3), Dept. of Inorg. and Org. Chemistry (4).

Dexrazoxane (DEX) is the only drug with well-established cardioprotective efficacy against anthracycline (ANT) cardiotoxicity in both clinical and experimental settings. Although mechanisms of its cardioprotective action are still unclear, it is traditionally believed that DEX acts via its iron-chelating metabolite ADR-925 which prevents ANT-induced oxidative damage. However, direct evidence for this hypothesis is lacking. Our previous experiments confirmed DEX (60 mg/kg) is effective cardioprotectant against chronic ANT cardiotoxicity induced in rabbits with daunorubicin (DAU 3 mg/kg/week for 10 weeks) and also against DAU (1.2 μM) toxicity to neonatal rat ventricular cardiomyocytes (NVCM; DEX 10-100 μM). Our pharmacokinetic experiments demonstrated that direct administration of ADR-925 (60 mg/kg, inf. alone or with additional s.c. dose in 150^{th} min) is able to reach comparable or higher concentrations of ADR-925 in plasma and heart than those after administration of parent drug (DEX). Similarly, exposure of NVCM to ADR-925 (100 μM) resulted into higher intracellular concentrations than after DEX. These findings allowed us to directly assess the cardioprotective effects of ADR-925 using the same models. The results of these investigations clearly showed that ADR-925 is unable to protect neither NVCM cells nor rabbit hearts against ANT cardiotoxicity regardless of schedule of administration. This message is based on survival, functional, morphological, histological, molecular and biochemical findings (e.g. index of systolic function LV dP/dt_{max} decreased by 46%, 39% and 41% as compared to controls in the DAU and both ADR-925 combination groups, respectively, $p<0.05$). All these findings markedly contrasted with excellent protective efficacy of DEX, which was induced by the same or lower concentrations of ADR-925 at the sites of its putative action. In conclusion, these data for the first time show that iron-chelating agent ADR-925 is not responsible for cardioprotective effects of DEX against ANT cardiotoxicity. Instead, other mechanisms, presumably associated with parent DEX molecule (eg. interaction with topoisomerase IIβ), may be involved and deserve further study.

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Title of the project: The influence of preservatives on the composition of microbiome and the development of Crohn's disease in genetically susceptible host

Grant Agency: Charles University ***Project Number:*** 906613

Principal Investigator: L. Hrnčířová

Co-investigators: J. Krejsek, T. Hrnčíř, N. Gabrielová, E. Trčková

Starting date: 1.4.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 830

Summary of 2015 results

Title of the presentation: Antimicrobial food additives influence the composition of human gut microbiota

Authors: L. Hrnčířová (1,2), J. Krejsek (1), T. Hrnčíř (2), N. Gabrielová (3), E. Trčková (3)
Fac. Med., Charles Univ., Hr. Králové, Dept. of Clinical Immunology and Allergology (1), Dept. of Gnotobiology, Inst. of Microbiology, Ac. Science CR, Nový Hrádek (2), Fac. Med., Charles univ., Hr. Králové (3)

There is accumulating evidence that gut microbiota play an important role in the induction and maintenance of various allergic, autoimmune, metabolic diseases and cancer. The ratio of beneficial (anti-inflammatory) versus harmful (pro-inflammatory) microbiota seems to play a central role. The composition of gut microbiota is influenced by genetic and environmental factors. The single most important environmental factor is diet. A preservative is naturally occurring or synthetically produced substance that is added to food to prevent microbial growth or undesirable chemical changes. The aim of the project is to evaluate whether and to which extent commonly used food additives modify the composition of gut microbiota. We performed in vitro studies, where we tested the inhibitory effect of widely used antimicrobial food additives (AMFAs) on the growth of single bacteria isolated from human gut microbiota, and in vivo studies (we exploit a humanized mouse model), where we tested the influence of dietary AMFAs on the composition of human gut microbiota and the impact of AMFA-modified microbiota on the development of immune system. We have found that the inhibitory effect of four common AMFAs is different for each tested aerobic bacteria and AMFAs, and can be synergistic in some conditions, so we hypothesize that the presence of many different AMFAs in diet can influence the growth of susceptible gut bacteria and contribute to dysbiosis.

When we tested the effect of AMFAs in diet in vivo, we have found that even low AMFA concentrations decrease the diversity of human gut microbiota, specifically the Actinobacteria and Verrucomicrobia phyllum disappear, and the frequency of the Proteobacteria phyllum increases. The high AMFA concentrations in diet entirely disrupt the gut microbiota ecosystem with the Proteobacteria phyllum overgrowth. Analysis of the immune system by flow cytometry have shown shift to proinflammatory tuning of the gut immune system.

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Title of the project: The development of a diagnostic panel for the monitoring of perioperative small bowel injury

Grant Agency: Ministry of Health ***Project Number:*** NT/13536-4

Principal Investigator: R. Hyšpler

Co-investigators: Z. Zadák, A. Tichá, M. Kaška, I. Svobodová, A. Ferko, E. Havel, L. Žaloudková, M. Drahošová

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 5412

Summary of 2015 results

Title of the presentation: Markers of Perioperative Bowel Complications in Colorectal Surgery Patients

Authors: Radomír Hyšpler (1), Alena Tichá (1), Milan Kaška (2), Lenka Žaloudková (3), Lenka Plíšková (3), Eduard Havel(2), and Zdeněk Zadák (1)
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3Department of Clinical Chemistry, University Hospital Hradec Kralove

Colorectal cancer is a clinical condition whose treatment often involves intestinal resection. Such treatment frequently results in two major gastrointestinal complications after surgery: anastomotic leakage and prolonged ileus. Anastomotic leakage is a serious complication which, more often than not, is diagnosed late; to date, C-reactive protein is the only available diagnostic marker. A monocentric, prospective, open case-control study was performed in patients undergoing colorectal surgery. Intestinal fatty acid binding protein (i-FABP), citrulline, D-lactate, exhaled hydrogen, Escherichia coli genomic DNA, and ischemia modified albumin (IMA) were determined preoperatively, postoperatively, and on the following four consecutive days. Bacterial DNA was not detected in any sample, and i-FABP and D-lactate lacked any distinct potential to detect postoperative bowel complications. Exhaled breath hydrogen content showed unacceptably low sensitivity. However, citrulline turned out to be a specific marker for prolonged ileus on postoperative days 3-4. Using a cut-off value of 20 μmol/L, a sensitivity and specificity of ~75% was achieved on postoperative day 4. IMA was found to be an efficient predictor of anastomosis leak by calculating the difference between preoperative and postoperative values. This test had 100% sensitivity and 80% specificity and 100% negative and 20% positive predictive value.

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Title of the project: The risk factors of dental caries and periodontal diseases in children with very low birth weight (VLBW)

Grant Agency: Ministry of Health ***Project Number:*** NT/14336-3

Principal Investigator: V. Merglová

Co-investigators: R. Koberová Ivančaková, Z. Broukal, J. Dort

Starting date: 1.1.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 2963

Summary of 2015 results

Title of the presentation: Mothers related risk factors of ECC in very low birth weight children.

Authors: R. Koberová Ivančaková[1], V. Merglová[2], Z. Broukal[3], J. Zemánková[4], L. Ryšková[5], Z. Janovská[1]

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Background: Health complications and poorer oral health of pregnant women may lead to pre-term delivery a very low birth weight (VLBW) of children.

Aim: The aim of the study was to identify relevant risk factors of early childhood caries (ECC) in mothers delivered their child pre-maturely with very low birth weight (VLBW) in comparison to those delivered eutrophic, full-term children. The study was approved by the ethical committees of University Hospitals in Hradec Králové and Pilsen. Design: Altogether 104 age-matched mothers of one-year old children have been included in the study, 56 with VLBW children, 48 with full-term children (30.9 vs. 31 yrs) based on their written informed consent. Mothers were dentally and periodontally examined by calibrated examiners and basic oral health data were calculated (DMFT, PBI). Health history was obtained by the questionnaire. Statistics – Fisher exact test, t test ($p<0.05$). Results: Risk pregnancy was reported more frequently in mothers with VLBW children (64.3% vs. 16.7% - $p<0.05$). Systemic diseases and complications of pregnancy were more frequent in women delivering pre-maturely as compared with those with full-term deliveries (17.9% vs. 4.2% - $p<0.05$). The most of mothers from both groups were non-smokers (83.9% vs. 93.7% - $p=0>0.05$). Oral health was slightly better in mothers delivered full-term compared to pre-term (DMFT 9.5 vs. 11.4, PBI 16.5 vs. 29.9 – in both parameters $p>0.05$).

Conclusion: Risk pregnancy, frequently associated with poorer general and oral health may lead to pre-mature delivery and VLBW of the child and thus can be taken as a relevant risk factor of perinatal complications of new-borns and of the ECC in these children. Further research is needed to confirm this hypothesis.

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Title of the project: Cervical fluid - noninvasive prediction of histological chorioamnionitis and funisitis in pregnancies complicated by preterm prelabor rupture of membranes

Grant Agency: Ministry of Health ***Project Number:*** NT/14104-3

Principal Investigator: M. Kacerovský

Co-investigators: M. Procházka, P. Janků, O. Šimetka

Starting date: 1.4.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 3347

Summary of 2015 results

Title of the presentation: Bedside vaginal fluid interleukin-6 testing in pregnancies complicated by preterm prelabor rupture of membranes

Authors: Marian Kacerovský, Ivana Musilová, Tomáš Bestvina, Martina Hudeckova, Igor Michalec

Preterm prelabor rupture of membranes (PPROM) is frequently complicated by specific infectious and inflammatory conditions such as microbial invasion of the amniotic cavity (MIAC), intra-amniotic inflammation (IAI) and microbial-associated IAI. Bedside testing of amniotic fluid interleukin (IL)-6 has been shown to be a clinically relevant approach to assessing the status of the amniotic cavity. The invasiveness of amniocentesis makes clinicians hesitant to use it broadly in clinical practice, and therefore a shift from amniotic fluid sampling towards a non-invasive procedure is needed. Therefore, the main goal was to determine the diagnostic indices and predictive value of the bedside assessment of vaginal fluid IL-6 concentration in the identification of MIAC, IAI, and microbial-associated IAI in patients with PPROM.

One-hundred-twenty women with singleton pregnancies were included in this study. Vaginal fluid was obtained from the posterior vaginal fornix by aspiration with a sterile urine sample tube with a suction tip. Amniotic fluid was obtained by transabdominal amniocentesis. IL-6 concentrations were assessed with a lateral flow immunoassay in both fluids immediately after sampling.

The bedside assessment of IL-6 in vaginal fluid was possible to perform in 90% (108/120) of the women. A strong positive correlation was found between the IL-6 concentrations in vaginal and amniotic fluids (Spearman rho 0.71; $p<0.0001$). The presence of MIAC, IAI or microbial-associated IAI was associated with higher vaginal fluid interleukin-6 concentrations in both crude and adjusted analyses. A vaginal fluid interleukin-6 of concentration of 2500 pg/mL was determined to be the best cutoff value for the prediction of IAI (sensitivity of 67%, specificity of 90%, positive predictive value of 61%, negative predictive value of 92%, and likelihood ratio of 7.3) or microbial-associated IAI (sensitivity of 100%, specificity of 90%, positive predictive value of 55%, negative predictive value of 100%, and likelihood ratio of 9.6). The bedside assessment of IL-6 in vaginal fluid seems to be an easy, rapid, non-invasive, and inexpensive method for the prediction of IAI and microbial-associated IAI in PPROM pregnancies, showing good specificity and negative predictive value.

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Title of the project: The relationship between bacterial load in amniotic fluid and the intensity of intraamniotic inflammatory response in women with preterm prelabor rupture of membranes

Grant Agency: Ministry of Health ***Project Number:*** NT/13461-4

Principal Investigator: M. Kacerovský

Co-investigators: C. Andrýs, R. Sleha

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 3968

Summary of 2015 results

Title of the presentation: Intra-amniotic inflammation in pregnancies complicated by preterm prelabor rupture of membranes

Authors: Marian Kacerovský, Ivana Musilová, Lenka Plíšková, Radka Kutová, Martin Štěpán

Objective: The main aim was to characterize subgroups of preterm prelabor rupture of membranes and short-term neonatal outcomes based on the presence and absence of intra-amniotic inflammation and/or microbial invasion of the amniotic cavity.

Methods: One hundred and sixty-six women with singleton pregnancies were included in this study. Amniotic fluid samples were obtained by transabdominal amniocentesis and were assayed for interleukin-6 levels by a lateral flow immunoassay. The presence of *Ureaplasma* species, *Mycoplasma hominis, Chlamydia trachomatis*, and 16S rRNA was evaluated in the amniotic fluid. Intra-amniotic inflammation was defined as amniotic fluid interleukin-6 values, measured by a point of care test, higher than 745 pg/mL.

Results: Microbial-associated intra-amniotic inflammation (intra-amniotic inflammation with microbial invasion of the amniotic cavity) and sterile intra-amniotic inflammation (intra-amniotic inflammation alone) were found in 21% and 4%, respectively, of women with preterm prelabor rupture of membranes. Women with microbial-associated intra-amniotic inflammation had higher microbial loads of *Ureaplasma* species in the amniotic fluid than women with microbial invasion of the amniotic cavity alone. No differences in the short-term neonatal morbidity with respect to the presence of microbial-associated intra-amniotic inflammation, sterile intra-amniotic inflammation and microbial invasion of the amniotic cavity alone were found after adjusting for the gestational age at delivery in women with preterm prelabor rupture of membranes.

