Laboratory of Transgenic Models of Diseases

Transgenesis, embryogenesis, proteases and their inhibitors, aging and epigenetics, neural development

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With an exceptional role in IMG, our department serves as an incubator in which research projects and groups of the BIOCEV project as well as national research infrastructure develop. Although thematically distinct, all groups, projects and activities are based on the usage of mouse models as a tool to reveal gene functions in the complexity of the whole organism.

Proteases in physiology and disease. One part of the department is focused on proteases, particularly on matrix metalloproteinases (MMP), a disintegrin and metalloproteinase (ADAM), and kallikreins (Klk). MMP and Klk proteases are partly responsible for controlling extracellular matrix-cell interactions affecting cell differentiation, survival, migration, and other processes. ADAM10 & ADAM17 proteinases release ligands and their receptors from the cell surface, thus guiding bioavailability of many important regulatory molecules. The balance among the proteases and their natural inhibitors determines whether biological processes are to be initiated or terminated.

Ubiquitylation-mediated processes in health and disease. Using mutant mouse models we address the role of several ubiquitin ligases and deubiquitinases in mediating responses to environmental stressors. A main focus of these studies is to understand the role of ubiquitylation in regulating intestinal barrier function and to characterize links with human inflammatory bowel disease.

Stem cell pluripotency and early embryonic development. Stochastic processes underlie much of early pre-implantation development but later, especially during gastrulation, increasingly deterministic signalling restricts the developmental fate. Using unique mouse models and environmental stressors we address the molecular mechanisms influencing cell fate decisions probabilistically and the effects this has on embryonic development, stem cell pluripotency, and embryonic robustness to environmental stressors and teratogens.

Stem cell dynamics and aging. In building a quantitative model of epigenetic silencing, we have uncovered an important role for probability-based events. Using several novel mouse mutants found in an unbiased forward genetics screen to alter these odds (including Foxo3a, which has already been linked to human longevity) we are gaining new understanding about how probabilistic cellular events underlie many aspects of the aging process.

Fig. 1. TALEN-assisted targeting of the ROSA locus: expression of turboRFP in founder mice was manifested by red colour of the skin. Photographs were taken at the age of 2 days (left) and 4 weeks (right). Strong expression of TurboRFP in founder mice was confirmed using fluorescent microscopy of tail biopsies (right). Expression of TagBFP in the flippase-positive embryo (left) derived from breeding of founder B7 with a flippase expressing mouse.

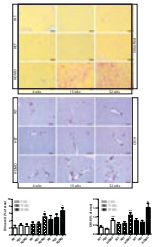

Fig. 2. Mutant mouse with liver-specific ablation of ADAM10 develops spontaneous fibrosis.

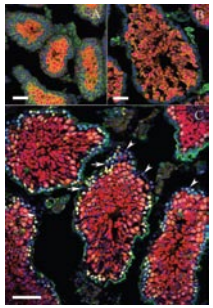

Fig. 3. Expression of EGFP protein in the testis of LRAT-EGFP reporter transgenic mouse from postnatal day 14 to adulthood. From postnatal day 14 to adulthood, EGFP protein (red) expression in the pLrat□GFP 17 reporter mouse is highly expressed in meiosis round spermatocytes (SCP3 positive) and in post meiosis spermatids (SCP3 negative), which are located more luminal.

- GACR, GAP303/10/2044 – The Impact of a liver-specific deficiency of growth factor sheddase ADAM10 on liver development and pathology, 2010-2013, R. Sedláček
- GACR, GAP305/10/2143 – Generation of mouse models for targeting stellate cells and myofibroblasts in the liver, 2010-2013, R. Sedláček
- GACR, GAP302/11/2048 – Function of metalloproteinases in colon epithelium and during development of experimental colitis and colon cancer, 2011-2014, R. Sedláček
- GACR, GA13-01710S – Reactivity of lung vessels in pulmonary hypertension, 2013-2017, K. Chalupský
- GACR, 14-33798P – Genomic instability and cardiovascular aging: the role of local and systemic mechanism, 2014-2016, M. Ďurík
- FP7 EU, 284501 INFRACOMP – Coordinating the cooperation of the ESFRI project Infrafrontier with the International Phenotyping Consortium (IMPC), 2011-2014, R. Sedláček
- FP7 EU, 312325 Infrafrontier-I3 – Development of mouse mutant resources for functional analyses of human diseases - Enhancing the translation of research into innovation, 2013-2016, R. Sedláček
- MEYS, EC OP CZ.1.07/2.3.00/20.0102 – Founding an expert team for the Centre for Phenogenomics, 2011-2014, R. Sedláček
- MEYS, EC OP CZ.1.07/2.3.00/30.0027 – Founding the Centre of Transgenic Technologies, 2012-2015, R. Sedláček, V. Kořínek, Z. Kozmík
- MEYS, EC OP CZ.1.07/2.3.00/30.0050 – Founding the expert platform for phenotyping and imaging technologies, 2012-2015, R. Sedláček, P. Hozák
- MEYS, LM2011032 INFRAFRONTIER-CZ – Infrafrontier-CZ/Czech Centre for Phenogenomics as a national centre of „The European infrastructure for phenotyping and archiving of model mammalian genomes": Integration of the Czech national centre into international network, 2012-2016, R. Sedláček
- MEYS, 7AMB13AT012 – Structural and functional analysis of interaction between calmodulin and plectin isoform 1a, 2013-2014, M. Gregor
- MEYS, LH14276 LH - KONTAKT II – Novel causative genes identification and functional study for selected Mendelian disorders, 2014-2016, R. Sedláček
- MH, IGA NT14451 – New technology for correction of mutations in monogenetic diseases by targeted reparation of mutations using specific nucleases, 2013-2015, R. Sedláček
- TACR, TA03011057 – Development of new methods to analyse environmental genotoxic stress and mutagenicity of potential pharmaceutical compounds, 2013-2016, R. Sedláček

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From the left:
Down: Makéta Pícková / Technician, Silvia Petrezselyová PhD / Postdoctoral Fellow, Lenka Sarnová MSc / Technician, Agnieszka Kubik-Zahorodna PhD / Research Associate, Olga Žbodáková MSc / Research Assistant, Zuzana Ileninová PhD / Postdoctoral Fellow, Dana Kopperová Msc / Technician, Monika Volčková MSc / Technician, Henrieta Pálešová MSc / Technician
Middle: Radislav Sedláček PhD / Head of Laboratory, Veronika Grešáková MSc / PhD Student, Shohag Bhattacharyya MSc / PhD Student, Björn Schuster PhD / Research Associate, Jana Šafránková B.A. / Project Manager, Veronika Libová MSc / Technician, Petr Kašpárek MSc / PhD Student, Attila Juhasz / Technician, Anna Laštůvková MSc / Technician, Inken M. Beck, Libor Daněk M.A. / Project Manager, Benoit Piavaux PhD / Postdoctoral Fellow
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