3rd CCP Phenogenomics Conference 2021

Virtual Conference

16 – 17 September 2021

Abstract Book

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Czech Centre for Phenogenomics

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MINISTRY OF EDUCATION, YOUTH AND SPORTS

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Back to Content [page 4]

Content

Dear colleagues,

It is my great pleasure to welcome you at the third CCP Phenogenomics Conference. This year, the conference is held as a virtual meeting due to the continuing uncertainty about travel.
The scientific committee has selected two main thematic focuses. The first day is dedicated to immunology, infectious diseases, and human diseases models. Among other interesting topics, this day covers Covid-19 related research and the translation of basic research results into application. The second day is specifically dedicated to preclinical development and advances in neuroscience.

Even though, taking place only in a virtual environment, we believe that the Conference will provide an excellent opportunity to support networking and interactions among the CCP users and experts.

I would also like to thank our partners and sponsors for their continuous support to our annual conference.

We are looking forward to meeting you virtually in September 2021.

On behalf of the CCP Organizing Committee,
Radislav Sedláček
Director of the Czech Centre for Phenogenomics

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Back to **Content** [page 4]

ORGANIZER – CZECH CENTRE FOR PHENOGENOMICS

The Czech Centre for Phenogenomics (CCP) is a large research infrastructure unique in combining genetic engineering capabilities, advanced phenotyping and imaging modalities, SPF animal housing and husbandry, as well as cryopreservation and archiving, all in one central location – at BIOCEV campus.

Through its membership in INFRAFRONTIER and IMPC, CCP is a partner in a global network that aims to comprehensively and systematically analyze the effect of loss of function gene mutations in mice. The goal is to produce a comprehensive 'encyclopaedia' of gene function, that will help identify causative factors of human diseases as well as novel targets for therapeutic intervention.

www.phenogenomics.cz

ACKNOWLEDGEMENTS:

MINISTRY OF EDUCATION, YOUTH AND SPORTS

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Operational Programme Research, Development and Education (OP RDE)
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Thursday 16 September 2021

DAY 1

	Session 1 – Opening - 10th IMPC Anniversary	Chair: Radislav Sedláček
10:00 – 10:20	Welcoming lecture	Radislav Sedláček, Institute of Molecular Genetics Czech Academy of Sciences, Czech Republic
10:20 – 11:00	**Keynote lecture:** Illuminating the dark genome: genome-wide approaches for understanding the genetic basis of disease	Steve Brown, MRC Harwell Institute, UK
	Session 2 – Immunology and infections	Chair: Radislav Sedláček
11:00 – 11:20	Neutralizing antibodies for prophylaxis and therapy of viral infections	Daniel Růžek, Institute of Parasitology, Biology Centre, Czech Academy of Sciences, Czech Republic
11:20 – 11:40	A new mouse model of shedding and transmission of the pertussis agent	Peter Šebo, Institute of Microbiology, Czech Academy of Sciences, Czech Republic
11:40 – 12:00	Pre-clinical mouse models of immune disorders and immunotherapies	Bernard Malissen, Centre d'Immunologie de Marseille-Luminy & Center for Immunophenomics, Marseille, France
12:00 – 12:30	Discussion with speakers	
12:30 – 14:00	Lunch break	
	Session 3 – Short technology talks (commercial talks)	Chair: Vendula Novosadová
14:00 – 14:10	Multimodal molecular imaging in (pre) clinical research	Milan Kopecek, FUJIFILM Visualsonics, Amsterdam, Netherlands
14:10 – 14:20		Sable Systems
14:20 – 14:30	IntraVital Microscopy (IVM): In Vivo Live Cell Imaging Platform	Pilhan Kim, Graduate School of Medical Science and Engineering, KAIST, Korea Accela sponsored talk
14:30 – 14:40	Automated cognitive & behavioral screening of individual mice living in social groups, reducing stress component	Dilip Verma, TSE Systems Berlin, Germany
	Poster session 1	
14:40 – 15:40	Interactive poster viewing	
	Session 4 – Disease models	Chair: Petr Kašpárek
15:40 – 16:00	Modelling human mitochondrial translation dysfunction in mice	Aich Abhishek, University Medical Center Göttingen, Germany
16:00 – 16:20	Dangerous liaisons: A rogue PACS1/HDAC6 interaction in PACS1 Syndrome	Gary Thomas, University of Pittsburgh, US
16:20 – 16:40	Discussion with speakers	

Back to Content [page 4]

Friday 17 September 2021

DAY 2

9:30 – 10:00	**Keynote lecture**	Jakub Abramson, Weizmann Institute of Science, Israel
	Session 5 – Advances in neurosciences (A)	Chair: Jan Rozman
10:00 – 10:15	Introduction to the session "Advances in Neurosciences"	Jan Rozman, Institute of Molecular Genetics Czech Academy of Sciences, Czech Republic
10:15 – 10:35	Translational issues beyond data quality	Sabine Hölter-Koch, Helmholtz Zentrum Munich, Germany
10:35 – 10:55	Integrative home cage-based phenotyping of mouse models of emotional and cognitive dysfunction	Oliver Stiedl, VU University Amsterdam, Netherlands
10:55 – 11:15	Characterization of alpha-synuclein transgenic mice and rats for prodromal Parkinson´s disease	Stephan von Hörsten, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany
11:15 - 11:35	Discussion with speakers	
11:35 – 11:50	Break	
	Session 5 – Advances in neurosciences (B)	Chair: Jan Rozman
11:50 – 12:10	Linking neuropsychiatry to quantitative biology: a translational and transdiagnostic approach	Martien Kas, University of Groningen, Netherlands
12:10 – 12:30	Neural stem cells, human-specific genes, and neocortex expansion in development and human evolution	Wieland Huttner, MPI-CBG, Germany
12:30 – 12:45	Discussion with speakers	
12:45 – 14:00	Lunch break	
	Session 6 – Preclinical development	Chair: Karel Chalupský
14:00 – 14:20	Validation of drug targets and testing of new compounds in mixed-lineage leukemia using xenograft and humanized knock-in mouse models	Vladimír Divoký, Palacky University Olomouc, Faculty of Medicine, Czech Republic
14:20 – 14:40	Epigenetic inhibitor increasing HDR efficiency	Cord Brakebusch, University of Copenhagen, Biotech Research & Innovation Centre, Denmark
14:40 – 15:00	The second generation of therapeutic antibodies against COVID-19	Branislav Kovacech, AXON Neuroscience, Slovakia
15:00 – 15:15	Discussion with speakers	

Back to Content [page 4]

	Session 7 – Short talks selected from poster presentations	Chair: Vendula Novosadová
15:15 – 15:25	Studying breast development and lactation biology using mouse models	Zuzana Koledová, Masaryk University, Faculty of Medicine, Czech Republic
15:25 – 15:35	Unique stem cell subpopulation ensures mesenchymal regeneration of continuously growing teeth	Jan Křivánek, Masaryk University, Faculty of Medicine, Czech Republic
15:35 – 15:45	Defining and establishing clinical blood chemistry reference intervals for the International Mouse Phenotyping Consortium	Roldan Medina De Guia, Institute of Molecular Genetics Czech Academy of Sciences, Czech Republic
15:45 – 15:55	Cytoplasmic polyadenylation by TENT5A is essential for teeth and bone formation	Goretti Aranaz Novaliches, Institute of Molecular Genetics Czech Academy of Sciences, Czech Republic
15:55 – 16:05	Analysis of human brain tissue derived from DBS surgery	Reetta Hinttala, University of Oulu, Finland
16:05 – 16:20	Break	
	Poster session 2	
16:20 – 17:00	Interactive poster viewing	
	Closing	
17:00 – 17:40	**Keynote lecture:** Dissecting the genetics of human syndromic disorders causing cognitive dysfunction using animal models	Yann Herault, Institut de Génétique et de Biologie Moléculaire et Cellulaire, France
17:40 – 18:00	Closing	Radislav Sedláček, Institute of Molecular Genetics Czech Academy of Sciences, Czech Republic

Professor Steve Brown FRS FMedSci

"Illuminating the Dark Genome: Genome-wide approaches for Understanding the Genetic Basis of Disease"

Director, MRC Harwell Institute, United Kingdom

Steve Brown did his PhD at Cambridge University and before he joined the MRC, he was Professor of Genetics at Imperial College, London.

His research interests cover mouse functional genomics, including the use of large-scale mouse mutagenesis and comparative genomic analysis to study the genetic basis of disease and to develop pre-clinical disease models. A particular focus has been the use of mouse models to study the molecular basis of genetic deafness. Along with Karen Steel, he discovered myosin VIIA as the gene underlying the shaker1 mutant, one of the first deafness genes to be identified. Over the last ten years he has led a substantial research effort in the genetics of otitis media or glue ear, a common cause of hearing loss in children, employing mouse models to elaborate the key genetic pathways involved and develop novel therapeutic strategies.

He has served on numerous advisory boards and his current appointments include the Advisory Council for the National BioResource Centre, Japan; Strategic Policy Committee, Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC) Strasbourg; and the Advisory Board for the Czech Centre for Phenogenomics (CCP). He is the past Chair of the International Mouse Phenotyping Consortium (IMPC) Steering Committee.

He is a Fellow of the Royal Society, a Fellow of the Academy of Medical Sciences, a member of the European Molecular Biology Organisation and in 2009 was the recipient of the Genetics Society Medal.

Back to Content [page 4]

Yann Herault, PhD

"Dissecting the Genetics of Human Syndromic Disorders Causing Cognitive Dysfunction Using Animal Models"

Institut de Génétique et de Biologie Moléculaire et Cellulaire, France
Leader of the Mouse Clinical Institute (MCI/ICS)

Yann Herault is a geneticist and neurobiologist with training in cellular and molecular biology. He worked on gene regulation and cellular transformation during his PhD then he was interested in the regulation of the HoxD gene complex during embryonic development with a specific focus on limb. Now his research focused on evaluating the consequences of gene dosage effect and copy number variation on cognition and to investigate the physiopathology of intellectual disabilities (ID) and Autism Spectrum Disorder (ASD). He has worked on Down Syndrome (DS, or Trisomy 21), other intellectual disabilities associated with copy number variation, such as 16p11.2 or 17q21.31 syndromes, or single gene mutated in ID and ASD (Ptchd1, Arx, Ehmt1, Setbp1,..).

Yann Herault has developed several therapeutic approaches to rescue behaviour and cognition in DS and ASD models. Working with human geneticists who identified new mutations in rare intellectual disabilities, he has generated new models and produced a standard analysis of more than 50 genes for ID and ASD. Recently he has developed rat models for Down syndrome and for 16p11.2.

Yann Herault is also leading the Mouse Clinical Institute (MCI/ICS) a centre devoted to serve the community for making or analysing more mouse and rat models. In addition he is directing the French National infrastructure CELPHEDIA and PHENOMIN, partner of European infrastructure (www.infrafronier.org) Over the years he have built several collaboration with privates industries, both small and large biopharmaceutical companies.

Back to **Content** [page 4]

KEYNOTE LECTURES

- Thursday, 16 September 2021 (10:20 – 11:00) - Steve Brown:
  Illuminating the Dark Genome:
  Genome-wide Approaches for Understanding the Genetic Basis of Disease
- Friday, 17 September 2021 (17:00 – 17:40) - Yann Herault:
  Dissecting the Genetics of Human Syndromic Disorders Causing Cognitive Dysfunction Using Animal Models

Illuminating the Dark Genome: Genome-wide Approaches for Understanding the Genetic Basis of Disease

- **Steve Brown, MRC Harwell Institute, Harwell, UK; and the IMPC**

E-mail of the presenting author: s.brown@har.mrc.ac.uk

The function of the majority of the genes in the human and mouse genomes remains dark. A major challenge for biomedical sciences is to build a comprehensive understanding of gene function that will support studies of rare and common disease and underpin advances in genomic and precision medicine. The International Mouse Phenotyping Consortium (IMPC) is building a catalogue of mammalian gene function by the generation and broad-based phenotyping of a knockout mouse line for every protein-coding gene. To date, nearly 10,000 knockout mouse lines, many for poorly understood genes, have been generated and over 8,500 phenotyped in a coordinated effort involving 21 global research centers and dedicated publicly-available online resources. The data enables an unprecedented view of the mammalian genome landscape including the enrichment of human Mendelian disease genes among the embryonic lethal strains, the pervasive and wide-ranging sexual dimorphism of phenotypic traits in both wild-type and mutant mice, and the identification of novel disease genes and mechanisms in areas as diverse as metabolism, hearing and vision. The plethora of new genetic disease models as well as the basic and translational knowledge that has arisen from our analysis is being applied in collaboration with rare disease, biobank and other consortia to provide a more profound understanding of the function of human genetic variation.

Back to Content [page 4]

Dissecting the Genetics of Human Syndromic Disorders Causing Cognitive Dysfunction Using Animal Models

- **Yann Herault, Institut de Génétique et de Biologie Moléculaire et Cellulaire, France**

E-mail of the presenting author: herault@igbmc.fr

Aneuploïdy or large copy number variation are causing several syndromic disorders in human. Investigating the genetics of these disorders is essential to better understand the pathophysiology of the disease and propose strategies to alleviate the conditions. To this end, animal models are used, even when the genetics is really complex, to achieve the identification of driver genes or pathways, and to carry on the evaluation of preclinical intervention. Here, I will present recent advances in the field of Down syndrome research, the most frequent form of intellectual disabilities leading to decipher the genotype to phenotype relationship, to identify targets, to validate preclinical proof-of-concept to decrease the burden of the disease.

