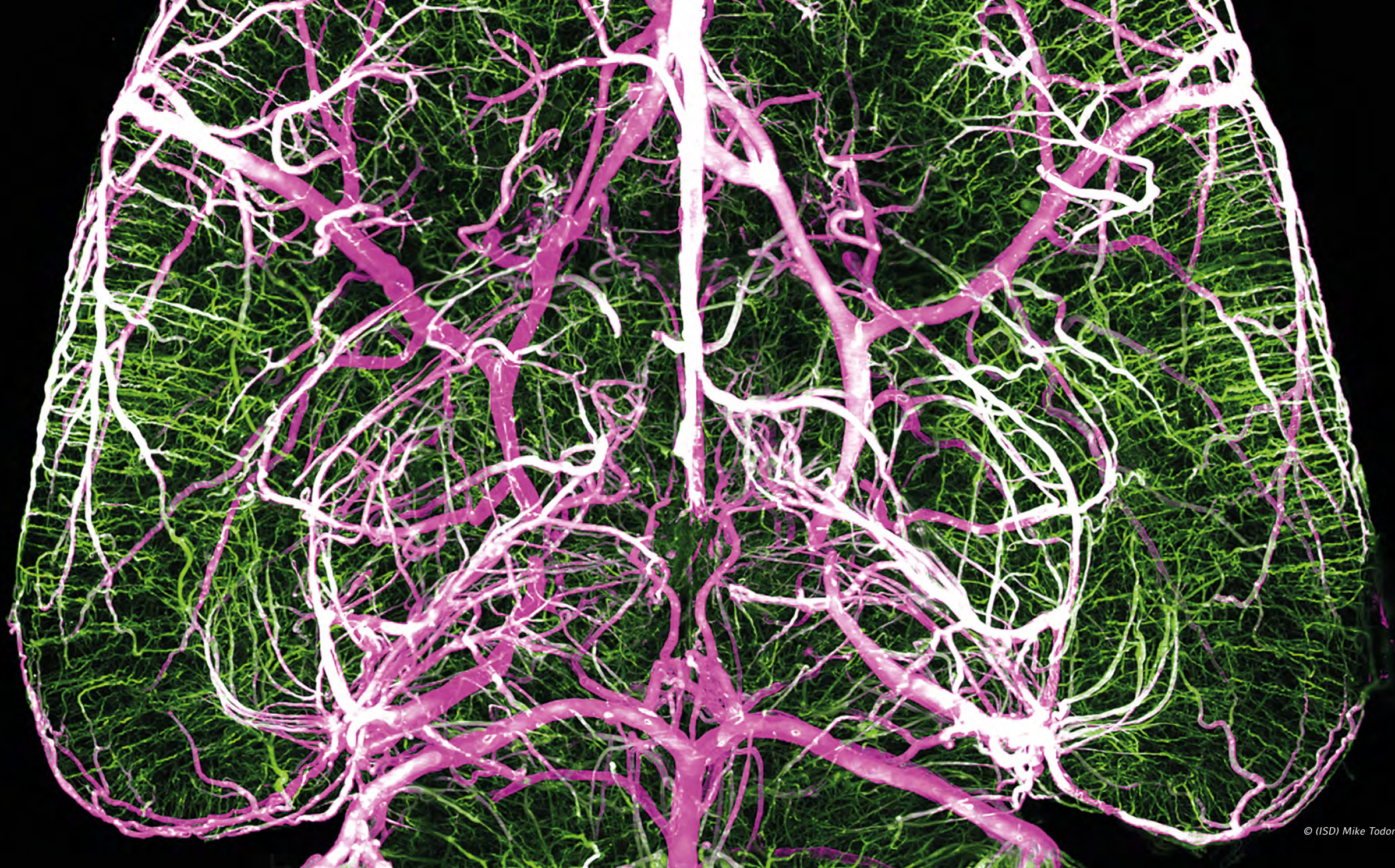
ANNUAL REPORT 2017/2018

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



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Center for Stroke and Dementia Building
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Foreword

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

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/MR), 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 installment of a human magnetic resonance imaging (MRI) research scanner operating at 3 Tesla (Siemens, Magnetom Prisma), a micro PET/MRI scanner (Mediso, nanoScan) 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

Center for Stroke and Dementia Research (CSD)

MISSION STATEMENT

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

We are equally committed to comprehensive patient care and 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-Żak, who sought to create an internationally recognized centre providing highly competitive interdisciplinary and translational research in the fields of stroke and dementia. In July 2008 the Solorz-Żaks, the Ludwig-Maximilians University (LMU), the State of Bavaria, and the Klinikum der Universität München (KUM) agreed on a long-term collaboration to 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*

Organisation

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Director, Dept. of Neurology, University Hospital,
RWTH Aachen, Germany

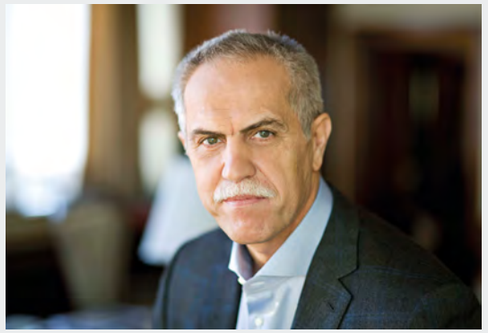
Founders

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

Klinikum der Universität München

Ludwig-Maximilians-Universität München

Bayerisches Staatsministerium für Wissenschaft,
Forschung und Kunst



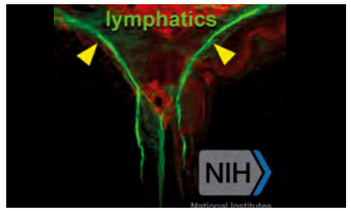
Zygmunt Solorz-Żak

News

11/2018

NIH R01 GRANT ON BRAIN LYMPHATICS

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.



09/2018

SYNERGY CLUSTER APPROVED FOR CONTINUATION

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.

SyNergy
Munich Cluster for
Systems Neurology

08/2018

ERC STARTING GRANT FOR ARTHUR LIESZ

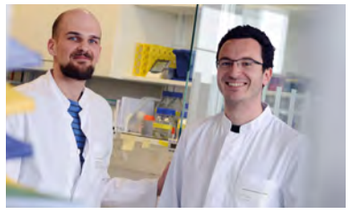
The European Research Council (ERC) Starting Grants are the first in a series of highly prestigious awards offered by the European Commission (EC). The 1.5M € award will enable the Liesz group to expand its research on inflammatory mechanisms in the recovery after acute stroke.

erc European Research Council

07/2018

ROLF-BECKER PRIZE 2018 AWARDED TO ISD SCIENTISTS

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.



07/2018

HUMAN MRI RESEARCH SCANNER INSTALLED

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.

05/2018

YOUNG INVESTIGATOR AWARD 2018 BY ESOC

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.

News

05/2018

SECOND FUNDING PERIOD OF SFB1123 APPROVED

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).

03/2018

ACTION PLAN FOR STROKE IN EUROPE 2018-2030

Munich, March 21-23, the European Stroke Organisation (ESO) in collaboration with the Stroke Alliance for Europe (SAFE) convened leading experts in stroke research and care to an international workshop targeted at identifying current challenges in the prevention and treatment of strokeand set the goals for the next decade.

10/2017

ERA-NET NEURON MULTI-NATIONAL GRANT

Farida Hellal and Nikolaus Plesnila were awarded an ERA-NET NEURON multi-national grant on multi-scale investigation of synaptic dysfunction after stroke (MISST). Consortium partners from Germany, France, Spain, Poland and Latvia will collaborate to unravel the mechanisms underlying long-term disability after stroke.

09/2017

ADOLF WALLENBERG PRIZE

Marco Düring 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.

08/2017

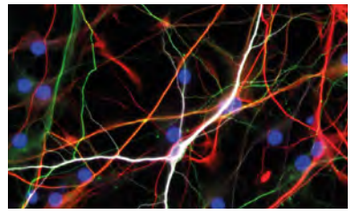
SCIENTIFIC REVIEW BY INTERNATIONAL ADVISORY BOARD

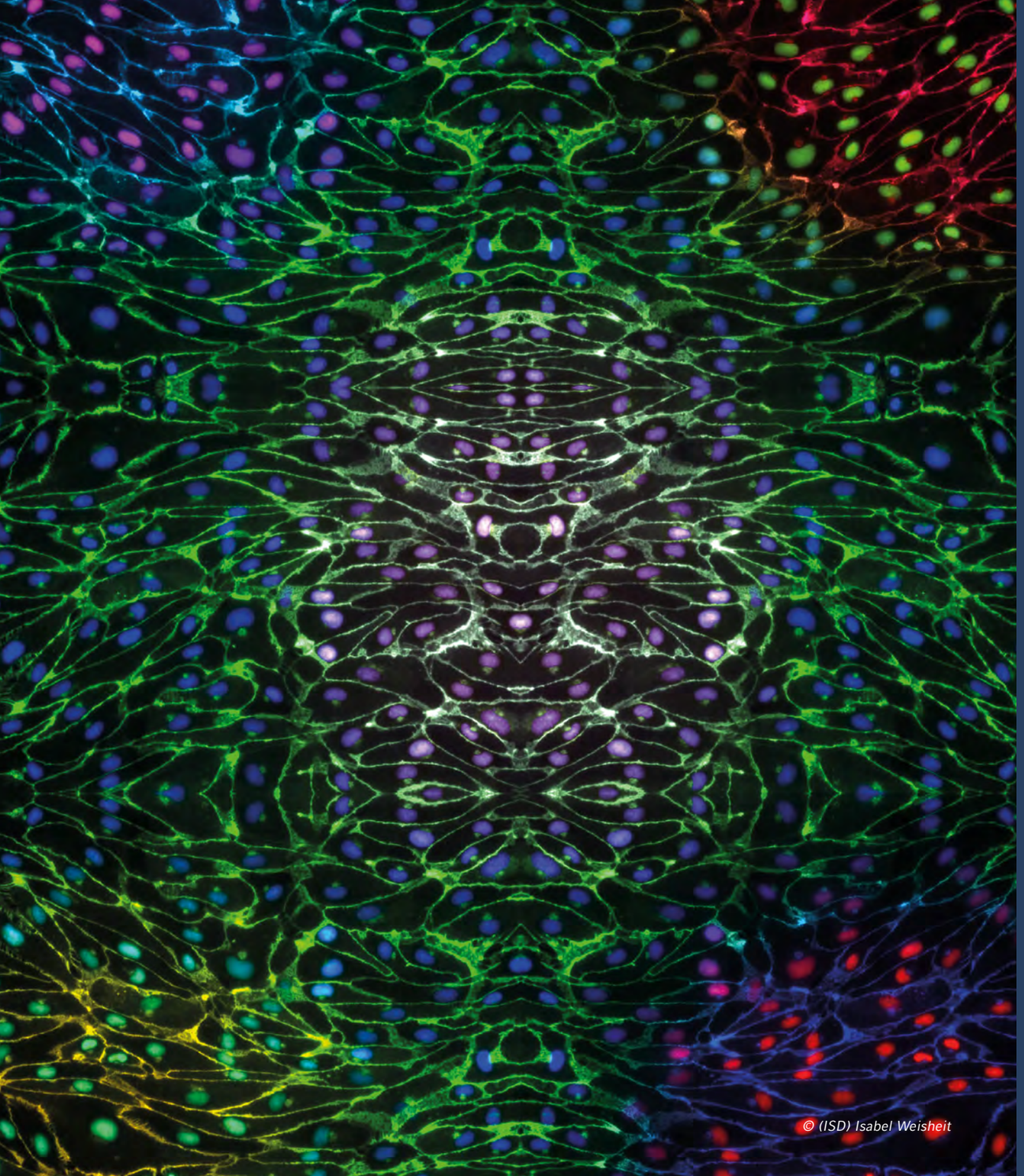
The Review (August 8th and 9th) started with an overview about major developments and achievements since 8/2015 and a review of research strategies followed by talks and discussions about current research projects. Details on projects were presented in a poster session during the breaks. The ISD remains very grateful for the advice provided by its board.

