UNIVERSITY HOSPITAL

Department of Neurology

Division of Molecular Neurology

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Research focus
- Neurodegenerative diseases
- Translational neurosciences
- Clinical research and development

Structure of the Division

Professorships: 2
Personnel: 20
- Doctors (of Medicine): 7
- Scientists: 3 (thereof funded externally: 2)
- Graduate students: 7

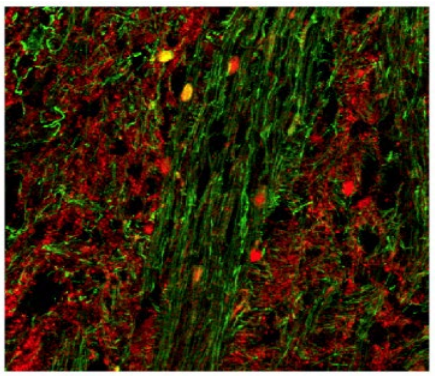
Clinical focus areas
- Outpatient clinical and research center for neurodegenerative movement disorders
- Center of the National Network for Parkinson's disease and European Huntington's disease Center
- Rare genetic movement disorders (Center for rare diseases)
- Atypical Parkinsonian syndromes

Research

The Division of Molecular Neurology focusses on the functional, behavioural, cellular, and pathological alterations in neurodegenerative diseases. The academic outpatient clinic provides state-of-the-art care for patients with neuro-degenerative movement disorders with particular focus on diagnostic work-up and treatment of Parkinsonian Disorders, Huntington's Disease and Motor Neuron Diseases. We participate in numerous national and international clinical studies. Furthermore, by applying medical engineering methods, an objective and opti-mized monitoring of patients with movement disorders is being developed in the framework of interdisciplinary research networks at the University Erlangen. By applying modern stem cell technologies, patient-based insights into cellular and biochemical disease mechanisms are studied.

Neurodegenerative diseases
The scientific focus of the Division of Molecular Neurology emphasizes on stem cell biology and neurodegenerative mechanisms in the context of sporadic Parkinson's disease, Multiple System Atrophy, Huntington's disease, and Hereditary Spastic Paraplegia. Neuroregenerative mechanisms with particular interest in the generation of new neurons and glial cells in the adult brain (adult neuro- and gliogenesis) are analyzed using cell culture systems (induced pluripotent stem cells) and transgenic disease models. In a complementary approach, neuro-degenerative mechanisms underlying the interplay of intra- and extracellular α-synuclein are analyzed in detail in order to better understand the molecular mechanisms underlying the pathogenesis of Parkinson's disease. The interaction between neuro-degenerative and inflammatory pathomechanisms within the central nervous system (CNS) is an additional major focus.

Translational neuroscience
A biobank for patient specific induced pluripotent stem cells (IPSCs) and its progeny is established and further developed in the framework of the Bavarian Network ForIPS and ForInter. Cell culture and molecular techniques have been established to delineate and modify pathological mechanisms associated with neuronal and oligodendroglial protein aggregation, degradation, and extracellular secretion mechanisms of alpha-synuclein in sporadic and atypical Parkinsonian syndromes. Alterations in protein degradation can lead to severe damage in neuronal and glial cells. Therefore, the experimental work focuses on the molecular causes, as well as possible therapeutic approaches that cause increased protein turnover in the lysosome. Moreover, we characterize myelin producing oligodendrocytes, which are affected in Multiple System Atrophy, showing a pronounced demyelination. The comprehensive analysis of cellular and molecular biological processes on patient derived material provides a unique opportunity to better understand molecular pathogenesis in neurodegenerative diseases and to analyze patients on an individual basis.
This translational neuroscience research work is supported in several interdisciplinary projects.
Funding: DFG, BMBF, Bavarian State Ministry of Economic Affairs and Media, Energy and Technology, Bavarian State Ministry of Education, Science, and the Arts, IZKF, Michael J. Fox Foundation.



Alpha-synuclein aggregation (red) in neuronal cells (synapsin: green) in the basal murine forebrain/thalamus region.

Clinical research and development
The Movement Disorders Outpatient Clinic and Center for Rare Movement Disorder, focus on clinical neuroscience research of sporadic Parkinson's disease (PD), rare Parkinsonian syndromes (Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA)) and Huntington's Disease. Another research focus is on Hereditary Spastic Paraplegia. The outpatient clinic, as a university center works in close cooperation with colleagues in private practice to provide continuous care for patients in the region. In particular, we participate in numerous national and international trial registries (e.g. for Huntington's Disease and PSP) and in innovative drug trials (antisense oligo-nucleotides; ASO). Together with the new professorship for stereotactic neurosurgery (Prof. Dr. T. Kinfe), deep brain stimulation was successfully reestablished at the University Hospital.
The outpatient centers scientific work focusses on the investigation of new biomarkers, that allow a better differential diagnosis of movement disorders, and facilitate monitoring of disease progression and therapeutic effects. In addition, the effects of tailored exercise therapy in Parkinson's disease are being investigated. The following projects are in progress:
- Differential diagnosis of MSA by means of 3T and 7T MRI (in close cooperation with the Department of Neuroradiology)
- Progression assessment of idiopathic Parkinson's Disease using non-motor symptoms such as anhedonia and constipation (microbiome; supported by the Adalbert-Raps Foundation)
- Sensor-based gait analysis as an early differential diagnostic biomarker and progression marker of Huntington's disease (funded by the Huntington Foundation of the Deutsche Huntington Hilfe)
- Sensor-based analysis of hyperkinetic movement disorders for differential diagnostic classification
- Sensor-based monitoring of gait impairment in patients with Hereditary Spastic Paraplegia (BMBF project "treatHSP")
- Validation of digital mobility outcomes and measurement methods using wearable sensor devices - the clinical validation study 'Mobilise-D' (EU project, Innovative Medicines Initiative), https://www.mobilise-d.eu/
- MOBILITY APP: Physiotherapy for atypical Parkinsonian syndromes in the clinical setting and in everyday life (D-A-CH project)
- Development of digital signatures of spastic gait patterns: self-learning algorithms for the calculation of clinically relevant gait parameters (funded by the Förderverein für HSP-Forschung e.V., https://hsp-hilfe.de/foer-derprojekt-gaitlab-ganganalyse/)
- Individualized, digital exercise in Parkinson's disease" (funded by the Manfred Roth Foundation and the Medical Research Foundation of the University Hospital Erlangen)
-Gait monitoring in the home environment (project "FallRiskPD", Medical Valley Award)

