Institute of Clinical and Molecular Virology
Division of Experimental Therapy

Address
Palmsanlage 5
91054 Erlangen
Phone: +49 9131 8523504
Fax: +49 9131 8523502
www.fpz.uni-erlangen.de

Head of Division
Prof. Dr. med. Stephan von Hörsten

Contact
Dr. rer. nat. Anja Schulze-Krebs
Phone: +49 9131 8523566
Fax: +49 9131 8523502
Anja.Schulze-Krebs@uk-erlangen.de

Research Focus
- Mechanisms of pathogenic protein cross-seeding in neurodegenerative disorders (Cross-Seeds)
- Therapeutic modulation of the cholinergic system in a rat model of amyloidosis
- Characterization of the contribution of transglutaminase 6 to Huntington’s and Alzheimer’s disease
- Characterization of the role of glutaminyl-cyclase and its isoform during Huntington’s disease
- Potentiation of Neuropeptide Y (NPY) mediating effects in stress-associated and neurodegenerative disorders via NPY-degradation inhibitors

Structure of the Division

Professorships: 1
Personnel: 6
- Doctors (of Medicine): 1
- Scientists: 2 (thereof funded externally: 1)
- Graduate students: 3

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, Huntington’s disease, Parkinson’s disease, 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, dipetidyl-peptidase 4, glutaminyl-cyclase and its isoform ultimately trying to identify novel intervention 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.

Therapeutic modulation of the cholinergic system in a rat model of amyloidosis
AD is a devastating neurodegenerative disorder that impairs memory and causes progressive cognitive and psychiatric deficits. Loss of memory (episodic memory, declarative memory) is usually the most common symptom lamented by affected patients. The cholinergic system is involved in regulating a number of physiological functions, including motor control and sensory processing, additionally to cognition and sleep. Cholinergic dysfunction is particularly relevant to AD because it emerges early on during the pathology. Pharmacological treatments aimed at potentiating cholinergic neurotransmission are approved interventional strategies that produce some positive effects in the early stages of the disease, although their effects wear out as the pathology progresses. Aims of the project are a) to pin down the contribution of attention deficit and hyper-activity to the behavioral symptoms associated with amyloid pathology in a transgenic rat model of AD; b) to analyze the impact of cholinergic-enhancing drugs on the observed phenotype(s); c) to demonstrate the efficacy of chronic cotinine administration as a novel pharmacological intervention in this animal model.

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 (Aβ) proteins inducing posttranslational modifications via transglutaminase-catalyzed intermolecular cross-links resulting in stable, rigid and insoluble protein complexes. Focusing on the role of TG6 in HTT and Aβ 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 particularly into TG6 dependent mechanisms contributing to HTT/Aβ aggregation potentially identifying targets and novel therapeutic approaches in neurodegenerative disorders.

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 ko mice. Furthermore, experimental therapy by active immunization against QC/isoQC posttranslational modified huntingtin fragments is performed.

Potentiation of Neuropeptide Y (NPY) 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 analyse 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.

Comprehensive phenotyping on behavioral, morphological, and physiological levels is used for the evaluation of the therapeutic potential of specific enzyme inhibitors targeting dipeptidyl-peptidase IV, glutaminyl cyclases, and transglutaminase 6 in transgenic animal models for human neurodegenerative disorders. Novel technologies, such as intra-home-cage-phenotyping and advanced telemetry, are applied.

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


Wagner L, Björkqvist M, Lundh SH, Wolf R, Börgel A, Schlenzig D, Ludwig HH, Rahfeld JU, Leavitt B, Demuth HU,