02/2017

STATE-OF-THE-ART FACILITY FOR STEM CELL RESEARCH

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.





Outpatient Clinic

Outpatient Clinic

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

Major aims and topics of our clinical studies are:

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

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

Outpatient clinic staff

Bay, Berkant, MSc / study assistant
Bertram, Désirée / neuropsychologist
Berwein, Michael, MSc / neuropsychologist
Borunda Vasquez, Lara, MSc / neuropsychologist
Bürger, Katharina, PD Dr. med. / senior physician
Catak, Cihan, Dr. med. / physcian
Cizmic, Deni / study assistant
Coloma Andrews, Lisa, Dr. phil. / neuropsychologist
Dichgans, Martin, Prof. Dr. med. / director
Dörr, Angelika / study nurse
Fertig, Alexandra / social worker
Hein, Sandra / study nurse
Hill, Julia / study nurse
Jakl, 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
Schöftenhuber, 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

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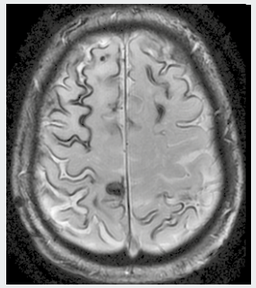
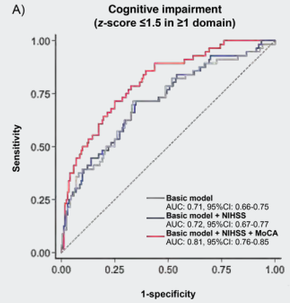
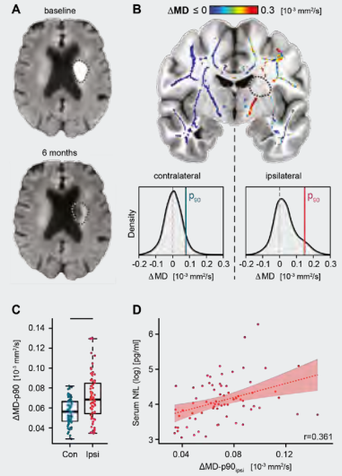
Katharina Bürger, MD, in consultation with a patient



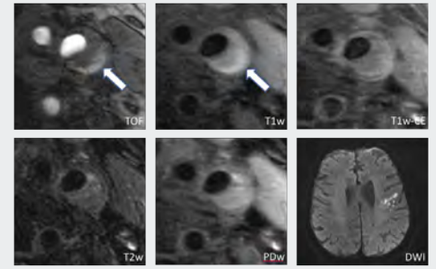
Prognostic relevance of cortical superficial siderosis (cSS) in patients with suspected cerebral amyloid angiopathy (CAA). Shown is a patient with disseminated cSS marked by multiple linear signals (black) along the cortical ribbon. Modified from Wollenweber et al. Neurology 2019



Baseline cognitive screening by the Montreal Cognitive Assessment (MoCA) predicts multiple adverse outcomes after stroke. Shown are the receiver operating characteristic (ROC) curves for the prediction of cognitive impairment after stroke (3-years interval post-stroke) obtained from three different models. Data are from the Determinants of Dementia after Stroke (DEDEMAS) study and STROKDEM study (Collaboration, R. Bordet, Lille, France). Modified from Zietemann et al. Neurology 2018.



Serum NfL levels correlate with secondary degeneration of major white matter tracts. (A) Co-registered DWI scans from a representative IS patient obtained at baseline (top) and 6 months post-stroke (bottom). (B) Upper panel: coronary view showing the change in mean diffusivity (ΔMD) from baseline to 6 months post-stroke within the main white matter tract skeleton (color-coded); lower panels: histograms of ΔMD quantified across the main white matter tract skeletons contralateral (left) and ipsilateral (right) to the infarct. (D) Association of serum NfL levels and ΔMD-p90 ipsilateral to the infarct. Modified from Tiedt et al. Neurology 2018



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

->„culprit plaque"

Stroke Prevention Unit

Senior physician:
PD Dr. med. Frank A. Wollenweber

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

Publications:

Wollenweber FA, Opherk C, Zedde M Catak C, Malik R, Duering M, Konieczny MJ, Pascarella R, Samões R, Correia M, Martí-Fàbregas J, Linn J, Dichgans M. *Prognostic relevance of cortical superficial siderosis in cerebral amyloid angiopathy.* **Neurology.** 2019 Jan 23. pii: 10.1212/WNL.0000000000006956.

Georgakis M, Duering M, Wardlaw JM, Dichgans M. *WMH and long-term outcomes in ischemic stroke: a systematic review and meta-analysis.* **Neurology.** (in press)

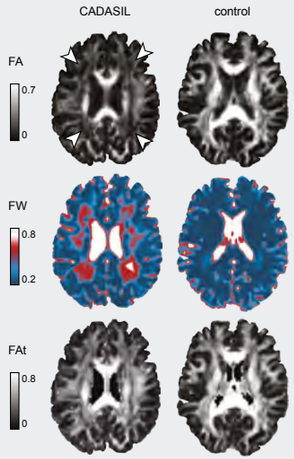
Tiedt S, Duering M, Barro C, Kaya AG, Boeck J, Bode FJ, Klein M, Dorn F, Gesierich B, Kellert L, Ertl-Wagner B, Goertler MW, Petzold GC, Kuhle J, Wollenweber FA, Peters N, Dichgans M. *Serum neurofilament light: A biomarker of neuroaxonal injury after ischemic stroke.* **Neurology**. 2018 Oct 2;91(14):e1338-e1347

Zietemann V, Georgakis MK, Dondaine T, Müller C, Mendyk AM, Kopczak A, Hénon H, Bombois S, Wollenweber FA, Bordet R, Dichgans M. E*arly MoCA predicts long-term cognitive and functional outcome and mortality after stroke.* **Neurology**. 2018 Nov 13;91(20):e1838-e1850.

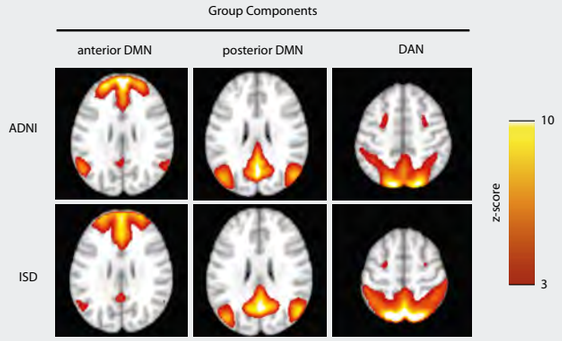
Tiedt S, Prestel P, Kautzky V, Düring M, Northoff B, Malik R, Klein M, Dorn F, Krohn K, Teupser D, Holdt L, Dichgans M. *RNA -seq identifies circulating miR-125a-5p, miR-125b-5p and miR-143-3p as potential biomarkers for acute ischemic stroke.* **Circ Res** 2017 121(8):970-980.

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

For a full account of ongoing clinical studies see page 52.



Free water determines diffusion alterations and clinical status in cerebral small vessel disease. Shown are representative images of a patient with hereditary small vessel disease (CADASIL, left) and a healthy control individual (right). Note the increase in cerebral free water on the free water (FW) map; top: conventional FA, middle: FW map; bottom: tissue compartment. FA, fractional anisotropy; FW, free water; MD, mean diffusivity; FAt, tissue compartment FA. From Duering et al. Alzheimer's and Dementia 2018.



ICA results. Resting-state networks identified via group independent component analysis (depicted in radiological convention). Group components for both study samples (ADNI and ISD) are superimposed on an MNI template and thresholded at a z-score >3.

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.

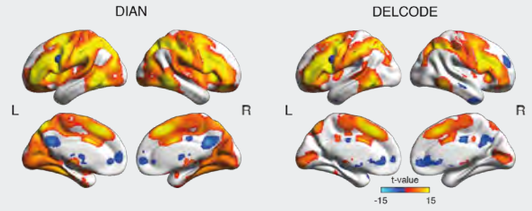
Memory Clinic

Senior physician:
PD Dr. med. Katharina Bürger

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 dementing conditions and make use of new PET ligands for neurodegenerative disease (including for ß-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.

Seed-based LFC connectivity pattern. Surface renderings of significant LFC-connectivity in the DIAN and DELCODE sample at a voxel threshold of α < 0.001, family-wise error corrected at the cluster level at α < 0.05. The LFC-region of interest that was used for seed-based functional connectivity analyses is superimposed as a blue sphere on the left hemisphere.



Selected Publications:

Franzmeier N, Buerger K, Teipel S, Stern Y, Dichgans M, Ewers M; Alzheimer's Disease Neuroimaging Initiative (ADNI). *Cognitive reserve moderates the association between functional network anti-correlations and memory in MCI.* **Neurobiol Aging.** 2017 Feb;50:152-162.

Duering M, Finsterwalder S, Baykara E, Tuladhar AM, Gesierich B, Konieczny MJ, Malik R, Franzmeier N, Ewers M, Jouvent E, Biessels GJ, Schmidt R, de Leeuw FE, Pasternak O* Dichgans M* *Free water determines diffusion alterations and clinical status in cerebral small vessel disease.* **Alzheimer's & Dementia.** 2018; 14(6):764-774.

Franzmeier N, Düzel E, Jessen F, Buerger K, Levin J, Duering M, Dichgans M,Haass C, Suárez-Calvet M, Fagan AM, Paumier K, Benzinger T, Masters CL, Morris JC, Perneczky R, Janowitz D, Catak C, Wolfsgruber S, ..., Bartels C, Araque Caballero MÁ, ..., Ewers M. *Left frontal hub connectivity delays cognitive impairment in autosomal-dominant andsporadic Alzheimer's disease.* **Brain**. 2018 Apr 1;141(4):1186-1200.