Conclusions: Microbial-associated but not sterile intra-amniotic inflammation is common in women with preterm prelabor rupture of membranes The gestational age at delivery but not the presence of inflammation affects the short-term neonatal morbidity of newborns from pregnancies complicated by preterm prelabor rupture of membranes.

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Title of the project: Characterization of the diagnostic potential of native polypeptides in amniotic fluid

Grant Agency: Ministry of Health ***Project Number:*** NT/13599-4

Principal Investigator: J. Lenčo

Co-investigators: M. Kacerovský

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 3913

Summary of 2015 results

Title of the presentation: Characterization of the diagnostic potential of native polypeptides in amniotic fluid

Authors: M. Vajrychová (1, 2), K. Pimková (2), V. Tambor (2), J. Lenčo (1), M. Kacerovský (3), University of Defence, Faculty of Military Health Sciences, Department of Molecular Pathology and Biology (1), University Hospital Hradec Králové, Biomedical research center (2), University Hospital Hradec Králové, Department of Obstetrics and Gynaecology (3)

The analysis of endogenous peptides from amniotic fluid has proved to be technically much more challenging than was anticipated at the beginning of the project. That is why great efforts have been devoted primarily to the technical aspects of the analysis. We have particularly dealt with the development of a method for preparation of endogenous peptides for quantitative nanoLC-MS/MS analysis and evaluation of MS/MS data. One of the variant of the endogenous peptides preparation method developed by us allowed performing exploratory analysis of changes in amniotic fluid peptidome between PPROM patients (preterm prelabour rupture of membranes) with microbial invasion of the amniotic cavity (MIAC) and histological chorioamnionitis (HCA) and PPROM patients without MIAC and HCA (n=11 in both groups). The method enabled on average identification of 510 high confidence endogenous peptides in MIAC and HCA positive samples whereas 442 species were on average found in MIAC and HCA negative samples. Peptides were derived from various groups of parent proteins but most of the peptides came from distinct collagen molecules such as collagen alpha-1(III) chain, collagen alpha-1(I) chain and collagen alpha-2(I) chain, which clearly points to extensive proteolysis of fetal membranes in PPROM. Good reproducibility of signals of eight spiked standard peptides in recorded nanoLC-MS/MS data (RSD of all peptides between 11-18%) enabled also quantitative evaluation using a label-free approach. Totally, 57 peptides showed statistically significant quantitative change. At the moment, the most promising potential endogenous peptide markers of MIAC and HCA in PPROM patients include sequences ASGPPVSELITK, SLPPDMYECLRV and IDQSRVLNLGPIT from histone, lumican and uromodulin respectively. In the near future, we will focus on validation of the exploratory data using an independent replication cohort through targeted nanoLC-MS proteomic analysis.

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Title of the project: Personalized antibiotic therapy in surgical patients affected by important bacterial infection and significant liquids sequestration.

Grant Agency: Ministry of Health ***Project Number:*** NT/14089-3

Principal Investigator: M. Kaška

Co-investigators: E. Havel, J. Martínková, D. Solichová, I. Selke-Krulichová, J. Kočí, A. Fousková, L. Kujovská-Krčmová, I. Práznovec, V. Salavec, P. Šafránek

Starting date: 1.5.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 4625

Summary of 2015 results

Title of the presentation: Personalized antibiotic therapy in surgical patients affected by important bacterial infection and significant liquids sequestration.

Authors: Kaška M. et al. (above-mentioned)

Background: In critically ill patients, multi-trauma and intensive therapy can influence the pharmacokinetics (PK) and pharmacodynamics (PD) of antibiotics with time-dependent bacterial killing. Consequently, PK/PD targets (%fT>MIC) - crucial for antimicrobial effects - may not be attained.

Methods: Twenty two patients admitted to the surgical ICU of the University Hospital in Hradec Králove for multiple-trauma or septic peritonitis were given piperacillin/tazobactam or meropenem by 1-hour IV infusion 4/0.5g every 8h or 3-hours IV infusion 1-2g every 8h. In the prospective study 17 patients were enrolled: for multiple-trauma (10) or for septic peritonitis (7). Other were analysed individually for complications caused with their comorbidity or technical problems of evaluation. PK variables: total and renal clearance (CLtot, CLR), volume of distribution (Vd), and elimination half-life (T1/2) were calculated, followed by glomerular filtration rate (MDRD) and cumulative fluid balance (CFB-total fluid volume based on 24-h registered fluid intake minus output). The PK/PD target attainment (100%fT>MIC) was defined as free (f) piperacillin/meropenem plasma concentrations that remain during entire dosing interval (T) above minimum inhibitory concentration (100%fT>MIC) within day 2-8 (when CFB culminates and disappears). Piperacillin / meropenem concentrations were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and corrected for unbound fraction (22%).

Results: Patients on piperacillin: %fT correlated positively with CFB ($rs = 0.75$, $p = 0.007$) and negatively with CLcr ($rs = -0.77$, $p = 0.01$). The PK/PD target was attained in 2/10 patients (20%) who experienced CLcr<130 mL/min associated with CFB 12-35L. 8/10 patients (80%) with CLcr > 130 mL/min only attained 50%fT>MIC. Septic patients on meropenem: the PK/PD target was reached in every patient. %fT negatively correlated with CLcr ($rs = -0.86$, $p = 0.014$). Three patients (43%) were overdosed.

Conclusion: Without dose up-titration with regard to covariate effects and individual drug PK/PD, patients are at risk for drug under- or overdosing. Cmin is recommended to verify every two days. CFB and CLcr should be monitored daily.

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Title of the project: With optimisation of perioperative surgical therapy to its more successful outcomes

Grant Agency: Ministry of Education ***Project Number:*** 260180

Principal Investigator: M. Kaška

Co-investigators: A. Ferko, J. Harrer, M. Broďák, P. Šponer, S. Řehák, J. Tošner, P. Rozsíval, V. Chrobok, R. Slezák, V. Černý, J. Manďák, J. Vojáček, P. Žáček, M. Kanta, P. Dostál, J. Špaček, H. Langrová, N. Jirásková, A. Šimůnek, R. Koberová-Ivančaková, F. Raiskup, M. Kacerovský, J. Studnička, P. Čelakovský, and the Doctor Study Program students in 1st - 4th year of their study

Starting date: 1.1.2015 ***Duration (years):*** 1

Total funds allocated for project - Kč (thousands): 950

Summary of 2015 results

Title of the presentation: New surgical and pharmacotherapeutic methods in surgical therapy

Authors: M. Kaška et al. (above-mentioned co-investigators)

Special physician (students of DSP) groups of individual surgical disciplines were focused on very recent problems of medical management during pre-, per-, and postoperative phase of this process during 2015 year. **Surgeons** were performing experiments with laboratory animals – pigs and rats. It was found that use of absorbable sewing materials allows good results in repair of lesional vas deferens according to the rat model in laboratory experiment. Negative results with non-absorbable materials were found in the same study. Investigation of microcirculation in a bowel anastomosis region (pig model) brought results, which certificated a possibility of special glues using for this frequent surgical therapeutic approach. **Gynaecologists** focused on detection of intra-amniotic inflammations. They found the interleukin-6 can be useful marker of this process for obstetricians. **Cardio-surgeons** and **thoracic surgeons** published their useful experiences for clinical daily practice in new hemostat applying in thoracic surgery and recommendations for management of inflammatory processes in chest generally. **Neurosurgeons** performed analysis of aggressive vertebral haemangioma treatment and recommendation in management of improving access for endonasal endoscopic frontal sinus surgery. **Ophthamologists** carried up some new possible therapy methods in retinal artery obstruction and an applying of navigated laser photocoagulation of chronic diabetic macular edema. Next their clinical research was concentrated on possibility of a femtosecond laser applying in cataract surgery in Marfan syndrome, preservation of photoreceptor inner/outer segment junction in dry age-related macular degeneration, and therapy of diabetic macular edema with micro-pulse laser. **Dentists** published good clinical experiences with use pharmacological therapeutic management in stomatology- therapeutic preparates as Zovirax Duo, Filmogel URGO Afty, Xerostom, Emofix etc. can be used successfully recently as in near future, experiences with therapy of biophosphonate-related osteonecrosis of the jaw and problems with applying of imunnoglobulin G4 in a new diagnostic algorithm. **Urologists** announced in a special journals their the first good experience with introducing of a laparoscopic cystectomy in routine clinical urology practice and possible use of extra-anatomic stent instead nephrostomy. **Othorhinolaryngologists** found new diagnostic methods for patients with chronic obstructive pulmonary disease, detection of squamous cell cancer, and in narrow band imaging.

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Title of the project: Factors affecting apoptosis in the colonic mucosa

Grant Agency: Ministry of Health ***Project Number:*** NT/13413-4

Principal Investigator: D. Kohoutová

Co-investigators: J. Cyrany, I. Tachecí, J. Bureš, P. Morávková, V. Buchta, M. Morávková, M. Drahošová, J. Vávrová, J. Pejchal, D. Šmajs

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 5781

Summary of 2015 results

Title of the presentation: Apoptosis of the colonic epithelial cells

Authors: D. Kohoutová

The aim of our project was to investigate apoptosis of the colonic epithelial cells and to assess the role of some factors which might influence the degree of apoptosis in the large intestine.

We enrolled 100 individuals (20 healthy subjects, 20 patients with non-advanced adenoma (NAA), 20 patients with advanced adenoma (AA), 20 individuals with colorectal cancer (CRC) and 20 subjects with inflammatory bowel disease (IBD)) into our study. Peripheral blood samples and painless biopsies during the colonoscopy were obtained. Apoptosis and bacteriocin production were assessed in the biopsy samples, investigation of S100 proteins, anti-porin antibodies and/or anti-glycoprotein antibodies were performed.

With respect to the character of kinetics of cell population in the large intestine, apoptosis was measured in three different compartments: in the superficial compartment, which is in the contact with the lumen, in upper and lower part of the crypts. During the transformation of healthy mucosa into the tissue of a NAA, significant difference in apoptotic activity in all compartments was observed ($p \leq 0,05$). The most significant increase in apoptotic activity was present in the superficial compartment. Further significant increase in apoptotic (and mitotic) activity was found out in the upper part of the crypts in AA when compared to NAA ($p \leq 0,05$). Significant decrease in apoptotic activity was detected in all compartments of CRC tissue when compared to NAA and AA ($p \leq 0,05$).

Colicins, the best decribed bacteriocins, possess antimicrobial, apoptotic, probiotic and antineoplastic activity. Large intestinal mucosa of patients with more advanced colorectal neoplasia (including AA and advanced CRC when assessed with TNM classification) had significantly higher production of bacteriocins when compared to those with less advanced colorectal neoplasia. Anti-porin antibodies aimed at porin C in the outer membrane of gram-negative bacteria were significantly higher in patients with CRC when compared to controls. It is therefore highly suspicious that large intestinal microbiota (with their substances) may influence apoptosis of the epithelial cells and play role in the colorectal carcinogenesis.

Our papers published in 2015: Kohoutova et al. Folia Microbiol 2015; published online 26 Nov 2015; Moravkova et al. Gastroenterol Res Pract; accepted for publication in Nov 2015.

Address for correspondence: D. Kohoutová, MD, PhD, 2nd Department of Internal Medicine - Gastroenterology, Charles University in Praha, Faculty of Medicine at Hradec Králové, University Teaching Hospital, Sokolská 581, 500 05 Hradec Králové, Czech Republic.
E-mail: Darina.Kohoutova@fnhk.cz

Title of the project: Risk factors of acute pancreatitis as a complication of double balloon enteroscopy

Grant Agency: Ministry of Health ***Project Number:*** NT/13414-4

Principal Investigator: M. Kopáčová

Co-investigators: J. Bureš, I. Tachecí, S. Rejchrt, J. Vávrová, V. Palička

Starting date: 2.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 8467

Summary of 2015 results

Title of the presentation: Risk factors of acute pancreatitis as a complication of double balloon enteroscopy

Authors: Kopáčová M., Bureš J., Tachecí I., Rejchrt S., Vávrová J., Palička V.

Kopáčová M., Bureš J., Tachecí I., Rejchrt S., Vávrová J., Palička V.

Double balloon enteroscopy (DBE) allows complete visualisation, biopsy, and treatment in the small bowel. The complications of DBE are rare, acute pancreatitis is one of the most redoubtable ones. The incidence of acute pancreatitis after diagnostic DBE is 0.3 % in most studies. The causal mechanism of post-DBE acute pancreatitis is uncertain; there are several theories in the literature. On the contrary, hyperamylasemia after DBE seems to be a rather common condition. Our project tried to identify in advance patients in a higher risk of acute pancreatitis associated with DBE. We have investigated 30 healthy volunteers and 117 consecutive patients (indicated for oral DBE). We have concentrated on several laboratory markers before DBE, 4 hours and 24 hours after DBE (serum cathepsin B, lactoferrin, E-selectin, SPINK 1, procalcitonin, S100 proteins, alpha-1-antitrypsin, hs-CRP, malondialdehyde, serum and urine amylase and serum lipase). We have not recorded any DBE-associated acute pancreatitis in this series. Serum amylase and lipase rose significantly with the maximum 4 hours after DBE ($p < 0.001$ and $p < 0.001$). We found significant difference between group of healthy volunteers and patients before DBE in serum cathepsin B ($p< 0.001$), lactoferrin ($p< 0.001$), SPINK1 ($p< 0.029$), procalcitonin ($p< 0.001$), alpha-1-antitrypsin ($p< 0.019$), hs-CRP ($p< 0.001$), and malondialdehyde ($p< 0.007$). Serum protein S100 rised significantly 4 hours after DBE compared to healthy controls and patient values before DBE ($p< 0.008$), alpha-1-antitrypsin decreased significantly 4 hours after DBE ($p< 0.002$). Serum amylase and lipase rised 4 hours after DBE ($p< 0.001$ and $p< 0.005$), while hs-CRP rised 24 hours after DBE ($p< 0.001$). We found statistically significant correlation between significant pain after DBE and serum amylase ($p< 0.039$) and lipase ($p< 0.005$) levels.

