Department of Neurology

Molecular Mechanisms in Neurodegenerative Diseases

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The Department of Neurology at Ulm University focuses its clinical and experimental work mainly on understanding the molecular mechanisms underlying such neurodegenerative diseases as Alzheimer's, Parkinson's and Huntington's disease, frontotemporal dementias, and amyotrophic lateral sclerosis/ motor neuron disease (ALS/MND). Structurally, it consists of a number of large outpatient clinics each serving their respective patient populations in addition to a clinical trial centre, which specializes in the clinical studies of selected groups of patients. There is also a gene and biobank, an inpatient clinic for acutely neurologically ill patients, and an experimental section in which more than fifty scientists work in ten basic neuroscience groups. These groups perform experimental research on the basic mechanisms of the diseases mentioned above.

The group of Prof. Dr. von Arnim conducts in vitro and in vivo experimental studies on Alzheimer's disease (AD) and is interested in the processing, sorting and signaling of the β-amyloid precursor protein (APP) and associated proteins (including motor proteins), and their subcellular compartimentalization. The work focuses on aspects of trafficking in AD by employing novel molecular imaging techniques (FLIM, TIRF). The ultimate goal of these studies is the translation of the findings into clinical therapeutic approaches which can be supported by imaging techniques in small animals and humans.

The group of Dr. Witting investigates the role of inflammation and its regulation by metabolic processes in neurodegenerative diseases, with a special focus on amyotrophic lateral sclerosis and Huntington's disease. The metabolic aspects of neurodegenerative diseases are further investigated in other tissues

and cells in collaboration with the groups of Dr. Dupuis, Dr. Weydt and Dr. Lindenberg. This integrated research might open new avenues of therapeutic interventions for these devastating diseases.
Studies on the etiology and pathogenesis of ALS/MND are the focal point of Prof. Dr. Ludolph's group. Experimental studies on etiology and pathogenesis center on resistance to hypoxia, neuritic transport and their associated proteins, and neuroinflammation, both in vitro and in vivo. The final goal of these experimental studies is the development of clinical interventions. This includes both preclinical intervention for the prevention of the disease and the development of therapies in the clinical phase to influence the human disease therapeutically.
The group of Jun. Prof. Dr. Danzer works on alpha-synuclein oligomer secretion from living neurons and transmission of oligomers in Parkinson's disease, which complements the immunohistopathological studies of Prof. Dr. Braak in this field of research. The work focuses on the identification of key players in the secretion process and deciphering the molecular mechanisms of initiation and propagation of neurodegenerative proteins both in vitro and in vivo. New in vivo models for Parkinson's disease built the basis for direct translation from basic research to clinics and will allow the identification of new pharmaceutical targets.
The group of Prof. Dr. Weishaupt works on cell and molecular biological aspects of ALS and Parkinson's disease. Members of the group are focused either on posttranslational modifications (specifically sumoylation) as regulators of pathological protein aggregation, the development of ALS protein aggregation assays for high-throughput screening or in vivo modeling of ALS-associated protein oligomerization and spreading of pathology. Further central topics of the Weishaupt team comprise the role of innate immunity as well as genetics and epigenetics in ALS, including next generation sequencing of genetic DNA or microRNA.

The group of Jun. Prof. Dr. Grabrucker investigates biometals in the brain, especially their influence on excitatory post synapses and specifically on scaffold proteins of the ProSAP/Shank family. These proteins play fundamental roles in the nascent assembly and function of glutamatergic synapses and are linked to Autism Spectrum Disorders, Alzheimer's disease and Schizophrenia. For this purpose, they use novel drug carriers, i.e. nanoparticles, and characterize them in regard to their potency to influence synapse formation, maturation and plasticity.

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Selected Publications:

- *Danzer KM, Kranich LR, Ruf WP, Cagsal-Getkin O, Winslow AR, Zhu L, Vanderburg CR, McLean PJ (2012): Exosomal cell-to-cell transmission of alpha synuclein oligomers. Mol Neurodegener. 7(1):42. Epub ahead of print*
- *Ingre C, Landers JE, Rizik N, Volk AE, Akimoto C, Birve A, Hübers A, Keagle PJ, Piotrowska K, Press R, Andersen PM, Ludolph AC, Weishaupt JH (2012): A novel phosphorylation site mutation in profilin 1 revealed in a large screen of US, Nordic, and German amyotrophic lateral sclerosis/frontotemporal dementia cohorts. Neurobiol Aging. Epub ahead of print*
- *Jesse S, Lehnert S, Jahn O, Parnetti L, Soininen H, Herukka SK, Steinacker P, Tawfik S, Tumani H, von Arnim CA, Neumann M, Kretzschmar HA, Kulaksiz H, Lenter M, Wiltfang J, Ferger B, Hengerer B, Otto M (2012): Differential sialylation of serpin A1 in the early diagnosis of Parkinson's disease dementia. PLoS One. 7(11). Epub*
- *Beyer A.-S., von Einem B, Schwanzar D, Thal DR, Ingelsson M, Makarova A, Deng M, Chhabra ES, Pröpper C, Böckers TM, Hyman BT, von Arnim CAF (2010): Engulfment adaptor PTB domain containing 1 interacts with and affects processing of the amyloid-beta precursor protein. Neurobiol Aging. 2012 Apr;33(4):732-43. Epub*
- *Lebedeva E, Stingl JC, Thal DR, Ghebremedhin E, Strauss J, Özer E, Bertram L, von Einem B, Tumani H, Otto M, Riepe MW, Ludolph AC, von Arnim CAF (2010): Genetic variants in presenilin genes and correlation to cerebrospinal β- amyloid 42 concentrations and diagnosis of Alzheimer's disease. Neurobiol Ageing. 2012 Jan;33(1):201.e9-201.e18. Epub*
- *Ferger AI, Campanelli L, Reimer V, Muth KN, Merdian I, Ludolph AC and Witting A (2010): The effect of mitochondrial dysfunction on the immunological properties of microglia, J. Neuroinflammation 7:45.*