10th Student Symposium on Molecular Medicine

Perspectives in Neuroscience

ulm university universität uulm

6 May 2017
Symposium Programme

MOLECULAR MEDICINE ULM
CONNECTING TWO WORLDS

Morning Session

09:00	**Introduction**	
09:05 - 09:50	**Kelly Del Tredici-Braak** *Center for Biomedical Research, Ulm University*	200 years James Parkinson, 20 years alpha-synuclein
09:50 - 10:35	**Jochen Weishaupt** *Department of Neurology, University Medical Center Ulm*	Amyotrophic lateral sclerosis genetics – gains and losses of function
	Sarah Brockmann *Department of Neurology, University Medical Center Ulm*	CHCHD10 – A Novel ALS Gene
10:35 - 11:00	**Coffee Break**	
11:00 - 11:45	**Mikael Simons** *TU Munich/DZNE/Munich/ MPI Exp Med Göttingen* **Mar Bosch Queralt** *TU Munich/DZNE/Munich*	Regenerative approaches for multiple sclerosis
11:45 - 12:15	**Student Representatives** *Ulm University*	Master Programme & International Graduate School in Molecular Medicine
12:15 - 13:30	**Lunch Break incl. Poster Session**	

Afternoon Session

12:45 - 13:30	**Poster Session**	
13:30 -14:15	**Moritz Helmstaedter** *Department of Connectomics* *MPI for Brain Research, Frankfurt*	Connectomics: mapping the brain's networks
	Meike Schurr *Department of Connectomics* *MPI for Brain Research, Frankfurt*	Scaling up connectomics to the order of a cubic millimeter
14:15 - 14:25	**Poster Prize Award Ceremony**	
14:25 - 15:00	**Coffee Break**	
15:00 - 15:45	**Andreas Grabrucker** *Dept. of Biological Sciences, University of Limerick, Ireland*	Convergence of non-genetic factors in Autism Spectrum Disorders
15:45 - 16:30	**Mike-Andrew Westhoff** *Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm*	A red queen, fluffy bunnies and hungry squirrels escaping from Alcatraz - Developing novel cancer therapies based on Darwinian principles
	Valerie Bezler *Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm*	
16:30 - 16:35	**Closing Remarks**	

20:30	**After-Symposium-Party at the Hudson Bar, Ulmer Gasse 6**

Abstracts

200 years James Parkinson, 20 years α-synuclein

Kelly Del Tredici-Braak, M.D., Ph.D.
Center for Biomedical Research, Ulm University

This year, it is 200 years since James Parkinson published the first complete clinical description of the disease bearing his name, 50 years since the introduction of high-dose L-DOPA therapy, and 20 years since the role of α-synuclein aggregation in Lewy pathology was discovered. In sporadic and inherited Parkinson's disease (PD), 60% have Lewy pathology – idiopathic PD comprises >90% of PD cases. Full diagnostic certainty of PD is impossible during life, with autopsy being necessary to confirm the clinical diagnosis. Autopsy-based studies have shown that α-synuclein aggregates in nerve cells develop in different regions of the central nervous system according to a predictable sequence in 6 neuropathological stages. PD differs from other neurodegenerative diseases, such as Alzheimer's disease, in that the entire human nervous system becomes involved, including the peripheral and enteric nervous systems. It is still unclear where Lewy pathology begins and how it spreads throughout the nervous system in PD, but there is growing experimental evidence in model systems for the existence of prion-like mechanisms for propagating α-synuclein aggregates. If at-risk persons could be reliably identified, it may become possible to develop strategies for delaying or preventing disease progression because PD has a long preclinical phase.

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Abstracts

Amyotrophic lateral sclerosis genetics – gains and losses of function

Prof. Dr. Jochen Weishaupt
Department of Neurology, University Medical Center Ulm

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that affects primarily motor neurons and leads to a progressive paralysis. Although 90% of ALS cases occur sporadically, approximately 5% of the newly diagnosed patients have already a positive family history for the disease, and genetic factors play an important role for disease pathogenesis. Almost two dozens of ALS genes have been discovered in recent years. ALS thus represents a model disease to demonstrate the role of human genetics and monogenic disease causes for neurodegeneration as well as their contribution to the understanding of pathogenic mechanisms. The talk will highlight some of the recently identified ALS genes, the routes that lead to their discovery, and exemplarily outline the possible different downstream sequelae induced by the respective mutations.

