

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 transglutaminase 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 neurodegenerative 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 (A β) proteins inducing posttranslational modifications via transglutaminase-catalyzed intermolecular crosslinks resulting in stable, rigid, and insoluble protein complexes. Focusing on the role of TG6 in HTT and A β 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 mech-

anisms contributing to HTT/A β 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 aminopolycarboxylic 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 glutaminyl-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 neurodegenerative 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 pre-clinical 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

Thangaratnarajah C, Dinger K, Vohlen C, Klaudt C, Nawabi J, Lopez Garcia E, Kwapiszewska G, Dobner J, Nüsken KD, van Koningsbruggen-Rietschel S, von Hörsten S, Dötsch J, Alejandro Alcázar MA. Novel role of NPY in neuroimmune interaction and lung growth after intrauterine growth restriction. *Am J Physiol Lung Cell Mol Physiol*. 2017 Sep 1;313(3):L491-L506

Amato D, Canneva F, Nguyen HP, Bauer P, Riess O, von Hörsten S, Müller CP. Capturing schizophrenia-like prodromal symptoms in a spinocerebellar ataxia-17 transgenic rat. *J Psychopharmacol*. 2017 Apr;31(4):461-473

Uzunecer TC, Schindehütte M, Dere E, von Hörsten S, Kornhuber J, Grömer TW, Müller CP. Schizophrenia dimension-specific antipsychotic drug action and failure in amphetamine-sensitized psychotic-like rats. *Eur Neuropsychopharmacol*. 2018 Dec;28(12):1382-1393

Siebzehnrbül FA et al. Early postnatal behavioral, cellular, and molecular changes in models of Huntington disease are reversible by HDAC inhibition. *Proc Natl Acad Sci U S A*. 2018 Sep 11;115(37):E8765-E8774

Timotius IK, Canneva F, Minakaki G, Pasluosta C, Mocerì S, Casadei N, Riess O, Winkler J, Klucken J, von Hörsten S, Eskofier B. Dynamic footprint based locomotion sway assessment in alpha-synucleinopathic mice using Fast Fourier Transform and Low Pass Filter. *J Neurosci Methods*. 2018 Feb 15;296:1-11

Plank AC, Canneva F, Raber KA, Urbach YK, Dobner J, Puchades M, Bjaalie JG, Gillmann C, Bäuerle T, Riess O, Nguyen HHP, von Hörsten S. Early Alterations in Operant Performance and Prominent Huntingtin Aggregation in a Congenic F344 Rat Line of the Classical CAGn51trunc Model of Huntington Disease. *Front Neurosci*. 2018 Jan 25;12:11

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