"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."

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.

Public Reachout

Clinical staff | outpatient clinic	
function	total
physicians	6
neuropsychologists	4
study nurses	7
social workers	1
technical assistants	1
outpatient office	3
clinical data manager	3
total	25

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 €
total	1,043,400 €

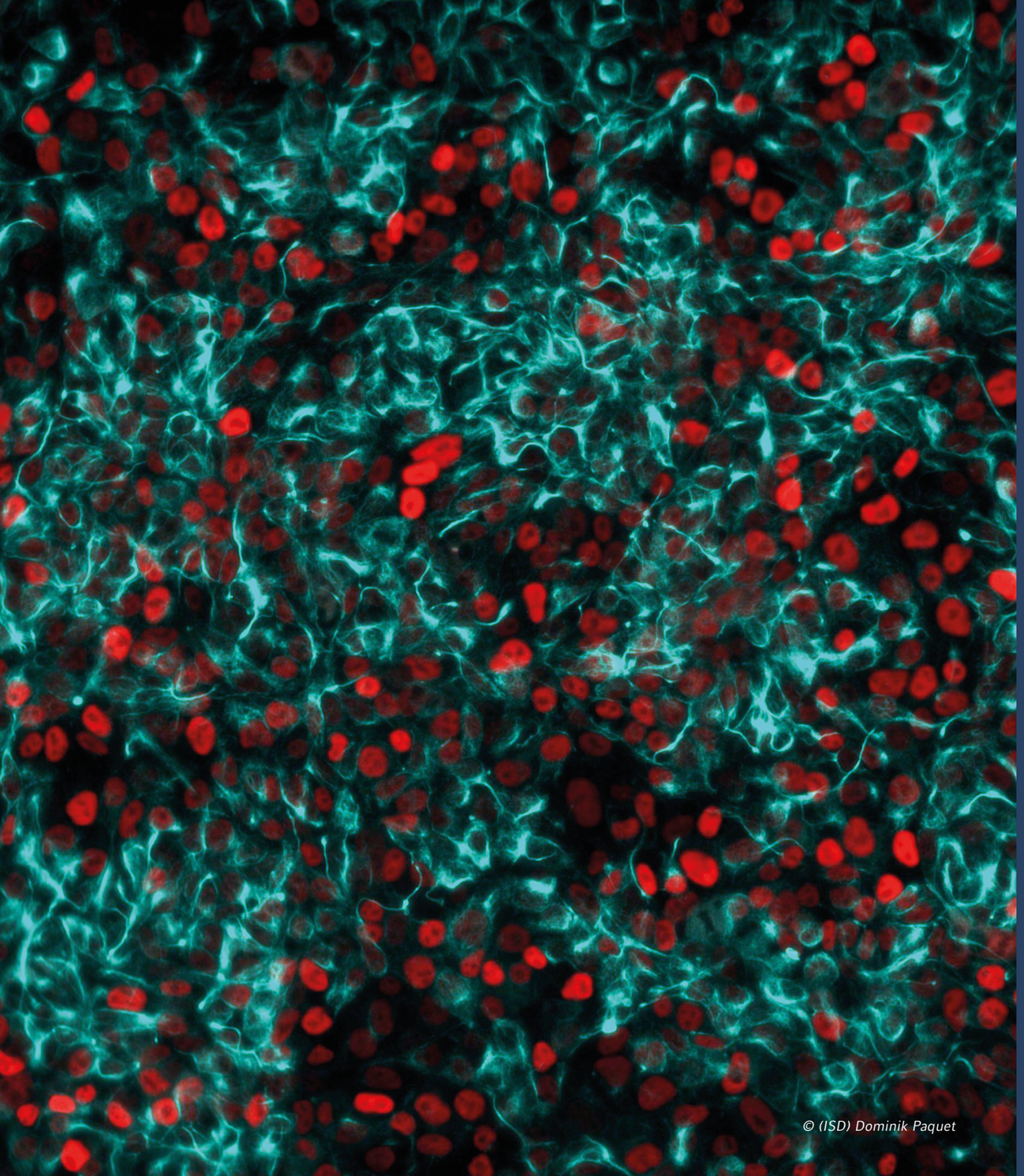
Statistics | Outpatient Clinic

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

Administrative Support

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Research at the ISD

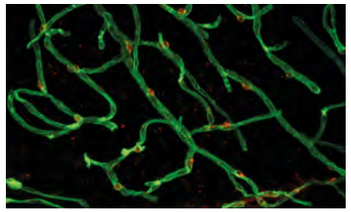
Scope of research

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

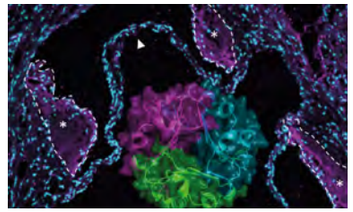
Methodological approaches include

- 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
- Immune cell phenotyping | FACS
- 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

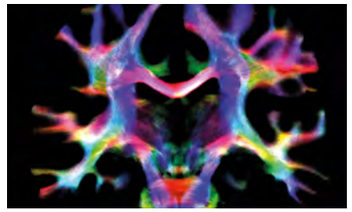
Translational Stroke and Dementia Research
PI: Martin Dichgans
(page 30)



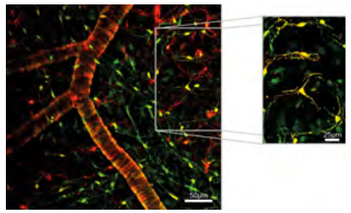
Vascular Biology
PI: Jürgen Bernhagen
(page 32)



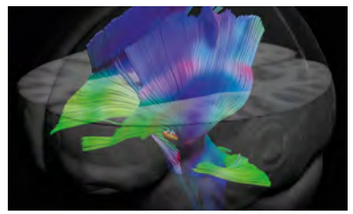
Vascular Cognitive Impairment
PI: Marco Düring
(page 34)



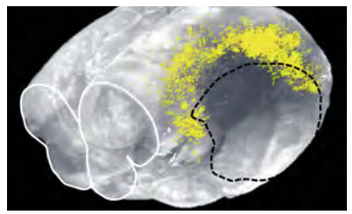
Experimental Stroke Research
PI: Nikolaus Plesnila
(page 36)



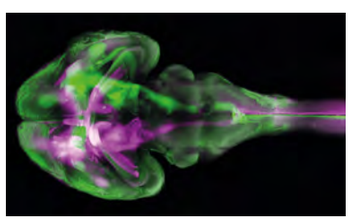
Brain Imaging and Biomarkers
PI: Michael Ewers
(page 38)



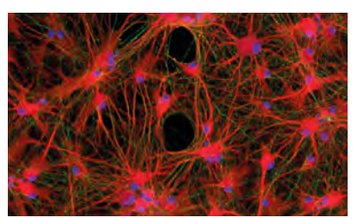
Stroke Immunology
PI: Arthur Liesz
(page 40)



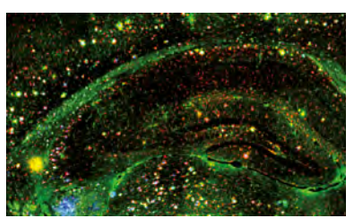
Acute Brain Injury
PI: Ali Ertürk
(page 42)

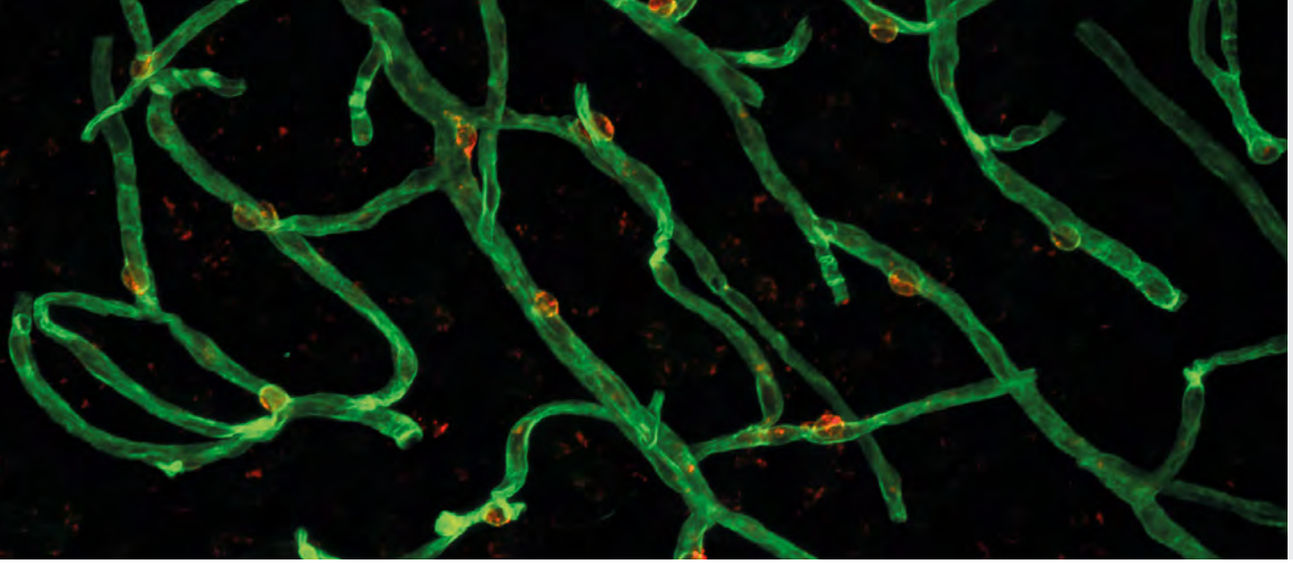


Neurobiology
PI: Dominik Paquet
(page 44)



Systems Neuroscience
PI: Ozgun Gokce
(page 46)





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

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

A major starting point of our work are patients with stroke that are examined through prospective clinical studies along with healthy individuals. We apply genetic (GWAS and sequencing) and other omics techniques to identify novel targets and pathways relevant to specific mechanistically defined stroke subtypes.

We use this information to explore relationships with informative intermediate (e.g. vascular, metabolic) and related phenotypes (e.g. coronary artery disease). We have established genetic mouse models for cerebral small vessel disease (SVD) derived from the genetic discoveries (e.g. Notch3, HtrA1, Foxf2) and use these models to identify and characterize key molecular (e.g. TGF-ß 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.

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Key Publications

Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, … [175 authors] …, Fornage M, Markus HS, Howson JMM, Kamatani Y, Debette S and Dichgans M. *Multi-ancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes.* **Nat Genet** 2018; 50(4):524-537.

