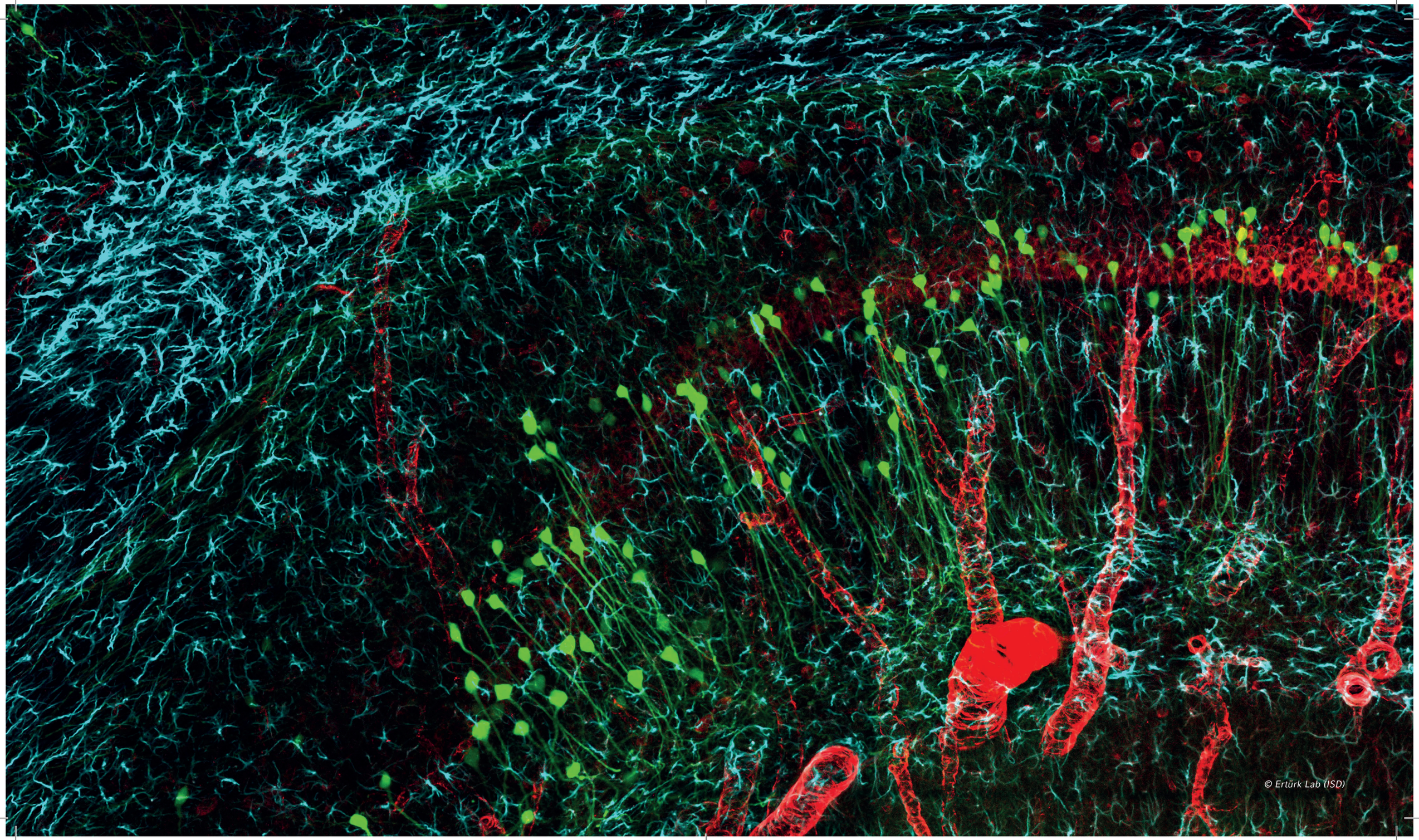
ANNUAL REPORT 2015/2016

Institute for Stroke and Dementia Research (ISD)
Klinikum der Universität München
Ludwig-Maximilians-Universität München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Content

Foreword

The Institute for Stroke and Dementia Research (ISD)

Stroke and Dementia rank among the most frequent diseases worldwide and the most pressing health problems in ageing societies (WHO Report 2002). Stroke is the leading cause of permanent disability in high-income countries and the second leading cause of death worldwide (Global Burden of Disease Study 2015). In Europe, more than 5 million people suffer from dementia disorders with almost two thirds accounted for by Alzheimer's disease (AD) and cerebrovascular disease (CVD).

The Institute for Stroke and Dementia Research (ISD) was launched in 2010 through the extraordinary generosity and vision of Zygmunt Solorz-Żak who recognized the promise of integrating patient care with clinical and basic research to transform medicine. Mr. Solorz-Żak saw the need to empower physicians and scientists from different fields to work together to realize that promise. His founding gift was intended to provide the resources necessary to allow the institute to maintain a high degree of flexibility within a rapidly moving field. Munich's pre-eminent University Hospital, the Ludwig-Maximilians University, and the State of Bavaria shared Mr. Solorz-Żak's vision and joined together with him as the founding partners of the Institute for Stroke and Dementia Research.

Center for Stroke and Dementia Research

Since its inauguration in 2010, and move-in into the new Center for Stroke and Dementia Research (CSD) building the ISD has grown to more than 99 people including 66 scientists ranging from master and Ph.D. students to full professors. Currently, the ISD hosts nine research groups that are highly connected and offer complementary methodological expertise. The ISD further operates an outpatient clinic for patients with stroke and cerebrovascular disease and a memory clinic. Within the new CSD building the ISD closely collaborates with its partnering institution – the German Center for Neurodegenerative Diseases, DZNE.

Scientists at ISD are acquiring increasing amounts of third party funding with 1,640,624 million Euro spent in 2015 and more than 2,085,338 million Euro spent in 2016. Within this period ISD investigators published more than 160 papers in peer-reviewed journals including leading journals in the fields of Genetics, Neuroscience, and Medicine.

Among the most recent recruits are Prof. Jürgen Bernhagen who holds the chair for Vascular Biology and Prof. Dominik Paquet who runs a research group on Neurodegeneration and Neurovascular Dysfunction. Both Bernhagen and Paquet were appointed through the DFG-funded cluster of excellence (SyNergy – Munich cluster of excellence for Systems of Neurology). The ISD is further glad to welcome Ozgun Gokce an expert on single cell sequencing and new junior research group leader. Arthur Liesz recently obtained a DFG-funded Emmy Nöther award offering further support for his research program on Stroke Immunology, which also integrates into the SyNergy cluster.

The ISD is part of a still growing neuroscience community in Munich and is heavily involved in the SyNergy cluster. SyNergy started operations in early 2013 and has generated a major momentum with unprecedented opportunities for new infrastructure and collaboration across institution. Building on the success of the first funding period SyNergy will apply for continuation of funding with an even more developed strategic plan. The ISD further entertains close links with the collaborative research center CRC1123 on atherosclerosis and is strongly involved in other national, and international research hubs including EU FP7 and Horizon2020-funded networks some of which are coordinated by the ISD.

Center for Stroke and Dementia Research, courtyard

Among the plans for 2017/18 are the installment of a human 3Tesla MRI scanner fully dedicated to research and an animal PET/MRI. This new infrastructure will be shared with investigators from other institutions and further complement ISDs focus on neuroimaging and cross-species analyses.

We are grateful for the opportunities provided to us and wish to report on our activies below. In the following we highlight major activities and developments in 2015/2016.

Prof. Dr. med. Martin Dichgans
Director, Institute for Stroke and Dementia Research

Center for Stroke and Dementia Research (CSD)

MISSION STATEMENT

The Institute for Stroke and Dementia Research (ISD) strives to advance therapeutic options in stroke and dementia.

We are equally committed to comprehensive patient care and research. The ISD strives to provide the highest quality in preventing, recognizing and treating both stroke and cognitive decline thus offering the best service to patients, their families, and referring physicians.

BACKGROUND

Stroke and Dementia rank among the ten most frequent diseases worldwide and the most pressing health problems in ageing societies (WHO Report 2002). Each year, about 15 million people suffer a stroke. Of these, 5 million die as a direct consequence of stroke, another 5 million are permanently disabled. In European countries, the number of strokes is likely to increase from 1.1 million in 2000 to about 1.5 million in 2025. The number of people with dementia is estimated to increase from about 25 million worldwide in 2005 to more than 80 million by 2040.

The foundation of the Institute for Stroke and Dementia Research (ISD) bears on the initiative of Zygmunt Solorz-Żak, who sought to create an internationally recognized centre providing highly competitive interdisciplinary and translational research in the fields of stroke and dementia. In July 2008 the Solorz-Żaks, the Ludwig-Maximilians University (LMU), the State of Bavaria, and the Klinikum der Universität München (KUM) agreed on a long-term collaboration to set up a dedicated center for stroke and dementia research.

RESEARCH INFRASTRUCTURE

The Center for Stroke and Dementia Research (CSD) hosts comprehensive research infrastructure including the following:

- *clinical trials unit (CTU) embedded into the outpatient clinic. The outpatient clinic is specialized on the diagnosis and treatment of stroke, cerebrovascular disease, and neurodegenerative diseases causing cognitive decline.*
- *human MRI research scanner, expected for 12/2017*
- *animal MRI/PET expected for 12/2017*
- *proteomics unit*
- *electron microscopy*
- *two-photon microscopy*
- *light sheet imaging for tissue clearing*
- *confocal microscopy*
- *life cell imaging*
- *high-content screening*
- *light-sheet microscopy*
- *isotop labs*
- *zebrafish facility*
- *seminar rooms*
- *wet labs*

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Highlights

11/2016

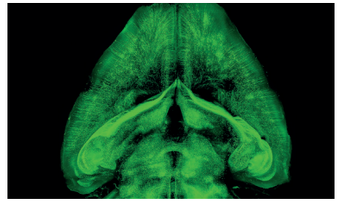
HUMAN MR SCANNER APPROVED BY THE DFG

A dedicated human MR research scanner has been approved for funding by the DFG. MR imaging has become an integral part of ISD research. The new scanner is part of a long-term strategic plan for the development of neuroimaging at LMU that also involves pre-clinical MRI / PET and ultra-high-field MR imaging. The new 3T MR research scanner will be positioned right next to the Center for Stroke and Dementia Research (CSD) building and offer immediate access from the ISD outpatient clinic. Operations are expected to start in 2017. Clinical scanning will be paralleled by MR/PET imaging in experimental models. Preparations for the installment of a pre-clinical MRI / PET facility within the CSD building have already started.

08/2016

NEW CLEARING TECHNOLOGY

The Acute Brain Injury Group led by Ali Ertürk developed new clearing technology that allows making entire adult rodents transparent for



whole-body imaging at subcellular resolution (Nat Methods, Aug 2016). The new technology called ultimate (u)DISCO provides the basis to map neuronal, glial, and vascular connections in entire lab animals and post-mortem material from humans. The work was highlighted by media worldwide including the New York Times, Wall Street Journal, NBC news, Discovery Channel, Nature and Science magazines. The cover image was chosen as one of the best scientific images of 2016 by Nature.

03/2016

EU-FUNDED NETWORK ON SMALL VESSEL DISEASES

An international consortium of mostly European investigators recently launched a major collaborative research program to uncover

SVDS @target

mechanisms and pathways in different forms of small vessel disease (coordinator: Martin Dichgans). The new network titled “Small vessel diseases in a mechanistic perspective: Targets for Intervention – Affected pathways and mechanistic exploitation for prevention of stroke and dementia (SVDs@target)” is funded through the European Union’s Horizon 2020 research and innovation program. A major objective of the 6 million Euro, 5-year project is to identify common molecular, cellular and physiological mechanisms that compromise the funcion of microvessels in different SVDs. SVDs@target was one of 450 funded projects in this heavily oversigned EU call.

01/2016

EU-FUNDED NETWORK ON STROKE AND DEMENTIA

The Horizon 2020 project CoSTREAM aims to improve our understanding of the co-occurrence of stroke and Alzheimer’s

CoSTREAM
UNDERSTANDING STROKE AND ALZHEIMER

disease. It has long been known that both diseases share underlying causes, but their exact interaction or link is not fully understood. CoSTREAM combines multiple factors to identify and investigate these common mechanisms, ranging from genetics and metabolomics, to brain structure and function. The project builds upon large data sets on both diseases, with follow-up studies performed up to 25 years. In the end, CoSTREAM will lead to increased knowledge about shared pathways, and can lead to new therapeutic approaches.

12/2015

EMMY-NOETHER-PROGRAM

Arthur Liesz has been admitted to the Emmy-Noether-Program of the German Research Foundation (DFG). His group will be funded with 1.3 million Euro over 5 years to investigate mechanisms of „Brain-released alarmins in acute brain ischemia“. This long-term project will be based on on a recetly published proof-of-concept study (Liesz et al., J Neurosci, 2015). Specifically, three subprojects will focus on the role of alarmins in mediating critical comorbidities of stroke: sickness behavior, immunosuppression and chronic vascular inflammation. Better understanding of alarmin-driven immunological cascades after stroke are of direct translational relevance with potential clinical use. The three investigated stroke comorbidities contribute to a large proportion of post-stroke complications and morbidity and might have a common trigger: the release of pro-inflammatory alarmins after stroke.

11/2015

3RD ESO STROKE SCIENCE WORSHOP, EIBSEE

More than 125 stroke experts met on Nov. 19 to 21 at lake Eibsee (Garmisch-Partenkirchen) to discuss the latest and hottest topics

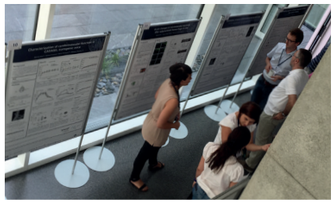
ESO
EUROPEAN STROKE ORGANISATION

in clinical, basic, and translational stroke research (Dichgans et al. Stroke 2016). The meeting is now in its third year and was organized by Heini Mattle and Martin Dichgans.

08/2015

SCIENTIFIC REVIEW BY ADVISORY BOARD

The ISD Advisory Board Meeting in August 3rd and 4th started with an Overview about all major developments since the last Meeting and



new aims and was followed by talks an discussions about all current research projects.

05/2015

OPENING CEREMONY

The Center for Stroke and Dementia Research was inaugurated officially by the state minister Dr. Ludwig Spaenle when

numerous guests followed the symbolic hand over of keys. “This is an important day for science and a great day for our patients” said Prof. Karl Walter Jauch, director of the Klinikum der Universität München. Representatives from the ISD, DZNE, and both medical faculties joined for round table discussion.

02/2015

CNSAFLAME

Ali Ertürk and Nikolaus Plesnila were awarded a multi-national grant from Era-Net Neuron. Consortium (CnsAflame) partners from

Germany, Sweden, France, and Israel will try to unravel the role of neuroinflammation in cognitive decline after traumatic brain injury.

11/2015

Jürgen Bernhagen moved his lab to ISD on 2015 to become an ISD PI. He was appointed **Chair of Vascular Biology** at LMU and is a member of SyNergy and SFB1123. Following his PhD and a postdoc in New York, Prof. Bernhagen previously held positions as a group leader at Fraunhofer IGB in Stuttgart and as a Professor of Biochemistry and Molecular Cell Biology at RWTH Aachen University. His research centers on mechanisms in inflammatory and cardiovascular diseases with a focus on cytokines, atypical chemokines, cellular signaling complexes, and atherosclerosis, a main underlying condition of ischemic stroke. In addition to gaining basic mechanistic insight into vascular pathobiology, these mechanisms will be specifically... *(more on page 32)*

02/2016

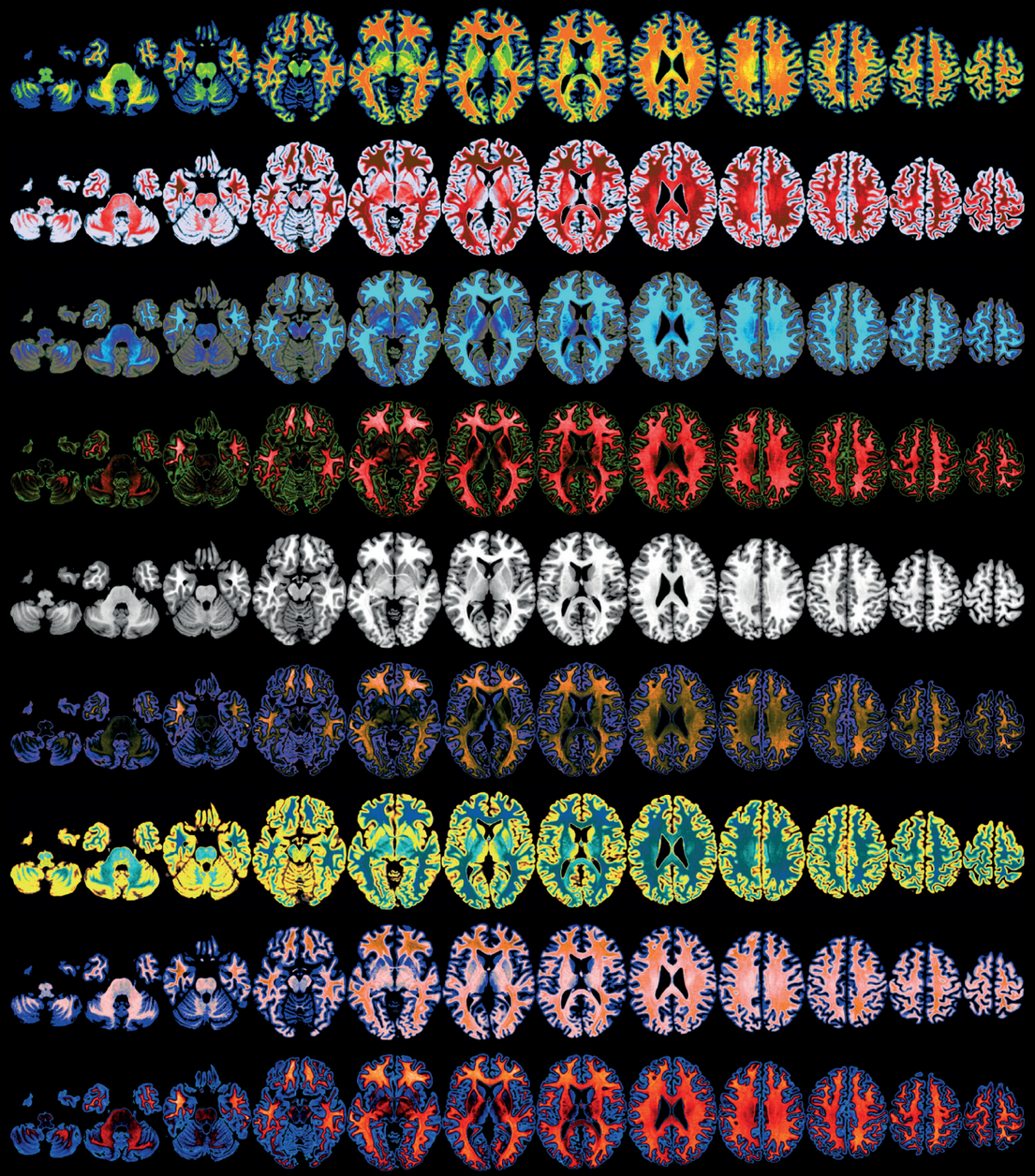
Özgun Gökçe is a molecular biologist with an interest in cell identity and cell-cell interactions. Coming from Stanford (USA) his team combines state-of-the-art animal models with high throughput single cell approaches to define and functionally explore

individual cell types relevant to human disease processes. Özgun Gökçe studied molecular biology in Bogaziçi University, Turkey, and received his PhD in EPFL, Switzerland. As a postdoctoral fellow, he joined the laboratory of Thomas C. Südhof at Stanford University, USA. He is a recipient of a NARSAD award and a NIH Pathway to Independence Award (K99/R00)... *(more on page 46)*

12/2016

Coming from The Rockefeller University (New York, USA), **Dominik Paquet** has joined the ISD. He was appointed Professor for Neurobiology and is a member of the Munich Cluster for Systems Neurology (SyNergy). Following his PhD at the LMU Munich, Prof. Paquet worked as a New York Stem Cell Foundation Druckenmiller Fellow in the laboratory of Marc Tessier-Lavigne, where he pioneered the use of CRISPR/Cas9 gene editing in induced pluripotent stem cells to study diseases of the human brain... *(more on page 44)*

New Recruits



Outpatient Clinic

Outpatient Clinic

We strive to provide the highest quality in recognizing, preventing, and treating cerebrovascular disease and cognitive decline thus offering the best service to patients, their families and referring physicians. While meeting this priority further progress is urgently needed. Much of our efforts go in the planning and conduct of investigator-initiated clinical studies and trials. We further collaborate with industry through participiation into industry-driven multi-center studies.

Major aims and topics of our clinical studies are:

- the identification of disease mechanism through genetic and other omics approaches and through brain imaging.
- the development of diagnostic and prognostic markers (MR imaging, PET, blood, CSF)
- testing novel therapeutic strategies in randomized controlled trials.