We confirmed our hypothesis that significant pain is most important indicator of threatened pancreatitis.

We found no laboratory markers that would identify in advance those patients in a higher risk of acute pancreatitis after DBE yet.

Address for correspondence: Marcela Kopacova, Prof, MD, PhD, 2nd Department of Medicine - Gastroenterology, Charles University Teaching Hospital, Sokolska 581, 500 05 Hradec Kralove, Czech Republic.

Title of the project: Teaching of properties and durability of mechanical structures of artificial bone grafts and implants - (Innovation in education - practical examples)

Grant Agency: Ministry of Education ***Project Number:*** IP 2015

Principal Investigator: M. Kopeček

Co-investigators: J. Záhora, D. Kordek, M. Smutný, A. Bezrouk

Starting date: 1.1.2015 ***Duration (years):*** 1

Total funds allocated for project - Kč (thousands): 245

Summary of 2015 results

Title of the presentation: 3D Printed Implants - design, manufacture and testing

Authors: M. Kopecek

Fac. Med., Charles Univ., Hr. Králové: Dept. of Medical Biophysics

Innovation project leads students to gain practical experience in the creation of prosthesis and artificial bone grafts and implants using the latest 3D technology. The measuring workplace was developed. Here the student can practically verify the properties and durability of created artificial replacements and compare different designs and production. Tested components are made by DLP 3D printing technology with the use of special materials based on photopolymer resins.

The durability of created implants and their destructive mechanical properties will be studied. The measuring workplace is used by students in optional course. Project was supported by the Ministry of Education.

Address for correspondence: M. Kopecek, Department of Medical Biophysics, Charles University in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, Czech Republic

Title of the project: Utilization of Ultra High Performance Liquid Chromatography with mass spectrometry detection for determination of vitamin D and its metabolites for clinical practice

Grant Agency: Ministry of Health ***Project Number:*** NT/14265-3

Principal Investigator: L. Kujovská Krčmová

Co-investigators: D. Solichová, L. Sobotka, M. Bláha, B. Červinková, E. Kasalová

Starting date: 11.4.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 4471

Summary of 2015 results

Title of the presentation: New modern UHPLC-MS/MS methods for determination of vitamin D and its metabolites used in clinical practice

Authors:: L. Kujovská Krčmová (1,2), D. Solichová (1), L. Sobotka (1), M. Bláha (3), B. Červinková (1,2), E. Kasalová (1,2), L. Javorská (1,2)

(1) 3rd Internal Gerontometabolic Clinic, University Hospital Hradec Králové, (2) Department of Analytical Chemistry, Faculty of Pharmacy, Charles University, (3) 4th Internal Clinic of Hematology, University Hospital Hradec Králové

New modern methods using Ultra High Performance Liquid Chromatography coupled with tandem Mass Spectrometry detection (UHPLC-MS/MS) for determination of vitamin D and its metabolites were developed and validated using FDA and EMA guidelines (1,2). Modern separation technique was combined with fast and simple sample preparation procedure using small volume of human serum.

Newly developed methods were used for determination of vitamin D and its metabolites in patients with familiar hypercholesterolemia treated by LDL apheresis and in control groups of the patients treated by extracorporeal rheohemapheresis with different basic diagnosis. Levels of vitamin D and its metabolites were measured before and after treatment. For statistical evaluation NCSS (Kaysville, USA) statistical software was used.

Our results show that there are statistically significant changes in vitamin D levels before and after LDL apheresis. Different vitamin D levels (with statistical significance) were also observed between all tested groups of the patients before treatment. These results are very important for further treatment and care of patients treated by extracorporeal elimination of lipids.

Literature:

1.http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf (26.12.2015)

2.http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf (26.12.2015)

Address for correspondence: Lenka Kujovská Krčmová, 3rd Internal Gerontometabolic Clinic, Sokolská 581, University Hospital Hradec Králové, 50005 Czech Republic, lenkakrcmova@seznam.cz

Title of the project: Concept of non-quaternary reactivators AChE as the antidotes of organophsophorus poisoning - a new hope or a blind way?

Grant Agency: Czech Republic ***Project Number:*** 15-16701S

Principal Investigator: K. Kuča

Co-investigators: K. Musílek, O. Soukup, J. Korábečný, E. Nepovimová, D. Jun, P. Jošt, V. Šepsová, M. Hrabinová

Starting date: 1.1.2015 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 7049

Summary of 2015 results

Title of the presentation: Concept of non-quaternary reactivators AChE as the antidotes of organophsophorus poisoning - a new hope or a blind way?

Authors: K. Kuča

Acetylcholinesterase (AChE) reactivators based on pyridinium aldoximes (obidoxime, HI-6) are used as causal antidotes in case of nerve agent or pesticide poisonings. Due to the presence of quaternary nitrogen, they have low blood-brain barrier (BBB) permeation and thus they are not capable to fully reactivate AChE in the central nervous system, where nerve agents or pesticides can be responsible for the chronic neural disorders. For this reason, development of novel centrally acting non-quaternary reactivators that can more efficiently cross BBB is one of the most promising strategies. However, from the practical point of view, several drawbacks of physico-chemical, pharmacological and toxicological origin are expected for these non-quaternary antidotes. In this project, all the benefits and negatives of non-quaternary AChE reactivators will be investigated to decide whether this new strategy is a really promising approach or just another blind way in the search for the new type of antidotal therapy.

Address for correspondence: kamil.kuca@fnhk.cz

Title of the project: Development of multi-target drugs for Alzheimer´s disease: combination of AChE inhibitor and melatonin derivative

Grant Agency: Ministry of Health ***Project Number:*** 15-30954A

Principal Investigator: K. Kuča

Co-investigators: J. Říčný, O. Soukup, M. Doležal, M. Hrabinová, E. Nepovimová, J. Korábečný, E. Mezeiová, K. Špilovská

Starting date: 1.5.2015 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 9105

Summary of 2015 results

Title of the presentation: Development of multi-target drugs for Alzheimer´s disease: combination of AChE inhibitor and melatonin derivative

Authors: K. Kuča

We would like to exploit the obtained preliminary data in preparation of more active hybrids combining derivative of melatonin and AChE inhibitor – huprine. Such compounds should exert multipotent profile in Alzheimer´s disease treatment by combining beneficial effect of mainly, but not exclusively, cholinergic enhancement and antioxidant activity. Funnel-like drug development process from design and synthesis though in vitro efficacy and safety evaluation to in vivo validation involving kinetic, toxic, pharmacodynamic and behavioral examination will be applied in order to select the best drug candidate. In this project, basic research (9%) represent the synthesis of novel compounds and the structure-biological activity relationship (SAR) evaluation. Applied research (91%) represents majority of the project, thus, the funnel-like selection of a drug candidate, its in vivo validation and subsequent patent protection application with commercial utilization.

Address for correspondence: kamil.kuca@fnhk.cz

Title of the project: Biomedical photonic devices for advanced medicinal diagnostics and therapy

Grant Agency: Ministry of Health ***Project Number:*** 15-33459A

Principal Investigator: M. Kuneš

Co-investigators: O. Lyutakov, P. Peterka

Starting date: 1.6.2015 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 17137

Summary of 2015 results

Title of the presentation: Preparation, modification and characterization of biocompatibile and biodegradable polymers

Authors: O. Lyutakov (1), K. Bastekova (1), O. Guselnikova (1), V. Svorcik (1), M. Kuneš (2, 3) Institute of Chemical Technology (1), University Hospital Hradec Králové: Biomedical Research Centre (2), Dept. of Surgery (3)

Proposed project involves development of novel optical system for fiber-optic based local monitoring, sensing and treatment. Aim of initial experiments was to develop and test polymer materials for adequate biodegradable and biocompatible properties. The influence of polymer–substrate interaction and spatial confinement of macromolecular chains in the ultrathin polymer films on lower critical solution temperature (LCST) was investigated under different pH conditions. Shift and broadening of the LCST temperature range was observed from the critical thickness of polymer film. It was also found that the substrate plays a key role in this shift. The observed phenomenon was applied for the temperature-controllable release of a small molecular dopant (crystal violet, CV) from the ultrathin polymer films. Finally, doped ultrathin polymer films were examined for their antibacterial activity by in-contact and drop methods. It was observed that polymer thickness and support substrate can influence both CV release and antibacterial properties. Despite the fact that the concentration of CV used was constant and thinner films contained a significantly smaller amount of CV than thicker ones, the antibacterial activity of thin films was found to be greater in several cases. Subsequently, poly L-lactic acid (PLLA) surface was modified with different organic compounds, allowing us to increase or decrease surface wettability and to modify surface properties. As binded organic compounds fluorinated, allowed to prepare the repellent surface, -NH2, -NO2, -COOH, CxHy were used and succesfully attached to polymer. Samples surface was characterized using IR spectroscopy, XPS, AFM, SEM, Z-potential, water, whole blood and blood plasma contact angle measurements. Three methods of surface modification were used: activation of PLLA surface by plasme; activation of diazonium salt by chemical reductant; and their combination. The best results were obrained in the last case. Potential application of the used methods lies in the tissue engineering and implants preparation.

Address for correspondence: M. Kuneš, Dept. of Surgery, University Hospital Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic

Title of the project: Rationalization of the systemic treatment of age-related macular degeneration with rheohemapheresis

Grant Agency: Ministry of Health ***Project Number:*** NT/14037-3

Principal Investigator: H. Langrová

Co-investigators: E. Rencová, M. Bláha, J. Studnička, A. Stepanov, J. Breznayová, M. Burová, V. Bláha, M. Lánská, H. Dvořáková, J. Kvasnička

Starting date: 1.5.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 7690

Summary of 2015 results

Title of the presentation: Five-years outcomes of rheohaemapheresis in the treatment of dry form of age-related macular degeneration

Authors: H. Langrová, E. Rencová, M. Bláha, J. Studnička, A. Stepanov, J. Breznayová, M. Burová, V. Bláha, M. Lánská, H. Dvořáková, J. Kvasnička

Purpose: To determine long-term effects of rheohaemapheresis on the dry form of age-related macular degeneration

Methods: We treated 65 patients, average age of 69.3 years, treated with rheohemapheresis and 55 patients, average age of 73.5 years, comprising the control group. In the treatment group, soft drusen and confluent soft drusen were present in 68 eyes, drusenoid pigment epithelium detachment (DPED) was found in 48 eyes. In the control group, soft drusen were present in 54 eyes and DPED in 38 eyes. Wet form of AMD was found in 14 eyes of treated patients and in 18 eyes of controls and these eyes were not included into the evaluation. Minimum follow-up period was 5 years. Each treated patient received series of 8 rheohaemaphereses of 1.5 plasma volume within 10 weeks. We evaluated rheological parameters and measured size of soft drusen area, size of DPED, best-corrected visual acuity (BCVA), electroretinography (ERG) at baseline and every 6 months.

Results: In the treatment group, the baseline mean BCVA was 73.6 letters of ETDRS optotypes followed by slight improvement of values upto 2 years and thereafter slight decrease to final BCVA of 73.8 letters. In the control group, the baseline mean BCVA was 71.2 letters and it decreased stadily, significantly after 4 years, to final BCVA of 64.8 letters ($p = 0.031$). We found improvement of the morphological findings in 62% of treated patients and only in 7% of controls, whereas progression to the wet form of disease or geographic atrophy was noted in only 7% of treated patients and in 37% of controls. DPED area became smaller in 80% of patients, whereas it enlarged in 47% of controls. We found preserved integrity of IS/OS photoreceptor junction in fovea in 68% of treated pacients and its defect in fovea in 67% of controls. We found stabilization of the activity of ganglion cells, cone system and central retinal region with eccentricity between 1,8° and 30° in treated patients and its alteration in controls, which was significant in follow-ups at 3.5 years and longer.

Conclusion: We demonstrated positive effect of rheopheresis on both anatomical and functional findings of treated patients that persisted over many months.

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Title of the project: Optimisation of Treatment and Management of Schizophrenia in Europe: Optimise Trial

Grant Agency: 7 FP EU ***Project Number:*** OPTiMiSE

Principal Investigator: R. Kahn

Co-investigators: J. Libiger, R. Köhler

Starting date: 1.7.2011 ***Duration (years):*** 5

Total funds allocated for project - Kč (thousands): 4871

Summary of 2015 results

Title of the presentation: Optimise trial reaches the final stage

Authors: Libiger J.

The objectives, methods and the scope of the Optimise Trial were described in the summary abstract at the last Faculty Research Conference in January 2015.This is not a separate presentation, just a continuation report for the Czech centre. The main goal of the project is to establish the optimal use and sequence of antipsychotics in the initial treatment of the first episode schizophrenia (FEP).