CHCHD10 – A Novel ALS Gene

Sarah Brockmann, M.Sc.
Department of Neurology, University Medical Center Ulm

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting both upper and lower motor neurons leading to a progressive paralysis. Just recently, we and others found a novel ALS disease gene called coiled-coil-helix-coiled-coil-helix domain containing 10 (CHCHD10). CHCHD10 is a mitochondrial protein that is enriched at cristae junctions of mitochondria and possibly plays a role in cristae structure, respiratory chain regulation and mtDNA stability. In this study we analyze the impact of three missense variants found in ALS patients (R15L, P34S and G66V) on the structure and stability of CHCHD10. Analysis of CHCHD10 protein levels in patient cells show a decreased protein level upon ALS-causing mutation. These results are in line with increased protein turnover rates and considerable structural changes of the R15L and G66V mutant proteins compared to wild-type CHCHD10. The P34S variant has similar properties as the wild-type protein. These results match most recent genetic evidence indicating that the R15L and G66V variants of CHCHD10 are pathogenic while P34S is not significantly associated with neurodegenerative diseases. Additionally, we observe a motility phenotype including muscle and motor neuron abnormalities in CHCHD10 morphant zebrafish. We thus hypothesize that mutations of CHCHD10 induce a structural disturbance and loss-of-function of CHCHD10.

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Abstracts

Regenerative approaches for multiple sclerosis

Prof. Dr. Mikael Simons

TU Munich/DZNE/Munich/MPI Exp Med Göttingen

Myelin is formed by the spiral wrapping of oligodendrocyte plasma membrane around axons of the central nervous system. One important goal is to understand how oligodendrocytes form myelin, how they select axons for myelination and how they regulate myelin thickness/intermodal length. A model will be presented how myelin elongates along and wraps around axons to form a tightly compacted multilayered membrane structure. Myelin disorders are among the most prevalent and disabling diseases in young adults. Although poorly understood, a consistent feature of myelin in various white matter diseases is the intralamellar vacuolization and fragmentation of the membrane. A model of how myelin may loose its stability in such diseases will be presented. Furthermore, data will be shown how myelin loses its stability in the aging brain. In addition, we will discuss and present data on how the myelin sheath provides trophic support to neurons to maintain functional axon-glial units over long time.

Mar Bosch Queralt, M.Sc.

TU Munich/DZNE/Munich

Myelin damage occurs in several autoimmune diseases including multiple sclerosis (MS). Myelin loss is followed by remyelination, a process by which new myelin sheaths are generated by oligodendrocytes. Although remyelination can occur in some MS patients, it is in most cases insufficient, but the reasons underlying this failure are poorly understood. Previous studies have shown that myelin removal by phagocytes is essential for myelin repair. In this project, we aim at understanding the different functional states of macrophages/microglia and how these contribute to the resolution of inflammation and tissue repair. We hope that this approach will not only shed light on the mechanisms of myelin reapair, but also open the door to new therapeutic avenues in white matter tissue repair.

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Abstracts

Connectomics: mapping the brain's networks

Dr. Moritz Helmstaedter
Department of Connectomics, Max Planck Institute for Brain Research, Frankfurt

Brains are highly interconnected networks of millions to billions of neurons. For a century, we have not been able to map these connectivity networks. Only recently, using novel electron microscopy techniques and machine-learning based data analysis, the mapping of neuronal networks has become possible at a larger scale. This new field of connectomics is still limited by technology and requires next-generation human-machine interaction for data analysis, but it is already starting to provide exciting insights into how neuronal circuits operate in the brain. Our goal is to make connectomics a high-throughput screening technique for neuroscience, to use connectomes for discovering brain-implemented algorithms, which may inspire novel machine learning, to map the imprints of sensory experience onto neuronal networks in the brain, and to investigate connectome alterations in models of psychiatric disease.