Outpatient service at ISD is provided by board certified neurologists and psychiatrists, neuropsychologists, social workers, and specially trained staff for the conduct of observational studies and clinical trials. Our efforts are targeted towards the implementation of validated treatments and the search for novel therapeutic approaches. We are committed to providing the best possible treatment to individual patients while acknowledging that individuals differ with respect to medical and non-medical factors (tailored treatment, precision medicine).

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Dr. med. Cihan Catak
Dr. phil. Lisa Coloma Andrews
Margit Deschner
Prof. Dr. med. Martin Dichgans
Angelika Dörr
PD Dr. med. Marco Düring
Alexandra Fertig
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Dr. med. Claudia Müller
Dorothea Reinartz
Sandra Schreiner
Dr. med. Steffen Tiedt
Viktoria Wiedmann
PD Dr. med. Frank Wollenweber
Adelgunde Zollver

Stroke Prevention Unit

Senior physician:
PD Dr. med. Frank Wollenweber

As a tertiary referral center our stroke prevention unit (SPU) takes care of the whole spectrum of neurovascular diseases with a special focus on primary and secondary prevention of stroke. The risk of a first or recurrent stroke can be efficiently reduced through preventive actions. To be successful preventive interventions require early recognition of risk factors and their targeted treatment.

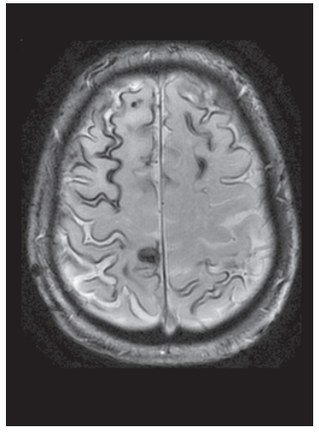


Figure: cortical superficial siderosis (disseminated)

The SPU offers comprehensive diagnostic assessment, counselling and personalized treatment to patients and individuals at risk for developing a stroke or cardiovascular events. The clinic is part of the Interdisciplinary Stroke Center Munich (www.iszm.de). It closely collaborates with neighboring disciplines such as neuroradiology, neurosurgery, and vascular surgery. The SPU unit also serves as a platform for the planning, conduct and coordination of investigator-initiated trials (IITs)

Major research topics of the SPU are:
- post stroke dementia (PSD)
- small vessel disease
- cerebral amyloid angiopathy (CAA) and cortical superficial siderosis (cSS)
- carotid artery disease (non-stenosing vulnerable plaques)

For a full account of ongoing clinical studies see page 52

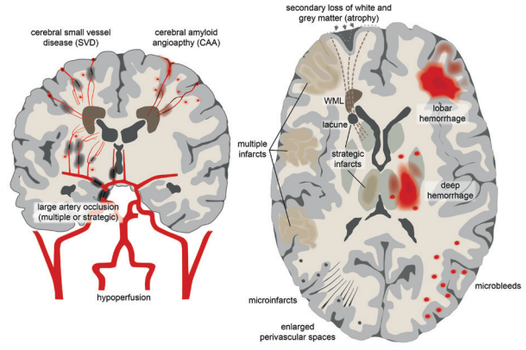
Publications:

Dichgans M, Leys D. *Vascular Cognitive Impairment.* **Circ Res.** 2017 Feb 3;120(3):573-591

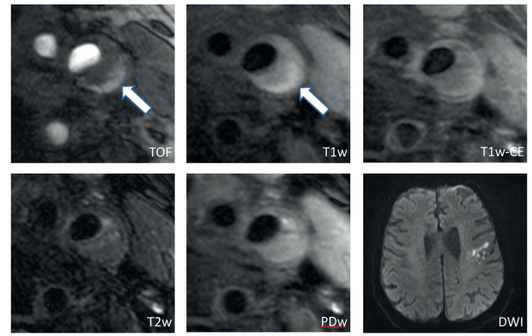
Baykara E, Gesierich B, Adam R, Tuladhar AM, ..., Ertl-Wagner B, **Ewers M**, Schmidt R, de Leeuw FE, Biessels GJ, **Dichgans M, Duering M.** *A Novel Imaging Marker for Small Vessel Disease Based on Skeletonization of White Matter Tracts and Diffusion Histograms.* **Ann Neurol.** 2016 Oct;80(4):581-92.

Wollenweber FA, Därr S, **Müller C, Duering M, Buerger K, Zietemann V, Malik R**, Brendel M, Ertl-Wagner B, Bartenstein P, Rominger A, **Dichgans M**; *Prevalence of Amyloid Positron Emission Tomographic Positivity in Poststroke Mild Cognitive Impairment*. **Stroke** 2016 Oct;47(10):2645-8.

Malik R, Traylor M, Pulit SL, Bevan S, Hopewell JC, Holliday EG, Zhao W, Abrantes P, Amouyel P, Attia JR, Battey TWK, Berger K, Boncoraglio GB, Chauhan G, Cheng YC, Chen WM, Clarke R, Cotlarciuc I, Debette S, Falcone GJ, Ferro JM, Gamble DM, Ilinca A, Kittner SJ, Kourkoulis CE, Lemmens R, Levi CR, Lichtner P, Lindgren A, Liu J, Meschia JF, Mitchell BD, Oliveira SA, Pera J, Reiner AP, Rothwell PM, Sharma P, Slowik A, Sudlow CLM, Tatlisumak T, Thijs V, Vicente AM, Woo D, for the METASTROKE collaboration, the Wellcome Trust Case Control Consortium 2 (WTCCC2), the NINDS Stroke Genetics Network (SiGN), Seshadri S, Saleheen D, Rosand J, Markus HS, Worrall BB, **Dichgans M**. *Low-frequency and common genetic variation in ischemic stroke: The METASTROKE collaboration.* **Neurology** 2016 Mar 29;86(13):1217-26.



Major mechanisms underlying Vascular Cognitive Impairment



AHA-LT VI Plaque
- *Extensive positive (i.e.outward) remodeling*
- *Large lipid-rich / necrotic core*
- *Extensive intraplaque hemorrhage (arrow)*
- *Irregular luminal surface*
- *Ulceration (not depicted; appx. 6 mm lower)*
- *Previous ipsilateral stroke at BL*

->„culprit plaque“

Memory Clinic

Senior physician:
PD Dr. med. Katharina Bürger

A decline of cognitive skills such as memory or attention may be normal and age-related or attributable to disease processes such as vascular disease, depression, metabolic malfunction and potentially to neurodegenerative dementia including Alzheimer's disease (AD).

Recent clinical trials have emphasized the potential of preventive treatment particularly, when initiated in the pre-symptomatic phase. Hence, more than ever, early recognition is critical. Our memory clinic offers comprehensive diagnostic workup, counselling and treatment to individuals at risk of developing cognitive decline as well as to patients suffering from early or advanced stages of dementia.

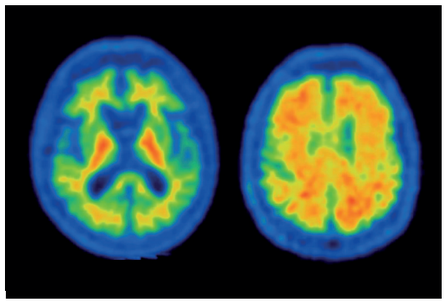


Figure 1: 3T-MRI with corresponding (18F-Flutemetamol) Amyloid-PET-Scan; left: Amyloid negative imaging of a cognitively healthy patient; right: Amyloid positive imaging of patient with AD.

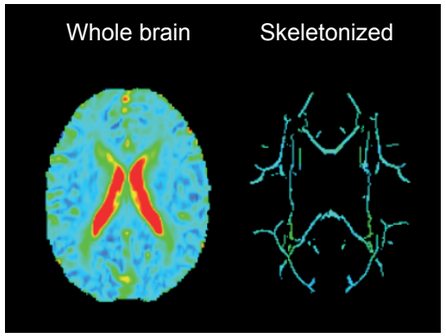


Figure 2: Novel MR-based biomarkers (Baykara et al.)

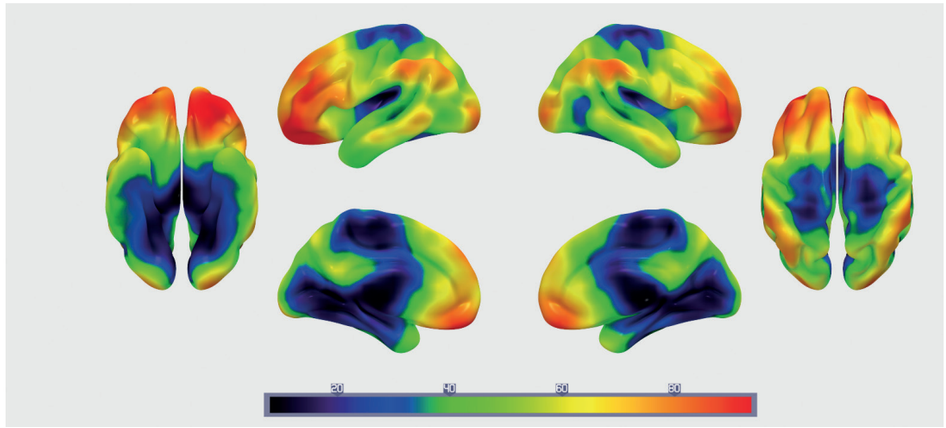


Figure 3: FMRI assessed Hubs of functional connectivity

Major research topics of the Memory Clinic are:
- pre-MCI and MCI (mild cognitive impairment)
- Alzheimer's disease (AD)
- frontotemporal lobar degeneration (FTLD)
- vascular cognitive impairment (VCI)
- cerebral small vessel disease (SVD)

Our diagnostic algorithms are optimized to detect pre-symptomatic stages of dementing conditions and make use of new PET ligands for neurodegenerative disease (Figure 1), novel laboratory-based biomarkers, and novel MR-based biomarkers (Figure 2) developed in part at the ISD.

Taylor AN, **Kambeitz-Ilankovic L**, **Gesierich B, Simon-Vermot L, Franzmeier N, Araque Caballero MÁ**, Müller S, Hesheng L, Ertl-Wagner B, **Bürger K**, Weiner MW, **Dichgans M, Duering M, Ewers M;** *Tract-specific white matter hyperintensities disrupt neural network function in Alzheimer's disease*. **Alzheimer's & dementia** 2016 Jul 16. pii: S1552-5260(16)32660-7.

Dichgans M, Wardlaw J, Smith E, **Zietemann V**, ..., **Düring M**, ..., **Malik R**, ..., Yang YH. *METACOHORTS for the study of vascular disease and its contribution to cognitive decline and neurodegeneration: An initiative of the Joint Programme for Neurodegenerative Disease Research*. **Alzheimers Dement.** 2016 Dec;12(12):1235-1249.

Suárez-Calvet M, Kleinberger G, **Araque Caballero MÁ**, Brendel M, Rominger A, ..., Crispin A, E**wers M**, Haass C. *sTREM2 cerebrospinal fluid levels are a potential biomarker for microglia activity in early-stage Alzheimer's disease and associate with neuronal injury markers*. **EMBO Mol Med.** 2016 May 2;8(5):466-76.

Figure 4: Outpatient Clinic

Patients' events

in cooperation with the Munich Alzheimer Association

Patients cooking for researchers and other CSD staff with support from the Munich Alzheimer Association.

ISD physicians and researchers inform patients and their caregivers about dementia and preventive option.

Alzheimer Gesellschaft München

Mit neuer Zuversicht!

Munich Alzheimer Association

We also offer support programs to patients and their families and regularly provide educational talks and presentations to the public to inform about AD and other types of dementia.

We closely cooperate with other players in the health care system including the Munich Alzheimer Association, service centers for the elderly living at home, day care institutions, and charity organizations.

Statistics | Outpatient Clinic

The total number of appointments in 2015 and 2016 was 2,541 and 2,848 respectively which corresponds to an increase of 35% compared to 2014.

The total number of clinical appointments was 1,987 (2015) and 2,093 (2016) and thus remained relatively stable. The total number of research visits was 550 (2015) and 755 (2016), which corresponds to an increase of 52% percent compared to 2014.

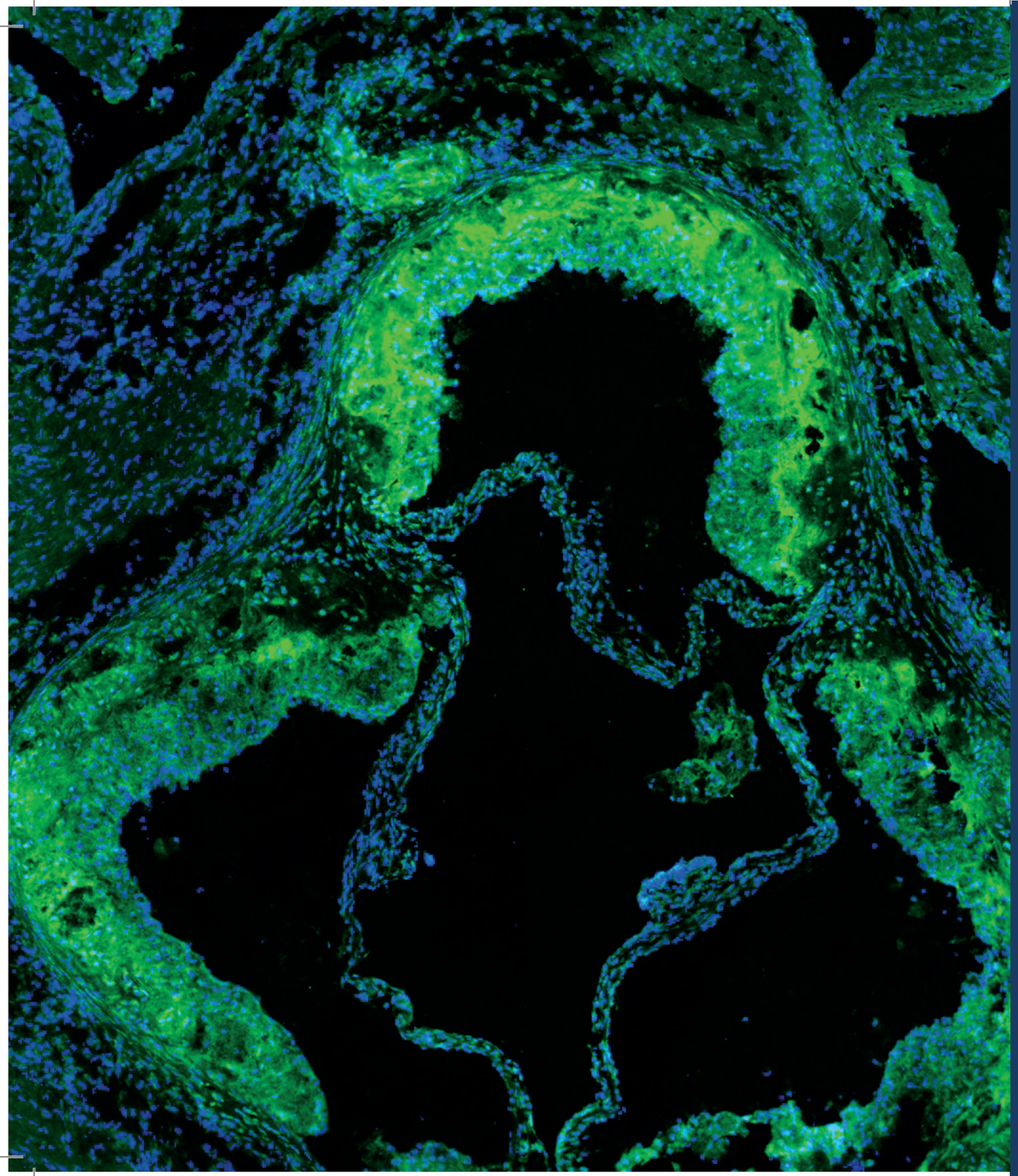
Patients presenting to the SPU most often had one of the following diagnoses:
1. Previous stroke or transient ischemic attack
2. Specific risk factors for ischemic stroke e.g. carotid artery stenosis, cervical artery dissection, patent foramen ovale
3. Specific risk factors for hemorrhagic stroke e.g. previous intracranial hemorrhage, cerebral microbleeds, cortical superficial siderosis, cavernoma or aneurysma
4. A high cardiovascular risk profile e.g. with hypertension, hyperlipidemia, obesity, smoking
5. Leukoencephalopathy of unknown origin or presumed vascular origin
6. Suspected isolated CNS vasculitis

A special focus of the SPU is on rare genetic stroke etiologies such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Fabry disease or an hereditary Moya-Moya disease.

Patients presenting to the memory clinic usually had one of the following diagnoses: subjective cognitive disorder, mild cognitive impairment (MCI, including both amnestic MCI and non-amnestic MCI, both single- and multiple-domain), vascular dementia (VaD), Alzheimer's disease (AD), other neurodegenerative dementias like frontotemporal lobar degeneration (FTLD), dementia with Lewy bodies (DLB), primary progressive aphasia (PPA) and mixed vascular and neurodegenerative dementia.

Clinical staff	outpatient clinic
function	total
physicians	5
neuropsychologists	2
study nurses	6
social workers	1
technical assistants	1
outpatient office	3
clinical data manager	2
total	20

Costs	outpatient clinic
In 2016 the total costs for the outpatient clinic amounted to 881,607 €. 73% of these costs were covered by the Vascular Dementia Research Foundation.	
personnel	736,860 €
material	39,953 €
travel expenses	4,849 €
investments	2,025 €
miscellaneous	97,920 €
total	881,607 €



Research

Scope of research
The focus of ISD research is on the following project areas:
- Small vessel disease | Microvessels
- Atherosclerosis
- Stroke-Immunology
- Vascular cognitive impairment | Post-stroke dementia
- Neurodegeneration (AD, FTLD)
- Secondary Neurodegeneration following acute brain injury
- Atherosclerotic stroke and mechanisms of atherosclerosis and inflammation

Technology – Methodological approaches include:
- Prospective investigator-initiated clinical studies and trials
- Genetics and second generation omics approach
- Single cell sequencing
- Genome editing
- Inducible pluripotent stem cells | organ in a dish Immunology
- In vivo microscopy (two-photon, light-sheet, confocal)
- MRI & PET (human and mouse)

Contact
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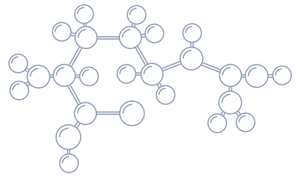
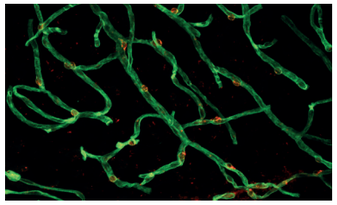
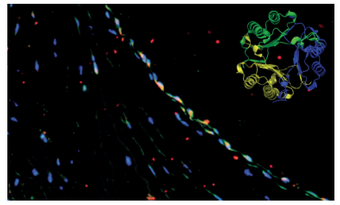
Research at the ISD



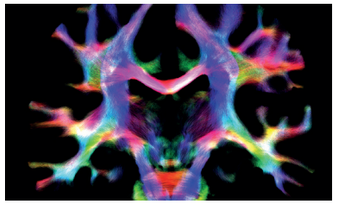
Translational Stroke and Dementia Research
PI: Martin Dichgans *(page 30)*



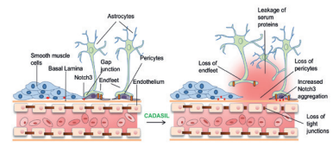
Vascular Biology
PI: Jürgen Bernhagen
(page 32)



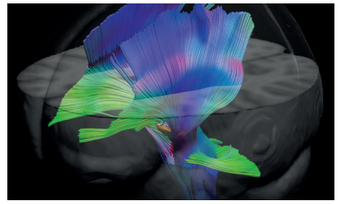
Vascular Cognitive Impairment
PI: Marco Düring
(page 34)



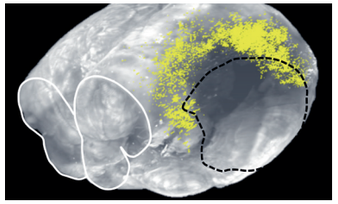
Experimental Stroke Research
PI: Nikolaus Plesnila
(page 36)



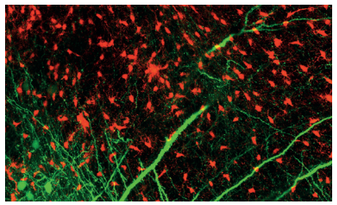
Brain Imaging and Biomarkers
PI: Michael Ewers
(page 38)



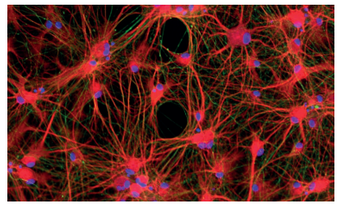
Stroke Immunology
PI: Arthur Liesz
(page 40)



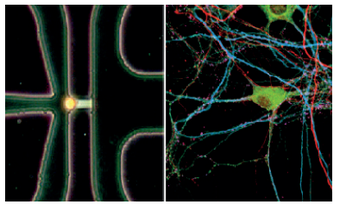
Acute Brain Injury
PI: Ali Ertürk
(page 42)



Neurobiology
PI: Dominik Paquet
(page 44)

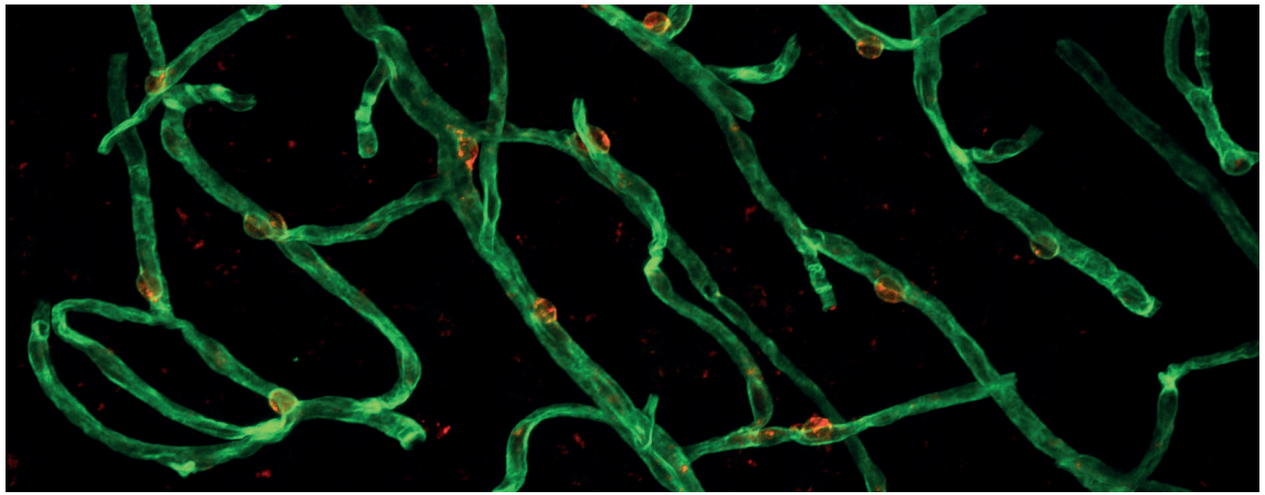


Systems Neuroscience
PI: Ozgun Gokce
(page 46)



Translational Stroke and Dementia Research Research Group – PI: Martin Dichgans

We are interested in the molecular, cellular, and physiological mechanisms of stroke and cerebrovascular disease. We use genetic approaches to identify novel risk genes and explore their functional role in vitro and in vivo using genome-editing, proteomics, and imaging technology. We are particularly interested in cerebral small vessel disease and large artery atherosclerotic stroke.