The present state of the trial reflects the development after reducing the number of collaborating centres and closing the academic sites in Austria, Belgium, France, Czech Republic, Switzerland, Germany and England. In all those centres, there were either low recruitment rates, or patients improved already in phase I of the trial and there were no recruits for the double blind phase of the trial. The remaining 12 sites, most of them in Spain, Poland and Israel, continue to admit patients. The number of subjects in the trial reached 446, and although the remission rate after the first stage of the trial (open amisulpride) remains higher than expected, the number of patients in the phase II and eventually also phase III increased. The exact data are partly not known or they are not publishable as yet. The Czech centre in Hradec Králové completed the follow -up after one year in previously admitted patients and sent off the collected blood samples for proteomic and eventually genomic analyses. The closing visit by the project-monitor from Utrecht´s Julius Centre took place in September 2015. Final administrative work-up of the project and preparation for relevant publication topics were the remaining activities at the site.

In 2015, there were published two introductory publications on the project in a leading professional journal:

Leucht S, Winter-van Rossum I et al The Optimisation of Treatment and Management of Schzophrenia in Europe (OPTiMiSE) Trial: Rationale for its Methodology and Review Effectivness of Switching Antipsychotics.
Schizophr. Bull, 2015;41: 549-558

Arango C, Kapur S, Kahn RS Going Beyond "Trial and Error" in Psychiatric Treatments: OPTiMiSEing the Treatment of First Episode Schziophrenia, Schizophr.Bull,2015;41:546-548

Address for correspondence: prof. MUDr. Jan Libiger, CSc. Psychiatric Clinic, Charles University Faculty of Medicine and Faculty Hospital at Hradec Králové, 500 05, Czech Republic

Title of the project: Pathophysiological mechanisms of diseases – possibilities of prevention, new diagnostic and therapeutic approaches – year 2015

Grant Agency: Ministry of Education ***Project Number:*** 260179

Principal Investigator: S. Mičuda

Co-investigators: M. Červinka, V. Geršl, Z. Červinková, J. Hanuš, M. Řezáčová, J. Mokrý, Z. Fiala

Starting date: 1.1.2015 ***Duration (years):*** 1

Total funds allocated for project - Kč (thousands): 1000

Summary of 2015 results

Title of the presentation: Pathophysiological mechanisms of diseases – possibilities of prevention, new diagnostic and therapeutic approaches

Authors: S. Mičuda (1), M. Červinka (2), V. Geršl (1), Z. Červinková (3), J. Hanuš (4), M. Řezáčová (5), J. Mokrý (6), Z. Fiala (7). Fac. Med., Charles Univ., Hr. Králové: Dept. of Pharmacology (1), Dept. of Medical Biology and Genetics (2), Dept. of Physiology (3), Dept. of Medical Biophysics (4), Dept. of Medical Biochemistry (5), Dept. of Histology and Embryology (6), Dept. of Hygiene and Preventive Medicine (7)

The rationale of the present project was to support research of postgraduate students grouped around seven Subject Co-ordination boards at the Theoretical Departments of Faculty of Medicine in Hradec Králové. Finally, 28 postgraduate students and 17 of their supervisors have participated to the project. The central theme of the research was to evaluate the new diagnostic or therapeutic strategies in various diseases and possibilities of their prevention. With respect to ongoing activities of involved research groups, the project spanned over preclinical as well as clinical topics. The preclinical works with laboratory animals were focused on the pathological changes of heart, liver, kidney, and lungs, which were induced by administration of drugs (e.g. anthracycline chemotherapy), toxins (e.g. endotoxin of gram-negative bacteria) or food components (e.g. high-fat diet). Cellular studies were mainly aimed at elucidation of cancer cell biology, responsible regulatory pathways and the effect of new promising chemotherapeutics, but tissue regeneration and role of stem cells was also investigated. Clinical part of the project was based on the epidemiological studies of harmful influence of polycyclic aromatic hydrocarbons and occupational stress. Taking together, project allowed completion of several articles in journals with impact factor and 4 postgraduate students from the team successfully finished their theses.

Project was supported by the Charles University project No. SVV-2015-260179.

Address for correspondence: S. Mičuda, Dept. of Pharmacology, Charles University in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, Czech Republic

Title of the project: Modulators of mitochondrial enzymes for treatment of neurodegenerative disorders

Grant Agency: Ministry of Health ***Project Number:*** 15-28967A

Principal Investigator: K. Musílek

Co-investigators: Z. Fišar

Starting date: 1.5.2015 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 8134

Summary of 2015 results

Title of the presentation: Modulators of mitochondrial enzymes for treatment of neurodegenerative disorders

Authors: K. Musílek

The mitochondrial enzymes seem to be next target for molecular design in term of Alzheimer Disease (AD) treatment. They are well known for their interaction with β-amyloid and they are subsequently responsible for disruption of cell homeostasis and cell death. The inhibition of β-amyloid interaction with mitochondrial enzymes by small modulators might prevent neuronal cell loss and thus improve progress of AD. Up-to-date, only few mitochondrial enzyme modulators were published and their design, synthesis and evaluation will be highly progressive in near future. The main aim of the project is development of convenient candidates (small molecules) for further preclinical research.

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Title of the project: Preparation of dosage forms with controlled release of glucose to prevention of hypoglycemic states

Grant Agency: Ministry of Health ***Project Number:*** NT/14479-3

Principal Investigator: A. Franc

Co-investigators: J. Muselík, D. Neumann

Starting date: 1.5.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 181

Summary of 2015 results

Title of the presentation: Preparation of dosage forms with controlled release of glucose to prevention of hypoglycemic states

Authors: D. Neumann1, A. Franc2, J. Muselík2

1 Dpt. of Paediatrics, University Hospital Hradec Kralove, 2 University of Veterinary and Pharmaceutical Sciences Brno

Pellets with controlled release of glucose and a diameter of 0,6 mm with in-vitro lag-time profiles of 120 and 240 minutes were manufactured in 2014/2015 year. The real-life characteristics were examined using 13C stable isotope technique. Clinical and in-vitro lag times fit even in different grades of physical activity of tested subjects. Further development was directed to stability and food processing.

The data were published as follows:

Franc A, Dvořáčková K, Muselík J, Žvaková M, Slováková V, Vetchý D, Sabadková D, Neumann D, Goněc R. Formulation of cores for the controlled release of glucose for prevention of hypoglycemia in diabetes patiens. Čes. Slov. Farm. 2014; 63, 206-212

Franc A, Sabadková D, Neumann D, Pavloková S, Kopecká P, Muselík J. Interdiction of hypoglycaemia in diabetic children by multiparticulate dosage form with controlled glukose repase. Pharm Dev Technol 2015 Sep 3; 1-8

Franc A, Muselík J, Sabadková D, Neumann D. Preparation of pellets with controlled release of glucose as prevention of hypoglycaemia in paediatric patients. Eur. J. Pharm. Sci 2015; 75: 72-80

Franc A, Muselík J, Neumann D, Sabadková D. Pelety s glukózou k prevenci hypoglykémií. Prakt. Lékáren. 2015; 11 (3): 100-102

Address for correspondence: David Neumann, Dpt. of Paediatrics, University Hospital Hradec Kralove, Sokolska 581, 500 05 Hradec Kralove, The Czesch Republic

Title of the project: Parametric monitoring the quality of TME as a tool to reduce local recurrence after surgery for rectal cancer

Grant Agency: Ministry of Health ***Project Number:*** NT/13726-4

Principal Investigator: J. Hoch

Co-investigators: A. Ferko, J. Örhalmi

Starting date: 1.1.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands):

Summary of 2015 results

Title of the presentation: Parametric monitoring the quality of TME as a tool to reduce local recurrence after surgery for rectal cancer

Authors: J. Örhalmi, A. Ferko, Department of Surgery, Faculty of Medicine and University Hospital Hradec Králové, Czech Republic.

Introduction**:** Quality of total mesorectal excision (TME) is an independent prognostic factor for recurrence of rectal cancer. Evaluation of quality of TME is not standardized in Czech Republic and therefore, the quality of rectal resections varied. The aim of this study is to evaluate the quality of TME in individual workplaces in the country.

Methods: Retrospective data collection was carried out in 2012. The project involves six teaching hospitals, where the number of resections of the rectum exceeds the number 50. After evaluation of retrospective data is continued entering patient data prospectively.

Results: 291 patients were evaluated in the first phase. There was evaluated biometric data, examinations before surgery, tumor staging before and after surgery, share of neoadjuvant chemoradiotherapy, type of surgery, TME quality, radicality of surgery.

Prospective data collection was terminated in 2015. Our institution has commissioned data from 563 patients since 2008. 200 in the first phase and 363 in the prospective phase (2012 – 2015). There are known only results from the first phase. The results from the second phase are processed. Several workshops were implemented for histopathological evaluation of resection and workshops for correct technique of TME. TME is implanted in all six teaching hospitals as a standard procedure at the present.

Address for correspondence: J. Örhalmi, Department of Surgery, Faculty of Medicine and University Hospital Hradec Králové, Sokoslká 587, 50005 Hradec Králové, Czech Republic.

Title of the project: The introduction of new practical trainig in Biochemistry focused on the importance of preanalytical errors.

Grant Agency: Ministry of Education ***Project Number:*** IP 2015

Principal Investigator: E. Peterová

Co-investigators: A. Mrkvicová

Starting date: 25.03.2015 ***Duration (years):*** 1

Total funds allocated for project - Kč (thousands): 295

Summary of 2015 results

Title of the presentation: The introduction of new practical exercises of Biochemistry focused on the effects of preanalytical

Authors: E. Peterová, A. Mrkvicová

During clinical practice, doctors are constantly confronted with the results of biochemical assays. The testing process includes the preanalytical, analytical and postanalytical phases and ends with the results ready for interpretation. The preanalytical stage occupies the most erroneous part of the total testing.

The main goal of the project is to confront medical students with critical evaluation of experimental data in the new practical training. During the theoretical part we concentrate on the blood collection equipment, technique of the blood collection and the factors interfering with biochemical tests. In the practical part of the training, students will collect their own blood samples for the further analysis of glucose, cholesterol and the total protein levels. In addition improper handling of the samples will be included in the measurement interpretation. The funds were used to purchase instrumentation eg. centrifuge for plasma collection, water bath for simulation of improper storage of the sample and adjustable pipettes. We prepared manuals as well as theoretical introduction for the new practical training.

In this practical training we integrate the application of critical thinking into biochemical testing and data interpretation.

Address for correspondence: E. Peterová, Dept. of Medical Biochemistry, Teaching and Research Center at Charles University in Hradec Králové, Zborovská 2089, 500 09 Hradec Králové

Title of the project: Role of miRNA 302/367 in cellular reprogramming

Grant Agency: Charles University ***Project Number:*** 1854214

Principal Investigator: R. Pisal

Co-investigators: J. Mokrý, P. Beznoska, D. Garcia, H. Hrebíková, J. Chvátalová, A. Mrkvicová

Starting date: 21.5.2014 ***Duration (years):*** 2

Total funds allocated for project - Kč (thousands): 254

Summary of 2015 results

Title of the presentation: Role of miRNA 302/367 in cellular reprogramming

Authors: R. Pisal

***Results*:** Parameters were standardized for cloning miR 302/367 cluster into pcDNA 3.1 (mammalian expression plasmid) and pLNCX (Retroviral plasmid) vectors. Transient and stable transfection of miR 302/367 cloned in pcDNA 3.1 was performed; stable transfection gave rise to characteristic induced pluripotent stem cell colonies (iPSC). These colonies differentiated few days after emerging probably due to lack of sustained expression of miR 302/367. Hence retroviral method of gene delivery was chosen. Initial experiment for determining virus titer and multiplicity of infection (MOI) was performed.

Since miR belongs to group of non-coding RNA's their expression can be determined using qPCR which requires destruction/killing of cells. Expression of cloned miR can be confirmed by cloning miR in specially designed construct in which an open reading frame (ORF) of a gene encoding florescent protein is interrupted by an intron; this intron bears restriction sites for cloning miR. Expression of miR can be confirmed by visualizing fluorescence since intron needs to be spliced and exons rejoined for the florescent protein to be expressed. The excised introns are further processed by cellular machinery for expressing the cloned miR.

An intron was introduced in a gene encoding Red fluorescent protein. Further work needs to be performed to optimize the system for miR expression.

Future tasks: Optimizing conditions for reprogramming human fibroblasts using miR 302/367 cluster with retrovirus as mode of gene delivery. Fine tuning parameters for designing a fluorescent indicator for expression of miR 302/367.