SESSION 1 – OPENING – 10TH IMPC ANNIVERSARY

Thursday 16 September 2021 (10:00 – 11:00)

- 10:00 – 10:20 Radislav Sedláček:
  Welcoming lecture
- 10:20 – 11:00 Steve Brown:
  Illuminating the Dark Genome:
  Genome-wide Approaches for Understanding the Genetic Basis of Disease

Illuminating the Dark Genome: Genome-wide Approaches for Understanding the Genetic Basis of Disease

- **Steve Brown, MRC Harwell Institute, Harwell, UK; and the IMPC**

E-mail of the presenting author: s.brown@har.mrc.ac.uk

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Back to Content [page 4]

SESSION 2 – IMMUNOLOGY AND INFECTIONS

Thursday 16 September 2021 (11:00 – 12:30)

- 11:00 – 11:20 Daniel Růžek:
  Neutralizing Antibodies for Prophylaxis and Therapy of Viral Infections
- 11:20 – 11:40 Peter Šebo:
  A New Mouse Model of Shedding and Transmission of the Pertussis Agent
- 11:40 – 12:00 Bernard Malissen:
  Pre-clinical Mouse Models of Immune Disorders and Immunotherapies
- 12:00 – 12:30 Discussion with speakers

A New Mouse Model of Shedding and Transmission of the Pertussis Agent

- **Peter Šebo, Institute of Microbiology, Czech Academy of Sciences, Czech Republic**

E-mail of the presenting author: sebo@biomed.cas.cz

Pertussis is a strictly human respiratory infectious disease that can be fatal to young children and elderly. The currently used mouse models of intracerebral or pulmonary B. pertussis infection served remarkably well in characterization of B. pertussis virulence factors and development of efficacious pertussis vaccines. However, B. pertussis transmission could not be reproduced in adult mice due to limited proliferation of the human pathogen in the upper airways of mice. Therefore, we inoculated nasal cavities of immunodeficient MyD88 knock-out mice to achieve a human-like level of nasal mucosa infection. This allowed triggering of rhinitis and catarrhal shedding of bacteria from mouse nasal cavities and efficient transmission of the infection onto co-housed adult animals. Testing a set of bacterial mutants, we identified two bacterial adhesins as key transmission factors. Combined with the power of mouse and bacterial genetics approaches, this newly established mouse model of the catarrhal phase of the whooping cough disease will enable deciphering of the mechanisms that underlie B. pertussis transmission to new hosts.Session 3 – Short technology talks (commercial presentations)

SESSION 3 - SHORT TECHNOLOGY TALKS (COMMERCIAL PRESENTATIONS)

Thursday 16 September 2021 (14:00 – 14:40)

- 14:00 – 14:10 Milan Kopeček, FUJIFILM Visualsonics:
  Multimodal Molecular Imaging in (pre) Clinical Research
- 14:10 – 14:20 Sable Systems
- 14:20 – 14:30 Pilhan Kim, KAIST, Korea:
  IntraVital Microscopy (IVM): In Vivo Live Cell Imaging Platform (sponsored by Accela)
- 14:30 – 14:40 Dilip Verma, TSE Systems:
  Automated Cognitive & Behavioral Screening of Individual Mice Living in Social Groups, Reducing Stress Component

Multimodal Molecular Imaging in (pre) Clinical Research

- **Milan Kopeček, Regional Sales Manager CEE, FUJIFILM Visualsonics, Amsterdam, The Netherlands**

E-mail of the presenting author: milan.kopecek@fujifilm.com

Photoacoustic (PA) imaging is a hybrid imaging modality, for non-invasive detection of tissue structural and functional anomalies. The approach is based on optical absorption, which uses pulsed laser-induced ultrasound from specific endogenous tissue chromophores (e.g., melanin or hemoglobin) to map their distribution.The technique combines the advantageous properties of optical and ultrasound imaging. In contrast to purely optical imaging, PA imaging retains good spatial resolutions at higher imaging depths since ultrasound waves are not scattered as highly as photons inside biological tissue. So the PA imaging has a potential for identifying both the anatomical features and functional activity of tissues at higher depths. Spectroscopic PA imaging can provide information of tumor oxygenation, and can serve as a tool for diagnosing malignancy. Some important applications of this technique include breast cancer detection, skin cancer visualization and small animal imaging.

IntraVital Microscopy (IVM): In Vivo Live Cell Imaging Platform

- **Pilhan Kim, Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology (KAIST), 291 Daehak-ro, Yuseong, Daejeon, Republic of Korea 305-338**

E-mail of the presenting author: pilhan.kim@kaist.ac.kr

Intravital microscopy can visualize various in vivo cellular-level dynamics such as cell trafficking, cell-to-cell or cell-to-microenvironment interactions in a living animal. Intravital imaging of cellular dynamics in natural in vivo microenvironment inside live animal model can provide unprecedented insights in the dynamic pathophysiology of human diseases those were impossible to obtain through conventional histological observation of ex vivo sample or in vitro culture sample. During the last decade, the intravital microscopy has become a highly valuable, indispensable technique in wide areas of biomedical sciences such as immunology, neuroscience, developmental and tumor biology. In vivo visualizations of gene expression, protein activity, cell trafficking, cell-cell / cell-microenvironment interactions and various physiological responses to external stimuli have been achieved. Additionally, it's a unique tool for the development of new therapeutics and diagnostics by providing improved accuracy and reliability in in vivo target validation with delivery monitoring and efficacy assessment. It has been used to directly analyze the delivery and efficacy of new biopharmaceuticals such as antibodies, cell therapy, gene therapy, nucleic acids and exosome in an in vivo microenvironment.

In this talk, a real-time laser-scanning intravital confocal/two-photon microscopy system will be introduced. The imaging system has been extensively optimized for in vivo cellular-level imaging of internal organs in live animal model for various human diseases, which can acquire a real-time multi-color fluorescence microscopic image in sub-micron resolution. Intravital microscopic imaging of various organs including skin, liver, spleen, pancreas, kidney, small intestine, colon, retina, lung, heart, lymph node, and bone marrow will be briefly introduced. Subsequently, recent studies utilizing the real-time intravital imaging technique to investigate dynamic cellular-level pathophysiology of various human diseases will be introduced.

Keyword: Intravital microscopy, Two-photon microscopy, Confocal microscopy, In vivo imaging, Fluorescence imaging.

Automated Cognitive & Behavioral Screening of Individual Mice Living in Social Groups, Reducing Stress Component

- **Dilip Verma, TSE Systems GmbH, Barbara-McClintock-Straße 4, 12489 Berlin, Germany**

E-mail of the presenting author: Dilip.Verma@tse-systems.com

A large part of data variability observed within or across labs is caused by unpredictable changes in the lab environment, experimenter's interference, or differential conditions in testing and housing. To combat such problems, TSE Systems introduced a standardized home cage testing system (IntelliCage) to automatically test group-housed animals within their social environment. The system requires no experimenter's interference and allows high-throughput behavioral phenotyping over several days or weeks.

IntelliCage allows a transfer of validated behavioral paradigms into automated setup, as comparative studies revealed the effects on learning and memory processes similar to the findings from e.g., Morris Water Maze or Vogel Conflict Test. Studies using behavioral flexibility- and response-inhibition tasks proved that the IntelliCage reliably assesses the executive functions. Transferring of established behavioral paradigms to the IntelliCage has shown to significantly reduce inter- and intra-lab variability.

SESSION 4 - DISEASE MODELS

Thursday 16 September 2021 (15:40 – 16:40)

- 15:40 – 16:00 Aich Abhishek:
  Modelling Human Mitochondrial Translation Dysfunction in Mice
- 16:00 – 16:20 Gary Thomas:
  Dangerous Liaisons: A Rogue PACS1/HDAC6 Interaction in PACS1 Syndrome
- 16:20 – 16:40 Discussion with speakers

Modelling Human Mitochondrial Translation Dysfunction in Mice

- **Aich Abhishek, Department of Cellular Biochemistry, University Medical Center Gottingen; Gottingen, Germany**
- Rehling Peter, Department of Cellular Biochemistry, University Medical Center Gottingen; Gottingen, Germany

E-mail of the presenting author: abhishek.aich@med.uni-goettingen.de

Protein assembly in the mitochondria is orchestrated by the seamless integration of nuclear and mitochondrial encoded proteins into single enzyme complexes. One such enzyme complex, the cytochrome c oxidase, is the terminal enzyme of the respiratory chain. Hence, an error due to mutations in any of the factors involved in the assembly process is always detrimental, leading to postnatal deaths in most of the cases. Thus, it is not possible to study the pathophysiology of such mutant genes in a systemic background. Generation of transgenic mouse models carrying knock-ins is the only inevitable step. This talk deals with few such models, generated for mimicking human patient mutations, and how they enabled the study of disease progression. The talks would also highlight a few critical methodologies necessary for proper assessment of mitochondrial health and physiology in these models.

Dangerous Liaisons: A Rogue PACS1/HDAC6 Interaction in PACS1 Syndrome

- Sabrina Villar Pazos[1], Kun Chen[1], Laurel Thomas[1], Yunhan Yang[1], Troy Krzysiak[2], Ana Almeida Rojo[3], Angela M. Gronenborn[2], Yanhua Huang[3] and **Gary Thomas**[1]

Departments of Microbiology and Molecular Genetics[1], Structural Biology[2] and Psychiatry[3], University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

E-mail of the presenting author: thomasg@pitt.edu

PACS1 Syndrome is a recently identified neurodevelopmental disorder caused by a recurrent de novo missense mutation in PACS1 (p.Arg203Trp). Patients carrying this missense mutation share several developmental deficits, including intellectual disability, seizures and autism. The mechanism by which PACS1^{R203W} causes PACS1 Syndrome is unknown and no curative treatment is available. PACS1 is a multifunctional sorting protein that facilitates cytoplasmic protein traffic and genome integrity. This multifunctionality depends on a small segment of PACS1 called the furin-binding region (FBR), which binds a broad range of client proteins, sorting adaptors and signaling molecules. The R203W mutation is located in the FBR, suggesting the possibility of an altered interaction between PACS1 and one or more of its client proteins in PACS1 Syndrome. Our studies suggest PACS1^{R203W} increases binding to the deacetylase HDAC6 to profoundly disturb membrane traffic and impair neuronal function. Our findings on the consequences of PACS1R203W/HDAC6 on neuronal function in patient cells and mouse models, as well as strategies to neutralize the toxic effects of PACS1^{R203W}/HDAC6 will be discussed.

SESSION 5 – ADVANCES IN NEUROSCIENCES (A)

Friday 17 September 2021 (10:00 – 11:35)

- 10:00 – 10:15 Jan Rozman: Introduction to the Session "Advances in Neurosciences"
- 10:15 – 10:35 Sabine Hölter-Koch: Translational Issues beyond Data Quality
- 10:35 – 10:55 Oliver Stiedl: Integrative Home Cage-based Phenotyping of Mouse Models of Emotional and Cognitive Dysfunction
- 10:55 – 11:15 Stephan von Hörsten: Characterization of Alpha-synuclein Transgenic Mice and Rats for Prodromal Parkinson´s Disease
- 11:15 – 11:35 Discussion with speakers

Introduction to the Session "Advances in Neurosciences"

- **Jan Rozman, Czech Centre for Phenogenomics, Institute of Molecular Genetics, Czech Academy of Sciences, Czech Republic**

E-mail of the presenting author: jan.rozman@img.cas.cz

The session „Advances in Neuroscience" will address basic, applied, and preclinical research in neuroscience. The use of experimental animal models to study certain aspects of human disease has been heavily criticized for lack of reproducibility and unclear translation to humans. At a time when certain diseases are on the rise worldwide, including, for example, neurodegenerative diseases, the development, and testing of new therapeutic approaches or drugs is getting so difficult that unacceptable delays occur. In addition, the risk of failure is so substantial that the pharmaceutical industry even considers withdrawing from certain areas.

An interesting question to be asked is whether the high attrition rates affect all disease areas equally or whether certain types are particularly susceptible. For example, most of our basic knowledge about neuroendocrine signaling in energy balance regulation comes from studies that included animal experiments. Thus, in this area, experimental animal models are extremely important and are likely to remain so for some time.

We have succeeded in attracting speakers for this session who have a great deal of expertise in the field of neuroscience, but also in the limitations and problems as well as opportunities for improvement in this area. The CCP is networking with many of them through international collaborations such as INFRAFRONTIER, IMPC, EBRA-PREMOS, and TEATIME. The speakers will discuss translational issues and data quality, home cage-based phenotyping, transgenic mouse and rat models for prodromal Parkinson´s disease, links between neuropsychiatry and quantitative biology, and neocortex expansion in development and human evolution.

Translational Issues beyond Data Quality

- **Sabine Hölter, Helmholtz Zentrum München, Germany**

E-mail of the presenting author: hoelter@helmholtz-muenchen.de

Due to a lack of major breakthroughs in understanding neuropsychiatric disease etiologies and in the development of improved treatments for decades, preclinical studies have been scrutinized and deemed largely irreproducible. This has spurred several initiatives to increase the robustness of preclinical data, which mainly focus on training, documentation, experimental design, data analysis and interpretation, and statistical approaches. While these improvements are highly necessary and timely, they may not solve the problem alone.

Importantly, they do not directly expand our knowledge about the causes of neuropsychiatric diseases, which in turn influences our choice of model systems for preclinical studies. Translation from insights of preclinical studies in animals and other model systems can not only fail because of data quality-related reasons, but also because of neurobiology-related reasons, e.g. because the study addresses aspects that are not causal for the disease, or because the relevant biological mechanism is not conserved between the species under study and humans. This talk introduces PREMOS, an initiative that tries to reach a broad consensus on a strategy how to address this issue and to increase the predictive value of the use of model systems. PREMOS is supported by the European Brain Research Area (EBRA) as an EBRA cluster; for more information see https://www.ebra.eu/premos/.