A major starting point of our work are patients with stroke that are examined through prospective clinical studies along with healthy individuals. We apply genetic (GWAS and sequencing) and other omics techniques to identify novel targets and pathways relevant to specific mechanistically defined stroke subtypes. We use this information to explore relationships with informative intermediate (e.g. vascular, metabolic) and related phenotypes (e.g. coronary artery disease). We have established genetic mouse models for cerebral small vessel disease (SVD) derived from the genetic discoveries (e.g. Notch3, HtrA1, Foxf2) and use these models to identify and characterize key molecular pathways (e.g. TGF-ß signaling) and cellular targets (e.g. brain pericytes) relevant to the pathogenesis of SVD.

Another area increasingly moving into the focus of our research is atherosclerosis. We in collaboration with others recently identified several risk loci for large artery stroke and are currently exploring the role of relevant genes (e.g. HDAC9, TSPAN2) in atherogenesis and vascular injury.

Key Publications

Beaufort N, **Scharrer E**, Lux V, Ehrmann M, **Haffner C**, **Dichgans M**. *Reply to Liu et al.: Loss of TGF-β signaling in CARASIL pathogenesis.* **Proc Natl Acad Sci U S A** 2015 Apr 7;112(14):E1694.

Malik R, Freilinger T, Winsvold BS, Anttila V, ... Palotie A; International Headache Genetics Consortium, **Dichgans M**; METASTROKE Collaboration of the International Stroke Genetics Consortium. *Shared genetic basis for migraine and ischemic stroke: A genome-wide analysis of common variants.* **Neurology** 2015 May 26;84(21):2132-45.

Malik R, Traylor M, ..., Worrall BB, **Dichgans M;** ISGC Analysis Group.; METASTROKE collaboration.; Wellcome Trust Case Control Consortium 2 (WTCCC2).; NINDS Stroke Genetics Network (SiGN).*Low-frequency and common genetic variation in ischemic stroke: The METASTROKE collaboration.* **Neurology** 2016 Mar 29;86(13):1217-26.

Gormley P, Anttila V, ..., **Malik R**, Heath AC, M..., Belin AC, **Dichgans M**, Wessman M,..., Nyholt DR, Palotie A; *Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine.* **Nat Genet.** 2016 Aug;48(8):856-66.

Malik R, Dau T, Gonik M, Sivakumar A, Deredge D, Edeleva EV, Götzfried J, van der Laan SW, Pasterkamp G, **Beaufort N,** ..., Saleheen D, International Stroke Genetics Consortium, Rothwell P, ..., Braun D, Markus HS , Wintrode P, Berger K, Jenne D, **Dichgans M.** *A common coding variant in SERPINA1 increases the risk for large artery stroke***. Proc Natl Acad Sci U S A.** 2017 (in press)

Dichgans M, Leys D. *Vascular Cognitive Impairment.* **Circ Res.** 2017 Feb 3;120(3):573-591

Team:
Dichgans, Martin, Prof. Dr. med. / PI
Asare, Yaw, Dr. rer. nat. / Postdoc
Beaufort, Nathalie, Dr. rer. nat. / Postdoc
Bokov, Yuri / Ph.D. student
Gernert, Jonathan / Ph.D. Student
Guangyao, Yan / Ph.D. student
Haffner, Christof, PD Dr. rer. nat. / Postdoc
Kopczak, Anna, Dr. med. / Postdoc
Lindner, Barbara / Technical assistant
Malik, Rainer, Dr. rer. nat. / Postdoc
Paulenz, Lina / Team assistant
Prestel, Matthias, Dr. rer. nat. / Postdoc
Schneider, Melanie / Technical assistant
Tiedt, Steffen / Clinician scientist
von Brauchitsch, Sophie / Ph.D. student
Waegemann, Karin, Dr. rer. nat. / Research coordinator
Yu, Luya / Ph.D. student
Zellner, Andreas / Ph.D. student
Ziesch, Natalie / Technical assistant
Zietemann, Vera, Dr. rer. nat, MPH / Postdoc

Vascular Biology

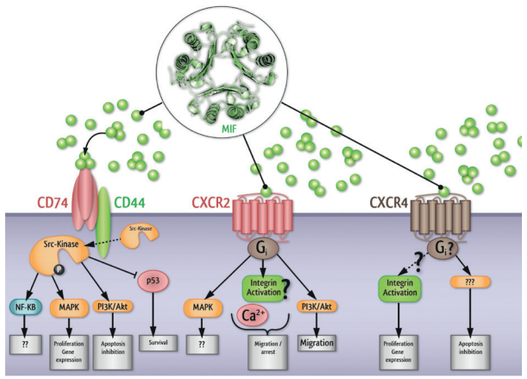
Research Group – PI: Jürgen Bernhagen

We are interested in the molecular and cellular mechanisms of cardiovascular disease and inflammation. A focus is on atypical chemokines, inflammatory signaling pathways, and leukocyte recruitment processes in atherosclerosis, a chronic inflammatory condition of arterial vessels and the main underlying condition of ischemic stroke. We study these mechanisms from basic vascular biology to clinical translation.

We have discovered the cytokine MIF in **inflammatory and vascular disease** and have characterized it as a protagonistic member of the class of '**atypical chemokines**' (Bernhagen et al., Nat. Med. 2007). Relying on biochemical and vascular biology methodologies in combination with transgenic mouse models and clinical approaches, we broadly study the **MIF protein family** (i.e. MIF, MIF-2/D-DT, CXCR2, CXCR4, CXCR7, CD74, sCD74) **and related classical chemokines in atherosclerosis, ischemic stroke, and myocardial infarction** (*Stoppe et al., Antiox Redox Signal 2015; Alampour-Rajabi et al., FASEB J 2015).* This involves deciphering the receptor complexes *(Rajasekaran et al., J Biol Chem 2016)* and pathways driving atherogenic recruitment of leukocyte sub-populations, but we also focus on site- and disease-specific oxidized isoforms as encountered under ischemic/oxidative stress as well as on chemokine-like alarmins such as HMGB1.

Another focus is on **atheroprotective signaling pathways maintained by the COP9 signalosome (CSN)** in atherogenic endothelium. The CSN is a multifunctional protein complex that regulates SCF cullin-RING E3-ligase (CRL) NEDDylation status, controlling ubiquitin/26S-proteasome-mediated degradation of cell-regulatory proteins. Based on our discovery of a link between CSN5/JAB1 and inflammation *(Kleemann et al., Nature 2000)*, we currently study atheroprotective effects of CSN5 via NFκB signaling.

We are also interested in cardioprotective mechanisms of some of these mediators *(Lüdike et al., Circulation 2012)* and how they compare with corresponding effects in ischemic stroke and cerebral/(micro)vascular pathogenesis but also other inflammatory diseases. Lastly, capitalizing on various collaborations, we increasingly pursue **links between inflammation and neurodegeneration,** i.e. inflammasome and amyloid/chaperone-type mechanisms.



Key Publications

Yoo SA, Leng L, ..., Sauler M, **Bernhagen J**, Ritchlin CT, Lee P, Cho CS, Kim WU, Bucala R. *MIF allele-dependent regulation of the MIF coreceptor CD44 and role in rheumatoid arthritis.* **Proc Natl Acad Sci U S A.** 2016 Dec 6;113(49):E7917-E7926.

Rajasekaran D, Gröning S, **Schmitz C**, ..., **Bernhagen J;** *Macrophage Migration Inhibitory Factor-CXCR4 Receptor Interactions: Evidence for Partial Allosteric Agonism in Comparison to CXCL12.* **J Biol Chem.** 2016 Jul 22;291(30):15881-95.

Przybyl L, ..., Stoppe C, **Bernhagen J**, ..., Herse F; *CD74-Downregulation of Placental Macrophage-Trophoblastic Interactions in Preeclampsia.* **Circ Res.** 2016 Jun 24;119(1):55-68.

Roger T, Schneider A, Weier M, Sweep FC, Le Roy D, **Bernhagen J**, Calandra T, Giannoni E. *High expression levels of macrophage migration inhibitory factor sustain the innate immune responses of neonates.* **Proc Natl Acad Sci U S A** 2016 Feb 23;113(8):E997-1005.

Alampour-Rajabi S, El Bounkari O, ..., **Bernhagen J**. *MIF interacts with CXCR7 to promote receptor internalization, ERK1/2 and ZAP-70 signaling, and lymphocyte chemotaxis.* **FASEB J**. 2015 Nov;29(11):4497-511.

Stoppe C, Rex S, ..., Weber C, **Bernhagen J.** *Interaction of MIF Family Proteins in Myocardial Ischemia/Reperfusion Damage and Their Influence on Clinical Outcome of Cardiac Surgery Patients.* **Antioxid Redox Signal.** 2015 Oct 10;23(11):865-79.

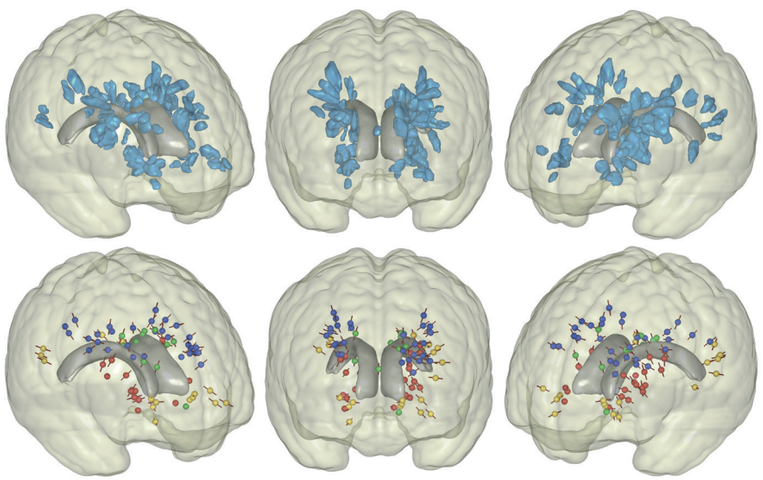
Djudjaj S, Lue H, ..., Ostendorf T, **Bernhagen J**, Boor P. *Macrophage Migration Inhibitory Factor Mediates Proliferative GN via CD74.* **J Am Soc Nephrol.** 2016 Jun;27(6):1650-64.

Team:
Atzler, Dorothee. Dr. rer. nat. / Postdoc
El Bounkari, Omar, Dr. rer. nat. / Postdoc & technical laboratory head
Bourilhon, Priscila, M.Sc. / Technical assistant
Brandhofer, Markus, M.Sc. / Ph.D. student
Dixit, Mahesh, B.Sc. / Master student, intern
Emontspohl, Christoph, M.Sc. / Ph.D. student (external)
Chen, Hong-Ru Christina, M.Sc. / Ph.D. student
Holz, Claudia / Student assistant
Heinrichs, Daniel, Dr. rer. nat. / Postdoc (external)
Honke, Anna / Student assistant
Krammer, Christine, M.Sc. / Ph.D. student
Lacy, Michael, M.Sc. / Technical assistant
Milic, Jelena, M.Sc. / intern
Schindler, Lisa, M.Sc. / Ph.D. student
Schmitz, Corinna, M.Sc. / Ph.D. student
Sinitski, Dzmitry, Dr. rer. nat. / Postdoc
Stangl, Edith / Team assistant
Thavayogarajah, Tharshika, cand. med. / MD doctoral student
Tursch, Marlies, VD / doctoral student
Wang, Siljia, M.D. / Ph.D. trainee

Vascular Cognitive Impairment

Research Group – PI: Marco Düring

We are interested in the mechanisms by which vascular dysfunction causes cognitive decline. The major focus of our work is on cerebral small vessel disease (SVD), the most common cause of vascular cognitive impairment (VCI) and also a frequent finding in patients with neurodegenerative disease including Alzheimer's disease.



Our methodological expertise is in structural and functional neuroimaging in humans using advanced analytical and statistical techniques.

We use datasets from large cohorts including population-based samples as well as patients with stroke and genetically defined forms of SVD. A specific focus of our group is on CADASIL, an inherited form of SVD and model disease for pure VCI.

A major theme is the development of biomarkers for VCI. We recently established a novel, fully automated and robust biomarker based on diffusion tensor imaging. A toolbox for the calculation of this novel biomarker is available publicly (www.psmd-marker.com).

Another focus of our work is on the interplay between vascular and neurodegenerative pathology. Thus, for example, our group recently revealed a link between subcortical infarcts and changes of cortical morphology implying a role for remote, secondary neurodegeneration in stroke and VCI.

Key Publications

Baykara E, Gesierich B, Adam R, Tuladhar AM, Biesbroek JM, Koek HL, Ropele S, Jouvent E; Alzheimer's Disease Neuroimaging Initiative, Chabriat H, Ertl-Wagner B, **Ewers M,** Schmidt R, de Leeuw FE, Biessels GJ, **Dichgans M, Duering M.** *A Novel Imaging Marker for Small Vessel Disease Based on Skeletonization of White Matter Tracts and Diffusion Histograms.* **Ann Neurol.** 2016 Oct;80(4):581-92.

Duering M, Righart R, Wollenweber FA, Zietemann V, Gesierich B, Dichgans M. *Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts.* **Neurology** 2015 Apr 21;84(16):1685-92.

Duering M, Gesierich B, Seiler S, Pirpamer L, **Gonik M**, Hofer E, Jouvent E, Duchesnay E, Chabriat H, Ropele S, Schmidt R**, Dichgans M.** *Strategic white matter tracts for processing speed deficits in age-related small vessel disease.* **Neurology** 2014 Jun 3;82(22):1946-50.

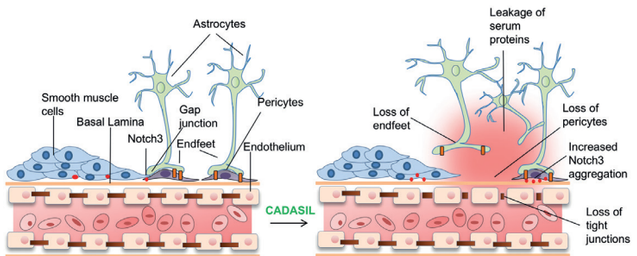
Duering M, Csanadi E, **Gesierich B,** Jouvent E, Hervé D, Seiler S, Belaroussi B, Ropele S, Schmidt R, Chabriat H, **Dichgans M.** *Incident lacunes preferentially localize to the edge of white matter hyperintensities: insights into the pathophysiology of cerebral small vessel disease.* **Brain.** 2013 Sep;136(Pt 9):2717-26.

Duering M, Righart R, Csanadi E, Jouvent E, Hervé D, Chabriat H, **Dichgans M.** *Incident subcortical infarcts induce focal thinning in connected cortical regions.* **Neurology** 2012 Nov 13;79(20):2025-8.

Team:
Achmüller, Melanie / MD student
Adam, Ruth, Ph.D. / Postdoc
Baykara, Ebru, M.Sc. / Ph.D. student (GSN)
Düring, Marco, PD Dr. med. / PI
Gesierich, Benno, Ph.D. / Postdoc
Hübner, Mathias, Dipl.Biol. MPH / Technician
Konieczny, Marek / Ph.D. student (MMRS)
Pietsch, Hedwig / Team assistant
Vlegels, Naomi / Master student

Laboratory of Experimental Stroke Research Research Group – PI: Nikolaus Plesnila

The main interest of the laboratory is to study the role of cerebral vessels for the pathophysiology of acute and chronic brain injury and to use the evolving knowledge for the development of novel therapeutic strategies for patients. For this purpose we use clinically relevant mouse models for acute and chronic brain injury and investigate neuro-vascular morphology and function by in vivo microscopy using conventional and 2-photon fluorescence microscopy.



CADASIL-associated aggregation of mutated NOTCH3 extracellular domain induces pericyte dysfunction and loss well before white matter damage occurs. As a consequence tight junctions open up, astrocytic end-feet detach from cerebral microvessels, and the blood-brain barrier becomes leaky to neurotoxic plasma components.

The work of the Laboratory of Experimental Stroke Research currently focuses around two topics: 1) the role of the cerebral microcirculation for brain injury after subarachnoid hemorrhage (SAH) and 2) the function of cerebral microvessels in physiological and pathological aging. Regarding SAH we discovered that early surgical decompression results in an increased rate of secondary bleedings thereby significantly worsening outcome (5) and that inhaled nitric oxide reduces cerebral microvasospasms by -85% and blunts mortality (2). Further, we demonstrated that pial and intraparenchymal microvessels show a complete loss of CO2 reactivity after SAH (1). This finding suggests that SAH induces severe neuro-vascular dysfunction already within the first few hours after brain hemorrhage.

Experiments on the aging brain demonstrated that already normal aging results in severe dysfunction of cerebral microvessels. While young vessels dilate and remain dilated upon repetitive neuronal activation, vessels from only eight month old mice dilate less and start to constrict with ongoing neuronal activity (4). These findings suggest that rather vascular and not necessarily neuronal dysfunction may be responsible for the reduced attention span at older age.

Finally, we could demonstrate that the first pathological alteration in a mouse model of CADASIL is the retraction and death of microvascular pericytes. As a consequence the blood brain barrier becomes dysfunctional, plasma protein enter the brain, and astrocytic end-feed detach from cerebral capillaries. These changes start to occur at an age of 4-8 month and precede white matter damage by more than one year (3). Accordingly, pericytes may represent the primary target for the cure of CADASIL.

Team:
(from left to right): Rehberg, Markus, PD Dr. rer. nat. / Hellal, Farida, PhD / Sellner, Sabine / Ghosh, Mitrajit, PhD / Seker, Burcu, PhD / Auffenberg, Eva, Dr. med. / Heumos, Nicole / Lourbopoulos, Athanasios, MD, PhD / Terpolilli, Nicole, Dr. med. / Shrouder, Joshua / Liu, Hanhan, MD / Mao, Xiang, MD / Westermayer, Irina / Nekolla, Katharina / Katzdobler, Sabrina / Nehrkorn, Kathrin, DVM, PhD / Valero Freitag, Susana / Mamrak, Uta / Pietsch, Hedwig / Plesnila, Nikolaus, Prof. Dr. med.
(Not on the picture): Exner, Carina / Fan, Ziyu, MD / Groschup, Bernhard / Rauen, Katrin, Dr. med. / Reichelt, Lara / Schwarzmaier, Susanne, Dr. med. / Schwicht, Charlotte / Sienel, Rebecca

Key Publications

Balbi M, Koide M, **Schwarzmaier SM**, Wellman GC, **Plesnila N**. *Acute changes in neurovascular reactivity after subarachnoid hemorrhage in vivo.* **J Cereb Blood Flow Metab** 2017 Jan;37(1):178-187.

