FNUSA ICRC

FAKULTNÍ NEMOCNICE U SV. ANNY V BRNĚ
MEZINÁRODNÍ CENTRUM KLINICKÉHO VÝZKUMU

Strategický dokument výkonného ředitele FNUSA-ICRC

2021-2025 a dál

Tvoříme budoucnost medicíny

Pavel Iványi, MBA, LL.M.

IMPRINT

Koordinace
Eva Špillingová

Design
Jiřina Kapcárová

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icrc@fnusa.cz

Obsah

BUDOUCNOST MEDICÍNY PO ROCE 2020

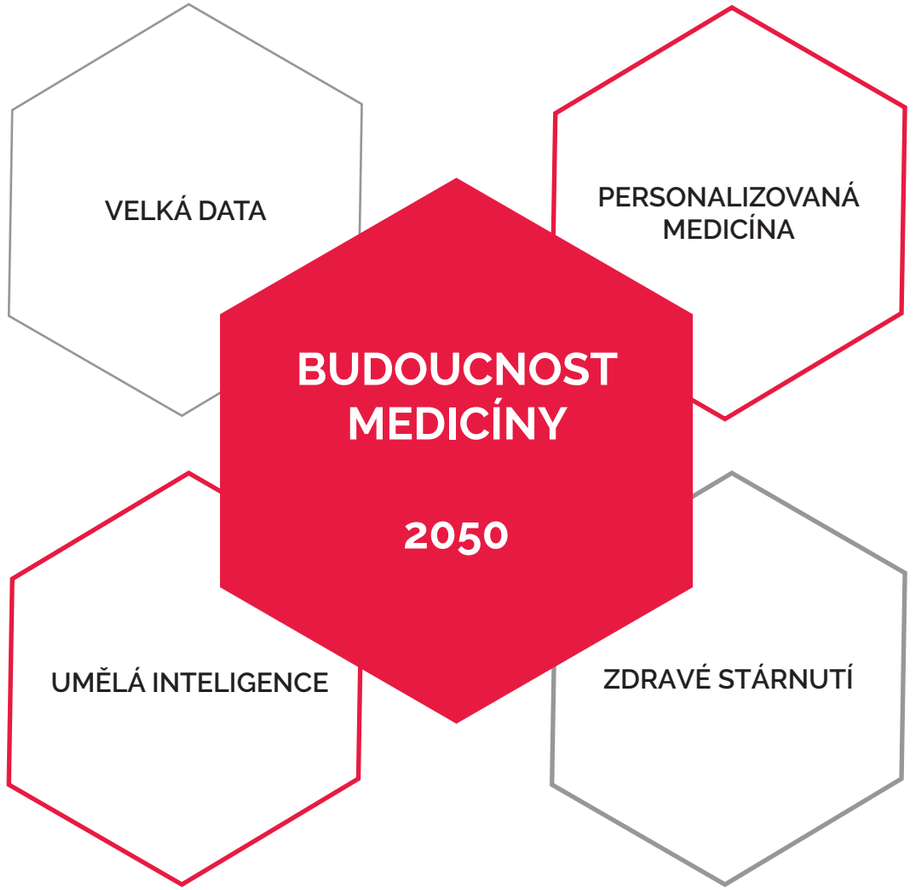
V roce 2018 zveřejnil časopis Nature[1] náhled do budoucnosti medicíny, kde v úvodu představil některé z hlavních trendů, které svět medicíny čekají. Uvedl, že „pokud se uskuteční jen zlomek toho, co je prezentováno, může se lidstvo těšit na zdravější budoucnost".

Aby se zabránilo tomu, že rezistence na antibiotika zničí pokrok, kterého lidstvo v minulém století dosáhlo, vědci závodí o doplnění antibakteriálního arzenálu. Velký význam má využití dat, která generují všudypřítomné počítače a smartphony, k lepšímu předvídání ohnisek infekčních nemocí.

Vzhledem k velkému potenciálu pro dosažení výsledku hraje prevence nemocí v medicíně stále větší roli. Intervence na ochranu lidí před chronickými onemocněními by mohla začít v prvních okamžicích po narození. A přestože se úbytek zdraví s přibývajícím věkem může zdát normální, stále probíhá debata o tom, kde končí zdravé stárnutí a kde začíná nemoc.

Snaha o větší kontrolu nad negativními reakcemi imutního systému, stejně jako snaha o vývoj technologických řešení při ochrnutí se ukazuje jako slibná. Nástup editace genomu CRISPR-Cas vyvolal naděje na široké využití genové terapie; zatím tato technologie pomáhá při hledání nových léků. Dokud bude možné překonávat překážky v přístupu k nejlepší dostupné léčbě, budoucnost medicíny může být skutečně zářivá.

Členové komunity FNUSA-ICRC – managementu, Dozorčí rady, Mezinárodního vědeckého poradního sboru a další - byli požádáni, aby napsali pár slov o tom, jak vidí vývoj medicíny v příštích 20 až 30 letech, a tím přispěli k naší vizi budoucnosti medicíny. Pochopení možných scénářů je klíčem k vytvoření naší mise. Z jejich příspěvků vzešly čtyři hlavní oblasti:



[1] Hodson, R., 2018. The future of medicine. Nature. doi:10.1038/d41586-018-02472-6

Věříme, že pokrok v molekulární a buněčné medicíně, bioinženýrství a umělé inteligenci otevírá možnosti získat dosud nedosažitelné znalosti o lidských nemocech. Navíc se zřetelem na genetický původ, kulturní specifika a vlivy prostředí. Všechny tyto poznatky budou nepochybně znamenat revoluci v moderní zdravotní péči a medicíně jako takové.

Dvě oblasti, které již nesmírně ovlivnily moderní medicínu a budou ji ovlivňovat i v následujících desetiletích: porozumění a úprava genomu a umělá inteligence v kombinaci s biomedicínskými vědami."

prof. dr. Aleš Blinc, dr. med.
University Medical Centre of Ljubljana

Reálně si dovedu představit, že dojde k užší integraci technologie do lidského těla – implantování technologie do lidské anatomie na úrovni nervových a jiných spojení díky propojení informací, zvýšení a rozšíření možností lidského těla po traumatu.
Bude dále rozvíjena globální širokopásmová síť schopná pojmout a přenášet obrovské objemy dat.
Bude existovat silná koncentrace nesmírného množství informací, které budou využity pro různé účely (snad pozitivní).

Ing. Pavel Leinveber
FNUSA-ICRC

Klinické projevy mnoha lidských onemocnění se nyní zdají být rozmanitější, než se původně očekávalo. Toto zjištění vyžaduje další klinické studie. Lidské nemoci reagují velmi odlišně na konkrétní terapeutické možnosti a v mnoha případech bude potřeba terapeutické přístupy přizpůsobit, aby lépe pomohly pacientům.

Výsledkem účinnějších preventivních opatření a pokročilých terapeutických možností v medicíně je významně rostoucí průměrný věk populace, současně však není dostatečně rozvinuté efektivní řízení zdravotní péče o seniory.

"Budou vyvinuty a implementovány nové metody, které umožní účinnou a personalizovanou léčbu závažných onemocnění. Tyto metody budou těžit z výhod velkých dat, která se v současné době shromažďují v biologii. Například proteinové sekvence získané sekvenováním nové generace nebo informace ohledně jejich aktivity a stability shromážděná vysoce výkonnými laboratorními technikami. Na tato data budou systematicky aplikovány algoritmy umělé inteligence a pro rychlý vývoj „optimálních" proteinů budou použity matematické modely.

prof. Mgr. Jiří Damborský, Dr.
FNUSA-ICRC a Loschmidtovy laboratoře

Ve způsobu, jakým se technologie dostávají k populaci, bude skok vpřed, ať už ve formě významné výpočetní síly nebo takzvaného „internetu věcí." Tyto prvky budou mít naprosto zásadní dopad na každodenní život nás všech - budou zahrnuty do všech oblastí lidského fungování a úsilí.

Ing. Pavel Leinveber
FNUSA-ICRC

"Neustále získáváme lepší porozumění o způsobu, jakým stárneme na molekulární úrovni. Toto porozumění povede k vývoji nových preventivních opatření i léčebných terapií, které prodlouží délku životního období, kdy budeme aktivní a zdraví."

prof. Mgr. Jiří Damborský, Dr.
FNUSA-ICRC a Loschmidtovy laboratoře

• Eliminace klinických projevů pokročilé aterosklerózy (infarkt myokardu, velká část ischemických cévních mozkových příhod, gangréna končetin) prostřednictvím genové terapie, přinese výhody velmi nízké hladiny LDL-cholesterolu pro široké spektrum populace,
• hlavní pokroky v léčbě rakoviny díky porozumění a úpravy kauzálních mutací, které vedou k různým typům rakoviny,
• inteligentní implantabilní technologie a spojení těla se strojovým rozhraním,
• lepší pochopení mechanismů demence a tlumení jejího postupu.

prof. dr. Aleš Blinc, dr. med.
University Medical Centre of Ljubljana

Prof. Blinc poznamenal:

"Historie nemá konce a předpovědi pro vzdálenou budoucnost jsou notoricky nepřesné - stejně jako dlouhodobé předpovědi počasí".

Tyto předpovědi nám však pomáhají vytvářet a definovat naši misi. Misi, která identifikuje nejdůležitější prvky strategie FNUSA-ICRC.

MISE FNUSA-ICRC

Naším posláním je být profesionální, mezinárodně uznávanou a viditelnou institucí s vynikajícím výzkumem, který je založen na vysoce kvalitní výzkumné infrastruktuře, a atraktivním zaměstnavatelem s vysokým standardem profesionálního prostředí.

Věříme, že můžeme zlepšit zdravotní péči a kvalitu života propojením klinické péče, výzkumu, vývoje, vzdělávání, a spolupráce s průmyslovým sektorem. Naším cílem je podpořit inovace ve zdravotnictví, objevy v chápání progrese lidských onemocnění a zlepšení prevence, diagnostiky a léčby těchto onemocnění s přímým dopadem na zdravotní péči.

Na základě vizí o budoucím vývoji a poslání, ke kterému jsme se přihlásili, předkládám strategický dokument FNUSA-ICRC pro rok 2021 a následující období. Samozřejmě to je a bude živý materiál, doplněný strategiemi všech výzkumných týmů a Core Facilit. Společně tyto dokumenty nabízejí jak vodítko, tak vhled na to, kam FNUSA-ICRC směřuje.

Pavel Iványi, MBA, LL.M.
Výkonný ředitel Mezinárodního centra klinického výzkumu Fakultní nemocnice u sv. Anny v Brně

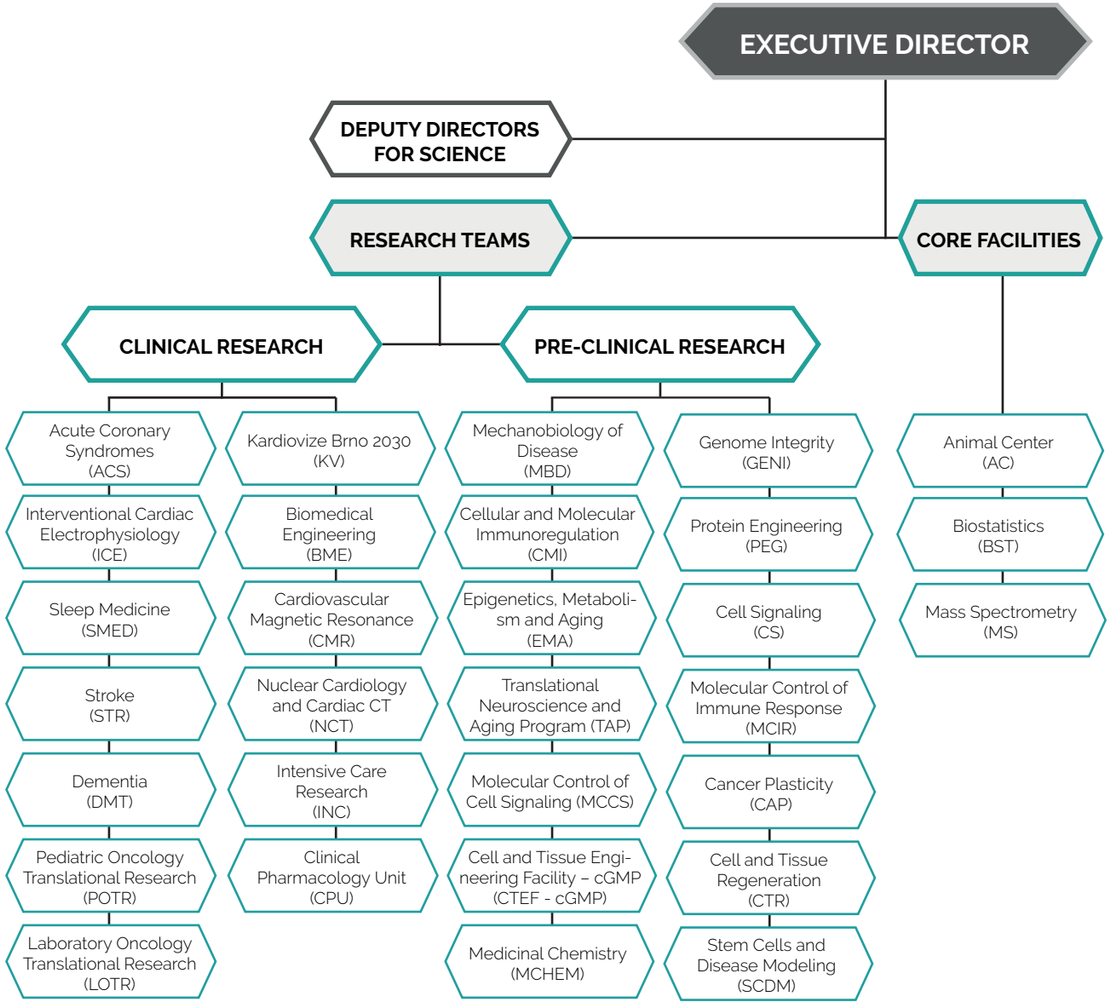
KDO JSME

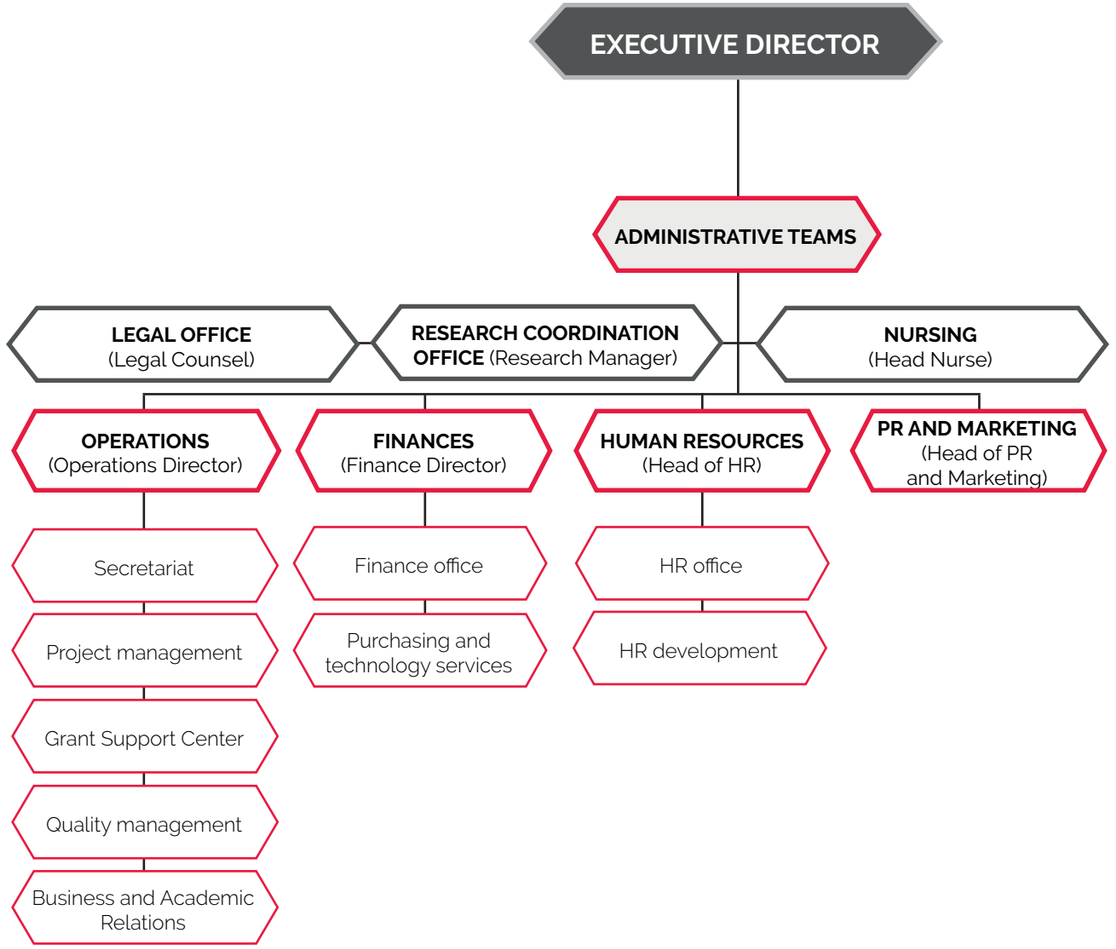
Mezinárodní centrum klinického výzkumu (FNUSA-ICRC) bylo založeno v roce 2011 jako nedílná součást Fakultní nemocnice u sv. Anny v Brně (FNUSA) a je jedinou infrastrukturou medicínského výzkumu financovanou EU v České republice. FNUSA-ICRC bylo vybudováno jako jedinečná výzkumná infrastruktura v rámci FNUSA za účelem aplikace základních vědeckých poznatků do klinických postupů, současně však i hledání příčin klinických nálezů v laboratorních podmínkách pre-klinického výzkumu. FNUSA-ICRC má autonomii v oblasti výzkumu, řízení a financí s cílem integrovat mezinárodní multidisciplinární výzkum se vzděláváním a výcvikem prostřednictvím intenzivní mezinárodní výměny znalostí a personálu ve prospěch pacientů nejen ve FNUSA.
Strategické partnerství s Mayo Clinic mělo významnou roli v úspěšném zřízení výzkumného centra. Klíčovým je od počátku aplikace „motta tří štítů": integrace výzkumu, klinické praxe a lékařského vzdělávání do přístupu zaměřeného na pacienta.

Během 10 let od založení vybudovalo FNUSA-ICRC infrastrukturu pro výzkum, mezinárodně konkurenceschopné výzkumné portfolio, představilo management řízený Dozorčí radou a zahájilo hodnocení výzkumných týmů Mezinárodním vědeckým poradním sborem (ISAB). Vytvořili jsme síť spolupráce s akademickou obcí a průmyslem a patentovali jsme naše první objevy. FNUSA-ICRC se stalo centrem excelence v oblasti klinického, translačního a pre-klinického výzkumu. V současné době je hrdým zaměstnavatelem více než 480 lidí (290 FTE) z 30 zemí.

ISAB se skládá z mezinárodně uznávaných odborníků v oblasti lékařských věd. Úlohou ISAB je poskytovat rady a doporučení vedení FNUSA-ICRC v otázkách dlouhodobé strategie, doporučovat klíčové priority výzkumu a plánování a hodnotit výzkumné týmy.

FNUSA-ICRC přímo sleduje cíle Inovační strategie České republiky 2019-2030 v oblasti inovačních a výzkumných center (Country for Excellence). Jedním z hlavních cílů je podpora klíčových trendů v klinické medicíně a bio-medicíně. Jsme jediné takové „centrum excelence" v oblasti medicíny v České republice financované z Národního programu udržitelnosti (NPU II).


EXECUTIVE DIRECTOR
DEPUTY DIRECTORS FOR SCIENCE
RESEARCH TEAMS
CORE FACILITIES
CLINICAL RESEARCH
PRE-CLINICAL RESEARCH
Acute Coronary Syndromes (ACS)
Interventional Cardiac Electrophysiology (ICE)
Sleep Medicine (SMED)
Stroke (STR)
Dementia (DMT)
Pediatric Oncology Translational Research (POTR)
Laboratory Oncology Translational Research (LOTR)
Kardiovize Brno 2030 (KV)
Biomedical Engineering (BME)
Cardiovascular Magnetic Resonance (CMR)
Nuclear Cardiology and Cardiac CT (NCT)
Intensive Care Research (INC)
Clinical Pharmacology Unit (CPU)
Mechanobiology of Disease (MBD)
Cellular and Molecular Immunoregulation (CMI)
Epigenetics, Metabolism and Aging (EMA)
Translational Neuroscience and Aging Program (TAP)
Molecular Control of Cell Signaling (MCCS)
Cell and Tissue Engineering Facility – cGMP (CTEF - cGMP)
Medicinal Chemistry (MCHEM)
Genome Integrity (GENI)
Protein Engineering (PEG)
Cell Signaling (CS)
Molecular Control of Immune Response (MCIR)
Cancer Plasticity (CAP)
Cell and Tissue Regeneration (CTR)
Stem Cells and Disease Modeling (SCDM)
Animal Center (AC)
Biostatistics (BST)
Mass Spectrometry (MS)


EXECUTIVE DIRECTOR
ADMINISTRATIVE TEAMS
LEGAL OFFICE (Legal Counsel)
RESEARCH COORDINATION OFFICE (Research Manager)
NURSING (Head Nurse)
OPERATIONS (Operations Director)
FINANCES (Finance Director)
HUMAN RESOURCES (Head of HR)
PR AND MARKETING (Head of PR and Marketing)
Secretariat
Project management
Grant Support Center
Quality management
Business and Academic Relations
Finance office
Purchasing and technology services
HR office
HR development

FNUSA-ICRC V ČÍSLECH

Naši výzkumníci publikovali téměř **1 500** článků v časopisech indexovaných na Web of Science, s více než **18 400** citacemi.

Více než **65%** těchto článků je výsledkem spolupráce s mezinárodními partnery.

Téměř **40%** článků je v Q1 časopisech.

Téměř **50%** je publikováno v režimu Open Access.

V minulém období jsme získali **3** patenty a vytvořili více než **50** dalších aplikovaných výsledků jako je software, užitný vzor apod.

Výsledky jsou výstupem více než **120** národních i mezinárodních projektů, které získali klinici a výzkumníci FNUSA-ICRC.

Oddělení klinických studií koordinovalo více než **500** klinických studií, které přinášejí pacientům nové terapeutické možnosti.

Více než **8 000** pacientů každoročně benefituje z vybudované technologické infrastruktury.