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Title of the project: Predictive Immunological Markers in Patients Infected by the Hepatitis C Virus

Grant Agency: Ministry of Health ***Project Number:*** NT/14072-3

Principal Investigator: P. Chalupa

Co-investigators: S. Plíšek, P. Boštík, J. Kapla, J. Košťálová, J. Krejsek, K. Kondělková

Starting date: 1.5.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 1101

Summary of 2015 results

Title of the presentation: Predictive Immunological Markers in Patients Infected by the Hepatits C Virus

Authors: S. Plisek (1), P. Bostik (1), J. Kapla (1), J. Kostalova (1), J. Krejsek (2), K. Kondelkova (2); Fac. Med., Charles Univ. and Teaching Hospital, Hr. Králové: Dept. of Infectious Diseases (1) and Institute of Clinical Immunology (2)

Infection with Hepatitis C virus (HCV) represents a serioud problem with a poor therapeutic response in some patients. The goal of this project was to identify immunologic parameters, which could serve as predictors of HCV treatment response using 2 cohorts of HCV infected patients - one treated with regular regimen and one with a spontaneous clearance of the virus. The analysis of selected immune parameters revealed that the levels of TGF-beta during the first 12 weeks of the treatment gradually decreased and, conversely, the numbers of Tregs gradually increased during the treatment. The level of expression of the activation marker CD38 on CD8+ T cells also gradually increased. On the contrary, the expression of activation marker HLA-DR on CD8+ T cells decreased during the first four weeks of the treatment. Further analysis showed that numbers of Tregs in the HCV patients were significantly higher than those of healthy controls and persons with the spontaneous elimination of HCV. Similarly, the percentage of CD8+ T cells expressing simultaneously both activation markers, i. e. CD38 and HLA-DR, was significantly higher in HCV patients in comparision to both healthy controls and persons with spontaneous HCV elimination. Finally, the expression of CD38 on CD8+ T cells was higher in the HCV patients group in comparison to persons with spontaneous HCV elimination. In addition, the percentage of Tregs in the blood correlated positively with the serum levels of TGF-beta. Furthemore, the levels of expression of the CD38 and HLA-DR markers on circulating CD8+ T cells, as well as the numbers of CD8+ T cells expressing simultaneously CD38 and HLA-DR correlated positively with VL.

In conclusion, our data suggest that chronic HCV infection is resposible for a significant modulation of immune responses. Although certain immunostimulatory effects of the IFN-based therapy could have been expected, we observed a suppression of CTLs and the gradual rise of Tregs during the treatment. These findings indicate an important role of HCV in a modulation of immune responses and also a potential clinical usefulness of selected immune parameters for the monitoring of the chronic HC treatment efficacy.

Address for correspondence: S. Plisek, Dept. of Infectious Diseases, Teaching Hospital and Charles University in Prague, Faculty of Medicine in Hradec Králové, Sokolská 581, 500 05 Hradec

Title of the project: Rational design of novel immunomodulators - potential vaccine adjuvans - based on TLR4 ligands

Grant Agency: Czech Republic ***Project Number:*** 15-11776S

Principal Investigator: R. Prymula

Co-investigators: J. Honegr, D. Maliňák, R. Doležal, Š. Salajková

Starting date: 1.1.2015 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 3405

Summary of 2015 results

Title of the presentation: Rational design of novel immunomodulators based on TLR4 ligands

Authors: R. Prymula, J. Honegr, D. Malinak, R. Dolezal, S. Salajkova, Biomedical Research Center, University Hospital Hradec Kralove, Sokolska 581, 500 05 Hradec Kralove, Czech Republic

Aim of the project is to identify novel potential TLR4 ligands as novel potential vaccine adjuvants.

We have undergone in-silico virtual high throughput screening (vHTPS) of 10000 compounds, utilizing the resources of Czech national supercomputing center. 9700 compounds was chosen from Zinc database (a free database of more than 2 000 0000 commercially available drug-like compounds for virtual screening), 200 compounds was chosen from our database of compounds and 100 compounds were specifically designed based on results from previously published works. For narrowing the broad spectrum of available compounds from Zinc database the open source software Screening Assistant 2 was employed. 10000 compounds were subsequently docked into the active spot of TLR4 and bonding energy for each compound were calculated.

From this vHTPS screening we have obtained 60 compounds with high bonding energy to the receptor TLR4. From these sixty compounds obtained from vHTPS we have selected 10 compounds are suitable for alteration of their structures. Some of the compounds were synthesized, some were purchased for evaluation of their in vitro activity on cell line stably expressing human TLR4 receptor. From those compounds we have chosen two lead structures (based both on their physic-chemical properties and on their internal activity). We have designed ten derivatives of those two lead compounds (total 20 compounds) using basic principles of medicinal chemistry to find more suitable drug candidates (taking into account solubility, π-π interactions, etc) that could act as potential immunomodulators on the innate immunity system. First batch of ten compounds (derivatives of lead compound 1) was already synthesized and tested on the cell line. We have found some potentially interesting compounds, that shows in-vitro 50-70% activity of MPLA. In next year we will continue to synthesize rest of the 20 compounds and test them. We will test candidate structures on mouse BMDCs and donor PBMCs to investigate its ability to trigger immune response on immunocompetent cells.

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Title of the project: Targeted proteomic analysis in hypertrophic cardiomyopathy

Grant Agency: Ministry of Health ***Project Number:*** NT/13721-4

Principal Investigator: R. Pudil

Co-investigators: J. Stulík, L. Horáková

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 5893

Summary of 2015 results

Title of the presentation: Targeted proteomic analysis in hypertrophic cardiomyopathy

Authors: R. Pudil (1), J. Stulík, (2), A. Fučíková (2), L. Horáková (3), H. Řehulková (2), P. Řehulka (2)

1- Faculty of Medicine in Hradec Králové, 2 - Institute of Molecular Pathology, Faculty of Military Health Sciences, Hradec Králové, 3 - University Hospital Hradec Králové

The main objective of the proposed project was to verify the analytical potential of selected protein biomarkers of peripheral blood for diagnostics of hypertrophic cardiomyopathy. The project was focused on verification and validation of the relative concentration of these proteins in peripheral blood of patients with hypertrophic cardiomyopathy in the comparison with the results of the healthy population and other diseases that are accompanied by structural changes in the myocardium (dilated cardiomyopathy, ischemic heart disease, arterial hypertension and aortic stenosis).

The 2015 results: During the final year of the project, we finished all proteomic analyses (a comparative iTRAQ and SWATH semiquantitative proteomic analyses were finished in patient and all control groups: aortic stenosis, arterial hypertension, dilated cardiomyopathy, chronic coronary artery disease and healthy controls). Individual samples from all groups were also analysed using targeted proteomic approach; a group of selected potential biomarkers was targeted. We also performed statistical and bioinformatical analyses.

We found 128 plasma proteins whose abundances were uniquely regulated among the analyzed cardiovascular pathologies. Most of them have not been described yet. Additionally, application of statistical exploratory analyses of the measured protein profiles indicated the relationship in pathophysiology of the examined cardiovascular pathologies.

In a group of patients with hypertrophic cardiomyopathy, we performed analysis of the clinical severity parameters and biomarkers. We found significant association of some parameters (vascular endothelial growth factor and heart fatty acid binding protein (VEGF, hFABP) and clinical parameters (especially, increased VEGF level is associated with structural and functional parameters in patients with HCM, and serves as a potential tool for diagnostic process of these patients).

The results of our research project were presented in scientific meetings. Until know, we have published two original scientific publications (one in IF journal), and others are under review.

Address for correspondence: Prof. MUDr. R. Pudil, Ph.D., Charles University in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, Czech Republic

Title of the project: Increasing of the R&D capacity at Charles University through new positions for graduates of doctoral studies

Grant Agency: Ministry of Education ***Project Number:*** CZ.1.07/2.3.00/30.0061

Principal Investigator: M. Moravová

Co-investigators: J. Mokrý, S. Mičuda, R. Pudil

Starting date: 1.7.2012 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 9231

Summary of 2015 results

Title of the presentation: POSTDOC II: Increasing of the R&D capacity at Charles University through new positions for graduates of doctoral studies

Authors: R. Pudil, M. Moravová, Grants and International Division, Dean's Office, Faculty of Medicine in Hradec Králové

The project was the second phase of the project POSTDOC I.
The aim of the project was to support the establishment, development and mobility of the research teams of the Faculty of Medicine in Hradec Králové. The project was organized by Charles University and was supported from the European Structural Founds and Ministry of Education, Youth and Sports. The project allowed to establish seven new research positions for recent PhD graduates (post doc positions) in our medical faculty. The main activities of the postdocs were focused on three fields. The main field is the research.
For all period of the project duration, the students were joining the research teams at our faculty, they also participated in the teaching of the pre- and postgraduate students, and had a possibility to stay in foreign scientific institutions with the aim to learn new research methods and to transfer them in our faculty.
Compared to project POSTDOC I, the project POSTDOC II started later.

Research characteristics of the postdoc positions:

Postdoc 01: The research was focused on the development and research application of the new methods for the study of nuclear receptors regulating gene transcription. This research was focused on genes important for liver hemostasis of endo- and xenobiotics and the interaction with medication.

Postdoc 02:
The research was focused on the stem cell biology: new methods in cultivation of the mezenchymal and pluripotent stem cells and its differentiation. The special attention was paid to characterization of the biological properties of the stem cells in vitro, evaluation of the cellular kinetics, their potential for differentiation.
The realisation of the project fulfilled all project aims and indicators.

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Title of the project: Influencing colorectal cancer by targeted therapy - in vitro study

Grant Agency: Ministry of Health ***Project Number:*** NT/14150-3

Principal Investigator: A. Ryška

Co-investigators: S. John, J. Soukup, L. Krbal, E. Rudolf, V. Hanušová

Starting date: 1.1.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 2274

Summary of 2015 results

Title of the presentation: Development of preparation and basic characterization of primary cell cultures of colorectal carcinoma *in vitro*

Authors: A. Ryška, S. John, J. Soukup, L. Krbal, V. Hanušová, E. Rudolf

Colorectal carcinoma is one of the most prevalent malignant neoplasms in developed countries. Despite all efforts to diagnose these tumours in their initial stage, there are (at least in Czech Republic) many cases diagnosed late as advanced, frequently already metastatic, disease.

Patients with advanced colorectal carcinoma are in addition to surgical resection of the primary tumour treated also by systemic postoperative chemotherapy, which is in majority of generalized patients accompanied by some kind of targeted (biological) treatment. Currently, there are two major options for biological treatment targeting either VEGF or EGFR pathway depending on activating mutations in KRAS and NRAS genes as negative predictive factors. The antiEGFR treatment targets directly the intracellular signaling in the neoplastic cells, whereas antiVEGF treatment blocks angiogenesis in the tumor by targeting the endothelial cells.

The main aim of the presented project was to develop a procedure of explantation of neoplastic tissue from the resected colorectal cancer and preparation of primary cell cultures, which would be later used for further testing of standardized treatment.

This has been succesfully done and we have the protocol for cultivation of neoplastic cells. At the end of our project we obtained samples from 35 patients where 33 samples were from primary site of the tumour and 20 samples from lymph node metastasis. There are 13 cell lines from primary tumours and 14 lines from the affected lymph node available. Total effectiveness of the derivation from primary tumours was 39,4% and 70% from lymph nodes respectively.

All derived cell lines were histologically and immuhistochemically compared to the tumour from the site of extraction.

We evaluated the metastatic potencial of these cell lines in comparison to the immortalized colorectal model cell lines SW-480 and SW-620 (migration assay, expression of adhesion/invasion markers). Selected cell lines were also tested for changes of viability after treatment with chemotherapeutic agents (irinotecan, oxaliplatine) and anti-VEGF or anti-EGFR targeted therapy (bevacizumab, cetuximab, panitumumab).

Results of this study confirm the potential of cell cultures isolated from patients in individualization of colorectal cancer therapy.

Address for correspondence: Prof. Aleš Ryška, MD, Ph.D.; The Fingerland Department of Pathology; Charles University Medical Faculty Hospital; CZ-500 05 Hradec Králové; CZECH REPUBLIC; mailto:ryskaale@fnhk.czryskaale@fnhk.cz

Title of the project: New methods and approaches in diagnostics and search for predictive and prognostic markers in neoplastic disorders

Grant Agency: Ministry of Education ***Project Number:*** 260181

Principal Investigator: A. Ryška

Co-investigators: V. Buchta, A. Krajina, J. Krejsek, P. Živný

Starting date: 1.1.2015 ***Duration (years):*** 1

Total funds allocated for project - Kč (thousands): 750

Summary of 2015 results

Title of the presentation: New methods and approaches in diagnostics and search for predictive and prognostic markers in neoplastic disorders

Authors: Ryška A, Buchta V, Krajina A, Krejsek J, Živný P

Malignant neoplasms are one of the major causes of morbidity and mortality in developed countries. In the past decade, there has been an enormous development in our understanding of pathogenesis, diagnostic procedures as well as treatment options. This resulted in significant improvement of prognosis for many oncologic patients. Thus, cancer remains in the focus of interest of many researchers. For the optimal choice of therapeutic approach is essential not only precise knowledge of etiopathogenesis of different types of cancer, but also our better understanding of heterogeneity and plasticity of tumors. In our project, we have focused on search for predictive and prognostic markers from different points of view (imaging, biochemical markers, histologic features, immunologic data, interaction of neoplastic population with the host, etc.).

Individual sub-projects included among others (altogether 28 sub-projects): Study of metylation of tumorsupressor genes in hepatocelular carcinoma, Changes in tissue perfusion during the perioperative phase of heart surgery, evaluation of influence of selected antiepileptic drugs and on levels endocanabinoids in rat serum and brain tissue; microRNA as potential biomarkers for early detection of renal injury induced by contrast medium used in invasive imaging, immunopathogenesis of Sjögren syndrome, evaluation of contribution of various biochemical markers in diagnostics of bone fracture, immunological response in patients after heart surgery; study of intestinal immune system - influence of intestinal microbiome, study of pre-resection embolization of portal vein in patients with hepatic metastases with intention to induce hyperthophy of residual liver parenchyma; molecular subtyping of lung adenocarcinoma, study of serrated lesions of the large intestine.

Altogether, 6 fulltext papers were published, several additional manuscript are currently under the peer review, 2 doctoral theses were succesfully defended.