Terpolilli NA, Feiler S, Dienel A, Müller F, **Heumos N**, Friedrich B, Stover J, Thal S, Schöller K, **Plesnila N**. *Nitric oxide inhalation reduces brain damage, prevents mortality, and improves neurological outcome after subarachnoid hemorrhage by resolving early pial microvasospasms.* **J Cereb Blood Flow Metab** 2016, 36(12): 2096–2107

Ghosh M, **Balbi M**, **Hellal F**, **Dichgans M**, Lindauer U, **Plesnila N**. *Pericytes are involved in the pathogenesis of CADASIL.* **Ann Neurol** 2015, 78:887-900

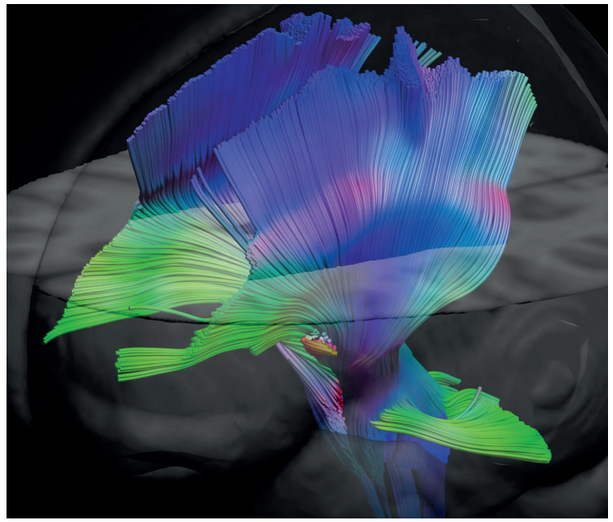
Balbi M, **Ghosh M**, Longden TA, Jativa Vega M, **Gesierich B**, **Hellal F**, **Lourbopoulos A**, Nelson MT, **Plesnila N**. *Dysfunction of mouse cerebral arteries during early aging.* **J Cereb Blood Flow Metab** 2015, 35:1445-1453

Bühler D, Azghandi S, Schüller K, Plesnila N. *Effect of decompressive craniectomy on outcome following subarachnoid hemorrhage in mice.* **Stroke** 2015, 46:819-26

Brain Imaging and Biomarker

Research Group – PI: Michael Ewers

We are interested in the detection of brain changes that precede the manifestation of dementia symptoms in Alzheimer's disease. A first major focus is the detection of protective brain mechanisms that delay the onset of cognitive impairment. Another topic of our research is the development of markers for the early detection of AD. We primarily employ fMRI and DTI-based analysis of functional networks along with biochemical analysis of cerebrospinal fluid markers.



Early life-experiences such as education and higher IQ enhance cognitive reserve, i.e. mitigate the impact on brain pathology on cognition in AD. Using DTI, multi-task fMRI and combined EEG-fMRI, we map functional networks associated with protective factors. We recently identified a highly connected hub in the frontal cortex as a key brain region underlying cognitive reserve in AD. We are testing non-invasive techniques such as tDCS and TMS to enhance such functional brain mechanisms.

Together with Prof. Yaakov Stern (Columbia University, USA) and Prof. Gael Chetelat (INSERM, France) we recently initiated the professional interested area (PIA) on "Reserve, resilience and protective factors" hosted by the Alzheimer's Association, open to any interested collaborators.

For our second major research topic, i.e. the development of markers for the prediction of AD, we are combining multi-modal imaging and biochemical markers. We use pattern recognition algorithms to extract the best combination of markers for the prediction of cognitive decline and early diagnostic classification.

Another area currently moving into the focus of our research are markers of the brain's neuroimmune response in AD. Together with our collaborator Prof. Christian Haass (DZNE, Munich), we found changes in CSF TREM2, a marker of microglia activity, to occur up to 5 years before the onset of AD dementia. We are currently investigating the potentially protective effects of TREM2 in AD.

Key Publications

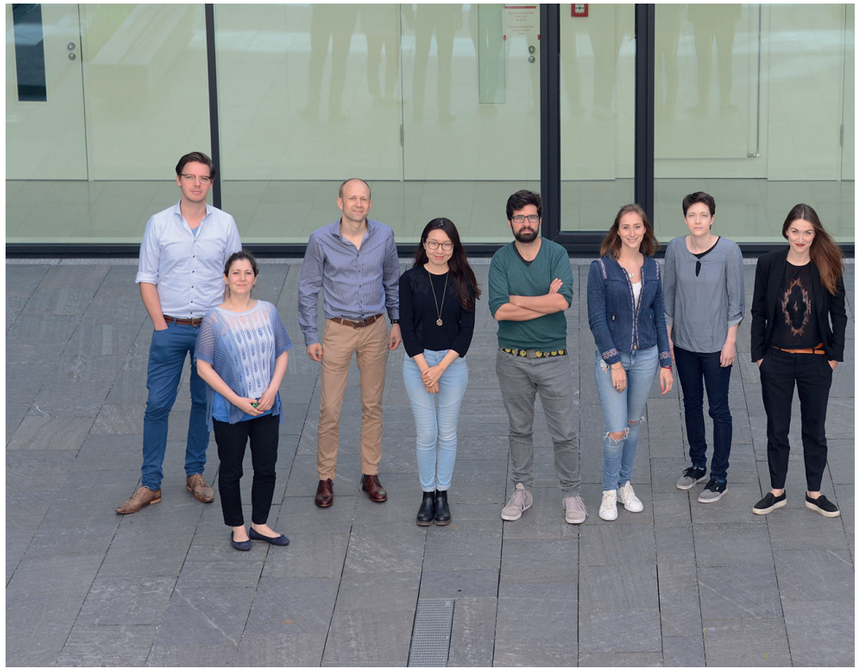
Franzmeier N, Buerger K, Teipel S, Stern Y, **Dichgans M, Ewers M.** *Cognitive Reserve Moderates the Association between Functional Network Anti-Correlations and Memory in MCI***. Neurobiol Aging.** 2017 Feb;50:152-162.

Suarez-Calvet M, **Araque Caballero MA, ..., Ewers M*, Haass C*.** *Early changes of CSF sTREM2 in Dominantly Inherited Alzheimer's Disease follow marker markers of amlyoid deposition and neuronal injury.* **Science Transl Medicine** (in press) *Contributed equally to the work

Franzmeier N, Duering M, Weiner M, **Dichgans M, Ewers M.** *Global functional connectivity in frontal cortex is a potential neural substrate of cognitive reserve in prodromal AD***. Neurology** (in press).

Molinuevo JL, ...**, Ewers M,** ..., Jessen F; Subjective Cognitive Decline Initiative (SCD-I) Working Group. *Implementation of subjective cognitive decline criteria in research studies.* **Alzheimer's & dementia** 2016 Nov 5. pii: S1552-5260(16)33019-9.

Zhang Y, Simon-Vermot L, Araque Caballero MÁ, Gesierich B, Taylor AN, Duering M, Dichgans M, Ewers M; Alzheimer's Disease Neuroimaging Initiative; *Enhanced resting-state functional connectivity between core memory-task activation peaks is associated with memory impairment in MCI*. **Neurobiol Aging.** 2016 Sep;45:43-9.



Team:
Ewers, Michael, Prof. Dr.
Araque, Miguel, Dr. rer. nat.
Franzmeier, Nicolai
Simon-Vermot, Lee
Hartmann, Julia Clarissa
Lehner, Lisa
Ren, Jinyi
Pietsch, Hedwig

Stroke-Immunology

Research Group – PI: Arthur Liesz

We are interested in the interplay between the brain and the immune system after stroke. Acute brain lesions disturb the well-balanced interconnection between both systems. Hence, our research focuses on both directions of brain-immune interaction: The impact of immune mechanisms on neuronal damage and recovery and the systemic immunomodulation after stroke.

Our methodical spectrum covers diverse brain ischemia models, transgenic animal models, a broad spectrum of cutting-edge immunological techniques as well as histological, biomolecular and behavioral analysis tools.

A focus of our work is the role of pro- and anti-inflammatory lymphocyte subpopulations in stroke and their neurotoxic and – protective functions. Following our previous work in this field (e.g. Nature Medicine, 2009, The Journal of Neuroscience, 2013) we have recently characterized a key role of the intestinal microbiome in modulating lymphocyte function after stroke (The Journal of Neuroscience, 2016).

Another focus of our research is the migration of pro-inflammatory leukocytes to the ischemic brain (Brain, 2011). Here, we are currently investigating pathophysiological mechanisms of leukocyte-endothelial interaction and novel therapeutic approaches for translational use (Science Translational Medicine, 2015).

A third research area investigates alarmin-driven mechanisms of peripheral immune alterations after brain ischemia. We aim to characterize alarmins – humoral mediators released by the necrotic brain tissue – as modulators of the systemic immune system (The Journal of Neuroscience, 2015)

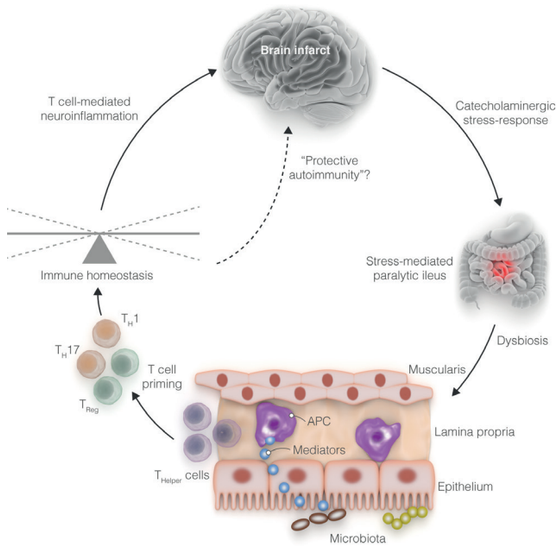


Figure: Dysbiosis of gut microbiota following acute infarct primes the post-stroke neuroinflammatory response.

Key Publications

Singh V, Roth S, Llovera G, Sadler R, Garzetti D, Stecher B**, Dichgans M, Liesz A.** *Microbiota Dysbiosis Controls the Neuroinflammatory Response after Stroke.* **J Neurosci.** 2016 Jul 13;36(28):7428-40.

Llovera G, ..., Dirnagl U, Planas AM, **Plesnila N**, Vivien D, **Liesz A**. *Results of a preclinical randomized controlled multicenter trial (pRCT): Anti-CD49d treatment for acute brain ischemia.* **Sci Transl Med** 2015 Aug 5;7(299):299ra121.

Liesz A, Zhou W, Na SY, Hämmerling GJ, Garbi N, Karcher S, Mracsko E, Backs J, Rivest S, Veltkamp R. *Boosting regulatory T cells limits neuroinflammation in permanent cortical stroke.* **J Neurosci.** 2013 Oct 30;33(44):17350-62.

Liesz A, Zhou W, Mracsko E, Karcher S, Bauer H, Schwarting S, Sun L, Bruder D, Stegemann S, Cerwenka A, Sommer C, Dalpke A, Veltkamp R. *Inhibition of lymphocyte trafficking shields the brain against deleterious neuroinflammation after stroke* **Brain** 2011 Mar;134(Pt 3):704-20.

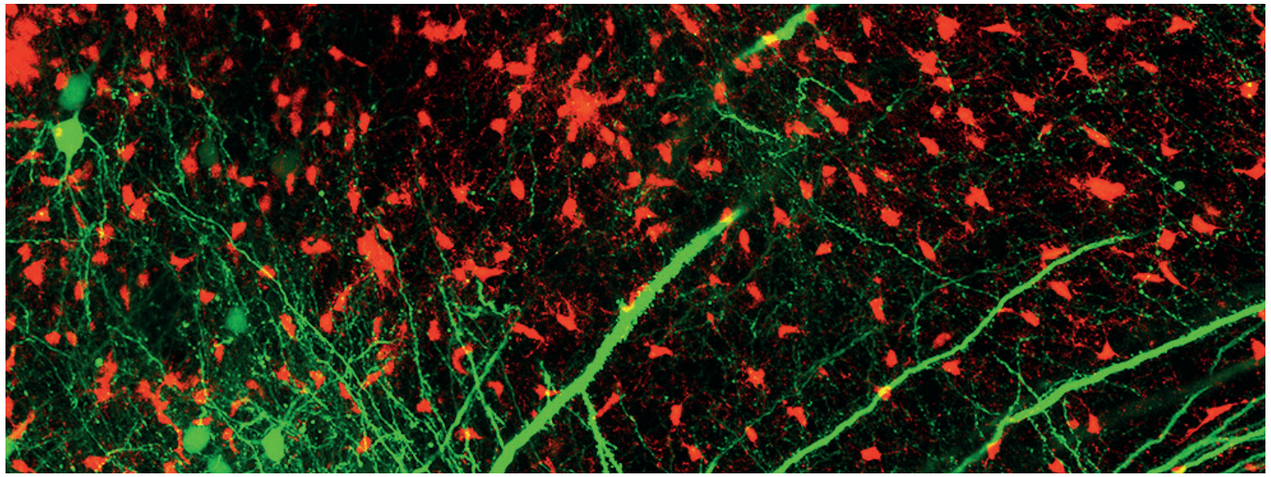
Liesz A, Suri-Payer E, Veltkamp C, Dörr H, Sommer C, Rivest S, Giese T, Veltkamp R. *Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke* **Nat Med.** 2009 Feb;15(2):192-9. doi: 10.1038/nm.1927.

Team:
Liesz, Arthur, PD Dr. med.
Corinne Benakis, Ph.D.
Singh, Vikramjeet, Ph.D.
Llovera Garcia, Gemma, M.Sc.
Roth, Stefan, M.Sc.
Sadler, Rebecca, M.sc.
Yang, Jun, M.D.
Thuß-Silczak, Kerstin
Cramer, Julia
Heindl, Steffanie
Ritter, Helena

Acute Brain Injury Research

Research Group - PI: Ali Ertürk

My laboratory is interested in understanding key mechanisms leading to neurodegeneration in acute brain injuries and dementia.. We use the cutting-edge technologies to investigate mechanisms of inflammation and degeneration in the injured and ageing brain.



Patients with acute brain injury often develop chronic complications including early onset dementia, epilepsy and neuropsychiatric disorders. While these complications are suggestive of continuous alterations in the injured brain circuitry, virtually nothing is known about how the initial injury alters the brain structure and ultimately its function. We recently discovered an unknown widespread neurodegeneration of synapses and associated chronic neuroinflammation in the entire brain upon trauma. We are now exploring if caspase-3 and/or activated immune cells are involved in spine stripping in acute brain injury.

Nervous system works as an entity in 3D, with long neuronal projections that can be extend from head to toe. Hence, ideally, the changes in neuronal circuitry are best studied in the intact whole nervous system. However, traditional tissue histology yields only fragments of neuronal circuitry hindering how it is altered neurological diseases. To address this major shortcoming, we recently developed a new technology called ultimate (u) DISCO that can image neuronal and vascular connections at sub-cellular resolution in the entire adult mouse. We now utilize uDISCO to study mechanisms of chronic neurodegeneration and develop new therapeutics for stroke and dementia.

Key Publications

Pan C, Cai R, Quacquarelli FP, Ghasemigharagoz A, Lourbopoulos A, Matryba P, Plesnila N, Dichgans M, Hellal F, Ertürk A; *Shrinkage-mediated imaging of entire organs and organisms using uDISCO.* **Nat Methods.** 2016 Oct;13(10):859-67. (Cover of Nature Methods 2016 October Issue)

Ertürk A*, Mentz S, Stout E et al., *Interfering with the Chronic Immune Response Rescues Chronic Degeneration After Traumatic Brain Injury.* **J Neurosci.** 2016 Sep 21;36(38):9962-75. *Corresponding author.

Ertürk A, Wang Y, Sheng M. *Local pruning of dendrites and spines by caspase-3-dependent and proteasome-limited mechanisms.* **J Neurosci.** 2014 Jan 29;34(5):1672-88.

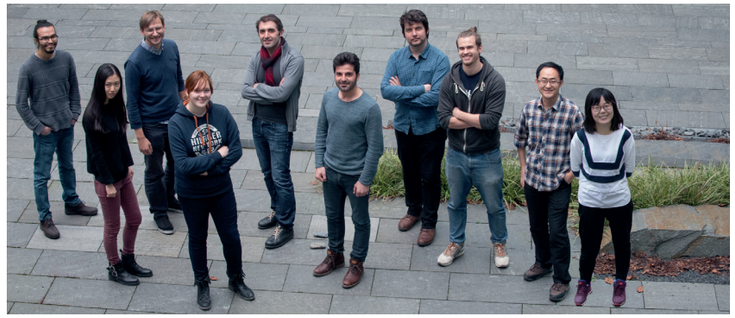
Ertürk A, Becker K, Jährling N, Mauch CP, Hojer CD, Egen JG, Hellal F, Bradke F, Sheng M, Dodt HU. *Three-dimensional imaging of solvent-cleared organs using 3DISCO.* **Nat Protoc.** 2012 Nov;7(11):1983-95. (Cover article of the 2012 November Nature Protocols issue).

Ertürk A, Mauch C.P., **Hellal F.**, Forstner F., Keck T., Becker K., Jahrling N., Steffens H., Richter M., Hubener M., et al. *Three-dimensional imaging of the unsectioned adult spinal cord to assess axon regeneration and glial responses after injury.* **Nat Med.** 2012 (Cover article of the 2012 January Nature Medicine issue).

Ylera B*, **Ertürk A*, Hellal F,** Nadrigny F, Hurtado A, Tahirovic S, Oudega M, Kirchhoff F, Bradke F; C*hronically injured adult sensory axons in the CNS acquire regenerative competence following a lesion of their peripheral process.* **Curr Biol.** 2009 Jun 9;19(11):930-6. *Co-first author.

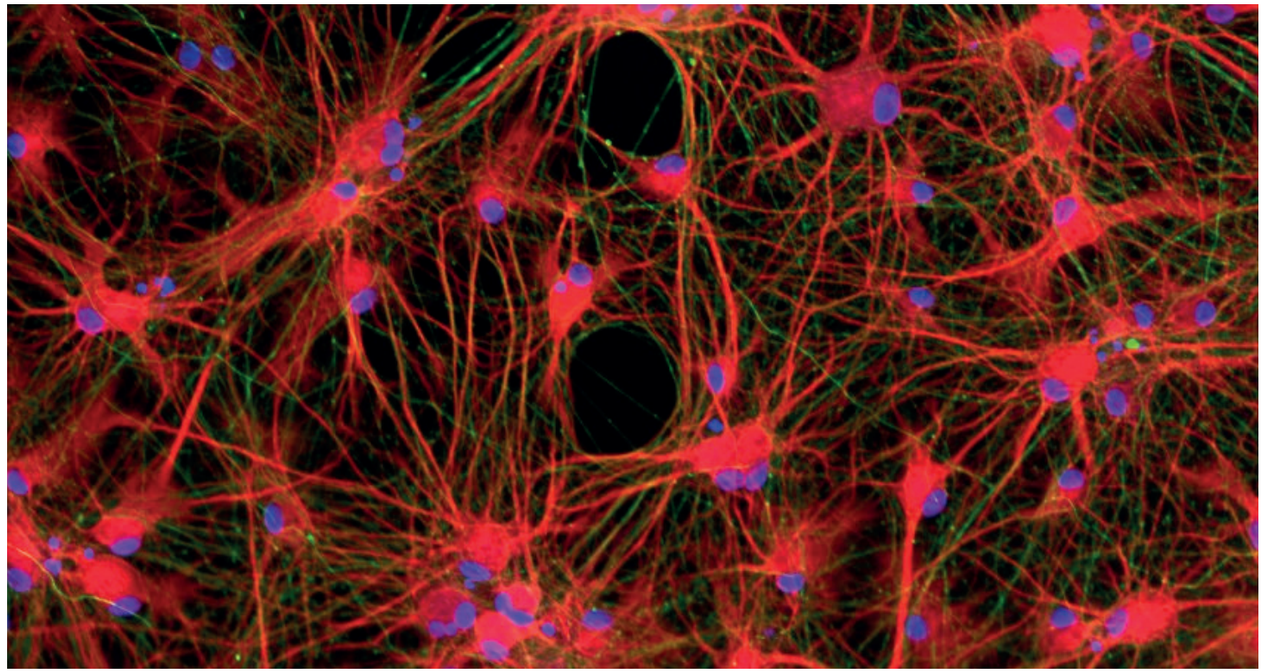
Ertürk A, Hellal F, Enes J, Bradke F (2007): *Disorganized microtubules underlie the formation of retraction bulbs and the failure of axonal regeneration.* **J Neurosci.** 2009 Jun 9;19(11):930-6

Ertürk, Ali / PI
Pan, Chenchen / Ph.D. student
Cai, Ruiyao / Ph.D. student
Todorov, Mihail / Ph.D. student
Zhao, Shan / Ph.D. student
Ghasemi, Alireza / Engineer
Parra Damas, Arnaldo / Postdoc
Förstera, Benjamin / Postdoc
Mrowka, Leander / Master student
Baum, Josephine / Technician
Paulenz, Lina / Team assistant



Neurodegeneration and Vascular Dysfunction Research Group - PI: Dominik Paquet

We are interested in the molecular and cellular mechanisms leading to neuronal death and cognitive decline in patients with neuropsychiatric disorders (e.g. Alzheimer's disease and Frontotemporal dementia) and neurovascular impairments (stroke and vascular cognitive impairment). Our main focus is on building advanced human in vitro model systems recapitulating these diseases using induced pluripotent stem cells and genome editing with CRISPR/Cas9.