FNUSA-ICRC – HRDÝ ČLEN MEZINÁRODNÍCH SÍTÍ A VÝZKUMNÝCH INFRASTRUKTUR

Alliance4Life
Alliance for Life Sciences: Closing Research and Innovation Divide in the European Union

HBM4EU
Human Biomonitoring Initiative

EATRIS
European Infrastructure for Translational Medicine

RES-Q
Register of Stroke Care Quality

FNUSA ICRC
FAKULTNÍ NEMOCNICE U SV. ANNY V BRNĚ
MEZINÁRODNÍ CENTRUM KLINICKÉHO VÝZKUMU

ECRIN
European Clinical Research Infrastructure Network

ESO-EAST
East-European Network of the European Stroke Organization

ELIXIR
European Life-sciences Infrastructure for Biological Information

ESADA
European Sleep Apnea Database

VÝZKUM – DŮVOD NAŠÍ EXISTENCE

FNUSA-ICRC se zaměřuje na výzkum orientovaný na pacienta s důrazem na translační medicínu.
Výzkum je řízen následujícími 3 pilíři:
• KLINICKÉ VÝZKUMNÉ týmy se zaměřením na pokrok v pochopení a léčbě hlavních lidských chorob. Většina z nich je součástí klinických oddělení FNUSA.
• TÝMY PRE-KLINICKÉHO VÝZKUMU převádí klinické poznatky do buněčných a zvířecích modelů lidských onemocnění a zpět, s konečným cílem navrhnout nové diagnostické metody, a identifikovat terapeutická řešení. Pracují na prohlubování porozumění lidským chorobám a na vývoji nových nástrojů souvisejících s vylepšenou diagnostikou a terapií.
• CORE FACILITY fungují jako servisní platformy poskytující sofistikovanou podporu výzkumu od správy dat po identifikaci nových biomarkerů. Kromě toho jsou Core Facility klíčovým synergickým partnerem klinických studií a některé také provádějí vlastní výzkum.

Podle údajů Českého statistického úřadu jsou nejčastějšími příčinami úmrtí v České republice srdeční choroby, maligní novotvary, cévní mozkové choroby, Alzheimerova choroba a další demence. Výzkum FNUSA-ICRC je zaměřen na oblast neurologického, kardiovaskulárního, onkologického a interdisciplinárního výzkumu, se zvláštním důrazem na zdravé stárnutí. FNUSA-ICRC má v České republice jedinečné postavení s řadou významných grantů zaměřených na stárnutí.

Neurologický výzkum je zaměřen na dvě hlavní oblasti – cévní mozkovou příhodu a demenci.
Výzkumné aktivity v oblasti cévní mozkové příhody zahrnují vývoj a implementaci inovativní léčby a prevence akutní ischemické cévní mozkové příhody. Cílem je snížit dopady cévní mozkové příhody, zlepšit následné schopnosti pacientů a dosáhnout lepší kvality života po cévní mozkové příhodě.
Výzkum demence je založen na české studii stárnutí mozku – jedinečné národní, dlouhodobé prospektivní populační studii s cílem studovat časné funkční, metabolické a strukturální biomarkery Alzheimerovy choroby a dalších neurodegenerativních onemocnění.

Hlavním cílem **onkologického výzkumu** je porozumět biologii rakoviny, abychom zajistili účinnou prevenci a léčbu prostřednictvím přístupu Bench-to-Bedside. Toto mezioborové úsilí zahrnuje několik konkrétních témat, včetně rakovinných kmenových buněk, plasticity rakovinných buněk, buněčné signalizace, epigenetických mechanismů nebo recidivy rakoviny a chemoterapie. Ve výsledku se snažíme nabídnout inovativní terapeutické koncepty a prognostické nástroje pro klinickou onkologii se zvláštním důrazem na dětskou onkologii. Jedním ze společných cílů je vývoj specifické léčby nádorů rezistentních na terapii a také syntetické usmrcování geneticky podmíněných typů rakoviny.

Kardiovýzkum je zaměřen jak na intervenční léčbu, tak na neinvazivní diagnostiku například infarktu myokardu, či srdečních arytmií. Významným výsledkem úzké spolupráce s Mayo Clinic je vývoj nových katétrů pro ablace srdečních arytmií. Naši vědci jsou průkopníky primárního perkutánního koronárního a arytmologického intervenčního programu v České republice a zaměřují se na neustálé zlepšování neinvazivní diagnostiky. Inovace zobrazovacích protokolů pro hodnocení ischémie myokardu, ať už prostřednictvím magnetické resonance, nebo nukleární kardiologie, je jednou z nejdůležitějších oblastí výzkumu. Dalším důležitým směrem je studium role spánkové apnoe a její léčby při infarktu myokardu, srdečním selhání nebo náhlé srdeční smrti. Pre-klinický výzkum vychází z našich dlouholetých zkušeností s lidskými pluripotentními kmenovými buňkami, což je vynikající nástroj pro vytváření in vitro modelů srdečních onemocnění. Zvláštní pozornost je také věnována chorobám, které vedou ke kardiomyopatii a srdečnímu selhání.

Jedním z hlavních cílů je identifikace buněčných mechanosenzorů a / nebo vhodných biomarkerů, které se podílejí na vzniku srdečních patologií.

Interdisciplinární výzkum se zaměřuje na konkrétní biomedicínská témata spojená s hlavními směry našeho výzkumu. Zvláštní pozornost je věnována pluripotentním kmenovým buňkám, jak embryonálním, tak indukovaným, a dospělým kmenovým typům, které jsou rovněž studovány. Mechanismy zánětlivých procesů a imunologie sepse spojuje naše kliniky, pre-klinické výzkumníky a translační odborníky. Dalším příkladem společného cíle je vývoj nových protizánětlivých léků a strategií pro terapeutickou kontrolu zánětlivých poruch. Samostatná pozornost je věnována buněčné signalizaci, konkrétně funkci receptorových tyrosin kináz (RTK), hlavnímu molekulárnímu nástroji komunikace mezi buňkami. Medicínská chemie nabízí cenné nástroje pro další specifický výzkum a / nebo klinické studie věnované přípravě netriviálních malých molekul spolu s proteinovým a metabolickým inženýrstvím. Zvláštní důraz je kladen na stárnutí s více odkazy na kardiovaskulární, neurologické, neurodegenerativní a další onemocnění.

EXCELENTNÍ VÝSLEDKY VÝZKUMU

KARDIOVIZE BRNO 2030
Jedinečný výzkumný program zaměřený na identifikaci hlavních rizikových faktorů závažných srdečních chorob a jejich minimalizaci prostřednictvím preventivních programů, které zlepšují zdraví široké veřejnosti. Osloveno bylo více než 2000 dobrovolníků.

Spánková laboratoř
Jediná evropská certifikovaná kardiovaskulární laboratoř zaměřená na léčbu poruch dýchaní ve spánku.

PanCareFollow Up project
Regionální model pro dlouhodobé sledování mladých post onkologických pacientů při přechodu z pediatrické péče na péči pro dospělé jako platforma ke studiu dlouhodobých toxicit, rizikových faktorů a možných způsobů, jak snížit zátěž léčby.

Mezinárodní registr RES-Q pacientů s cévní mozkovou příhodou
Více než 200 000 registrovaných pacientů.

Jedinečné softwarové nástroje
Ve výzkumu Alzheimerovy choroby, akutní cévní mozkové příhody, predikce účinku specifických mutací DNA na lidské zdraví.

Biomedicínské inženýrství
Jedinečná infrastruktura umožňuje získávání velmi slabých a širokospektrálních elektrofyziologických signálů v České republice a ve střední Evropě.

Intervenční srdeční elektrofyziologie
Unikátní stereotaktický navigační robot umožňuje přesnější a šetrnější léčbu srdečních arytmií.

ZAMĚŘENÍ BUDOUCÍHO VÝZKUMU

Srdeční infarkty a arytmie	Poruchy spánku	Cévní mozková příhoda
Demence	Zánětlivé mechanismy při sepsi	Disregulace imunitního systému
Epigenetika gastroenterického systému	Achondroplázie	Vybrané typy rakoviny - medulloblastoma etc.

Toto spektrum nemocí bude i nadále objektem našich výzkumných zájmů, zejména pokud jde o:
- **Charakterizaci klinických fenotypů** prostřednictvím rozsáhlých nejmodernějších klinických databází a databází vzorků,
- **vývoj nových a zdokonalení stávajících diagnostických přístupů** - nové biomarkery, pokročilé elektrofyziologické přístupy, nové zobrazovací protokoly,
- zavádění **správné klinické praxe**,
- Identifikaci účinných **preventivních opatření** a pokrok v **terapeutickém úsilí** - testování jedinečných léků, poskytování špičkových klinických studií, vývoj a testování nových terapeutických zařízení.

VÝZKUM ZAMĚŘENÝ NA PACIENTA S DŮRAZEM NA TRANSLAČNÍ MEDICÍNU A STÁRNUTÍ

ODBORNÉ ZNALOSTI V

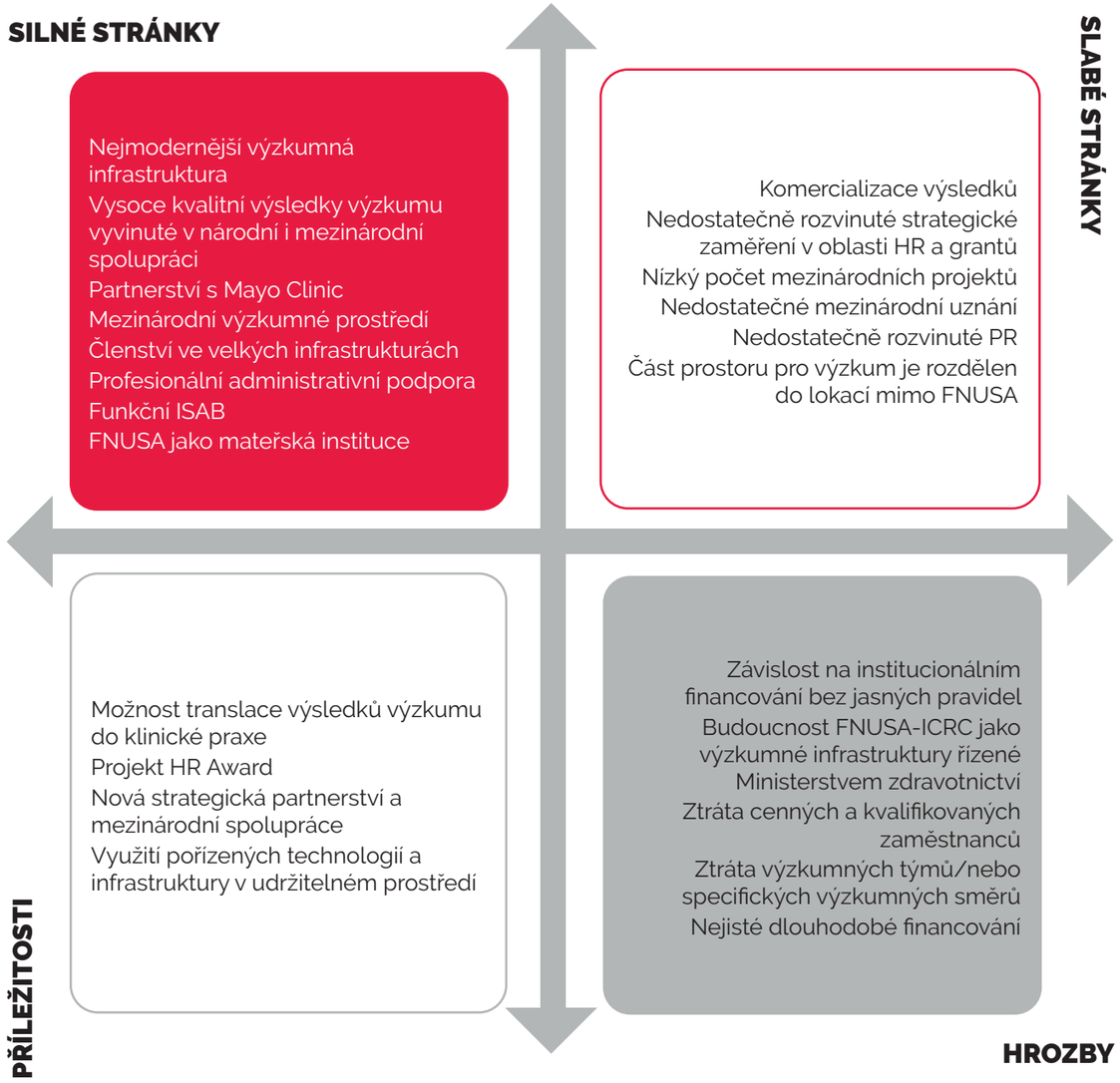
- CHEMII
- MOLEKULÁRNÍ A BUNĚČNÉ BIOLOGII
- IMUNOLOGII
- EPIGENETICE
- BUNĚČNÉ SIGNALIZACI
- NEUROVĚDÁCH
- MECHANOBIOLOGII
- ONKOLOGII

• **Pokročit v porozumění mechanismů**, které jsou základem rozvoje a progrese nemocí, a převedení nových poznatků do klinických aplikací a do praxe.
• Posunout vývoj a poznání řady molekul, signálních drah, buněčných a zvířecích modelů souvisejících s lidskými chorobami, které jsou **relevantní pro translaci do klinického výzkumu**. Od buněčných modelů hypertrofie myokardu a arytmií, přes buněčné modely poškození DNA a epigenetických odchylek až po nové zvířecí modely mrtvice a Alzheimerovy choroby.

PŘEVÁDĚNÍ OBJEVŮ VÝZKUMU V MOLEKULÁRNÍ A PRECIZNÍ MEDICÍNĚ

• **Komplexní přístup Bench-to-Bedside** se zvláštním důrazem na stárnutí, lidské choroby související s věkem a stárnutím.
• Od **nových diagnostických biomarkerů** a dalších diagnostických nástrojů po **několik nových molekul** s léčivými vlastnostmi a originálními terapeutickými přístupy.
• Pro maximalizaci tohoto úsilí plánujeme průběžnou **aktualizaci a rozšiřování** klinických a preklinických databází.

SWOT ANALÝZA



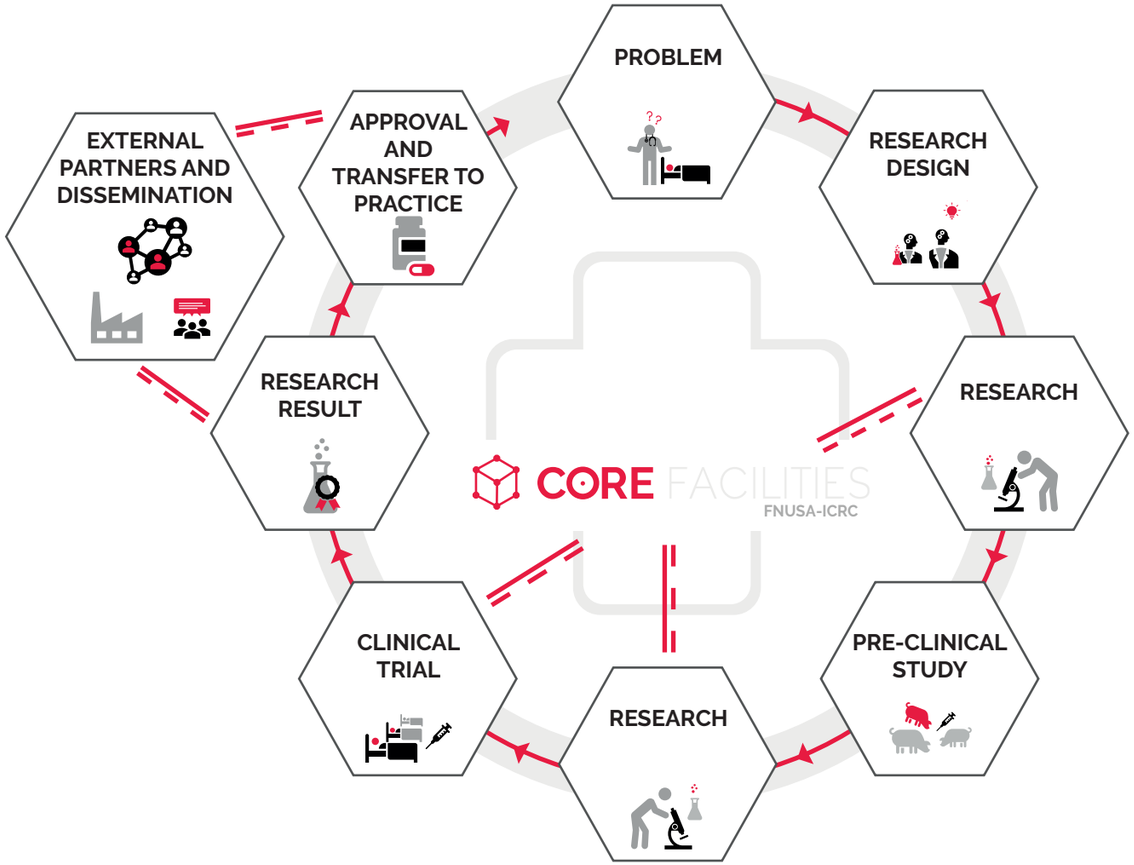
NAŠE VIZE

Profesionální, mezinárodně uznávaná instituce s vynikajícím výzkumem, založená na vysoce kvalitní výzkumné infrastruktuře a nabízející atraktivní zaměstnání v profesionálním prostředí s vysokým standardem.

2030

NAŠE VIZE JE

- Zlepšit zdravotní péči a kvalitu života propojením klinické péče, výzkumu a vývoje, vzdělávání a spolupráce s průmyslovým sektorem.
- Posílit inovace ve zdravotnictví s objevy v porozumění vývoji a progrese lidských onemocnění.
- Zlepšit prevenci, diagnostiku a terapii lidských chorob s přímým dopadem na zdravotní péči.
- Posílit pozici FNUSA-ICRC na mapě uznávaných translačních výzkumných institucí.
- Být respektovaným partnerem při rozvoji regionálních a národních strategií v oblasti medicíny a biologických věd.
- Aktivně přispívat společnosti prostřednictvím vzdělávání, přenosu znalostí do praxe a rozvíjením veřejné debaty.
- Stát se atraktivním zaměstnavatelem s profesionálním a otevřeným pracovním prostředím, silnou firemní identitou a vnitřní kulturou.


PROBLEM
RESEARCH DESIGN
RESEARCH
PRE-CLINICAL STUDY
RESEARCH
CLINICAL TRIAL
RESEARCH RESULT
APPROVAL AND TRANSFER TO PRACTICE
EXTERNAL PARTNERS AND DISSEMINATION
CORE FACILITIES
FNUSA-ICRC

STRATEGICKÁ PRIORITA EXCELENTNÍ VÝZKUM

Naším strategickým cílem je konsolidovat dosavadní vědecké úspěchy a posílit pozici centra jako mezinárodně uznávané referenční instituce s hlavním zaměřením na:

- nárůst výsledků výzkumu a kvality publikací
- transfer výsledků výzkumu do klinické péče
- dosažení ekonomického dopadu výsledků výzkumu
- kontrolu a hodnocení výzkumných týmů na základě zpětné vazby ISAB (Haldonův princip)
- vysokou kvalita výzkumné infrastruktury

Úspěchem FNUSA-ICRC je nezávislost, svoboda a vysoká úroveň odpovědnosti daná výzkumným týmům a vedoucím výzkumných týmů. Jedná se o důležitý a jedinečný princip, který zachováme za každou cenu. Strategie, cíle a plány všech výzkumných týmů jsou nedílnou součástí konceptu naší strategie a jsou přílohou tohoto strategickému dokumentu.

V nadcházejícím období doplníme naši organizační strukturu o představitele managementu vědy a výzkumu. Může to být vědecký ředitel, tým zástupců ředitele nebo vědecká rada s výkonnými povinnostmi souvisejícími s definováním strategie a řízení výzkumu.

Dobrá praxe vědeckého publikování a strategie Open Access, která bude nastavena v souladu s Národní strategií otevřeného přístupu k vědeckým informacím České republiky, patří k hlavním zásadám FNUSA-ICRC.

FNUSA-ICRC vyvinula jedinečnou moderní výzkumnou infrastrukturu, která je přímo spojena s pacienty a translačním výzkumem. Tento technologický most spojuje klinickou péči s hi-tech laboratořemi, Animálním centrem a preklinickým výzkumem a vede ke klinickým aplikacím. Specifickými laboratořemi jsou tkáňové laboratoře cTEF, laboratoře HiSEM pro vysoce citlivá měření a NIOBE II pro magnetickou navigaci katétrů. FNUSA-ICRC vyvinula koncepci Core Facilit poskytujících efektivní způsob, jak výzkumníkům zpřístupnit nejmodernější přístroje a služby. Koncept Core Facilit budeme dále rozvíjet.