Georgakis MK, Gill D, Rannikmäe K, Traylor M, Anderson CD, MEGASTROKE consortium of the International Stroke Genetics Consortium, Lee JM, Kamatani Y, Hopewell JC, Worrall BB, Bernhagen J, Sudlow CLM, Malik R, Dichgans M. *Genetically Determined Levels of Circulating Cytokines and Risk of Stroke: Role of Monocyte Chemoattractant Protein-1.* **Circulation** 2019 Jan 8;139(2):256-268.

Malik R, Rannikmäe K, Traylor M, Georgakis MK, Sargurupremraj M, Markus HS, Hopewell JC, Debette S, Sudlow CLM, Dichgans M. MEGASTROKE consortium and the International Stroke Genetics Consortium. *Genome-wide meta-analysis identifies 3 novel loci associated with stroke.* **Ann Neurol.** 2018 Dec;84(6):934-939.

Tiedt S, Duering M, Barro C, Kaya AG, Boeck J, Bode FJ, Klein M, Dorn F, Gesierich B, Kellert L, Ertl-Wagner B, Goertler MW, Petzold GC, Kuhle J, Wollenweber FA, Peters N, Dichgans M. *Serum neurofilament light: A biomarker of neuroaxonal injury after ischemic stroke.* **Neurology**. 2018 Oct 2;91(14):e1338-e1347.

Malik R, Dau T, Gonik M, Sivakumar A, Deredge D, Edeleva EV, Götzfried J, van der Laan SW, Pasterkamp G, Beaufort N, ..., Saleheen D, International Stroke Genetics Consortium, Rothwell P, ..., Braun D, Markus HS , Wintrode P, Berger K, Jenne D, Dichgans M. *A common coding variant in SERPINA1 increases the risk for large artery stroke.* **Proc Natl Acad Sci U S A.** 2017 Apr 4;114(14):3613-3618.

Tiedt S, Prestel M, Malik R, Schieferdecker N, Duering M, Kautzky V, Stoycheva I, Böck J, Northoff BH, Klein M, Dorn F, Krohn K, Teupser D, Liesz A, Plesnila N, Holdt LM, Dichgans M. *RNA-Seq Identifies Circulating miR-125a-5p, miR-125b-5p, and miR-143-3p as Potential Biomarkers for Acute Ischemic Stroke.* **Circ Res**. 2017 Sep 29;121(8):970-980.

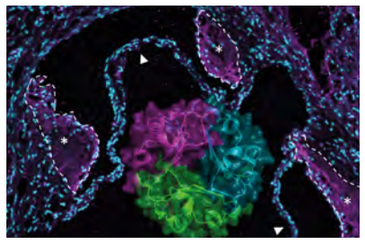
Vascular Biology

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 2011*). 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; Stoppe et al., Antiox Redox Signal 2015; Schmitz et al., FASEB J 2018; Stoppe et al., Sci Transl Med 2018*). This involves deciphering the **ligand/receptor complexes and pathways** *(Rajasekaran et al., J Biol Chem 2016; Soppert et al., JAHA 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 (*Schindler et al., Redox Biol 2018; Roth et al., Sci Transl Med 2018*).

Another focus is on **signaling mediated by the COP9 signalosome (CSN) and NF B-regulating pathways** in atherogenesis and neurovascular inflammation. The CSN is a multi-protein complex that regulates SCF 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 *(Kleemann et al., Nature 2000)*, using conditional gene knockout and pharmacological augmentation approaches, we discovered an atheroprotective effect of CSN5 via NF B in endothelium and myeloid cells (*Asare et al., Thromb Haemost 2013; Asare et al., PNAS 2017*). 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).



Shown are atherosclerotic plaques (; stained in magenta) from ApoE-/- mice (valve level, indicated by arrowheads; cell nuclei in blue). For illustration purposes, the inflammatory cytokine MIF (subunits colored in magenta, green, blue), which promotes atherogenic leukocyte recruitment and plaque formation, is shown.*

Key Publications

Atzler D, McAndrew D, ..., Neubauer S, Lygate C. *Dietary Supplementation with Homoarginine Preserves Cardiac Function in a Murine Model of Post-Myocardial Infarction Heart Failure.* **Circulation**. 2017 Jan 24;135(4):400-402.

Asare Y, Ommer M, ..., Gijbels MJ, Schmitz C, Sinitski D, Tilstam PV, Lue H, ..., Weber C, Dichgans M, Jankowski J, Pardi R, de Winther MP, Noels H*, Bernhagen J.* *Inhibition of atherogenesis by the COP9 signalosome subunit 5 in vivo.* **Proc Natl Acad Sci U S A.** 2017 Mar 28;114(13):E2766-E2775. *corresponding authors

Stoppe C*, ..., Rex S, Ochi A, Leng L, Moeckel G, Linkermann A, El Bounkari O, Zarbock A, Bernhagen J*, Djudjaj S, Bucala R, Boor P*. *The protective role of macrophage migration inhibitory factor in acute kidney injury after cardiac surgery.* **Sci Transl Med.** 2018 May 16;10(441). *corresponding authors

Schmitz C, Noels H, El Bounkari O, Straussfeld E, ..., Krammer C, Tilstam PV, Gerdes N, Bürger C, Kapurniotu A, Bucala R, Jankowski J, Weber C, Bernhagen J*. *Mif-deficiency favors an atheroprotective autoantibody phenotype in atherosclerosis.* **FASEB J.** 2018 Aug;32(8):4428-4443. *corresponding author

Spanopoulou A., ..., Grammatikopoulos A., Bernhagen J., Zacharias M., Rammes G., Kapurniotu A. *Designed Macrocyclic Peptides as Nanomolar Amyloid Inhibitors Based on Minimal Recognition Elements.* **Angew Chem Int Ed Engl.** 2018 Oct 26;57(44):14503-14508

Baeza Garcia A, .., Ulmer JB, Bernhagen J, Fikrig E, Geall A, Bucala R. *Neutralization of the Plasmodium-encoded MIF ortholog confers protective immunity against malaria infection.* **Nat Commun.** 2018 Jul 13;9(1):2714.

Roth S, Singh V, Tiedt S, Schindler L, Huber G, ..., Holdt LM, Harris HE, Engelhardt B, Bianchi ME, Vivien D,

Haffner C, Bernhagen J, Dichgans M, Liesz A. *Brain-released alarmins and stress response synergize in accelerating atherosclerosis progression after stroke.* **Sci Transl Med.** 2018 Mar 14;10(432)

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Sabrina Lukanovic, LL.M. / team assistant
Adrian Hoffmann, Dr. med. / Metiphys clinician scientist
Sinitski, Dzmitry, Dr. rer. nat. / postdoc
Bourilhon, Priscila, MSc / technical assistant
Simona Gerra, MSc / technical assistant
Sijia Wang, MD / PhD student
Marlies Tursch, VD / student
Brandhofer, Markus, MSc / PhD student
Christoph Emontzpohl, MSc / PhD student (external)
Christine Krammer, MSc / PhD student
Jelena Milic, MSc / PhD student
Lisa Schindler, MSc / PhD student
Tian Yuan, MSc / PhD student
Ying Gao, MD / PhD trainee
Chunfang Zan, MD / PhD trainee
Sabrina Reichl, cand. med., / MD student
Leon Zwißler, cand. med. / MD student
Tharshika Thavayogarajah, cand. med. / MD doctoral student (external)
Alexander Harjung, BSc / student assistant
Anna Honke, BSc / student assistant
Verena Bolini, BSc / student assistant

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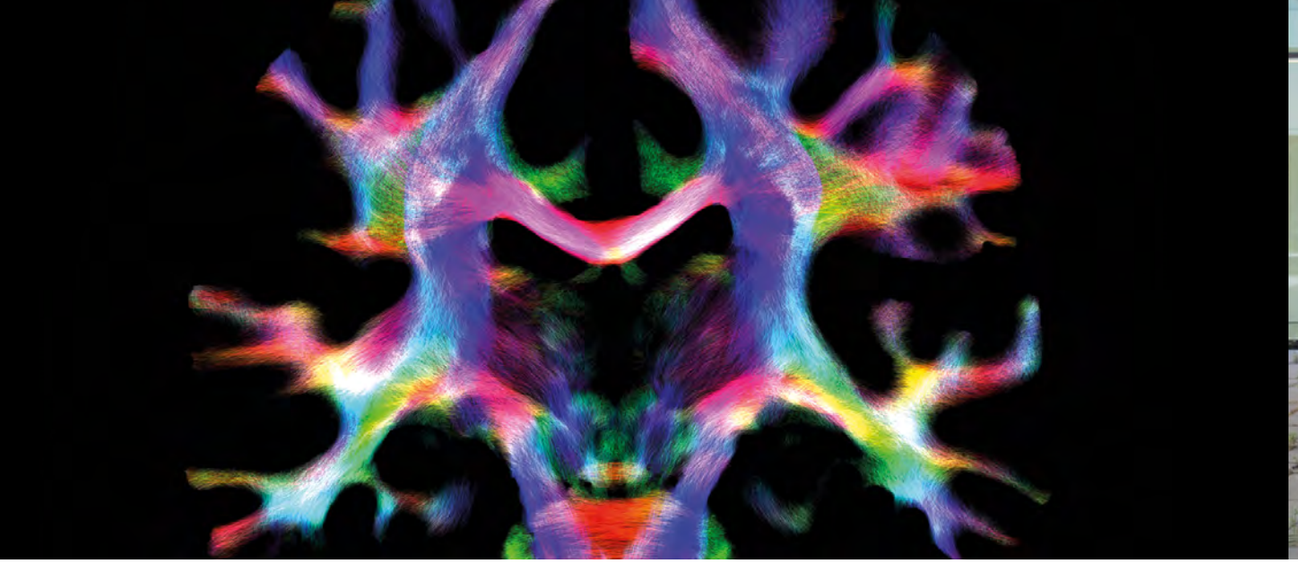

Team:
Achmüller, Melanie / MD student
Araque Caballero, Miguel Á., PhD / Postdoc
Cubillos-Pinilla, Leidy, BSc / Master student
Duering, Marco, PD Dr. med. / PI
Finsterwalder, Sofia, MSc / PhD student
Gesierich, Benno, PhD / postdoc
Habash, Susan / radiographer (MTRA)
Hübner, Mathias / research assistant
Konieczny, Marek, MSc / PhD student
Pietsch, Hedwig / team assistant
Schillinger, Ulrike, Dr. med. vet. / veterinary physician

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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

Duering M, Finsterwalder S, Baykara E, Tuladhar AM, Gesierich B, Konieczny MJ, Malik R, Franzmeier N, Ewers M, Jouvent E, Biessels GJ, Schmidt R, de Leeuw FE, Pasternak O, Dichgans M. *Free water determines diffusion alterations and clinical status in cerebral small vessel disease.* **Alzheimers Dement.** 2018 Jun;14(6):764-774.