Due to the inaccessibility of human brain cells for molecular research, neurodegenerative diseases have mostly been studied in animal and simplified cellular models, which have significantly broadened our knowledge, but have drawbacks limiting successful translational research. We aim to address this gap by developing human model systems based on patient-derived induced pluripotent stem cells, which have the genetic configuration of the patients and allow differentiating and studying somatic cell types directly affected by disease, such as neurons, glia or endothelial cells. In addition, these models are accessible for genetic manipulation and amenable to drug development, which facilitates molecular studies with disease-affected human cell types and can accelerate the identification of novel therapeutic approaches.

We have recently developed efficient technologies to introduce and remove patient mutations in human induced pluripotent stem cells using the CRISPR/Cas9 gene editing system and have also developed protocols for the optimized differentiation of neuronal and glia cell types of the human brain. We have applied these technologies to generate and study isogenic sets of human neurons with mutations in disease-associated genes, such as APP, PSEN or TAU.

We aim to further optimize the genetic configuration, cell type composition and culture parameters of these and further models to elicit the most disease-relevant phenotypes, and then exploit them to reveal molecular disease mechanisms.

Team:
Mentz, Susanne / Technicial assistant
Paulenz, Lina / Team assistant
Paquet, Dominik, Prof. Dr. / PI
Klimmt, Julien / Ph.D. student

Key Publications

Kwart D*, **Paquet D***, Teo S, Tessier-Lavigne M. *Precise and efficient scarless genome editing in stem cells using CORRECT.* **Nat Protoc.** 2017 Feb;12(2):329-354. *equal first authors

Paquet D, ..., Tessier-Lavigne M. *Efficient introduction of specific homozygous and heterozygous mutations using CRISPR/Cas9.* **Nature.** 2016 May 5;533(7601):125-9.

Paquet D, Plucińska G, Misgeld T. *In vivo imaging of mitochondria in intact zebrafish larvae.* **Methods Enzymol.** 2014; 547:151-64.

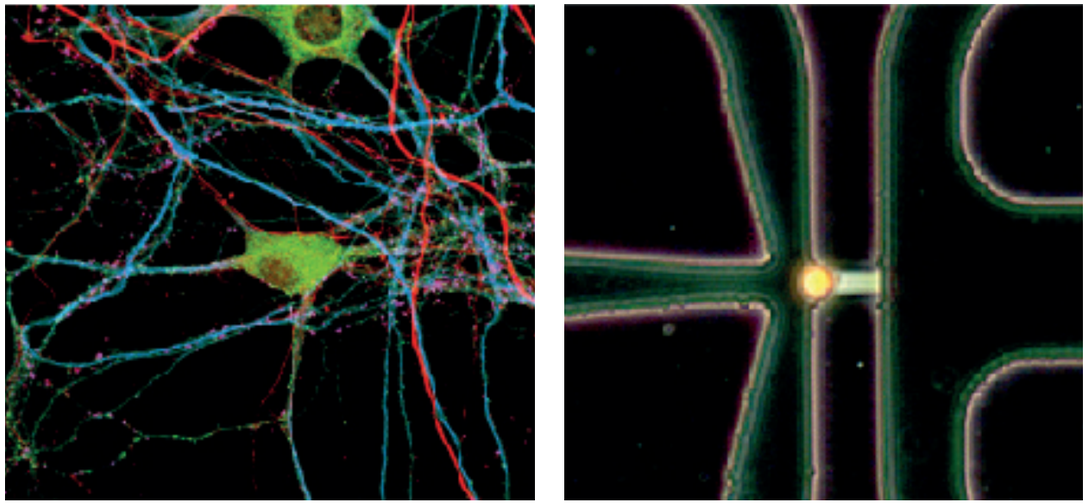
Plucińska G*, **Paquet D***, Hruscha A, Godinho L, Haass C, Schmid B, Misgeld T. *In vivo imaging of disease-related mitochondrial dynamics in a vertebrate model system.* **J Neurosci.** 2012 Nov 14;32(46):16203-12. *equal first authors

Paquet D, ... Haass C. *A zebrafish model of tauopathy allows in vivo imaging of neuronal cell death and drug evaluation.* **J Clin Invest.** 2009 May 5(119);1382-1395.

Systems Neuroscience

Research Group - PI: Özgun Gökçe

We use experimental and computational approaches to study the connectivity of the basal ganglia circuit to identify regulators of the vascular-glial-neuron triad connections during health and neurological disorders.



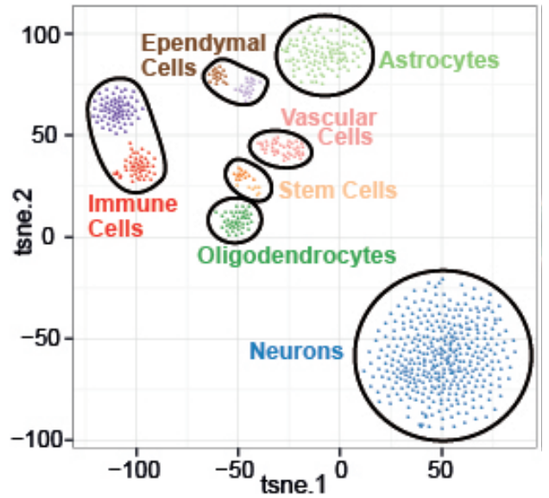
Neuronal cells and Microfluidic Single cell capture for RNA-sequencing

The neuronal network is a highly organized dynamic system that generates our thoughts, actions and feelings. Such a complex network requires a cell type-specific recognition code that identifies the right connections and alters them through experience.

Our laboratory seeks to understand how neuron-glia-vascular communications are regulated by cell type-specific adhesion molecules during both health and disease.

The importance of cell adhesions in brain function is highlighted by the fact that mutations in cell adhesion genes are associated with vascular, neurodegenerative and psychiatric disorders.

We use a combination of single cell transcriptomics, live imaging and molecular approaches to elucidate the cellular and molecular mechanisms regulating the interconnected vascular-glial-neuron triad.



Reconstruction of mouse brain from single cell transcriptomic data

Team:
Besson-Girard, Simon, M.Sc. / Ph.D. student
Bulut, Buket, BS / Master student
Gokce, Ozgun, Ph.D. / PI
Nguyen, Phuc, M.Sc. / Ph.D. student
Stangl, Edith, / Team assistant
Usifo, Fumere, M.Sc. / Technician

Key Publications

Gokce O, Stanley GM, Treutlein B, Neff NF, Camp JG, Malenka RC, Rothwell PE, Fuccillo MV, Südhof TC, Quake SR; *Cellular Taxonomy of the Mouse Striatum as Revealed by Single-Cell RNA-Seq*. **Cell Rep.** 2016 Jul 26;16(4):1126-37.

Fuccillo MV*, Földy C*, **Gokce O***, Rothwell PE, Sun GL, Malenka RC, Südhof TC. *Single-Cell mRNA Profiling Reveals Cell-Type-Specific Expression of Neurexin Isoforms.* **Neuron.** 2015 Jul 15;87(2):326-40 *Co-first author

Treutlein B*, **Gokce O***, Quake SR, Südhof TC. *Cartography of neurexin alternative splicing mapped by single-molecule long-read mRNA sequencing.* **Proc Natl Acad Sci U S A.** 2014 Apr 1;111(13):E1291-9. *Co-first author

Gokce O & Südhof T. C. *Membrane-Tethered Monomeric Neurexin LNS-Domain Triggers Synapse Formation,* **J Neurosci.** 2013 33(36), 14617–14628.

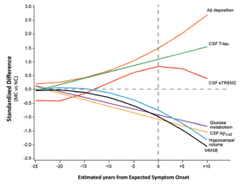
Gokce O, Runne H., Kuhn A. & Luthi-Carter R. 2009 *Short-term striatal gene expression responses to brain-derived neurotrophic factor are dependent on MEK and ERK activation* **PLoS ONE** 2009;4(4):e5292.

Research Highlights

12/2016

TRACING THE NEUROIMMUNE RESPONSE IN AD

The emergence of neuroinflammation in the pathological cascade of Alzheimer's disease is still unknown. The teams of C. Haass

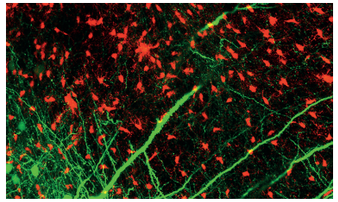


(DZNE) and M. Ewers (ISD) demonstrated dynamic changes in the novel biomarker of microglia activity, called TREM2, to be closely coupled to neurodegeneration occurring several years before symptom onset (...). *Suárez-Calvet M, ..., Ewers M, Haass C; ... Early changes in CSF sTREM2 in dominantly inherited Alzheimer's disease occur after amyloid deposition and neuronal injury. Sci Transl Med. 2016*

11/2016

INTERFERING WITH THE CHRONIC IMMUNE RESPONSE

Traumatic brain injury (TBI) frequently causes chronic complications including epilepsy and dementia. A new study by Ali Ertürk

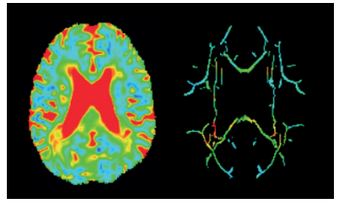


and colleagues shows that TBI causes a long-lasting brain immune response that parallels neurodeneration. Limiting the invasion of immune cells prevents neurodegeneration and improves motor function. *Ertürk A, Mentz S, S..., Sheng M. Interfering with the Chronic Immune Response Rescues Chronic Degeneration After Traumatic Brain Injury. J Neurosci. 2016*

10/2016

NEW BIOMARKER FOR SMALL VESSEL DISEASE

In a large, collaborative study, ISD researchers established and validated a novel imaging biomarker for cerebral small vessel disease. The

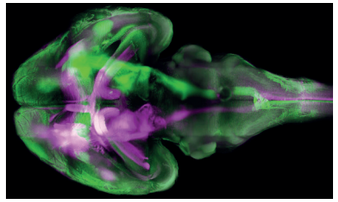


marker is based on skeletonization of white matter tracts and diffusion histograms. *Baykara E, Gesierich B, Adam R, ..., Duering M. A Novel Imaging Marker for Small Vessel Disease Based on Skeletonization of White Matter Tracts and Diffusion Histograms. Ann Neurol. 2016*

08/2016

SEEING THROUGH ENTIRE ORGANISMS

Ali Ertürk and colleagues have developed a major technology that allows making entire organs and organisms transparent. The new

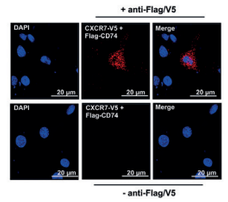


method provides the basis to map neuronal, glial, and vascular connections in the entire lab animals and potentially in deceased human brains. The work has been published in Nature Methods and highlighted by media worldwide including New York Times, Wall Street Journal, Business Insider and Science magazine: *Pan C, Cai R, Quacquarelli FP, Ghasemigharagoz A, Lourbopoulos A, Matryba P, Plesnila N, Dichgans M, Hellal F, Ertürk A. Sh. Nature Methods 2016*

07/2016

UNRAVELING MIF RECEPTOR MECHANISMS

In two biochemical studies, the Bernhagen unraveled novel receptor mechanisms for the chemokine-like inflammatory cytokine MIF that

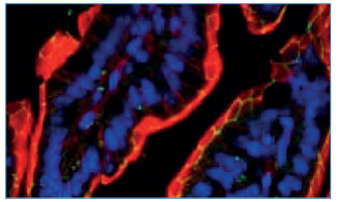


has a role in atherosclerosis and ischemic stroke. One study provided biochemical evidence that the chemokine scavenger receptor CXCR7 is a novel MIF receptor. Work focusing on the chemokine receptor CXCR4 that is pivotal in regulating leukocyte homing and atherogenesis, deciphered differential binding regions in CXCR4 that determine interaction of this receptor with the cognate ligand CXCL12 versus the alternative ligand MIF. This work is a basis to specifically target atherogenic MIF-CXCR4 engagement while sparing homeostatic CXCL12-CXCR4 interactions. *Alampour-Rajabi et al., FASEB J. 2015; Rajasekaran et al., JBC 2016*

07/2016

ROLE OF THE GUT MICROBIOME IN STROKE

A recent study by the team of Arthur Liesz reveals a bidirectional interaction between the brain and gut microbiome after experimental

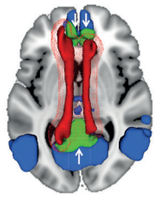


stroke. Post-stroke dysbiosis induces a neurotoxic immune response. The study was published in the Journal of Neuroscience and was featured by various media reports. *Singh V, Roth S, Llovera G, Sadler R, Garzetti D, Stecher B, Dichgans M, Liesz A. Microbiota Dysbiosis Controls the Neuroinflammatory Response after Stroke. J Neurosci. 2016*

06/2016

TRACT-SPECIFIC WMH AND NETWORK FUNCTION IN AD

A study by Michael Ewers and team published in Alzheimer's and Dementia shows that age-related white matter hyperintensities

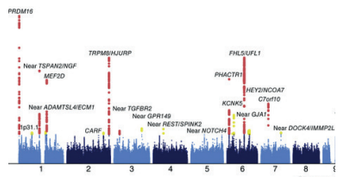


(WMH) in specific vulnerable WM tracts are associated with impaired network function in patients with Alzheimer's disease (AD). *Taylor AN, Kambeitz-Ilankovic L, Gesierich B, Simon-Vermot L, Franzmeier N, Araque Caballero MÁ, Müller S, Hesheng L, Ertl-Wagner B, Bürger K, Weiner MW, Dichgans M, Duering M, Ewers M. Tract-specific white matter hyperintensities disrupt neural network function in Alzheimer's disease. ; Alzheimer's Disease Neuroimaging Initiative (ADNI). Alzheimers Dement. 2016*

05/2016

ROLE OF VASCULAR FACTORS IN MIGRAINE

A Genome-wide association study with involvement of ISD investigators has identified 38 susceptibility loci for migraine including 28 novel

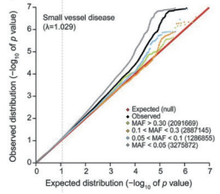


loci. The results lend further weight to a vascular etiology of migraine and emphasize genetic overlap with stroke. *Gormley P, ..., Malik R, Dichgans M... Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet. 2016*

04/2016

NOVEL RISK LOCI FOR LARGE AND SMALL VESSEL STROKE

In a series of genome-wide association studies (GWAS) ISD investigators in collaboration with other scientists from the international

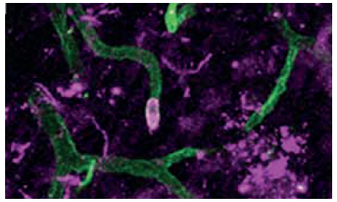


stroke genetics consortium (ISGC) recently identified several risk loci for ischemic stroke. The work is published in three papers in Lancet Neurology and Neurology. *(...) (CHARGE), (SiGN), (ISGC) Identification of additional risk loci for stroke and small vessel disease: a meta-analysis of genome-wide association studies, Lancet Neurol. 2016 / (SiGN), (ISGC) Loci associated with ischaemic stroke and its subtypes (SiGN): a genome-wide association study, Lancet Neurol. 2015 / Malik R et al. Low-frequency and common genetic variation in ischemic stroke: The META-STROKE collaboration. Neurology. 2016*

12/2015

ROLE OF PERICYTES IN CADASIL

A study by Ghosh and colleagues (Plesnila lab) published in the Annals of Neurology demonstrates that pericytes are critically involved

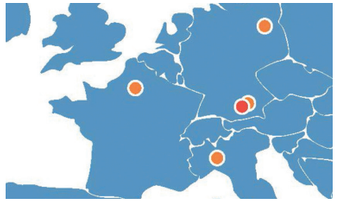


in the initiation of CADASIL, an inherited small vessel disease. Hence, protecting pericytes may represent a novel therapeutic strategy for this disorder. *Ghosh M, Balbi M, Hellal F, Dichgans M, Lindauer U, Plesnila N Pericytes are involved in the pathogenesis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Ann Neurol. 2015*

08/2015

THE FIRST PRECLINICAL RCT

An international team coordinated by Arthur Liesz completed the first preclinical RCT as a response to the replication crisis in translational re-



search. The study validated the efficacy of the anti-CD49d antibody in brain ischemia. The results were published in August 2015. *Science Translational Medicine. Llovera G, Hofmann K, Roth S, S..., Plesnila N, Vivien D, Liesz A. Results of a preclinical randomized controlled multicenter trial (pRCT): Anti-CD49d treatment for acute brain ischemia. Sci Transl Med. 2015*

05/2015

SHARED GENETIC BASIS FOR MIGRAINE AND STROKE

By analyzing genome-wide data from stroke and migraine consortia ISD investigators showed that common variants at a substantial

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number of genetic loci influence risk of both ischemic stroke and migraine, with strongest overlap between migraine without aura and both large artery stroke and cardioembolic stroke. *Malik R, Freilinger T, ... Dichgans M Shared genetic basis for migraine and ischemic stroke: A genome-wide analysis of common variants. Neurology. 2015*

Investigator Initiated Studies *(Selection)*

ISD investigators coordinate and run a number of investigator-initiated clinical studies and trials (IIT) including both interventional and observational studies (for additional information also see www.clinicaltrials.gov).

DEMDAS (The DZNE Mechanism of Dementia after After Stroke; NCT01334749)

Risk of dementia is high after stroke but the mechanisms of post stroke dementia (PSD) are insufficiently understood. Specifically, there are few data on how vascular and neurodegenerative mechanisms interact in determining cognitive decline after stroke. 600 patients with an acute stroke and without prior dementia will be followed for 5 years with assessments at baseline (< 120 h after onset of stroke), and at 3, 6, 12, 24, 36, 48, and 60 months. Baseline assessments include variables previously demonstrated to be associated with PSD as well as novel variables. Brain MRI (structural MRI and resting state fMRI) in combination with detailed neuropsychological testing and blood draws will be done at 6, 12, 36, and 60 months. Patients developing cognitive impairment (with or without dementia) and a subgroup of matched individuals without cognitive decline will be examined by brain FDG-PET and Amyloid-PET scanning. DEMDAS is a non-interventional study. However, it is designed to prepare for a future targeted trial. For one, DEMDAS will determine the mechanisms underlying secondary improvement and recovery of cognitive function after stroke as this might provide clues for the development of targeted therapeutic strategies. The respective analyses will cover aspects of structural and functional reorganization after stroke including secondary neurodegeneration. Second, DEMDAS will result in the identification of biomarkers (imaging, blood, CSF) for secondary neurodegeneration and cognitive decline after stroke (e.g. see Baykara et al. Ann Neurol. 2016). Third, DEMDAS will enable us to derive and validate a risk score for PSD and PSCIND for use in daily clinical practice.
From 2017 on two collaborative translational projects will be added to DEMDAS to establish a translational link between the clinical trial and basic research at DZNE Munich and Bonn. These projects will open a clear perspective towards the development of novel therapeutic strategies in vascular disease, secondary neurodegeneration and dementia.

The study was initially started as a monocentric study (DEDEMAS [Determinants of Dementia AfterStroke]) at ISD and subsequently extended as a multicenter study through funding from the DZNE (additional: sites Bonn, Berlin, Göttingen, Magdeburg, Munich-TUM).
Sample size DEDEMAS (ISD): 141
Planned sample size DEMDAS: 600
Started May 2013
Current enrollment: 367
(148 at ISD + 219 from additional study centres)
Estimated date for study completion: 2021
Coordinator: M. Dichgans
Project management: F. Wollenweber, K. Waegemann
Funding: Munich Cluster for Systems Neurology (SyNergy) & DZNE.