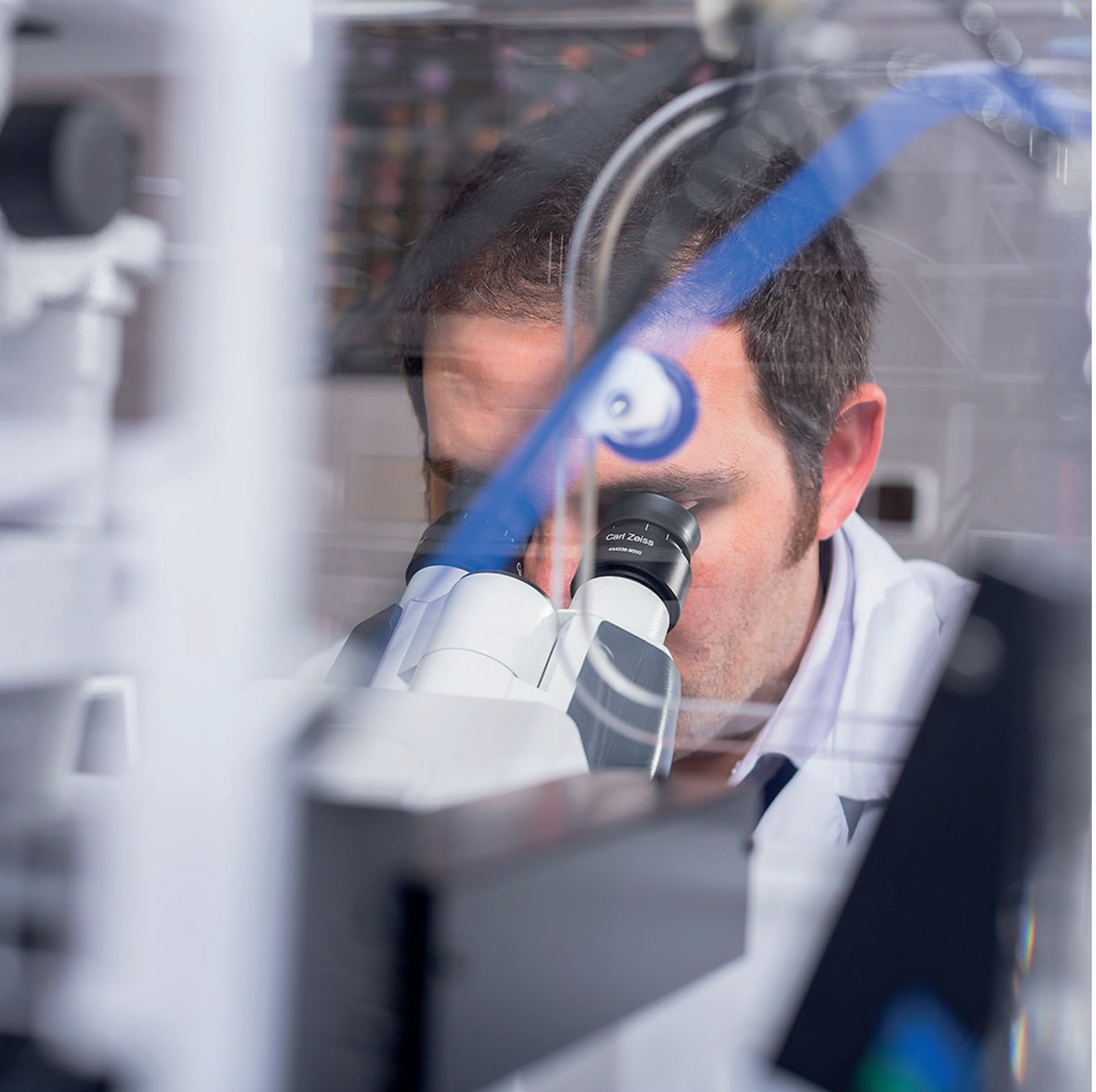
Naše hlavní Core Facility jsou Animální centrum, Biostatistika a Mass Spectrometry. Animální centrum je rozděleno do několika lokalit, z nichž některé se ukazují jako méně ideální. Toto nastavení tedy budeme dále optimalizovat. Animální centrum by mělo vyrůst v zařízení nabízející služby péče o zvířata všem výzkumným týmům v excelentní kvalitě, s odpovídající certifikací, flexibilním přístupem a konkurenceschopnými náklady. Mass Spectrometry se v současnosti reviduje kvůli nutnosti investice do nového vybavení. Hledáme partnerství s další institucí za účelem sdílení investičních a provozních nákladů. Další Core Facility (Zařízení pro buněčné a tkáňové inženýrství, Jednotka klinické farmakologie a Biomedicínského inženýrství) budou zařazeny mezi výzkumné týmy pre-klinického výzkumu. Budou od nich vyžadovány vlastní výzkumné projekty a zajištění grantového financování, zároveň budou i nadále nabízet služby a svá zařízení. Oddělení klinických studií, které nabízí služby jak FNUSA-ICRC, tak klinikám FNUSA, bude podřízeno oddělení Obchodních a akademických vztahů, kde soustředíme veškeré obchodní činnosti, správu a služby externí spolupráce.

Detailní hodnocení priorit výzkumu a výsledků výzkumných týmů FNUSA-ICRC je založeno na standardizovaném procesu hodnocení. Férové, transparentní, specifické, podrobné a hodnotné pro zúčastněné týmy. Vědci by měli být hodnoceni zase pouze vědci. Výzkum je hodnocen ve smysluplných intervalech s klíčovou rolí ISAB. Hodnocení mají být zdrojem informací pro management a výzkumné týmy. Mohou být zdrojem pro stanovení priorit a nástrojem pro výběr nejlepších týmů pro posílení a podporu.

Spolupráce s průmyslem je klíčovým prvkem komercializace našich výsledků. Chceme zapojit průmysl do našeho výzkumu v mnohem ranějších fázích, než tomu bylo dříve. Školící programy pro vědce podpoří jejich všeobecné znalosti o komerční hodnotě výzkumu. Pro období 2021-2023 je plánováno vyvinutí více než 40 aplikovaných výsledků.
FNUSA-ICRC úzce spolupracuje s rozsáhlou sítí národních a mezinárodních partnerů, stejně jako s významnými akademickými institucemi a komerčními partnery. Aktivní účast v mezinárodních platformách a výzkumných infrastrukturách je klíčem k úspěchu. FNUSA-ICRC je jednou ze zakládajících výzkumných institucí Alliance4Life, konsorcia výzkumných institucí z EU-13 v oblasti přírodních věd, a je aktivním členem sedmi mezinárodních výzkumných infrastruktur. Naši vědci se podíleli na více než 60 společných projektech s finančním podílem téměř 500 mil. Kč. Naším cílem je zvýšit mezinárodní viditelnost centra podporou výsledků výzkumů, řešením aktuálních problémů v medicíně a přírodních vědách, zdůrazňováním vzdělávání studentů a účastí na mezinárodních projektech. Mezinárodní mobilita zaměstnanců vytváří náš vlastní diplomatický sbor.
Pro nadcházející období posilíme naši aktivní roli ve stávajících partnerstvích a konsorciích, zejména v kontextu nadcházejícího klastrování velkých výzkumných infrastruktur s cílem rozšířit zapojení FNUSA-ICRC do nových výzkumných infrastruktur a pokud možno být koordinační institucí, nejen partnerskou. FNUSA-ICRC má v nadcházejícím období v úmyslu podílet se na přípravě regionálních a národních strategií týkajících se výzkumu a vývoje, čímž přispěje ke směřování národních politik a financování výzkumu.

Budeme pokračovat a rozšiřovat mezinárodní akademickou spolupráci, např. s Mayo Clinic a Yale University, budeme zkoumat nové možnosti, jak se stát významným partnerem v mezinárodní akademické spolupráci.

Vzdělávání, stáže a kariérní rozvoj studentů na všech úrovních jsou jednou z hlavních priorit FNUSA-ICRC. Jako nedílná součást FNUSA se FNUSA-ICRC podílí na vzdělávání vysokoškolských studentů v úzké spolupráci s Lékařskou fakultou MU. Projekt Akademie FNUSA-ICRC je prostředkem k motivaci nadaných studentů středních a vysokých škol k vědecké kariéře v oblasti lékařského výzkumu, jakož i platformou pro popularizaci výsledků výzkumu. Akademie FNUSA-ICRC bude dále rozvíjena jako strukturovaný koncept popularizace, vzdělávání, motivace a zapojení studentů do výzkumných aktivit FNUSA-ICRC v rámci projektu HR Award Dále budeme pokračovat v zapojení studentů a doktorandů do výzkumu prostřednictvím stáží a zaměstnání ve výzkumných týmech a Core Facilitách



NAŠE HLAVNÍ CÍLE V EXCELENTNÍM VÝZKUMU

Podporovat priority výzkumu ve FNUSA-ICRC
- Podpora jasně definovaných priorit výzkumných týmů

Zvýšit současnou vysokou kvalitu výzkumných infrastruktur
- Sdílení investic a reinvestic do výzkumných infrastruktur

Hodnocení výzkumu a zvýšení kvality výzkumu a publikací
- Pravidelné hodnocení týmů Mezinárodním vědeckým poradním sborem
- Zvýšení podílu publikací v T5, T10, Q1 a nad mediánem

Vylepšit naši mezinárodní stopu
- Posílit současný výzkum a akademickou spolupráci
- Identifikovat nové příležitosti pro strategickou akademickou spolupráci a partnerství
- Získat mezinárodní výzkumné granty jako hlavní příjemce nebo partner
- Zvýšit počet členství / koordinace konsorcií

Zvýšení ekonomického dopadu výsledků výzkumu
- Počet udělených patentů a užitných / průmyslových vzorů
- Objem příjmů z komercializace a smluvního výzkumu

Posílit pozici FNUSA-ICRC jako partnera pro tvorbu politiky na regionální a národní úrovni
- Politické dokumenty vytvořené ve spolupráci s FNUSA-ICRC
- Účast na konferencích na národní a mezinárodní úrovni

Podpora vzdělávání aktivním šířením výsledků výzkumu a popularizací vědy
- Počet účastníků Akademie FNUSA-ICRC – studenti středních škol, bakalářských a magisterských studijních programů
- Počet studentů a stážistů vzdělávaných nebo mentorovaných výzkumnými pracovníky FNUSA-ICRC
- Počet veřejných akcí pořádaných FNUSA-ICRC a akcí s účastí FNUSA-ICRC

HLAVNÍ NÁSTROJE

- Revize a další **rozvoj pravidelného hodnocení ISAB** pro zajištění jeho vyšší důvěryhodnosti.

- **Dokončení hodnotící databáze** v souladu s potřebami uživatelů na všech úrovních - hodnotitelé, výzkumníci, administrativní podpora, management FNUSA-ICRC.

- Podpora **mezinárodních partnerství a spolupráce**, upevnění stávajících partnerství a aktivní vyhledávání nových příležitostí.

- Vytvoření a implementace strategie Open Access v souladu s požadavky Národní strategie otevřeného přístupu České republiky k vědeckým informacím.

- **Udržitelný finanční model Core Facilit** včetně plánu reinvestic a poplatků za využívání služeb.

- **Aktivní členství v mezinárodních výzkumných infrastrukturách** a účast na jejich činnostech, včetně dalšího rozvoje, sdílení osvědčených postupů a vytváření sítí zaměstnanců na všech úrovních.

- **Podpora infrastruktury a administrativních služeb FNUSA-ICRC** pro interní i možné externí klienty.

- Budování **pevných vztahů se zúčastněnými stranami a tvůrci politik** na regionální a národní úrovni, aktivní komunikace s ministerstvy a dalšími příslušnými institucemi v oblasti medicínského výzkumu a přírodních věd.

- **Rozvinutí činnosti Akademie FNUSA-ICRC** a popularizace vědecké kariéry mezi studenty


LINET

STRATEGICKÁ PRIORITA PROFESIONÁLNÍ MANAGEMENT

Cílená administrativní podpora je klíčovým faktorem pro bezproblémový provoz jakéhokoli výzkumného centra. Ve FNUSA-ICRC jsou kompetence rozděleny do několika logických jednotek umožňujících jeho efektivní řízení. Odpovědnosti jsou jasně definovány, což zabraňuje jejich překrývání. Za agendu lidských zdrojů odpovídá oddělení HR. Provoz je řízen provozním ředitelem, který odpovídá za každodenní administrativu, podporu grantů a řízení projektů. Finance spravuje Finanční oddělení, agendu rozvoje spolupráce s podnikovou sférou řídí oddělní Obchodních a akademických vztahů, a to včetně transferu technologií a klinických studií. Za výzkumné výsledky, bibliometrii a hodnocení výzkumu odpovídá Oddělení pro koordinaci výzkumu.

FNUSA-ICRC je nedílnou součástí Fakultní nemocnice u sv. Anny v Brně. FNUSA zajišťuje podporu FNUSA-ICRC v technických záležitostech, údržbě, účetnictví a zadávání veřejných zakázek. Symbióza FNUSA a FNUSA-ICRC je zásadní - klinický výzkum je prováděn na pacientech na klinikách; nemocnice těží z moderní technologické infrastruktury, která se částečně používá pro klinickou péči; výsledky výzkumu jsou rychle přeneseny do klinické péče a zlepšují poskytované standardy.

Náklady na administrativní oblast prošly v roce 2020 velkou revizí, což vedlo k jejich výraznému snížení. Budeme i nadále sledovat míru těchto nákladů a udržovat flexibilní a efektivní organizaci administrativy sloužící pro podporu výzkumu. Věříme, že nová organizace administrativy bude vhodnou podporou pro FNUSA-ICRC v klíčových administrativních úkolech a povinnostech. Dosáhne úrovně nákladů odpovídající celkové velikosti centra a také úrovně, kde bude další snížení možné pouze s důsledkem ohrožení kvality a spolehlivosti prováděných administrativních úkolů.

Pochopení a sdílení stejných hodnot pomáhá maximalizovat vnitřní úsilí o dosažení stanovených cílů. Používáme etický kodex a komunikační principy - tato pravidla poskytují doporučení pro všechny zaměstnance a pomáhají udržovat úroveň spolupráce, profesionálního přístupu a efektivity celého systému. Jako nástroj zpětné vazby jsme implementovali systém řízení stížností, který pomáhá shromažďovat podněty z celé instituce.

Naše nadcházející výzvy jsou silně spojeny s implementací HR standardů. Jejich cílem je posílení strategického rozvoje FNUSA-ICRC prostřednictvím institucionálního nastavení podmínek řízení v souladu s mezinárodními standardy kvality a HR Award. HR Award rovněž zahrnuje přijetí strategie rozvoje lidských zdrojů, která bude základem pro udržitelný systém průběžného vzdělávání zaměstnanců ve výzkumu a vývoji.

Řízení kvality se bude zabývat certifikací ISO 9001, která bude zahrnovat nová zařízení a environmentální management. Rostoucí datové kohorty v epidemiologických studiích vyžadují přesně definovanou a kontrolovanou správu dat. Vnitřní výbor pro kvalitu FNUSA-ICRC definuje priority v rámci předběžné analýzy, která byla dokončena spolu s přípravou HR Award.

Profesionální PR strategie je nezbytnou součástí každé výzkumné instituce, která chce ovlivňovat oblasti lékařského výzkumu. Naším cílem je efektivní šíření výsledků výzkumu a osvědčených postupů. To zahrnuje moderní webové stránky, sociální média, profesionální propagační materiály a aktivní vyhledávání nových propagačních kanálů.

NAŠE HLAVNÍ CÍLE V PROFESIONÁLNÍM MANAGEMENTU

Konsolidace a další rozvoj profesionálních administrativních služeb

Proaktivní administrativní služby zaměřené na přínos pro výzkumné pracovníky
Udržování vysoké úrovně kvality se sníženým počtem zaměstnanců prostřednictvím vylepšených a optimalizovaných pracovních procesů

Efektivní politika PR a interní komunikace

Zvýšení počtu mediálních výstupů
Zlepšení kvality mediálních výstupů s výraznějším zapojením vědců
Jasná interní komunikace, transparentnost a přístup k informacím

Personální politika a jasné definování personálních procesů

Revize všech předpisů personální politiky a zajištění jejich maximální uživatelské přívětivosti
Udržení nízké fluktuace zaměstnanců
Poskytování přehledů benefitů a jejich využití pro všechny zaměstnance
Revize kritérií pro nábor zaměstnanců a zajištění flexibility
Udržení a případné navýšení počtu vynikajících mezinárodních vědců

Efektivní řízení kvality

Vytvoření efektivní strategie pro řízení kvality

Správa velkých dat

Vytvoření efektivní strategie pro správu dat

HLAVNÍ NÁSTROJE

- **Maximalizace potenciálu projektu HR Award** a úspěšné získání HR Excellence in Research Award.
- **Redefinování HR procesů**, harmonizace s mezinárodními standardy a pravidelné hodnocení.
- **Budování pevných vztahů s mateřskou organizací FNUSA** a jasná definice role FNUSA-ICRC ve struktuře nemocnice.
- **Další vývoj Informačního systému FNUSA-ICRC.**
- **Funkční Welcome Office** poskytující služby novým zaměstnancům již před nástupem a po celou dobu jejich zaměstnání ve FNUSA-ICRC, pomoc při jednání zahraničních zaměstnanců s úřady.
- Přehled shromažďovaných **dat a jejich struktura**, analýza možností jejich uložení a další využití pro rozhodování managementu.
- **Rozšíření managementu výzkumných dat** v nemocničním prostředí v souladu s pravidly GDPR.
- **Podpora a rozvoj profesionálních administrativních týmů**, včetně strategie dalšího rozvoje odborných kompetencí zaměstnanců.
- **Profesionalizace** webových stránek a další rozvoj všech komunikačních kanálů.
- **Aktivní prezentace** centra a jeho úspěchů na mezinárodních akcích.

FNUSA ICRC

ST. ANNE'S UNIVERSITY HOSPITAL BRNO
INTERNATIONAL CLINICAL RESEARCH CENTER

Table of contents

ACUTE CORONARY SYNDROMES

MUDr. Ota Hlinomaz, CSc.

Established in 2016*

Key words
Interventional cardiology, stent, scaffold, coronary artery disease, myocardial infarction, percutaneous coronary intervention, tako-tsubo cardiomyopathy, ST-Elevation myocardial infarction

Research focus
The Acute Coronary Syndrome Research team belongs amongst pioneers of primary percutaneous coronary intervention programs in the Czech Republic and is also one of the largest centers. The main activity of the ACS Research team is interventional cardiology, treatment of coronary artery disease by percutaneous coronary interventions and treatment of acute coronary syndromes. The main research is focused on a new stent and scaffolds development, treatment of ST-Elevation Myocardial Infarction (STEMI) patients with multivessel disease, anti-aggregation therapy after acute coronary syndromes, Tako-tsubo Cardiomyopathy, new imaging methods of coronary arteries and atherosclerotic plaque progression.

Research objectives
- Evaluate unstable coronary plaques by optical coherence tomography and near infrared spectroscopy.
- Test newly developed coronary stents and scaffolds in animal models and humans.
- Test the role of genetic polymorphisms on pharmacokinetics of antiplatelet drugs used for acute coronary syndromes treatment.

* *The team was originally established in 2011 as a research subprogram of the Operational Programme Research and Development for Innovation (OP RDI).*

STRATEGY FOR THE PERIOD 2021 - 2025

The Acute Coronary Syndrome Research team belongs amongst pioneers of primary percutaneous coronary intervention program in the Czech Republic and is also one of the largest centers. The main activity of the ACS Research team is interventional cardiology, treatment of coronary artery disease by percutaneous coronary interventions and treatment of acute coronary syndromes. The main research is focused on treatment of ST-Elevation Myocardial Infarction (STEMI) patients with multivessel disease, a new stent and scaffolds development, Tako-tsubo Cardiomyopathy, spontaneous coronary artery dissections (SCAD), new imaging methods of coronary arteries and atherosclerotic plaque progression.
We participate in the multicenter, international, randomized DAPT-SHOCK PRAGUE-23 trial, which compares cangrelor to ticagrelor in patients with cardiogenic shock due to acute myocardial infarction. Most of the patients are evaluated by MRI and echocardiography. The hypothesis is that cangrelor is superior to ticagrelor in these high-risk patients.
We will work on the 10-year follow up of the patients in Prague-13 trial comparing the PCI versus the conservative treatment of non-culprit coronary stenoses in patients with STEMI treated by primary PCI. We expect better long-term results in the PCI group.
We will publish the results of our analysis comparing the 15-year and 20-year survival amongst patients presenting with chronic stable angina who had smooth coronary vessels, no obstructive and obstructive coronary artery disease on invasive coronary angiography.
We will evaluate unstable coronary plaques by optical coherence tomography and near infrared spectroscopy. These unstable plaques will be treated by stent implantation. We expect a better prognosis in these patients in comparison to conservatively treated patients.
Newly developed coronary stents and scaffolds will be tested in humans and compared to currently used stent.
Patients with spontaneous coronary artery dissections will be deeply examined and followed. We will participate at the European multicenter registry. We hope to find the factors that influence the long-term prognosis of our patients.
Patients with advanced heart failure due to reduced systolic function of the left ventricle will be treated by the AccuCinch system. Improved exercise tolerance and better prognosis after device implantation is expected. We will participate in pilot clinical trial with this system.
We will collaborate with CINRE hospital in Bratislava, Slovakia, Institute of Cardiology in Minsk, Belarus, Bulgarian Cardiac Institute in Pleven and Varna, Leicester Research Group from England and Mayo Clinic, USA.

INTERVENTIONAL CARDIAC ELECTROPHYSIOLOGY

MUDr. Zdeněk Stárek

Established in 2016*

Key words

Cardiac Electrophysiology, Cardiac Arrhythmia, Stem Cell Therapy, Epicardial Pacing, Ablation, Defibrillation, Electroporation, Apoptosis, In-vitro models

Research focus

The Interventional Cardiac Electrophysiology Research team is focused on clinical research of catheter navigation, 3D imaging of heart structures and image integration during catheter ablations of cardiac arrhythmias. Our main aim is prototype catheter testing and its development in animal models, based on the collaboration with researchers from Mayo Clinic, USA. The ICE team is further focused on the development of catheters for epicardial stimulation, defibrillation and ablation towards chronic experiments and new catheters with direct visualization of ablated tissue. Further areas are regenerative strategies of bradyarrhythmias, using stem cell technologies and novel ablation modalities. There is also ongoing brain vasculature research with neurologists and neurosurgeons. The magnetically navigated micro-catheter is utilized for endovascular mapping of deep brain structures in animal models, in order to help patients with epilepsy and to improve the quality of brain structures mapping. The ICE Research team is also running research on microRNA in atrial fibrillation.

Research objectives

- Development of new catheters and devices for interventional treatment of cardiac and brain diseases.
- Clinical research of catheter navigation, 3D imaging of heart structures and image integration during catheter ablations of cardiac arrhythmias.
- Translational focus on stem cell-derived cardiomyocytes and regeneration strategies.

Main partners

- Mayo Clinic, Rochester, MN, USA
- Mount Sinai Hospital, New York, USA
- Herzzentrum Leipzig, Leipzig, Germany

Offered services and expertise

- Catheter testing both in human and in animal models.
- Technical assistance on animal studies involving imaging and electrophysiology equipment.
- Human electrophysiology clinical evaluation.
- Registry setup.

** The team was originally established in 2011 as a research subprogram of the Operational Programme Research and Development for Innovation (OP RDI).*

STRATEGY FOR THE PERIOD 2021 - 2025

Current situation, research focus

Everything is related to everything. The research of the Interventional Cardiac Electrophysiology (ICE) team has three tightly connected branches. Human research, animal research and in vitro pre-clinical research. Effective research needs an experienced team, money and patients. Research of the ICE team depends on the strong clinical program of the catheter ablation of arrhythmias. About 600 catheter ablations are performed per year. Critically important is education of the things, without experienced electrophysiologists, technicians, biomedical engineers and nurses, any research is unthinkable. A large clinical program allows us to enroll patients into clinical studies and investigate initiated research projects. A pool of data from clinical patients, clinical studies and contracted research allow to publish in respected journals and to improve the prestige of the EP center, which increases the chances of being involved in further contracted researches. The payment from the clinical and contracted research also improves overall financing of our team. But without a strong clinical program and great results, there are no contracted projects or clinical studies.

A similar situation is also in place with animal and pre-clinical research. Support of an experienced team and funding from various sources, including money from clinically contracted research, is necessary. ICE performs both its own animal experiments, financed from grants, and contracted animal experiments, with a similar context as in clinical research regarding the funding. Pre-clinical research supports animal and clinical research and is funded from several sources, which are connected to clinical and animal research and takes place at the facilities of collaborating teams.

