# Institute of Clinical and Molecular Virology

## Division of Experimental Therapy

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**Research focus**

- Mechanism of pathogenic protein cross-seeding in neurodegenerative disorders (Cross- Seeds)
- Characterization of the contribution of trans-glutaminase 6 to Huntington's and Alzheimer's disease
- Examination of behavioral abnormalities in rats after injection with gadolinium based contrast agents: Neurobehavioral findings resulting from experiments
- Characterization of the role of glutaminyl-cyclase and its isoform during Huntington's disease
- Potentiation of Neuropeptide Y mediated effects in stress-associated and neurodegenerative disorders via NPY-degradation inhibitors
- Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition

## Structure of the Division

Professorship: 1
Personnel: 7

- Doctor (of Medicine): 1
- Scientist: 1
- Graduate students: 4

**Special structural features**

- Location within the Preclinical Experimental Animal Center (PETZ)
- Contribution to services and teaching offered by PETZ

## Research

Research is focused on experimental therapeutic studies in animal models of human neurodegenerative and psychiatric disorders (Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), Spinocerebellar ataxia type 17, Schizophrenia, stress-induced disorders, attention deficit hyperactivity disorder). After comprehensive phenotyping of a certain disease model, we search for, characterize, and target post-translational protein-modifications by transglutaminases, dipeptidyl-peptidase 4, glutaminyl-cyclase and its isoform ultimately trying to identify novel interventional approaches. A present focus is on neurodegenerative processes in the course of protein aggregation disorders.

**Mechanisms of pathogenic protein cross-seeding in neurodegenerative disorders (Cross-Seeds)**
This project is based on the hypothesis that a number of brain disorders, including AD, PD, and HD, share common pathogenic mechanisms leading to neurodegeneration. A traditional view on these devastating disorders focuses on individual, disease-specific enzymes and/or aggregating proteins contributing to aspects of neuropathology. Here, we combine interdisciplinary approaches to identify cross-disease pathways leading to pathogenic protein aggregation. All three clinical conditions addressed have at least one feature in common: Aggregation of pathogenic proteins associated with neurodegeneration. We use mice and rats transgenic for AD, PD, and HD in order to screen for cross disease protein aggregation between the pathogenic proteins.

**Characterization of the contribution of transglutaminase 6 to Huntington's and Alzheimer's disease**
Mammalian transglutaminases (TG) catalyze calcium-dependent irreversible post-translational modifications of proteins and their enzymatic activities contribute to the pathogenesis of several human neuro-degenerative diseases. Our overall hypothesis is that the neuronal isoform of transglutaminases, transglutaminase 6, significantly contributes to protein aggregation in HD and AD. TG6 may interact with polyglutamine (HTT) or amyloid-precursor-derived (Aß) proteins inducing posttranslational modifications via trans-glutaminase-catalyzed intermolecular crosslinks resulting in stable, rigid, and insoluble protein complexes. Focusing on the role of TG6 in HTT and Aß aggregation *in vitro* and *in vivo*, we therefore study TG6 expression and function in HD/AD cell culture systems, transgenic mouse and rat models including novel loss-of-function mutant mice (TG6ko mice). We expect deeper insight into the role of TG6 in the CNS and particular into TG6 dependent mechanisms contributing to HTT/Aß aggregation potentially identifying targets and novel therapeutic approaches in neurodegenerative disorders.

**Examination of behavioral abnormalities in rats after injection with gadolinium based contrast agents: Neurobehavioral findings resulting from experiments**
The objective of this study was to investigate the potential effect of a signal intensity (SI) increase and the presence of Gadolinium (Gd) in the brain after repeated administration of the Gd-based contrast agents (GBCAs) Omniscan and Gadovist on general health, motor coordination, anxiety-related behaviors as well as cognition. GBCAs represent a family of aminopolyarboxylic acid ligands chelated to gadolinium and are commonly used in patients for T1-weighted magnetic resonance imaging (MRI) for diagnostic purpose. Since a few years it is known that repeated administration of some, but not all GBCAs, is associated with T1-weighted signal intensity increase in the deep cerebral nuclei dentate nucleus and globus pallidus of the patients. Genesis, clinical consequences, reversibility, and potential comorbidity of this Gd-accumulation is not known yet. The American Food and Drug Administration as well as the European Medicines Agency prompted all manufacturer of GBCAs to investigate potential functional consequences of this Gd-accumulation.

**Characterization of the role of glutaminyl-cyclase and its isoform during Huntington's disease**
Aim of the present project is to investigate the role of glutaminyl-cyclase (QC) and iso-glutaminyl-cyclase (isoQC) during the neuropathological processes associated with HD in the rodent brain. Among other approaches, HD transgenic animals are phenotyped and the impact of the enzyme glutaminy-cyclase (QC) and its isoform (isoQC) is characterized after cross- breeding with QC and isoQC knockout-mice. Furthermore, experimental therapy by active immunization against QC/isoQC posttranslational modified huntingtin fragments is performed.

