Institute of Biochemistry – Emil-Fischer-Center

Professorship of Molecular Medicine with focus on Molecular Imaging

Address
Fahrstraße 17
91054 Erlangen
Phone: +49 9131 8524622
Fax: +49 9131 8524605
www.biochemie.med.fau.de/research/ag-lie-en

Head of Division
Prof. Dr. med. Dieter Chichung Lie

Contact
Prof. Dr. med. Dieter Chichung Lie
Phone: +49 9131 8524622
Fax: +49 9131 8524605
chi.lie@fau.de

Dr. rer.nat. Ruth Beckervordersandforth
Tel.: +49 9131 8524194
ruth.beckervordersandforth@fau.de

Research focus
- Transcriptional programs in the regulation of adult neurogenesis
- Role of autophagy and lysosome activity in stem cell function and adult neurogenesis
- Functional characterization of intellectual disability factors
- Hippocampal astrocyte development, dynamics and functional diversity

Structure of the Professorship

Professorship: 1
Personnel: 7
- Scientists: 3 (there of funded externally: 1)
- Graduate students: 5

Dr. Ruth Beckervordersandforth (PI)
- Scientists: 1 (DFG funded)
- Graduate students: 1 (DFG funded)
- medical students: 5 (2 DFG and 3 IZKF funded)

Special structural feature
The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, as well as the professorships of Bioinformatics and of Molecular Medicine with focus on Molecular Imaging.

Research

Neurons and glia cells form functional networks that are the structural basis for learning, cognition, and behavior. Perturbation of the formation, maturation, and plasticity of neural circuits contributes to the pathogenesis of neurodevelopmental disorders, such as intellectual disability and neuropsychiatric diseases, like schizophrenia. Our research aims to better understand the genetic and cell biological mechanisms that regulate development and homeostasis of neural networks.

Transcriptional programs in the regulation of adult neurogenesis
PI: Prof. Dr. D.C. Lie
The discovery of adult neurogenesis, i.e. the lifelong generation of new hippocampal and olfactory bulb neurons from stem cells, has added a new layer of complexity to our understanding of the mechanisms underlying plasticity and regeneration in the mammalian central nervous system. There is strong evidence that adult neurogenesis significantly contributes to hippocampus-dependent learning and memory processes as well as to the pathophysiology of cognitive and affective symptoms during aging and in neurodegenerative and neuropsychiatric diseases. Thus, understanding of the mechanisms regulating adult neurogenesis is of major basic neuroscientific and clinical interest. The generation of new functional neurons from stem cells is a complex multistep process. Current data indicate that each developmental step is controlled by stage-specific transcription factors. We have now found that the Wnt/β-catenin signaling pathway regulates a transcriptional program that controls the functional integration of adult-generated hippocampal neurons. Interestingly, we also observed that ageing-associated impairments in adult hippocampal neurogenesis are paralleled by a decline in Wnt/β-catenin signaling activity. Strikingly, enhancing Wnt/β-catenin signaling activity is sufficient to ameliorate age-associated deficits in adult neurogenesis. In ongoing work, we are investigating the mechanisms regulating Wnt/β-catenin signaling activity in the hippocampus as well as the mechanisms underlying ageing-associated decline in the activity of this key regulatory pathway.
Funding: DFG

Role of autophagy and lysosome activity in stem cell function and adult neurogenesis
PI: Dr. Iris Schäffner, Prof. Dr. D.C. Lie
Degradation and recycling of dysfunctional cellular components are critical pathways for cellular homeostasis. Somatic stem cells are particularly dependent on degradation and recycling pathways to maintain their lifelong capacity for regeneration. We recently demonstrated that the longevity and ageing associated transcription factors of the FoxO family are critical to regulate autophagy, i.e., a central pathway for proteins and organelles, in adult neural stem cells. Loss of FoxOs does not only impair activity of the autophagic pathway, but is associated with stem cell dysfunction and impaired integration of adult-born neurons. We have now found that FoxOs regulate autophagy by controlling lysosome activity and identified molecular targets of FoxOs in this process. Notably, reconstitution of lysosome activity was sufficient to ameliorate FoxO-deficiency associated dysfunction of stem cells and neurons. Inspired by these findings, we are presently testing the hypothesis that enhancing lysosomal activity may counter age-associated deficits in stem cell function.
Funding: IZKF Erlangen