Our research takes place at the two well equipped EP labs (human clinical projects), animal catheterization lab on the Veterinary University in Brno (VFU) and several other collaborating labs (Biology dpt. of Faculty of Medicine, Masaryk University, team of Vladimír Rotrekl; Institute of Biophysics of the Czech Academy of Sciences, team of dr. Jan Víteček; Faculty of Electrical Engineering and Communication, BUT, team of dr. Dalibor Červinka).

Strategy for future five years

Our team will continue with the work described above. We would like to enlarge further the number of clinical patients (up to 800-900 per year), increase the number of team members to allow the increase of the volume of research. Due to the long time problems in communication with the management of VFU, which have led to a high decrease in the number of animal experiments, animal research is being moved to the Veterinary Research Institute (VRI) in Brno. In order to ensure development of animal research, our goal in cooperation with ICRC Animal center is to completely move research equipment, including Stereotaxis, from VFU to VRI and to build a functioning center for animal experiments and animal electrophysiology workshops planned for the near future. New animal models – sheep and rabbits will be employed in planned experiments, which will increase the scope of applicable species, each suitable for a different research task.

In the area of pre-clinical research, experimentation supporting clinical and animal research will be expanded in collaboration with our basic research partners.

Collaborating institutions

- University of Silesia, Katowice, Poland
- Cardiology Department of Institute for Clinical and Experimental Medicine Prague, Prague
- Semmelweis University Heart and Vascular Center in Budapest
- Biology dpt. of Faculty of Medicine, Masaryk University, Brno
- Institute of Biophysics of the Czech Academy of Sciences, Brno
- Faculty of Electrical Engineering and Communication, BUT, Brno

SLEEP MEDICINE

prof. MUDr. Ondřej Ludka, Ph.D.

Established in 2016*

Key words
Sleep Disordered Breathing, Myocardial Infarction, Atrial Fibrillation, Heart Failure, Sudden Cardiac Death, MicroRNA, Hypertension

Research focus
The Sleep Medicine Research team plans to initiate three crucial research studies on assessing the role of sleep apnea treatment, prognosis of patients after myocardial infarction and prevention of sudden cardiac death and atrial fibrillation recurrence. An important part of the SMED team activities will be continuous data analysis from projects where enrollment of patients has already been completed. This way we can evaluate a rising opportunity to identify severe risk factors and to eliminate it via a corresponding therapy. The SMED Research team would like to establish one of the first centers capable of monitoring the frequency and appropriate use of technologies for SA treatment. The center of telemonitoring will be established as an integral part of the current Cardiovascular Sleep Research Center and its support will be crucially important to improve the reliability of outcomes of the above described sleep research studies.

Research objectives
- To characterize the role of sleep apnea and its treatment in myocardial infarction, heart failure, sudden cardiac death and atrial fibrillation.
- Elucidate pathophysiological mechanisms underlying sleep apnea.
- Evaluate the relationship between sleep apnea and metabolic disorders.

Main partners
- The Charité - Universitätsmedizin Berlin, Berlin, Germany
- The University of Milan, Milan, Italy
- Mayo Clinic, Rochester, MN, USA

Offered services and expertise
- Fully functional Sleep lab certified by Czech Sleep Research and Sleep Medicine Society and also certified as a research center by European Sleep Research Society.
- Polygraphy and manual or automatic titration of positive airway pressure therapy (CPAP, BiPAP, ASV, AVAPS etc.).
- Full polysomnography.

** The team was originally established in 2011 as a research subprogram of the Operational Programme Research and Development for Innovation (OP RDI).*

STRATEGY FOR THE PERIOD 2021 - 2025

Sleep is a state of physiological rest for the cardiovascular system and sleep-disordered breathing (SDB) disrupt this state. The most common type of SDB is obstructive sleep apnea (OSA) in up to 66% of patients after myocardial infarction (MI) as shown in our unique and the world's largest group of consecutive patients after MI (SAPAMI study). OSA is associated with increased mortality in these patients and is also a modifiable risk factor. Early diagnosis and treatment can therefore not only improve the quality of life, but also reduce the morbidity and mortality of these patients. The primary aim of our planned interventional clinical trial will be to address whether Continuous Positive Airway Pressure (CPAP) treatment of acute MI patients with moderate to severe OSA will reduce the combined rate of MACE (cardiovascular mortality, stroke, myocardial infarction and the need for a new revascularization) in these subjects over a 3-year period.
We will continue on microRNA work in OSA patients with resistant hypertension. The aim of the study is to determine diagnostic potential of circulating microRNAs in identifying sleep apnea patients in a hypertensive (coronary artery disease in the future) population.
These two works will be a priority for our lab.
We plan to continue research focused on the occurrence of SDB in patients with achondroplasia, which should be due to the disproportionate development of the cranial base and associated upper respiratory tract dysmorphism and also these two studies; ORTOSA – effect of different anesthetic procedures on OSA exacerbations in the postoperative period and MICROSA - microcirculatory heterogeneity in patients with OSA.
The European Sleep Apnea Database (ESADA) serves as a reference database for European sleep apnea patients and current research is focused on the identification of specific sleep apnea phenotypes. The ESADA also serves as a bridge for education and knowledge transfer between the various participating centers. Our center is very active and respected in this database as evidenced by the fact that this year ICRC hosted the ESADA meeting.
Related with the team structure, we plan to collaborate with Mayo Clinic and the Charite Hospital Berlin. Part of our research is also contracted research (eg Honeywell – testing devices to detect the risk of falling asleep in the cockpit, ResMed, Linde, Saegeling – telemonitoring, BTL, Cardion etc).

STROKE

prof. MUDr. Robert Mikulík, Ph.D.

Established in 2016*

Key words
Stroke Diagnosis and Acute Treatment; Stroke Logistics

Research focus
Research actives of the Stroke research team (STR) include development and implementation of innovative methods for the evaluation, treatment, and prevention of acute ischemic stroke. Research portfolio is designed across translational axis from basic science to clinical research and implementation research. The emphasis is on a translational approach so that knowledge gained through basic research is applied and tested in clinical practice and then translated into health care system and population.

Research objectives
- Research on implementation of evidence-based treatments.
- Development of in vitro and animal model for stroke to test new diagnostics (e.g. basic thrombus imaging) and therapeutic strategies (e.g. new recanalization methods).
- Identification of better stroke awareness methods including program on stroke awareness in children.

Main partners
- European Stroke Organisation, Switzerland
- ANGELS Initiative, The world-wide stroke support project, Germany
- University of Calgary, Canada
- Network of Stroke Centers in Central and Eastern Europe

Offered services and expertise
- Simulation training and methodology- is intended for stroke teams and professionals in stroke.
- System Engineering/Software Developing and data management.
- Preclinical Research: highly sophisticated in vitro flow models and small animal models of stroke.
- Web-based platform for education of children and lay public in Stroke.
- Coordination of clinical trials.

* *The team was originally established in 2011 as a research subprogram of the Operational Programme Research and Development for Innovation (OP RDI).*

STRATEGY FOR THE PERIOD 2021 - 2025

The Stroke Research team will continue the development of novel methods of diagnostics, treatment and prevention of stroke. Our general research strategy is translational, i.e. from bench to bed and from evidence to the health care system and the community. Therefore, areas of our activities will include preclinical, clinical, and implementation research and we will further reinforce the translation between these areas. We will further develop and leverage the infrastructures and tools that we have built: a) STROKE BRNO as infrastructure for preclinical research, b) Czech Stroke Research Network as platform for multicenter clinical research, and c) the RES-Q Registry in Stroke Care Quality as platform and tool for implementation research. STROKE RBNO brings to the table the collaboration of several teams and institution, especially from Brno. The Czech Stroke Research Network is consortium of 20 clinical stroke centers in the Czech Republic under our leadership and RES-Q is our registry, which has become global platform to improve stroke care within 1500 hospitals from 70 countries. We have also established a Public Health Group, which covers and supports activities and research in stroke awareness, prevention and epidemiology. The Stroke Public Health Group activities should affect both the local community and the international population. Our general aim is to create the future of stroke care and medicine through strengthening partnership with both Czech and international institutions, as well as with companies and through engagement of experts in clinical, preclinical and implementation research during all stages of their careers.

DEMENTIA

prof. MUDr. Jakub Hort, Ph.D.

Established in 2016*

Key words
AD, MCI, Non-Alzheimer Dementia, Longitudinal Study, CBAS

Research focus
The current research of the Dementia Research team is based on the Czech Brain Aging Study (CBAS) – a unique, national, multicentric and longitudinal prospective cohort study. The aim of CBAS is to study the early functional, metabolic, structural and genetic biomarkers of Alzheimer´s Disease and other dementias in blood, CSF and magnetic resonance imaging with a focus on synucleinopathies, tauopathies and TDP--43-pathies. These studies are complemented by animal studies with emphasis on translational aspect of the used methodology. CBAS also explores the effects of lifestyle factors on the brain's maintenance using questionnaires and nonpharmacological interventions. CBAS team consists of two core synchronized sites – Cognitive Centers at ICRC St. Anne´s University Hospital Brno and at Motol University Hospital, Prague.

Research objectives
- Evaluation of neuropsychological and spatial navigation tests as an early markers of neurodegeneration.
- Defining structural, metabolic and functional biomarkers on MRI and PET in humans.
- Exploring epidemiological risk factors in primary and secondary prevention of dementia.

Main partners
- University of South Florida, Tampa, FL, USA
- Harvard University, Cambridge, MA, USA
- Nanjing Drum Tower Hospital, Nanjing, China
- EADC - European Alzheimer Disease Consortium
- eDLB - European DLB consortium
- Alzheon
- University of Gothenburg, prof. Kaj Blennow

Offered services and expertise
Translational research, data analysis, longitudinal study, biomarkers of neurodegenerative disorders, neuropsychology, neuroimaging, cerebrospinal fluid analysis, blood biomarkers, clinical trials.

* *The team was originally established in 2011 as a research subprogram of the Operational Programme Research and Development for Innovation (OP RDI).*

STRATEGY FOR THE PERIOD 2021 - 2025

The Dementia team will focus on evaluation of factors predicting conversion from subjective cognitive decline (SCD) to mild cognitive impairment (MCI) and dementia due to Alzheimer disease, frontotemporal dementia, Lewy body dementia, vascular dementia and related neurodegenerative disorders. Longitudinal analyses using data readily available will be used.
Metabolic biomarkers will be evaluated – total tau, phospho tau 217, 181, NFL-light, beta-amyloid, neurogranin and other. We will use both CSF and blood samples.
Amyloid PET will be correlated with other structural and metabolic markers and the early perfusion phase will be studied.
Epigenetics with focus on ApoE4 status will be studied including effects of diet, physical activity, mindfulness and other non-pharmacological interventions.

Main collaborations:
- Alzheon Biotech Company - developing new therapeutic strategies
- Prof. Kaj Blennow University of Gothenburg, Sweden – metabolic biomarkers
- University of South Florida, Tampa, FL, USA – epidemiological and longitudinal data

PEDIATRIC ONCOLOGY TRANSLATIONAL RESEARCH

prof. MUDr. Jaroslav Štěrba, Ph.D.

Established in 2016

Key words
Personalized Pediatric Oncology, Metronomic Chemotherapy, Long Term Follow Up

Research focus
Personalized precision pediatric oncology uses up to date theranostic approaches in order to increase survival and decrease long term morbidity and sequelae from the disease and the necessary therapies. POTR also focuses on rational incorporation of new anticancer drugs into earlier lines of treatment based on comprehensive DNA, RNA and proteomic analyses of the tumor and the patient as the host. As well as establishing functional regional models for long term follow up with transition of care from pediatric to adult services as the platform to study long term toxicities, risk factors and possible ways to decrease the treatment burden.

Research objectives
- Personalized precision pediatric oncology based on comprehensive assessment of the tumor and the host.
- Decreasing the disease and treatment related morbidity and mortality, while studying long term survivors and running juvenile animal studies for new anticancer medicines.
- The CSF proteomic project for children with brain tumors and leukemia and NHL. Analysis of possible biomarkers.

Main partners
- Medical University of Vienna, Vienna, Austria
- Floating Hospital for Children at Tufts Medical Center, Boston, MA, USA
- AP-HM, Marseille, France

Offered services and expertise
- Unique and well characterized population of young adults - former pediatric oncology patients who are at risk of late toxicity from the disease and the treatment, and who should be looked after and further studied in many areas, mainly cardiology, neurology, endocrinology, pulmonology.
- Established cooperation with international pediatric oncology centers in Europe and the US.

STRATEGY FOR THE PERIOD 2021 - 2025

2 main research focuses:
1) personalized/precision pediatric oncology
2) late effects and follow up for former pediatric oncology patients.

Hypothesis – personalized care leads to improved results and quality of life for children and AYA with cancer.
Main objectives – improve and verify multiomic approach using complementarity of advanced DNA, RNA and proteomic levels, together with tumor microenvironment and other host characteristics.
Collaboration is planned within the Brno region – ICRC proteomic facility, ICRC and St. Anne's University hospital clinical facilities for former pediatric oncology patients. Masaryk University – CEITEC and School of Medicine for DNA, RNA and phosphoproteomic levels.
Outside of Brno and the Czech Republic the main cooperation will remain to be with the Medical University Vienna, and the Pediatric Oncology Departments in Boston and Toronto.

LABORATORY ONCOLOGY TRANSLATIONAL RESEARCH

prof. RNDr. Renata Veselská, Ph.D., MSc

Established in 2016

Key words
Cancer Stem Cells, Signaling Pathways, Pediatric Solid Tumors, Precision Medicine

Research focus
Laboratory translational research - with the main focus being on pediatric oncology - in close cooperation with clinicians and pathologists represents an important approach to bringing new information concerning tumor biology from bench to bedside. This strategy encompasses especially the identification of activated signaling molecules within tumors that can be targeted by specific low-molecular-weight inhibitors. In addition to this, our research is also aimed at the investigation of cancer stem cell phenotype in relation to the tumorigenicity and resistance to conventional therapy.

Research objectives
- The identification of activated RTK and downstream signaling pathways as druggable molecular targets in relapsed / refractory pediatric solid tumors and giant cell tumor of the bone.
- Analysis of the expression of key stemness factors and p53 family proteins in relation to the tumorigenicity of sarcoma cells.
- Deciphering the role of mitochondrial dynamics and autophagy in acquisition of stemness using clinically relevant models of resistance development in pediatric solid tumors.

Main partners
- Children's Hospital of Philadelphia, PA, USA (Dr. Michael Hogarty)
- University of Porto, Portugal (Dr. Lucília Saraiva)
- University of Sydney, Australia (Dr. Patric Jan Jansson)
- Karolinska Institutet, Stockholm, Sweden / Medical University of Vienna, Austria (Prof. Dr. Igor Adameyko)

Offered services and expertise
- Primary cultures of human solid tumors.
- Functional assays on cancer stem cell phenotype (including in vivo tumorigenicity testing).
- Analyses of activated cell signaling pathways using phosphoprotein arrays.
- Detailed morphological and gene expression studies on tumor tissue samples, cancer cell lines and xenograft tumors.

STRATEGY FOR THE PERIOD 2021 - 2025

The LOTR research team focuses on providing new knowledge of mechanisms that promote cancer progression and resistance, with special efforts on identifying druggable molecular targets in otherwise refractory pediatric solid tumors. In close cooperation with clinicians and pathologists, we will continue on our mission of bringing such knowledge from bench to bedside through our two major lines of research: (1) investigating the potentially vulnerable mechanisms regulating aggressive cancer stem cells (CSCs), and (2) identification of activated signaling molecules within tumors, which can be targeted by specific low-molecular-weight inhibitors.

Therapy resistance and cancer recurrence remain a frustrating therapeutic challenge in oncology. While it is already known that refractory cancer cells exhibit stem-like traits, molecular mechanisms underlying therapy resistance of these CSCs are poorly understood, especially in childhood tumors, which precludes the development of effective anti-cancer therapies. We will build on our previous results and in a collaboration with our international partners we will investigate: (i) whether there is a link between the expression of key stemness factors, p53 proteins, and tumorigenicity of sarcoma cells, which could be therapeutically exploited using novel drugs re-activating p53 proteins, and (ii) if pharmacological inhibition of mitochondrial quality control may prevent the induction of stemness and drug resistance in pediatric solid tumors.

Direct and specific targeting of signal transduction by low-molecular-weight inhibitors or monoclonal antibodies represent one of the very promising strategies in precision medicine. The basic step for this personalized approach includes the precise characterization of the individual tumor regarding the receptor tyrosine kinase (RTK) pattern – both the expression and activation – as well as of downstream signaling pathways. We hypothesize that it is possible to identify specific relationships amongst activated signaling pathways, molecular alterations in genes, encoding these key signaling molecules, and therapeutic outcomes after targeted treatment as described above. Thus, we plan to evaluate the importance of analyzing and the impact of targeting the key signaling molecules in relapsed/refractory pediatric solid tumors, using in-depth analysis both in retrospective and continuous (prospective) cohorts of patients and subsequent validation of data from phospho-protein arrays by immunohistochemical detection of activated key signaling molecules. The results will be of high importance for further precision of targeted therapy according to the relevant results of molecular profiling, in order to achieve the most beneficial treatment with the best clinical outcomes for individual patients.

Planned collaborations:

- Dr. Michael Hogarty (Children's Hospital of Philadelphia, PA, USA)
- Dr. Lucília Saraiva (University of Porto, Portugal)
- Dr. Patric Jan Jansson (University of Sydney, Australia)
- Prof. Dr. Igor Adameyko (Karolinska Institutet, Stockholm, Sweden / Medical University of Vienna, Austria)

KARDIOVIZE BRNO 2030

Juan Pablo Gonzalez Rivas, MD

Established in 2016*

Key words
Prevention of Cardiovascular Diseases

Research focus
The Kardiovize team is one of FNUSA-ICRC international research teams, our mission includes data acquisition, analysis, publication and diffusion of relevant epidemiologic and public health topics focused on cardiovascular and mental risk factors. With this knowledge intervention programs are designed, implemented, and evaluated in order to reduce the burden of major risk factors and business opportunities are created as well, which contribute to the sustainability of the institution and promotes the health of the population.

Research objectives

- To assess the cardiometabolic and cognitive risk factors and their determinants in the Czech population.
- To implement and evaluate population and individual interventions in Brno, to reduce cardiovascular diseases and the cognitive decline risk, and create a portable model to be replicated in others cities in the region.
- To collaborate with researchers of low and middle-income countries to improve the understanding of the complex relationship among cardiometabolic, mental, and cognitive risk factors.
- To develop business opportunities evaluating new technologies and providing the population of Brno access to high-quality and high-technology evaluations and programs.
- To consolidate Kardiovize as a European leading center in cardiovascular disease prevention research.

Main partners

- Mayo Clinic, Rochester, MN, USA
- Mount Sinai, NU, NY, USA
- Charles University, Prague, Czech Republic

Offered services and expertise

- Recommended methodology of community intervention programs.
- Population-focused prevention programs, promotion of health education.
- Enterprise-focused prevention programs.
- Monitoring changes in awareness of risk factors for cardiovascular disease.
- Laboratory and diagnostic methods.

* *The team was originally established in 2011 as a research subprogram of the Operational Programme Research and Development for Innovation (OP RDI).*

STRATEGY FOR THE PERIOD 2021 - 2025

By 2021

- Kardiovize team will work as a consolidated team, trusting each other, sharing projects, creating inspiration among their partners.
- Kardiovize will have an established rhythm of production of high-quality impact articles, this knowledge will be spread and transferred to the community in Brno. The follow-up of the participants will be completed and will provide the support for these high-impact articles.
- Kardiovize data will be linked with the national registry to determine the main drivers of mortality in the country.
- Kardiovize team will coordinate the implementation of health programs within ICRC, like Yoga and lifestyle promotion, as a part of research programs, as well as the coordination of the HITS Diabetes Program and the Hypertension Control Program.
- The Kardiovize database will be a part of a global consortium of databases, like the Global Burden Disease Group and the Non-communicable Risk Factors Group, in order to contribute to the understanding of the burden of diseases and risk factors, globally.
- Kardiovize will be part of a solid network of researchers, working together with the Mayo Clinic U.S., the TH Chan Harvard School of Public Health in Boston, US, the Resolve Initiative, NY, US, the Foundation for Clinical, Epidemiological, and Public Health Research of Venezuela (FISPEVEN INC), Caracas, Venezuela, African Institutions, and others.
- Kardiovize will be a profitable center implementing a business model to collect and analyze data, and implementing private programs.
- The Kardiovize team will contribute to the evaluation of environmental risk factors.
- The **KARDIOVIZE CENTER** will be created as a strong and well-coordinated research structure with local and international researchers, in a favorable environment to promote research and health.

By 2022

Kardiovize Center will start to complete the data collection second cross-sectional survey in Brno, contributing to the understanding of the change of epidemiological risk factors. Kardiovize will continue with the sustained production of high-quality research articles, the implementation and coordination of health programs, and the alliance with other research institutions. Kardiovize will patents ideas based on Artificial Intelligence.

By 2025

Kardiovize Center will start the follow-up evaluations of the participants; this will provide data with more than 10 years of follow-up. Kardiovize Center will be consolidated as a strong research center with solid global networks, and will implement health programs in the city.

BIOMEDICAL ENGINEERING

Ing. Pavel Leinveber

Established in 2016*

Key words
Advanced Acquisition of Biological Signals, Data-Analyses in Cardiology and Neurology

Research focus
The Biomedical Engineering research team (BME) focuses on the development and testing of new methods and technologies for improved diagnostics for better stratification of heart and brain diseases. The BME aims its main research effort at progressive analyses of weak electrical signals emitted by the body organs through an advanced acquisition of these signals.
The BME team also offers high-quality technical engineering services for researchers in terms of biological signal measurement and analyses, as well as the research data management and mining.

Research objectives
- To research various frequency components in the ECG signal and their contribution to clinical practice – spatial and temporal distribution properties in the QRS complex on different frequencies using new ultra-high frequency ECG (UHF-ECG) methods and technologies.
- To analyze EEG high-frequency oscillations (HFOs) and their meaning in physiology and pathophysiology of the epileptic brain.
- To research EEG signal propagation – the brain connectivity in physiology and pathophysiology in epilepsy and Parkinson's disease.

Main partners
- Mayo Clinic, Rochester, MN, USA
- Institute of Scientific Instruments, Brno, Czech Republic
- University Hospital Královské Vinohrady, Prague, Czech Republic
- Gdansk University of Technology, Gdansk, Poland

Offered services and expertise
- Biological data acquisition and analysis.
- Clinical/research data management and mining.
- Electro-magnetically clean laboratories with shielding from low frequencies (0.1Hz) and specific multi-channel acquisition systems.
- Development of new diagnostic technologies and tools in neurology and cardiology.