Publications:*
- *Wollenweber FA et al., Int J Stroke 2014*
- *Duering M et al., Neurology 2015*
- *Wollenweber FA, et al., Stroke 2016*
- *Dichgans M et al., Alzheimers Dement 2016*

PROSCIS (Prospective stroke cohort with incident stroke; NCT01364168)
The primary aim of this study is to derive and validate risk scores for vascular endpoints (recurrent stroke, myocardial infarction, and other complications of stroke) and death following an incident stroke. 850 patients with an incident stroke will be followed for 36 months with additional assessments at 3, 12, and 24 months.
Planned sample size: 850
Started February 2011
Current enrollment: 580
We estimate to complete the study in 2018
Principle investigators: M. Dichgans, V. Zietemann

Publications:*
Liman T et al., Int J Stroke 2013
Zietemann V et al., Eur Stroke J 2016

BM-3N (Prospective stroke cohort with 3-month follow-up)

The primary aim of this study is to characterize all patients with acute stroke admitted to a tertiary level stroke unit. Assessments are done at baseline and after 3 months. A focus is on the identification of factors associated with functional and cognitive outcome 3 months post-stroke. Patients excluded from PROSCIS or DEMDAS or patients who refused to participate in these long-term studies are included.
Planned sample size: 3000
Started February 2011
Current enrollment: 780 patients
Principle investigators: M. Dichgans, V. Zietemann

Publications:*
- *Wollenweber FA et al. Stroke 2013*

CAPIAS (Carotid Plaque Imaging in Acute Stroke NCT01284933)

Even with extensive diagnostic workup the underlying etiology remains unidentified in about 25% of patients with acute ischemic stroke or transient ischemic attack (TIA). Current stroke classification schemes consider atherosclerotic lesions only as causative if associated with substantial luminal narrowing. However, the degree of luminal stenosis is an insufficient measure of plaque vulnerability. The aim of CAPIAS is to determine the frequency, characteristics, and consequences of complicated AHA lesion type VI carotid artery plaques in patients with cryptogenic stroke. For plaque characterization all patients undergo high resolution black-blood carotid MRI at 3.0-Tesla (hr-bb-MRI). The hypotheses driving this study are that i) a substantial proportion of cryptogenic strokes in the anterior circulation are caused by AHA-LT VI plaques; ii) these patients are at high risk of developing a recurrent stroke, TIA, or clinically silent lesion detectable by brain MRI; and iii) AHA-LT VI plaques are associated with specific infarct patterns. Furthermore we will search for biomarkers associated with AHA-LT VI plaques. CAPIAS will provide valuable insights into

stroke mechanisms, may have important implications for diagnostic decision making, and provide the basis for the planning of targeted interventional studies. The study was started in 2011 and subsequently extended as a multicenter study with additional sites in Munich (Technical University), Freiburg and Tübingen.
Planned sample size: 300
Started February 2011
Current enrollment: 130
Principle investigator: M. Dichgans, T. Saam
Project management: A. Kopczak

Publications:*
Bayer-Karpinska A et al., BMC Neurol. 2013
Schwarz F et al., .Neurology. 2013
Grimm JM et al., J Cardiovasc Magn Reson. 2014
Hyafil F et al., Eur J Nucl Med Mol Imaging. 2016
Bayer-Karpinska A et al., Neuroimaging Clin N Am. 2016
Saam T et al., J Cardiovasc Magn Reson. 2016,

SuSPect-CAA (Superficial Siderosis in Patients with suspected Cerebral Amyloid Angiopathy NCT01856699)

Non-traumatic cortical superficial siderosis (cSS) is a common finding in patients with cerebral amyloid angiopathy (CAA) and can be its sole imaging sign. The clinical features and course as well as the prognostic significance of cSS in CAA patients remain unclear. In a retrospective study we previously showed that cSS may be an important predictor for future intracranial hemorrhage. However, prospective data are missing. The SuSPect-CAA study is designed as a prospective observational multi-center cohort study. Primary objective of the study is to evaluate if cSS is a predictor for future stroke and mortality (primary endpoint: combined rate of stroke and death after 36 months). Secondary objectives of the study include 1) to evaluate if cSS represents a marker of future intracranial hemorrhage, especially at the site of initial siderosis, 2) to describe the clinical presentation and course of cSS, 3) to assess associated imaging findings, 4) to determine the differential diagnoses of cSS. All subjects presenting to the study center (out- or inpatient treatment with neuroimaging) will be screened. The study population consists of two patient groups: Study group: Patients meeting the modified Boston criteria for probable or possible CAA. Patients meeting the classical Boston criteria for possi≠ble or probable CAA but without any cSS were assigned to the control group. Enrollment was finished in December 2015 after inclusion of of 271 patients. Follow-up assessment at 6, 12, 24, and 36 months are currently performed by visits in the respective neurological outpatient clinic including a structured interview and neurological exam, neuropsychological tests, EEG and MRI. First results from the analyses of baseline data is expected for 2017.
Planned sample size: 200
Started May 2013
Last patient in December 2015 (Enrollment: 271)
Principle investigator: FA Wollenweber

Publications:*
Linn J et al., J Neurol. 2013

VASCAMY (Interaction between Vascular and Amyloid Brain Pathology in Alzheimer's Disease)

In Alzheimer's disease (AD), cerebrovascular disease frequently co-occurs with ß-amyloid (Aß). However, the specific roles of Aß and vascular pathologies in the development of neurodegeneration early in the course of AD are poorly understood. The overall aim of this study is to disentangle the specific contribution of Aß pathology and cerebrovascular disease to neuronal network impairment and cognitive decline in the early stage of AD. To this end, we have set up a prospective 5-year longitudinal neuroimaging study, which will include 80 non-demented subjects with mild cognitive impairment (MCI) of episodic memory or executive function and 60 elderly cognitively healthy subjects (HC). The deposition of Aß (as measured by amyloid PET) and ischemic brain damage (as measured by MRI and DTI) will be tested as predictors of neuronal network changes (DTI, fMRI) and cognitive decline during annual follow-up. In addition, we will include 50 subjects with CADASIL, an inherited small vessel disease and model for pure vascular cognitive impairment, to study the same parameters in patients with pure vascular disease. We expect that the results of this study will allow determining the specific impact of brain Aß and cerebrovascular pathology on neuronal network dysfunction and cognitive decline.
Planned sample size: 190
Started: July 2013
Current enrollment: 191 (VASCAMY & CADASIL)
Principle investigators: M. Ewers, M. Düring, K. Bürger

Publications:*
Taylor AN et al., Alzheimers Dement. 2013

DEEARLY-AD (The DZNE Early Onset Alzheimer's Disease Study)

Early-onset Alzheimer's disease (EOAD) accounts for 1-6% of AD cases and is highly genetically determined but only a minority of cases is autosomal-dominantly inherited. The amyloid-hypothesis is thought to be valid for early- and late onset AD (EOAD and LOAD). There is evidence, however, that production and degradation of beta-amyloid are differentially affected. The study will examine potential differences in beta-amyloid metabolism between EOAD and LOAD. Age-matched healthy individuals will serve as controls. Primary objective: To compare markers of beta-amyloid production and degradation in blood and cerebrospinal fluid between EOAD and LOAD. Secondary objectives: (1) To compare disease expression in EOAD compared to LOAD using neuropsychological and neurological examinations, and MRI. (2) To examine whether markers of beta-amyloid metabolism correlate to clinical disease expression. Recruitment goal: 75 EOAD and 75 LOAD patients as well as 50 control subjects within two years. The study is implemented in the DZNE's Clinical Register.
Started: July 2013
Current enrollment: 42
Principle investigator: K. Bürger

DELCODE (Longitudinal Cognitive Impairment and Dementia Study)

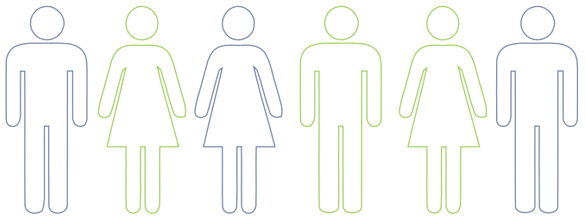
DELCODE capitalizes on the preclinical stage of AD with the aim to characterize the neuronal networks mechanisms of cognitive adaptation and decompensation. The focus of DELCODE is on episodic memory and working memory as potential indicators of preclinical AD. Effects on neuronal networks (e.g. topology, connections strength, consistencies) will be analyzed cross-sectionally and longitudinally and will be used as predictors for cognitive decline. DELCODE will also aim at the refined description of earliest cognitive alterations with neuropsychological tasks beyond the standard assessments. These will be also assessed longitudinally. Markers of disease pathology (amyloid and brain volume loss) as well as genetic and non-genetic risk factors and indicators of cognitive reserve will serve as independent variables, and their effect on neuronal network alterations in the presence of disease will be

assessed.
Planned sample size: 1000
Started: February 2014
Current enrollment: 100
Principle investigator: K. Bürger

eMIRgency (microRNAs in the acute stroke setting)

Recent work suggests a potential role of microRNAs as diagnostic and prognostic markers in cardiovascular disease. microRNAs are small non-coding RNAs that regulate protein expression intracellularly, but can also be released from lesion sites and circulate in the peripheral blood. The overall goal of this case-control study is to identify differences in microRNA patterns of acute stroke patients compared to healthy controls. Patients presenting within 24 hours of symptom onset are included and subjected to sequential blood draws during hospitalization. To characterize circulating microRNAs RNA will be isolated from cell-free plasma. Individual microRNA profiles will be characterized using state of the art technology such as RNA sequencing and qPCR. To control for potential confounders past medical history, medication, neuroimaging and clinical laboratory parameter are recorded. In addition to their potential diagnostic and prognostic value, functional analyses of stroke-relevant microRNAs will provide insights into stroke mechanisms.
Planned sample size: 150 patients and 150 controls
Started: February 2014
Current enrollment: 401
Principle investigator: M. Dichgans
Project management: S. Tiedt, M. Prestel

** for full list of publications see page 74.*



RESPECT-ESUS
Randomized, Double-blind, Evaluation in Secondary Stroke Prevention Comparing the EfficaCy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate (110 mg or 150 mg, Oral b.i.d.) Versus Acetylsalicylic Acid (100 mg Oral q.d.) in Patients With Embolic Stroke of Undetermined Source.
Local principle investigator: L. Kellert, F. Wollenweber
Status: started July 2016, recruiting

DESCRIBE
DZNE-Clinical Registry Study of Neurodegenerative Disorders.
Local principle investigator: M. Dichgans
Status: recruiting

SPACE 2 (BMT, CEA, CST ACI-Stenosis)
Stent-protected Angioplasty of asymptomatic Carotid stenosis vs. Endarterectomy.
Local principle investigator: M. Dichgans
Status: stopped recruitment.

EMERGE
A Phase III Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects with Early Alzheimer's Disease
Local principle investigator: K. Bürger
Status: recruiting

SIMaMCI
Randomized Controlled Trial of Simvastatin in Amnestic MCI Patients.
Local principle investigator: K. Bürger
Status: started July 2011, recruiting

Zoom@SVDs
Zooming in at microvascular malfunction in Small Vessel Diseases with 7T MRI.
Study sites: Utrecht, Munich
Local Principle Investigator: M. Dichgans
Status: will start recruitment in 2017

INVESTIGATE-SVDs
Imaging NeuroVascular, Endothelial and STructural InteGrity in prepAration to TrEat Small Vessel Diseases
Study sites: Edinburgh, Maastricht, Munich.
Local Principle Investigator: M. Dichgans
Status: will start recruitment in 2017

TREAT-SVDs
EffecTs of Amlodipine and other Blood PREssure Lowering Agents on Microvascular FuncTion in Small Vessel Diseases.
Study drugs: amlodipine, losartan, atenolol
Study sites: Munich, Oxford, Edinburgh, Maastricht, Utrecht.
Coordinating Investigator: M. Dichgans
Status: will start recruitment in 2017

Multicenter Trials *(Participation / Selection)*

Project Funding *(Selection)*

Munich Cluster for Systems Neurology (SyNergy) funded by the DFG Excellence initiative promotes integrative research on major neurological diseases (neurovascular, neurodegenerative, neurinflammatory), with the aim to improve pathomechanistic understanding and eventually therapeutic options. The central focus is to foster intense collaboration across the traditional boundaries of neurodegenerative, -inflammatory and –vascular diseases. SyNergy research projects are organized into 3 **Research Areas,** each targeted at one specific pathomechanistic "nexus". **Core-Projects** bundle systems neurology-specific expertise to make it accessible to all SyNergy projects. **Tandem Projects** are highly collaborative research projects. The projects combine expertise across traditional pathomechanisms, as well as systems biology and systems neuroscience tools. Many projects involve both basic scientists and academic clinicians.

ISD investigators participate in the following Projects:

Tandem Projects:
B 1: Contribution of pericytes in vascular insufficiency in CADASIL (PI: N. Plesnila)
B 3: Transcriptional regulation of HDAC9 (PI: M. Dichgans)
B 6: Role of the stroke-relevant HDAC9 gene in the cellular proteome & acetylome (PI: M. Dichgans)
B 9: Long non-coding RNAs involved in loss of dendritic spines and synapses (PI: A. Ertürk)
B 10: Degeneration and plasticity of connected areas after white matter ischemia (Tandem project Plesnila/ Dichgans)

Core-Projects:
Core 6: Development of novel methodology for the joint analysis of -omics data (PI: M. Dichgans)
Core 9: Non-apoptotic caspase activity in synapse loss and neuronal differentiation (PI: A. Ertürk)
Core-13: Detection of a Pro-2-oxidized variant of the chemokine MIF in vascular disease (PI: J. Bernhagen)

Clinician Scientist Group (PI: A. Liesz)
Clinician Scientist Program (PI: S. Tiedt)
Clinical Studies Hub (PI: M. Dichgans)

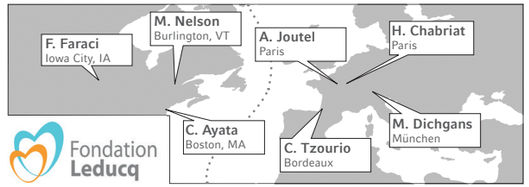
PI-Grundförderung im SyNergy-Cluster M. Dichgans
PI-Grundförderung im SyNergy-Cluster M. Plesnila

Funding of **W3-Professor for "Vascular Biology"**
J. Bernhagen
Funding of W2-Professor for "Neurobiology"
D. Paquet

SyNergy Board: M. Dichgans

For more information see www.synergy-munich.de

CVgenes@target (Exploitation of genomic variants affecting coronary artery disease and stroke risk for therapeutic intervention, funded by EU FP7)
Atherosclerosis and its most disabling sequelae, stroke and coronary artery disease (CAD), are leading causes of death in Europe. Until now, preventive and therapeutic interventions for these diseases aim at ameliorating the effects of established cardiovascular risk factors. More recently, results of genome-wide association (GWA) studies added to our perception of mechanisms leading to atherosclerosis. Collectively, over 50 genetic loci with a role in CAD and stroke have been identified. Some genes at these loci work through known risk factors such as lipids and, in fact, are already established or evolving treatment targets. However, this is not true for the majority of risk variants, which implies that key pathways leading to atherosclerosis are yet to be exploited for therapeutic intervention. The EU network CVgenes@target utilizes genomic variants affecting atherosclerosis risk for identification of both underlying genes and affected pathways in order to identify, characterize, and validate novel therapeutically relevant targets for prevention and treatment of CAD and stroke. Three interconnected programmes pave the way from discovery of CAD/stroke risk loci to therapeutically modifiable targets. Martin Dichgans is a leader of Work Package 4 on "In vivo/ex vivo studies for target validation, and compound characterization" *(Azghandi et al. Stroke 2015)* and contributes to Work package 3 on characterization of candidate genes and risk variants and Work Package 5 on assay development.
For more information see http://cvgenesattarget.eu/



The mission of Fondation Leducq is to improve human health through international efforts to combat cardiovascular and neurovascular disease. Each network is built around a transatlantic research alliance involving investigators from Europe and North America.

The ISD participates in a network: **Pathogenesis of Small vessel Disease of the Brain.** Small vessel diseases (SVD) account for 25% to 30% of ischemic strokes and are a leading cause of cognitive decline and disability worldwide. Very little is known about the underlying causes of SVDs. The central idea behind the project is that devastating monogenic forms of adult-onset SVD-CADASIL (missense mutations in NOTCH3) and CARASIL (loss-of-function mutations of HTRA1) - are invaluable paradigms for understanding the pathogenesis of SVD. The Network has three highly interconnected objectives that collectively seek to identify the fundamental mechanisms of CADASIL and CARASIL at molecular, biochemical, cellular, neurovascular-unit and whole-brain levels, and assess the contribution of these disease pathways to common SVD.
Martin Dichgans contributes to Aim 1 "To identify the network of genes/gene products that drive small vessel pathology in CADASIL and CARASIL" particularly in the mechanistic link between HTRA1 mutations and the TGF-ß pathway (Beaufort et al., PNAS, 2014) and in common disease pathways between CADASIL and CARASIL *(Kast et al, Acta Neuropathol Commun. 2014).*

For more information see *http://fondationleducq.org*

CRC 1123: Atherosclerosis - Mechanisms and Networks of Novel Therapeutic Targets

Vascular disease including coronary artery disease (CAD) and stroke remains the leading cause of death and morbidity worldwide. The underlying factor common to most of these conditions is atherosclerosis. In order to develop more effective strategies for the prevention and treatment of arterial disease, a better understanding of the pathogenesis and progression of atherosclerosis is crucial. It is the mission of the CRC 1123 to improve the in-depth understanding of molecular networks in atherogenesis, atheroprogression and atherothrombosis as the pathological sequence of CAD, leading to the identification of worthwhile targets for treating atherosclerosis.

ISD participates with two projects in this CRC.

Mechanisms of atherogenic recruitment by MIF family proteins and peptide-based therapeutic leads (A 03; PI: Jürgen Bernhagen): The chemokine-like inflammatory mediator MIF plays a critical role in the development of atherosclerosis. In this project, we aim to elucidate the binding determinants between MIF and its homolog MIF-2 and CXC chemokine receptors as a prerequisite for novel intervention strategies in cardiovascular disease. Structurally stabilized MIF-derived peptides will be devised both as molecular tools to scrutinize the mechanism(s) and as potential anti-MIF agents. The role of MIF-2 and its relationship with MIF in cardiovascular disease will be elucidated. Lastly, peptide-based CXCR-ectodomain mimics will be devised as a potential novel class of MIF/chemokine blockers.

Role of HDAC9 in Atherosclerosis (B 03; PI: Martin Dichgans): The HDAC9 gene region on 7p21.1 was identified as a major risk locus for carotid atherosclerosis and stroke. HDAC9 has previously been shown to control the maturation and function of FOXP3+ regulatory T (Treg) cells, which in turn have atheroprotective function. The inhibitory effect of HDAC9 on Treg cells renders these cells a promising candidate for targeted analyses. The main aims of the current project therefore are (1) to study the effects of HDAC9 deficiency on atherogenesis and atherothrombosis in mouse models, (2) to examine allele-specific effects on Treg cell function in humans, and (3) to determine allele-specific effects on plaque characteristics and HDAC9 expression in human atherosclerotic plaques. *(Haffner et al., J Cereb Blood Flow Metab 2016)*
For further information see
http://www.sfb1123.med.uni-muenchen.de/index.html

SVDS @target

Small vessel diseases in a mechanistic perspective: Targets for Intervention – Affected pathways and mechanistic exploitation for prevention of stroke and dementia.

Stroke and dementia rank among the most pressing health issues in Europe. Diseases in small blood vessels, known as cerebral small vessel diseases (SVDs) have emerged as a central link between these two major comorbidities. SVDs account for more than 30% of strokes and at least 40% of dementia cases. They encounter multiple distinct diseases that can be separated based on their underlying genetic defects, risk factors, and clinical presentations. Despite this profound impact on human health, there are no treatments with proven efficacy against SVDs.

The consortium which consists of 12 partners from 7 countries is coordinated by Martin Dichgans. It brings together basic scientists and academic clinicians and will make use of novel animal models, state-of-the art technologies (e.g. proteomics & ultra-high field MRI) and expertly phenotyped patient cohorts to identify key mechanisms common to multiple SVDs and determine how these mechanisms contribute to individual SVDs.

The five-year project which is funded with 6 Mio EUR through the European Union's Horizon 2020 program is organized around the **four major risk factors** and mechanisms that have recently emerged and for which evidence supports a role in SVDs:

Blood pressure variability **(WP1)**, Blood Brain Barrier **(WP2)**, Microvascular matrisome **(WP3)** and Inflammation **(WP4)**. New mechanisms will be validated in animal models and in humans **(WP5)**.

All work packages are led by a pre-clinical and a clinical investigator who collaborate on a specific problem. Hence, there will be rapid and efficient transfer of new knowledge from laboratory to bedside and back.

A major strength of the project is the access to large, thoroughly phenotyped cohorts of patients. In addition, the project includes three own sub-studies:

ZOOM@SVDs, a MRI study at ultra-high resolution (7T) to assess microvascular function and parenchymal damage.