Functional characterization of intellectual disability factors
PI: Dr. Sören Turan, Prof. Dr. D.C. Lie
Sox11 mutations were recently identified in a subset of patients suffering from Coffin-Siris Syndrome, a developmental disorder associated with intellectual disability. Using human pluripotent stem cells to model human neurodevelopment, we found that SOX11 is essential for the generation of neuroectoderm and that SOX11 regulates the balance between proliferation and differentiation in neural stem cells. These findings contribute to a better understanding of the pathogenetic mechanisms in Coffin-Siris Syndrome. This project is conducted in close collaboration with Prof. Dr. B. Winner (Division of Stem Cell Biology) and Prof. Dr. A. Reis (Institute of Human Genetics).
Funding: Bavarian State Ministry for Science and Art, Research Network ForInter

Hippocampal astrocyte development and dynamics
PI: Dr. Ruth Beckervordersandforth
For a long time it has been thought that hippocampal plasticity is predominantly driven by neurons, however, more recent data indicate an active participation of astrocytes. To date it is known that astrocytes contribute to such plasticity in two ways: firstly, by serving as radial glia-like neural stem cells (NSCs) that give rise to new neurons and glial cells, secondly, by serving as niche cells that control the activity of NSCs, and provide structural and functional support to neurons. Besides extensive investigations of the astrocyte-like radial NSC, the niche astrocyte compartment remains understudied and was considered to be static and homogeneous. We recently discovered that the hippocampal niche is constantly changing due to life-long generation of new astrocytes, a dynamic process able to react to external and internal stimuli such as voluntary exercise and aging. Interestingly, we identified that new astrocytes are not only generated by gliogenic division of NSCs, but also by proliferation of local astrocytes. While this mechanism has so far only been described in the developing cortex, our data show that this type of astrogenesis is an ongoing process from hippocampal development to aged stages. We are currently investigating which molecular factors are involved in both NSC- and astrocyte-mediated astrogenesis.
Funding: DFG

Morphological, molecular and functional diversity of hippocampal astrocytes
PI: Dr. Ruth Beckervordersandforth
Investigating astrocyte diversity on morphological, molecular and physiological levels, we present evidence that each anatomical layer of the adult mouse DG is populated by morphologically and molecularly distinct astrocyte populations. Region-specific diversification of astrocytes is further supported

by subtype-specific physiological functions such as the establishment of homotypic astrocyte networks as well as functional differences in Glutamate transport. Importantly, we found a number of key molecular and morphological features of murine astrocyte diversity also in humans, indicating that astrocyte diversity in the DG is highly conserved and relevant for human DG physiology. These findings suggest that diversity of astrocytes goes beyond the broad scale of developmental ancestry and affects - equivalent to what has been shown for neurons - also regional networks.
Funding: DFG

Teaching

The Professorship of Molecular Medicine with focus on Molecular Imaging contributes to the teaching curriculum of Medicine and Dentistry by offering obligatory and elective courses. It provides interdisciplinary training for students of the master degree program Molecular Medicine that is performed together with the departments of Psychiatry and Psychotherapy and of Nuclear Medicine, the Institute of Radiology, and the Division of Molecular Neurology. Aim is to theoretically and practically teach the students state-of-the-art technologies of molecular imaging.
Bachelor and master students as well as medical and scientific graduate students are supervised in our group to successfully finish their thesis projects.