SESSION 5 - ADVANCES IN NEUROSCIENCES (B)

Friday 17 September 2021 (11:50 – 12:45)

- 11:50 – 12:10 Martien Kas:
  Linking Neuropsychiatry to Quantitative Biology: a Translational and Transdiagnostic Approach
- 12:10 – 12:30 Wieland Huttner:
  Neural Stem Cells, Human-specific Genes, and Neocortex Expansion in Development and Human Evolution
- 12:30 – 12: 45 Discussion with speakers

SESSION 6 - PRECLINICAL DEVELOPMENT

Friday 17 September 2021 (14:00 – 15:15)

- 14:00 – 14:20 Vladimír Divoký:
  Validation of Drug Targets and Testing of New Compounds in Mixed-lineage Leukemia Using Xenograft and Humanized Knock-in Mouse Models
- 14:20 – 14:40 Cord Brakebusch:
  Epigenetic Inhibitor Increasing HDR Efficiency
- 14:40 – 15:00 Branislav Kovacech:
  The Second Generation of Therapeutic Antibodies against COVID-19
- 15:00 – 15:15 Discussion with speakers

SESSION 7 – SHORT TALKS SELECTED FROM POSTER PRESENTATIONS

Friday 17 September 2021 (15:15 – 16:05)

- 15:15 – 15:25 Zuzana Koledová:
  Studying Breast Development and Lactation Biology Using Mouse Models
- 15:25 – 15:35 Jan Křivánek:
  Unique Stem Cell Subpopulation Ensures Mesenchymal Regeneration of Continuously Growing Teeth
- 15:35 – 15:45 Roldan Medina De Guia:
  Defining and Establishing Clinical Blood Chemistry Reference Intervals for The International Mouse Phenotyping Consortium
- 15:45 – 15:55 Goretti Aranaz Novaliches:
  Cytoplasmic Polyadenylation by TENT5A is Essential for Teeth and Bone Formation
- 15:55 – 16:05 Reetta Hinttala:
  Analysis of Human Brain Tissue Derived from DBS Surgery

Back to Content [page 4]

Unique Stem Cell Subpopulation Ensures Mesenchymal Regeneration of Continuously Growing Teeth

- **Jan Krivanek, Department of Histology and Embryology, Faculty of Medicine, Masaryk University, Brno, Czech Republic**
- Josef Lavicky, Department of Histology and Embryology, Faculty of Medicine, Masaryk University, Brno, Czech Republic
- Adam Bogdanovic, Department of Histology and Embryology, Faculty of Medicine, Masaryk University, Brno, Czech Republic
- Petr Taus, Central European Institute of Technology, Masaryk University, Brno, Czechia
- Marcos Gonzalez Lopez, Department of Histology and Embryology, Faculty of Medicine, Masaryk University, Brno, Czech Republic
- Vladislav Rakultsev, Department of Histology and Embryology, Faculty of Medicine, Masaryk University, Brno, Czech Republic
- Marie Sulcova, Laboratory of Molecular Morphogenesis, Institute of Animal Physiology and Genetics, Czech Academy of Science, Brno, Czech Republic, Department of Experimental Biology, Faculty of Science, Masaryk University, Brno, Czech Republic
- Marcela Buchtova, Laboratory of Molecular Morphogenesis, Institute of Animal Physiology and Genetics, Czech Academy of Science, Brno, Czech Republic; Department of Experimental Biology, Faculty of Science, Masaryk University, Brno, Czech Republic

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In rodents and several other species, a continuously growing teeth have evolved. This adaptation on specialized style of living ensures permanent replenishing of dental tissues worn by constant gnawing and provides an attractive system for studying of stem cell niche, cell differentiation or injury-induced regeneration. Recent advances in single cells RNA sequencing and lineage tracing methods enabled to perform an unbiased and reliable analysis of this organ and to study different stem cell populations responsible for permanent growth. Using this approach, we found a novel, quiescent and long-lasting population of mesenchymal stem cells contributing to the permanent tooth growth. This, up to now unknown, stem cell population is spatially restricted and gives rise to all mesenchymal parts of dental pulp, including different types of dental pulp cells and dentin-producing odontoblasts. Further analyses showed a multipotent characteristic of this unique population and uncovered molecular background responsible for differentiation (bifurcations) into distinct terminally differentiated cell states. Based on our detailed study of this exemplary model system on single cell level we uncovered the role of the same type of stem cell population during embryonic development of several organ systems. Taken together we discovered a novel, highly specific mesenchymal stem cells which plays role during permanent adult tissue growth and contribute to formation of different organs during development.

Defining and Establishing Clinical Blood Chemistry Reference Intervals for The International Mouse Phenotyping Consortium

- **Roldan de Guia, Czech Centre for Phenogenomics (BIOCEV/IMG), Institute of Molecular Genetics of the Czech Academy of Sciences, Vestec, Czech Republic**
- Sharon Cheng, MRC Harwell Institute, Informatics Group, Harwell Campus, Oxfordshire, UK
- Karel Chalupsky, Czech Centre for Phenogenomics (BIOCEV/IMG), Institute of Molecular Genetics of the Czech Academy of Sciences, Vestec, Czech Republic
- Piia Keskivali-Bond, MRC Harwell Institute, Informatics Group, Harwell Campus, Oxfordshire, UK
- The International Mouse Phenotyping Consortium
- Jan Rozman, Czech Centre for Phenogenomics (BIOCEV/IMG), Institute of Molecular Genetics of the Czech Academy of Sciences, Vestec, Czech Republic

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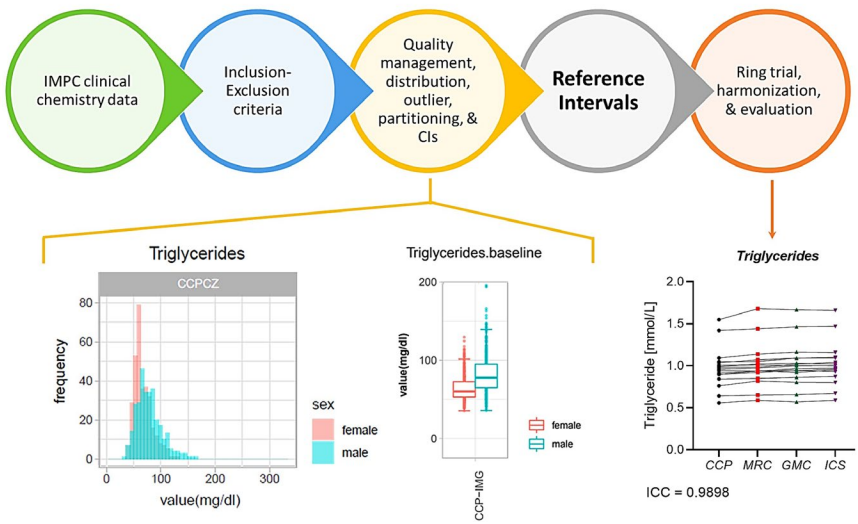
Clinical chemistry has the primary purpose of performing analytical procedures for the quantification of different ions, enzymes, biomolecules, and other serological components of a biological material. Standardized assays are essential for patient screening, diagnosis of diseases, and clinical management. Reference intervals (RIs) or decision limits are being used by clinical laboratories after a streamlined, established procedure following international guidelines set by the International Federation of Clinical Chemistry (IFCC) or Clinical and Laboratory Standards Institute (CLSI). This study aims to define and establish RIs in different IMPC research centres by implementing guidelines similar to IFCC/CLSI. Furthermore, we analyzed variability and robustness of different clinical chemistry parameters across 4 IMPC centres as part of external quality assessment (EQA) and post-analytical, RI validation.



Simplified schematic for the calculation of reference intervals from IMPC clinical chemistry data: The procedure follows the IFCC/CLSI guidelines. CCP Triglyceride is shown as an example for frequency distribution, outlier elimination, sex partitioning, and ring trial assessment. ICC – Intraclass correlation coefficient.

Cytoplasmic Polyadenylation by TENT5A is Essential for Teeth and Bone Formation

- **Goretti Aranaz Novaliches, Czech Centre for Phenogenomics, Institute of Molecular Genetics of the Czech Academy of Sciences, Vestec, Czech Republic**

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The TENT5A proteins are involved in many different human diseases. Importantly, TENT5A loss of function mutations has been found in patients with osteogenesis imperfecta. Tent5a deficient mice model was developed in our laboratory which exhibits a strong phenotype in teeth development and skeleton aberrations.

Here we show that TENT5A is a non-canonical poly (A) polymerase that is essential for proper bone and teeth mineralization. TENT5A is express in ameloblast in teeth, cells that synthesize enamel matrix proteins (EMPs) needed for enamel formation. Using nanopore direct mRNA sequencing we have identified that Tent5a polyadenylates amelogenin (Amelx) and other secreted proteins mRNA to increase their expression during amelogenesis. Therefore, this study mainly focuses on the role of Tent5a in amelogenesis. In Tent5a KO mice, we observed decreased enamel layer thickness and disrupted enamel patterning. When we analyzed the expression of EMPs, Ambn and Amelx, in the absence of Tent5a via immunofluorescence assays, the expression did not significantly differ but EMP self-assembly into the extracellular matrix was impaired. The ability of EMPs to assemble into the organic matrix is essential for enamel formation by directing hydroxyapatite deposition.

In conclusion, we aim to elucidate the molecular mechanisms underlying the Tent5a deficient phenotype in mice. We postulate that skeletal hypomineralization is just one of many possible manifestations in teeth and bone development and homeostasis.

Analysis of Human Brain Tissue Derived from DBS Surgery

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- Jaakko Teppo, University of Helsinki
- Maija J. Lahtinen, University of Oulu, Oulu University Hospital
- Anu Suoranta, University of Helsinki
- Bishwa Ghimire, University of Helsinki
- Pirkko Mattila, University of Helsinki
- Johanna Uusimaa#, University of Oulu, Oulu University Hospital
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We were the first to discover germline Phosphodiesterase 10A (PDE10A) variants in children affected by a hyperkinetic movement disorder (Diggle et al. 2016). PDE10A is enriched in the striatum, and animal data suggest that it is a key regulator of the cortical motor activity. PDE10A is a hydrolase, which plays an essential role in regulating cAMP/PKA and cGMP/PKG signalling cascades and its inhibitors are currently being evaluated in clinical trials for the treatment of neurological pathophysiologies such as schizophrenia, Huntington's disease, or addiction.

To further study the molecular pathways behind deficits in the basal ganglia we have developed an approach to collect fresh human brain tissue material from Deep Brain Stimulation (DBS) surgery. DBS is a neurosurgical treatment for advanced and medically refractory movement disorders, such as Parkinson's disease, essential tremor and dystonia. Fresh human brain tissue material is collected from guiding tubes for proteomics analysis by liquid chromatography-mass spectrometry and recording microelectrodes are used for RNA extraction and transcriptomics analysis by RNA sequencing.

Analysis of the proteomics and transcriptomics datasets showed that this approach can be used to obtain brain hemisphere-specific data from individual patients without any sample pooling and without any modifications to the standard surgical protocol. The approach described here was validated by comparing the previous approaches to collect brain derived tissue material and their related datasets. The method provides a source for fresh brain tissue material to be used for studying molecular aspects of movement disorders and information on the causative pathways that can be utilized in developing new treatment options

Back to Content [page 4]

POSTER SESSION

Thursday 16 September 2021 (14:40 – 15:40)

Friday 17 September 2021 (16:20 – 17:00)

- **Poster 1** – Raishbrook Miles:
  A Fast, non-Invasive Method to Assess Central Retinal Artery Occlusion in Mice
- **Poster 2** – Klara Dohnalova:
  Hyperbilirubinemia Is Associated with Changes in Cholesterol Metabolism and Fat Breakdown
- **Poster 3** – Veronika Iatsiuk:
  Cullin4 Regulates Colorectal Cancer Expansion through the Modulation of Intracellular Smad3 Trafficking
- **Poster 4** – Elisabetta Golini:
  Home Cage Detection of Sleep Disturbances in a Mouse Model of ALS
- **Poster 5** – Irena Jeníčková, Petr Kašpárek:
  Zygote Electroporation of Cre and Dre Proteins Enables Efficient Recombination in Mouse Embryos
- **Poster 6** – Ruberte Jesús:
  Precision Pathobiology for Disease Models (PATHBIO)

A) RESEARCH POSTER PRESENTATIONS

(PO-1) A Fast, non-Invasive Method to Assess Central Retinal Artery Occlusion in Mice

- **Miles Raishbrook,** Petr Macek, Jan Prochazka, Jan Rozman, Radislav Sedlacek,
  Czech Centre for Phenogenomics, Institute of Molecular Genetics of the Czech Academy of Sciences, Vestec, Czech Republic

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We have developed a fast, non-invasive method for measuring the Doppler flow of the central retinal artery (CRA) in mice from which important characteristics, such as the resistive index (RI), can be extrapolated to assess and potentially predict the onset of diabetic retinopathy (DR) in diabetic mouse models.

Although diagnosis and management of diabetes is well founded, DR is still the leading cause of blindness in the adult population and occurs in approximately one third of diabetics [1]. A DR risk factor is reduced blood -flow through the CRA, a vessel that branches from the ophthalmic artery and enters the eye at the optic disc supplying nourishment through the blood vessels of the inner neuronal layers of the retina. Diabetics have a significantly increased risk of CRA occlusion [2]. Reduced blood flow to this area contributes to the pathogenesis of DR, leading to retinal layer thinning, ganglion cell loss, increased vascular permeability and neovascularisation, all of which are considered when evaluating animal models of DR [3]. The RI of the CRA has been reported as a robust imaging biomarker for the prediction of the onset of DR in humans, with increases positively correlating with DR severity [4]. This, alongside other DR diagnostic techniques, paired with genetic or induced diabetic mouse models will provide an excellent platform on which to study the pathophysiology of this destructive disorder.

In order to briefly simulate altered blood flow through the CRA that can occur in DR, we injected adrenaline into the tail vein of anaesthetised C57Bl/6 mice and measured peak systolic velocity (PSV) and end diastolic velocity (EDV) to compare the RI before and after injection.

(PO-2) Hyperbilirubinemia Is Associated with Changes in Cholesterol Metabolism and Fat Breakdown

- **Klara Dohnalova, Institute of Molecular Genetics of the Czech Academy of Sciences, Czech Centre for Phenogenomics, Vestec and First Faculty of Medicine, Charles University, Prague**
- Krystof Klima, Institute of Molecular Genetics of the Czech Academy of Sciences, Czech Centre for Phenogenomics, Vestec
- Dagmar Zudova, Institute of Molecular Genetics of the Czech Academy of Sciences, Czech Centre for Phenogenomics, Vestec
- Libor Vitek, First Faculty of Medicine, Charles University, Prague
- Radislav Sedlacek, Institute of Molecular Genetics of the Czech Academy of Sciences, Czech Centre for Phenogenomics, Vestec
- Karel Chalupsky, Institute of Molecular Genetics of the Czech Academy of Sciences, Czech Centre for Phenogenomics, Vestec

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Elevated concentration of bilirubin in human plasma is associated with lower BMI. Animal studies also showed connection between high levels of unconjugated bilirubin and reduced adiposity. Physiologic function of bilirubin could also include protection against cardiovascular diseases where its role as an antioxidant agent has been proposed. Recent report showed that hyperbilirubinemia is associated with reduced fat mass and increased hepatic mitochondrial biogenesis, specifically in female animals, suggesting a dual role of elevated bilirubin and reduced UGT1A1 function on adiposity and body composition.

Our aim was to investigate the impact of unconjugated hyperbilirubinemia on metabolite and lipid composition in Gunn rats. Rat plasma of 14 weeks old animals of both genders was examined in metabolomics and lipidomics screening. Extracted plasma samples were measured on Orbitrap ID-X Tribrid using ZORBAX Eclipse Plus C18 column and on 6546 LC/Q-TOF using Accucore C30 column.