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Title of the project: Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)

Grant Agency: Ministry of Education ***Project Number:*** BBMRI_CZ

Principal Investigator: D. Valík

Co-investigators: A. Ryška, V. Palička, J. Laco, R. Kutová

Starting date: 1.1.2011 ***Duration (years):*** 5

Total funds allocated for project - Kč (thousands): 2900

Summary of 2015 results

Title of the presentation: The potential of cryopreserved paired tumor and blood samples from patients with selected malignant tumors for biomedical research

Authors: Laco, J., Ryška, A., Kutová, R., Palička, V.

Biomedical research in oncology and molecular medicine is more and more focused on tailoring of treatment in individual cancer patients. For this approach are needed studies focused on detection of not only prognostic, but also predictive markers of treatment efficacy. These markers are usually identified post hoc based on retrospective analysis of various molecules in tumor tissue or in the blood of treated patients with correlation of these values with clinical outcome.

For these purposes, there is an increased need for preserved tumorous tissues for future testing. With the means of cryopreservation, i.e. a process where tissues are archived as snap frozen in liquid nitrogene with blockage of any enzymatic activity (stopping of cell death, DNA, RNA and proteins decay), the tissues are kept intact for further biological and medical research.

During 2015, both participating laboratory departments, The Fingerland Department of Pathology and Institute of Clinical Biochemistry and Diagnostics, kept on collection, transport and storage of both patients' blood samples and fresh tumor tissue samples.

According to individual protocols for each tumor diagnosis the blood samples are collected. Close cooperation with other clinical departments (oncology, general surgery, head and neck surgery, dentistry, gynaecology and obstetrics) is fully established and routine collection of tumor tissue and blood samples is performed in selected diagnoses (breast carcinoma, colorectal carcinoma, hepatocellular carcinoma, head and neck carcinomas, ovarian carcinomas). The laboratories are equipped with consumables for isolation of DNA from both tumor tissue and blood. The crucial point is robust categorization of samples which must enable retrieval of samples on the basis of various clinico-pathological criteria. Thus, a computer based database has been developed to solve this issue. All samples are now categorized based on standard criteria, such as diagnosis, TNM, grading, follow up intervaletc. The infrastructure serves as a basis for several research projects (validation of liquid biopsy approach, research of role of miRNA in metastasizing of colorectal cancer, etc.

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Title of the project: Prediction of therapeutic response in ovarian cancer patients

Grant Agency: Ministry of Health ***Project Number:*** NT/14107-3

Principal Investigator: I. Sedláková

Co-investigators: M. Červinka, M. Naležinská, C. Andrýs, J. Nekvindová, R. Pudil, I. Karešová, J. Tošner, J. Laco, J. Špaček, K. Caltová, J. Chovanec, J. Umlauf

Starting date: 1.5.2013 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 7921

Summary of 2015 results

Title of the presentation: Prediction of therapeutic response in ovarian cancer patients

Authors: I. Sedláková (1), M. Červinka (2), M. Náležinská (3), J. Laco (4) C. Andrýs (5), J. Nekvindová (6), R. Pudil (7), I. Karešová (6), J. Tošner (1), J. Špaček (1), K. Caltová (2), J. Chovanec (3), J. Umlauf (3).

Dept. of Gynecology and Obstetrics University Hospital and Fac. Med. Hradec Králové (1)
Dept. of Medical Biology and Genetics Faculty of Med. Charles University in Prague (2), Masaryk Memorial Cancer Institute in Brno (3),
Dept. of Pathology University Hospital Hradec Králové (4), Dept. of Clinical Immunology and Alergology (5), Dept. of Clinical Biochemistry and Diagnostics (6), Dept. of Cardiology and Angiology (7),

The objective of the project was identification of molecular biology markers useful for prediction of therapeutic response in ovarian cancer patients by means of: 1) Determination of ABCB1, ABCC1, GST genetic polymorphisms (PCR), resistance proteins (P-glycoprotein (Pgp), Multidrug Resistance Associated Protein (MRP1)) by means of imunohistochemistry, drug resistance/drug sensitivity in vitro (MTT assay) from solid tumor in ovarian cancer patients. We observed it in ovarian cancer patients diagnosed from 2006 to 2009 and from 2013 to 2015. Evaluation of correlation between these characteristics and therapeutic response (progression free survival (PFS), overall survival (OS), side effects). 2) Analysis of polymorphisms of the Interleukin-8 gene, endoglin, FGF, angiopoetin gene expression in ovarian tumor (PCR) and pro-angiogenesis markers (VEGF, TGFά, TGFβ a bFGF) in venous blood (ELISA). Evaluation of correlation among these characteristics and kind of primary farmacotherapy and medical outcome (PFS, OS). 3) Analysis of cardiotoxicity of standard primary chemotherapy (Paclitaxel + Carboplatin) by ECG, blood pressure, echocardiography, markers of cardiotoxicity (NT-proBNP,cTnT,cTnI,CKMB,MYO,h-FABP, GPBB) (ECLIA, protein biochip technology) in ovarian cancer patients. Pgp and MRP1 expression were clinically significant in ovarian cancer patients. Pgp and MRP1 may be reliable independent predictive and prognostic factors regarding the clinical outcome of ovarian cancer. MRP3 is less important as a predictive and prognostic factor than MRP1 expression. Patients with primary ovarian cancer had a significantly higher plasma VEGF level compared with patients with benign ovarian tumors and healthy women. In our study levels of TGFa mRNA were elevated in tumor samples.

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Title of the project: Diagnostics and treatment of hoarseness - current diagnostic tools and treatment

Grant Agency: Ministry of Education ***Project Number:*** IP 2015

Principal Investigator: K. Smatanová

Co-investigators: V. Chrobok

Starting date: 1.1.2015 ***Duration (years):*** 1

Total funds allocated for project - Kč (thousands): 160

Summary of 2015 results

Title of the presentation: Vocal cord patholohy related hoarseness - aetiology, diagnosis and treatment

Authors: K. Smatanová, J. Dršata, V. Chrobok
Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Hradec Kralove, Charles University in Prague, Faculty of Medicine in Hradec Kralove

Hoarseness is a symptom which indicates vocal cord pathology. Aetiology can be various organic (congenital, inflammatory, traumatic, benign lesions, malignant lesions of vocal cord) or functional (paresis/paralysis, hypotonia/hypertonia, psychogenic). Literature: J. Dršata et al.: Foniatrie - hlas, 157 - 248, 2011.

To diagnose such pathology, there are various diagnostic tools available. One of the most important is laryngostroboscopy, which is a type of endoscopic examination. Using this technique, we can visualise anatomy of the vocal cord, asses it´s movement and mucosal wave. Aim of our work is to prepare an audiovisual lecture for medical students with organic and functional lesions of vocal cord. It is very important to be familiar with aetiology of hoarseness as it can indicate malignancy and hoarseness is a red flag symptom. We collected audiovisual data from our patients treated at Department of Otolaryngology and Head and Neck surgery in Hradec Králové. Patients are examined in our Phoniatry out - patients´ clinic, their examination is stored in Xion endoscopic unit. We focused on pre and post treatment of various vocal cord lesions such as extraesophageal reflux, vocal cord cyst, vocal cord polyp, vocal cord nodules, vocal cord granuloma, Reinke´s oedema, leukoplakia of vocal cord, carcinoma of vocal cord, laryngeal papillomatosis and vocal cord paralysis. Thanks to these recordings, medical students will not only see the initial pathology but also the result of either conservative or surgical treatment. This audiovisual file will be presented to students during their practical teaching at Otorhinolaryngology department, but it will be also available on line on the faculty´s website. With this project, we provide clinical information for students about diagnosis and treatment of hoarseness, support e - learning for students studying in both Czech and English language and help developing teaching methods and make information available for gaining more clinical skills.

Address for correspondence: K. Smatanová, Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Hradec Kralove, Charles University in Prague, Faculty of Medicine in Hradec Kralove

Title of the project: Complex assessment of microenvironment in chronic lymphocytic leukemia

Grant Agency: Ministry of Health ***Project Number:*** NT/13412-4

Principal Investigator: L. Smolej

Co-investigators: C. Andrýs, V. Řezáčová, D. Vokurková, F. Vrbacký, M. Šimkovič

Starting date: 1.1.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 3094

Summary of 2015 results

Title of the presentation: Expression of CD223, CD49d, CD31 and CD54 in patients with chronic lymphocytic leukemia.

Authors: Lukáš Smolej (1), Vladimíra Řezáčová (2), Martin Šimkovič (1), Pavel Vodárek (1), David Belada (1), Pavel Žák (1). University Hospital and Charles University in Prague, Faculty of Medicine in Hradec Králové: (1) 4th Department of Internal Medicine - Hematology, (2) Institute of Clinical Immunology and Allergology.

Chronic lymphocytic leukemia, the most common adult leukemic disorder in Western hemisphere, has a remarkably heterogeneous clinical course with overall survival ranging from months to decades. The bone marrow and lymph node microenvironment plays a crucial role in the prevention of apoptosis and proliferation of the leukemic clone. The optimal markers of microenvironment in CLL, however, have not yet been identified. In the present study, we assessed the membrane expression of CD223, CD49d, CD31 and CD54 by flow cytometry in 90 untreated CLL patients (median age, 66 years; males, 71%; Rai III/IV stages, 28 %; unmutated IGHV genes, 64 %) and evaluated their possible association with established prognostic factors and clinical course of the disease. We used flow cytometers Epics XL and Navios (Beckman Coulter, USA) and Monoclonal antibodies IgG1-PE (Caltag Laboratories, USA); CD223-PE, CD49d-PE, CD31-FITC, CD54-FITC (R&D Systems, USA). Expression higher than median was considered high. All markers were significantly elevated in CLL patients in comparison to healthy controls ($p< 0,0001$). Patients with unmutated IGHV genes had significantly higher expression of CD223 ($p=0.045$) and CD54 ($p=0.022$). Low expression of CD49d was significantly associated with longer time to first line treatment (median 0 months vs. not reached, risk ratio 0.52 [95% confidence interval 0.3-0.92], $p=0.016$). In conclusion, our results indicate that CD223, CD54 and CD49d play a role in biology and progression of CLL and thus warrant further investigation.

Address for correspondence: Lukáš Smolej, M.D., Ph.D., 4th Department of Internal Medicine - Hematology, University Hospital and Charles University in Prague, Faculty of Medicine in Hradec Králové, Czech Republic.

Title of the project: Analysis of clonal heterogeneity in chronic lymphocytic leukemia using next generation sequencing of B cell receptor. A national study.

Grant Agency: Ministry of Health ***Project Number:*** 15-30015A

Principal Investigator: L. Smolej

Co-investigators: F. Vrbacký, M. Šimkovič

Starting date: 1.5.2015 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 15469

Summary of 2015 results

Title of the presentation: Analysis of clonal heterogeneity in chronic lymphocytic leukemia.

Authors: Lukáš Smolej (1), Martin Šimkovič (1), Filip Vrbacký (1)
University Hospital and Charles University in Prague, Faculty of Medicine in Hradec Králové: (1) 4th Department of Internal Medicine – Hematology.

Chronic lymphocytic leukemia (CLL) is characterized by extraordinary heterogeneity concerning clinical presentation and molecular features.As the clonal disease of B lymphocytes, each case can be described by a specific immunoglobulin gene (IG) encoding for the B cell receptor. Extensive molecular evidence was provided on antigen stimulation operation in CLL, which is also supported by epidemiological studies. High throughput sequence analysis has not been applied extensively in research focused on IG due to several limitations. The current project aims to expertly implement advanced methodology for the high-throughput IG sequence analysis to produce, manage and delve into extensive immunogenetic sequence datasets in CLL. Furthermore, the obtained data will be associated with clinical, molecular and epidemiological features of CLL cases as these will be collected through the purpose-specific survey among Czech CLL patients. An extensive national-wide CLL database CLLEAR containing data on clinical course and molecular biomarkers is being used and extended during the project. The aims of the project are: 1. To explore the composition of CLL population diagnosed in the Czech Republic with respect to the clinical, biological and epidemiological features. 2. To perform molecular studies of immunoglobulin genes uncovering variety and diversity of B lymphocyte clones in newly diagnosed CLL using NGS.

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Title of the project: Predictive factors of pathologic response to neoadjuvant chemotherapy in patients with HER-2 positive or triple negative breast carcinoma

Grant Agency: Ministry of Health ***Project Number:*** NT/13564-4

Principal Investigator: B. Melichar

Co-investigators: H. Študentová, T. Adam, Z. Kolář, N. Zlámalová, K. Cwiertka, E. Hlídková, J. Ehrmann, D. Solichová, L. Krčmová, A. Ryška, H. Hornychová, J. Dvořák

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 9900

Summary of 2015 results

Title of the presentation: Association of urinary neopterin, neutrophil-to-lymphocyte, lymphocyte-to-monocyte and platelet-to-lymphocyte ratios with long-term survival of patients with breast cancer

Authors: B. Melichar(1), H. Študentová(1), D. Vitásková(1), V. Šrámek(1), L. Kujovská Krčmová(3), E. Pešková(4), D. Solichová(3), H. Kalábová(1), A. Ryška(5), K. Hrůzová(1), R. Havlík(2)

Departments of (1)Oncology and (2)Surgery, Palacký Univ. Medical School, Olomouc, (3)Third,(4)Forth Department of Medicine and (5) Fingerland Institute of Pathology, Charles Univ. Teaching Hospital, Hradec Králové

The aim of the present study was to evaluate correlations of peripheral blood cell count-derived ratios and urinary neopterin concentration with prognosis in breast cancer patients. Urinary neopterin, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) were retrospectively analyzed in cohorts of breast cancer patients. NLR and PLR correlated positively with each other and negatively with LMR, but no correlation between neopterin concentrations and PBC-derived ratios was observed. Increased urinary neopterin concentration was significant predictor of poor survival in breast cancer patients, but PLR, NLR or LMR were not significantly associated with survival in multivariate analysis. In conclusion, increased urinary neopterin predicts poor survival in patients with breast cancer and active disease.

