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The Institute for Stroke and Dementia Research (ISD)

Stroke and Dementia rank among the most common diseases worldwide and the most pressing health problems in ageing societies. Stroke is the leading cause of permanent disability and the second leading cause of death worldwide (Global Burden of Disease Study 2018). 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-Zak who recognized the promise of integrating patient care with basic and clinical research to transform medicine. Mr. Solorz-Zak 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-Zak’s vision and joined together with him as the founding partners of the Institute 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 112 people including 74 scientific staff ranging from master and PhD 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 6.3 million Euro spent in 2017 (including Human-MRI and PET/MRI), and more than 3.9 million Euro spent in 2018. Within this period ISD investigators published more than 120 papers in peer-reviewed international journals including leading journals in the fields of Genetics, Neuroscience, and Medicine.

Among the most recent accomplishments are the installation of a human magnetic resonance imaging (MRI) research scanner operating at 3 Tesla (Siemens, Magnetom Prisma), a micro PET/MRI scanner (Mediso, nano-Scan) that is first in line for PET imaging (also operating at 3 Tesla) and a femtopulse near-infrared laser multiphoton microscope (Leica SP8 DIVE, 1300 nm). 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 an ERC starting grant offering further support for his research program on Stroke Immunology, which also integrates into the SyNergy cluster.

The ISD is part of an ever 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 institutions. Building on the success of the first funding period SyNergy recently successfully applied 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, the clinician scientist program in vascular medicine (PRIME), and is involved in other national, and international research hubs including EU FP7, Horizon2020, and NIH-funded networks some of which are coordinated by the ISD.

Among the plans for 2019/20 are a new Professorship for Stroke Immunology, the set-up of the SyNergy-ISD funded “Macroscale” and “Mesoscale” technology hubs and an even stronger push towards education of clinician scientists, clinical translation, and interventional studies.

We are grateful for the opportunities provided to us and wish to report on our activities below. In the following, we highlight major achievements and developments in 2017/2018.

Prof. Dr. med. Martin Dichgans
Director,
Institute for Stroke and Dementia Research
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 top research. The ISD strives to provide the highest quality in preventing, recognizing and treating 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, almost 6 million die as a direct consequence of stroke, another 5 million are permanently disabled. In European countries, the number of strokes is expected 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 40 million worldwide in 2015 to about 100 million by 2040 (World Alzheimer Report 2015).

The foundation of the Institute for Stroke and Dementia Research (ISD) bears on the initiative of Zygmunt Solorz-Zak, 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-Zaks, the Ludwig-Maximilians University (LMU), the State of Bavaria, and the Klinikum der Universität München (KUM) agreed on a long-term collaboration to install 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 an outpatient clinic specialized on the diagnosis and treatment of stroke, cerebrovascular disease, and neurodegenerative diseases that cause cognitive decline
- state-of-the-art human MRI research scanner
- state-of-the-art micro MRI/PET scanner
- light-sheet microscopy
- facility for iPSC-related technology
- electron microscopy (DZNE)
- multi-photon microscopy with 1300 nm pulsed IR laser and FLIM-FRET
- confocal microscopy
- wide-field calcium imaging
- life cell imaging
- proteomics unit (DZNE)
- binding studies by dynamic mass redistribution and alpha-technology
- peptide array-based protein binding mapping
- single cell sorting and sequencing unit
- high-content screening
- isotope labs
- SPF facility
- zebrafish facility (DZNE)
- seminar rooms
- wet labs
- biobank
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Vascular Dementia Research Foundation

RA Erich Steinsdörfer (Vice Chairman)
Vascular Dementia Research Foundation

RA Josef Birka
Vascular Dementia Research Foundation

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Chairman, Integrated Center for Research and Treatment of Vertigo, Balance and Ocular Motor Disorders

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Director, Klinikum der Universität München

Prof. Dr. rer. pol. Bernd Huber
President, Ludwig-Maximilians-Universität München

Representative of the Bayerisches Staatsministerium für Wissenschaft, Forschung und Kunst

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Professor of Neuroscience Head of the Department of Molecular Neuroscience Chair of Molecular Biology of Neurological Disease at the UCL Institute of Neurology University College London, UK

Prof. Costantino Iadecola, MD
Anne Parrish Titzell Professor of Neurology, Professor of Neuroscience, Brain and Mind Research Professor of Neurology and Neuroscience, Weill Cornell Medical College, New York, USA

Prof. Peter M. Rothwell, MD. Ph.D, FRCP
Head of the Centre for the Prevention of Stroke and Dementia Professor of Clinical Neurology Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford University of Oxford, UK

Prof. Dr. med. Jörg B. Schulz (Chairman)
Director, Dept. of Neurology, University Hospital, RWTH Aachen, Germany

Founders

Zygmunt & Małgorzata Solorz-Zak (Benefactors), Warsaw, Poland

Klinikum der Universität München

Ludwig-Maximilians-Universität München

Bayerisches Staatsministerium für Wissenschaft, Forschung und Kunst
Steffen Tiedt, a clinician scientist at the ISD has been awarded the Young Investigator Award 2018 by the European Stroke Organisation (ESO) for his work on serum Neurofilament Light as a marker for neuroaxonal injury after stroke.

A new state-of-the-art scanner operating at 3T (Siemens MAGNETOM Prisma) that had been jointly funded by the German Research Foundation (DFG) and the Vascular Dementia Research Foundation has started operations. The scanner is located in a highly equipped new building next to the CSD and offers unprecedented opportunities for cutting-edge imaging studies in patients and healthy subjects.

Stefan Roth and Arthur Liesz were awarded the “Rolf-Becker” Prize for one of the top scientific outputs in 2017/18 by the Medical Faculty of LMU Munich and the foundation “Rufzeichen Gesundheit!” Baierbrunn. They received this prestigious award for their recent work published in Science Translational Medicine.

The DFG-funded Munich Cluster of Systems Neurology (SyNergy), which unites multiple investigators from the Munich Neuroscience community has been approved funding by the Excellence Commission. Funding will commence in January 2019 for an initial period of seven years with the possibility of another period of extension. The ISD is heavily involved in the clusters activities and remains grateful for the wonderful opportunities emerging from this unique project.

The European Research Council (ERC) Starting Grants are the first in a series of highly prestigious awards offered by the European Commission (EC). The 1.5M € award will enable the Liesz group to expand its research on inflammatory mechanisms in the recovery after acute stroke.

Ali Ertürk has received a research grant from the National Institute of Health (NIH, USA) to explore the role of brain lymphatic/glymphatic systems in dementia and ageing in collaboration with Maiken Nedergaard (Rochester University, New York). The project involves use of the latest clearing technology developed at the ISD.

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After joining the ISD in late 2016 Dominik Paquet (Neurobiology) opened a new stem cell research facility to explore the mechanisms and novel therapeutic approaches to dementia, stroke and related diseases in novel human brain tissue models derived from patient stem cells.

Marco Durin has been awarded the Adolf Wallenberg Prize for outstanding cerebrovascular research by the German Stroke Society (DSG) and German Neurological Society (DGN). The award recognizes his contribution to the understanding of cerebral small vessel disease and the mechanisms by which vascular brain lesions cause cognitive decline.

The Collaborative Research Center SFB1123 „Atherosclerosis – Mechanisms and Networks of Novel Therapeutic Targets” has been approved a second funding period. The ISD contributes to the LMU led network with projects led by Martin Dichgans/Yaw Asare (project B5) and Jürgen Bernhagen (project A3), as well as a flanking project by Arthur Liesz (C1).
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 participation 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 clinic 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).