INVESTIGATE-SVDs, a MRI study at 3T to assess blood brain barrier function, microvascular function, and perivascular flow.

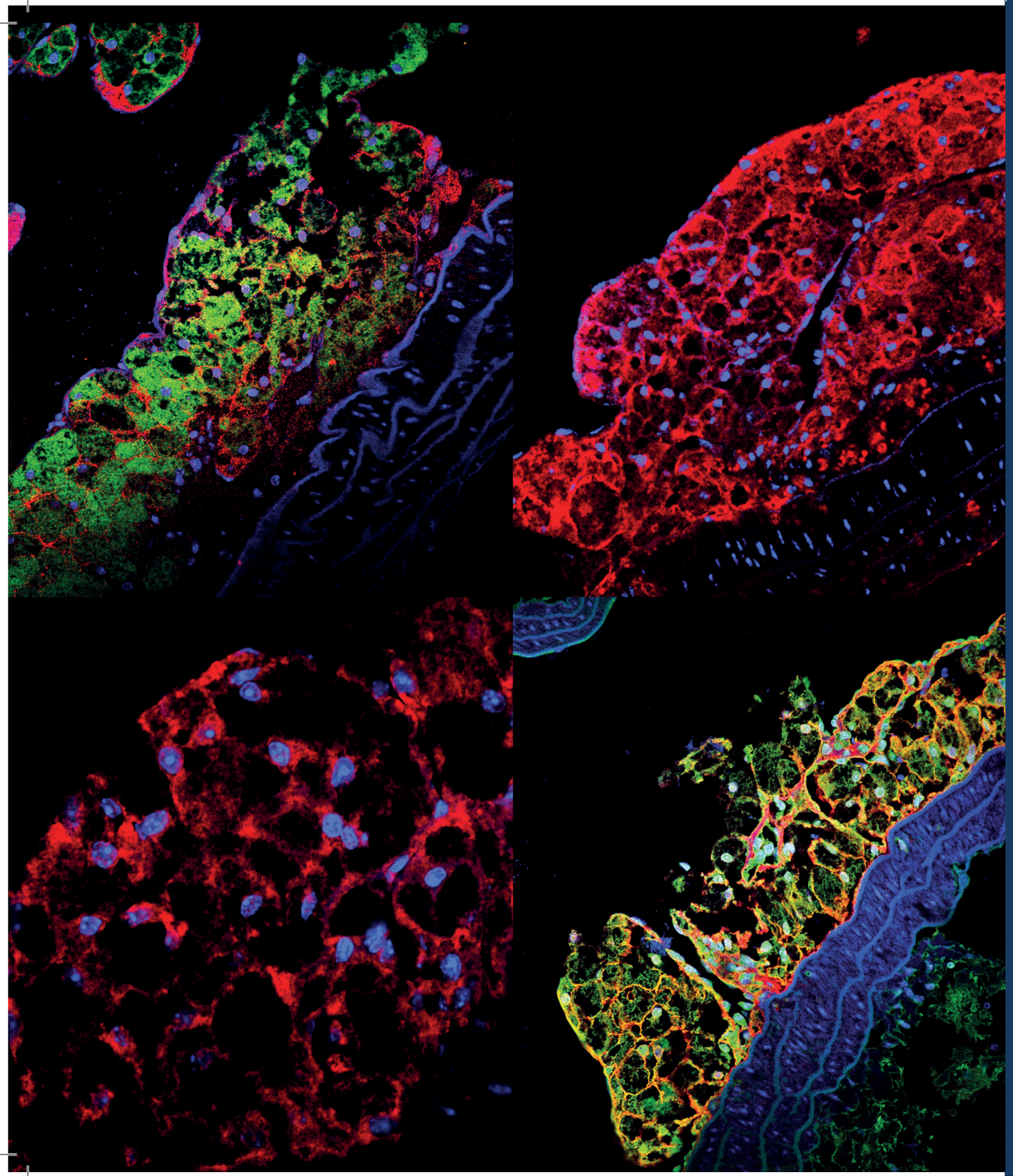
TREAT-SVDs, an interventional study to determine the effects of different blood pressure lowering agents on microvascular function in patients with distinct SVDs

Coordinator: M. Dichgans
For more information see http://www.svds-at-target.eu/

CoSTREAM

Common mechanisms and pathways in Stroke and Alzheimer's disease.

Stroke and Alzheimer's disease are major diseases imposing a huge burden on aging societies. It has long been recognized that stroke and Alzheimer's disease often co-occur, and it has been speculated that the two disorders have an overlapping pathogenesis. The Horizon 2020 project CoSTREAM aims to identify these common mechanisms and pathways in stroke and Alzheimer's disease by combining clinical, genetic, epidemiologic, metabolic and radiologic research to develop an organ-on-a-chip in vitro model for the blood-brain connection. The project builds upon large data sets on both diseases, with follow-up studies performed up to 25 years. In the end, CoSTREAM will lead to increased knowledge about shared pathways, and can lead to new therapeutic approaches. CoSTREAM is a 5-year research program that consists of three phases: aetiology, pathways, and translation. Together these form the basis for seven interrelated Work Packages. An essential feature is joint work across Work Packages that will thereby ensure smooth transition across the three phases. Martin Dichgans leads Work Package 1 on Genetics which aims to determine the genetic overlap between stroke and Alzheimer's disease as well as their subtypes and provide an estimate of the genetic correlation between the two. Furthermore, this Work Package will pinpoint specific genes or genomic regions that mediate risk to stroke or stroke subtypes, relevant MRI markers and Alzheimer's disease. Furthermore ISD contributes to Work Package 2 on Metabolomics, Work Package 3 on Brain Imaging and Work Package 6 on Therapeutics. PI: M. Dichgans
For more information see http://www.costream.eu/



Numbers & Facts

Project	*Funding Institution*	*Role*	*Period*	*Budget*
SyNergy **Munich Cluster for Systems Neurology** *Period I: Jan 2013 to Jun 2015* *Period II: Jul 2015 to Oct 2017* *Overall local budget (ISD): 3,465,000 €*	DFG (German Research Foundation)	Coordinator Research Area B: M. Dichgans Principle Investigator, Tandem Projects B3, B6, B5 and Core 6: M. Dichgans	Period I + II (Period I: Jan 2013 to Jun 2015 Period II: Jul 2015 to Oct 2017)	550,000 €
		Principle Investigator, Tandem Projects B1, B10: N. Plesnila	Period I + II	405,000 €
		Associate Investigator,Tandem Project B9 and Core 9: A. Ertürk	Period I + II	85,000 €
		W3-Professor for "Vascular Biology", Core 13: J. Bernhagen	Period II	55,000 €
		Clinical Studies Hub: M. Dichgans	Period I + II	377,000 €
		Clinician Scientist Group: A. Liesz	Period I + II	783,000 €
		Clinical Scientist Program: S. Tiedt	Period II	60,000 €
		SyNergy Professor: J. Bernhagen		300,000 €
		SyNergy Professor: D. Paquet		850,000 €
Emmy-Noether Research Award on „Brain-released alarmins as mediators of immunological comorbidities after stroke"	DFG German Research Foundation	Principle Investigator: A. Liesz	Jan 2016 to Jan 2021	1,260,000 €
Supporting funds for 3T MRI	DFG German Research Foundation	Principal Investigator: M. Dichgans	-	1,175,000 €
SVDs@target – Small vessel diseases in a mechanistic perspective: Targets for Intervention – Affected pathways and mechanistic exploitation for prevention of stroke and dementia.	EU/Horizon 2020	Coordinator: M. Dichgans	Jan 2016 to Dec 2020	Overall budget: 5,998,300 € Local budget: 975,167 €
DEMDAS – DZNE Mechanisms of Dementia after Stroke.	DZNE	Coordinator and Principal Investigator: M. Dichgans	Period I: Jan 2013 to Dec 2016 Period II: Jan 2017 to Dec 2021	Overall budget: 1,333,283 € Local budget: 846,889 € (Period I)

Third Party Funding

Project	*Funding Institution*	*Role*	*Period*	*Budget*
SFB 1123 Atherosclerosis – Mechanisms and networks of novel therapeutic targets	DFG German Research Foundation	**Role of HDAC9 in Atherosclerosis.** Principal Investigators: M. Dichgans, C. Haffner	Jul 2014 to Jun 2018	364,100 €
		Mechanisms of atherogenic recruitment by MIF family proteins and peptide-based therapeutic leads. Principal Investigators: J. Bernhagen, A. Kapurniotu (TUM)	Jul 2014 to Jun 2018	443,000 € Overall local budget ISD: 807,100 €
Genome-wide search for Quantitative Trait Loci for radiographic white matter hyperintensities in CADASIL	Corona-Foundation	Principal Investigator: M. Dichgans	Jan 2011 to Dec 2016	600,000 €
Fondation Leducq – Transatlantic Network of Excellence in Cardiovascular and Neurovascular Research	Fondation Leducq	Principal Investigator: M. Dichgans	Aug 2012 to Jul 2017	590,150 €
CVgenes-at-target – Exploitation of genomic variants affecting coronary artery disease and stroke risk for therapeutic tervention.	EU / FP7	Principal Investigator: M. Dichgans	Oct 2013 to Sep 2016	547,000 €
CoSTREAM – Common mechanisms and pathways in Stroke and Alzheimer's disease.	EU/Horizon 2020	Principal Investigator: M. Dichgans	Oct 2013 to Sep 2016	510,000 €
MESCOG – Mechanism of Small Vessel Related Brain Damage and Cognitive Impairment, Integrating Imaging findings from Genetic and Sporadic Disease (01 EW1207)	EU	FP6	ERA-NET NEURON	Coordinator/Principal Investigator: M. Dichgans	Mar 2012 to Dez 2015	Overall budget: 813,000 € Local budget: 487,484 €
Molekulare Charakterisierung der anti-fibrotischen Effekte von MIF in der Leberfibrose | **SFB-TRR57 „Mechanismen der Organfibrose"**	DFG German Research Foundation	Principal Investigators: J. Bernhagen, M. Berres (RWTH Aachen University)	Jan 2013 to Dec 2016	386,000 €
e:AtheroSysMed – Systems medicine of myocardial infarction and stroke.	BMBF	Principal Investigator: M. Dichgans	Dec 2013 to Nov 2016	Local budget: 290,151 €

Third party funds (spent) Source	Number of projects 2015	Funds spent 2015	Number of projects 2016	Funds spent 2016
DFG	15	939,936 €	23	1,251,776 €
BMBF, EU	9	430,689 €	12	584,164 €
Foundations (Fondation Leducq, Corona Stiftung…)	8	269,999 €	6	249,398 €
External third party funding spent		1,640,624 €		2,085,338 €
Others	11	332,759 €	12	960,767 €
Vascular Dementia Research Foundation*	1	4,636,700 €	1	3,866,073 €
Amount of further third party funding		4,969,459 €		4,826,840 €
Total third party funding spent		6,610,083 €		6,912,178 €

** (without outpatient clinic), also see p. 67*

Project	*Funding Institution*	*Role*	*Period*	*Budget*
Die Rolle von MIF innerhalb der kardialen ischämischen Präkonditionierung	DFG German Research Foundation	Principal Investigators: C. Stoppe (RWTH Aachen University), J. Bernhagen	Jan 2013 to Dec 2016	381,000 €
Neuroinflammatory mechanisms of chronic neurodegeneration and cognitive decline following traumatic brain injury	ERA-Net Neuron	Principal Investigators: A. Ertürk, N. Plesnila	Apr 2015 to Mar 2018	Overall budget: 1,203,143 € Local budget: 299,880 €
Macrophage migration inhibitory factor in renal fibrosis: a novel endogenous anti-fibrotic factor?	Else-Kröner-Fresenius-Stiftung (EKFS)	Principal Investigators: P. Boor (RWTH Aachen University), J. Bernhagen	Jan 2013 to Dec 2015	298,000 €
Protektion vor kardiovaskulären Veränderungen im Alter durch S-Nitrosierung des Zytokins macrophage migration inhibitory factor	Else-Kröner-Fresenius-Stiftung (EKFS)	T. Rassaf (Essen University Hospital), J. Bernhagen	Jan 2016 to Dec 2018	291,000 €
Molecular mechanisms of recessive and dominant mutations in the small vessel disease-related high temperature requirement protease HTRA1	DFG German Research Foundation	Principal Investigator: M. Dichgans	Jan 2017 to Dec 2019	251,350 €
		Principal Investigator: N. Beaufort		16,000 € Overall budget (ISD): 267,350 €
Structural and functional connectivity in cerebral small vessel disease	DFG German Research Foundation	Principal Investigator: M. Düring	Jan 2017 to Dec 2019	Overall budget: 470,006 €, local budget: 262,400 €
Bedeutung von Perizyten für die Störung der zerebralen Mikrozirkulation nach Subarachnoidalblutung	Else-Kröner-Fresenius-Stiftung (EKFS)	Principal Investigator: N. Plesnila	Mar 2014 to Feb 2017	244,000 €
Support fund for confocal microscope	DFG German Research Foundation	Principal Investigator: A. Ertürk	-	200,000 €
Leukocyte-Interaction with immunological brain barriers	DFG German Research Foundation	Principal Investigator: A. Liesz	Oct 2014 to Sep 2017	197,000 €
Assessing neurodegeneration throughout the entire brain at a single cell resolution in mice	DFG German Research Foundation	Principal Investigator: A. Ertürk	Feb 2017 to Jan 2020	192,000 €
StemForStroke – Secretome analysis of intrahecally applied bone marrow stromal cells in experimental stroke	EU	Principal Investigator: N. Plesnila	Mar 2014 to Feb 2016	169,000 €
Usage of tissue clearing technology to investigate brain regions that are involved in diabetics	Member of Helmholtz Alliance ICEMED	Principal Investigator: A.Ertürk	Nov 2016 to Oct 2018	120,000 €
Gaze behaviour during real spatial navigation | DSGZ Start-up Project	German Center for Vertigo and Balance Disorders (DSGZ)	Principal investigator: F. Schöberl, A. Zwergal, K. Bürger	Nov 2014 to Apr 2016	110,394 €

Project	*Funding Institution*	*Role*	*Period*	*Budget*
MicroFlow – Molecular mechanisms of microvascular dysfunction following hemorrhagic stroke	EU/FP7	Principal investigator: N. Plesnila	Jul 2012 to Jul 2016	100,000 €
VASCAMY – Interaction beween vascular and amyloid brain pathology in Alzheimer's disease	EU/Marie Curie	Principal investigator: M. Ewers	Jun 2013 to Jun 2017	100,000 €
Strukturelle und funktionelle Konnektivität als Biomarker der vaskulären kognitiven Störung	Else Kröner-Fresenius-Stiftung	Principal Investigator: M. Düring	Feb 2015 to Jan 2017	93,500 €
H4H2 – Homoarginine for Heart and Health	Junior Researcher Fund for D. Atzler	Principal Investigator: D. Atzler, J. Bernhagen	Jun 2016 to Dec 2016	78,000 €
HDAC9-mediated mechanismus underlying vascular inflammation.	Medical Faculty, FöFoLe	Principal Investigator: Y. Asare	Dec 2015 to May 2017	54,947 €
Characterization of neurodegeneration in the entire brain after TBI using novel 3D imaging approach.	Medical Faculty, FöFoLe	Principal Investigator: A. Ertürk	Sep 2016 to Mar 2018	54,262 €
Mechanismen der Leukozyten-Endothel Interaktion	Medical Faculty, FöFoLe	Principal Investigator: A. Liesz	Jan 2014 to Jan 2015	52,000 €
Alarmin-mediated sterila inflammation	LMU, LMUexcellent initiative	Principal Investigator: A. Liesz	Mar 2015 to Feb 2016	50,000 €
The gut microbiota in post-stroke neuronal plasticity	LMU, LMUexcellent initiative	Principal Investigator: A. Liesz	Mar 2016 to Feb 2017	50,000 €
Disentangling brain damage due to Alzheimer's and vasc. disease using DTI	Alzheimer Forschg. Initiative e.V.	Principal Investigator: M. Düring	Nov 2016 to Oct 2018	Overall budget: 100,000 €, local budget: 50,000 €
Stressvermittelte Immunschwäche nach Schlaganfall	Daimler und Benz Stiftung	Principal Investigators: A. Liesz	Feb 2014 to Jan 2015	28,000 €
The DZNE Early Onset Alzheimer's Disease Study – DEEARLY (additional funding for neurochemical analyses)	Dr. Helmut Legerlotz-Stiftung	Principal investigator: K. Bürger, D. Edbauer	Jan 2015 to Dec 2015	12,000 €

Third party funds (spent) | Courtesy of Vascular Dementia Research Foundation*	2015	2016
personnel costs	2,696,734 €	2,774,661 €
material costs	666,130 €	749,458 €
travel expenses	44,442 €	51,378 €
investments	1,229,395 €	290,575 €
total	4,636,700 €	3,866,073 €
**not including costs for outpatient clinic*		

Teaching

2015 | Faculty of Medicine

Bayer-Karpinska A, Dichgans M, Düring M, Liesz A, Opherk C, Tiedt S, Wollenweber F | **Blockpraktikum Neurologie und Neurochirurgie 1** (7M1407)

Bayer-Karpinska A, Dichgans M, Düring M, Liesz A, Opherk C, Tiedt S, Wollenweber F | **Blockpraktikum Neurologie und Neurochirurgie 2** (7M1408)

Bürger K, Wollenweber F | **Blockpraktikum Psychiatrie und Psychotherapie 1** (7M1410)

Bürger K, Wollenweber F | **Blockpraktikum Psychiatrie und Psychotherapie 2** (7M1411)

Dichgans M, Opherk C, Wollenweber F | **Interdisziplinäre Behandlung des Schlaganfalls** (7C0014)

Dichgans M, Opherk C | **Experimentelle Ansätze in der Schlaganfalltherapie** (7C0017)

Beaufort N, Dichgans M, Haffner C, Malik R, Opherk C, Prestel M | **Demenzen: Molekulare Grundlagen und pathophysiologische Konzepte** (7C0019)

Dichgans M, Opherk C | **Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder** (7C0025)

Ertürk A, Hellal F, Liesz A, Plesnila N, Schneider M | **Experimentelle Schlaganfallforschung** (7C0123)

Caballero M, Beaufort N, Dichgans M, Düring M, Ewers M, Haffner C, Hellal F, Liesz A, Malik R, Plesnila N, Prestel M, Schneider M | **Stroke and Dementia Research – News and Views** (7C0124)

Caballero M, Düring M, Ewers M, Malik R | **Neuroimaging of Brain Changes in Alzheimer's disease and Other Dementias** (7C0146)

Ertürk A, Liesz A | **Developments and trends in neuroimmunological research** (7C0155)

Plesnila N | **Tutorial on good scientific practice in experimental stroke research** (7C0156)

Malik R | **Genetische Analysen komplexer Erkrankungen** (7C0157)

Bürger K, Catak C, Dichgans M, Ewers M | **Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik** (7C0233)

Bürger K, Dichgans M, Düring M, Ewers M | **Strukturelle Magnetresonanztomographie in der Demenzforschung** (7C0248)

Caballero M, Düring M, Ewers M | **Multimodale Bildgebung zu Gehirnveränderungen bei der Alzheimer Demenz** (7C0263)

Bürger K, Catak C, Dichgans M, Ewers M | **Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik** (7P0602)

Dichgans M, Opherk C | **Neurologische Notfall- und Intensivmedizin** (7P0603)

Bürger K, Catak C, Dichgans M, Wollenweber F | **Interdisziplinäre Therapie von Demenzen** (7P0607)

Dichgans M, Opherk C | **Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder** (7P0609)

Dichgans M, Opherk C, Wollenweber F | **Interdisziplinäre Behandlung des Schlaganfalls** (7P0610)

2015 | Faculty of Biology

Caballero M, Ewers M, Düring M, Malik R | **P 10.2 Seminar - Neuroimaging of Brain Changes in Alzheimer Disease and Other Dementias**

Adam R, Düring M, Ewers M | **P 10.2 Seminar - Neuroimaging of the functional architecture of the brain**

Beaufort N, Dichgans M, Haffner C, Liesz A, Plesnila N | **P 2.5 Practical Course - Molecular Neurogenetics and Experimental Stroke Research**

Dichgans M, Liesz A | **P 2.5 Practical course - Neuroimmunological methods in experimental stroke research**

Dichgans M, Ertürk A, Malik R, Prestel M | **P 10.2 Practical Course - Methods in Clinical Neuroscience**

Dichgans M, Schneider M | **P 10.2 Practical course - Experimental stroke research - Introduction to laboratory animal science**

2016 | Faculty of Medicine

Bayer-Karpinska A, Catak C, Düring M, Janowitz D, Kopczak A, Opherk C, Tiedt S, Wollenweber F | **Bedside Teaching / Untersuchungskurs Neurologie und Neurochirurgie (7M1452)**