The project was supported by Ministry of Health Internal Grant Agency, No. NT13564-4/2012

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Title of the project: Tissue trauma and postoperative stress in patients with surgically treated early endometrial cancer stages

Grant Agency: Ministry of Health ***Project Number:*** NT/13566-4

Principal Investigator: R. Pilka

Co-investigators: B. Melichar, M. Kudela, D. Ondrová, T. Adam, D. Friedecký, D. Solichová, L. Krčmová

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 6986

Summary of 2015 results

Title of the presentation: Systemic inflammatory response after abdominalopen, laparoscopic and robotic staging surgery of in endometrial cancer patients

Authors: R. Pilka(1), R. Marek(1), T. Adam(3), M. Kudela(1), D. Ondrová(1), D. Neubert(1), J. Hambálek(1), M. Maderka(1), D. Solichova(4), L. Kujovska Krcmova(4), B. Melichar(2)

Departments of (1)Obstetrics and Gynecology, (2)Oncology and (3)Clinical Biochemistry, Palacký University Medical School and Teaching Hospital, Olomouc and (4)Third Department of Medicine, University Hospital Hradec Králové

Surgical intervention elicits an inflammatory response that is accompanied by oxidative stress. There are obvious differences between different therapeutic approaches in terms of tissue trauma and oxidative stress. Different biomarkers of inflammatory response include C-reactive protein (CRP), kynurenine/tryptophan ratio or neopterin. Systemic inflammatory response is also associated with decreased hemoglobin concentrations and higher platelet counts, and also with oxidative stress. Oxidative stress results in decreased concentrations of circulating antioxidants like alpha-tocopherol. The concentrations of alpha-tocopherol along with other lipid-soluble vitamins like retinol or vitamin D reflect also the nutritional status of the patients. The aim of this study was to compare an association between clinical indicators of surgical trauma with biomarkers of inflammatory response and nutritional balance in patients treated with three surgical approaches including open (laparotomy), laparoscopic and robotic surgery as well as in patients operated for benign disorders.

Present data demonstrate significant changes in the investigated biomarkers of nutrition and inflammatory response in the acute postsurgical phase in patients with endometrial cancer. In addition, the biomarkers of nutrition and inflammatory response correlated significantly with clinical parameters of surgical stress.

In conclusion, present data demonstrate a differential response to surgical trauma in patients with endometrial carcinoma.

The project was supported by Ministry of Health Internal Grant Agency, No. NT13566-4/2012

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Title of the project: Development of novel disinfectants against pathogens occuring in the hospital environment

Grant Agency: Ministry of Health ***Project Number:*** 15-31847A

Principal Investigator: O. Soukup

Co-investigators: P. Boštík

Starting date: 1.5.2015 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 7490

Summary of 2015 results

Title of the presentation: Development of novel disinfectants against pathogens occuring in the hospital environment

Authors: Ondrej Soukup (1), David Malinak (1), Jan Korabecny (1), Roman Prymula (1), Lenka Hobzova (1), Lenka Ryskova (1), Pavel Bostik (2), Vanda Bostikova (2), Daniel Jun (2), Jan Marek (2)

Biomedical Research Center, University Hospital Hradec Kralove (1), Faculty of Military Health Sciences, University of Defense (2)

In this project, we would like to develop new compounds based on quaternary ammonium salts with a strong disinfectant potential against nosocomial infections in hospital environment, thus bacterial, fungal and viral pathogens. The project is designed for development of various (3-6) mixtures with strong disinfecting properties and wide spectrum of efficacy by combining individual agents with more specific efficacy. In the first year, based on the preliminary data, approximately 60 analogues of quaternary ammonium salts (QAS) containing quaternary nitrogen and carbon chain of C12, C14, and C16 was prepared by the chemical synthesis. It is assumed that their effect is based on ability to interfere with the stability and functionality of microbial cell membranes of a wide range of infectious agents, which is ideal for topical use as disinfectants. According to the literature and our preliminary data, QAS were found to be effective against both bacteria and fungi. Furthermore, QAS were reported to be effective also against both encapsulated and non-encapsulated viruses. Such findings were confirmed by our pivotal in vitro screening using standard benzalkonium QAS and basic battery of microbes (S. aureus, E. coli, Cl. dificile C. albicans and VZ virus), which serves for the selection of effective concentration for future testing. Thus, newly prepared compounds will be evaluated for their in vitro effect at given concentration by means of standard qualitative screening methods during the next year.

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Title of the project: The use of the synthetic biomaterials in the treatment of the extensive skeletal defects in revision total hip arthroplasty

Grant Agency: Ministry of Health ***Project Number:*** NT/13477-4

Principal Investigator: P. Šponer

Co-investigators: E. Syková, K. Urban

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 7557

Summary of 2015 results

Title of the presentation: The application of the suspension of autologous mesenchymal stem cells into the femoral bone defects

Authors: P. Šponer (1), T. Kučera (3), S. Filip (1), V. Palička (1), K. Urban (3), Z. Kočí (2), E. Syková (2)

1 - Faculty of Medicine in Hradec Králové
2 - Institute of Experimental Medicine AS CR in Prague
3 - University Hospital in Hradec Králové

Bone regeneration enhancement using biological agents, including osteogenic growth factors and multipotent mesenchymal stromal cells (MSCs), is fast becoming a clinical practice. Here, we present the results of clinical trial utilizing expanded autologous MSCs for the regeneration of femoral bone defects. We compared healing quality in 18 patients after 12-months follow-up period. Ultraporous β-tricalcium phosphate synthetic graft material containing either expanded autologous MSCs (9 patients; trial group), or β-tricalcium phosphate alone (9 patients; control group), was implanted into femoral defects during revision total hip arthroplasty. Both groups were assessed clinically, radiographically and with DEXA scanning at 6 weeks, 3, 6 and 12 months postoperatively. Trabecular remodeling was found in all nine patients in the trial group and in 1 patient only in the control group. Over the 12-months follow-up period, the significant differences were documented between trial and control groups in the presence of radiolucency, and bone trabeculation through the defect ($P < 0.05$). At 6 months after surgery, there was only a mild decrease in median DEXA bone mineral density to 98% in the trial group with an increase in median bone mineral density to 111% at 12 months after surgery. In the control group, there was a marked decrease in median BMD to 88% at 6 months post operation with a subsequent return of median BMD to 100% at 12 months after operation. Our prospective study confirms a safety of the application of an ultraporous β-tricalcium phosphate synthetic graft material combined with expanded MSCs in management of bone defects with compromized microenviroment.

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Title of the project: Vulnerability and reparation possibility of peroperative vas deferens damage in experiment

Grant Agency: Charles University ***Project Number:*** 160315

Principal Investigator: R. Štichhauer

Co-investigators: M. Kaška, J. Koudelka, K. Petkov, A. Ryška, V. Krejčí

Starting date: 6.5.2015 ***Duration (years):*** 2

Total funds allocated for project - Kč (thousands): 215

Summary of 2015 results

Title of the presentation: Possibilities of lesional vas deferens repair in the experiment

Authors: R. Štichhauer, J. Koudelka, K. Petkov, A. Ryška, M. Kaška

Damage of vas deferens during a surgery of inguinal hernia is one of the most frequent iatrogenic injury in pediatric surgery. There is no recommendation for treatment of that injury. The main idea of our experimental study is a creation of some useful algorithm for injured vas deferens reparation under the conditions of basic paediatric surgery departments with the use of magnifying glasses only. We decided for a pilot prospective experimental study, which was performed on the rat. 48 animals were included into the study yet and they were divided in six subgroups according to the method of the vas deferens injury. The subgroups are: 1. contusion of the vas deferens by pressing in a pean for 2 sec, 2. anastomosis of the vas deferens by single absorbable stitches (Vicryl R 8/0), 3. joining of both ends each to other with the help of an intraluminally lead fibre of absorbable sewing material (PDS 7/0), 4. = 3. joining with a non-absorbable fibre of sewing material (Prolen 7/0), 5. anastomosis by absorbable sewing material (Vicryl R 8/0) with an intraluminally situated fibre of absorbable sewing material (PDS 7/0), 6. = 5. only an intraluminally situated fibre of non-absorbable sewing material (Prolen 7/0). The vas deferens was checked 3 months after the primary operation and than resected in a lenght of 20 mm with a line of artificial injury. These resected parts of the vas deferens were examined in function by the flow rate of methylene blue solution (μL/min). The pathologist after that performed morphologic evaluation of the resected vas deferens. Findings on the injured vas deferens were compared with those on the second side without surgery.

We found a normal liquid flow rate through the resected part of the vas deferens and morphological conditions in this subgroup with the contused vas deferens. The best results in flow rate through the transected vas deferens were evaluated in the subgroup with reparation performed by joining the transected vas deferens with the help of absorbable sewing material. Similar results were found in the subgroup anastomosis performed with absorbable stitch and with intraluminally situated absorbable stitch fibre.

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Title of the project: Interventional left atrial appendage closure vs. novel anticoagulation agents in high-risk patients with atrial fibrillation (PRAGUE-17)

Grant Agency: Ministry of Health ***Project Number:*** 15-29565A

Principal Investigator: P. Osmančík

Co-investigators: J. Šťásek, J. Bis, L. Haman

Starting date: 15.5.2015 ***Duration (years):*** 5

Total funds allocated for project - Kč (thousands): 2414

Summary of 2015 results

Title of the presentation: Interventional left atrial appendage closure vs. novel anticoagulation agents in high-risk patients with atrial fibrillation (PRAGUE-17)

Authors: J. Šťásek, J. Bis, L. Haman (center Hradec Kralové)

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence of 1-2%. Without antithrombotic treatment, the annual risk of a cardioembolic event is 5-6%. The source of a cardioembolic event is a thrombus, which usually forms in the left atrial appendage (LAA).

Prevention of cardioembolic events involves treatment with anticoagulant drugs, which were limited to, until recently, vitamin K antagonists (e.g. warfarin). Anticoagulant treatment with warfarin can lead to adverse bleeding events, some of which can be life threatening. Recently, two new options for thrombus prevention have been developed. The first is the novel anticoagulants (NOAC), which were associated with slightly better safety profiles due to a lower frequency of intracranial bleeding in large randomized trials. The second option involves interventional occlusion of the LAA. The aim of this project is to compare the LAA occlusion intervention to NOAC pharmacological treatment in a randomized multicenter study of AF patients at high risk of a cardioembolic event.

The aim of the project is to compare LAA occlusion with NOAC in a randomized multicenter study of AF patients at the greatest risk.

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Title of the project: Wireless capsule endoscopy in diagnostics of enteropathy induced by non-steroidal anti-inflammatory drugs

Grant Agency: Ministry of Health ***Project Number:*** NT/13532-4

Principal Investigator: I. Tachecí

Co-investigators: J. Bureš, M. Kopáčová, T. Douda, P. Bradna, S. Rejchrt

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 4967

Summary of 2015 results

Title of the presentation: Wireless capsule endoscopy in diagnostics of enteropathy induced by non-steroidal anti-inflammatory drugs

Authors: I. Tachecí, P. Bradna, T. Douda, D. Baštecká, M. Kopáčová, S. Rejchrt and J. Bureš
2nd Dpt of Internal Medicine-Gastroenterology, Charles University in Prague, Faculty of Medicine and University Hospital in Hradec Králové

Background: The goal of our project was to evaluate the prevalence of NSAID-induced enteropathy by means of capsule endoscopy, to describe the endoscopic characteristics of this disease, and to identify possible laboratory and/or clinical predictors of the disease in patients with rheumatoid arthritis and/or osteoarthritis.

Methods**:** 143 rheumatoid arthritis (74) or osteoarthritis (69) patients (101 women, mean age 59 and 42 men, mean age 59) treated with NSAIDs (>1 month) and 42 healthy volunteers entered the study and underwent capsule endoscopy (EndoCapsule; Olympus), laboratory tests, and filled in questionnaires. We observed no clinical complications during capsule endoscopy, patient compliance to the investigation was 100 %.

Results**:** The overall prevalence of the disease was 45 % in NSAID users and the prevalence of NSAID-compatible lesions was 12 % in the control group of healthy volunteers (p = 0,000). Mild (red spots or erosions), moderate (10–20 erosions) and severe enteropathy (>20 erosions or ulcers) was described in 36 %, 4 %, 5 % patients and in 12 %, 0%, 0% healthy volunteers. The most frequent findings were so-called red spots (mucosal erythema foci) and small intestinal erosions (up to 10). The clinical significance of those lesions is almost questionable. There was no correlation observed between the enteropathy presence or severity and type of NSAID used (p = 0,758, p= 0,361). On the other hand, strong correlation between the presence or severity of enteropathy and dose of NSAIDs was identified (p = 0,000, p = 0,000). We also focused on laboratory and/or clinical predictors for NSAID-induced enteropathy. After statistical evaluation, all anaemia (haemoglobin, erythrocytes, mean corpuscular volume, serum iron levels, ferritin), nutrition (albumin, pre albumin) or inflammatory markers (CRP, thrombocytosis, erythrocyte sedimentation rate) can not be recommended for diagnostics of NSAID-induced enteropathy or its severity. Clinical markers (age, sex, dyspepsia) appeared not to be very reliable either.