Outpatient clinic staff
Bay, Berkant, MSc / study assistant
Bertram, Deüre / neuropsychologist
Berwein, Michael, MSc / neuropsychologist
Borunda Vasquez, Lara, MSc / neuropsychologist
Bürger, Katharina, PD Dr. med. / senior physician
Catak, Cihan, Dr. med. / physician
Cizmic, Deni / study assistant
Coloma Andrews, Lisa, Dr. phil. / neuropsychologist
Dichgans, Martin, Prof. Dr. med. / director
Dörö, Angelika / study nurse
Fertig, Alexandra / social worker
Hein, Sandra / study nurse
Hill, Julia / study nurse
Jaki, Veronika, Dr. med. / physician
Janowitz, Daniel / physician
Kopczak, Anna, Dr. med. / physician
Küster, Bettina, Dr. med. / physician
Lorbeer, Mariya / study nurse
Markov, Eva / study nurse
Prothiwa, Stephanie / reception
Schöntenhuber, Valentina / reception
Schreiner, Sandra / reception
Tiedt, Steffen, Dr. med. / physician

Wiedmann, Viktoria / technical assistant
Wollenweber, Frank, PD Dr. med. / senior physician
Zollver, Adelgunde / study nurse

Contact
Institute for Stroke and Dementia Research (ISD) Klinikum der Universität München Feodor-Lynen-Straße 17, 81377 München Internet: www.isd-muc.de E-Mail: ambulanz.isd@med.uni-muenchen.de Tel.: +49-89-4400-46046

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

The SPU offers comprehensive diagnostic assessment, counselling and personalized treatment to patients and individuals at risk. 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:
- cerebral small vessel disease
- post stroke dementia (PSD)
- cerebral amyloid angiopathy (CAA)
- carotid artery disease

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Major research topics of the SPU are:
- cerebral small vessel disease
- post stroke dementia (PSD)
- cerebral amyloid angiopathy (CAA)
- carotid artery disease

Publications:


For a full account of ongoing clinical studies see page 52.
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, there is a growing interest into improved options for early diagnosis. 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.

Major research topics of the Memory Clinic are:
- • pre-MCI and MCI (mild cognitive impairment)
- • Alzheimer’s disease (AD)
- • vascular cognitive impairment (VCI)
- • cognitive reserve & mechanisms of resilience
- • frontotemporal lobar degeneration (FTLD)

Our diagnostic algorithms are optimized to detect pre-symptomatic stages of dementia conditions and make use of new PET ligands for neurodegenerative disease (including for β-amyloid, tau, microglia) Figure 1.), novel laboratory-based biomarkers, and novel MR-based biomarkers (e.g. Baykara et al. Ann Neurol 2016) developed in part at the ISD.

Selected Publications:


“After learning about my diagnosis of Alzheimer’s disease from the doctors here at the ISD I joined one of their treatment trials. Over my visits, I have come to value the unique atmosphere, professionalism, and empathy of the team. My wife says, I would be missing something if I weren’t allowed to come here, and I think she is right.”

Selected Publications:
Reaching out to the public is part of the ISD’s efforts to promote research.

For instance, the ISD actively contributed to Messe 66, the largest senior fair in Germany, through an information booth. Several of ISD’s medical professionals, physicians and scientists took turns to inform more than 300 interested visitors, patients, and their relatives, and distributed relevant material.

They reached out to people, answered questions, raised interest in the ISD’s clinical and research activities and offered participation into clinical studies.

Clinical staff | outpatient clinic

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<td>study nurses</td>
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<tr>
<td>social workers</td>
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</tr>
<tr>
<td>technical assistants</td>
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<tr>
<td>outpatient office</td>
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<td>clinical data manager</td>
<td>3</td>
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Costs | outpatient clinic

In 2018 the total costs for the outpatient clinic amounted to 1,043,400 €. 78% of these costs were covered by the Vascular Dementia Research Foundation.

| personnel     | 905,270 € |
| material      | 63,820 €  |
| travel expenses | 2,975 €   |
| investments   | 10,054 €  |
| miscellaneous | 61,281 €  |
|                      | 1,043,400 € |

Statistics | Outpatient Clinic

The number of appointments in 2017 and 2018 amounted to 3,193 and 3,008 respectively which collectively corresponds to a 7% increase compared to 2016. The total number of clinical appointments was 2,269 (2017) and 2,054 (2018) and thus remained relatively stable. The total number of research visits was 924 (2017) and 954 (2018), which corresponds to an increase of 26.2% percent compared to 2016.

Patients presenting to the SPU most often had one of the following diagnoses:

1. Previous stroke or transient ischemic attack
2. Risk factors for ischemic stroke e.g. carotid artery stenosis, cervical artery dissection, patent foramen ovale
3. Risk factors for hemorrhagic stroke e.g. previous intracranial hemorrhage, cortical superficial siderosis, cerebral microbleeds, cavernoma or arteriovenous malformations
4. General vascular risk factors e.g. 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), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), or Fabry 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.
Research
The focus of ISD research is on the following topics:

- 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

Methodological approaches include

- Prospective investigator-initiated observational and interventional studies in patients
- Genetics and second-generation -omics
- Mendelian randomization studies
- Single cell sequencing | Computational biology
- CRISPR/Cas genome editing
- Induced pluripotent stem cells (iPSCs) | Tissue engineering | Advanced in vitro models
- Biochemistry | Proteomic techniques
- Receptor-ligand interaction profiling
- Experimental stroke models (ischemia, hemorrhage, subarachnoid hemorrhage)
- Experimental atherosclerosis models (chronic atherogenesis, neointima formation, hyperlipidemia)
- In vivo microscopy (multi-photon, FLIM-FRET, light-sheet, confocal)
- Tissue clearing & light sheet microscopy
- Behavioral testing
- MRI & PET (human and mouse)
- Advanced image postprocessing analysis
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, Fox2) and use these models to identify and characterize key molecular (e.g. TGF-β signaling) and physiological (e.g. blood-brain-barrier) pathways and cellular targets (e.g. vascular endothelial cells and 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, SCARF1) in atherogenesis and vascular injury.

Key Publications


Tiedt S, Prestel, Martin, Prof. Dr. med. / clinician scientist
Thomas, Krya / MD student
Völgyi, Kata / MD student
Wagner, Emanuel / MD student
Zielke, Natalie / technical assistant

http://DichgansLab.isd-muc.de
@ISD_Research
https://twitter.com/isd_research
Vascular Biology

Research Group – PI: Jürgen Bernhagen

We are interested in the molecular and cellular mechanisms of cardiovascular disease and inflammation. The main 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 discovered the cytokine MIF in inflammatory and vascular disease and characterized it as a key member of the emerging class of atypical chemokines (Bernhagen et al., Nature 1993; Bernhagen et al., Nat. Med. 2007; Heinrichs et al., PNAS 2019). Relying on biochemical and vascular biology methods in combination with multi-photon microscopy, single cell RNAseq, proteomics, transgenic mouse models and clinical approaches, we study the MIF protein family (MIF, MIF-2, CXCR2, CXCR4, CXCR7, CD74, SCD74, novel MIFs and related chemokines in atherosclerosis, ischemic stroke, and myocardial infarction (Merk et al., PNAS 2011; Steppe et al., Antioxid Redox Signal 2015; Smits et al., FASEB J 2018; Steppe et al., Sci Transl Med 2018). This involves deciphering the ligand/receptor complexes and pathways (Jayasekaran et al., J Biol Chem 2016; Soppert et al., JAMA 2018) driving atherogenic recruitment of leukocytes, but we also focus on disease-specific oxidized isoforms as encountered in ischemic stress as well as on chemokine-like alarmins such as HMGB1 (Bernhagen et al., Nature 1993; Bernhagen et al., Nat. Med. 2007; Heinrichs et al., PNAS 2019). We currently study the role of the CSN holo-complex, early versus advanced atherogenesis models and evaluate CSN-based translational opportunities. We are also interested in cardioprotective mechanisms of (atypical) chemokines (Lüdike et al., Circulation 2012; Pohl et al., Thromb Haemost 2016) and how they compare with related effects in ischemic stroke and cerebrovascular pathogenesis but also other inflammatory diseases. Lastly, capitalizing on local and international collaborations, we pursue links between inflammation and neurodegeneration, e.g. in Alzheimer disease (AD) and amyotrophic lateral sclerosis (ALS).