** The team was originally established in 2011 as a research subprogram of the Operational Programme Research and Development for Innovation (OP RDI).*

STRATEGY FOR THE PERIOD 2021 - 2025

The Biomedical Engineering research team (BME) has its long-term focus on the development and testing of new methods and technologies for improved diagnostics for better stratification of heart and brain diseases. The BME aims its main research effort at progressive analyses of weak electrical signals emitted by the body's organs through an advanced acquisition of these signals.
A small part of BME will keep serving as a BME Core Facility (BME-CF) to offer high-quality technical engineering services for researchers in terms of biological signal measurement and analyses, as well as the research data management and data-mining services.
In the cardiology area, we will mainly study the diagnostic potential of novel ultra-high frequency ECG (UHF-ECG) method on multichannel non-invasive mapping of electrical depolarization of heart ventricles, diagnostic relevance of UHF depolarization maps on the prediction of patients susceptibility to the negative effect of long-term myocardial pacing in the right heart ventricle, and optimal placement of pacing electrodes into the heart chambers. We will also explore the possible diagnostic advantages of UHF-ECG in patients with a high risk of sudden cardiac death.
In neurology, our research focus will be on high-frequency intracranial EEG, where we investigate high-frequency oscillations (HFOs) and their meanings in physiology and pathophysiology of the epileptic brain. As well as intracranial EEG signal propagation – the brain connectivity in physiology and pathophysiology in epilepsy and Parkinson's disease. We will perform this research using novel analytical methods and artificial intelligence algorithms. Apart from clinical neurology, we will also investigate memory encoding processes of the normal human brain.

Planned collaborations:
- Mayo Clinic, Rochester, MN, USA
- Institute of Scientific Instruments, Brno, Czech Republic
- University Hospital Kralovske Vinohrady, Prague, Czech Republic
- Maastricht University, Maastricht, Netherland
- McGill University, Montreal, Canada
- Gdansk University of Technology, Gdansk, Poland

CARDIOVASCULAR MAGNETIC RESONANCE

doc. MUDr. Roman Panovský, Ph.D.

Established in 2018

Key words
Cardiovascular Magnetic Resonance, Non-Invasive Cardiology, Heart Imaging

Research focus
The Cardiovascular Magnetic Resonance research team (CMR) is focused on the development of new protocols of heart imaging and identifying novel imaging biomarkers for the prediction of early myocardial dysfunction. The main purpose is to improve the non-invasive diagnostics of early forms of myocardial diseases, contributing especially to heart failure. Early and accurate diagnosis of myocardial dysfunction and structural abnormalities that are known to precede the development of manifest symptomatic heart failure can provide several potential benefits and can also lead to better short-term and long-term prognosis of patients, the decrease of patient morbidity and mortality, improving their quality of life and potentially saving public resources.

Research objectives
- To test for a novel CMR protocol to improve early detection of myocardial injury in Duchenne and Becker muscular dystrophy patients.
- To prove that CMR can detect higher prevalence and earlier stages of cardiac involvement in patients with sarcoidosis, in comparison with the commonly used methods.
- To find novel CMR and laboratory markers for the diagnosis of cardiotoxicity in oncological groups of patients after cardio toxic chemotherapy.

STRATEGY FOR THE PERIOD 2021 - 2025

The CMR team is going to continue to realize the main research focus - to develop new imaging protocols of heart imaging and identifying novel imaging biomarkers for the prediction of early myocardial dysfunction. In the following period, some advanced phases of the running projects are going to continue and new projects are planned to commence. Regarding already running projects, the long imaging follow up study is scheduled for both the Duchenne muscular dystrophy (DMD) cohort and DMD carriers to test a prognostic value of imaging biomarkers. The project ONCOHEART - novel biomarkers in detection of cancer therapeutics-related cardiotoxicity as a part of the ENOCH grant will be finished in cooperation with Pediatric Oncology Translational Research (POTR). After the data analysis, the follow-up of the team will be considered.
Several new projects are planned for realization. In cooperation with Interventional cardiac electrophysiology team (ICE), the left atrium assessment by cardiac magnetic resonance in patients with atrial fibrillation before radiofrequency ablation will be prepared with an intent to gain more detailed information about the left atrium before radiofrequency ablation, as well as to find prognostic biomarkers. The comparison of the heart phenotype imaged by CMR parameters is planned to compare with genetic profile of patients with hypertrophic cardiomyopathy. Also new pulmonary circulation biomarkers acquired with CMR, like pulmonary transit time (PTT), pulmonary transit beats (PTB) and pulmonary blood volume index (PBVI), will be studied in different cohorts of patients to prove their value of non-invasive assessment of congestion and pulmonary circulation.
Besides the above-mentioned projects, CMR team would like to play an important role in machine learning and artificial intelligence, ideally in cooperation with industrial vendors, like Philips (Master Research Agreement is currently finalized), GE Healthcare and Circle cardiovascular imaging. Currently, the CMR team is taking part in a large international project submitted to the Horizon 2020 call (SC-1-BHC-06-2020, development of artificial intelligence and machine learning analysis in early diagnosis and risk stratification in frequent cardiac disorders).

NUCLEAR CARDIOLOGY AND CARDIAC CT

doc. MUDr. Vladimír Kincl, Ph.D.

Established in 2018

Key words
Non-invasive cardiology, Cardiac Imaging Methods

Research focus
The Nuclear Cardiology and Cardiac CT team (NCT) is equipped with one of the two cadmium-zinc-telluride SPECT cameras in the Czech Republic. The NCT focuses on new imaging protocols that use the cadmium-zinc-telluride technique in nuclear cardiology. The team has successfully tested and published feasibility of low-dose myocardial perfusion protocol using 201-thallium. Further research is now focused on the diagnostic and prognostic verification of this low-dose protocol. The team also plans to commence imaging of myocardial sympathetic innervation using 123-iodine in patients with heart failure and perform multimodality imaging of myocardial viability in collaboration with the Cardiovascular Magnetic Resonance team.

Research objectives
- The development and testing of low-dose imaging protocols in nuclear cardiology.
- Improvement of imaging protocols used for assessment and quantification of myocardial ischemia.
- Improvement of the risk stratification in patients with heart failure.
- Subclinical impairment of cardiac function in Duchenne dystrophy gene carriers.
- Impairment of cardiac functions in patients with Parkinson´s disease.

STRATEGY FOR THE PERIOD 2021 - 2025

In nuclear cardiology we plan to develop new imaging protocols using our dedicated cardiac SPECT scanner with cadmium-zinc-telluride (CZT) technology (GE Discovery NM 530c). We´d like to focus on cardiac sympathetic innervation imaging for the localization of arrhythmogenic centers in the heart and risk stratification of sudden cardiac death. In the field of non-invasive cardiology, we plan to continue with ongoing projects: 1) The Oncoheart project – evaluation of late cardiotoxic effects in adult patients who underwent cardiotoxic chemo- and radiotherapy for cancer during their childhood. This project is being realized in collaboration with the Pediatric Oncology team and Cardiac Magnetic Resonance team. 2) The Duchenne dystrophy project – assessment of the subclinical cardiac dysfunction in Duchenne dystrophy gene carriers, collaboration with the Cardiac Magnetic Resonance team. 3) Heart and Parkinson´s disease – collaboration with the Dep. Of Neurology and CEITEC research group as well as the Cardiac Magnetic Resonance (CMR) team, this study plans to elucidate the relation between Parkinson´s disease and cardiac function impairment, including echocardiography, ECG Holter monitoring, ECG stress testing and advanced CMR parameters. This project was submitted to the AZV grant call with Dept. of Neurology as main investigator and dr. Kincl as a member of the research team, the results of the call are still not available.
Besides above-mentioned projects and collaborations, the NCT team takes part in a large international project submitted to Horizon 2020 call, category SC1-BHC-06-2020; the development of artificial intelligence and machine learning analysis in early diagnosis and risk stratification in frequent cardiac disorders. Our team also plans to develop our collaboration with Dep. Of Nuclear Medicine in Olomouc University Hospital (prof. Kaminek, who is also member of our team), where another CZT cardiac scanner GE Discovery NM 530c is planned to be installed by the end of this year.

INTENSIVE CARE RESEARCH

MUDr. Martin Helán, Ph.D.

Established in 2018

Key words
Sepsis, Septic shock, SIRS, Post-sepsis Syndrome, Oxidative Stress, Biomarkers, Immunology

Research focus
The Intensive Care Research team (INC) focuses on a clinical, patient-oriented investigation of the mechanisms of development, progression and outcomes of critical illness. The cooperation with several pre-clinical research labs provides us wide opportunities for a translational scientific approach, by combining clinical with cellular and molecular data. Thanks to the cooperation with the Cellular and Molecular Immunoregulation team, the project focusing on Immunology of sepsis has been running smoothly and bringing promising results. One of our objectives is to test novel biomarkers of critical illness. Therefore, we investigate several circulating substances and monocytic surface markers in predictions of patient mortality, therapeutic response and onset of complications. Our secondary focus is peri-operative medicine and anestheziological management of at-risk patients.

Research objectives
- To bring novel insights into immuno-pathophysiology of sepsis, septic shock, MODS and SIRS, which could potentially improve treatment of critically ill patients and reduce their mortality.
- To develop novel biomarkers of critical illness, which could better stratify patients with the highest risk and identify the individuals suitable for specifically targeted therapy.
- To bring novel findings, which could identify patients with increased peri-operative risk and develop novel approaches to optimize patients before, during and after surgery.

Main partners
- Jan Frič – internal cooperation (CMI, ICRC)
- Marcela Vlková – internal cooperation (Department of Allergology and Immunology, FNUSA)
- Jiří Pařenica – University Hospital Brno-Bohunice, CZ
- Y. S. Prakash – Mayo Clinic, USA

Offered services and expertise
- Recruitment of critically ill patients, collection and analysis of clinical data.
- Cooperation and expertise in the field of intensive care and peri-operative medicine.

STRATEGY FOR THE PERIOD 2021 - 2025

Research focus
Sepsis – The primary interest of the team. Sepsis is a very heterogeneous syndrome, which makes it difficult to study. Our objective is to describe novel mechanisms in pathogenesis of sepsis, potentially useful for development of new diagnostic and therapeutic approaches. We mainly focus on the immunology of sepsis, septic shock and multi-organ dysfunction syndrome (MODS), including sepsis induced by the Covid-19 disease.
Peri-operative medicine – Novel findings could identify patients with increased peri-operative risk of complications and develop novel approaches to optimize patients before, during and after surgery. Moreover, surgery represents a clearly defined trauma at a clearly defined time followed by SIRS (non-infectious systemic inflammatory response). Thus, this makes for a good model for SIRS investigation.

Research projects

Running projects
Immunology of sepsis
- The project focuses on the role of monocytes in sepsis development, progression and recovery. Patients diagnosed with sepsis admitted to the ICU are recruited to the study. Clinical data and samples are collected at admission (T1), 3-5 days after (T2) and after recovery from sepsis (T3). Pre-clinical research analyses are performed in cooperation with CMI: phagocytosis, CD14/CD16 monocyte subsets, expression of other surface structures (HLADR), cytokine production, transcription factors activity, monocyte metabolism, etc. This project is co-funded by the AZV grant until 2021, but is anticipated to be continued in following years.
- In cooperation with dr. Frič's team (CMI-ICRC).
- Projected timeline: until 2025.

Biomarkers in sepsis
- Pilot analysis of endothelial- and oxidative stress-related biomarkers in septic shock patients has been done. Preliminary results selected biomarkers with promising potential in mortality prediction. Soluble endoglin (sEng) was identified as the most significant predictor. Subsequently, we are analyzing this marker in our cohort of septic patients to confirm its predictive and diagnostic power. Additionally, we are investigating the in vitro effects of sEng treatment on monocytes and sEng expression and secretion in inflammatory conditions.
- In cooperation with dr. Pařenica (CCU, University Hospital Brno-Bohunice) and dr. Frič's team (CMI-ICRC).
- Projected timeline: until 2022.

Influence of different degree of obesity on Oxygen Reserve Index
- Oxygen reserve index (ORi) is a non-invasive and continuous parameter showing a patient's oxygen status in the moderate hyperoxic range - defined as a patient's oxygen "reserve". Prior to the induction of general anesthesia, the hyperoxia is induced by artificial oxygen administration (preoxygenation). ORi could be used to assess the level of hyperoxia during preoxygenation. We expect that obese patients will have a lower ability to achieve a sufficient level of hyperoxia. We test this hypothesis experimentally on volunteers. Non-obese and obese volunteers will be preoxygenated by different means and the ORi will be measured.
- Projected timeline: until 2021.

Projects in preparation
Phenomenon of trained immunity
- Investigation of immunologic characteristics of patients with/without latent toxoplasmosis and

with/without a history of anti-tuberculosis vaccination. Results could provide new insight into the pathophysiology of severe respiratory infections, including SARS-Cov2 and explain reasons for different susceptibility to viral infection amongst different populations.
- In cooperation with dr. Frič's team (CMI, ICRC).
- Projected timeline: 2020-2023.

Role of monocytes and neutrophils in surgery-induced SIRS
- Based on our results from the septic cohort we plan to investigate immunity in non-infectious systemic inflammatory conditions (SIRS), with a particular focus on subsets of neutrophil granulocytes and monocytes. This project has been submitted for AZV 2021.
- In cooperation with dr. Vlková (ÚKIA, FNUSA) and dr. Frič's (CMI, ICRC).
- Projected timeline: 2021-2025.

ORi in ICU patients
- After finishing the first ORi experiment on volunteers we plan to test the usefulness of ORi in critically ill patients. We expect that ORi could be used to control undesirable levels of hyperoxia in ICU patients on mechanical ventilation and thus to improve the care of critically ill patients.
- Projected timeline: 2021-2022.

Anti-inflammatory effect of vagal nerve stimulation
- Vagal nerve stimulation (VNS) has been shown to have promising anti-inflammatory and immunomodulatory functions. Most of the research has been done on animal models. We plan to test VNS in patients undergoing severe surgical operations in order to reduce post-operative infectious complications (sepsis) and inflammatory response (SIRS).
- In cooperation with prof. Matějovič (Pilsen, CZ).
- Projected timeline: 2022-2025.

Expiratory H2S in septic patients
- H2S functions as a "gasotransmitter". It is endogenously produced and has several pathophysiological functions (regulation of inflammation, vasodilation, bronchodilation, anti-oxidative functions, cytoprotective effects, etc.). We plan to measure H2S concentrations in expiratory breath from ventilator circuits of artificially ventilated ICU patients in sepsis and ARDS. Furthermore, we are already cooperating with a basic research lab (prof. Prakash, Mayo Clinic, USA) and are investigating in vitro effects of H2S on immune and lung cells – the first results have already been published in 2020.
- In cooperation with prof. Y.S. Prakash (Mayo Clinic, USA) and dr. Frič's team (CMI, ICRC).
- Projected timeline: 2021-2025.

Effect of cannabis treatment on patient's immune cells
- We plan to collect blood from patients before and after the initiation of treatment with cannabis and investigate differences in morphology and the function of immune cells.
- In cooperation with dr. Hřib (CPLB, FNUSA-ICRC).
- Projected timeline: 2021-2024.

Collaborations
Running
- Jan Frič – internal cooperation (CMI, ICRC)
- Marcela Vlková – internal cooperation (Department of Allergology and Immunology, FNUSA)
- Jiří Pařenica – University Hospital Brno-Bohunice, Czech Republic
- Y.S.Prakash – Mayo Clinic, USA

In preparation
- Marcin Osuchowski - Wien
- Martin Matějovič – Pilsen university hospital and Biomedical Centre, Pilsen, Czech Republic.
- MUDr. Radek Hřib – internal cooperation, CPLB, FNUSA

CLINICAL PHARMACOLOGY UNIT

MVDr. Ing. Václav Trojan, Ph.D.

Established in 2016

Key words
Pharmacokinetics, Pharmacodynamics, Pathophysiology, Internal Medicine, Biological Treatment, Intensive care, Biological Monitoring, Cannabis Research

Research focus
The Clinical Pharmacology Unit (CPU) is a certified Unit working under ISO 9001, GCP and national legislation. It executes clinical trials with pharmaceuticals or medical devices (phases I., II., III. and IV.). Main interests are pharmacokinetics (PK) and pharmacodynamics (PD) of the drug and its early phase of development. In this field, CPU realizes sponsored as well as academic studies. The latest academic trial had the aim to study the influence of different drug application forms used in the intensive care unit during nasogastric tube (NGT) applications. One of the topics of CPU is the handling and monitoring of sepsis in intensive care. Other study topics are from the field of rheumatology (Phase I), gastroenterology (Phase II), diabetology (Phase I) and oncology (Phase I). As an important step to provide IIT clinical trials, the unit prepares their own protocols. Since 2019 CPU has been developing clinical cannabis research as the first Centre in Czech Republic. Cannabis growing and medicament production is GMP and GACP certified.

Research objectives
- To change Pk/Pd of the drugs primarily in the critically ill.
- To improve the results of perioperative care in high-risk patients.
- To grow medical cannabis according to the GMP standard.
- To produce new forms of cannabis in Hospital pharmacies.
- To study the effect of cannabis on patients (current/new).
- To study and confirm cannabis product safety.
- Contract research.

Main partners
- Masaryk Memorial Cancer Institute, Brno, Czech Republic Thomayer Hospital, Prague, Czech Republic, Masaryk University Brno, Czech Republic
- University of Veterinary and Pharmaceutical Sciences Brno, Brno, Czech Republic

Offered services and expertise
- Complete service for conducting clinical trials
- Pk/Pd of various drugs in different patient groups and diseases
- Sepsis in the critically ill
- Monitoring of haemodynamics (invasive and non-invasive)

STRATEGY FOR THE PERIOD 2021 - 2025

Strategy for the period 2021-2025
Cannabis Research Center - Worldly unique infrastructure as a part of FNUSA-ICRC
We can produce and provide research material in standardized conditions, to prepare dry floss or press extract into new pharmaceutical forms. CPU wants to test security/safety on volunteers and patients with proper diagnoses, for which treatment can be indicated.
Standardized material /cannabis plant in standardized condition/ is the crucial base for upcoming research.

World unique structure in ISO SYSTEM
production - preclinical studies - clinical studies

Plant research
- Breeding program – new varieties development, DNA testing, hybridization
- Production optimization – internal/external factors testing (lights, nutrition, photo period, etc.)
- Preservation – tissue cultures lab, multiplication

Preclinical research
- Options of extractions, molecules separation, storage conditions
- Molecules testing on stem cells, also in cooperation with other ICRC teams

Clinical research
The Clinical Pharmacology Unit (CPU) is a certified Unit working under ISO 9001, good clinical practice (GCP) and national legislation. It executes clinical trials with pharmaceuticals or medical devices (phases I., II., III. and IV.). Main interests are pharmacokinetics (PK) and pharmacodynamics (PD) of the drug and its early phase of development. In this field, CPU realizes sponsored as well as academic studies. One of the topics of CPU is the handling and monitoring of sepsis in intensive care. Other study topics are from the field of rheumatology (Phase I), gastroenterology (Phase II), diabetology (Phase I) and oncology (Phase I). As an important step to provide clinical trials, the unit prepares their own protocols.

MECHANOBIOLOGY OF DISEASE

Giancarlo Forte, Ph.D.

Established in 2016

Key words
Cell Mechanobiology, Cardiac Pathologies, Cardiomyocytes, iPSCs, Bioengineered Tissues, 3D organoids

Research focus
The Mechanobiology of disease (MBD) team is mainly interested in correlating defects in tissue-specific cell mechanobiology system with the onset of aging pathologies with and a specific focus on those affecting the cardiovascular system. The working hypothesis of MBD is that defects in the function of the apparatus cells use to perceive and respond to external mechanical cues – the mechanosensing apparatus – which contributes to aging-associated pathologies.

MBD researchers adopt loss- and gain-of-function approaches, microfluidics and micropatterning technologies to manipulate the mechanosome of adults, pluripotent stem cells and stem cell-derived cardiac cells. MBD takes the advantage of cutting-edge technologies for live imaging, cell separation and high-throughput gene and protein analysis to highlight perturbations in the mechanosensing apparatus occurring in the cardiac tissue and cells derived from patients.

Research objectives
- Identification of potential cellular mechanosensors involved in the onset of cardiac pathologies and suitable as bio-markers of the diseases.
- Identification of novel molecular processes involved in cardiac phenotype acquisition.
- Generating valuable in vitro models of cardiac diseases.

Main partners
- University of Porto, Porto, Portugal
- Katholieke Universiteit Leuven, Belgium
- University Campus Bio-Medico, Rome, Italy
- University of Trieste Italy

Offered services and expertise
- Multicolor high quality confocal imaging.
- Live imaging in confocal microscopy.
- 3D confocal rendering.
- Automated MACS cell separation.
- Real Time PCR and PCR arrays.
- Multiphoton analysis of thick biological tissues.

STRATEGY FOR THE PERIOD 2021 - 2025

Defects in cell homeostasis might be responsible for the inefficient replenishment of functional cells during the establishment and progression of aging diseases, including cardiovascular diseases and cancer [1].

The Mechanobiology of disease team (MBD) is mainly interested in correlating defects in tissue-specific cell mechanobiology system with the onset of aging pathologies with a special focus on those affecting the cardiovascular system.

The working hypothesis of MBD is that defects in the function of the apparatus cells use to perceive and respond to external mechanical cues – the mechanosensing apparatus – which contributes to aging-associated pathologies.

This hypothesis is the basis of the concepts of mechanotargeting and mechano-therapeutics, which recently made their way into the medical vocabulary to describe a new class of drugs and treatments targeting mechanically activated pathways involved in pathologies.

The scientific questions MBD plans to answer in the near future are the following: (1) is the regulation of mechanosensing pathways involved in the setting and progression of aging-associated diseases? (2) can we exploit our knowledge on cell mechanosensing to counteract aging-associated pathologies?

Recently, our team contributed to unveil the molecular processes underlying the intracellular mechanical responsiveness of neonatal cardiomyocytes [2], mesenchymal progenitors [3, 4], skeletal myoblasts [5] and pluripotent stem cells [Pagliari et al, in revision]. Also, we provided the first high resolution 3D map of nanostructure remodeling associated with heart failure in human patients (Perestrelo et al, in revision) and identified a mechanosensitive component of the cardiomyocyte RNA splicing apparatus involved in cardiac diseases (Martino et al, in revision). More importantly, our team provided the first evidence that the mechanically active protein YAP controls cell-ECM interaction and tumor cell migration by promoting focal adhesion gene transcription [6].

We additionally described how the mechanical control of mechanosensitive pathways can be exploited in breast cancer cells to hijack their genetic program. In particular, we proposed a novel strategy to mechanically reprogram tumor cells to exit the cell cycle and progress towards the harmless adipogenic phenotype [7].

In the near future, MBD researchers plan to continue combining loss- and gain-of-function approaches, microfluidics and micro patterning technologies to manipulate the mechanosome of adults, pluripotent stem cells and stem cell-derived cardiac cells.