Bayer-Karpinska A, Düring M | **C-StaR Neurologie (7M1825)**

Dichgans M, Opherk C, Wollenweber F | **Interdisziplinäre Behandlung des Schlaganfalls (7C0014)**

Dichgans M, Opherk C | **Experimentelle Ansätze in der Schlaganfalltherapie** (7C0017)

Beaufort N, Dichgans M, Haffner C, Malik R, Opherk C, Prestel M | **Demenzen: Molekulare Grundlagen und pathophysiologische Konzepte** (7C0019)

Dichgans M, Opherk C | **Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder** (7C0025)

Ertürk A, Hellal F, Liesz A, Plesnila N, Schneider M | **Experimentelle Schlaganfallforschung** (7C0123)

Caballero M, Beaufort N, Dichgans M, Düring M, Ertürk A, Ewers M, Haffner C, Hellal F, Liesz A, Malik R, Plesnila N, Prestel M, Schneider M | **Stroke and Dementia Research – News and Views** (7C0124)

Caballero M, Düring M, Ewers M, Malik R | **Structural connectomics in disease: Applied diffusion tensor imaging (DTI) and fiber tracking. A practical course** (7C0146)

Ertürk A, Liesz A | D**evelopments and trends in neuroimmunological research** (7C0155)

Plesnila N | **Tutorial on good scientific practice in experimental stroke research** (7C0156)

Malik R | **Genetische Analysen komplexer Erkrankungen** (7C0157)

Caballero M, Düring M, Ewers M, Malik M | **Functional connectomics in disease: Applied diffusion tensor imaging (DTI) and fiber tracking. A practical course** (7C0170)

Bürger K, Catak C, Dichgans M, Ewers M | **Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik** (7C0233)

Bürger K, Dichgans M, Düring M, Ewers M | **Strukturelle Magnetresonanztomographie in der Demenzforschung** (7C0248)

Caballero M, Düring M, Ewers M | **Multimodale Bildgebung zu Gehirnveränderungen bei der Alzheimer Demenz** (7C0263)

Bernhagen J, Brandhofer M, El Bounkari O, Schmitz C | **Current developments in vascular biology: mechanisms and pathologies** (7C0375)

Bernhagen J, El Bounkari O | **Doktorandenkolloqium: kardiovaskuläre Pathologien - Atherosklerose und Schlaganfall** (7C0376)

Bernhagen J, Dichgans M, Liesz A, Plesnila N | **Interdisziplinäre Vorlesung: Promotionsstudium Molekulare Medizin und Systembiologische Medizin** (7C0422)

Ewers M | **Diskussion aktueller Forschungsbefunde zur Alzheimer Demenz** (7C4046)

Bernhagen J, Brandhofer M, El Bounkari O, Schmitz C | **Aktuelle Themen der Molekularen Atheroskleroseforschung** (7C4047)

Bürger K, Catak C, Dichgans M, Ewers M | **Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik** (7P0602)

Dichgans M, Opherk C | **Neurologische Notfall- und Intensivmedizin** (7P0603)

Bürger K, Catak C, Dichgans M, Wollenweber F | **Interdisziplinäre Therapie von Demenzen** (7P0607)

Dichgans M, Opherk C | **Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder** (7P0609)

Dichgans M, Opherk C, Wollenweber F | **Interdisziplinäre Behandlung des Schlaganfalls** (7P0610)

Adam R, Caballero M, Ewers M, Düring M, Malik R | **P 10.2 Seminar - Structural Connectomics in Disease: Applied diffusion tensor imaging (DTI) and fiber tracking**

Adam R, Düring M, Ewers M | **P 10.2 Seminar - Functional Connectomics in Disease: Applied Resting State Imaging**

2016 | Faculty of Biology

Beaufort N, Bernhagen J, Dichgans M, El Bounkari O, Gökçe Ö, Haffner C, Liesz A, Plesnila N, Prestel M | **P 2.5 Practical Course - Molecular Neurogenetics and Experimental Stroke Research**

Dichgans M, Liesz A | **P 2.5 Practical course - Neuroimmunological methods in experimental stroke research**

Dichgans M, Ertürk A, Malik R, Prestel M | **P 10.2 Practical Course - Methods in Clinical Neuroscience**

Ertürk A | **P 2.5 Practical Course - Advanced fluorescence microscopy techniques: Super resolution, light-sheet and others**

Ertürk A | **P 2.5 Practical Course - Tissue clearing and 3D imaging for mapping the brain in health and disease**

Participation in Graduate Schools:

Munich Center for Neurosciences – Brain and Mind: ISD staff actively participates into teaching programs offered within the graduate school of the MCN.

The training concept of the Graduate School of Systemic Neurosciences (GSN) is designed to offer:

1) an optimally structured and student-centered teaching program in English;

2) comprehensive and state of-the-art scientific training regarding topics and methods - exceptionally broad scope of the Munich neuroscience research spectrum for neuroscience-related projects and theses (M.Sc., Ph.D.);

3) ECTS based grading, fully compatible with the Bologna System;

4) personal career planning and intensive individual coaching for scientific and related careers;

5) various options for lab rotations within the Munich Graduate Program, with collaborating institutions at Ludwig-Maximilians-Universität München, Technische Universität München, Max-Planck-Institutes, Helmholtz Center Munich, DLR, etc. and their international research partners;

6) an international network for future careers in academia and RTD projects for graduates, Ph.D. students and postdocs (see www.mcn.lmu.de). ISD staff further participates in the graduate program molecular medicine (Promotionsstudiengang Molekulare Medizin).

M. Dichgans is a scientific board member of the GSN. ISD staff further participates in the graduate program molecular medicine (Promotionsstudiengang Molekulare Medizin).

Habilitations & Theses

Ph.D. students

Advanced diffusion models in cerebral small vessel disease. M. Konieczny, planned degree: PhD, started Sep 2016

The choroid plexus in post-stroke lympocyte invasion. G. Llovera, planned degree: Dr. rer. nat., started Aug 2013

The role of brain-released alarmins in post-stroke atheroprogression. S. Roth, planned degree: Dr. rer. nat., started Aug 2013

Microbiota-derived metabolites in modulating post-stroke recovery. R. Sadler, planned degree: Ph.D. (GSN), started Oct 2015

Functional brain mechanism underlying cognitive reserve in Alzheimer's disease. N. Franzmeier, planned degree: Ph.D. (GSN), started Oct 2014

Structural and functional connectivity in vascular cognitive impairment. E. Baykara, planned degree: Ph.D. (GSN), started Aug 2013

Using resting state fMRI to predict impairment of task-related memory network activation in preclinical Alzheimer's disease. L. Simon-Vermot, planned degree: Ph.D. (GSN), started Feb 2013

Role of HDAC9 in atherosclerotic mouse models. S. Azghandi, Ph.D. (GSN), completed Nov 2016

Characterization and treatment of cerebrovascular dysfunction in CADASIL mutant mice. M. Balbi, Ph.D. (GSN), completed Nov 2015

Mechanism of microvasospasm following subarachnoid hemorrhage. K. Nehrkorn, Ph.D. (GSN), completed Apr 2016

Transcriptional regulation of the stroke risk gene HDAC9 by the E2F3/Rb1 complex. C. Prell, Dr. rer. nat., completed Jan 2015

Consequences of HtrA1 deficiency on TGF-β signaling. E. Scharrer, Dr. rer. nat., completed Jan 2015

Proteomic approach to study molecular pathomechanisms in hereditary small vessels disease. A. Zellner, planned degree: Dr. rer. nat., started Oct 2014

Pathological Notch3 aggregation: Role of cysteine-sparing mutations and antiaggregatory strategies in CADASIL. P. Hanecker, Dr. rer. nat., completed Dec 2016

Role of the stroke-relevant HDAC9 gene in proteome & acetylome. F. Söllner, planned degree: Dr. rer. nat., started Jan 2015

Functional characterization of the conserved cis-regulatory element at the HDAC9 locus – a major risk locus for atherosclerosis. G. Yan, planned degree: Dr. rer. nat., started Apr 2015

Medical theses

Platelet-derived MIF: A novel platelet chemokine with distinct recruitment properties. T. Wirtz, Dr. med., completed Dec 2015

Die Rolle von MIF (macrophage migration inhibitory factor) innerhalb der Anästhetika-induzierten Präkonditionierung. L. Siry, Dr. med., completed Nov 2016

Die Rolle von macrophage migration inhibitory factor (MIF) bei der Rekrutierung von endothelialen Progenitorzellen (EPC) nach myokardialer Ischämie / Reperfusion. L. Helemdag, Dr. med., completed Sept 2016

Wide-field calzium-imaging of neuronal activity for post-stroke connectivity. J. Cramer, planned degree: Dr. med, started Feb 2016

Brain-released alarmins in post-stroke systemic immunomodulation. J. Yang, planed degree: Dr. hum. biol., started Nov 2015

Plasticity of vascular smooth muscle cells in familial small vessel disease. T. Landinger, planned degree: Dr. med., started Feb 2014

Role of astrocytic gpx4 following cerebral ischemia. I. Rynarzewska, planned degree: Dr. med., started Apr 2013

Rolle von CYLD im Schlaganfallmodell bei Mäusen. P. Scheffler, planned degree: Dr. med., started Apr 2013

Rolle von NADPH-Oxidasen nach Subarachnoidalblutung. D. Bühler, planned degree: Dr. med., started Feb 2013

The role of regional cortical atrophy in mild cognitive impairments. T. Klöpping, planned degree: Dr. med., started Oct 2012

The influence of personality factors on the effect of a cognitive intervention in subjects with amnestic mild cognitive impairment. J. Kramer, Dr. med., completed Dec 2016

Role of HDAC9 in proatherogenic processes in vascular cells. Y. Bokov, planned degree: Dr. med., started Apr 2016

HDAC9-mediated atherogenic mechanisms in macrophages and regulatory T cells. L. Yu, planned degree: Dr. med., started Aug 2016

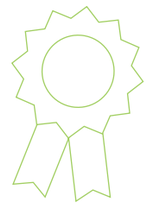
Habilitations

Immunologische Mechanismen nach akuter zerebraler Ischämie. A. Liesz, Habilitation in Experimental Neurology, Sep 2016

Kognition und funktionelles Outcome nach Schlaganfall. F. A. Wollenweber, Habilitation in Clinical Neurology, Dec 2015

Honors & Awards

- C. Benakis | Marie Curie Individual Fellowship, 2017
- S. Tiedt | Stipend by the Josef-Hackl-Stiftung
- A. Liesz | Young Investigator Award European Stroke Organization, 2015
- A. Liesz | Emmy-Noether-Program of the German Research Foundation (DFG), 2015
- N. Terpolilli | Hannelore Kohl Foundation Award 2015
- M. Dichgans | President, German Stroke Society (DSG)
- M. Dichgans | Editorial Board, Annals of Neurology
- D. Atzler | LMUexcellent Junior Investigator Award
- C. Schmitz | Young Investigator Fellowship / European Atherosclerosis Society 2016
- A. Ertürk | Chair, Society of Neuroscience Minisymposia (Clearing and Labeling Methods for High Resolution Imaging of Intact Biological Specimens), 2015
- A. Ertürk | Associate Investigator, Graduate School of Systemic Neurosciences (GSN-LMU), 2014
- A. Ertürk | Sofja Kovalevskaja Award, Alexander von Humboldt Foundation 2014 (offer)
- M. Düring | Young Investigator Award VASCOG, 2015



ISD staff has been or is significantly involved in the organization of the following conferences and events (selection):

Scientific Conferences & Symposia

ESO Stroke 2016, Stockholm (Sweden, Nov 2016) Session: „IV Thrombolysis – dosing of alteplase" | M. Dichgans: scientific chair

5th European Immunology and innate immunity Conference (Berlin, Jul 2016) J. Bernhagen: Organizing Committee and Speaker

4th International Conference on Innate Immunity Barcelona (Spain, Jul 2015) J. Bernhagen: Organizing Committee and Speaker

Cardiac Regeneration and Vascular Biology Conference San Servolo (Italy, Jun 2016) | J. Bernhagen: Session Chair

7th International MIF Symposium Weizmann Institute of Science, Rehovot (Israel, Oct 2015) | J. Bernhagen: Organizing Committee, Speaker, and Session Chair

Society of Neuroscience (SFN) Minisymposia titled "Clearing and Labeling Methods for High Resolution Imaging of Intact Biological Specimens", Chicago (USA, Oct 2015) | Ali Ertürk: Chair

2**nd European Stroke Organisation Conference ESOC Barcelona** (Spain, May 2016) Session: Genetics and Biomarkers | M. Dichgans: scientific chair

1st European Stroke Organisation Conference ESOC Glasgow (UK, Apr 2015) Session: Small Vessel Disease | M. Dichgans: scientific chair

I**SC Nashville** (USA, Feb 2015) "Diagnosis of Stroke Etiology Oral Abstracts I" | M. Dichgans: moderator

Alzheimer's Association International Conference (AAIC), Washington (USA, Jul 2015) | M. Ewers: symposium chair and speaker

Professional Interest Area: Reserve, AAIC, Toronto (Canada, Jul 2016) | M. Ewers: organizing committee and speaker

10th World Stroke Congress (WSC), Hyderabad (India, Oct 2016) Session: The new stroke genetics: Implications for clinical practice | M. Dichgans: scientific chair

89th DGN-Kongress (Mannheim, Sep 2016) Session: Demenz | M. Dichgans: scientific chair

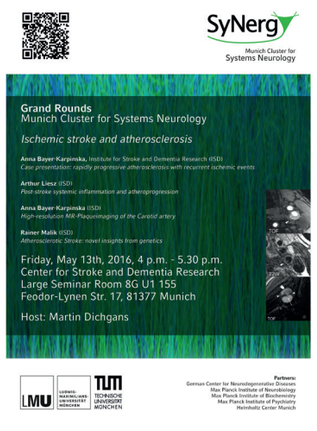
89th DGN-Kongress (Mannheim, Sep 2016) Fortbildungsakademie: HTK 22 - Schlaganfall | M. Dichgans: scientific chair

89th DGN-Kongress (Mannheim, Sep 2016) Session: Schlaganfall – Hot Topics | M. Dichgans: scientific chair

9th International Symposium on Neuroprotection and Neurorepair (Leipzig, Oct 2016) | N. Plesnila organizing committee, speaker, and session chair

DGN (Düsseldorf, Sep 2015) „Neue diagnostische und therapeutische Ansätze in der Schlaganfallforschung" | M. Dichgans: scientific chair

Conferences, Trainings and Events *(Selection)*



International Ethics and Advisory Board of the Dutch Heart-Brain Consortium Amsterdam (NL, Mar 2016) Support Masterclass for PhD candidates and postdocs | M. Dichgans: scientific chair

Annual Conference 33rd ANIM (Berlin, Jan 2016) Symposium DSG | M. Dichgans: scientific chair

2. Stroke-Unit-Betreiber-Treffen (Berlin, Mar 2016) Session: Erfahrungen mit bisherigen Audits | M. Dichgans: scientific chair

Annual Conference 32nd ANIM (Berlin, Jan 2015) Symposium DSG | M. Dichgans: scientific chair

Further events

Advisory Board Meeting (ISD) (Munich, Aug 2015)

3D Imaging and Tissue Clearing Workshop (Munich, Jul 2015 & 2016)

ISD Research Retreat (Lake Ammersee, Jul 2015 & 2016)

Patient information event: Stroke and Dementia Prevention, (Munich Oct 2015 & 2016)

Patient information Munich Memory Alliance (Munich, Apr 2016)

Kick-off meeting EU Horizon 2020 programme SVDs@target (Munich, Nov 2015)

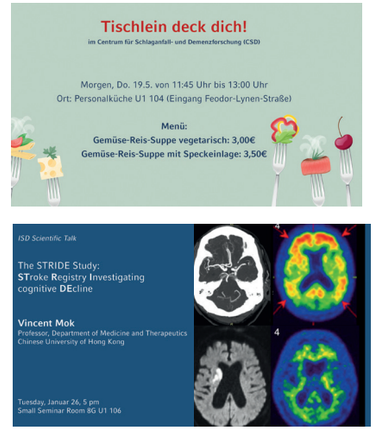
General Assembly EU Horizon 2020 programme CoSTREAM (Munich, Nov 2015)

17th Stroke Unit Day (Munich, Nov 2015)

Center for Stroke and Dementia Research Opening Event (Munich, May 2015)

External Speakers in ISD Talks (Selection)

Laura T. Haas, Yale, USA / Ivan Dikic, Frankfurt, Germany / Katherine LaClair, Baltimore, USA / Luc Dupuis, Strasbourg, France / Herwig Baier, Munich, Germamy / Vincent Mok, Hong Kong, China / Alain Chédotal, Paris, France / Heidi Noels, Aachen, Germany / Richard I. Morimoto, Evanston, USA / Manuel Mayr, London, GB / Halina Offner, Oregon, USA / Adriano Aguzzi, Zurich, Switzerland / Hiroki R. Ueda, Tokyo, Japan / Marcelo Bozza, Rio de Janeiro, Brazil / Denis Vivien, Normandie, France / Elisabeth Tournier-Lasserve, Paris, France / Loes Rutten-Jacobs, Cambridge, GB / Tim Magnus, Hamburg-Eppendorf, Germany / Angela Ruohao WU, Hong Kong, China/ Wulf Paschen, Durham, USA / Hilal A. Lashuel, Lausanne, Switzerland / Stefan Teipel, Rostock, Germany / Monika Chanu Chongtham, Göttingen, Germany / Marco E. Bianchi Milan, Italy / Ana Buvac, Göttingen, Germany / Arn van den Maagdenberg, Leiden, The Netherlands / Prof. Marcelo Bozza, Rio de Janeiro, Brazil / Monika Chanu Chongtham, Göttingen, Germany / Cristina Iobbi, Braunschweig, Germany / Sarah Pendlebury, Oxford, GB



Dichgans M, Leys D. *Vascular Cognitive Impairment.* **Circ Res.** 2017 Feb 3;120(3):573-591

Malik R, Dau T, Gonik M, ..., **Beaufort N**,..., **Dichgans M**. *A common coding variant in SERPINA1 increases the risk for large artery stroke.* **Proc Natl Acad Sci U S A.** 2017 (in press) (IF 9.4)

Ling Y, De Guio F, **Duering M,** Jouvent E, Hervé D, Godin O, **Dichgans M,** Chabriat H. *Predictors and Clinical Impact of Incident Lacunes in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy.* **Stroke**. 2017 Feb;48(2):283-289. (IF 5.8)

Balbi M, Koide M, Wellman GC, **Plesnila N.** *Inversion of neurovascular coupling after subarachnoid hemorrhage in vivo.* **J Cereb Blood Flow Metab.** 2017 Jan 1:271678X16686595 (IF 4.9)

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	2015		2016		2015/2016	
	number	IF total / IF Ø	number	IF total / IF Ø	number	IF total / IF Ø
Total Articles	75	502.9 / 7.2	84	645.2 / 8.3	159	1148.1 / 7.8
First and/or Senior Authorship	28	191.2 / 6.8	28	213.0 / 7.9	56	404.2 / 7.3
Original Articles	71	472.6 / 7.3	80	577.3 / 7.9	151	1049.9 / 7.6
First and/or Senior Authorship	24	166.9 / 7.0	25	188.0 / 7.5	49	354.9 / 7.3

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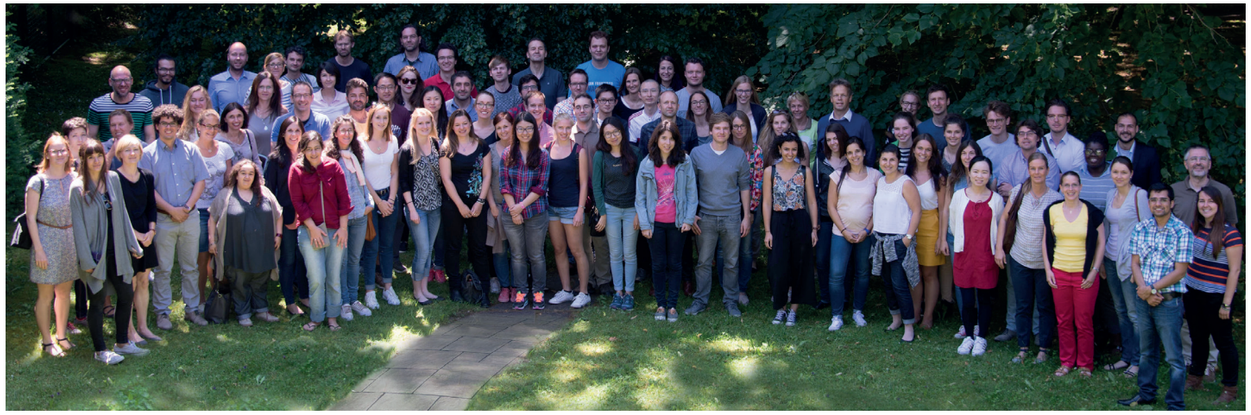

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