Conclusions**:** Capsule endoscopy is a safe, accurate, non-invasive endoscopy method for identification of NSAID-induced enteropathy in the rheumatoid arthritis or osteoarthritis patients. The prevalence of small bowel damage is 45 %, mostly mild. Severe damage of small bowel (ulcers or multiple erosions) was identified in 9% of long-term NSAID users. No simple clinical or laboratory markers of the presence or severity of NSAID-induced enteropathy were recognized.

Address for correspondence: I. Tachecí 2nd. Dpt. of Internal Medicine - Gastroenterology, University Hospital, Hradec Králové

Title of the project: MEFANET – clinical reasoning

Grant Agency: Ministry of Education ***Project Number:*** CZ.1.07/2.2.00/28.0038

Principal Investigator: D. Schwarz

Co-investigators: I. Tachecí

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 7035

Summary of 2015 results

Title of the presentation: Virtual Cases in Internal Medicine Education

Authors: Ilja Tachecí 1, Aleš Ryška 2

1 - 2nd Dpt. of Internal Medicine - Gastroenterology and 2 - The Fingerland Dpt. of Pathology, Charles University Medical Faculty and University Hospital Hradec Kralove

Virtual patients represent a useful tool in undergraduate teaching of clinical reasoning skills. Virtual cases (www.e-kazuistiky.cz) have been developed as an interactive problem-based learning system, which uses anonymized clinical data and test results from real patients, covering different fields of internal medicine, and with the help of unique IT algorithms generates sets of individual virtual patients. According to user-predefined program settings (spectrum of diagnoses, number of patients and criteria for passing the course), sets of virtual patients can be prepared on demand of each teacher. The total number of 62 peer-reviewed clinical cases covering several internal medicine subspecialties were published in the system so far. Basic clinical information including personal data, medical history, symptoms, laboratory values, etc. is generated for each virtual patient. The main task for the student is to determine the optimal diagnostic algorithm (choose adequate diagnostic steps in the correct order), and to determine the correct diagnosis in each virtual patient. Results of diagnostic tests, imaging methods and clinical findings are presented utilizing a multimedia presentation (images, video-sequences, audio-recordings). Evaluation of students includes not only assessment of correctly determined diagnosis, but also the diagnostic pathway, which led the user to the specific diagnosis. Thus, the system enables assessment of appropriateness of each test as well as reasonable sequencing of tests. A unique feature of the system is evaluation of financial aspects of all selected examinations (teaching of consideration of economic issues of medical care). The original system was prepared as interactive web based environment, in addition applications for Android or iOS compatible mobile devices were developed.

The system is currently routinely used in the undergraduate curriculum at the Medical Faculty in Hradec Králové (in the 4th year - internal medicine).

The Virtual cases program is a useful tool for undergraduate medical education with positive feedback from both students and teachers. The main advantages are flexibility, potential for further growth and no restrictions regarding particular disease, clinical discipline, diagnostic procedure, etc.

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Title of the project: Role of oxidative stress in the interplay between cellular senescence and apoptosis

Grant Agency: Czech Republic ***Project Number:*** 15-03379S

Principal Investigator: Z. Hodný

Co-investigators: V. Tambor, K. Pimková, R. Dzijak

Starting date: 1.1.2015 ***Duration (years):*** 3

Total funds allocated for project - Kč (thousands): 8832

Summary of 2015 results

Title of the presentation: Development of a redox proteomics quantitative assay for a cellular senescence and apoptosis model

Authors: V. Tambor (1), K. Pimková (1), R. Dzijak (2), Z. Hodný (2)
Biomedical Research Center, University Hospital Hradec Kralove (1), Institute of Molecular Gentetics, Academy of Sciences Czech Republic (2)

Cellular senescence, an essentially permanent cell cycle arrest, represents an essential anticancer barrier. Yet there is evidence that accumulation of senescent cells in normal and cancer tissues can promote proinflammatory milieu, which may result in enhancement of tumorigenic or metastatic potential of tumour cells. Besides mitochondrial energy metabolism, NADPH oxidases, the key enzymes involved in redox signalling, represent a second major cellular source of free oxygen and nitrogen radicals. Uncontrolled activity of these enzymes play an important role in several pathological processes associated with onset of cancer. The current project aims at elucidating the redox balance in a cellular model of senescence using proteomics by assessing reduced vs. oxidized protein forms at a whole-proteome level. In order to distinguish native reduced protein forms, free thiol groups are tagged using a particular flavor of iodo tandem mass tags labels (Thermo Fisher Scientific, Germany). The oxidized cysteine residues are in turn reduced in vitro and the newly formed thiol groups are then tagged by another variant of the iodoTMT labels. The sample is then analyzed using liquid LCMS in order to obtain information on a) the protein content of the sample and b) the ratio between the reduced and oxidized forms of individual proteins. During the first year, we focused at method development. Our results show that we can routinely assess the levels of ~2700 proteins based on the ~18 000 peptides. From these, ~2600 peptides are cysteine containing and thus carry the reduced/oxidized ratio information, which provides sufficient coverage for subsequent evaluation. Importantly, the tagging efficiency of the iodoTMT labels exceeds 95%, which is crucial for precise quantitation. In order to enhance the selectivity of the analysis, we will focus on cysteinyl peptide enrichment in the following experiments. Ultimately, these newly developed methods will be used for the analysis of a cellular senescence model.

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Title of the project: Identification of early and late nosocomial pneumonia bacterial agents in patients at intensive care through genetic analysis of bacterial DNA and determine their propagation

Grant Agency: Ministry of Health ***Project Number:*** NT/14263-3

Principal Investigator: Z. Turek

Co-investigators: P. Paterová

Starting date: 1.5.2013 ***Duration (years):*** 2

Total funds allocated for project - Kč (thousands): 732

Summary of 2015 results

Title of the presentation: Identification of early and late nosocomial pneumonia bacterial agents in patients at intensive care

Authors: Turek (1), P. Paterová (2)

Fac. Med., Charles Univ., Hr. Králové: Dept. of Anesthesiology and Intensive Care (1), Dept. of Clinical Microbiology (2)

The financial sources have been available since 6/2013, at this time, patient's selection and their enrolment into study at University hospital Hradec Kralove has been completed at 12/2014 according to the study schedule. Since 6/2013 to 12/2014 total of 88 patients were enroled into study and total of 173 microbiological specimens have been taken and sent to University Hospital Olomouc for further genetic analysis of bacterial genome. The mortality rate in study group reached during the study 15%. Total of 164 episodes of new onset of ventilator associated pneumonia (VAP) were diagnosed according to determined classification criteria. VAP associated with culture of non-fermenting gramm negative bacteria (NFGNB) comprising bacterial strains of Stenotrophomonas spp., Burgholderia spp. and Achromobacter reached 57 episodes of all VAP diagnosed throughout the study in 32 patients. Preceding therapy with carbapenems has not been recognised as a risk factor for colonisation a respiratory tract infection with positive culture of NFGNB.

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Title of the project: New analytical methods for effective monitoring of biomarkers

Grant Agency: Czech Republic ***Project Number:*** TA04010954

Principal Investigator: Z. Zadák

Co-investigators: R. Hyšpler, A. Tichá, I. Svobodová, M. Vacková

Starting date: 1.7.2014 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 16756

Summary of 2015 results

Title of the presentation: Biomarkers in various type diseases

Authors: Z. Zadák, A. Tichá, R. Hyšpler, I. Svobodová, M. Vacková

At present, a selection of priority sections has been made. The centre of investigation in the year 2015 was searching for the indicators of the disorder of the intestinal function. Indoxyl sulfate was considered already in the past to be the indicator of the damage of the intestine and intestinal ileus. Urine samples has been collected from patients in whom a disorder of intestinal passage has been diagnosed and where the finding of 3-indoxyl sulfate is expected as an indicator. The collection of urine samples from the patients concerned suffering from disorders of passage is stored for analytical experiments and as the substrate for the search for an advantageous analytical method, which would enable not only a rapid recognition of the existing disorder of passage but also the development of its risk. Another way is quantification of the modified structure of albumin by means of copper ions. According to quite recent items of knowledge in the site of insufficient blood supply due to hypoxia of the tissue an increase in the concentration of simple aldehydes, above all methylglyoxal, is observed. These aldehydes are capable, by means of the process of the so-called glycation, to covalently bind to several last N-terminal amino acids, which results in the loss of the ability of the albumin molecule to bind copper ions Cu2+. Examination of this modification is especially valuable because analytical determination of methylglyoxal in ex vivo samples is, due to its high reactivity, very difficult and in routine practice nearly impossible. Our aim is application of IMA (ischemia modified albumin) to predict dehiscence of anastomosis, which according to our research seems to be very promising. Early diagnosis is of essential importance for successful management of this complication.

Literature:

1. Eom, J.E., Lee, E., Jeon, K.H., et al. Development of an albumin copper binding (ACuB) assay to detect ischemia modified albumin. Anal Sci, 2014, 30(10), 985-990.

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3. Hyšpler, R., Tichá, A., Kaška, M., et al.: Markers of Perioperative Bowel Complications in Colorectal Surgery Patients. Disease Markers, 2015, Article ID 428535, 7 pages.

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Title of the project: Risk factors for development of CMV virostatic resistance in the patients after allogeneic stem cell transplantation

Grant Agency: Ministry of Health ***Project Number:*** NT/13691-4

Principal Investigator: P. Hubáček

Co-investigators: P. Sedláček, M. Zajac, E. Klapková, P. Žák, L. Plíšková, E. Vejražková, R. Kutová, M. Lengerová, J. Winterová, P. Cetkovský

Starting date: 1.4.2012 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 9827

Summary of 2015 results

Title of the presentation: Ganciclovir treatment failure in adult allogeneic hematopoietic stem cell transplant recipient with cytomegalovirus infection – a single centre experience

Authors: E. Vejrakova (2), P. Hubacek (1), J. Kutova (2), L. Pliskova (2), V. Štěpánová (5), A. Zavřelová (2), J. Radocha (2), E. Malá(6), P. Žák (2) (5 Dept. of Microbiology and 6 Dept. of Clinical Immunology and Allergology Univ. Hospital Hradec Kralove)

In 2012 and 2014, 40 patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) for hematological malignancies and were treated for human CMV reactivation/disease were followed up prospectively. In pts with treatment failure, CMV-DNA was isolated and analysed by nucleotide sequence analysis of the UL97 and UL54 genes conferring resistance to the virostatic agent.

Results: The treatment failure occurred in seven patients, but ganciclovir resistance conferring mutations were only detected in two of them (mutation L595F and M460I in the UL97 gene). Another mutation in the UL97 gene (N510S) was found in patient with recurrent CMV replication who needed to be retreated but did not meet the criteria for treament failure.

Conclusion: The low incidence of genetically confirmed ganciclovir - resistant CMV isolates in HSCT recipients with relatively common clinical treatment failure suggest that the mechanism underlying slower viral clearence is often other than mutations conferring ganciclovir resistance to the virus.

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Title of the project: National study of leukemia cell mutation and clonality in patients diagnosed with acute myeloid leukemia

Grant Agency: Ministry of Health ***Project Number:*** 15-25809A

Principal Investigator: Z. Ráčil

Co-investigators: P. Žák, M. Čulen, P. Cetkovský, P. Jindra, T. Szotkowski

Starting date: 31.5.2015 ***Duration (years):*** 4

Total funds allocated for project - Kč (thousands): 14526

Summary of 2015 results

Title of the presentation: National study of leukemia cell mutation and clonality in patients diagnosed with acute myeloid leukemia

Authors: Z. Ráčil, P. Žák

The main goal of the project is a mutational analysis of the wide spectrum of genes in a large cohort of the AML patients and determination of the detected mutations' frequency, type, mutual coexistence, clonality and stability in the course of the disease. Based on the comparison with clinical data, we will be able to design broadened classification for the prognostic/risk groups as well as to determine new markers for minimal residual disease monitoring. Apart from this, we aim to reveal novel genes, which are consistently deregulated by aberrant DNA methylation in AML with defined mutational background and determine the affected pathways.

Common part of the project - mutational analysis

1. To detect mutations and assess their frequency using the panel of 54 genes in a large cohort of AML patients at the time of diagnosis from five hematological centers in the Czech Republic and comparison of the results with the clinical data, stratification of the patients into prognostic/risk group
2. To assess the type of the mutations, analyze their mutual coexistence and clonality at the AML diagnosis and during the course of the disease (disease remission, primary resistance or relapse), and correlation with the mutational status of the separated bone marrow CD34+ cells
3. To evaluate the mutations origin (somatic/germinal) and its stability during the disease (identification of stable markers for possible MRD monitoring)

Our center doesn´t participate on subprojects A (To correlate the mutational status of a patient and corresponding xenograft and to find links between xenograft). To assess the role of mutations in repopulation of immunodeficient mice and determine if the same mechanisms apply in patient leukemogenesis or disease progression) and B (Transcriptional and DNA methylation effects of the mutations in DNA methylation regulators in AML).

Selection of the retrospective symplex and collection of the new clinical material from the curatively treated AML patiens and DNA isolation from the samples. DNA library preparation and sequencing of the first cohort of 96 samples, optimization ofthe sequencing method on the NextSeq system.

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