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

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

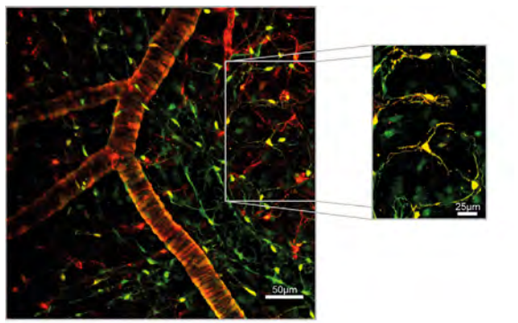
Duering M, Gesierich B, Seiler S, Pirpamer L, Gonik M, Hofer E, Jouvent E, Duchesnay E, Chabriat H, Ropele S, Schmidt R, Dichgans M. *Strategic white matter tracts for processing speed deficits in age-related small vessel disease.* **Neurology.** 2014 Jun 3;82(22):1946-50.

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

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

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

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 pearl-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 **inversed** later than 24 hours after SAH. These finding indicate that metabolic signals coming from activated neurons do not only not dilate cerebral vessels, but cause vasoconstriction, i.e. neurovascular coupling is inversed. On a functional level this may suggest that after SAH any neuronal activity, either by physiological or pathological stimuli, e.g. handling of the patient or cortical spreading depolarization, may cause a mismatch between flow and metabolisms on the level of the cerebral microcirculation thereby causing **micro-ischemia** and subsequent brain damage. In search for therapeutic options for this process, we tested **endothelin receptor** antagonists and **calcium channel inhibitors** and demonstrated that neither of these strategies previously used in patients with large artery vasospasms is able to improve micro-ischemia. The only therapy being identified as effective in our hands is the external application of **nitric oxide by inhalation**. This is further supported by the fact that dysfunction of the endothelial NO synthase massively worsens outcome after experimental SAH. Therefore, we will further focus our efforts to understand the mechanisms responsible for neurovascular dysfunction after SAH.



In vivo 2-photon image of cerebral pericytes (yellow) in a NG2-Dsred/PDGFR-eGFP double-transgenic mouse. This mouse line generated in our laboratory is currently used to isolate and characterize capillary pericytes in normal and ischemic brain by single cell analysis.

Team (from left to right):
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Mao, Xiang / MD student
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Tsitos, Stergios / MD student
Saicic, Stefan, MD student

Key Publications

Liu H, Dienel A, Schöller K, Schwarzmaier SM, Nehrkorn K, Plesnila N*, Terpolilli NA* *Microvasospasms After Experimental Subarachnoid Hemorrhage Do Not Depend on Endothelin A Receptors.* **Stroke.** 2018; 49(3):693-699

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Balbi M, Koide K, Wellman G, Plesnila N. *Inversion of neurovascular coupling after subarachnoid hemorrhage in vivo* **J Cereb Blood Flow Metab.** 2017; 37(11): 3625-3634

Lourbopoulos A, Mamrak U, Roth S, Balbi M, Shrouder S, Liesz A, Hellal F, Plesnila N *Inadequate food and water intake determine mortality following stroke in mice* **J Cereb Blood Flow Metab.** 2017; 37(6):2084-2097

Krieg SM, Trabold R, Plesnila N. *Time-Dependent Effects of Arginine-Vasopressin V1 Receptor Inhibition on Secondary Brain Damage after Traumatic Brain Injury.* **J Neurotrauma.** 2017; 34(7):1329-1336

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

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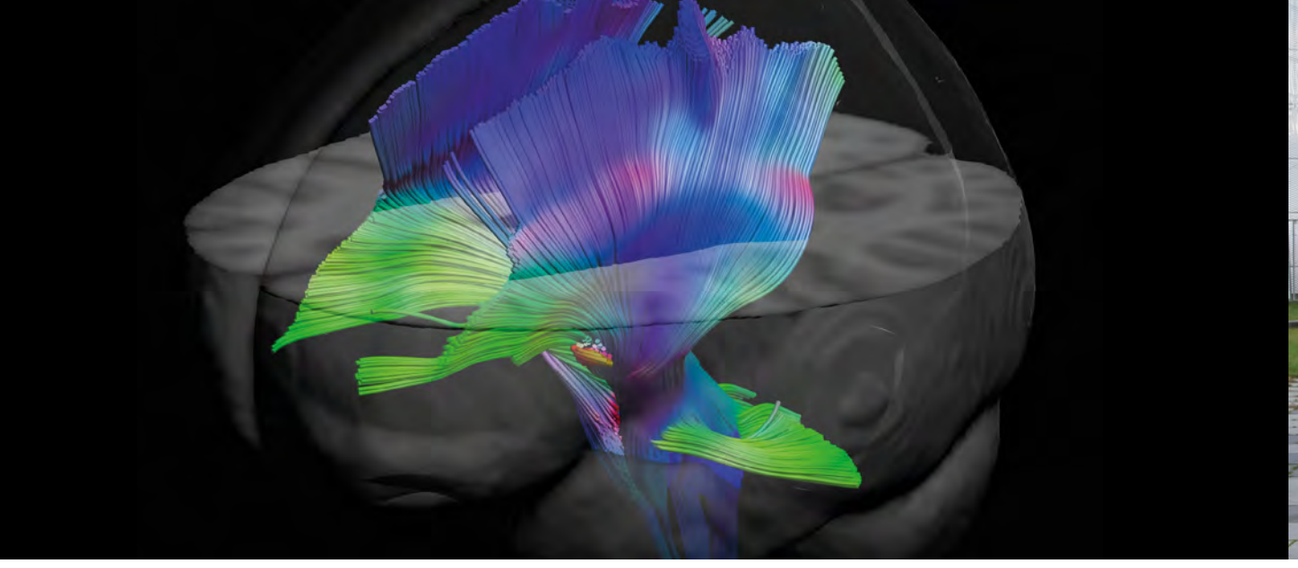

Team:
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Brain Imaging and Biomarker

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

Araque Caballero MÁ, Suárez-Calvet M, Duering M, Franzmeier N, ..., Dichgans M, Jucker M, Karch C, Masters CL, ..., Hassenstab J, Schofield PR, Haass C, Ewers M; *White matter diffusion alterations precede symptom onset in autosomal dominant Alzheimer's disease.* **Brain.** 2018 Oct 1;141(10):3065-3080.

Franzmeier, N., Duzel, E., Jessen, F., Buerger, K., Levin, J., Duering, M., Dichgans, M., Haass, C., ..., Janowitz, D., Catak, C., Wolfsgruber, S., ..., Araque Caballero, M. Á., ..., Bateman, R. and Ewers, M. *Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease.* **Brain.** 2018; 141(4):1186-1200.

Franzmeier N, Duering M, Weiner M, Dichgans M, Ewers M. Alzheimer's Disease Neuroimaging Initiative (ADNI), *Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease.* **Neurology**. 2017 Mar 14;88(11):1054-1061

Taylor AN, Kambeitz-Ilankovic L, Gesierich B, Simon-Vermot L, Franzmeier N, Araque Caballero MÁ, ..., Bürger K, Weiner MW, Dichgans M, Duering M, Ewers M; Alzheimer's Disease Neuroimaging Initiative (ADNI). *Tract-specific white matter hyperintensities disrupt neural network function in Alzheimer's disease.* **Alzheimers Dement**. 2017 Mar;13(3):225-235.

Suarez-Calvet M, Araque Caballero MA, ..., Ewers M*, Haass C*. *Early changes of CSF sTREM2 in dominantly inherited Alzheimer's Disease follow marker markers of amlyoid deposition and neuronal injury.* **Sci Transl Med.** 2016 Dec 14;8(369):369ra178. (*contributed equally)

Ewers M, Sperling RA, Klunk WE, Weiner MW, Hampel H. *Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia.* **Trends Neurosci.** 2011 Aug;34(8):430-42.

Stroke-Immunology

Research Group – PI: Arthur Liesz

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

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

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

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

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

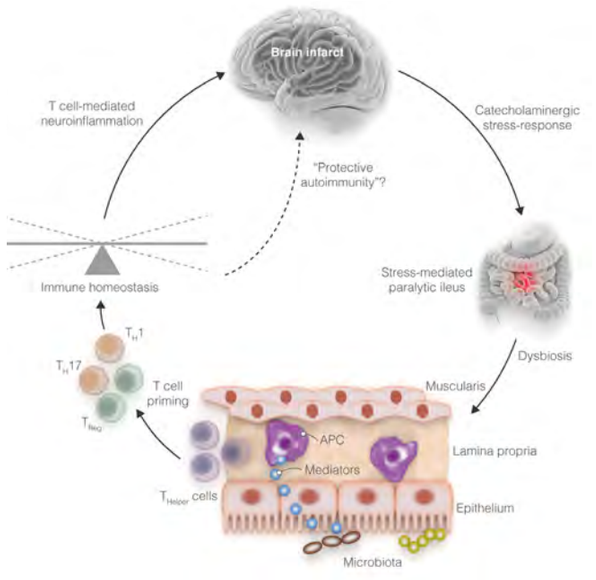

Figure: Dysbiosis of gut microbiota following acute infarct primes the post-stroke neuroinflammatory response.

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Key Publications

Roth S, Singh V, Tiedt S, Schindler L, ..., Haffner C, Bernhagen J, Dichgans M, Liesz A. *Brain-released alarmins and stress response synergize in accelerating atherosclerosis progression after stroke.* **Sci Transl Med.** 2018 Mar 14;10(432).

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

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

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

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

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

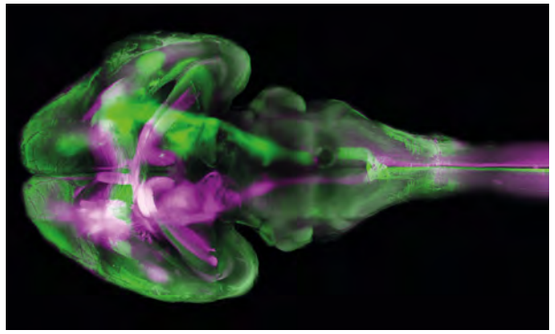
Acute Brain Injury Research

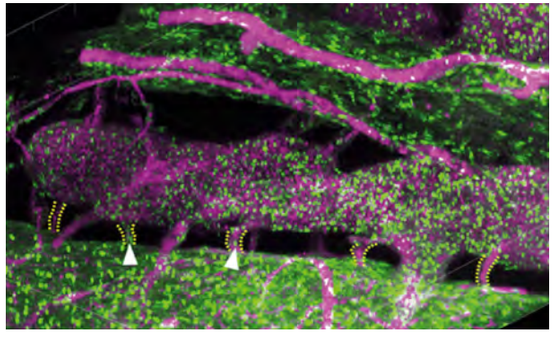
Research Group – PI: Ali Ertürk

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 MRI/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.

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.