Selected publications

Braun, K., Häberle, B.M., Wittmann, M.T., Lie, D.C. (2020) Enriched environment ameliorates adult hippocampal neurogenesis deficits in Tcf4 haploinsufficient mice. BMC Neurosci. Nov 23;21(1):50. doi: 10.1186/s12868-020-00602-3.

Heppt, J., Wittmann, M.T., Schäffner, I., Billmann, C., Zhang, J., Vogt-Weisenhorn, D., Prakash, N., Wurst, W., Taketo, M.M., Lie, D.C. (2020) β-catenin signaling modulates the tempo of dendritic growth of adult-born hippocampal neurons. EMBO J. Nov 2;39(21):e104472. doi: 10.15252/embj.2020104472. Epub 2020 Sep 15.

Boerstler, T., Wend, H., Krumbiegel, M., Kavyanifar, A., Reis, A., Lie, D.C., Winner, B., Turan, S. (2020) CRISPR/Cas9 mediated generation of human ARID1B heterozygous knockout hESC lines to model Coffin-Siris syndrome. Stem Cell Res. Jun 29;47:101889. doi: 10.1016/j.scr.2020.101889.

von Wittgenstein, J., Zheng, F., Wittmann, M.T., Balta, E.A., Ferrazzi, F., Schaffner, I., Haberle, B.M., Valero-Aracama, M.J., Koehl, M., Miranda, C.J., Kaspar, B.K., Ekici, A.B., Reis, A., Abrous, D.N., Alzheimer, C. & Lie, D.C. (2020) Sox11 is an Activity-Regulated Gene with Dentate-Gyrus-Specific Expression Upon General Neural Activation. Cereb Cortex. doi: 10.1093/cercor/bhz338

Wedel, M., Frob, F., Elsesser, O., Wittmann, M.T., Lie, D.C., Reis, A. & Wegner, M.(2020) Transcription factor Tcf4 is the preferred heterodimerization partner for Olig2 in oligodendrocytes and required for differentiation. Nucleic Acids Res. doi: 10.1093/nar/gkaa218

Turan, S., Boerstler, T., Kavyanifar, A., Loskarn, S., Reis, A., Winner, B. & Lie, D.C. (2019) A novel human stem cell model for Coffin-Siris Syndrome like syndrome reveals the importance of SOX11 dosage for neuronal differentiation and survival. Hum Mol Genet. doi: 10.1093/hmg/ddz089

Fiebig, C., Keiner. S., Ebert, B., Schaffner, I., Jagasia, R., Lie, D.C. & Beckervordersandforth R. (2019) Mitochondrial Dysfunction in Astrocytes Impairs the Generation of Reactive Astrocytes and Enhances Neuronal Cell Death in the Cortex Upon Photothrombotic Lesion. Front Mol Neurosci 12: 40. doi: 10.3389/fnmol.2019.00040

Beckervordersandforth, R. & Rolando, C. (2020) Untangeling human neurogenesis to understand and counteract brain disorders. Current Opinion in Pharmacology 2020.50:67-73. doi: 10.1016/j.coph.2019.12.002

Schneider, J., Karpf, J. & Beckervordersandforth, R. (2019) Role of astrocytes in the neurogenic niches. Methods in Molecular Biology, vol.1938. doi: 10-1007/978-1-4939-9068-9-2

International cooperations

Dr. D.N. Abrous, Neurocentre Magendie U1215, INSERM and Université de Bordeaux, Bordeaux, France

Prof. A. Ballabio, Telethon Institute of Genetics and Medicine (TIGEM), Neapel, Italien

Dr. A. McNeill, Sheffield University, Sheffield, England

Prof. K. Nakashima, Kyushu University, Fukuoka, Japan

Prof. M.M. Taketo, Kyoto University, Kyoto, Japan

Dr. Jan Beckervordersandforth, Maastricht University Medical Centre, Maastricht, Netherlands

Prof. Dr. Onur Basak, University Medical Centre Utrecht, Utrecht, Netherlands

Dr. Felipe Ortega, Complutense University of Madrid, Madrid, Spain