Another focus is on signaling mediated by the COP9 signalosome (CSN) and NF-κB-regulating pathways in atherogenesis and neurovascular inflammation. The CSN is a multi-protein complex that regulates SCD cullin-RING E3-ligase NEDDylation status, controlling ubiquitin-proteasome-mediated degradation of cell-regulatory proteins. Based on our discovery of a link between CSN5 and inflammation-regulating pathways (Kleemann et al., Neutralization of the Plasmodium-encoded MIF ortholog confers protective immunity against malaria infection. Nat Commun. 2018 Jul 13;9(1):2714. *corresponding authors)

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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


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.

In the past two years the work of the Laboratory of Experimental Stroke Research further focused on the role of cerebral microvessels for ischemic brain damage after subarachnoid hemorrhage (SAH). Previously we demonstrated that within a few hours after SAH pial arterioles show pear-string like constrictions and cerebral perfusion is reduced by more than 60%. Since this reduction of CBF is not sufficient to explain cerebral ischemia after SAH, we focused our investigations on cerebrovascular function. Our results in a clinically relevant mouse SAH model demonstrate that pial and intraparenchymal microvessels show a complete loss of CO2 reactivity already three hours after SAH which lasts for at least one week. Further and more importantly, the coupling between neuronal activation and vessel dilatation is not only lost, but also reversed later than 24 hours after SAH. These findings indicate that metabolic coupling between neuronal activation and cerebral vessels is not only lost, but also reversed after SAH.

Key Publications


http://PlesnilaLab.isd-muc.de @ISD_Research https://twitter.com/ISD_research
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 major focus of our work is the detection of protective brain mechanisms that delay the onset of cognitive impairment. Another focus 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 reserve capacity, i.e. mitigate the impact of brain pathology on cognition in AD. Using DTI and multi-task fMRI, we map functional networks associated with protective factors.

We have recently identified a highly connected hub in the frontal cortex as a key brain region underlying reserve capacity in AD (Franzmeier et al. Brain 2018). We are currently testing in longitudinal studies whether enhancing frontal hub connectivity may have a beneficial effect on the clinical expression of dementing conditions. Together with Prof. Yaakov Stern (Columbia University, USA) and Prof. Gael Chetelat (INSERM, France) we recently founded the professional interested area (PIA) on “Reserve, resilience and protective factors” hosted by the Alzheimer’s Association. We are currently building a consortium to collect multiple data sets for replication of neuroimaging results on reserve and thus enhance reproducibility and transparency of our findings (https://www.survio.com/survey/d/H3A1L1E8M9I3A5L1D). For our second focus, 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.

A recent focus has been centered on 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 in data from the international DIAN study (https://dian.wustl.edu/). We are currently investigating the potentially protective effects of TREM2 in AD.

Key Publications


Team:
Ewers, Michael, Prof. Dr. / PI
Franzmeier, Nicolai, Dr. / postdoc
Neitzel, Julia, Dr. / postdoc
Ren, Jinyi / PhD student
Rubinski, Anna / PhD student
Pietzch, Hedwig / team assistant

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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).

Key Publications


http://LieszLab.isd-muc.de
@LieszLab
https://twitter.com/LieszLab

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

Research Group – PI: Ali Ertürk

Key Publications


We recently found that there are direct vascular connections between the skull and the meninges (which we named skull-meninges connections, SMCs), which mediate the exchange of cells and molecules between the skull and the brain, especially after a stroke (Cai, ..., Ertürk *BioRxiv* 2018) Nature Neuroscience, in press). This discovery suggests that the skull marrow cells might be directly involved in brain function in health and disease. Therefore, a better understanding of the skull bone marrow – meninges – brain interactions could reveal novel therapeutics and diagnostics. Easier accessibility of the skull compared to brain parenchyma makes it also attractive to study, which might eliminate hurdles of drug delivery into the brain, especially to control neuroinflammation.

We use artificial intelligence based algorithms (deep learning) to analyze our biological data, in particular those coming from the imaging of entire transparent organs and rodent bodies. This approach provides an unbiased view on biological mechanisms in action, and helps us to identify previously unpredicted key mechanisms such as the involvement of skull marrow in brain pathologies.

My laboratory is interested in understanding key mechanisms leading to neurodegeneration and inflammation in acute brain injuries and dementia. In particular, we are interested in studying the skull-meninges connections that we recently discovered. Towards this goal, we use methods such as 2-photon imaging and MR/PET as well as unbiased approaches such as single cell RNaseq, proteomics by Mass Spec, and deep tissue antibody labeling and imaging by clearing technologies that we have developed.
human cortical neurons with mutations in the Alzheimer-associated genes APP and PSEN1.

We aim to extend this work by generating all cell types that are relevant for neurodegenerative or neurovascular disease in the human brain from iPSCs, and combining them in a human brain tissue model, in which we can elicit and study disease phenotypes and investigate underlying mechanisms. In addition, because such models are accessible for genetic manipulation and amenable to drug development, we plan to apply them for translational studies to accelerate the identification of novel therapeutic approaches.

Key Publications


Team:
Paquet, Dominik, Prof. Dr. / PI
Stüven, Andrea / team assistant
Klimmt, Julien / graduate student (GSN)
Crusius, Dennis / technical assistant
Dansert, Angelika / graduate student (GSN)
Gonzalez-Gallego, Judit / graduate student (GSN) – co-supervised with Martin Dichgans
Pedro-Domingues, Liliana / graduate student (GSN) – co-supervised with Mika Simons / DZNE

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Neurodegeneration and Vascular Dysfunction Research Group – PI: Dominik Paquet

The PaquetLab aims to understand the molecular and cellular mechanisms leading to nerve cell death and cognitive decline in patients with neuropsychiatric disorders (e.g. Alzheimer’s disease, frontotemporal dementia and related disorders) and neurovascular impairments (stroke and vascular cognitive impairment). We apply cutting-edge technologies, such as CRISPR/Cas genome editing, differentiation of induced pluripotent stem cells (iPSCs) into human brain cells, and tissue engineering to build advanced human in vitro model systems recapitulating these diseases.

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 iPSCs, which have the genetic configuration of the affected patients and allow differentiating and studying somatic cell types directly affected by disease, such as neurons, astrocytes, microglia, oligodendrocytes, smooth muscle cells and endothelial cells.

We have recently established protocols for the optimized differentiation of major cell types of the human brain, and also developed efficient technologies to introduce and remove patient mutations using CRISPR/Cas genome editing. In a recent study (Paquet et al. Nature 2016) we have already demonstrated the potential and feasibility of our approach, by generating and studying isogenic sets of human cortical neurons with mutations in the Alzheimer-associated genes APP and PSEN1.

We aim to extend this work by generating all cell types that are relevant for neurodegenerative or neurovascular disease in the human brain from iPSCs, and combining them in a human brain tissue model, in which we can elicit and study disease phenotypes and investigate underlying mechanisms. In addition, because such models are accessible for genetic manipulation and amenable to drug development, we plan to apply them for translational studies to accelerate the identification of novel therapeutic approaches.

Key Publications


Our group aims to characterize genomic changes at single cell resolution and to reveal mutagenic mechanisms leading to diseases. We primarily use single-cell sequencing technologies to characterize phenotypes and use molecular biology and animal models to understand the effects of somatic mutations on disease pathologies.

Our major research focus is genomic instability in brain during post stroke pathologies and neurodegeneration.

We use single-cell sequencing to measure the accumulation of genomic mutations in animal models. Our aim is to identify mechanisms leading to genomic instability in cell types of the brain and to develop therapies to slow genomic aging.

Together with Jürgen Bernhagen, we also analyze B-cell development at the single-cell resolution, as they are a key player in cardiovascular disease and atherosclerosis which is the main risk factor for stroke. B-cell maturation involves somatic hypermutation and genetic recombination generating antibody diversity. We specifically study the role of atypical chemokines in B-cell development in order to reveal their function in the development and induction of the somatic mutations.