Ertürk, Ali, Dr. / PI
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Bhatia, Harsharan Singh, Dr. / postdoc
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Kolabas, Ilgin / Master student
Paetzold, Johannes / master student
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Todorov, Mihail / PhD student
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Key Publications

Pan C, Schoppe O, …, Ertürk A. *Deep learning reveals cancer metastasis and therapeutic antibody targeting in whole body.* **BioRxiv** (in preprint)

Cai R, Pan C, …, Ertürk A. *Panoptic imaging of transparent mice reveals whole-body neuronal connectivity and skull-meninges connections.* **Nat Neuroscience.** (in press)

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Garvalov B, Ertürk A. *Seeing whole-tumour heterogeneity.* **Nat Biomed.** Eng. (2017).

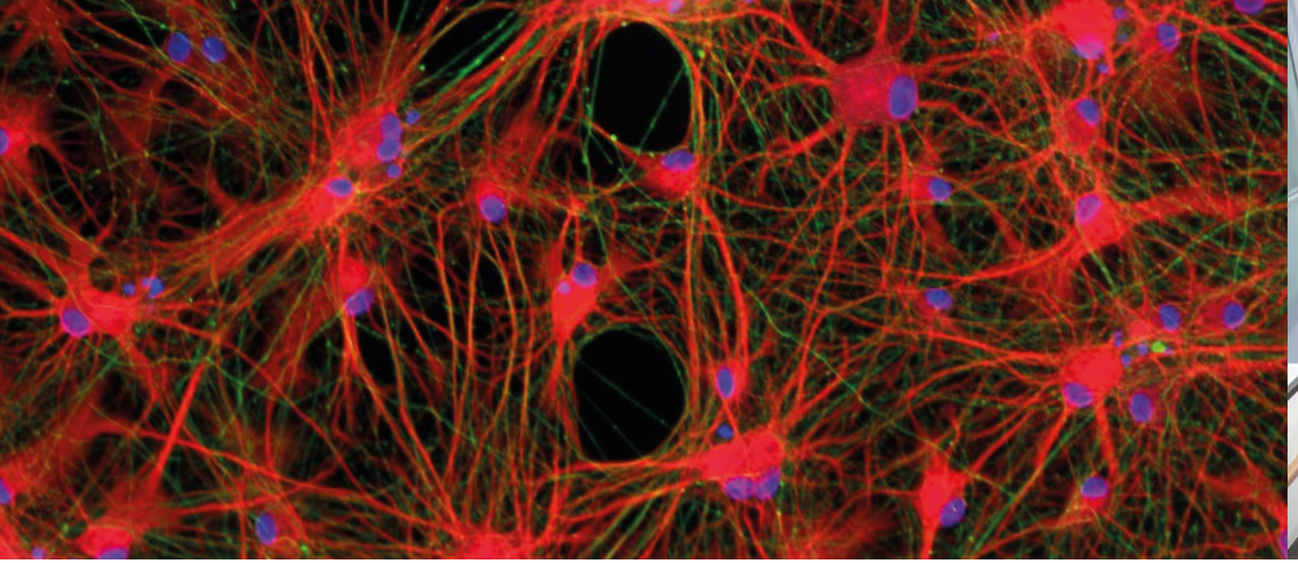
Pan C, Cai R, Quacquarelli FP, Ghasemigharagoz A, Lourbopoulos A, Matryba P, Plesnila N, Dichgans M, Hellal F, Ertürk A; *Shrinkage-mediated imaging of entire organs and organisms using uDISCO*. **Nat Methods**. 2016 Oct;13(10):859-67. (Cover of Nature Methods 2016 October Issue)

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

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

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

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



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Weisheit, Isabel / graduate student (GSN)
Crusius, Dennis / technical assistant
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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

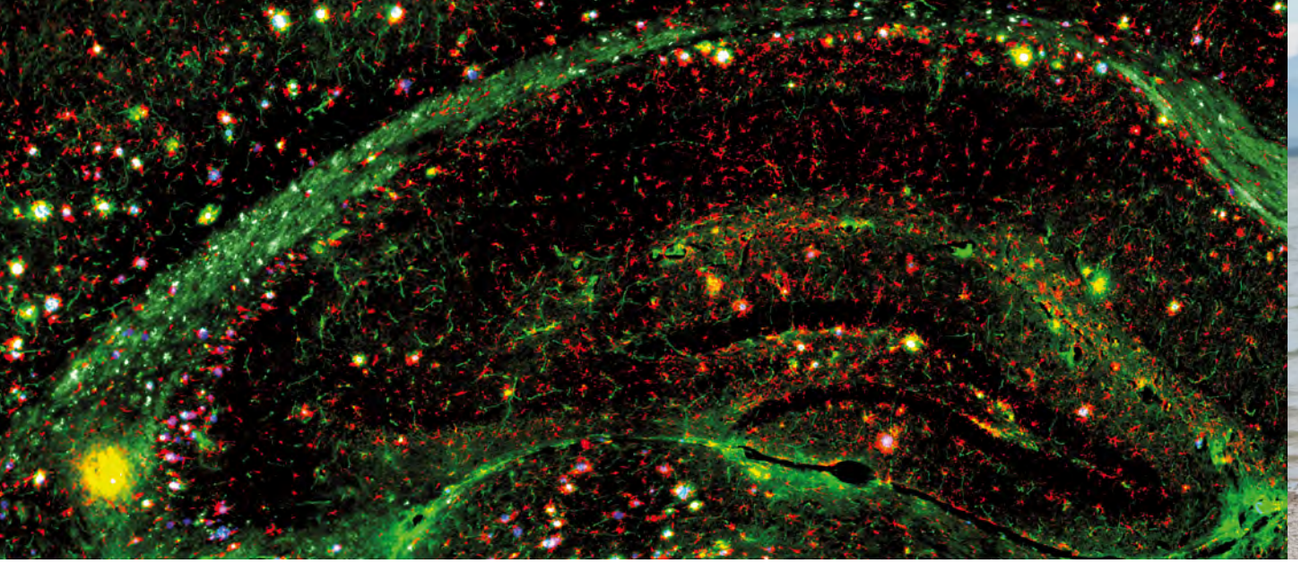
Kwart D*, Paquet D*, Teo S, Tessier-Lavigne M. *Precise and efficient scarless genome editing in stem cells using CORRECT.* **Nat Protoc.** 2017 Feb;12(2):329-354. *equal first authors

Paquet D, Kwart D, Chen A, Sproul A, Jacob S, Teo S, Olsen KM, Gregg A, Noggle S, Tessier-Lavigne M. *Efficient introduction of specific homozygous and heterozygous mutations using CRISPR/Cas9*. **Nature.** 2016 May 5;533(7601):125-9.

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

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

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



Team:
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Systems Neuroscience

Research Group – PI: Özgün Gökçe

Changes in the genome, called mutations, are the driving force of evolution. These mutations continue to shape us from the moment we begin life as a single cell to the end of our life by altering the genome of each cell. During development, these somatic mutations provide important benefits including fighting infections by developing B-cells antibody diversity, but they are also the underlying cause of almost all age-related diseases, particularly cancer and neurodegeneration. Yet, we do not know how many mutations accumulate in each cell and what the key mutagenic mechanisms are.

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

Zhang B., Gokce O., Hale D.W., Brose N., Südhof T.C. Autism-Associated *Neuroligin-4 Mutation Selectively Impairs Glycinergic Synaptic Transmission in Mouse Brainstem Synapses.* **J Exp Med.** 2018 May 215(6): 1543-1553

Wang W., Penland L., Gokce O., Croote D., Quake S.R., *High fidelity hypothermic preservation of primary tissues in organ transplant preservative for single cell transcriptome analysis.* **BMC Genomics.** 2018 Feb 19: 140.

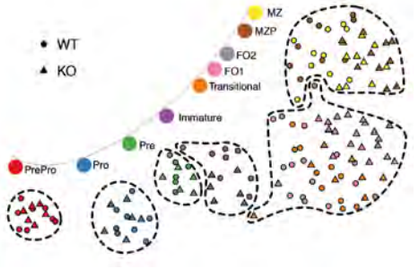
Chen L.Y., Jiang M., Zhang B., Gokce O., Sudhof T.C. *Conditional Deletion of All Neurexins Defines Diversity of Essential Synaptic Organizer Functions for Neurexins* **Neuron.** 2017 May 94 (3), 611-625. e4

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

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

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

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

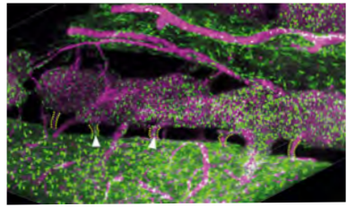


News

12/2018

SKULL-MENINGES CONNECTIONS REVEALED BY vDISCO

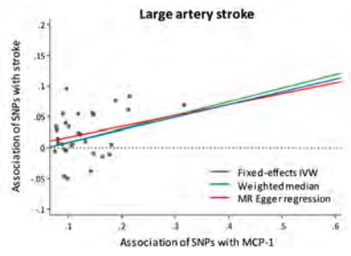
The Erturk group developed a nanobody-based immunolabeling method, vDISCO, that enables imaging subcellular details in transparent mice. They uncovered neuronal projections and skull–meninges connections in whole adult mice that are likely to have relevance in both health and disease.
Cai R et al., Panoptic imaging of transparent mice reveals whole-body neuronal projections and skull-meninges connections. **Nat Neurosci.** *2018 Dec 31.*



10/2018

ROLE OF MONOCYTE CHEMO-ATTRACTANT PROTEIN-1 IN STROKE

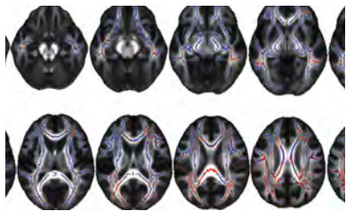
Using a Mendelian Randomization approach and data from >800.000 individuals ISD investigators showed that genetic predisposition to higher levels of the inflammatory cytokine MCP-1 is associated with a higher risk of stroke, in particular large artery stroke and cardioembolic stroke. These findings inform the planning of future clinical trials.
Georgakis MK et al., Genetically Determined Levels of Circulating Cytokines and Risk of Stroke: Role of Monocyte Chemoattractant Protein-1. **Circulation** *2019 Jan 8;139(2):256-268.*



09/2018

WHITE MATTER ALTERATIONS PRECEDE SYMPTOM ONSET IN AD

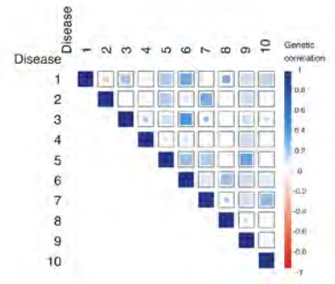
By studying patients with familial Alzheimer's disease (AD) Michael Ewers and his team found the evolution of white matter alterations to start in callosal fibers already 10 years before estimated symptoms onset in familial AD. They further found associations between white matter integrity and CSF markers of AD and soluble TREM2.
Araque Caballero MÁ et al., White matter diffusion alterations precede symptom onset in autosomal dominant Alzheimer's disease. **Brain.** *2018 Oct 1;141(10):3065-3080.*