The most prominent differences in plasma metabolite composition were found in female cohort of Gunn rats. 4 subclasses of metabolites were found: bile acids, flavonoids, fatty acids, phenylalanine and, as expected, bilirubin and its metabolites. As opposed to male Gunn rats, lipidomic data analysis in female Gunn rats revealed substantial decrease of all measured lipid classes in comparison with control, with a main difference in compounds containing long unsaturated fatty acids.

This is the first study to comprehensively assess metabolomics and lipidomics in hyperbilirubinemic rats. Our findings show that hyperbilirubinemia, specifically in female animals, is associated with changes in cholesterol metabolism and breakdown of fat.

(PO-3) Cullin4 Regulates Colorectal Cancer Expansion through the Modulation of Intracellular Smad3 Trafficking

- **Veronika Iatsiuk, Laboratory of Transgenic Models of Diseases and Czech Centre for Phenogenomics, Institute of Molecular Genetics of the Czech Academy of Sciences, Prague, Czech Republic**
- Jolana Tureckova, Laboratory of Transgenic Models of Diseases and Czech Centre for Phenogenomics, Institute of Molecular Genetics of the Czech Academy of Sciences, Prague, Czech Republic
- Michaela Prochazkova, Laboratory of Transgenic Models of Diseases and Czech Centre for Phenogenomics, Institute of Molecular Genetics of the Czech Academy of Sciences, Prague, Czech Republic
- Frantisek Spoutil, Czech Centre for Phenogenomics, Institute of Molecular Genetics of the Czech Academy of Sciences, Prague, Czech Republic
- Pavel Talacko, BIOCEV proteomics core facility, Faculty of Science, BIOCEV, Charles University, Vestec, Czech Republic
- Vendula Novosadova, Czech Centre for Phenogenomics, Institute of Molecular Genetics of the Czech Academy of Sciences, Prague, Czech Republic
- Radislav Sedlacek, Laboratory of Transgenic Models of Diseases and Czech Centre for Phenogenomics, Institute of Molecular Genetics of the Czech Academy of Sciences, Prague, Czech Republic
- Jan Prochazka, Laboratory of Transgenic Models of Diseases and Czech Centre for Phenogenomics, Institute of Molecular Genetics of the Czech Academy of Sciences, Prague, Czech Republic

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Colorectal cancer is a second leading cause of cancer-associated mortality. Among others, cancer development is associated with alteration in ubiquitination process. Cullin4-RING E3 ubiquitin ligase (CRL4) is an important complex, responsible for regulation of signaling pathways. The core component is CUL4A that work as a scaffold protein by assembling the multicomponent CRL4. Aberrant expression of the Cul4a gene is a cause of many tumor types, including colorectal cancer. Thereby, in this study we aim to identify the role of CRL4 in the alteration of the regulatory pathways, resulting in the gastro-intestinal homeostasis disorders and tumor expansion.

Current research showed that Cul4a is expressed in crypt base population and knockout cause the anomalies in the intestine development. We have showed abnormal localization of Lys+ Paneth cell (PC) population in the crypt base, which might be a cause of morphology and homeostasis disorders. We have observed that Cul4KO on ApcMin colorectal carcinoma background leads to the tumor development in the distal colon, what is only occasionally observed in ApcMin mice. However, Cul4KO mice on ApcMin background showed prolonged lifespan while developing tumors that could be associated with changes in tumor invasiveness. Followed molecular studies leads us to the suggestion that observed phenotype could a cause of Cul4a influence on the intracellular trafficking of Smad3 transcriptional factor.

So, our results show that Cul4a is a critical regulatory element in intestine homeostasis that is associated with colorectal cancer progression and invasiveness.

(PO-4) Home Cage Detection of Sleep Disturbances in a Mouse Model of ALS

- **Elisabetta Golini, Intitute of Biochemistry and Cell Biology, CNR-National Research Council, Monterotondo Scalo (RM), Italy**
- Mara, Rigamonti, Tecniplast, Buguggiate (VA), Italy
- Fabio, Iannello, Tecniplast, Buguggiate (VA), Italy
- Carla, De Rosa, Intitute of Biochemistry and Cell Biology, CNR-National Research Council, Monterotondo Scalo (RM), Italy
- Ferdinando, Scavizzi, Intitute of Biochemistry and Cell Biology, CNR-National Research Council, Monterotondo Scalo (RM), Italy
- Marcello, Raspa, Intitute of Biochemistry and Cell Biology, CNR-National Research Council, Monterotondo Scalo (RM), Italy
- Silvia, Mandillo, Intitute of Biochemistry and Cell Biology, CNR-National Research Council, Monterotondo Scalo (RM), Italy

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Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease that affects central and peripheral nervous systems, leading to the degeneration of motor neurons, and resulting in muscle atrophy, paralysis and death. Sleep disturbances are common in patients with ALS and other neurodegenerative diseases, causing even further deteriorated quality of life.

We used an automated home cage monitoring system (DVC®) to capture irregular activity patterns potentially associated with rest disturbances and to disease progression in the SOD1G93A mouse model. DVC® enables non-intrusive 24/7 long term activity monitoring, assessed together with body weight decline and neuromuscular function deterioration (grid hanging and grip strength tests) in males and females from age 7 until 24 weeks.

Activity of SOD1G93A mice start becoming irregular at 14 weeks, especially during day time, with frequent bouts not observed in controls or younger SOD1G93A mice. We created the Regularity Disruption Index (RDI) to quantify these irregularities of activity.

RDI is a robust measure for detecting home cage activity related to rest/sleep disturbances. Its rise during early symptomatic stages parallels neuromuscular and weight decline. The non-intrusive long-term continuous monitoring of activity can been instrumental in discovering novel activity patterns potentially correlated with sleep disturbances in models of neurodegenerative disorders.

Reference: Golini E, Rigamonti M, Iannello F, De Rosa C, Scavizzi F, Raspa M, Mandillo S. A non-invasive digital biomarker for the detection of rest disturbances in the SOD1G93A mouse model of ALS. 2020, Frontiers in Neuroscience 14: 896. doi: 10.3389/fnins.2020.00896.

(PO-5) Zygote electroporation of Cre and Dre proteins enables efficient recombination in mouse embryos

- **Irena Jenickova[a], Petr Kasparek[a,b], Silvia Petrezselyova[a,b], Jan Elias[b], Jan Prochazka[a,b], Jana Kopkanova[a], Michal Navratil[c], Cyril Barinka[c] and Radislav Sedlacek[a,b]**

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Zygote electroporation is an efficient technique for mouse genome engineering using CRISPR/Cas system. Here, we demonstrate that the same procedure can be used for efficient delivery of Cre and Dre recombinases to mediate allele conversions in 1-cell stage mouse embryos. The method is simple, inexpensive, and enables highly efficient allele conversion in newborn animals. Proof of concept experiments were performed with Rosa26-tdTomato-EGFP and Rosa26-VFRL-EGFP reporter lines, carrying a transgenic casettes for Cre/Dre -dependent expression of GFP protein. We have achieved 91 % and 98 % of fully converted animals after Cre and Dre protein zygote electroporation, respectively. Moreover, the technique can be combined with in vitro fertilization leading to fast generation of tm1b converted animal models with the efficiency 67-100% in relation to the tm1a allele. This dramatically reduces time and costs needed for generation of desired models, especially when compared with traditional methods based on breeding with Cre-deleter mouse lines. Furthermore, we believe that simple and accessible option to utilize less common recombinases such as Dre, can lead to generation of more complex and versatile mouse models in the future.

(PO-6) Precision Pathobiology for Disease Models (PATHBIO)

- **Ruberte Jesús and the PATHBIO consortium, Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès, Spain**

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Background

Mouse-based studies nowadays are essential for all Precision Medicine Initiatives, which aim to transform current medical practice to personalized healthcare. However, the scientific community lacks sufficient human resources and expertise in mouse pathology to effectively and reproducibly characterize and validate these animal models.

Despite this increasing demand for mouse experts, there is a proven deficiency of specialized training opportunities for veterinary, medical and biomedical researchers to acquire the necessary expertise with recognized programs in Higher Education. Furthermore, no single European University has all the expertise, resources and personnel required to design and establish a strong educational program.

For this reason several universities, research institution and companies have come together to develop an educational program to bring highly qualified researchers to the field of Precision Pathobiology.

Innovative aspect

PATHBIO has brought a new concept of Mouse Precision Pathobiology, breaking the boundaries between anatomical and histological laboratories integrating mouse morphology and functional anatomy through its different levels from the organic, passing through the histological level, to the cellular and subcellular levels and ending with mouse images obtained by X-ray, Computed Tomography (CT), and Magnetic resonance (MRI), thanks to the possibility to compare them with their equivalent histopathological images.

The combination of all these fields has increased the accuracy of morphological mouse phenotyping. This integrative view has been the basis for the design and establishment of our strong educational program in Mouse Precision Pathobiology, which integrates pathology, anatomy, embryology, imaging, ontologies and informatics.

Impact

In the past 3 years, PATHBIO in collaboration with the IMPC and INFRAFRONTIER consortia has organized 9 Summer Courses (Mouse Anatomy and Embryology, Mouse Imaging, and Mouse Pathology).

During these years, a total of 351 students (102 of them non-European) from 45 different countries have taken the courses (see map), which shows the high interest that exists in the field of Mouse Pathobiology for an official, innovative and specialized teaching.

Also, with the expertise gathered in these courses, the Consortium has been able to design an Erasmus Mundus Joint Master.

Back to Content [page 4]

B) INFRASTRUCTURE POSTER PRESENTATIONS

- **Poster 7** - Biochemistry and Haematology Unit (Roldan M. de Guia & Jan Rozman)
- **Poster 8** - Bioimaging & Embryology Unit (Jan Procházka)
- **Poster 9** - Cardiovascular Unit (Jiří Lindovský)
- **Poster 10** - Hearing & Electrophysiology Unit (Jiří Lindovský)
- **Poster 11** - Histopathology Unit (Dagmar Zudová)
- **Poster 12** - Immunology Unit (Jana Balounová)
- **Poster 13** – Lung Unit (Václav Žatečka)
- **Poster 14** – Metabolism Unit (David Pajuelo Reguera)
- **Poster 15** - Metabolomics Unit (Karel Chalupský)
- **Poster 16** - Neurobiology & Behaviour Unit (Agnieszka Kubik-Zahorodna)
- **Poster 17** - PDX & Cancer Models Unit (Petra Králová Viziová)
- **Poster 18** – Vision Unit (Marcela Pálková)
- **Poster 19** - Bioinformatician Unit (Vendula Novosadová)
- **Poster 20** – Transgenic and Archiving Module (Petr Kašpárek)
- **Poster 21** – Preclinical testing at the Czech Centre for Phenogenomics (Gizela Koubková)

(PO-7) Biochemistry and Haematology Unit

Head: Roldan M. de Guia & Jan Rozman
Team: Mariya Glushchenko, Eva Štefancová, Yu-chieh Wu

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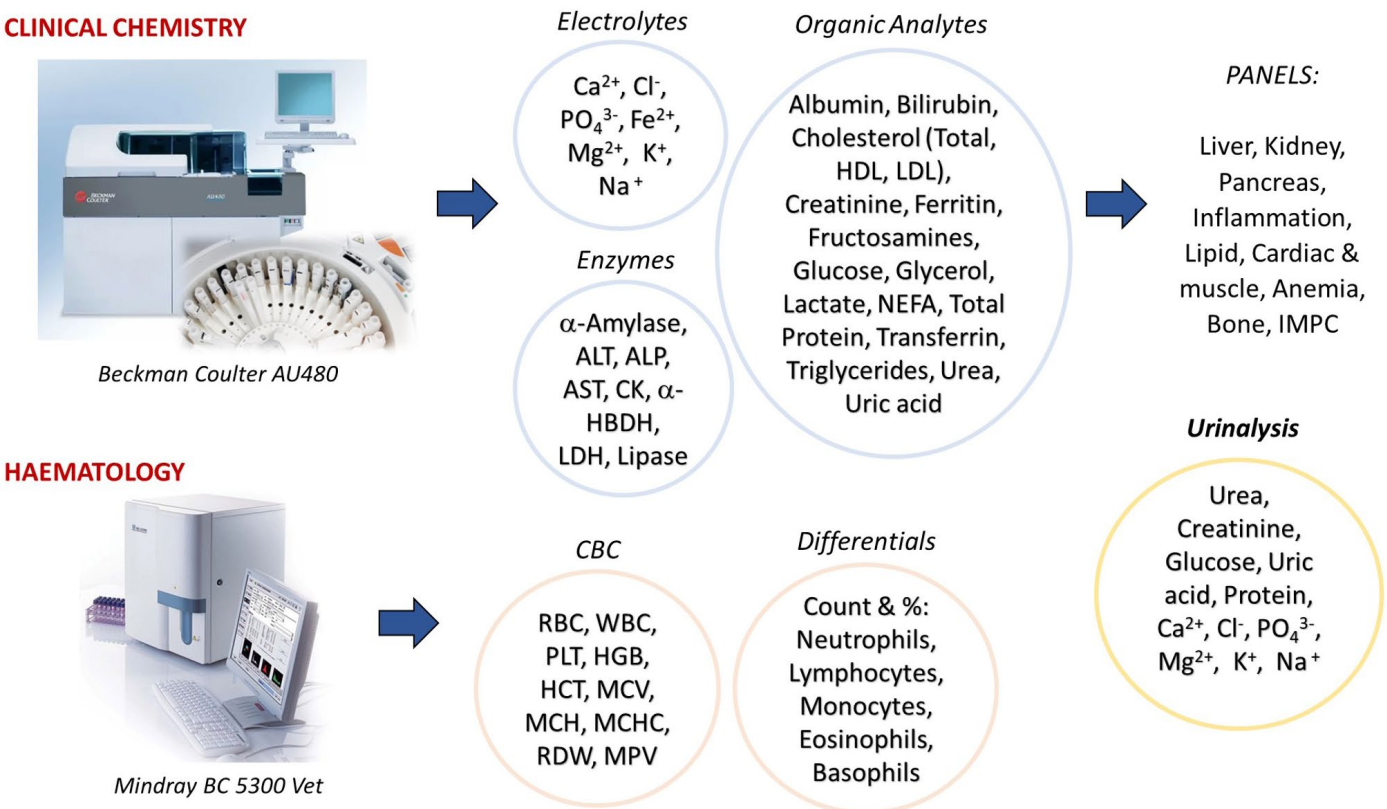
We use advanced analytical platforms maintained at high standards with methodologies following robust screening protocol by the International Mouse Phenotyping Resource of Standardized Screens (IMPReSS). **Clinical chemistry** analyses of plasma/serum, urine, and other biological materials comprise of metabolites, ions, enzymes, and serological quantifications that could be used to assess metabolic and functional abnormalities of different organs of the body. Examination of whole blood for **hematology** may reveal pathologies or treatments that affect blood parameters. We can measure multitude of biomolecules from a single sample using different panels for multiplex **immunoassays** and tested kits for individual analytes. Furthermore, the unit can conduct tests under Good Laboratory Practice (GLP). More information at www.phenogenomics.cz/phenotyping/biochemistry-and-haematology/.