**Key Publications**


A proteomic analysis of isolated brain vessels from CADASIL patients and biochemical analyses imply loss of HTRA1 proteolytic function as a critical step in the pathogenesis of CADASIL, the most common hereditary cause of cerebral small vessel disease (cSVD). The study suggests shared molecular pathways between genetically distinct causes of cSVD.


Complex heart surgery may lead to organ dysfunction such as acute kidney injury (AKI) or ischemic stroke. A researcher team led by Aachen University and the Bernhagen lab found that patients with high blood levels of the cytokine MIF had a reduced risk of developing AKI. The study is published in an issue of Sci Transl Med.


A large scale genetic study on major brain diseases including stroke and Alzheimer’s disease revealed shared genetic influences between multiple brain disorders and relevant phenotypes, including cognitive measures. The results highlight the value of heritability-based methods in understanding the etiology of neurological and psychiatric disorders. ISD investigators were on the steering committee of this long term project.


Using a Mendelian Randomization approach and data from >800,000 individuals ISD investigators showed that genetic predisposition to higher levels of the inflammatory cytokine MCP-1 is associated with a higher risk of stroke, in particular large artery stroke and cardioembolic stroke. These findings inform the planning of future clinical trials.


The Erturk group developed a nano-body-based immunolabeling method, vDISCO, that enables imaging subcellular details in transparent mice. They uncovered neuronal projections and skull-meninges connections in whole adult mice that are likely to have relevance in both health and disease.

Using RNA sequencing and qRT-PCR in three independent samples of acute ischemic stroke patients ISD researchers established a set of 3 circulating microRNAs (miR-125a-5p, miR-125b-5p, and miR-143-3p) as a promising blood-based diagnostic marker for the early phase of ischemic stroke.


ISD researchers have identified the choroid plexus as a previously unrecognized key structure for cerebral T cell invasion into the brain after stroke. These findings are of high relevance for clinical trials targeting immune cell infiltration in stroke patients.


Some patients with Alzheimer’s disease show a remarkable resilience against the impact of brain pathology. A new ISD study revealed a hub region in the brain that plays a key role in delaying dementia symptoms even in genetically caused AD.


Diffusion changes are a major hallmark of cerebral small vessel disease. A recent study from ISD investigators shows that these changes are largely driven by increased extracellular fluid and not the degeneration of white matter fiber tracts. The results support the accumulating evidence of disturbed blood-brain barrier function in small vessel disease.


In a series of studies involving almost 900,000 individuals from around the world an international GWAS effort led by ISD investigators identified 35 risk loci for stroke. Two studies published in Nature Genetics and Annals of Neurology demonstrate shared genetic variation with related vascular traits, including blood pressure, cardiovascular traits, and venous thromboembolism. The results further provide novel targets for mechanistic studies and perspectives for drug development.

Another important lesson from the two studies is that some genes implicated in Mendelian forms of stroke also contribute to sporadic stroke through common genetic variants.


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Ischemic stroke symptoms, regardless of severity, are often accompanied by 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 (e.g., Wollenweber et al. Stroke 2016). 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 DEDEMAS: 600
- Started May 2013
- Current enrollment: 602 (completed)
- 2764 at ISD + 338 from additional study centers
- Estimated date for study completion: 2023
- Coordinator: M. Dichgans
- Project management: F. Wollenweber, K. Waegemann
- Funding: German Center for Neurodegenerative Diseases (DZNE)
- Publications: Wollenweber FA et al., Int J Stroke 2014

**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. 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 are done at 6, 12, 36, and 60 months. Patients developing cognitive impairment

**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 2013
- Current enrollment: 1,192 patients
- Principle investigators: M. Dichgans, V. Zietemann
- Publications: Wollenweber FA et al., Stroke 2013

**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: 754
- We estimate to complete the study in 2019
- Principle investigators: M. Dichgans, Marios Georgakis
- Publications: Liman T et al., Int J Stroke 2013
- Zietemann V et al., Eur Stroke J 2016
- Malisch C et al., Plos One 2018

**CAPIAS (Carotid Plaque Imaging in Acute Stroke; NCT01284933)**
Even with extensive diagnostic work-up 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 withcryptogenic 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 (TUM), Freiburg and Tübingen.

**Planned sample size: 300**
- Started February 2011
- Current enrollment: 234
- Principle investigator: M. Dichgans, T. Saam
- Project management: A. Kopczak
- Publications: Bayer-Karpinska A et al., BMC Neurol 2013
- Schwarcz P et al., Neurology 2013
- Grimm JM et al., J Cardiovasc Magn Reson 2014
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, IMRI) and cognitive decline during annual follow-up. In addition, we will include 50 subjects with CADDASIL, 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 investigator:** M. Ewers, M. Dürring, K. Bürger

**Publications:**

- Taylor AN et al., Alzheimers Dement 2013
- Baykara et al., Ann Neurol 2016
- Franzmeier N et al., J Alzheimers Dis 2017
- Taylor AN et al., Alzheimers Dement. 2017
- Simon-Vermot L et al., Front Aging Neurosci 2018
- Franzmeier N et al., Alzheimers Res Ther 2018
- Duering et al., J Stroke 2018
- Duering et al., Alzheimers Dement 2018

**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:** 2000

**Started:** February 2014

**Current enrollment:** 1811 (USD)

**Principle investigator:** K. Bürger

**CIRCLUCAS (CIRCUlating biomarkers After Stroke)**

Currently, clinical decision-making in the acute phase of stroke is guided by neuroimaging, which lacks accuracy and is not available worldwide. Blood-based biomarkers are predicted to be an integral element of future precision medicine and their detection has been facilitated by recent technological advances. However, despite various attempts, no blood-based biomarker has been established for stroke. CIRCLUCAS is a case-control study aimed at identifying novel blood-based biomarkers to support decision-making in the acute phase of stroke such as the separation of patients with ischemic stroke and patients with transient ischemic attacks, stroke mimics, and hemorrhagic stroke. Compared to previous biomarker studies, CIRCLUCAS’ focus on biosampling of patients with suspected stroke allows for unprecedented coverage of timepoints starting at hospital arrival and follow-up until day 90. Assessments include detailed documentation if the clinical course, past medical history, and medication, neuroimaging and clinical laboratory parameters.

**Started:** February 2014

**Planned sample size:** 2000 patients

**VASCAMY (Interaction between Vascular & Amyloid Pathology in Alzheimer’s Disease)**

In Alzheimer’s disease (AD), cerebrovascular disease frequently co-occurs with β-amyloid (ß). However, the specific roles of AB 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, IMRI) and cognitive decline during annual follow-up. In addition, we will include 50 subjects with CADDASIL, 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. Dürring, K. Bürger

**Publications:**

- Taylor AN et al., Alzheimers Dement 2013
- Baykara et al., Ann Neurol 2016
- Franzmeier N et al., J Alzheimers Dis 2017
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- Simon-Vermot L et al., Front Aging Neurosci 2018
- Franzmeier N et al., Alzheimers Res Ther 2018
- Duering et al., J Stroke 2018
- Duering et al., Alzheimers Dement 2018

**TREAT-SVDs**

**Effect of Amlodipine and other Blood PREssure Lowering Agents on Microvascular Function in Small Vessel Diseases**

TREAT-SVDs is a prospective, multi-centre, multinational, randomised, open-label, 3 sequence crossover clinical trial phase III b study with blinded endpoint assessment (PROBE design). The trial enrolls patients with lacunar stroke, vascular cognitive impairment, and CADDASIL. We hypothesise that the function of cerebral microvessels can be influenced by medication and that this influence can be measured by assessing changes in blood flow response to a stimulus such as CO2. Cerebrovascular reactivity to CO2 is known to be impaired after stroke as a marker for endothelial dysfunction. Endothelial dysfunction increases arterial stiffness in other vascular beds. In large arteries vascular stiffness leads to an increase in pulse wave velocity which is an independent risk factor for cardiovascular disease. Short-term variability of 24-hour systolic blood pressure (BP) shows an independent relation to aortic stiffness in hypertension. While it is well established that hypertension is a risk factor for SVDs, stroke and dementia, there is novel evidence that BP variability is a major independent risk factor. TREAT@SVDs will compare the effect of different antihypertensive drug classes on microvascular function, assessed by cerebrovascular reactivity and BP variability, in SVDs. All patients meeting eligibility criteria are randomly allocated to one of three sequences of antihypertensive treatment (each for 4 weeks) which are given in standard dose in the following order: Group 1: amlodipine > losartan > atenolol; Group 2: atenolol > amlodipine > losartan; Group 3: losartan > atenolol > amlodipine. Studying the effects of different
antihypertensive drug classes on microvascular function, assessed by CVR and BP variability, holds great promise for improving our mechanistic understanding of SVDs, stroke, and dementia.