Furthermore, MBD plans to invest more into the generation of patient-specific iPSC-based organoid disease models with the goal of exploiting multi-organ-on-chip approaches to better mimic and study the pathophysiological role of mechanically activated pathways. Of note, we plan to offer this cutting-edge technology to the study of SARS-COV-2 tropism and effects in human organs (heart, brain, lungs, intestine).

Also, we plan to start a large-scale analysis of small molecules able to tune the function of mechanically activated pathways.

Finally, MBD researchers plan to scale-up some of the novel mechano-therapeutics identified in cell cultures closer to the clinic, by testing their activity on patient-derived cells to obtain 3D organoids.

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CELLULAR AND MOLECULAR IMMUNOREGULATION

Mgr. Jan Frič, Ph.D.

Established in 2016

Key words
Innate Immunity, Inflammation, Immunosenescence, Immunosuppression, Sepsis, Tissue Organoids

Research focus
The team focuses on different aspects of the human immune response and on how the underlying mechanisms of immunity are linked with the development of disorders and pathologies. The main objectives are addressing i) new key events in myeloid cell signaling, describing the role of the Calcineurin–NFAT axis in the control of myeloid cell response to pathogens; (ii) novel important roles of immune response in the progression of human sepsis; (iii) the research in the field of immune senescence, addressing the immunosenescent phenotype in a number of cohorts of patients with various disorders and in child cancer survivors; iv) the development of 3D models of human mucosal tissues to mimic and study the immunocompetence of these complex microenvironments. Our tight collaboration with clinicians creates the opportunity to perform pre-clinical research with a strong translational approach, filling the gap between bench and bedside.

Research objectives
- Description of the role of pattern recognition receptors in acute immune response, chronic inflammation and tissue regeneration using immune cells and mucosal tissue 3D organoids.
- Characterization of dynamic changes of the immune system during onset and progression of septic shock.
- Description of molecular crosstalk between innate immune signaling and metabolic changes in myeloid cells.
- Describing the mechanisms responsible for the onset of innate immune memory as a tool to reduce the susceptibility of patients to respiratory infections.
- Develop translational research in the field of immunosenescese and inflammaging through analysis of various cohorts of the elderly, patients with chronic inflammatory disorders and child cancer survivors.

Main partners
- Department of Pathophysiology, Third Faculty of Medicine, Charles University in Prague, Czech Republic
- Veterinary Research Institute, Brno
- Institute of Hematology and Blood Transfusion in Prague
- Czech Centre for Phenogenomics, Institute of Molecular Genetics, Prague
- Central European Institute of Technology, Brno
- University of Perugia, Italy
- Latvian Institute of Organic Synthesis, Riga

Offered services and expertise
- FACS sorting of cells using MoFlo.
- Multiparametric FACS analysis.
- Histology and imaging techniques.
- Tailored cell signaling reposter cell lines.
- Screening of signaling processes using various human primary immunocytes.

STRATEGY FOR THE PERIOD 2021 - 2025

Our team focuses on different aspects of the human immune response and on how the underlying mechanisms of immunity are linked with the development of disorders and pathologies. In the last years, we have successfully established our main research niches: (i) we focused on new key events in myeloid cell signaling, describing the role of the Calcineurin–NFAT axis in the control of myeloid cell response to pathogens; (ii) we addressed novel important roles of immune response in the progression of human sepsis; (iii) we established our research in the field of immune senescence, addressing the immunosenescent phenotype in a number of cohorts of patients with various disorders and in child cancer survivors; (iv) we developed 3D models of human mucosal tissues to mimic and study the immunocompetence of these complex microenvironments. Our tight collaboration with clinicians creates the opportunity to perform pre-clinical research with a strong translational approach, filling the gap between bench and bedside.
In the next years, we aim to dissect the major changes occurring in immune cell subsets, including their hematopoietic progenitors. During the onset and progression of sepsis we will use new as well as already collected sepsis patients' samples. By performing deep immunophenotyping of clinical samples and revealing immune-metabolic patterns of these cells, we aim to provide novel tools for a precise and timely diagnosis and prognosis of this complex pathology. Furthermore, we plan to tackle the mechanisms responsible for the onset of innate immune memory in myeloid cells and use this as a tool to reduce the susceptibility of patients to respiratory infections, including COVID-19.
We plan to expand our translational research addressing the early onset of immune senescence and its link with chronic inflammatory pathologies and the burden of anti-cancer therapies in child cancer survivors. Signs of immune senescence onset will be compared across different cohorts and linked with experimental data about candidate drivers of this process, including chronic low-grade inflammation, persistent infections and other chronic systemic disorders.
Furthermore, we will keep developing our research in the mucosal immune-environment to better understand host-pathogen interactions. Using our well-established models of human intestinal and lung organoids, we aim to develop novel tools and approaches for the resolution of complex human inflammatory disorders.
Our team greatly benefits from established local and international collaborations, including the University of Perugia (fungal immunology), the Latvian Institute of Organic Synthesis in Riga, the Institute of Molecular Genetics and BIOCEV in Prague (metabolomics), the Institute of Hematology and

Blood Transfusion in Prague (flow cytometry), and the Veterinary Research Institute in Brno (SARS--CoV-2). Strong established intramural cooperation with ICRC FNUSA teams (including POTR, INC, CNR, DMT, CAP) and the support of ICRC core facilities (BST, MS) will continue to be essential for our pre-c-linical and translational research.

EPIGENETICS, METABOLISM AND AGING

Manlio Vinciguerra, Ph.D., MSc

Established in 2016

Key words
Epigenetics, Nutrition, Gastrointestinal Cancers, Senescence, Aging, Immunity, Stem Cells

Research focus
The research focus of the Epigenetics in Metabolism and Aging team consists of 3 research lines. The major research interest is to understand how histone variants, an exquisite epigenetic mechanism of regulation of gene expression in mammals, affects cell metabolism, reprograming and cancer. The EMA studies how large histone variants called macroH2A1.1 and macroH2A1.2, splicing isoforms of macroH2A1, function as energy sensors and oncogenes in many cancer types and during induced pluripotent stem cells reprograming. The second line of investigation concerns the study of new-patented senolytics, drugs that kill selectively senescent cells in liver physiology and pathology. The third line of investigation involves the detailed study of the role of a rejuvenating factor, identified through parabiotic screening called Growth Differentiation Factor 11 (GDF11) in nutrient metabolism in mice.

Research objectives
- Study the epigenetic macroH2A1 isoforms and DNA-damage components of endothelial cells repro-graming into induced pluripotent stem cells (iPSC).
- Identification of the central and systemic effects of senolytics (dasatinib+guercetin, and a new-patented one) in mice.
- Uncovering the side effects of the „youth factor" GDF11 in obese mice and humans.

Main partners
- University College London, London, UK
- University of Southern California, Los Angeles, USA
- University of Barcelona, Barcelona, Spain

STRATEGY FOR THE PERIOD 2021 - 2025

The research focus of EMA team is on the epigenetics and cellular mechanisms that contribute to aging of an individual, which is the main risk factor for the majority of illnesses. As a major epigenetic mechanism, EMA team studies histone variants and in particular histone macroH2A1, and as mechanism driving aging the team studies cellular senescence, a phenomenon that is both physiological and pathological.

At EMA we have 4 research objectives, which address outstanding open questions:

- Can we create induced pluripotent stem cells (iPSC) more stable, and suitable for regenerative therapies by manipulating the expression of macroH2A1? Investigations on DNA damage and differentiation *Collaborations: Prof. Irena Koutna (ICRC), Prof. Lumir Kreici (MU/ICRC), Dr. Martin Mistrik (IMTM, Olomouc), Prof. Jiri Bartek (Karolinska Institute, Stockholm, Sweden).*
- Can we delay aging by eliminating selectively senescent cells in the organism? Investigations on senolytics. *Collaborations: Dr. Martin Mistrik/Prof. Marjan Haiduch (IMTM, Olomouc), Dr. Sylvia Badurek (VBCF, Vienna), Dr. Dmitry Bulavin (IRCAN, Nice, France).*
- Can we use blood circulating histones as new liquid biopsies to stratify patients with diabetes, cancer and by age? Investigations using patient cohorts and ImageStream ® based analysis. *Collaborations: Dr. Jan Cerveny (Czech Globe), Dr. Anna Alisi (Pediatric Hospital Bambin Gesu, Rome, Italy).*
- What are the side effects of the most promising "anti-aging" factors? Investigations on Growth Differentiation Factor 11 (GDF11) in vivo. *Collaborations: Prof. Michelangelo Foti (University of Geneva, Switzerland), Prof. Francesc Villarroya (University of Barcelona, Spain).*

TRANSLATIONAL NEUROSCIENCE AND AGING PROGRAM

Gorazd Bernard Stokin, Ph.D., MD

Established in 2016

Key words
Aging, Alzheimer`s Disease, Traumatic Brain Injury, Stem Cell, Axonal Transport

Research focus
The TAP team aims at furthering our understanding of aging and age-related disorders, in particular, neurodegenerative ones. TAP focuses on understanding the murky grey zone between physiological aging and preclinical and early symptomatic neurodegenerative disorders such as Alzheimer`s disease. Intriguingly, traumatic brain injury recapitulates many of the features found in aging and early symptomatic Alzheimer`s disease. Uniquely TAP takes advantage of its clinical, as well as basic, scientific knowledge and experience to bring further progress in its specific research field of interest. Thorough understanding of behavioral and cognitive neurology is coupled to stem cells and animal models of aging and neurodegeneration, with particular attention to synaptic and axonal changes.

Research objectives
- Identification of the earliest change of aging and neurodegeneration.
- Understanding the mechanism underlying aging and neurodegeneration.
- Generation of human stem cells derived neuronal and glial lineages to address aging and neurodegeneration.

Main partners
- Mayo Clinic, Rochester, MN, USA
- University of California, San Diego, CA, USA
- University of Buenos Aires, Buenos Aires, Argentina

Offered services and expertise
- Behavioral and cognitive testing.
- Real time in vivo imaging.
- Production of human stem cells derived neuronal and glial lineages.
- Automated immunochemistry scoring.

STRATEGY FOR THE PERIOD 2021 - 2025

Background
A recent exponential increase in people reaching old age has translated into increased incidence of neurodegenerative disorders such as Alzheimer's disease, which today represent an unprecedented economic burden and above all a major global health emergency. The Translational Aging and Neuroscience (TAP) team was founded with the goal to advance our knowledge about aging with a particular focus on neurodegenerative disorders, such as Alzheimer's disease. Today, TAP consists of an international group of researchers including Dr Stokin as the Principal investigator, Drs Bhat, Carna, Lacovich, Novotny, Onyango and Pozo Devoto as post-doctoral fellows, Ms Feole and Velezmoro-Jauregui as PhD students and Ms Texlova, Dragisic and Ernstbergerova as technical experts. In the near future, TAP plans to employ Ms Ivanyi to provide psychological expertise in clinically relevant studies. In addition, Ms Klosterman, University of Arizona, will be joining next year as an already awarded Fulbright fellow and possibly Dr Das, University of California San Diego, as a Marie Sklodowska Curie fellow. TAP research evolves around the identification of the earliest clinical features and in elucidating basic mechanisms underlying the development of Alzheimer's and related disorders. This research capitalizes from Dr. Stokin's expertise in axonal biology and his previous discoveries of the axonal role in neurodegeneration in combination with his experience as a behavioral and cognitive neurologist. Major general objectives of research planned by TAP in 2021 - 2025 can be summarized as follows:

General objective 1 - Examining the role of axons in neurodegeneration
In order to augment our knowledge about the role of axons in aging and neurodegeneration, we test several aspects of the axonal biology and pathology here, primarily by exploiting human stem cell derived neuronal and other cultures. First, to date, we developed novel methodological approaches to understand basic principles of microtubule-based axonal transport. Next, we want to exploit these approaches to understand how mutations in genes, linked to neurodegeneration, perturb axonal transport. Second, we have recently established cellular phenotypes produced by mosaic amyloid precursor protein (APP) mutants, recently linked to sporadic Alzheimer's disease. We have now created several APP deletion mutants, which will help us elucidate the mechanisms underlying mosaic AP mutants in Alzheimer's disease. Third, we spent several years assessing mechanisms underlying the development of axonal swellings, the major axonal pathology found in Alzheimer's and related disorders. By developing novel axonal injury assay and using animal models we have managed to validate our assay and test for morphological changes and functional consequences of axonal swelling formation. In the future we plan to link observed changes in calcium to the cytoskeletal adaptation of the axons in response to injury, and to test whether similar mechanism also take place in the formation of axonal swellings in Alzheimer's disease. And last, but not least, considering APP and microtubule-protein tau play a major role in Alzheimer's and related disorders, significant effort is made to better understand their pathophysiology using stem cells and animal models.

General objective 2 - Assessing the role of glia in axonal biology and neurodegeneration
Although axons are surrounded by glial cells from oligodendrocytes to astrocytes and microglia, interaction between axons and glial cells are poorly understood. In order to elucidate functionally the interaction between axons and glia we have developed novel protocols to generate isogenic glial cell lines. In the future, we plan to continue our efforts to understand how APP and Alzheimer's disease linked APP mutations affect astrocytes and to rigorously test the effects of glia on axonal transport, in particular, in reactive astrocytes. Most importantly, since we have recently generated a conditional transgenic mouse overexpressing APP, we next plan to test which brain cell type is most affected in Alzheimer's disease.

General objective 3 – Screen and identify early markers of aging and Alzheimer's disease
In order to clinically test the relevance of the identified mechanisms underlying the development of aging and Alzheimer's disease (General objectives 1 and 2), one must be able to match the mechanistic findings to a clinically measurable outcome. However, today there are relatively few clinically measurable outcomes available. As a result, to date, we completed a cross-sectional analysis of healthy cognition in the middle aged and established that the major risk factors for suboptimal healthy cognition in the middle aged are psychological factors ranging from anxiety to depression. Importantly, we have also identified a failure of choroid plexus and identified several microRNAs specific to early Alzheimer's disease. In the future, we plan to test for association between the middle aged and their parents for changes in cognition, including possible genetic risk factors, as well as to establish longitudinally changes in cognition with aging. Last, but not least, following several years of work we have finally completed the development of a novel learning and memory test, we now plan to first validate the test and then explore its usefulness in a multicentric trial.

Other research
In order to continue contributing as researchers to the society at large, TAP examined longitudinally the effects of COVID-19 on mental health and plans to continue monitoring how future COVID-19 developments might influence mental health in the future. This work is currently under consideration for publication and will continue being published to enhance global fight against COVID-19.
TAP business mindset
TAP believes strongly in the collaboration with industry, as this is the fastest way to translate research discoveries into practice benefiting people. Consequently, we have long ago established collaboration with Psychogenics, a world leader in preclinical pharmacological testing established by the Novel laureate Paul Greengard. We plan to continue and possibly expand this collaboration in the years to come. In addition, we have been developing: 1. several novel methods, in example examining axonal transport and pathology, 2. paradigms, such as the axonal injury, one for which we have already submitted patent application, 3. high throughput screening assays, such as for testing impairments in axonal transport, 4. novel CRISPR-Cas9 modified isogenic human stem cell derived cell models mimicking neurodegenerative diseases, 5. Conditional transgenic mouse models allowing to test Alzheimer's disease pathology in specific brain cell populations, 6. Antibodies with therapeutic potential and 7. a CRISPR-Cas13 assay to eliminate mutant expression of RNAs involved in neurodegeneration. Although we have already started submitting patent applications for some of these novel tools and instruments, we plan to continue patenting in the years to come.

Collaborations
Over the years TAP, ICRC, collaborated productively with TAP, Mayo Clinic. Considering key collaborator of TAP, Mayo Clinic, recently moved to the Barrow Neurological Institute, TAP, ICRC, will most like-

ly establish a novel collaboration with the Barrow Neurological Institute, while exploring the option of continuing the collaboration with Mayo Clinic. TAP also plans to continue collaborations with the University of California San Diego, several institutions in Buenos Aires as well as with Imperial and King's Colleges in London. TAP is currently awaiting the signing of the annex for the collaboration with the University Clinical Centre Ljubljana in order to jump-start mutual clinical research. TAP is also awaiting the signing of the collaboration with the University of Nairobi with which it plans to explore axonal biology of big animals. Last, but not least, based on TAP research, several potential collaborations may be desired by TAP in the near future, and these include collaborations with the University of Brisbane and Emory University among others.

MOLECULAR CONTROL OF CELLULAR SIGNALING

Dr. Jaeyoung Shin

Established in 2019

Key words
Targeted therapy, Cancer, Cellular signaling, Organoid model, Drug development, Metastatic Cancer

Research focus
The research theme is Molecular control of signaling in cancer associated with aging. To study signal transduction molecules, scientific interests are in understanding the molecular signaling machinery controlling fundamental cellular processes like cell death/survival, migration and cellular differentiation. This project has specifically added mitochondria and aging. With this in view, a comprehensive analysis of these MAPK signaling will provide important insights into the molecular mechanisms involved in the development of cancer. Understanding MAPK signaling, our team should be able to develop innovative therapeutic concepts that will enable us to attack tumor cells. The mechanistic understanding gained from these studies will improve diagnosis, lead to the development of treatment strategies to arrest invasion at the pre-malignant stage, and thus prevent patient overtreatment.

Research objectives
- The RAF/MEK/ERK pathways controlled by protein kinases are involved in the initiation and progression cancer forms.
- To ensure understanding of cancer associated with aging, new therapeutic options for tumor genesis should be developed.
- Biomarker strategy development and implementation for oncology clinical trials.
- Investigating the impact of the 3D organoid cell culture on the targeted therapeutic response and signaling pathway activity of MAPKs, with a view to identifying potential targets to improve therapeutic response.

Main partners
- Masaryk Memorial Cancer Institute (MMCI), Czech republic
- Cell Signaling and Targeted Therapy Research Group at UIT The Arctic University of Norway
- Natural Science group at Dankook University in Korea

Offered services and expertise
- Advanced immunoblotting.
- 3-dimensional models of primary tumor tissue.
- shRNA library directed against the entire human genome.
- CRISPR-based gene knock-in.

STRATEGY FOR THE PERIOD 2021 - 2025

Summary
There is a great need to develop systems in which the course for initiation and progression of cancer, and therapies directed at these steps, can be studied directly in mouse and human cells, and over time courses relevant to real world tumorigenesis. While engineered mouse models are valuable, there is a need to develop complementary systems where meaningful, relatively rapid in vitro work can yield substantial pre-clinical insights leading to final animal testing. In this regard, we have developed an organoid model, which is yielding important data for studying the progression of breast cancer. This proposal directly addresses the unmet need by developing a novel three-dimensional in vitro organoid model that does recapitulate key hallmarks of cancer progression. The mechanistic understanding gained from these studies will improve diagnosis, lead to the development of treatment strategies to arrest invasion at the pre-malignant stage, and thus prevent patient overtreatment. It is straightforward to generalize our system to other tumor types, development of tumor/stromal co-culture, and drug screening.

Research plans
2021: In this investigation, our main focus will be on how the actions and interplay of the currently identified MAPK signaling molecules are controlled by phosphorylation and protein-protein interaction. In a first set of experiments, we will continue our analysis on the modification state of affinity purified targeted protein from human breast cancer tissue for a specific molecular type of cancer tissue, cancer cells and human epithelial cells.
2022: We will investigate, for the first time, the spatial distribution and origin of the migratory phenotype. We will use CRISPR-based gene knock-in (FP-labeling), automated image analyses, and a deep-learning algorithm to track and visualize the emergence of migratory phenotypes from the hypoxic core outward to the periphery or from the migratory front. The development of this 3D organoid model and completion of the proposed work will analyze in the progression of invasive breast cancer. We will obtain a shRNA library directed against the entire human genome and have gained access to the CRISPR/Cas9, all in one vector system. Identification of biomarker and MAPKs substrates relevant for cancer cells infection can be done.
2023: We will further employ this approach of profiling kinase expression in organ specific cancer cell lines, which have revealed substantial kinome reprogramming during cancer progression and demonstrated an excellent correlation between the anti-proliferative effects of kinase inhibitors and the expression levels of their target kinases. Affinity columns immobilized with kinase inhibitors have been employed as capture ligands for the enrichment of kinases, and approximately 200 protein kinases could be identified and quantified by subsequent LC-MS/MS analyses. Additionally, we will enrich ATP binding site by modifying MAPKs proteins from stable cell lines, expressing His-tagged Ub and perform Western blotting against the endogenous candidates.
2024: Organoids are three-dimensional models of primary tumor tissue obtained from fresh biopsies. We will demonstrate that breast cancer tissue cultured in 3D express a higher sensitivity to target molecules than those cultured in 2D, as the cells of the 3D cultures display an increased activation and dependence on MAPK signaling. To gain further insights into the potential role of target molecules in epithelial morphogenesis and differentiation, we will study target molecules' expression levels by employing three-dimensional (3D) gastrointestinal organoids that reflect either murine intestinal or human gastric architecture and cell composition.
2025: We will investigate the impact of the 3D organoid cell culture on targeted therapeutic response and signaling pathway activity of MAPKs with the view to identifying potential targets, to improve therapeutic response. With the addition of a new technique, tumor organoid culture, to our repertoire of pre-clinical cancer models, it is important to evaluate the translational potential of this new model system. The use of cancer organoids, as both models and methods, is expanding in the fields of basic and preclinical cancer research. Drug screening systems using cancer organoids could potentially be applied to determine the most beneficial drug for each individual patient.

Role within the Collaborative Research Centre
Within this project, we have established a collaboration with the Masaryk Memorial Cancer Institute (MMCI) about organoids as reliable breast cancer research models.
Regarding MAPK signaling within the cancer research has established collaborative with Cell Signaling and Targeted Therapy Research Group at UIT The Arctic University of Norway.
We also have established a collaboration with the Natural Science group at Dankook University in Korea.

CELL AND TISSUE ENGINEERING FACILITY – cGMP

doc. RNDr. Irena Koutná, Ph.D.

Established in 2016

Key words
Cell and Tissue based therapy

Research focus
The CTEF-cGMP facility represents a unit for Cell-based Medicinal Products (CBMPs) or Advanced Therapy Products (ATPs) including cell therapy and tissue engineered products. These products are manufactured from viable autologous, allogeneic or xenogeneic cells and they can also contain non-cellular components (chemical/biological compounds, matrices, scaffold etc.). All manufacturing and production control activities in CTEF are carried out in accordance with the principles of cGMP quality. This is in order to provide the authorization for the manufacturing of investigation of all medical products within the clinical trials. Environmental Monitoring and Assessment is conducted continuously during the production processes.

Research objectives
- Development of clinical-scale manufacturing processes based on cell and tissue engineering.
- Development of analytical methods for product characterization and release.
- GMP manufacturing and quality control of releasing clinical–grade products.