In the primary standard screen, the following parameters can be measured:



Back to Content [page 4]

Secondary and custom-tailored analysis:

Projects in selected publications:

- Identification of genetic elements in metabolism by high-throughput mouse phenotyping. Nat Commun. 2018 Jan 18;9(1):288. doi: 10.1038/s41467-017-01995-2.
- KLK5 and KLK7 Ablation Fully Rescues Lethality of Netherton Syndrome-Like Phenotype. PLoS Genet. 2017 Jan 17;13(1)

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RESEARCH AREAS & PANELS:

Aging, Acute phase proteins, Cardiovascular diseases, DNA damage, Signaling pathways, Pituitary hormones, Stress hormones, Sex & thyroid hormones, Histone post-translational modifications, Antibody isotyping, Cytokines/Chemokines, Diabetes, Metabolic hormones, Adipokines, Myokines, Neuropeptides, Amyloid beta, Angiogenesis, Immuno-oncology checkpoints, Bone metabolism, Vascular injury, Kidney toxicity, Liver injury

(PO-8) Bioimaging & Embryology Unit

Head: Jan Prochazka
Team: Frantisek Spoutil, Michaela Prochazkova, Ivana Bukova, Veronika Martinkova, Tereza Michalcikova, Sarah Clewell

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The Bioimaging and Embryology unit is focused on functional morphology projects using state of art 3D imaging technologies of adult mice and rats as well as tiny samples as murine embryos. The anatomical annotation of skeleton dysmorphologies and developmental disorders offered by the unit is a key feature for interpretation of morphology phenotypes. The Bioimaging and Embryology unit also provides the knowledge base for conditional gene inactivation during development, embryonic tissue isolation and dissections for OMICs procedures or establishment of primary cell cultures.

The most prominent focus of the unit is to provide functional morphological analysis of phenotypes in adult mice and rat models and also during their embryonic development. The important knowledge base lies in 3D imaging of either adult tissues or embryos with microCT technology which allows scanning of not only hard mineralized tissues but also soft tissues and embryos with use of appropriate contrast protocols. The microCT technology provides the best cost effective approach for 3D visualization of phenotypes and the unit provides full data analysis platform for state of art 3D data processing. Besides 3D imaging the Bioimaging and Embryology unit is equipped with whole body imaging system that is suitable for imaging of fluorescence and bioluminescence reporters in mice and rats in vivo and is very advantageous especially for imaging of cancer models derived from cancer cell lines or PDX. For non-invasive imaging and cell labelling the set of lentiviral and AAV reporters is available. Beside cancer cells, the physiological processes like inflammation, kidney function or specific enzyme activity can be also non-invasively imaged. Beside stated imaging modalities the unit also provides experience in functional assays on primary cells or their isolation for multiOMICs technologies. The embryological tissues can be dissected and primary cell lines or organ cultures can be established as well as immortalized cell lines from knock out phenotypes can be delivered. These approaches can help to accelerate the research of mutants with embryonic lethal phenotypes.

Technologies available:
In vivo microCT with spatial resolution down to 9µm, Ex vivo microCT with spatial resolution from 0,5µm, In vivo microCT with spatial resolution 50µm with scanning time 30s. Clarity system for tissue clearing, Fluorescence microscope, In vivo whole body optical imaging system, Primary cell tissue culture equipment, Lentiviral & AAV particle assembly pipeline + fluorescence, genetic and luminescence reporters.

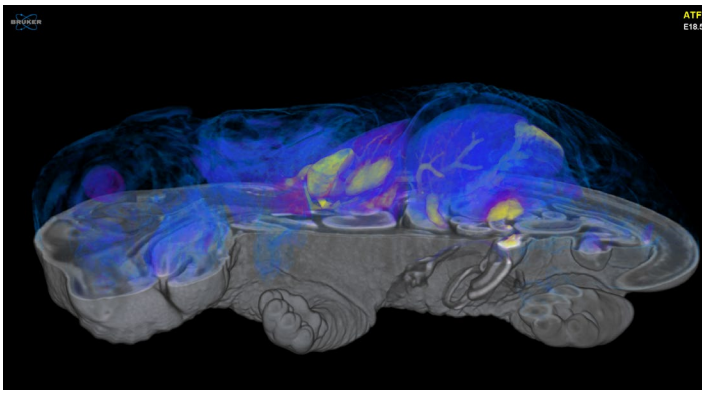
Example of succesful projects:
Embryo colection, conditonal gene inactivation and embryonal tissue dissection in scientific article: WNT5A is transported via lipoprotein particles in the cerebrospinal fluid to regulate hindbrain morphogenesis. Kaiser K, Gyllborg D, Procházka J, Salašová A, Kompaníková P, Molina FL, Laguna-Goya R, Radaszkiewicz T, Harnoš J, Procházková M, Potěšil D, Barker RA, Casado ÁG, Zdráhal Z, Sedláček R, Arenas E, Villaescusa JC, Bryja V. Nat Commun. 2019

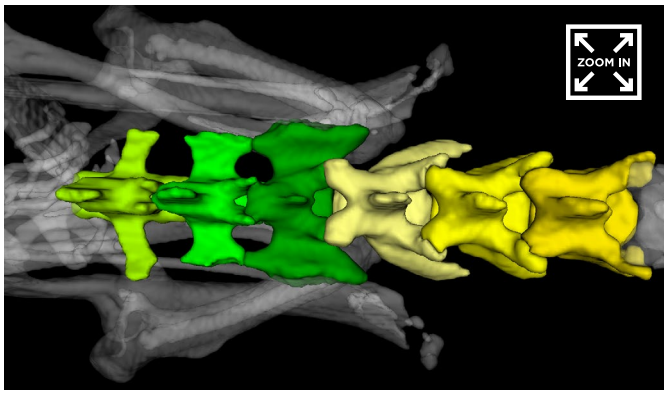
Back to Content [page 4]

A cellular and spatial map of the choroid plexus across brain ventricles and ages. Dani N, Herbst RH, McCabe C, Green GS, Kaiser K, Head JP, Cui J, Shipley FB, Jang A, Dionne D, Nguyen L, Rodman Ch, Riesenfeld SJ, Prochazka J, Prochazkova M, Sedlacek R, Zhang F, Bryja V, Rozenblatt-Rosen O, Habib N, Regev A, Lehtinen MK. Cell 2021.

Imaging and fucntional analysis of tooth enamel in scientific article: Intrinsically disordered proteins drive enamel formation via an evolutionarily conserved self-assembly motif. Wald T, Spoutil F, Osickova A, Prochazkova M, Benada O, Kasparek P, Bumba L, Klein OD, Sedlacek R, Sebo P, Prochazka J, Osicka R. Proc Natl Acad Sci U S A. 2017

Imaging and fucntional analysis of bone in scientific article: Cytoplasmic polyadenylation by TENT5A is required for proper bone formation. Gewartowska O, Aranaz-Novaliches G, Krawczyk PS, Mroczek S, Kusio-Kobiałka M, Tarkowski B, Spoutil F, Benada O, Kofroňová O, Szwedziak P, Cysewski D, Gruchota J, Szpila M, Chlebowski A, Sedlacek R, Prochazka J, Dziembowski A. Cell Reports 2021.





(PO-9) Cardiovascular Unit

Head: Jiri Lindovsky
Team: Jiri Lindovsky, Petr Macek, Sarka Karbanova

Contact: ccp-pm-cardiovascular@img.cas.cz

The Cardiovascular Unit provides investigators with services to assess cardiovascular phenotypes in mice and rats. To perform rapid and in-depth analysis of the mouse or rat heart and circulatory system in both normal and disease states, we employed several state-of-the-art instrumentation that allows for sensitive screening of phenotypic variations. The Cardiovascular Unit uses a variety of non-invasive in vivo techniques for the monitoring of physiological and bioelectrical variables, including heart rate, ECG, and blood pressure in conscious animals. Treadmill stress tests are used to assess functional cardiovascular capacity. For imaging of the animal heart and vascular system we use Vevo2100 or Vevo3100 High-Frequency Ultrasound Imaging System (echocardiography). It is well known for its outstanding image quality in all modalities-cardiac, vascular and general echography and high frame rates. It also offers Color and Power Doppler modes for blood flow quantification and M-mode acquisition for high-temporal resolution in left ventricular analysis, and comes with VevoStrain analysis software for high-resolution image analysis of chamber dimensions, wall thickness, and ventricular function in lightly sedated mice or rats. While the central focus of the Unit is cardiovascular research, the techniques that are employed may also be useful to investigators in other fields, such as cancer, neurobiology and developmental biology. The ultrasound system allows imaging of numerous anatomic structures other than the heart and vascular system, namely: abdominal (kidney, spleen, liver, larger abdominal vessels), pelvic (bladder, ovaries, prostate) organs and other (e.g. eye, testes), including tumors. For developmental studies, it is possible to monitor living mouse/rat embryos in uterus and follow the development of cardiac structures as well as changes in blood flow velocities in the heart and umbilical artery. We are also establishing injection techniques of micro- or nanoliter volumes under ultrasound image guidance, such as intracerebral or intraocular delivery of transfection vectors or drugs.

Instrumentation & technologies:
Vevo 2100 & Vevo3100 High-Frequency Ultrasound System (VISUALSONICS), Kent Coda 8 blood pressure monitor system (Kent Scientific), ECGenie electrocardiogram recording system (Mouse Specifics, Inc.)

Back to Content [page 4]

(PO-10) Hearing & Electrophysiology Unit

Head: Jiri Lindovsky
Team: Jiri Lindovsky, Ján Majerník, Miles J. Raishbrook

Contact: ccp-pm-hearing@img.cas.cz

The unit provides electrophysiological methods for functional testing of hearing and vision in mice and rats.

In principal, techniques used are based on recording of electric potentials of sensory pathways evoked by relevant stimuli. Presence or absence and size or form of the evoked potentials is then interpreted as a correlate of activity and functional status of individual structures of the nervous system. The primary test of hearing is the Auditory Brainstem Response (ABR), which is an acoustically evoked potential recorded by subdermal needle electrodes placed on the top of animal's head. It represents a sum of activity of neurons responsible for sound processing starting at the level of the auditory nerve, through the cochlear nucleus and the superior olivary complex, up to the inferior colliculus. Vision is tested using Electroretinography (ERG) and Visual Evoked Potentials (VEP). ERG measures electrical responses of the retina evoked by light stimulation. The signal recorded from an eye surface and obtained under various light conditions, stimulation intensities and timing protocols allows to individually assess the function of different retinal cell types. Recently, we started establishing a recording technique that allows to independently test subregions of the retina, multifocal electroretinography (mfERG). VEP is recorded on the back of animal's head and corresponds to activation of the ultimate level of the visual pathway – the visual cortex.

We also provide a direct measurement of force of isometric muscle contraction ex-vivo. This method is useful for quantifying normal or abnormal work of skeletal muscles of various subtypes (white, red) as well as that of neuro-muscular junctions.

Instrumentation & technologies:
Hearing: 6m^3 sound attenuated chamber, Tucker-Davis Technologies System 6 hardware, Tucker-Davis Technologies BioSig software, Matlab programming language for customized data analysis. Frequency range of sound stimulation 0 – 50 kHz. Vision: Roland Consult RETIanimal Ganzfeld Q450 hardware, Roland Consult RETI system software, Matlab programming language for customized data analysis.

Muscle contraction force: Digitimer Neurolog System, custom made recording chamber, Matlab.

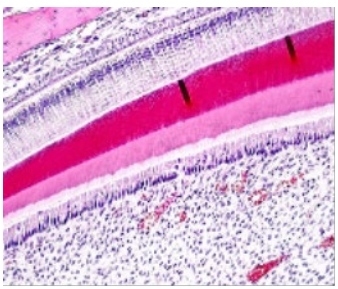
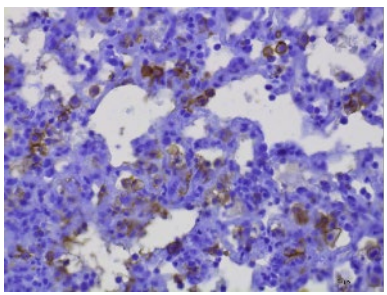
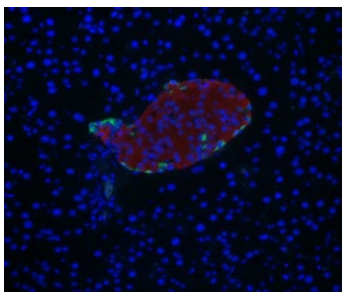
(PO-11) Histopathology Unit

Head: Dagmar Zudova
Team: Barbora Pavlu, Veterinary Pathologist; Sarka Suchanova, GLP manager & Customer services; Linda Kutlikova, lab manager; Technicians: Lien Duongova, Christine Sophia Canada, Aneta Cestrova, Attila Juhasz

Contact: ccp-pm-histopathology@img.cas.cz

The Histopathology unit is one of the largest units of the CCP Phenotyping Module and provides service for a broad range of research community including users working with non-rodent material. The unit is particularly engaged in experimental pathology. The work flow of the histopathology laboratory covers all procedures from gross morphology through various staining techniques and fluorescent slide scanning to pathology description. Complete necropsy of mouse/rat is performed by veterinary pathologist and all macroscopic findings are documented. Almost all steps in tissue processing and slide preparation are automatized to achieve the highest levels of reproducibility and quality. The lab offers H&E staining done by automated stainer, wide range of special stains and immunochemistry. The microscopic evaluation of histological samples is done by veterinary pathologist and complex report with picture documentations is a standard. Most of activities are conformed to Good Laboratory Practices (GLP).