Study sites: Munich, Oxford, Edinburgh, Maastricht, Utrecht
Coordinating Investigator: M. Dichgans
Project management: A. Kopczak
Status: recruiting
Started February 2018
Planned sample size: 105 (30 genetic SVDs + 75 sporadic SVDs)
Estimated date for study completion: July 2019
Funding: EU Horizon2020 research and innovation programme

INVESTIGATE-SVDs
Imaging NeuroVascular, Endothelial and StrucTructural InteGriTY in PrepaRation to TReat Small Vessel Diseases

INVESTIGATE-SVDs is a multi-center observational study including an interventional study paradigm. Our working hypothesis is that blood pressure (BP), BP variability, and age-related molecular changes in microvessels have profound effects on the regulation of cerebral blood flow as well as on the barrier and clearance functions of small brain vessels. Over time, this burden of compromised function results in structural brain alterations such as changes in the perivascular space, white matter lesions, and infarcts as well as haemorrhages, which ultimately lead to stroke and dementia, the two major manifestations of SVDs. INVESTIGATE-SVDs will advance our knowledge of SVD pathophysiology by assessing the factors responsible for altered brain microvascular function. Specifically, it will assess the relationship between increased blood brain barrier (BBB) permeability, decreased cerebrovascular reactivity to CO2, BP variability and clinical and structural features of SVD. Our hypothesis is that greater BBB permeability will be associated with more reduced cerebrovascular reactivity. We hypothesise that (i) it will be possible to have increased BBB permeability without decreased cerebrovascular reactivity as this should occur at an earlier point in the pathogenesis of SVDs; (ii) enlarged perivascular spaces on structural imaging correlate with increased BBB permeability and reduced cerebrovascular reactivity, and (iii) more variable blood pressure worsens BBB permeability and cerebrovascular reactivity, and that this effect will be greater than the effect of hypertension alone. The study is exploratory and will provide key information on several components of microvascular function.

Study sites: Edinburgh, Maastricht, Munich
Local Principle Investigator: M. Dichgans
Project management: A. Kopczak, K. Waegemann
Status: recruiting
Started July 2017
Planned sample size: 75 (30 genetic SVDs at ISD + 45 sporadic SVDs at other study sites)
Current enrollment: 45 (16 genetic SVDs at ISD + 29 sporadic SVDs at other study sites)
Estimated date for study completion: July 2019
Funding: EU Horizon2020 research and innovation programme

Zoom@SVDs
Zooming in at microvascular malfunction in Small Vessel Diseases with 7T MRI

Zoom@SVDs is a longitudinal observational study with 7T MRI in 60 patients with sporadic SVDs and 30 healthy controls. In addition, 20 patients with CADASIL as a hereditary form of SVDs and 10 matched healthy controls will be enrolled. Primary objective is to determine which novel 7T markers of microvascular malfunction most clearly differentiate patients with SVDs from healthy controls. Secondary objectives are to explore the relation between microvascular function and parenchymal lesion presence at baseline and lesion progression after 24 months. The study will relate microvascular function to (i) blood pressure and blood pressure variability and to (ii) cognitive function in the cross sectional study design as well as to (iii) cognitive decline in the longitudinal study design. All 7T MRI scans will be performed at the University Medical Center Utrecht (UMCU). For the 20 CADASIL patients and 10 healthy controls recruitment, informed consent, core clinical work-up and follow up will be done at the ISD. These patients will travel to Utrecht to undergo 7T MRI.

Study sites: Utrecht, Munich
Local Principle Investigator: M. Dichgans
Project management: A. Kopczak, K. Waegemann
Status: recruiting
Started March 2017
Planned sample size: 120 (90 UMCU + 30 ISD)
Current enrollment: 61 (33 UMCU + 28 ISD)
Estimated date for study completion: December 2020
Funding: EU Horizon2020 research and innovation programme

Industry-sponsored Trials

TANGO
Randomized, double-blind-placebo-controlled, parallel-group study to assess the safety, tolerability, and efficacy of BIIB092 in subjects with mild cognitive impairment due to Alzheimer’s disease or with mild Alzheimer’s disease.
Protocol number 251AD201
Sponsor: Biogen USA/UK
Status: recruiting

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: ongoing

SiMaMCI
Randomized Controlled Trial of Simvastatin in Amnestic MCI Patients.
Local principle investigator: K. Bürger
Status: ongoing
Funding & Education
**Funding**

SyNergy promotes integrative research on major neurodegenerative, inflammatory and vascular diseases. SyNergy research projects are organised into four research areas, each targeted at neurodegenerative and -vascular diseases. SyNergy research projects are conducted 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 additionally supported to research clusters and introduce an additional element of interaction between the Cluster scientists. Projects combine expertise across traditional pathomechanisms, as well as systems biology and systems neuroscience tools – many of them involving both basic scientists and academic clinicians. 

**Tandem Projects**

- Munich Cluster for Systems Neurology (SyNergy) (DFG funded Excellence Initiative) 
- Munich Cluster for Systems Neurology 
- Munich Cluster for Systems Neurology

For more information see [www.synergy-munich.de](http://www.synergy-munich.de)

**Project Funding**

**SyNergy Board:** M. Dichgans

**Clinician Scientist Program** (PI: S. Tiedt) 
**Clinician Scientist Group** (PI: A. Liesz)

**SyNergy Professor:** J. Bernhagen

**Munich Cluster for Systems Neurology (SyNergy)**

**B1 – Systems neurology of cell-type specific mitochondrial pathology in neurodegeneration and ischemia models (A. Liesz)**

- Identifying key regulators of neuronal replacement after neurodegeneration and stroke (M. Dichgans; A. Liesz; N. Plesnila)

**B2 – Small vessel disease (SVD) – multiscale imaging from models to patients (M. Dichgans; A. Liesz; N. Plesnila)**

**B3 – Exploring disorders of the neuro-glio-vascular unit in isogenic human iPSC-derived in vitro models** (D. Paquet; M. Dichgans; N. Plesnila)

**B1** – Systems neurology of cell-type specific mitochondrial pathology in neurodegeneration and ischemia models (A. Liesz)

- Identifying key regulators of neuronal replacement after neurodegeneration and stroke (M. Dichgans; A. Liesz; N. Plesnila)

- B3 – Small vessel disease (SVD) – multiscale imaging from models to patients (M. Dichgans; A. Liesz; N. Plesnila)

- C3 – Exploring disorders of the neuro-glio-vascular unit in isogenic human iPSC-derived in vitro models (D. Paquet; M. Dichgans; N. Plesnila)

**D1 – Microglial activity markers: from mouse models to humans (M. Dichgans)**

**D2 – Pharmacological inhibition of HDAC9 for atheroprotection and its effect on neuroprotection (M. Dichgans; A. Liesz; J. Bernhagen; N. Plesnila)**

**Technology hubs**

**Mcroscale hub** (A. Ertürk) involves: 
- Tailored virus vectors for cell labelling and tracing; 
- RV-based trans-synaptic tracing for network analysis; 
- Methods development in tissue clearing; light-sheet imaging for whole-brain analysis.