Motion analysis and therapy projects are carried out in close cooperation with the Machine Learning and Data Analytics Lab (Prof. Bjoern Eskofier, Dr. Felix Kluge), the companies Portabiles GmbH and Portabiles HealthCare Technologies GmbH as well as the German Parkinson Association – Regional Group Erlangen (Christine Enders, Wolf-Jürgen Aßmus). Particularly noteworthy is the EU project Mobilise-D, which aims to measure mobility in a total of 2.400 patients in everyday life using wearable sensor technology. The consortium includes 34 university centers that want to submit a so-called digital biomarker to EMA and FDA for approval in five years (2019-2024) in order to be able to use it as an objective endpoint in clinical studies (project leaders PD Dr. Heiko Gaßner, Prof. Dr. Jürgen Winkler). The concept for digital exercise training developed in the department was awarded with the Hertie Prize for Commitment and Self-Help in 2020 (PD Dr. Heiko Gaßner).

We have studied new MRI sequences in a murine model of MSA, suggesting that these sequences may dramatically facilitate the differential diagnosis of Parkinsonian syndromes, especially MSA (Lambrecht et. al; 2020). Currently, these sequences are being tested in a cross-sectional study in the clinic.

The symptoms anhedonia and constipation are early non-motor symptoms of PD. We analyze these symptoms with respect to disease progression. While the microbiome in PD patients is characterized by deficient probutyrogenic taxa, it may not be a suitable biomarker. We therefore aim to evaluate the therapeutic possibilities of dietary-based microbiome alterations (Cosma-Grigorov et al., 2020).

Sensor-based gait analysis in Huntington's Disease is a technical biomarker in the assessment of disease stage and motor impairment (Gaßner et el., 2020) and will be studied further.

At the Center for Rare Movement Disorders, numerous rare hyperkinetic movement disorders have been causally elucidated (e.g., McLeod syndrome (1:10,000,000), ERCC4-induced chorea) and contributed to national case series to better classify these disorders.

Teaching

The Division of Molecular Neurology participates in the teaching activities of the medical faculty in clinical neurology, the master's program Molecular Medicine, and at the technical faculty (medical technology). The focus on neuroscience in the Interdisciplinary Center of Neuroscience could be supported, a medical-technical project could be included in a research group application, and a neuroscientific research group (GRK 2162: Development and Vulnerability of the Central Nervous System; see separate report) could successfully be funded.

Within the scope of the supervision of scientific-academic work, bachelor's and master's theses as well as medical, physiotherapeutic, sports science, engineering and natural science doctorates are supervised.

Selected publications

Regensburger M, Minakaki G, Kettwig M, Huchzermeyer C, Eisenhut F, Haack TB, Kohl Z, Winkler J (2020), Novel Biallelic CTSD Gene Variants Cause Late-Onset Ataxia and Retinitis Pigmentosa. Mov Disord 35:1280-1282, 10.1002/mds.28106

Cosma-Grigorov A, Meixner H, Mrochen A, Wirtz S, Winkler J and Marxreiter F (2020) Changes in Gastrointestinal Microbiota Com-position in PD—A Pivotal Role of Covariates. Front. Neurol. 11:1041. doi: 10.3389/fneur.2020.01041

Gaßner H, Sanders P, Dietrich A, Marxreiter F, Eskofier BM, Winkler J, Klucken J.J; Clinical Relevance of Standardized Mobile Gait Tests. Reliability Analysis Between Gait Recordings at Hospital and Home in Parkinson's Disease: A Pilot Study. J Parkinsons Dis. 2020;10(4):1763-1773.

Lambrecht V, Hanspach J, Hoffmann A, Seyler L, Mennecke A, Straub S, Marxreiter F, Bäuerle T, Laun FB, Winkler J.; Quantitative susceptibi-lity mapping depicts severe myelin deficit and iron deposition in a transgenic model of mul-tiple system atrophy. Exp Neurol. 2020 Apr 14;329:113314.

Wanner P, Winterholler M, Gaßner H, Winkler J, Klucken J, Pfeifer K, Steib S (2020). Acute exercise following skill practice promotes motor memory consolidation in Parkinson's disease. Neurobiology of Learning and Memory 178; 107366

International cooperations

Prof. Dr. F. H. Gage, Laboratory of Genetics-Gage, The Salk Institute for Biological Studies, La Jolla: USA

Prof. Dr. B. Bloem, Radboud University Medical Center, Nijmegen: The Netherlands

Prof. Dr. E. M. Masliah, Department of Neurosciences, University of California, San Diego, La Jolla: USA

Prof. Dr. G. Wenning, University Hospital of Innsbruck, Innsbruck: Austria

Prof. Dr. R. Krüger, University of Luxemburg, Luxemburg: Luxemburg