Instrumentation & technologies:
Tissue processing: Leica ASP6025 - The most modern vacuum tissue processor
Sectioning fresh specimens: Vibratom Leica 1200, automated vibrating blade microtome
Slide staining: MultistainerLeica ST5020 in conjuction with Leica CV5030 Coverslipper- an exceptionally versatile stainer-coverslipper workstation,
Ventana Benchmark Speial Stains -Automated slide stainer for special stains
Ventana Discovery ULTRA - Automated stainer for immunohistochemistry and in situ hybridization
Microscopy and analysis: Carl Zeiss Axio Imager.Z2- motorized microscope imaging station, capable of both brightfield and fluorescence capture
Leica DM3000 - Semi automated high-throughput brightfield microscope system
Slide scanning:
Carl Zeiss Axio Scan.Z1 -Combined brightfield and fluorescence slide scanner with ability to also scan histotopograms. Equiped with ultra-fast LED fluorescent module and 7 different excitation/emission filters.

Back to Content [page 4]

Projects in selected publications:

- De Gasparo R, Pedotti M, Simonelli L, **Nickl P,** Muecksch F, Cassaniti I, Percivalle E, Lorenzi JCC, Mazzola F, Magrì D, **Michalcikova T,** Haviernik J, Honig V, **Mrazkova B, Polakova N,** Fortova A, **Tureckova J, Iatsiuk V,** Di Girolamo S, Palus M, **Zudova D,** Bednar P, **Bukova I,** Bianchini F, Mehn D, Nencka R, Strakova P, Pavlis O, **Rozman J,** Gioria S, Sammartino JC, Giardina F, Gaiarsa S, Pan-Hammarström Q, Barnes CO, Bjorkman PJ, Calzolai L, Piralla A, Baldanti F, Nussenzweig MC, Bieniasz PD, Hatziioannou T, **Prochazka J, Sedlacek R,** Robbiani DF, Ruzek D, Varani L Bispecific IgG neutralizes SARS-CoV-2 variants and prevents escape in mice. **Nature 2021**
- Šedová, L.; **Prochazka, J.; Zudová,** D.; Bendlová, B.; Včelák, J.; **Sedlacek, R.;** Šeda, O. Heterozygous Nme7 Mutation Affects Glucose Tol-erance in Male Rats. Genes 2021, 12, 1087.
- **Bukova I, Szczerkowska KI, Prochazkova M,** Beck IM, **Prochazka J, Sedlacek R** Loss of Wiz Function Affects Methylation Pattern in Palate Development and Leads to Cleft Palate. **Front Cell Dev Biol 2021** 9: 620692.

(PO-12) Immunology Unit

Head: Jana Balounova
Team: Kristína Vičíková, Michaela Šímová, Carlos Eduardo Madureira Trufen, Kamila Křížová (maternity leave)

Contact: ccp-pm-immuno@img.cas.cz

As an integral part of the terminal screen, immunophenotyping involves characterization of particular immune cell populations in terms of their cellularity and phenotype using multicolor flow cytometry (FCM). The procedures are based on standard immunophenotyping protocols of the Adult and Embryonic Phenotype Pipeline that has been agreed by the research institutions involved: IMPReSS -International Mouse Phenotyping Resource of Standardised Screens. According to these guidelines, we utilize two panels (IMPC Panel A & Panel B) to discriminate various populations of lymphoid and myeloid cells in the mouse spleen or other tissues (peripheral blood, lymph nodes, thymus, bone marrow, peritoneal lavage, intestine). We have developed FCM assays to analyze cell populations in mouse blood, embryonic as well as adult hematopoiesis, thymus and tumor microenvironment. We collaborate closely with the PDX Unit and analyze human leukocytes in humanized mice. Moreover, we can design a suitable staining panel to detect, characterize or purify cell populations of interest by FCM.

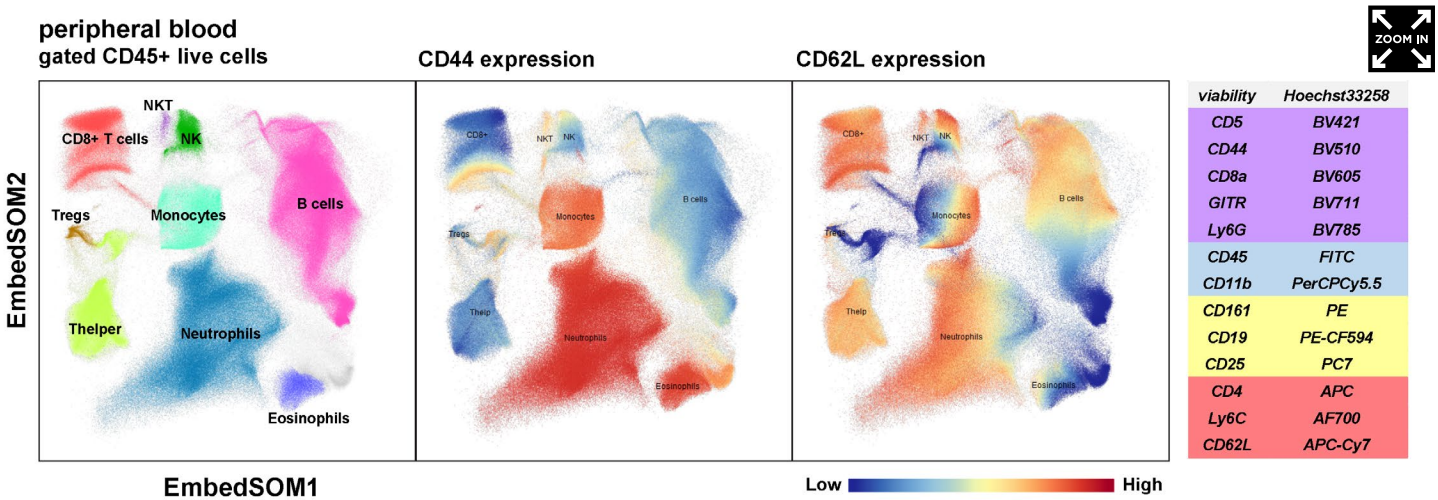
Instrumentation & technologies:
The Unit is equipped with Cytek Aurora spectral flow cytometer. With 5 lasers (355, 405, 488, 532, 635nm), three scattering channels, and 64 fluorescence channels and automated sample loader, the Aurora system is suitable to acquire high dimensional flow cytometry data in hightroughput. The FCM data is analyzed in FlowJo software and statistically evaluated. Furthermore, the Immunology Unit is equipped with gentleMACS tissue dissociator (Miltenyi Biotec) for tissue dissociation, EasySep cell separation magnet for column-free cell separation (StemCell Technologies), bright field automated cell counter for counting of viable cells (Cellometer Auto T4, Nexcelom Bioscience) and a microplate spectrophotometer - ELISA reader (BioTek Epoch).

Selected Publications:
Deletion of TLR2 + erythro-myeloid progenitors leads to embryonic lethality in mice. I Šplíchalová, **J Balounová,** M Vobořil, T Brabec, **R Sedlacek** and D Filipp. Eur J Immunol. 2021 Sep;51(9):2237-2250.
doi: 10.1002/eji.202049142.

Regulation of Inflammatory Response by Transmembrane Adaptor Protein LST1. M Fabisik, J Tureckova, N Pavliuchenko, J Kralova, **J Balounova, K Vicikova,** T Skopcova, F Spoutil, J Pokorna, P Angelisova, B Malissen, **J Prochazka, R Sedlacek,** T Brdicka. Front Immunol. 2021 Apr 27;12:618332. doi: 10.3389/fimmu.2021.618332

CRL4-DCAF12 Ubiquitin Ligase Controls MOV10 RNA Helicase during Spermatogenesis and T Cell Activation. T Lidak, N Baloghova, V Korinek, **R Sedlacek, J Balounova,** P Kasparek, L Cermak.
Int J Mol Sci. 2021 May 20;22(10):5394.doi: 10.3390/ijms22105394.

SOM-based embedding improves efficiency of high-dimensional cytometry data analysis.
M Kratochvil, A Koladiya, **J Balounova,** **V Novosadova,** **R Sedlacek,** K Fiser, J Vondrasek and K Drbal. bioRxiv (2019): 496869.



(PO-13) Lung Unit

Team: Vaclav Zatecka

Contact: ccp-pm-lung@img.cas.cz

The Czech Centre for Phenogenomics is the only phenotyping center which routinely screens for mechanical properties of the lungs in their standard pipeline. For this we use the Flexivent FX (Scireq), a modular, computer controlled animal ventilator. We have developed a method which allows us to perform the measurements in intubated mice, thus allowing for repeated measurements in the same animal. The device can be equipped with a nebulizer for the measurement of dose response curves to broncho-constrictive agents (e.g. methacholine) or for the administration of compounds directly to the lungs. For the high-throughput projects we can offer measurements with the 'multiple subject extension', which allows us to measure up to 8 animals simultaneously (4 animals per machine). However, for technical reasons, these measurements can only be performed in tracheotomized animals.

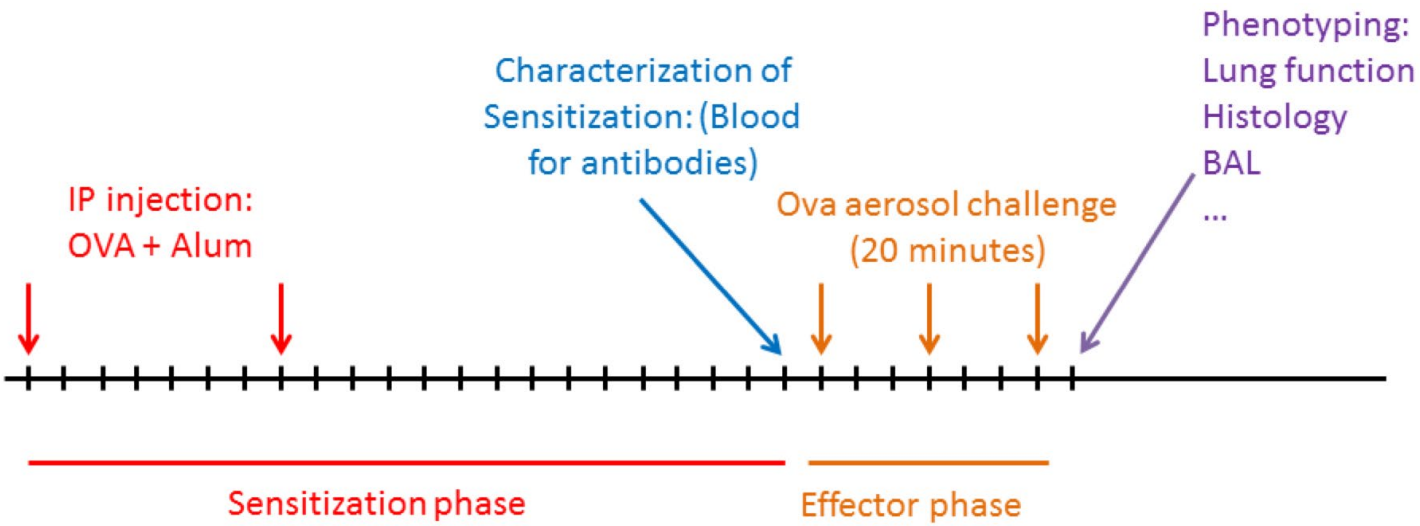
The Unit also performs standard models of pulmonary diseases, like asthma, emphysema, fibrosis, or more complex models on request. All other services of our facility can be added to come to comprehensive package that suits our customers' needs as well as possible. We also perform and train people for the administration of drugs compounds to the lungs, through intubation, oro-pharyngeal instillation or via nebulization.

Models:
Mouse model of severe OVA-induced allergic asthma; Mouse model of mild OVA-induced allergic asthma; Mouse model of sub-cutaneous immunotherapy for allergic asthma; Mouse model of occupational asthma; Mouse model of house dust mite induced allergic asthma; Mouse model of elastase induced pulmonary emphysema; Mouse model of bleomycin induced pulmonary fibrosis; Mouse model of acute lung injury, AAV based gene delivery to lung, AAV humanization of lung epithelia for Covid-19 research.

Instrumentation & technologies:
Flexivent FX with FX1 and FX2 modules (for measurement of animals between 8 and 65g)
Flexivent Multi subject extension (MSX, for measurement of 4 adult mice simultaneously per machine)
Aeroneb ultrasonic nebulizers for compound administration under ventilation
Pari LC star jet nebulizers for whole body aerosol exposure
Nonin 2500A Vet pulse-oximeter
Mouse intubation set-up
Set-up to inflate lungs with fixative
Semi-quantitative evaluation of pulmonary oedema by echography

The multi-subject extension for measurement of 4 mice simultaneously

Back to Content [page 4]



Typical time-course for a model of severe OVA-induced allergic asthma.

(PO-14) Metabolism Unit

Head: David Pajuelo Reguera
Team: Rajasree Sain

Contact: ccp-pm-metabolism@img.cas.cz

Rodent models, especially genetically modified mouse models, are key scientific tool for the discovery of gene functions directly or indirectly involved in energy metabolism and glucose homeostasis.
For first-line phenotyping, we perform intraperitoneal glucose tolerance tests, non-invasive body composition and indirect calorimetry as a starting point for further in-depth and hypothesis-driven studies.
Climate chambers with controlled light:dark regimes, humidity, and temperature allow us to perform cold challenges, studies in thermoneutrality, or variation in light:dark rhythms while acquiring indirect calorimetry data in mice or rats. As an additional service, we can evaluate the effect of feeding a certain diet, for example, a high-fat diet, on overall metabolism.

For the more in-depth study of glucose metabolism, we have implemented several tests in our metabolic pipeline: Basal and peak blood insulin concentration can be determined during glucose tolerance tests; to evaluate insulin sensitivity we conduct insulin tolerance tests; finally hepatic gluconeogenesis can be investigated by pyruvate tolerance tests. These complementary methodologies help to interpret possible defects in glucose metabolism caused by genetic modification or specific treatment.

Another recently integrated methodology is the telemetry of physiological parameters such as body temperature at two locations in the body or, very soon, the real-time measurement of blood glucose levels. These parameters can be measured in home-caged mice as well as in combination with indirect calorimetry. The combination of telemetry with indirect calorimetry opens a wide range of new possibilities to monitor metabolic functions in real-time and under ad libitum or challenging conditions or, under some specific treatment with minimum human intervention during the experiments.

We are able to perform body composition analysis based on TD-NMR technology providing a quick and precise method to determine the weight of lean and fat tissue, as well as free fluids in living mice and rats. This procedure provides a non-destructive and non-invasive analysis tool for rat and mouse phenotyping. The advantage that the animal does not have to be anesthetized and that the analysis is very fast allows repeated measurements of body composition in time series to detect effects of genetic alteration or treatment over time.

