



# Laboratory of Transgenic Models of Diseases

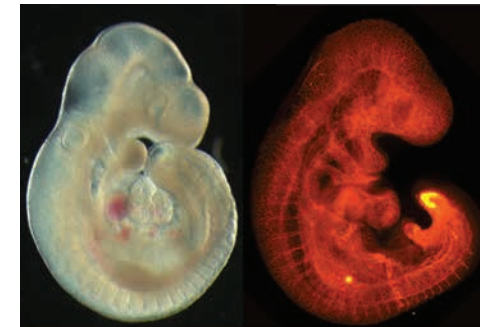
Proteases and their inhibitors, transgenesis, embryogenesis, aging and epigenetics, neural development

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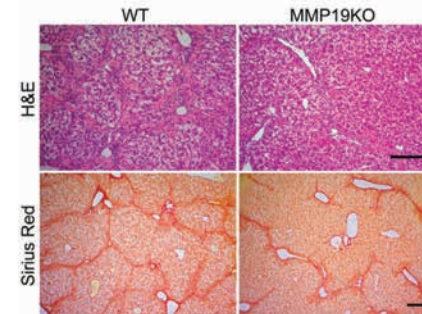
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Our department has an exceptional role in IMG, serving as an incubator in which new research projects and groups as well as research infrastructure [partly core facilities] develop for the project of BIOCEV. Although thematically distinct, all groups and projects 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]. While MMP and Klk proteases are largely responsible for controlling extracellular matrix-cell interactions affecting cell differentiation, survival, migration, and other processes, the ADAM proteinases such as ADAM 10 and ADAM17 [TACE] 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 tissues and organ architecture are to be built up or disrupted, or whether biological processes are to be initiated or terminated. This balance is pivotal for tissue homeostasis and its disturbance may lead to development of various pathologies. 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. Molecular mechanisms of neural development and neurodegeneration. Tight regulation of signalling cascades and molecular mechanisms controlling neuron polarization and axon guidance are essential for normal neural development and function of the nervous system. Their defects or aberrant activation in adult neurons are associated with onset of neurodegenerative disorders, e.g. Alzheimer's disease. Using in vitro systems and in vivo mouse models, we focus on the regulation of signalling cascades by conformational changes, and their role in the nervous system development, aging and disease.



**Fig. 1.** 9.5 days post coitus mouse embryo; left panel: fresh preparation, right panel: fixed and stained with VE-cadherin antibody to visualize developing vasculature



**Fig. 2.** 6 week CCl4 treatment results in lower liver damage in MMP19KO mice compared to WT mice. H&E staining showed larger bridging necrosis areas in WT mice than in MMP19KO mice. Scale bars=200 µm.

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From the left:

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Not in the picture:

Markéta Jíroušková, PhD / Research Fellow [maternity leave] · Agnieszka Kubik-Zahorodna, PhD / Research Associate [since 2012] · Jolana Turečková, PhD / Research Associate · Dana Průková, PhD / Postdoctoral Fellow · Gizela Koubková, PhD / Research Assistant [since 2012] · Eliška Machalová / Technician [maternity leave] · Václav Gergelits / Diploma Student · Halka Buryová / Diploma Student (until 2012)