Main partners
- Institute of Hematology and Blood Transfusion, Praha, Czech Republic
- Masarykova Univerzita, Brno, Czech Republic
- The Institute of Genetic Medicine, Newcastle, United Kingdom

Offered services and expertise
- The facility provides licensed manufacturing and testing of cGMP grade cell-based medical products for pre-clinical and clinical trials and is available to scientists in the academic and private sector.
- Taking care of project licenses and authorization processes.

STRATEGY FOR THE PERIOD 2021 - 2025

RESEARCH FOCUS
Advanced Therapy Medicinal Products (ATMPs) offer significant promise for the long-term management, and even cure, of disease, especially in areas of high unmet medical need. The current clinical treatment approaches to cancer, heart disease, diabetes, stroke and other conditions will be changed by ATMPs. These therapies will impact many treatment pathways by exploiting techniques and methods to repair, replace, regenerate and re-engineer human genes, cells, tissues or organs in order to restore or establish normal function. Future plans will need to consider other advanced therapies and parallel healthcare innovations that will affect strategic implementation.

GLOBAL MAIN OBJECTIVES:
- Gene therapy (i.e. the transfer of genetic material into the cells of a patient's body to treat the cause or symptoms of a specific disease).
- Cell therapy (i.e. the transfer of intact, live cells into a patient to help lessen or even cure a disease). These cells may originate from the patient themselves or a donor.
- Tissue engineered product (i.e. a regenerative medicine that replaces or regenerates human cells, tissues or organs to restore or establish normal function).

GLOBAL KEY PRIORITIES:
- Regulatory Compliance, Quality and Safety
- Workforce Development
- Clinical trials
- Academic* and Company collaboration

SPECIFIC AIMS 2021-2023
Production:

ATMP	SÚKL approved production from
Virus specific T-lymphocytes	1Q/2021
Peripheral blood mononuclear cells	1Q/2021
iPSCs	1Q/2021
hESCS	1Q/2021
MSC from Umbilical Cord	3Q/2021
MSC from Fat Tissue	3Q/2021
CAR-T GD2	4Q/2022
CAR-T PSMA	4Q/2022
Skin Graft production	4Q/2023
CHONDROSET	4Q/2023
QUALITY CONTROL TESTS	**SÚKL authorization from**
MTT-asay	1Q/2021
Immunogenicity T-cell test	1Q/2021

MEDICINAL CHEMISTRY

doc. Mgr. Kamil Paruch, Ph.D.

Established in 2016

Key words
Organic Synthesis, Medicinal Chemistry, Chemical Biology, Kinases, Nucleoside Analogs, Nucleases

Research focus
The research in our laboratory focuses on the development of synthetic methods and strategies for the preparation of structurally non-trivial small molecules for applications in biomedical research. Specifically, our project includes:
- Development of potent inhibitors of certain „non-routine" kinases (CLK, HIPK).
- Synthesis of new forskolin-based modulators of adenylyl cyclases.
- Identification inhibitors of selected DNA repair pathways (nucleases Mre11 and Mus81).
- Preparation of new small-molecules probes of cell differentiation, and fluorescent probes for biological systems.

Research objectives
- Total synthesis of new analogs of forskolin and testing their activity against human adenylyl cyclases.
- SAR development around the existing proprietary inhibitors of nucleases MRE11 and Mus81; identification of sub-micromolar inhibitors.
- Synthesis and biological profiling of new carbocyclic C-nucleosides.

Main partners
- Max Planck Institute for Molecular Physiology, Dortmund, Germany
- University of Oxford, Oxford, United Kingdom
- University of Oslo, Oslo, Norway

Offered services and expertise
- Organic synthesis of small-molecule organic compounds of medium complexity.
- Medicinal chemistry - optimization of early leads.
- Separation of racemic mixtures by HPLC on chiral stationary phase on semipreparative scale.

STRATEGY FOR THE PERIOD 2021 - 2025

The research in our laboratory focuses on the discovery of new (potentially patentable) organic compounds with targeted biological activity. Our research topics are the following:

Selective kinase inhibitors
Protein kinases regulate a wide range of cellular functions including initiation of cancer cells, tumor progression, and the development of metastatic diseases. Many of them therefore represent attractive targets for modern oncology. Up to this date, more than thirty kinase inhibitors have been approved for clinical use.
Part of our research is focused on the identification and development of new (patentable) potent and highly selective inhibitors of selected „non-routine" kinases, especially Haspin and ALKs, where we have already identified attractive early lead compounds. The ultimate ambition of these projects, which are run in close collaboration with top-class biologists, is the identification of state-of-the-art chemical biology probes and candidate compounds that would be suitable for further preclinical progression.

Inhibitors of DNA repair pathways
DNA nucleases are key enzymes responsible for processing strands of DNA following damage. Present in all cell types, nucleases are one of the first enzyme mediators recruited to the site of DNA damage in cells and play crucial roles in various DNA repair pathways, ensuring stability of the genome.
While nucleases have been relatively underexplored in terms of their pharmacological inhibition, we believe that nuclease inhibitors could have a broad potential as selective treatments for a range of cancers, particularly in tumors that have defects in their DNA repair processes and are reliant on alternative DDR pathways, which are mediated by nucleases. The opportunity may also exist to use nuclease inhibitors in combination with other cancer therapies, including the standard of care treatments, such as ionizing radiation, and potentially together with emerging therapies such as immuno-oncology treatments.

Chemistry and biology of forskolin
Structurally complex diterpene forskolin is a known allosteric activator of adenylyl cyclases, key enzymes involved in the production of second messenger cAMP. Semisynthetic analogs of forskolin provided an important proof-of-principle in therapeutic targeting of adenylyl cyclases (colforsin is a drug approved in Japan). The pharmacology of adenylyl cyclases is complex, however, much remains to be learned.
Our laboratory is re-examining the potential of forskolin. Towards this end, we recently reported a 24-step synthesis of this complex target and developed synthetic strategies toward novel forskolin analogs not accessible by semisynthesis. By profiling the new forskolin analogs in a panel of all isoforms of human adenylyl cyclases (in collaboration), we are hoping to identify molecules with improved potency and/or isoform selectivity.

Inhibitors of bacterial and eukaryotic ribosomes
A more recently initiated project in our laboratory is looking into analogs of the natural antibiotic bactobolin A to target bacterial and/or eukaryotic ribosomes. We have recently published the shortest synthesis of bactobolin A (16 steps) and used this approach to rapidly access new bactobolin A analogs. Prepared molecules will be examined in the context of antibiotics and selective cytotoxic agents.

GENOME INTEGRITY

doc. Mgr. Lumír Krejčí, Ph.D.

Established in 2016

Key words
Genome Integrity, DNA Repair, Homologous Recombination, Cancer, Small Molecule Inhibitors

Research focus
The Genome Integrity research focuses on deciphering the intrinsic functions of homologous recombination (HR) which has a dual role in the maintenance of genome stability. First, it promotes the faithful repair of DNA double-strand breaks belonging amongst the most lethal forms of DNA damage. Moreover, HR is also required for stabilizing stalled replication forks, promoting their reversal, protection and restart to ensure completion of replication and ensure genome maintenance. Inability to perform and regulate recombination is linked to human infertility, miscarriage and genetic diseases, particularly cancer, this further emphasizes the importance of a better mechanistic understanding of this pathway. Furthermore, the GENI team focuses on the detailed study of nucleases, which comprise an integral part of many DNA repair pathways and their inactivation leads to genomic instability and cancer.

Research objectives
- Characterizing the mechanism and regulation of homologous recombination and its intrinsic role in the maintenance of genome stability.
- Mechanistic understanding of the action of HR co-factors and their impact on genome integrity and cancerogenesis.
- Development of potent and selective inhibitors of nucleases for possible therapeutic use.

Main partners

- Francis Crick Institute, London, UK
- University of Zurich, Zurich, Switzerland
- IFOM, Milan, Italy

Offered services and expertise
- Various methods from biochemistry, structural biology, molecular biology, genetics and biophysics.
- Detailed studies of protein properties and activities including their interactions with other molecules such as DNA and small molecule inhibitors.

STRATEGY FOR THE PERIOD 2021 - 2025

Research Focus and Hypothesis
The Genome Integrity research focuses on deciphering the intrinsic functions of homologous recombination (HR) which has a dual role in the maintenance of genome stability. First, it promotes the faithful repair of DNA double-strand breaks belonging amongst the most lethal forms of DNA damage. Moreover, HR is also required for stabilizing stalled replication forks, promoting their reversal, protection and restart to ensure completion of replication and ensure genome maintenance. Inability to perform and regulate recombination is linked to human infertility, miscarriage and genetic diseases, particularly cancer, this further emphasizes the importance of a better mechanistic understanding of this pathway. Furthermore, the GENI team focuses on the detailed study of nucleases, which comprise an integral part of many DNA repair pathways and their inactivation leads to genomic instability and cancer. Using very interdisciplinary approach the GENI is developing specific inhibitors of nuclei for treatment of therapy-resistant tumors as well as synthetic killing of genetically defined cancers.

Main Objectives
- Characterizing the mechanism and regulation of homologous recombination and its intrinsic role in the maintenance of genome stability.
- Mechanistic understanding of the action of HR co-factors and their impact on genome integrity and cancerogenesis.
- Development of potent and selective inhibitors of nucleases for possible therapeutic use.

Planned Collaborations
- Francis Crick Institute, London, UK
- University of Zurich, Zurich, Switzerland
- IFOM, Milan, Italy

PROTEIN ENGINEERING

prof. Dr. Mgr. Jiří Damborský

Established in 2016

Key words
Alzheimer Disease, Biocatalysis, Bioinformatics, Computer Modelling, Lab-on-chip, Microfluidics, Metabolic Engineering, Mechanistic Enzymology, Protein Engineering

Research focus
The PEG research team focuses on protein and metabolic engineering for biomedicine. The team develops new theoretical concepts, software tools and lab-on-chip technologies for protein engineering. It uses these newly developed tools for the design of proteins with improved properties for biocatalysis, biodegradation, biosensing, cell culturing and differentiation. The team has published more than 180 original articles, 19 book chapters and filed 7 international patents and founded the biotechnology spin-off Enantis Ltd.

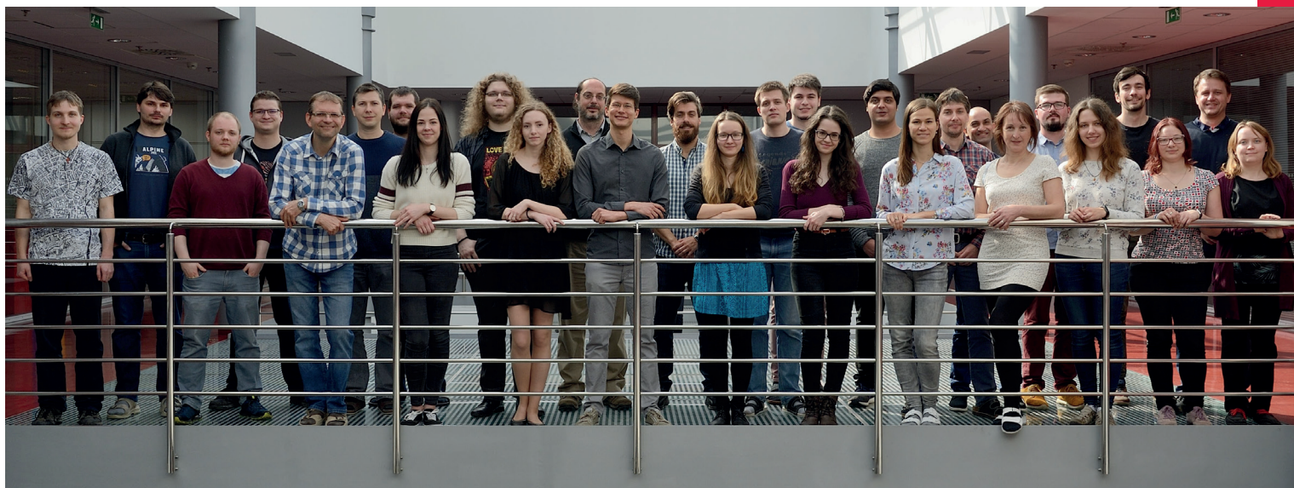
Research objectives
- Computational design and engineering of hyper stable proteins.
- Establishing new, theoretical concepts for protein engineering.
- Development of user-friendly software tools and microfluidic chips.

Main partners
- ETH Zurich, Switzerland
- Tohoku University, Katahira, Japan
- University of Cambridge, Cambridge, UK
- Novo Nordisk Foundation Center for Biosustainability (CFB), Copenhagen, Denmark
- Spanish National Research Council (CSIC), Madrid, Spain

Offered services and expertise
- Bioinformatics – identification of interesting genes in genomic databases for molecular cloning and experimental characterization.
- Lab-on-Chip Technologies – development of microfluidic lab-on-chip technologies for biochemical and biomedical research.
- Pathway Engineering – design and construction of bacterial strains expressing newly assembled biochemical pathways.
- Protein Stabilization – computational design of stabilizing mutations using evolutionary and energetic approach.

STRATEGY FOR THE PERIOD 2021 - 2025

PEG team is focused on the development of diagnostic and treatment tools in the domains of (i) Alzheimer's Disease, (ii) acute stroke, and (iii) cancer. Most recently, the PEG team responded to the urgent need to address (iv) the COVID pandemic and initiated a new project focused on the development of a novel computational technique for the identification of potential drug candidates. (I) We will study the molecular mechanisms of Alzheimer's Disease. We will focus on the interactions of the Abeta peptide with the APOE protein, which is critical for the homeostasis of the Abeta in the brain. We will use both experimental and theoretical approaches in this study. Understanding the molecular mechanism of the disease is critical to the identification of new molecular targets. (II) We will apply advanced methods of protein engineering to improve existing thrombolytic. We will also attempt to identify new thrombolytic enzymes by database screening using bioinformatics tools. (III) We will continue developing a new web tool PedictSNP Onco for the navigation of treatment for pediatric oncology patients. This tool integrates a large variety of structural bioinformatics tools and provides medical doctors with essential data for their decisions. (IV) We will conduct systematic screening of all FDA-approved drugs with the target spike (s) glycoprotein. We will analyze results using machine learning approaches and develop generally applicable mathematical models. The workflow developed within this project will be implemented in web applications. The internal collaborations include interactions with clinical teams (MUDr. Robert Mikulík – FNUSA; MUDr. Kateřina Sheardová – FNUSA; MUDr. Jaroslav Štěrba – FN Brno), which are important for the directing of projects towards the development of tests, materials and treatment strategies, which will be practically useful and beneficial for the patients. We also have several, critical international collaborations, which give us access to unique technologies (Dr. Stavros Stavrakis – ETH Zurich, Switzerland; Dr. Florian Hollfelder – University Cambridge, United Kingdom; Dr. Uwe Bornscheuer – University Greifswald, Germany).



CELL SIGNALING

Mgr. Pavel Krejčí, Ph.D.

Established in 2018

Key words
Morphogen Signaling, Receptor Tyrosine Kinases, Genetics of Bone Disorders, Primary cilia, Fibroblast Growth Factor, Achondroplasia, Drug Development and Repurposing

Research focus
Maintenance of tissue homeostasis depends on extracellular signals that govern basic cell functions. Receptor tyrosine kinases (RTKs) represent the major molecular tools of such cell-to-cell communication. RTK importance is further emphasized by evidence of their pathological functions, with more than 80 human pathologies associating with alterations in the RTK genes, including cancer, developmental disorders and metabolic syndromes. Our research focuses on several poorly known areas of the RTK functions, such as the composition of protein complexes associating with activated RTKs at the cell membrane, the nature of effectors utilized by RTKs to regulate specific cell functions, the mechanisms by which RTKs interact with primary cilia and morphogen signaling, and the molecular pathologies of skeletal disorders caused by RTK mutations.

Research objectives
- Unravel the mechanism of primary cilia regulation by RTKs.
- Determine the extent of transactivation among the human RTKs.'
- Develop new treatments for FGFR3-related chondrodysplasias.

STRATEGY FOR THE PERIOD 2021 - 2025

Cell signaling lab focuses on cell communication systems, which use polypeptide ligands and the cell surface receptors. These receptors bind growth factors, cytokines, morphogens, hormones, extracellular matrix components, and other ligands. We aim to answer questions related to many aspects of receptor signaling, ranging from molecular and cellular biology of receptor function to the development of receptor inhibitors. We also explore the biology of primary cilia, and determine how defects in cilia function lead to skeletal syndromes in humans. Finally, we develop new therapeutics for Achondroplasia and operate the first clinical registry for patients with Achondroplasia in the Czech Republic (www.achondroplasia-registry.cz). Finding a cure for Achondroplasia is also one of major goals of our research.
Future directions of research: (A) transactivation among receptor tyrosine kinases in cancer resistance, (B) cell communication during endoplasmic reticulum stress, and (C) the development of PROTAC therapeutics for oncogene kinases.
Cell signaling lab cooperates with the following foreign scientists, who contributed to our recently published work: Deborah Krakow, University of California Los Angeles (articles in Human Molecular Genetics, Science Signaling, Science Translational Medicine, Cellular Signaling, PNAS, and others); Huyk Wan Koo, Yonsei University, South Korea (articles in Human Molecular Genetics, PNAS); Gert Jensen, Erasmus MC, The Netherlands (articles in Human Molecular Genetics, PNAS); Jurgen Wesche, Oslo University, Norway (article in Science Signaling); Lin Chen, Third Military Medical University, Chongqing, China (article in Human Molecular Genetics); Zheng Fu, University of Virginia, USA (article in PNAS); Christophe Erneaux, Université Libre de Bruxelles, Belgium (article in Science Signaling, Advances in Biological Regulation); Malgorzata Zakrzewska, Wroclaw University, Poland (article in Biomaterials, CMLS); Lars Klimaschewski, Innsbruck University, Austria (article in Biomaterials).

MOLECULAR CONTROL OF IMMUNE RESPONSE

doc. Mgr. Lukáš Kubala, Ph.D.

Established in 2016

Key words
Hyaluronic Acid, Thrombolysis, Adenyl Cylases, Microfluidic Systems

Research focus
Molecular control of immune response research team (MCIR) is focused on elucidation of molecular mechanisms underlying acute and chronic inflammatory processes and of therapeutic targets. We investigate the role of hyaluronan in the course of healing and inflammatory processes. This will be used for the development of hyaluronan based pharmaceuticals and biomaterials in collaboration with biotech company Contipro. Secondly, our objective is to develop fluidic models to study the relationship between blood flow, vascular inflammation and vessel recanalization during ischemic stroke. The third objective is to evaluate the biological importance of different isoforms of adenylyl cyclases in collaboration with the Medicinal Chemistry research team.

Research objectives
- Identification of molecular mechanisms responsible for the development of endothelial dysfunction and tissue damage under conditions of acute and chronic inflammation including ischemic insults.
- Development of new anti-inflammatory drugs targeting cAMP signaling pathways, particularly specific isoforms of adenyl cylases.
- Identification of the regulatory role of phagocytes and their newly defined subpopulations in the course of acute and chronic inflammation.

Main partners
- Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany.
- BioMEMS Resource Center, Harvard Medical School, USA.
- Contipro a.s., Dolní Dobrouč, Czech Republic

Offered services and expertise
- Testing of anti-inflammatory drugs in *in vitro* models and evaluation of their efficiency in a variety of preclinical animal models.
- Studies employing endothelial cell seeded microfluidic systems that mimic microvascular system.
- Testing biocompatibility and regenerative potential of new materials and compounds, *in vitro* and *in vivo*.

STRATEGY FOR THE PERIOD 2021 - 2025

Inflammation is a fundamental response to infection and injury of virtually all multicellular organisms. Molecular control of immune response research team (MCIR) is focused on the elucidation of molecular mechanisms underlying acute and chronic inflammatory processes. Our main objectives are to explore new principles and mechanisms of action of molecules and enzymes and to identify their potential as new therapeutic targets. Primarily, we are investigating the role of hyaluronan, one of body's own biopolymers, in the course of healing and inflammatory processes. This will be used for development of hyaluronan based pharmaceuticals and biomaterials in collaboration with biotech company Contipro. Secondly, our objective is to develop fluidic models to study the relationship between blood flow and vascular inflammation and vessel recanalization during ischemic stroke. In collaboration with the Stroke research team, new strategies to potentiate thrombolysis are being studied. The third objective is to evaluate the biological importance of different isoforms of adenylyl cyclases in collaboration with the Medicinal Chemistry research team. The goal is to clarify the role of particular adenylyl cyclase isoforms in different immune cell responses and the potential for their specific modulation by newly developed compounds.
In addition to intensive collaborations with other clinical and translational research teams within ICRC, we are continuing our intensive coalition with international partners including assoc. prof. Anna Klinke at Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany and prof. Daniel Irimia at BioMEMS Resource Center, Harvard Medical School, USA.

CANCER PLASTICITY

Mgr. Karel Souček, Ph.D.

Established in 2016

Key words
Cancer Cell Plasticity, Epithelial-to-Mesenchymal Transition, Tumor Heterogeneity, Dissemination

Research focus
The major research interest is to understand the plasticity and heterogeneity of cancer cells and the role of the microenvironment in cancer progression. Cellular plasticity has been considered as a factor contributing to the resistance to cancer chemotherapy and poor prognosis. Simultaneously, recurrence and chemoresistance of many types of cancers are believed to be tightly linked with the biology of cancer stem-like cells or tumor-initiating cells (CSCs/TICs) and circulating tumor cells (CTCs). There is increasing evidence that cancer plasticity induced by different stimuli is a source of CSCs/TICs/CTCs. Currently, we have identified in vitro and in vivo experimental models showing heterogeneity in cancer cell plasticity in terms of CSC and the plasticity profile. We are characterizing single cells and single cell-derived clones to understand molecular mechanisms associated with cell plasticity and its role in cancer progression, therapy resistance and the generation of the cells with CSCs/TICs/CTCs-like properties.

Research objectives
- Correlation between the plasticity of cancer cells with aberrant signaling, dissemination capability and chemoresistance.
- Description of heterogeneity of expression of markers defining most aggressive cells at single cell level within a tumor.
- Introducing the methods for expansion and characterization of clinical samples maintaining its original phenotype (e.g. patient-derived xenografts, 3D in vitro cultures of organoids/tumoroids).

Main partners
- Institute of Biophysics, Czech Academy of Sciences, Brno, Czech Republic
- Masaryk University, Faculty of Science & Faculty of Medicine, Brno Czech Republic
- Masaryk Memorial Cancer Institute, Brno, Czech Republic
- Palacky University Olomouc, Faculty of Medicine & University Hospital Olomouc, Czech Republic
- Medical University of Innsbruck, Innsbruck, Austria
- Leiden University Medical Centre, Leiden, Nederland
- Karolinska Institutet, Stockholm, Sweden
- University of Zurich, Zurich, Switzerland
- University College Dublin, Dublin, Ireland

Offered services and expertise
- Complex analysis of cytokinetics – analysis of proliferation, differentiation and cell death using a variety of methods and approaches including single cell analysis techniques.
- Real-time analysis of cell energy metabolism.
- Pre-clinical in vivo imaging of tumor progression using immunodeficient mice.
- Targeted gene knock-out methodology.