As for all units in CCP, our metabolism services gain additional value by the combination with other units of the center, e.g. cardiology, metabolomics, or clinical biochemistry, thus allowing the comprehensive characterization of your model.

Instrumentation & technologies

- Indirect Calorimetry including activity, food and water monitoring intake (PhenoMaster TSE Systems).
- Stellar Telemetry antenna & wireless monitoring dual temperature transmitters (TSE Systems).
- Body composition analyzer by Time-domain Nuclear Magnetic Resonance (TD-NMR) using (Minispec LF90II, Bruker)

(PO-15) Metabolomics Unit

Head: Karel Chalupsky
Team: Krystof Klima, Lukas Kucera, Klara Dohnalova

Contact: ccp-pm-metabolomics@img.cas.cz

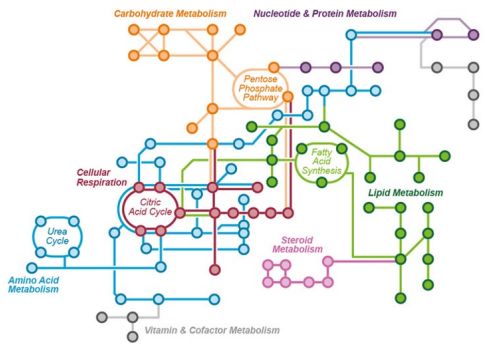
The Metabolomics unit is one of the newest extensions of the CCP expanding the method portfolio of the Metabolic and Clinical Biochemistry Units. The analysis of blood is part of our standard first-line phenotyping. We analyze about 30 biochemical parameters following IMPC IMPReSS. Measuring only a limited number of biochemical markers, increases the risk of missing the physiological impact of a studied gene or a treatment, or the early onset of a disease. Therefore, we implemented state-of-the-art metabolomics technology to analyze blood, serum or any other body fluid for molecules that may even give a hint to the mechanistic basis of a disease-relevant phenotype. Besides analysis based on liquid chromatography we also provide the mass spectrometry analysis of tissue samples by MALDI imaging.
Mass spectrometry imaging is mainly linked with histology and offer analysis of compounds in spatial context, which exceed the possibilities of classical histology. We are able to detect more than three hundreds of molecules on tissue slides.

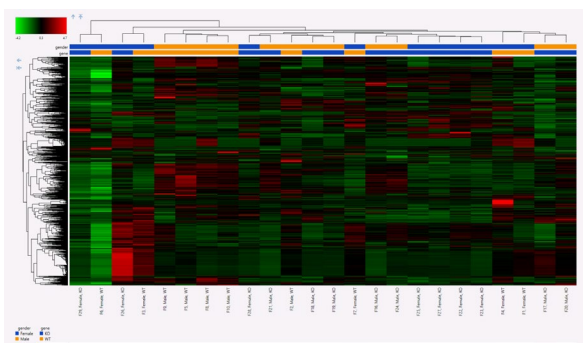
Our metabolomics unit has shown great potential in several biological applications. Discovery of diagnostic biomarkers, drug metabolization and their effects on whole metabolome, and progression of diseases are examples where studying metabolite profiles provided additional value also regarding translation to human disease. One of the biggest tasks in metabolomics is to obtain reliable and reproducible data in reasonable time. Over the past year, we have been able to optimize procedures so it was possible to collect and store mouse plasma from every mouse model produced and examined at the CCP. Using statistical methods such as PCA and others, allows to process and compare large data sets. Additional effort is put into the identification of unique metabolites and to map those to specific metabolic pathways which may be an important hint towards the molecular mechanism underlying the function of a gene.

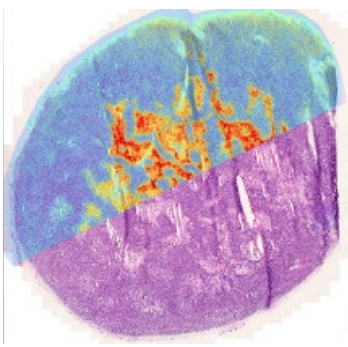
Our recent development in lipid detection is presented in poster section

Projects in selected publications:

- Microbiome and Metabolome Profiles Associated With Different Types of Short Bowel Syndrome: Implications for Treatment J Parenter Enteral Nutr. 2019 Apr 29







(PO-16) Neurobiology & Behaviour Unit

Head: Agnieszka Kubik-Zahorodna
Team: Katarina Kanasova, Pavlina Kucerova, Pavel Jina, Rozalie Novakova

Contact: ccp-pm-neuro@img.cas.cz

Genetic engineering opens an avenue of research opportunities to probe molecular bases of a variety of human diseases. Neurobehavioural tests using transgenic animal models make it possible to understand genetic mechanisms underlying neurological and psychiatric disorders including, but not limited to, anxiety, schizophrenia, mood disorders, and Parkinson's disease. The Neurobiology and Behaviour Unit employs a number of tests to examine motor abilities, cognitive functions, emotion, sensory processing as well as neurological, and gait impairments in transgenic mice.
Neurobiology and Behaviour module off¬ers standardized primary and secondary phenotype screens based on IMPC (International Mouse Phenotyping Consortium) protocols (https://www.mousephenotype.org/impress). Primary/mandatory screens include modified SHIRPA and dysmorphology evaluation, Open Field, Grip Strength, Acoustic Startle and PPI, Light/Dark Box, and Fear Conditioning.
The Unit also o¬ffers more specific secondary/optional screens that comprise tests evaluating animal emotionality and affect (Elevated Plus Maze, Forced Swim Test, Tail Suspension Test), cognitive function (Cued and Contextual Conditioning, Context Discrimination, Spontaneous Alternation, Barnes Maze, Novel Object Recognition), neuromotor abilities (RotaRod, Gait Analysis), pain sensitivity (Hot/Cold Plate, Tail Flick, Plethysmometer, von Frey Test), social preference, and last but not least evaluation of animal cognitive function and circadian activity in more natural conditions in IntelliCages.
Oversimplified „impoverished" environments together with stress from human handling may be responsible for substantial heterogeneity in the results of conventional behavioural tests. Social group housing in a large enclosure equipped with multiple gadgets in IntelliCage provides environmental enrichment beyond typically employed protocols. It also eliminates stressful interaction between the animal and the experimenter.
Mice behaviour often relies on intact olfactory system. Last year we added to our tests portfolio functional olfactory test – the habituation/dishabituation task. The test is based on the mice ability to recognise new odours and discriminate between them. The habituation/dishabituation task also requires neither extensive training nor prior food deprivation.

Instrumentation & technologies:
IntelliCage by NewBehaviour (TSE Systems) – state of the art equipment designed for automatic, long-term, studying cognitive functions of the rodents in the social groups while avoiding human factor.
DigiGait (Mouse Specifics Inc.) – state of the art equipment for gait analysis in various challenging conditions but unified for each animal.
ANY-maze controlled Fear Conditioning system (Stoelting, Ugo Basile SRL) – applied for standard cued and contextual fear conditioning, but also memory extinction, context discrimination etc.
Viewer for Animal Tracking (Biobserve) – with a variety of mazes covers testing in Barnes Maze, open field, light/dark box, elevated plus maze, novel object recognition, spontaneous alternation, forced swim test, 3-chamber sociability box.
Acoustic Startle Reflex (Med Associates Inc.) – used for sensorimotor gaiting evaluation. Startle reflex can be a subject to study its habituation, sensitization, or fear potentiation.
Tail Suspension Cage (Bioseb) – screening tool for antidepressants or studying depressive-like mouse phenotypes.
Rotarod (TSE Systems) – tests animal balance and coordination or motor learning on the rod.

(PO-17) PDX & Cancer Models Unit

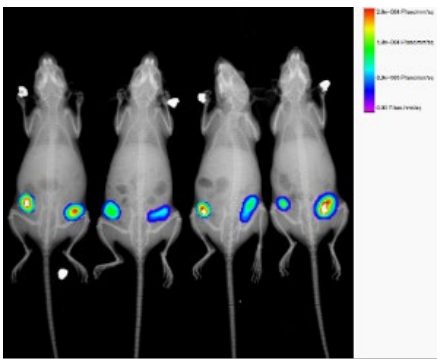
Head: Petra Kralova Viziova
Team: Andrea Hojna, Ana Rita da Silva Oliveira, Kristyna Hornova

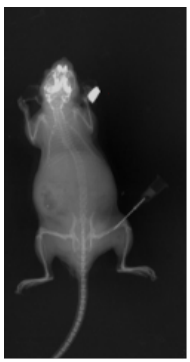
Contact: ccp-pm-pdx@img.cas.cz

The PDX (patient derived tumor xenograft)/Cancer Models Unit is dedicated to create novel orthotopic mouse/rat PDX and CDX models, to use them in cancer, immunology, and pharmacology research. PDX are models of cancer where the tissue or cells from a patient's tumor are implanted into a highly immunodeficient or humanized mouse. We use the well-suited NSG and NSG-SGM3 mouse strains to accomplish this purpose.

The samples for implantation or xenografts are placed orthotopicaly and then the tumor development and tumor size, as well as longevity, are followed to establish efficiency of treatment phase. Together with Bioimaging, Cardio, Immunology and Biochemistry units, the mice can be tested through in vivo approaches (luminescense, fluorescence, CT, ultrasound, blood parameters) to follow tumour and metastasis development and changes in blood profile. Mouse tumor samples can be viably stored in our cryobank and in parallel to evaluations in the CCP units (histopathology, hematology and biochemistry, immunology, bioimaging). Additionally samples may also be analyzed using uCT, MALDI imaging and/or metabolomics approaches. PDX mouse models represent therefore a promising research platform for personalized medicine including pharmacological and metabolic studies. The main benefit is the possibility of in-house multimodal analysis of the models.

The unit is also capable of cell/tissue culturing and freezing, and implantation of telemetric device as well. We recently developed a highly efficient intrafemoral xenografting for leukemia studies and microinvasive approach for mammary fat pad xenografts. Other surgery modalities include intrasplenic, subcapsular kidney, liver, intramuscular, ovary fat pad, testicular, intracaecal wall, intestinal wall, lung, subcutaneous xenograft etc. We have broad experience with cell culturing and cell line derived xenografts.
Our day-to-day monitoring of the animals allows us to collect important information such as healing times, changes in body weight, body condition score, changes on mucous membranes, skin reaction, behavioural tendencies, and prevalent disease symptoms during the study. We commit to a high level of biosafety and sterility, that allows us to proceed with long-term studies lasting up to several months.





Instrumentation & technologies
The unit is equipped with an X-RAD Biological Irradiator, a surgery microscope, all the necessary surgical instruments, a Tuttnauer autoclave, an inhalation unit, level 2 Biosafety cabinets, warming pads, and an oximeter for performing safe and accurate surgery on the animals.

Participation in projects:
- Participating as a member in the EuroPDX consortium (https://www.europdx.eu/).
- Research and therapy of myelodysplastic syndrome model with Biocev and 1st Faculty of Medicine (Charles University).
- Genotherapy of mammary and ovarian cancer on orthotopic models with IOCB.
- Testing of targeted polymeric conjugates for lymphoma therapy with IMG/IMC.
- PDX ALL3 intrafemoral leukemia model and testing of novel drugs with IOCB and The University Hospital (Brno).
- Immuno-oncology preclinical research on one side and dual flank mice model with IOCB.
- Rare lung cancer PDX models establishment with General University Hospital in Prague and Homolka hospital and 1st Faculty of medicine.
- Developing of pancreatic cancer model with Biocev.
- Implantation of telemetric devices for metabolism studies.
- Development of precise head-neck and ovarian cancer models for preclinical testing

Back to Content [page 4]

(PO-18) Vision Unit

Head: Marcela Pálková
Team: Marcela Pálková, Jiří Lindovský, Viktoriia Symkina, Ján Majerník

Contact: ccp-pm-vision@img.cas.cz

Vision unit is a part of phenogenomic center and is mainly focused on imaging, analyzing morphological structures and assessing morphological abnormalities in rodent eyes. These primary examinations are routinely performed in all mice coming to our unit. In special cases such as obvious morphological pathology of retina or special requests (e.g. mouse model for the retinopathy, diabetic disease etc.), the function of the retina is proved by electroretinography (ERG). Additional measurements of the intraocular pressure by rebound tonometer (IcareTonovet plus) provide us important information on the eye function and the health in the mice.

Imaging devices with high image quality and resolution are used to examine the anterior segment (Pentacam), retina (Optical coherent tomograph Heidelberg Engineering - OCT) and retinal vascular plexuses (OCT-A Heidelberg Engineering). All procedures are non-invasive, painless and allow long-term studies with repeated examination of eyes.

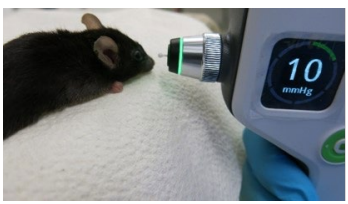
Pentacam scans the eye from 25-50 different angles and enables to measure many parameters of the cornea and the lens (e.g. surface, form, opacity, thickness and density) for each eye.

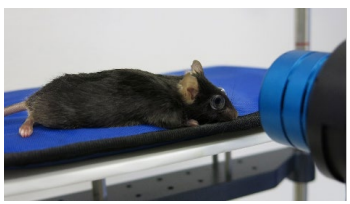
The OCT scan quantifies reflections of a light beam from individual layers of the retina and composes virtual cross-sectional images of the retina. The OCT-A scan enables us to detect and analyze four retinal vascular plexuses (svc - superficial and dvc - deep vascular complex, choriocapillaris and choroid). Each cross-section is evaluated and a variety of parameters are measured, e.g. the thickness and the gross morphology of the retina (retinal layers), form and the position of the optic disc, structure and pattern of the superficial blood vessels and parameters of the blood plexuses, e.g. density, number of blood vessel junctions and endpoints per region. To prove any morphological changes in the retina at different time points of life in mice, the consecutive scans could be done.

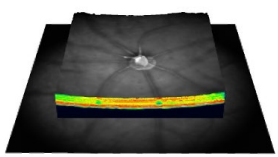
ERG measures electrical responses of different retinal cell types evoked by light stimulation. This examination enables us to compare/assess the physiological relevance of the morphological abnormalities in the retina for the vision and it is described in more detail in the Electrophysiological section.

Besides covering of the routine IMPC workflow, the unit also collaborated on many other research projects related to vision, such as the role of Zfp644 gene in the development of myopia (Szczerkowska et al. 2019). A strong retinal pathology discovered in Fam84b knockout strain initiated a more detailed longitudinal study which has become part of a master thesis and was presented at the conference last year.