**Potentiation of Neuropeptide Y mediated effects in stress-associated and neurodegenerative disorders via NPY-degradation inhibitors**
The concept of stress protection in the CNS via potentiation of endogenous stress-protective signaling is neither fully explored nor clinically translated. Neuropeptide Y (NPY) exerts many stress and neuroprotective actions in the brain and may well be pharmacologically modulated by inhibiting the corresponding enzymatic degradation. In addition, neurodegenerative disorders such as HD may benefit from such approaches. Surprisingly, in the degenerating striatum of HD patients, those medium spiny neurons expressing NPY survive. We will analyze this endogenous NPY-based neuroprotection in animal models of HD. Genetic and pharmacological inhibition of the NPY-degrading enzyme dipeptidyl-peptidase IV will be used to develop a novel HD delaying approach via inhibitor-mediated potentiation of NPY-mediated neuroprotection.

**Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition**
HD is an autosomal dominant neuro-degenerative disorder caused by expanded CAG repeats in the huntingtin gene. Although mutant HTT is expressed during embryonic development and throughout life, clinical HD usually manifests later in adulthood. A number of studies

document neurodevelopmental changes associated with mutant HIT, but whether these are reversible under therapy remains unclear. We identify very early behavioral, molecular, and cellular changes in preweaning transgenic HD rats and mice. Interventional treatment of this early phenotype with the histone deacetylase inhibitor (HDACi) LBH589 led to significant improvement in behavioral changes and markers of dopaminergic neurotransmission and complete reversal of aberrant neuronal differentiation *in vitro* and *in vivo*. Our data support the notion that neurodevelopmental changes contribute to the prodromal phase of HD and that early, presymptomatic intervention using HDACi may represent a promising novel treatment approach for HD.

## Teaching

The Division of Experimental Therapy contributes to the international degree program Molecular Medicine as well as to electives in Medicine. Our seminar on interdisciplinary preclinical studies using animal models of human disorders is much appreciated.
We supervise Bachelor's and Master's theses as well as MD and PhD theses in the fields of neurobiology and neuropathophysiology of neurodegenerative diseases.

**Selected publications**

Habermeyer J, Boyken J, Harrer J, Canneva F, Ratz V, Moceri S, . . . von Horsten S. (2020). Comprehensive phenotyping revealed transient startle response reduction and histopathological gadolinium localization to perineuronal nets after gadodiamide administration in rats. Sci Rep, 10(1), 22385.

Dietrich P et al. (2020). Molecular crosstalk between Y5 receptor and neuropeptide Y drives liver cancer. J Clin Invest, 130(5), 2509-2526.

Cheong RY, Tonetto S, von Horsten S, & Petersen A. (2020). Imbalance of the oxytocin-vasopressin system contributes to the neuropsychiatric phenotype in the BACHD mouse model of Huntington disease. Psychoneuroendocrinology, 119, 104773.

Konig C, Plank AC, Kapp A, Timotius IK, von Horsten S, & Zimmermann K (2020). Thirty Mouse Strain Survey of Voluntary Physical Activity and Energy Expenditure: Influence of Strain, Sex and Day-Night Variation. Front Neurosci, 14, 531.

Timotius, I. K., Moceri, S., Plank, A. C., Habermeyer, J., Canneva, F., Winkler, J., . . . von Horsten, S. (2019). Silhouette-Length-Scaled Gait Parameters for Motor Functional Analysis in Mice and Rats. eNeuro, 6(6).

Post JI, et al. (2019). Differential Levels and Phosphorylation of Type 1 Inositol 1,4,5-Trisphosphate Receptor in Four Different Murine Models of Huntington Disease. J Huntingtons Dis, 8(3), 271-289.

Minakaki, G et al. (2019). Treadmill exercise intervention improves gait and postural control in alpha-synuclein mouse models without inducing cerebral autophagy. Behav Brain Res, 363, 199-215.

Hartlage-Rubsamen M et al. (2019). Endogenous mouse huntingtin is highly abundant in cranial nerve nuclei, co-aggregates to Abeta plaques and is induced in reactive astrocytes in a transgenic mouse model of Alzheimer's disease. Acta Neuropathol Commun, 7(1), 79.

**International cooperations**

Dr. A.P. Osmand, Department of Biochemistry and Cellular and Molecular Biology, University of Tennessee, Knoxville: USA

Dr. S. Hunot, Brain & Spine Institute (ICM), Pierre et Marie Curie University, Paris: France

Dr. Å. Petersén, Translational Neuroendocrine Research Unit, Lund University, Lund: Sweden

Prof. Dr. J.G. Bjaalie, Institute of Basic Medical Sciences, University of Oslo: Norway