- Macroscale hub (M. Düring): µPET/MRI for longitudinal & molecular in vivo studies; ultra-scale, multi-parametric imaging: mice to men; dedicated research scanners and unified imaging protocols; development of new imaging-based disease markers.

- Genome hub (D. Paquet): Scarless CRISPR/Cas editing; mutation knock-ins, gene-corrections & larger genome edits; gene-edited iPSCs; differentiation into disease-relevant somatic cells.

**Clinician Scientist Group (PI: A. Liesz)**

**Clinician Scientist Program (PI: S. Tiedt)**

**SyNergy Professor:** J. Bernhagen

**Clinician Scientist Program** (PI: J. Bernhagen)

**SyNergy Board:** M. Dichgans

For more information see [www.synergy-munich.de](http://www.synergy-munich.de)
The five-year project which is funded with 6 Mio EUR through the European Commission’ 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 prospective sub-studies:

**ZOOMgSVDs**, an observational MRI study at ultra-high resolution (7T) to assess microvascular function and parenchymal damage.

**INVESTIGATE-SVDs**, an observational 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.

 Coordinates: M. Dichgans

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

The five-year project, which is funded with 6 Mio EUR through the European Commission 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 stroke (SVDs): Blood pressure variability, Blood Brain Barrier, Microvascular matrisome, and Inflammation. New mechanisms will be validated in animal models and in humans. All work packages are led by pre-clinical and clinical investigators who collaborate on specific problems. 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 prospective sub-studies:

- ZOOMgSVDs, an observational MRI study at ultra-high resolution (7T) to assess microvascular function and parenchymal damage.
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- 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/
Common mechanisms and pathways in Stroke and Alzheimer’s disease
Stroke and Alzheimer’s disease (AD) impose a huge burden on aging societies. Stroke and AD often co-occur, and it has been speculated that the two disorders have an overlapping pathogenesis. The Horizon 2020-funded project CoSTREAM aims to identify these common mechanisms and pathways in stroke and AD 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. 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 (WP). An essential feature is joint work across Work Packages that will thereby ensure smooth transition across the three phases. Martin Dichgans leads WP 1 on Genetics, which aims to determine the genetic overlap between stroke and AD as well as their subtypes and provide an estimate of the genetic correlation between the two. Furthermore, this WP will pinpoint specific genes or genomic regions that mediate risk to stroke or stroke subtypes, relevant MRI markers and AD. The ISD further contributes to WP 2 on Metabolomics, WP 3 on Brain Imaging and WP 6 on Therapeutics. PI: M. Dichgans
For more information see http://www.costream.eu/

### Third party funds (spent) | Courtesy of Vascular Dementia Research Foundation*

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<tr>
<th>Source</th>
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* (without outpatient clinic)
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<th>Role (PI=Principal Investigator)</th>
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<tr>
<td>SyNetro – Munich Cluster for Systems Neurology</td>
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<td>Associated Investigator, Tandem project B9, Core 9; A. Ertürk</td>
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<td>W3: Professor “Vaskuläre Biologie”, Core 13; J. Bernhagen</td>
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<th>Funding Institution</th>
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<th>Period</th>
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<tr>
<td>SFB 1123 – Atherosclerosis – Mechanisms and networks of novel therapeutic targets</td>
<td>DFG German Research Foundation</td>
<td>PI: M. Dichgans</td>
<td>Jul 2014 to Jun 2018</td>
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<td>Role of HDAC9 in Atherosclerosis. PIs: M. Dichgans, C. Haffner, Y. Azare</td>
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<td>Mechanisms of atherogenic recruitment by MIF family proteins and peptide-based therapeutic leads. PIs: J. Bernhagen, A. Kapusniok (TU)</td>
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<td>CoSTREAM – Common mechanisms and pathways in Stroke and Alzheimer’s disease</td>
<td>EU Horizon 2020</td>
<td>PI: M. Dichgans</td>
<td>Mar 2012 to Nov 2020</td>
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<td>Neuroinflammatory mechanisms of chronic neurodegeneration and cognitive decline following traumatic brain injury</td>
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<td>ERA-Net Neuron</td>
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<td>PIs: A. Ertürk, N. Plesnila</td>
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<td>Protectin vor kardiovaskulären Veränderungen im Alter durch S-Nitrosierung des Zytokins Macrophage Migration Inhibitory Factor</td>
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<td>Else-Kröner-Fresenius-Stiftung (EKFS)</td>
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<td>Molecular mechanisms of regressive and dominiant mutations in the small vessel disease-related high temperature requirement protease HTRA1</td>
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<td>DFG German Research Foundation</td>
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<td>Structural and functional connectivity in cerebrovasc. small vessel disease</td>
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<td>DFG German Research Foundation</td>
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<td>Bedeutung von Perizenten für die Störung der zerebralen Mikrozirkulation nach Subarachnoidalblutung</td>
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<td>Else-Kröner-Fresenius-Stiftung (EKFS)</td>
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<td>Leukocyte-Interaction with immunological brain barriers</td>
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<td>DFG German Research Foundation</td>
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<td>Assessing neurodegeneration throughout the entire brain at a single cell resolution in mice</td>
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<td>PI: A. Ertürk</td>
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<td>Usage of tissue clearing technology to investigate brain regions that are involved in diabetes</td>
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<td>Member of Helmholtz Alliance ICEMED</td>
<td>PI: A. Ertürk</td>
<td>Nov 2016 to Oct 2018</td>
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<td>VASCAMY – Interaction beween vascular and immune brain pathology in Alzheimer’s disease</td>
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<td>EU Marie Curie</td>
<td>PI: M. Ewers</td>
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<td>FöFoLe funding MD thesis: Sabrina Richter (&quot;Theoretical chemokine MIF and lymphocytes in atherosclerosis: emerging molecular and cellular links&quot;)</td>
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<td>FöFoLe funding, LMU/KUM</td>
<td>PI: T. Bernhagen</td>
<td>Jan 2018 to Dec 2019</td>
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<td>PI: O. Goke</td>
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<td>A novel oxidized MIF form, DZHK project PR.2-C</td>
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<td>DZHK Zentrum für Herz-/Kreislauferkrankungen (DZHKZ)</td>
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<td>(T. Rassaf, Essen)</td>
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<td>Entwickeln genetisch kodierter Ks Fluoreszenzensoren</td>
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### Project Funding