1. Szczerkowska et al.: Myopia disease mouse models: a missense point mutation (S673G) and a protein-truncating mutation of the Zfp644 mimic human disease phenotype. 2019; Cell & Biosci 9-21.







(PO-19) Bioinformatician Unit

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Bioinformatics unit of CCP assists other CCP units with computational, statistical, and analytical analyses and provides these services in this field to CCP external customers. The unit focuses, principally, on data analysis, biostatistics, tool and application development and occasional organization of training workshops in biostatistics and programming. We endeavor towards the automation of various interdisciplinary enterprises leveraging such novel approaches as deep learning. The group also maintains a continuous and indispensable effort in integrative bioinformatics as part of its involvement in phenotyping research by large-scale analysis of metabolomics datasets and image analysis. The unit takes care about all phenotyping data including quality control, statistical analysis, their storage and placing them into public web. We are also developing LIMS system and help people with daily routine process automatization.

As an example of our research activity is developing of new algorithm for merging metabolomics datasets. A crucial step in preprocessing LC—MS data is selecting appropriate peak detection parameters. Since m/z and retention time shifts are larger between batches than within batches, finding apt parameters for all samples of a large-scale multi-batch experiment while minimizing signal information loss becomes a daunting task. Preprocessing batches singly can curtail said problems but requires a method for aligning and combining them for further downstream analysis. We developed two different methods for aligning and combining individually preprocessed batches in multi-batch LC—MS experiments. These algorithms enable analyze single batches independently and combine them afterwards without necessity recalculation preprocessing of data again.

Instrumentation & technologies

For big data analysis, we utilize our own Supermicro 1029GQ-TRT server. This server consists of two Intel Xeon Gold 5120 @ 2.2 GHz processors each with 14 cores, 128 MB RAM, and two SSD drives in RAID 1, each with 240GB memory. For computational acceleration of deep learning/neural network approaches, we use one graphics card NVIDIA Tesla P100 16GB. Especially long-term one threaded tasks are dislocated to MetaCentrum which provides free membership for researchers and students of academic institutions in Czech Republic. Our main used tools in our bioinformatics unit are R, Python.

Projects in selected publications:

- Fam208a orchestrates interaction protein network essential for early embryonic development and cell division. Gresakova V, Novosadova V, Prochazkova M, Bhargava S, Jenickova I, Prochazka J, Sedlacek R. Exp Cell Res. 2019 May 18
- c-Myb regulates tumorigenic potential of embryonal rhabdomyosarcoma cells. Kaspar P, Prochazka J, Efenberkova M, Juhasz A, Novosadova V, Sedlacek R. Sci Rep. 2019 Apr 19
- Myopia disease mouse models: a missense point mutation (S673G) and a protein-truncating mutation of the Zfp644 mimic human disease phenotype. Szczerkowska KI, Petrezselyova S, Lindovsky J, Palkova M, Dvorak J, Makovicky P, Fang M, Jiang C, Chen L, Shi M, Liu X, Zhang J, Kubik-Zahorodna A, Schuster B, Beck IM, Novosadova V, Prochazka J, Sedlacek R. Cell Biosci. 2019 Feb 21

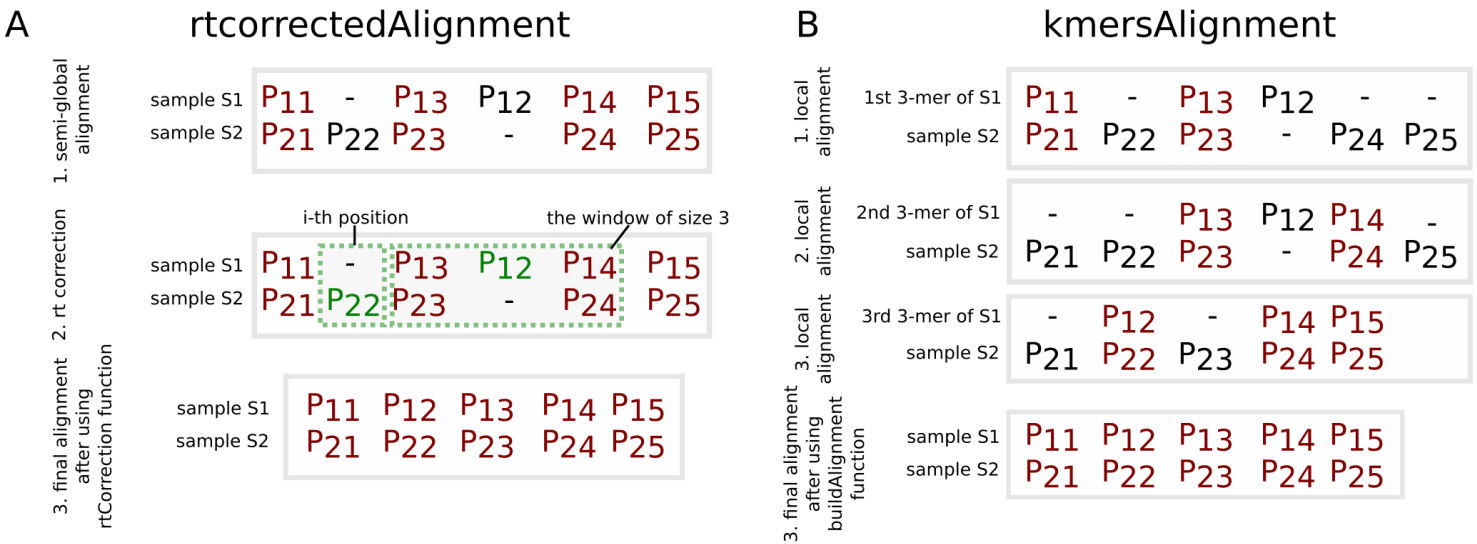
- Expression profile of miR-17/92 cluster is predictive of treatment response in rectal cancer. Kral J, Korenkova V, Novosadova V, Langerova L, Schneiderova M, Liska V, Levy M, Veskrnova V, Spicak J, Opattova A, Jiraskova K, Vymetalkova V, Vodicka P, Slyskova J. Carcinogenesis. 2018 Dec 13
- Rapid single-cell cytometry data visualization with EmbedSOM. Miroslav Kratochvíl, Abhishek Koladiya, Jana Balounova, Vendula Novosadova, Karel Fišer, Radislav Sedlacek, Jiří Vondrášek, Karel Drbal. bioRxiv 496869

sample S1 = ({P_{11} = (mz_1, rt_{11}, int_{11}), P_{12} = (mz_2, rt_{12}, int_{12}), P_{13} = (mz_3, rt_{13}, int_{13}), P_{14} = (mz_4, rt_{14}, int_{14}), P_{15} = (mz_5, rt_{15}, int_{15})}, $\leq_1^+$)

$\leq_1^+$ is a transitive closure of {(P11, P13), (P13, P12), (P12, P14), (P14, P15)}

sample S2 = ({P_{21} = (mz_1, rt_{21}, int_{21}), P_{22} = (mz_2, rt_{22}, int_{22}), P_{23} = (mz_3, rt_{23}, int_{23}), P_{24} = (mz_4, rt_{24}, int_{24}), P_{25} = (mz_5, rt_{25}, int_{25})}, $\leq_2^+$)

$\leq_2^+$ is a transitive closure of {(P_{21}, P_{22}), (P_{22}, P_{23}), (P_{23}, P_{24}), (P_{24}, P25)}



(PO-20) Transgenic and Archiving Module (TAM)

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Deputy head of the module: Petr Kasparek

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Transgenic and archiving module is a key part of Czech Centre for Phenogenomics, responsible for generation of novel genetically modified mice and rats using state-of-the-art technologies. TAM consists of subunits for the Genome Engineering & Model Generation and the Genotyping and Breeding, Cryopreservation & EMMA/Infrafrontier Services. Both subunits altogether provide complete service, from the initial gene-targeting design, generation of tools and transgenic rodent models to the genotyping and breeding of desired animal models.

The most commonly used genetic background in CCP is C57Bl/6N, but we are able to generate models on various backgrounds. Vast majority of newly generated mutant rodents are "knock-out" or "knock-in" models based on CRISPR/Cas9 targeting tools and zygote electroporation. Although classical transgenic models generation via pronuclear injection (PNI) of plasmid or BAC DNA is also used. Founder and G1 mice are analyzed to confirm germ line transmission (GLT). The successfully produced mouse/rat lines are cryopreserved (embryo or sperm cryopreservation). Furthermore, we offer mice production with the ES targeting technologies. Routinely we produce models from targeted embryonic stem cells originating from EUCOMM and KOMP repositories. Majority of modifications in these ES cell lines are so called "knockout-first" alleles that represent a LoxP-flanked critical exon with LacZ reporter element.

In cooperation with animal facility of CCP we provide consultation, assistance services, and information on the design and use of genetically modified transgenic mice. We also assist in animal rederivation (cleaning of the rodent line), reanimation (creating of the line from frozen embryos or sperms) as well as models import and export using cryopreserves sperm and embryos.

TAM provides services to a broad national and international scientific community. As a member of INFRAFRONTIER, we are contributing with mice generation to the IMPC project that aims to knockout all the mammalian genes. We also represent a Czech node of EMMA (European Mouse Mutant Archive), a non-profit repository for the collection, archiving (via cryopreservation) and distribution of relevant mutant mouse strains essential for basic biomedical research

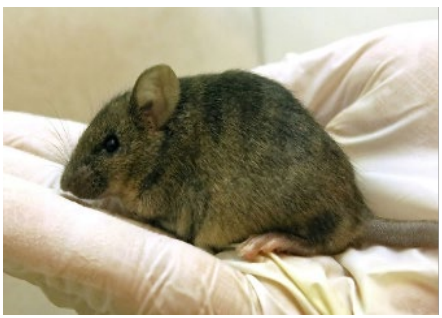
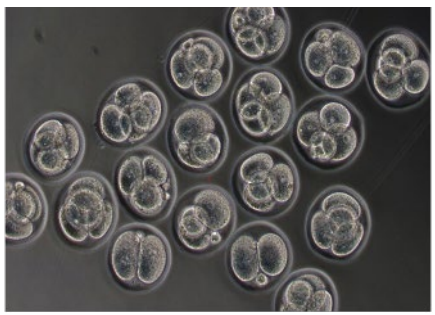
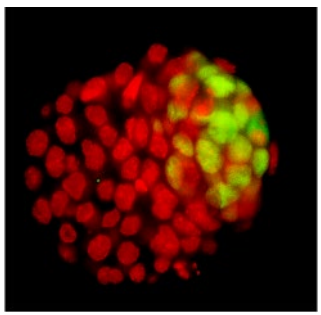
OUR SERVICE COMPRISES:

- Mouse/rat model generation using programmable nucleases (TALEN, CRISPR/Cas9)
- Classical plasmid and BAC transgene generation using PNI (pronuclear injection)
- Mouse model generation using ES cells, including usage of ES cells from EUCOMM and KOMP repositories
- CRE/FLP mediated allele conversions
- Embryo and sperm cryopreservation, and reanimation of strains from frozen material
- Ovary transplantation

- Rederivation/ cleaning of mouse/rat strains
- Genotyping service
- Import/ Export arrangements (together with the animal facility module

Instrumentation & technologies
NEPA 21 type II electroporator (NEPAGENE), micromanipulation microscopes Olympus IX83 equipped with TransferMan4r and XYRCOS (Hamilton Thorne) and Leica DMI6000B with FemtoJet4i. Freezing machine Asymptote EP600 (Grant), Micro-ePore pinpoint cell penetrator (WPI), sperm analyzer Mouse Traxx (Olympus CX41). Automatic capillary electrophoresis QIAxcel Advanced system.

Projects in selected publications:
- Efficient allele conversion in mouse zygotes and primary cells based on electroporation of Cre protein. **Irena Jenickova, Petr Kasparek,** Silvia Petrezselyova, Jan Elias, Jan Prochazka, **Jana Kopkanova,** Michal Navratil, Cyril Barinka, **Radislav Sedlacek** Methods 2021 Jul 191
- KLK5 and KLK7 Ablation Fully Rescues Lethality of Netherton Syndrome-Like Phenotype. **Kasparek P,** Ileninova Z, Zbodakova O, Kanchev I, Benada O, Chalupsky K, Brattsand M, **Beck IM, Sedlacek R.** PLoS Genet. 2017 Jan 17
- A viable mouse model for Netherton syndrome based on mosaic inactivation of the Spink5 gene. Kasparek P, Ileninova Z, Haneckova R, Kanchev I, **Jenickova I, Sedlacek R.** Biol Chem. 2016 Dec 1
- Efficient gene targeting of the Rosa26 locus in mouse zygotes using TALE nucleases. **Kasparek P,** Krausova M, Haneckova R, Kriz V, Zbodakova O, Korinek V, **Sedlacek R.** FEBS Lett. 2014 Nov 3

(PO-21) Preclinical testing at the Czech Centre for Phenogenomics

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The development of new drugs is an interdisciplinary, time-consuming, and costly process and critically depends on the selection of appropriate and predictive preclinical models. Developing safe and efficacious drugs requires thorough preclinical testing using in vitro, in vivo, and increasingly also in silico approaches. Due to the progress made in biomedical sciences, the number of potential biological disease targets has dramatically increased but translatability of those advances into significant health benefits is slowing down. It has also become evident that the drug development process is very inefficient and has high attrition rates contributing to what has recently been termed the translational gap. The reasons for this are poor hypotheses, irreproducible data, ambiguous preclinical models, statistical errors, insufficient transparency, and lack of data sharing in research.

Based on the experiences from high throughput phenotyping of mouse models, the Czech Centre for Phenogenomics (CCP) offers a broad portfolio of highly standardized, state-of-the-art test assays (some in GLP mode) that can be applied in preclinical studies in experimental rodent models reproducing certain features of human disease. Established preclinical tests comprise toxicity studies, hematological, and biochemical testing of samples taken from animals during toxicity studies, determination of active substances, and metabolites in plasma or other biological matrices, histopathology, PDX models, ECG and echocardiography for effects on cardiovascular functions, body composition analysis, monitoring of energy fluxes, substrate utilization, feeding and drinking behavior, and locomotor activity, as well as various imaging modalities. The CCP has also implemented neurobehavioral testing and established model systems in the field of asthma and lung fibrosis, liver fibrosis, and induced colitis models. Further model systems are under development including genetically modified mouse lines related to Covid-19 research.

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Back to Content [page 4]

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Back to Content [page 4]

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