STRATEGY FOR THE PERIOD 2021 - 2025

Tumor heterogeneity represents one of the major limitations of cancer therapy efficacy, which arises as a consequence of genetic instability, microenvironmental differences, and reversible phenotypic plasticity of cancer cells. Therefore, we aim to continue in the complex investigation of these processes and contribute to a better understanding of cancer progression and therapy resistance. Importantly, our effort will lead to the development of cancer-specific targeted therapies and the identification of new biomarkers, associated with cancer prognosis and dissemination. Our main objectives are i) deconvolute the heterogeneity of cancer using single-cell techniques and identify a set of molecules associated with tumor dissemination and therapy-resistance ii) explore selected signaling and metabolic pathways within tumor/metastatic microenvironment that can be utilized in the development of targeted anti-cancer therapy iii) further develop clinically relevant cancer models (3D cultures, xenografts) and imaging techniques for targeted therapy evaluation. We will continue in collaboration with our clinical partners at Masaryk Memorial Cancer Institute (prof. Svoboda, Dr. Adámková), Faculty Hospital Olomouc (prof. Študent), CLIP, University Hospital Motol (prof. Kalina), Medical University Innsbruck (prof. Culig), Faculty Hospital Brno (Dr. Múdry), St. Anne´s University Hospital Brno (prof. Hermanová) to be able to deliver clinically relevant outputs focused namely on melanoma, breast, prostate, colon, and bone cancers. We will also continue the intense collaboration with the Medicinal Chemistry team (ICRC), primarily in the preclinical testing of novel small-molecule kinase inhibitors.

CELL AND TISSUE REGENERATION

doc. MVDr. Aleš Hampl, CSc.

Established in 2016

Key words
Pluripotent Stem Cells, Embryonic Stem Cells, Genomic Stability, Cell Cycle Regulation

Research focus
The overall goal of research of the Cell and Tissue Regeneration team is to investigate the properties of human stem cells that are relevant to their utility in biomedicine. There is a particular focus on pluripotent stem cells, both embryonic and induced, but adult stem cell types are also studied. The biological phenomena that are being studied mainly include: a) genomic stability of stem cells because of its importance to safety in potential clinical applications, b) role of cell cycle regulators and non-coding RNAs in establishing and maintenance of differentiated phenotypes and also in pluripotency, and c) effects of extracellular biodomains on behavior of stem cells, with an emphasis on their contribution to the establishment of niche environments. Great effort is also dedicated to the understanding of stem cell-to-extracellular matrix interactions and to the development of methodologies for supporting growth of cells in engineered scaffolds as well as differentiation of stem cells towards defined somatic cell lineages (e.g. airway epithelia).

Research objectives
- Evaluation of the effects of distribution of regulatory biodomains on the behaviors of cells with use of the "molecular lawn" approach.
- Establishment of clinical grade (GMP quality) lines of human embryonic stem cells and their functional evaluation.
- Understanding and manipulating biological properties of human pluripotent stem cells that are relevant to their application in clinics.

Main partners
- Karolinska Institutet, Stockholm, Sweden
- University of Newcastle, Newcastle, UK
- Stem Cell Institute, MRC, Cambridge, UK
- Oslo University Hospital, Oslo, Norway

Offered services and expertise
Live cell imaging microscopy; transmission and scanning electron microscopy; stem cell phenotyping; establishment, propagation, and differentiation of human pluripotent stem cells; mass spectrometry-based cell fingerprinting.

STRATEGY FOR THE PERIOD 2021 - 2025

Focus & Objectives & Hypothesis
Our team traditionally focuses on various aspects of biology of human stem cells, particularly on stem cells originating from human embryo (hESC) and also pluripotent cells artificially produced by the process of dedifferentiation (hiPSC). The motivation and grounds for this focus is an unprecedented promise of biomedical and clinical applicability of these cell types combined with our long lasting leadership in this area of research (we were the first in the Czech Republic to establish hESC in 2003 and became part of the first ever European consortium funded by FP6 to study hESC).
Based on these facts, our focus will remain on biology and application of stem cells. We (and others) hypothesize that medical (tissue engineering) and bio-industrial (toxicity testing, drug screening, etc.) application of stem cells can only become reality when we harbor enough information on i) safety of stem cells (genetic and epigenetic stability), ii) strategies to differentiate stem cells to relevant organ-specific cell types, and iii) interaction of stem cells with man-made biomaterials to serve as scaffolds. It needs to be stressed that such complex knowledge can hardly be transferred and must be developed and mastered in place using multiple interdisciplinary interactions. We carry such interaction with colleagues inside ICRC and also with external collaborators (CEITEC VUT; Institute of macromolecular chemistry, ASCR; PSI Drásov).

Collaborations – Ongoing & Planned
There are two types of collaborative efforts that we currently carry and plan to further develop inside of the ICRC. The first one is reflecting genuine common research interests (some with external funding) amongst our team and the teams of other principal investigators. Most visibly these are collaborations with: i) Drs. Damborský, Kubala, and Mikulík on the development of thrombolytics, ii) Dr. Koutná on the transfer of basic knowledge on stem cells to clinical applications, iii) Drs. Paruch and Damborský (and TESCAN company) on the development of bioactive surfaces at nanoscale, and iv) Dr. Souček (and PSI company) on the development of instrumentation and bio-industrial application for high-content optical evaluation of 3D cell structures. The second type of collaboration builds on our methodological and technical expertise in the area of morphological examination of cells and tissues that we offer to our colleagues. Currently, we analyze pig hearts that are exposed to electric stimuli by the team of Dr. Stárek to model the effects of electroablation in humans. In the future, we will continue in all of these collaborative efforts, with maximizing those focused on clinical application of stem cells and on the development of unique instrumentation and methodologies for the bio-industry.

STEM CELLS DISEASE MODELING

Mgr. Vladimír Rotrekl, Ph.D.

Established in 2018

Key words
Disease Modelling, Pluripotent Stem Cells, Genome Stability, Cardiomyopathy, Stem Cell Metabolism, Cardiac Progenitors

Research focus
The Stem Cell and Disease Modeling research team (SCDM) builds on long term experience with human pluripotent stem cells, their cultivation and their differentiation. The current focus of the team aims at the use of human pluripotent stem cells to model human diseases, which lead to cardiomyopathy and heart failure. A special focus is put upon progressive cardiomyopathies caused by cardiac progenitor depletion and heart remodeling due to cardiac progenitor genome instability. The SCDM uses reprogrammed human patient cells, as well as human embryonic stem cells with edited genome, to create models of monogenic diseases involving cardiomyopathy. The team also complements stem cell based modeling with the analysis of both animal models and human samples. The SCDM team has also developed novel technology to analyze mechanoelectrical coupling in stem cell derived patients, specifically cardiac syncytium based on atomic force microscope.

Research objectives
- To determine the extent and mechanisms of heart progenitor depletion in human DMD patients using patient specific hiPSCs.
- To characterize novel DNA repair pathways in human pluripotent stem cells and determine the effect of its failure on the depletion of stem cells in human progressive heart failure with delayed onset (using DMD model).
- To determine the mechanism of autocrine and paracrine signaling of basic fibroblast growth factor in pluripotent stem cells.

Main partners
- University of Montpellier, Montpellier, France
- University of Texas, San Antonio, TX, USA
- University Medical Center Göttingen, Göttingen, Germany

STRATEGY FOR THE PERIOD 2021 - 2025

Introduction:
SCDM will follow its interest in modeling human diseases using pluripotent stem cells (hPSC) and apply its expertise in reprograming patient biopsies into human induced pluripotent stem cells. As well as its expertise in directed mutagenesis of human embryonic stem cells and its expertise in differentiation of the hPSCs into functional cells (e.g. cardiomyocytes, hepatocytes, adipocytes, hematopoietic stem cells etc.).
The strategy is based on our long-time experience with reprogramming of the primary cells obtained from patients (biopsies, blood), their reprogramming results in patient-specific pluripotent stem cells or/and editing human embryonic stem cells' genomes in order to create patient-like specific disease model. In our strategy between 2021 and 2025 we plan to address the accelerated development of cardiomyopathy in Duchene muscular dystrophy and Nijmegen breakage syndrome. We will focus also on electroconductive defects of the heart in 3 separate work packages.

WP1: Duchenne muscular dystrophy
Aim: To test the pharmacological effect of inhibition of NO synthase in mdx mice – animal model of DMD.
Hypothesis: SCDM recently discovered that DMD involves deregulation of NO synthase resulting in DNA damage in stem cells and cardiovascular precursor depletion in DMD patients as well as in hearts of animal models. Loss of cardiomoycytes is thus affecting not only disease suffering boys (X linked inheritance), but also presumably asymptomatic female carriers. We thus hypothesize, that NO synthase induced DNA damage affects the progenitor fate resulting in premature ageing like phenotype in cardiac tissue. We will exploit the discovery of NO synthase as potential therapeutic target in patients suffering Duchenne muscular dystrophy (DMD).
Objective: The pharmacological effect of inhibition of NO synthase in mdx mice – animal model of DMD – will be tested in the in-house animal facility. Analysis of available human heart samples during transplantations will continue previous search for cardiomyocyte precursor markers.
Collaborations: We expect collaboration with CMR (Roman Panovský, ICRC) in order to setup comparative criteria between human patients and mouse models for evaluation of the NOS inhibition effect on the experimental animals.

WP2: Nijmegen breakage syndrome (NBS)
Aim: To create a stem cell model of primary immunodeficiency and induced anticancer drug cardiotoxicity associated with Nijmegen breakage syndrome.
Hypothesis: a) DNA damage induced by mutation in NBS1 gene results in genome deterioration in hematopoietic stem cells affecting their fate and resulting in primary immunodeficiency. Modulation of DNA repair pathways in stem cells will allow to bypass the checkpoint arrest and fate modulation to improve the skewed ratio between myeloid and lymphoid lineages found in NBS patients. b) in vitro cardiac model derived from NBS patient specific hPSC will allow for the assessment/screening of cardiotoxicity and definition of its molecular basis.
Objective: a) New human pluripotent stem cell model of Nijmegen breakage syndrome will be constructed using both the patient specific hiPSC reprogramming and by directed mutagenesis of NBS1 gene in human embryonic stem cells. NBS hPSC will be differentiated into hematopoietic stem cells. A model of such will be used to study the effect of pharmacological modulation of DNA repair pathways on fate determination. b) NBS hESCs will be di-

fferentiated into functional cardiomyocytes allowing for functional assaying of cardiotoxic (cell death, troponin loss, contractility changes) effect of NBS relevant anticancer drugs and their combinations.
Collaborations: We will collaborate with POTR (Jaroslav Stěrba, ICRC) to identify relevant mutations and acquire primary cells from NBS patients. We will develop evaluation criteria for the comparison of stem cell derived models with human patients. Close collaboration with the POTR team will allow to translate our results into the clinics.

WP3: Electroconductive defects in cardiac tissue
Aim: to create a stem cell derived model of the cardiac conductive system using in vitro differentiated cardiac clusters, consisting of stem cell derived cardiomyocytes and supporting cell types. But also, a model of scar tissue, consisting of cardiac fibroblasts, in order to allow testing epigenetic methods to modulate local cellular/tissue conductivity.
Hypothesis: Atrioventricular block and ventricular arrhythmias arising in scar vicinity are frequent cardiac condition often leading to serious, even life-threatening conditions with limited treatment options. A robust and reliable in vitro model would allow for testing pharmacological intervention and/or cell therapy. We propose involvement of in situ local cardiac fibroblast/cardiovascular progenitor reprogramming or directed ion channel expression in order to modulate the conductivity. Alterations of the conductivity can be tested using our recently developed method of combining microelectrode array with atomic force microscopy.
Objective: Spontaneously beating hPSC derived clusters of cardiac cells, to be used in combination with cardiac fibroblasts and fibroblasts of either animal of hPSC origin to create in vitro heart block and scar model on MEA/AFM platform allowing for testing of both the pharmacological as well as the epigenetic intervention.
Collaborations: We plan on collaboration with ICE (Zdeněk Stárek, ICRC) to set up pharmacological testing on our model relevant for human patients.

We further collaborate and plan on maintaining collaborations with numerous internationally recognized laboratories, including Inserm U in Montpellier, France (Prof. Alain Lacampagne and Prof. Albano C. Meli), the Health Science Center in San Antonio, Texas University, USA (Prof. Christi A. Walter), the Jagiellonian University in Krakow, Poland (Prof. Jozef Dulak) and others.

ANIMAL CENTER

MVDr. Eduard Göpfert, Ph.D.

Established in 2016

Key words
Laboratory Animal Science, Animal Models, 3Rs Policy, Animal Facility, Preclinical Studies, Pig, Rodents

Main focus
AC is a research facility keen to provide knowledge, know-how and technologies for cutting edge in vivo research. AC supports other research teams all the way from experimental design to practical procedures, including ethical authorization steps.

AC is focused on standardization of animals housing and experimental procedures according to the European and national legislation and regulatory compliances (e.g. FDA and MHRA). We believe that good and reproducible data can only be achieved if optimal animal health and welfare are fulfilled.

Objectives
- Fulfilment of 3Rs Policy during in vivo research.
- Refinement of experimental procedures with implementation of the Systematic Review process.
- Compliance of pre-clinical research with current legislation and regulatory bodies.

Offered services and expertise
- LAR has experience with supervising and carrying out experimental procedures on rodents and pig models.
- Design of experimental procedures for preclinical research with rodents and pigs.
- Assuring of the project license and the authorization process.
- Carrying out experimental procedures.

Main partners
- University of Veterinary and Pharmaceutical Sciences Brno, Brno, Czech Republic
- Vienna Biocenter Core Facilities GmbH, Vienna, Austria
- Medical University of Vienna, Vienna, Austria
- Institute of Molecular and Translational Medicine; Faculty of Medicine and Dentistry; Palacky University Olomouc, Olomouc, Czech Republic

STRATEGY FOR THE PERIOD 2021 - 2025

Our vision, in cooperation with our partners, is to develop the AC – ICRC into a European centre of veterinary and biomedical research. To achieve this common goal, some important steps have already been made in the past, these are mainly thanks to the OPVV project, which allowed the forming of an excellent infrastructure and created the opportunity to hire exceptionally good specialists.
AC is focused mainly on animal experiments particularly in the field of cardiology and neurology. Our animal models are mouse, rat, rabbit, sheep and pig. The animal models mentioned above, as well as knowledge of effective legislation and the high level of up-to-date technology provide us with the possibility of conducting demanding experiments for the needs of researchers from ICRC and of our local and foreigner partners.
We conduct our experiments with state-of-the-art equipment and services for in vivo testing of mouse behaviour, metabolism, and physiology.
After training under expert supervision, researchers can perform experiments by themselves or use our services, which range from planning and performing experiments to final data analysis and interpretation.
In the framework of the cooperation between AC--ICRC and the Institute of Molecular and Translational Medicine (IMTM) in Olomouc, AC has extended its services of rodent behavioural testing with the use of the up-to-date technologies such as the phenomaster, motorater, intellicages, multiconditioning system, swimming pool and others.
In 2020 an important collaboration started with the Veterinary Research Institute (VRI) (Výzkumný ústav veterinárního lékařství – VÚVeL). Concerning this important cooperation, a common workplace for conducting experiments on big animals (pig, sheep) has been established. As a result, we can extend our experimental activities in the field of heart electrophysiology and neurology.
There are intensive negotiations underway concerning the continuation of the cooperation with the Faculty of Pharmacy of Masaryk University (FF MU) in 2021. Our activities at FF MU are focused on neurology and conducting experiments on mice, rats and rabbit models.
The cooperation with the Veterinary University involves experimental surgery with the use of the unique equipment (MRI, STEREOTAXIS) which is installed on-site, in the common animal centre.
AC is a member of international teams working on projects CResPAce and Enoch.
We do continue to search for other opportunities of international cooperation such as the COST project.
Furthermore, the team strategy includes AC specialists´ continuous deepening of expertise.
Team members are fully supported to present their results at scientific conferences and in publication activities.
The aim of AC as a Core Facility is to ensure the full service for all ICRC scientific teams who for their research activities use animal models, including consultation services concerning welfare, and the help with preparation of trial project applications.
AC team members are very active in searching for opportunities of cooperation in grants such as AZV, GAČR as co-proposer and/or as members of the research team.
AC's mission is to be a full-fledged partner in order to support all scientists in the field of animal experiments and preclinical testing.

BIOSTATISTICS

Mgr. Bc. Silvie Bělašková, Ph.D.

Established in 2016

Key words
Clinical data analysis, omic data, signal data, image data, analysis, data management, simulation study

Main focus
Provides biostatistical collaboration and supports medical and public health research.
The provided services are:
- Expertise for planning, conducting, analysis and interpretation and dissemination of research findings from clinical trials, epidemiologic and population-based studies, experiments in pre-clinical research, and other types of studies
- Advice and support in the preparation of grant applications
- Assistance with setup and management of high-quality databases which perform regular data quality checks, data entry, and data cleaning
- Education in the areas of study design, data collection, computerization, and statistical methods.

Objectives
- Clinical research
- Omic data analysis
- Data management (inquiries, forms, CRFs - fully customizable)
- Programming and analysis
- Simulations studies
- Signal and image data analysis in relation to clinical outcomes

Offered services and expertise
BST is a research institute oriented towards finding solutions of scientific projects and providing related services, especially in the field of biological and clinical data analysis, organization and management of clinical trials and syntheses.
- Biostatistics
- Bioinformatics
- Data management

Main partners
- Statistica, StatSoft CR s.r.o, Prague, Czech Republic
- DataFriends, Prague, Czech Republic
- Mayo Clinic, Rochester, USA
- Clinic of Reproductive Medicine and Gynaecology, Zlín, Czech Republic
- Imalab s.r.o., Zlín, Czech Republic

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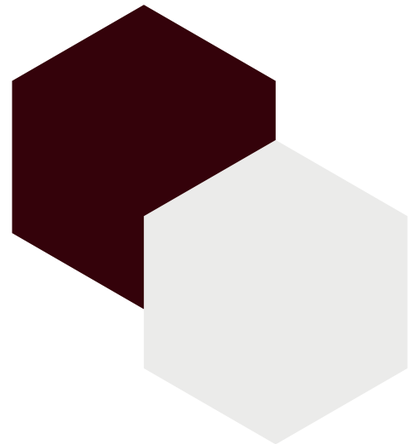
Facility Description:
The Biostatistics Core Facility exists to provide integrated information analytics services to scientists working in the physical, chemical, biological, or clinical sciences.
We assist bench scientists with their data generation and analysis from conceptualization to implementation and publication.
We are versed in a wide array of statistics and data analysis techniques, as they are used in a variety of academic fields. The Biostatistics Core Facility staff can tailor data analyses to the unique needs of journals in a specific field of research.
Where appropriate, the Biostatistics Core Facility staff will endeavor to develop new statistical methods to address the unique needs of your research laboratory.

Selected Areas of Expertise:
- Experimental Design Theory
- Verification of study design and eCRF
- Univariate and Multivariate Analysis
- Bayesian Analysis
- Nonparametric Analysis
- Asymptotic Theory
- Health Outcomes Research
- Efficiency and Productivity Analysis
- Omics data analysis
- Time series analyses
- Bio-Imaging

In general, the main goals are:
- Efficiently using biostatistics resources.
- Improving biostatistical contribution to science.

Continuously provide services of high standards based on requisition. Finalizing the validation of the RedCap platform for clinical trials according to SUKL regulation for the purpose of clinical trials. Specialization of MRI analysis as a part of the collaboration of the new Centre of Neurosciences MUNI and FNUSA. Focusing on big data analysis (clustering and neural networks) collaboration with BME and PEG. Correction of statistical tests in collaboration with Mayo Clinic (department of Statistics). Common research on higher-order asymptotic.



MASS SPECTROMETRY

Martin Eugenio Barrios-Llerena, Ph.D.

Established in 2017

Key words
Mass Spectrometry, Proteomics, Post-translational modifications, Metabolomics

Main focus
Optimization and development of MALDI imaging mass spectrometry (MALDI IMS) protocols to satisfy specific research needs is our main focus and opportunity for collaborative projects.

We also focus on development and optimization of methods using gas chromatography-mass spectrometry (GC-MS) for the characterization of volatile metabolites/markers produced by cell cultures, tissues and other biological sample.

Objectives
- Molecular imaging of neurotransmitters in brain tissue sections.
- MALDI-IMS mapping of tumor-associated proteins.
- MALDI IMS mapping of pharmaceuticals and their metabolites in biological tissues.
- Application of GC-MS for characterization of volatile markers of inflammatory disorders.

Offered services and expertise
- Development of MALDI IMS compatible protocols for formalin-fixed paraffin embedded tissues.
- Protein identification in complex mixtures.
- Relative quantification in complex mixtures.
- (Co)-IP-MS.
- MALDITOF profiling.
- MS data analysis and interpretation.
- GC-MS analyses of volatile metabolites.

Main partners
- TGen, the Translational Genomics Research Institute, Patrick Pirrotte PhD, Assistant Professor and Director of Collaborative Center for Translational Mass Spectrometry.
- Tel Aviv University, Department of Neurobiology, Dan Frenkel PhD, Laboratory Head, Assistant Professor.
- University of Applied Sciences Technikum Wien, Andreas Teuschl PhD, Head of Competence Team Signal Tissue.
- Institute of Organic Chemistry and Biochemistry of the CAS, Mass Spectrometry Research-Service Group, Martin Hubálek PhD, Research Scientist.
- Technische Universität Berlin, Department Food Chemistry and Toxicology, Dr. Claudia Keil

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The mass spectrometry core facility is focused in the implementation of mass-spectrometry-based proteomic methodologies for the analysis of biological samples, from cell to human tissue/biofluids. The application of these methodologies will provide a better understanding of human diseases in terms of pathophysiology; prevention; diagnosis and treatment; as well as the development of new biomarkers; drugs targets and therapies.
Our main objective is the development of robust methodologies for the application of shotgun proteomics, qualitative and quantitative, for the analysis of complex biological systems; and the continuous development/implementation of up-to-date proteomics methodologies for the analysis of samples from researchers at ICRC-FNUSA. For this purpose, we are actively looking for collaborations with clinicians and researchers at ICRC-FNUSA. At the moment, we are establishing collaborations with teams at Stroke and Pediatric Oncology Translational Research for the analysis of biofluids (serum and cerebrospinal fluid, respectively) from patient aiming to find candidates biomarkers for these illnesses.