<table>
<thead>
<tr>
<th>Project</th>
<th>Funding Institution</th>
<th>Role (PI=Principal Investigator)</th>
<th>Period</th>
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<tbody>
<tr>
<td>Structurelle und funktionelle Konnektivität als Biomarker der vasculären kognitiven Störung</td>
<td>Else-Kröner-Fresenius-Stiftung (EKFS)</td>
<td>PI: M. Düring</td>
<td>Feb 2015 to Jan 2017</td>
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<td>Notch3-Aggregation</td>
<td>VERUM Foundation</td>
<td>PI: D. Paquet</td>
<td>Dec 2018 to Nov 2020</td>
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<td>HDAC6-mediated mediated mechanisms underlying vascular inflammation</td>
<td>Medical Faculty, FFoLe</td>
<td>PI: Y. Asare</td>
<td>Dec 2015 to May 2017</td>
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<tr>
<td>Characterization of neurodegeneration in the entire brain after TBI using novel 3D imaging approach</td>
<td>Medical Faculty, FFoLe</td>
<td>PI: A. Ertürk</td>
<td>Sep 2016 to Mar 2018</td>
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<tr>
<td>Allergic-induced human brain tissue model to investigate neurodegenerative and vascular disorders</td>
<td>LMUnexcellent</td>
<td>PI: D. Paquet</td>
<td>Dec 2018 to Nov 2019</td>
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<tr>
<td>The gut microbiota in post-stroke neural plasticity</td>
<td>LMU, LMUnexcellent initiative</td>
<td>PI: A. Liesz</td>
<td>Mar 2016 to Feb 2017</td>
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<tr>
<td>Disentangling brain damage due to Alzheimer’s and vasoc disease using DTI</td>
<td>Alzheimer Forschung Initiative e.V.</td>
<td>PI: M. Düring</td>
<td>Nov 2016 to Oct 2018</td>
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<tr>
<td>Strategic Partnership LMU/Singapore within LMUlexc (&quot;Mechanisms of cardiovascular protection: from preconditioning to endothelial memory&quot;)</td>
<td>LMUlexc / DFG</td>
<td>PI: J. Bernhagen</td>
<td>Oct 2017 to Sep 2019</td>
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<td>Usage of tissue clearing in metabolic disorders</td>
<td>Helmholz</td>
<td>PI: A. Ertürk</td>
<td>Jun 2018 to Apr 2019</td>
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<td>Structural and functional features of skull-meningeal connections (SMcS)</td>
<td>LMU</td>
<td>PI: A. Ertürk</td>
<td>Jan 2018 to Dec 2019</td>
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<td>Age and AD related bottlenecks in glymphatic-lymphatic waste transport</td>
<td>NIF</td>
<td>PI: A. Ertürk</td>
<td>Sep 2017 to Aug 2022</td>
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<td>STREME: PNIN and DRR as CSF Biomarkers</td>
<td>Association for Frontotemporal Degeneration (AFTD)</td>
<td>PI: M. Ewers</td>
<td>Jan 2016 to Jan 2018</td>
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<tr>
<td>Die Rolle von MIF innerhalb der kardialen ischämischen Prämiktionierung</td>
<td>DFG</td>
<td>PI: J. Bernhagen</td>
<td>Nov 2015 to Oct 2018</td>
</tr>
<tr>
<td>K-REICHdom-MIF - Vergleichende Analyse der Funktion von Macrophage Migration Inhibitory Factor (MIF)-Proteinen in Tier- und Pflanzen-zellen</td>
<td>DFG</td>
<td>PI: J. Bernhagen</td>
<td>Jan 2017 to Dec 2019</td>
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<tr>
<td>Indikation von Inhibitoren der pathologischen Notch3-Aggregation</td>
<td>DFG</td>
<td>PI: C. Häflinger</td>
<td>Nov 2017 to Nov 2020</td>
</tr>
</tbody>
</table>
2018 | Faculty of Medicine

Dichgans M, Opherk C, Pfefferkon T, Wollenweber F I Interdisziplinäre Behandlung des Schlaganfalls (7C0014)

Dichgans M, Hamann G, Opherk C | Experimentelle Ansätze in der Schlaganfalltherapie (7C0376)

Bartenstein P, Bürger K, Catak C, Dichgans M, Ewers, Rominger M | Demonstration nuklearmedizinischer Befunde im Rahmen der Vascular Imaging; Vorstellung ausgewählter Krankheitsbilder (7P0609)

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

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

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

Dichgans M, Klein M, Opherk C, Straube A I Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder (7P0609)

Dichgans M, Opherk C, Pfefferkon T, Wollenweber F I Interdisziplinäre Behandlung des Schlaganfalls (7P0610)

Bürger K, Dichgans M, Düring M, Ewers M I Strukturelle Magnetresonanztomographie in der Demenzforschung (7C0374)


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

Paquet D I Experimental research on neurodegenerative and neurovascular disorders (7C0189)

Paquet D I Current developments in human in vitro research on neurodegenerative and neurovascular disorders (7C0190)

Bürger K | Brainblockpraktikum Psychiatrie u. Psychotherapie 1 (7M1463)


Bernhagen J, El Boukari O, Gökce O, Hoffmann A | Practical Course Molecular and Cellular Cardiovascular Medicine (7C0408)

Gökce O | Molecular biology and –omics approaches in the biomedical field – seminar (7C0124)

Alzheimer Demenz (7C4046)


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

Dichgans M, Klein M, Opherk C, Straube A I Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder (7P0609)

Bürger K, Catak C, Dichgans M, Wollenweber F | Interdisziplinäre Behandlung des Schlaganfalls (7P0610)

Dichgans M, Ewers M I Strukturelle Magnetresonanztomographie in der Demenzforschung (7C0374)

Caballero M, Düring M, Ewers M I Multimodal Bildgebung zur Gehirnveränderungen bei der Alzheimer Demenz (7C0233)

Dichgans M, Ewers M I Diskussion aktueller Forschungsbefunde zur Alzheimer Demenz (7C0124)


Clinician Scientist Program PRIME

Starting from January 2019 the DFG-funded clinician scientist PRIME program (PRIME, Coordinator: S. Massberg) will promote the clinical as well as scientific career of clinician scientists with a vascular research focus. PRIME will be integrated into the interdisciplinary Munich Clinician Scientist Program MCSP framework to pursue the following structural aims: 1) establish an institutionalized vascular clinician scientist program for eligible talented early career researchers as an optional track integrated into the resident programs of the participating disciplines; 2) provide flexible models of protected research time for clinician scientists adapted to the specific needs of the clinical training programs within the participating disciplines while minimizing delay in clinical training and board certification; 3) provide a scientific qualification program that specifically addresses the needs of clinician scientists with a vascular research focus; 4) expand and adapt the mentoring and role model program to the needs of PRIME to further enhance visibility and appeal of the program. PRIME convenes groups representing disciplines with a vascular focus. Specific measures will be implemented to grant equal opportunity of clinician scientists with family. Independent experts on governance and performance management in academic and research institutions will evaluate PRIME and provide the applicants and PIs with regular feedback. The ISD has a coordinating role in the PRIME Neurovascular Medicine Cluster.

Participation in Graduate Schools

Munich Center for Neurosciences - Brain and Mind: ISD staff actively participates in 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:
• an optimally structured and student-centered teaching program in English;
• 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 (MSc, PhD);
• ECTS based grading (Bologna System);
• personal career planning and intensive individual coaching for scientific and related careers;
• 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;
• an international network for future careers in academia and RTD projects for graduates, PhD students and post-docs (see www.mcn.lmu.de). M. Dichgans and Judit Gonzalez-Gallego (PhD students) are on the scientific board of the GSN.

Integrated PhD graduate program of the CRC 1123: Atherosclerosis

Doctoral researchers enrolled in the IRTG program are offered a three-year structured PhD program, allowing the students to collect the necessary ECTS points to obtain their PhD in Medical Research. MD students are welcome to join the study program for the duration of their medical thesis research project in the lab. The fundamental goal of the qualification program is to provide training specifically tailored to the needs and topic the CRC. The training program consists of:
• Basic principle seminars focusing on atherosclerosis and related innate and adaptive immunity;
• Advanced methodological courses with an emphasis on in vivo assays, animal models and state-of-the-art imaging tools;
• Soft skills seminars on communication, presentation and other topics equally relevant for a scientific, as well as a non-scientific, successful career;
• Scientific education provided by lecture series (by national and international renowned speakers in the field), annual retreats, workshops and international summer school;
• Doctoral Program and Degrees: As part of the IRTG1123 students will obtain a doctoral degree according to the guidelines from the MMRs at the LMU’s Medical Faculty. Depending on the students and supervisor’s academic backgrounds, one of the following degrees can be obtained:
• PhD (doctoral degree in Medical Research);
• Dr. rer. nat. (doctoral degree in Natural Sciences);
• Dr. hum. bio. (doctoral degree in Human Biology);
• Dr. med. (doctoral degree in Human Medicine); ISD staff further participates in the graduate program Molecular Medicine.
Role of the COP9 signalosome in atherosclerosis. Y. Tian, planned degree: PhD (MMRS), started Oc 2017

The role of brain-released alarmins in post-stroke systemic immunomodulation. C. Benakis | Marie Curie Individual Fellowship 2018

Honors & Awards

THE INSTITUTE FOR STROKE AND DEMENTIA RESEARCH | ANNUAL REPORT 2017/2018

PhD Theses
The role of Tau isoform expression in human iPSC-derived Tauopathy models A. Danner, planned degree: PhD (IGSN), started Dec 2018