06/2018

COMMON GENETIC BASIS OF COMMON BRAIN DISEASE

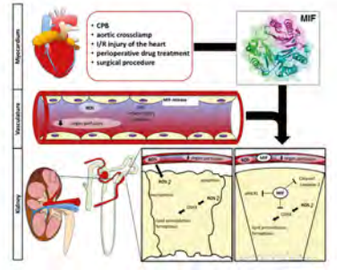
A large scale genetic study on major brain diseases including stroke and Alzheimer's disease revealed shared genetic influences between multiple brain disorders and relevant phenotypes, including cognitive measures. The results highlight the value of heritability-based methods in understanding the etiology of neurological and psychiatric disorders. ISD investigators were on the steering committee of this long term project... Brainstorm Consortium, ..., *Malik R et al., Analysis of shared heritability in common disorders of the brain.* **Science**. *2018 Jun 22;360(6395).*



05/2018

MIF PROTECTS FROM COMPLICATIONS AFTER CARDIAC SURGERY

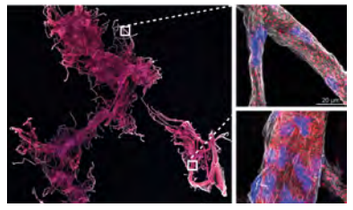
Complex heart surgery may lead to organ dysfunction such as acute kidney injury (AKI) or ischemic stroke. A researcher team led by Aachen University and the Bernhagen lab found that patients with high blood levels of the cytokine MIF had a reduced risk of developing AKI. The study is published in an issue of Sci Transl Med..
Stoppe C et al., The protective role of macrophage migration inhibitory factor in acute kidney injury after cardiac surgery. **Sci Transl Med.** *2018 May 16;10(441).*



04/2018

HTRA1 LOSS-OF-FUNCTION IN CADASIL

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
Zellner A et al., CADASIL brain vessels show a HTRA1 loss-of-function profile. **Acta Neuropathol.** *2018 Jul;136(1):111-125.*



03/2018

STROKE EXACERBATES ATHEROSCLEROSIS

Work by the Liesz lab reveals that experimental stroke exacerbates atheroprogression via alarmin-mediated propagation of vascular inflammation. Specifically, they demonstrate an HMGB1-induced monocyte and endothelial activation via the RAGE-signaling cascade and a synergizing effect of brain-released alarmins and stress response in accelerating atherosclerosis progression after stroke.

Roth S et al., Brain-released alarmins and stress response synergize in accelerating atherosclerosis progression after stroke. **Sci Transl Med.** *2018 Mar 14;10(432).*

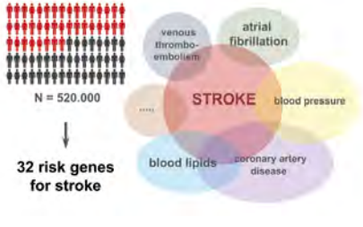
02/2018

25 NOVEL RISK LOCI FOR STROKE IDENTIFIED

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, cardiac 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.

Malik R et al., Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes **Nat Genet.** *2018 Apr;50(4):524-537.*

Malik R et al., Genome-wide meta-analysis identifies 3 novel loci associated with stroke. **Ann Neurol.** *2018 Nov 1. doi: 10.1002/ana.25369.*

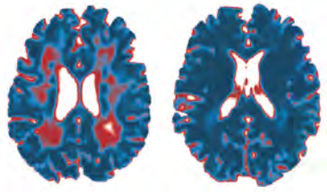


02/2018

INCREASED FREE WATER IN SMALL VESSEL DISEASE BRAINS

Diffusion changes are a major hallmark of cerebral small vessel disease. A recent study from ISD investigators shows that these changes are 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.

Duering M et al., Free water determines diffusion alterations and clinical status in cerebral small vessel disease. **Alzheimers Dement.** *2018 Jun;14(6):764-774.*

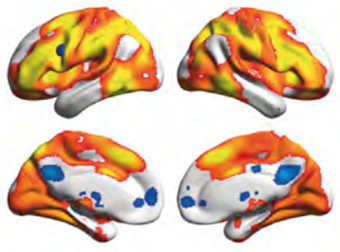


02/2018

PROTECTIVE HUB CONNECTIVITY IN ALZHEIMER'S DISEASE.

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...

Franzmeier N et al., Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease. **Brain.** *2018 Apr 1;141(4).*

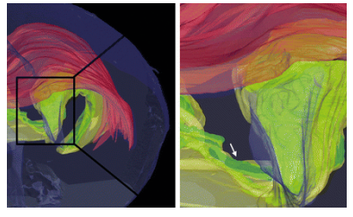


08/2017

THE CHOROID PLEXUS IS A KEY T CELL INVASION ROUTE

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

Llovera G et. al, The choroid plexus is a key cerebral invasion route for T cells after stroke. **Acta Neuropathol**. *2017 Dec;134(6):851-868.*

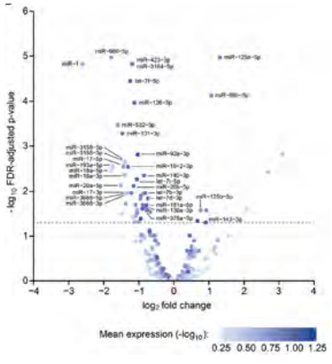


07/2017

MIRNA SET AS A NOVEL BIOMARKER FOR ISCHEMIC STROKE

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.

Tiedt S et al., RNA-Seq Identifies Circulating miR-125a-5p, miR-125b-5p, and miR-143-3p as Potential Biomarkers for Acute Ischemic Stroke. **Circ Res.** *2017 Sep 29;121(8):970-980.*



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

Investigator Initiated Studies *(Selection)*

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 (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 DEMDAS: 600
Started May 2013
Current enrollment: 602 (completed)
(216 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
Duering M et al., Neurology 2015
Wollenweber FA, et al., Stroke 2016
Dichgans M et al., Alzheimers Dement 2016
Zietemann V et al., Stroke 2017
Zietemann V et al., Neurology 2018

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
Malsch C et al,. Plos One 2018

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

The primary aim of this study is to characterize all patients with acute stroke admitted to a tertiary level stroke unit. Assessments are done at baseline and after 3 months. A focus is on the identification of factors associated with functional and cognitive outcome 3 months post-stroke. Patients excluded from PROSCIS or DEMDAS or patients who refused to participate in these long-term studies are included.

Planned sample size: 3000
Started February 2011
Current enrollment: 1.192 patients
Principle investigators: M. Dichgans, V. Zietemann
Publications:
Wollenweber FA et al., Stroke 2013

CAPIAS (Carotid Plaque Imaging in Acute Stroke NCT01284933)

Even with extensive diagnostic 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 with cryptogenic stroke. For plaque characterization all patients undergo high resolution black-blood carotid MRI at 3.0-Tesla (hr-bb-MRI). The hypotheses driving this study are that i) a substantial proportion of cryptogenic strokes in the anterior circulation are caused by AHA-LT VI plaques; ii) these patients are at high risk of developing a recurrent stroke, TIA, or clinically silent lesion detectable by brain MRI; and iii) AHA-LT VI plaques are associated with specific infarct patterns. Furthermore we will search for biomarkers associated with AHA-LT VI plaques. CAPIAS will provide valuable insights into stroke mechanisms, may have important implications for diagnostic decision making, and provide the basis for the planning of targeted interventional studies. The study was started in 2011 and subsequently extended as a multicenter study with additional sites in Munich (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
Schwarz F et al., Neurology 2013
Grimm JM et al., J Cardiovasc Magn Reson 2014
Hyafil F et al., Eur J Nucl Med Mol Imaging 2016
Bayer-Karpinska A et al., Neuroimag. Clin N Am 2016
Saam T et al., J Cardiovasc Magn Reso. 2016

SuSPect-CAA (Superficial Siderosis in Patients with suspected Cerebral Amyloid Angiopathy NCT01856699)
Non-traumatic cortical superficial siderosis (cSS) is a common finding in patients with cerebral amyloid angiopathy (CAA) and can be its sole imaging sign. The SuSPect-CAA study is a prospective observational multi-center cohort study. Its primary objective is to evaluate whether cSS is a predictor for future stroke and mortality (primary endpoint: combined rate of stroke and death after 36 months). Secondary objectives include 1) to determine, whether cSS represents a marker of future intracranial hemorrhage, 2) to describe the clinical presentation and course of cSS, 3) to assess associated imaging findings, and 4) to determine the differential diagnoses of cSS. All subjects presenting to the study center (out- and inpatients) will be screened. The study population consists of two patient groups: Study group: patients meeting the modified Boston criteria for probable or possible CAA. Patients meeting the Boston criteria for possible or probable CAA but without any cSS are assigned to the control group. Enrollment was finished in March 2016 after inclusion of 302 patients. Follow-up assessments at 6, 12, 24, and 36 months are currently ongoing. They include structured interviews, a neurological exam, neuropsychological tests, EEG and MRI.

Current recruitment: 302 (completed)
Started May 2013
Principle investigator: M. Dichgans, F. Wollenweber
Publications:
Linn J et al., J Neurol. 2013
Wollenweber F et al., Neurology 2019

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

Planned sample size: 190
Started: July 2013
Current enrollment: 191 (VASCAMY & CADASIL)
Principle investigators: M. Ewers, M. Düring, K. Bürger
Publications:
Taylor AN et al., Alzheimers Dement 2013
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: 1000
Started: February 2014
Current enrollment: 151 (ISD)
Principle investigator: K. Bürger

CIRCULAS (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. CIRCULAS 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, CIRCULAS' 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
Current enrollment: 1.346 patients
Principle investigator: M. Dichgans
Project management: S. Tiedt
Publications:
Tiedt S. et al., Circ Res 2017
Tiedt S. et al., Neurology 2018
Tiedt S, Dichgans M. Stroke 2018

TREAT-SVDs
EffecTs 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 CADASIL. 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 CO_2. Cerebrovascular reactivity to CO_2 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)
Current enrollment: 13 (3 genetic SVDs + 10 sporadic SVDs)
Estimated date for study completion: December 2020
Funding: EU Horizon2020 research and innovation programme

INVESTIGATE-SVDs

Imaging NeuroVascular, Endothelial and STructural 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 CO_2, 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 hypotheseis 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