Scaling up connectomics to the order of a cubic millimeter

Meike Schurr, M.Sc.
Department of Connectomics, Max Planck Institute for Brain Research, Frankfurt

Comprehensive EM-based 3D mapping of neuronal circuits is limited by the size and number of datasets which can be acquired within a reasonable amount of time. In order to cover a substantial part of (local) neuronal circuitry in mouse neocortex, volumes in the order of a cubic millimeter are required. Effective acquisition rates of fast single-beam scanning electron microscope (SEM) setups are in the order of 1-6 MHz. Thus, imaging of a cubic millimeter of neuronal tissue at nanometer resolution would take several years. The goal of this project is to scale up imaging techniques for routine screening of a cubic millimeter by the use of a 61 beam MultiSEM setup combined with an automated tape-collecting ultramicrotome (ATUM). First results show that this approach allows us to push data rates by two orders of magnitude up to 220 MHz at a voxel size of 4 nm x 4 nm x 35 nm. Together with an appropriate data infrastructure to process the amount of data (~ PB), this makes screening of a cubic millimeter possible within only 3 - 4 months and thus a tolerable resource investment.

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Convergence of non-genetic factors in Autism Spectrum Disorders

Assist. Prof. Andreas M. Grabrucker, Ph.D.
WG Cellular Neurobiology and Neuro-Nanotechnology, Dept. of Biological Sciences, School of Natural Sciences, University of Limerick, Ireland

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by their core symptoms - delayed acquisition of speech, deficits in social interactions and stereotypic behaviors. One in every one hundred Europeans born today is diagnosed with autism, with prevalence rates on the rise. The steep rise in the incidence rate of ASD makes it unlikely that purely genetic causes underlie ASD. Thus, genetic factors might be responsible or facilitate the occurrence of ASD but in addition to a combination of ASD-related genes, specific environmental factors act as risk factors triggering the development of ASD.
While from genetic studies, a list of hundreds of autism-linked genes was generated, much less agreement exists about which environmental factors contribute to ASD - and to what extent. Research in this area often yields inconsistent results, with only few factors (for example maternal infection) being broadly accepted. The reason for this lies in the difficulty to prove causality of non-genetic factors in ASD as epidemiological studies mostly used for investigating environmental risk factors only identify associations but fail to provide mechanistic insights. In this talk, I will present data from our latest mouse models for environmentally induced ASD, underlining our hypothesis that metal ion imbalance during pregnancy is an important player in ASD. Zinc status influences and is influenced by multiple factors and an interdependence of prenatal and early life stress, immune system abnormalities, impaired GI functions, and zinc deficiency can be hypothesized, linking several environmental factors in ASD mechanistically in a common pathology. In particular, we hypothesize that maternal zinc deficiency leads to brain and GI abnormalities in the offspring, and triggers inflammatory responses by changes in the microbiome, which produces altered signaling along a gutbrain axis.

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Abstracts

A red queen, fluffy bunnies and hungry squirrels escaping from Alcatraz

Developing novel cancer therapies based on Darwinian principles

Mike-Andrew Westhoff, PhD
Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm

Valerie Bezler
Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm

Molecular Medicine is a discipline that builds a potent bridge between biological theory and applied medicine. In this talk we will explore creative means by which knowledge can be transferred between different areas of expertise and thus open up novel therapeutic avenues to explore.
In particular, I will discuss Glioblastoma, the most common and lethal primary brain tumor, which – if current standard therapy is successful – leads to a mean patient survival of only 14 month. Glioblastoma comprises, like most cancers, different populations of (specialized) cells that display various forms of interaction. Of particular therapeutic interest are the highly motile, invasive cells that make complete tumor resection almost impossible. Applying concepts and ideas from the fields of population genetics and ecology the potential of two new treatment strategies will be highlighted:
1. Chronification – the RIST therapy is a complex combination therapy which is applied, in a compassionate use setting, to a wide variety of cancers, including Glioblastoma. While not curing the patient it has a potent effect on quality and quantity of life.
2. Isolation – two well characterized pharmacological substances, Disulfiram and Carbenoxolone, can potently block cell-substrate and cell-cell interactions, respectively, and thus form the basis of a novel anti-invasive treatment strategy.

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Symposium Organisation

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