Functional exploration of FoxQ2, a risk gene for cerebral small vessel disease. J. Gonzalez-Gallego, planned degree: PhD (IGSN), started Oct 2018

Post-stroke sterile inflammation in atherosclerotic plaque rupture and secondary infarctions. J. Cao, planned degree: PhD, started Sept 2018

MIF-2/DT in atherosclerosis and stroke. C. Zan, planned degree: PhD (GSN), started Oct 2018

Peptide-based inhibition strategies in atherosclerosis. Y. Gao, planned degree: PhD, started Sept 2018

Human iPSC-derived brain tissue models for Alzheimer’s disease. J. Klimmt, planned degree: PhD (GSN), started Sep 2018

The role of striatal circuit function and plasticity after stroke. PhD, started Sept 2018

The role of the COP9 signalosome in neuroinflammation, ischemic stroke and intracranial atherosclerosis. Y. Tian, planned degree: PhD (MMRS), started Oct 2017

Role of the COP9 signalosome in atherogenic inflammation. J. Milic, planned degree: PhD (IRTG1123), started Mar 2017

Investigating the nervous and immune system at the single cell resolution. S. Besson-Giraud, planned degree: PhD (IGSN), started Jan 2017

MIF proteins and their receptors in atherosclerosis: structure-activity-relationships and novel cellular routes. C. Kramer, planned degree: Dr. rer. nat. (IRTG1123), started Mar 2017

Advanced diffusion models in cerebral small vessel disease. M. Kneifetz, planned degree: PhD (MMRS), started Sep 2016

Heterogeneity of oligodendrocyte myelination in development and adulthood. L. Felten, planned degree: PhD (IGSN), started Jan 2016, co-supervised by Mika Simons, DZNE Munich

The atypical chemokine interactome in inflammation. M. Brandhofer, planned degree: Dr. rer. nat., started Apr 2016

Modification and regulation of MIF by innate immune cell-derived oxidants and other MIF-protein family isoforms. L. Schindler, planned degree: Dr. rer. nat., started Nov 2016

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

Proteomic approach to study molecular pathomechanisms in hereditary small vessel diseases. A. Zeller, planned degree: Dr. rer. nat., started Oct 2014

The chondroid plexus in post-stroke lymphocyte invasion. G. Löwera, planned degree: Dr. rer. nat., started Aug 2013

Medical Theses
Role and mechanism of the MIF protein family in ischaemic stroke. S. Wang, planned degree: Dr. med., started Jan 2017

Tryptophan metabolism is a key mechanism of microbeia-mediated immune alterations after acute stroke. P. Meller, planned degree: Dr. med., planned Sep 2018.

The role of oxidized species of the atypical chemokine MIF in early atherosclerosis. L. Zwiller, planned degree: Dr. med. (IRTG1123), started Mar 2018

MIF-mediated B-lymphocyte recruitment and tertiary lymphoid organs: molecular and cellular mechanisms and role in atherosclerosis. S. Reichl, planned degree: Dr. med., FoFoLab fellow for excellent structured MD thesis, started in Mar 2018

Role of FCGR1 in microglia-mediated synaptic pruning. C. Heisen, planned degree: Dr. med., FoFoLab MD thesis, started Mar 2018

The spatial relationship of acute infarcts and white matter hyperintensities. M. Aichmiller, planned degree: Dr. med., started Sep 2015

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

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

Role of HDAC9 in proatherogenic processes in vascular cells. L. Bokov, planned degree: PhD, started Apr 2016

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

Completed:

The Functional Role of the Macrophage Migration Inhibitory Factor Protein Family in Myocardial Fibrosis. J. Soppert, Dr. rer. nat., completed April 2015

Mechanism of macrophage migration inhibitory factor (MIF)-induced blood-brain barrier (BBB) dysfunction in ischemic stroke. H. Chen, PhD, completed October 2017

Neural memory of cognitive reserve in Alzheimer’s disease. N. Franzmeier, PhD (GSN), completed Dec 2017


Imaging Markers of Cerebral Small Vessel Disease. E. Baykara, PhD (GSN), completed Aug 2018

The protective role of MIF in acute kidney injury after cardiac surgery. L. Arendsen, MD, completed April 2018

The role of brain-released alarmins in post-stroke atheroprotection. S. Roth, Dr. rer. nat., completed Oct 2018

Honor’s & Awards

• C. Benakis | Marie Curie Individual Fellowship, 2017
• M. Düring | Adolf Wallenberg Award (OSGI), 2017
• M. Düring | Radboud Excellence Initiative Fellowship 2018
• J. Milic | Distingt Oravadic Scholarship Serbia, 2017

Theses, Honors & Awards

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Conferences, Trainings and Events (Selection)

World Health Summit (Berlin, Oct 2018) Dementia Prevention by Stroke Prevention (M. Dichgans: scientific chair)

10th International Symposium on Neuroprotection and Neurorepair (Dresden, Oct 2018) N. Plesnila: session chair, speaker

INTS NeuroTrauma 2018 (Toronto, Canada, Aug 2018) N. Plesnila: scientific chair, speaker


DGNKongress (Leipzig, Sep 2017) M. Dichgans: scientific chair


NNS 2017, 35th Annual Neurotrauma Symposium Snowbird (USA, Jul 2017) N. Plesnila: session chair, speaker

Heart & Brain Meeting (Düsseldorf, June 2017) M. Dichgans: scientific chair

Medical Ethics Workshop (Venice, Italy May 2017) N. Plesnila: organizing committee member

3rd European Stroke Organisation Conference (Prague, May 2017) M. Dichgans: conference chair

Arbeitskreis Neurologie, Sponsoring by Bayer Healthcare (Berlin, May 2017) M. Dichgans: scientific chair

BRAIN (Berlin, Apr 2017) 28th Symposium on Cerebral Blood Flow, Metabolism and Function, 13th Conference on Quantification of Brain Function with PET M. Dichgans: scientific chair


4th ESO Stroke Science Workshop (Garmisch-Partenkirchen, Nov 2017) M. Dichgans: scientific chair, organizing committee member

External Speakers in ISD Talks (Selection)
Hector Cabrera-Fuentes, Duke-NUS GMS and National Heart Research Institute of Singapore
Karim Hochrainer, Weil Cornell Medical College
John Cryan, BSc Biochemistry, Nat.University of Ireland, Galway
Dominik Michalski, Klinik und Poliklinik für Neurologie, Universitätstiklinikum Leipzig
Renaud Jolivet, CERN and University of Geneva
Willem Huijbers, Tilburg University, The Netherlands
Claudio D. Acuna Goycoolea, Anatomy and Cell Biology, Heidelberg University
Karsten Rusche, Wallenberg Neurosc. Center, Lund University
Tony Stöcker, DZNE Bonn
Paul G. Unscheid, Zentrum für dementielle Erkrankungen und Altersgesundheit Zürich
Angelika Dannert, Department of Cardiology, University Medical Center Göttingen
Christian Kupatt, Technische Universität München
Craig Ritchie, Edinburgh University
Jacek Szczypiorski, Institute of Neuropsychology, Saarland University Medical Center
Birgit Liss, Institut of Applied Physiology, Ulm University
Ana Martin-Villalba, German Cancer Research Center, DKFZ, Heidelberg

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

Scientific Conferences & Symposia

Arbeitskreis Neurologie, Sponsoring by Bayer Healthcare (Berlin, Dec 2018) M. Dichgans: scientific chair


Arbeitskreis Neurologie, Sponsoring by Bayer Healthcare (Berlin, Nov 2018) 4th ESO Stroke Science Workshop, Satellite Symposium, Mechanic Thrombectomy | M. Dichgans: scientific chair


Published in:

First and/or Senior Authorship

Number IF total / IF Ø number IF total / IF Ø

Total Publications 57 26 455.2 / 8.0 181.4 / 7.0 72 204.3 / 10.2 629.7 / 9.7

http://doi.org/10.1093/ps/efx034


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