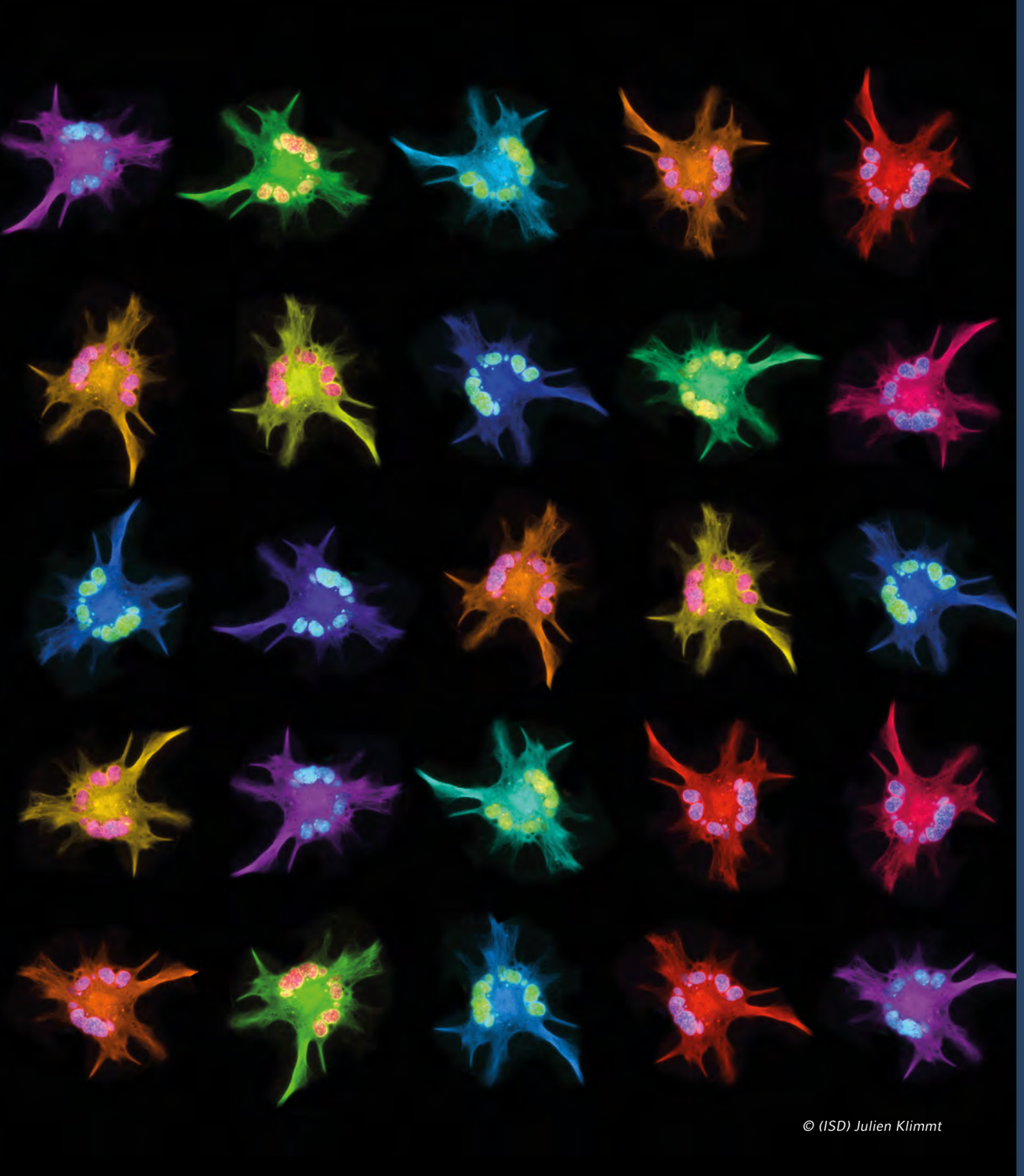
Randomized, double-blind-placebo-controlled, parallel-group study to assess the safety, tolerability, and efficacy of BIIB092 in subjects with mild cognitive impairment due to Alzheimer's disease or with mild Alzheimer's disease.
Protocol number 251AD201
Sponsor: Biogen USA/UK
Status: recruitung

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



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Funding & Education

Project Funding *(Selection)*

Munich Cluster for Systems Neurology (SyNergy) (DFG funded Excellence Initiative)
SyNergy promotes integrative research on major neurological diseases (neurovascular, neurodegenerative, neuroinflammatory), 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 organised into four research areas, each targeted at one specific pathomechanistic or translational nexus. Tandem projects are highly collaborative research projects involving multiple PIs. Technology hubs provide critical methodological support to Tandem Projects 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.

ISD investigators participate in the following:

Tandem Projects
A4 – Microglia heterogeneity in neurological disorders of neurodegenerative, inflammatory and vascular origin (M. Dichgans)
B1 – Systems neurology of cell-type specific mitochondrial pathology in neurodegeneration and ischemia models (A. Liesz)
B2 – 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
Mesoscale hub (A. Ertürk) involves: tailored virus vectors for cell labeling 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; ulti-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
PI-Support (M. Dichgans; A. Liesz; D. Paquet)
AI- Support (M. Düring; N. Plesnila; A. Ertürk; J. Bernhagen)
SyNergy Board: M. Dichgans
For more information see **www.synergy-munich.de**

The mission of Fondation Leducq is to improve human health through international efforts to combat cardiovascular and neurovascular disease. Each network is built around a transatlantic research alliance involving investigators from Europe and North America. The ISD participates in a network: **Pathogenesis of Small Vessel Disease of the Brain.** Small vessel diseases (SVD) account for 25% to 30% of ischemic strokes and are a leading cause of cognitive decline and disability worldwide. Very little is known about the underlying causes of SVDs. The central idea behind the project is that devastating monogenic forms of adult-onset SVD-CADASIL (missense mutations in NOTCH3) and CARASIL (loss-of-function mutations of HTRA1) - are invaluable paradigms for understanding the pathogenesis of SVD. The network has three highly interconnected objectives that collectively seek to identify the fundamental mechanisms of CADASIL and CARASIL at molecular, biochemical, cellular, neurovascular-unit and whole-brain levels, and assess the contribution of these disease pathways to common SVD.

Martin Dichgans contributes to aim 1 to identify the network of genes/gene products that drive small vessel pathology in CADASIL and CARASIL particularly in the mechanistic link between HTRA1 mutations and the TGF-fl pathway and in common disease pathways between CADASIL and CARASIL (Zellner et al., Acta Neuropathol, 2018).

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

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

ISD participates with two projects in this CRC:

Mechanisms of Atherogenic Recruitment by MIF Family proteins and peptide-based therapeutic leads (A 03; PI: Jürgen Bernhagen): MIF is an atypical chemokine (CK) that promotes atherosclerosis through CXCR2/4-dependent leukocyte recruitment. Based on results of the first funding period, we will study the entire MIF protein network in atherosclerosis; i.e. dissect the interplay between MIF and MIF-2 in atherogenesis and B cell autoreactivity (Aim 1), study previously unrecognized MIF gene products (MIF-3/4, MIF-AS1-lncRNA) (Aim 2), elucidate interactions between MIF proteins and classical CKs (Aim 3), and develop the identified CXCR ectodomain peptides into next-generation MIF protein-specific mimics as proof-of-concept atherosclerosis blockers (Aim 4).

Role of HDAC9 in Atherosclerosis (B03; PIs: Yaw Asare & Martin Dichgans): Our previous work established a pro-inflammatory and pro-atherogenic role of HDAC9 and identified an activating effect of HDAC9 on NF-κB signaling. We now aim to expand on these results by addressing the

following: (Aim 1) examine effects of HDAC9 on chromatin accessibility, the transcriptome, as well as the cellular proteome and secretome using ATAC-seq, RNA-seq, and LC-MS/MS; (Aim 2) investigate HDAC9-related alterations in NF-κB signaling under pro-inflammatory conditions; (Aim 3) study cell-specific effects of HDAC9 on atheroprogression and neointima formation using Hdac9flox/flox and atherogenic deleter mice.

For further information see
http://www.sfb1123.med.uni-muenchen.de/index.html

Small Vessel Diseases in a Mechanistic Perspective: Targets for Intervention
Affected pathways and mechanistic exploitation for prevention of stroke and dementia.
Stroke and dementia rank among the most pressing health issues in Europe.

Diseases in small blood vessels, known as cerebral small vessel diseases (SVDs) have emerged as a central link between these two major co-morbidities. SVDs account for more than 30% of strokes and at least 40% of dementia cases. They encounter multiple distinct diseases that can be separated based on their underlying genetic defects, risk factors, and clinical presentations. Despite this profound impact on human health, there are no treatments with proven efficacy against SVDs. The consortium which consists of 12 partners from 7 countries is coordinated by Martin Dichgans. It convenes basic scientists and academic clinicians and will make use of novel animal models, state-of-the art technologies (e.g. proteomics & ultra-high field MRI) and expertly phenotyped patient cohorts to identify key mechanisms common to multiple SVDs and determine how these mechanisms contribute to individual SVDs.

The five-year project which is funded with 6 Mio EUR through the European 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:

ZOOM@SVDs, 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

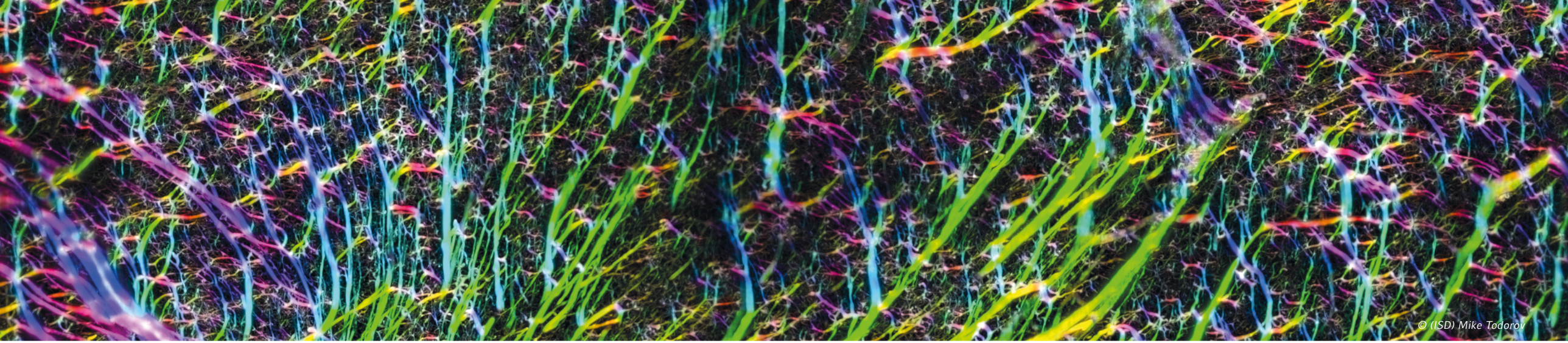
Coordinator: M. Dichgans
For more information see **http://www.svds-at-target.eu/**

Neuroinflammatory mechanisms of chronic neurodegeneration and cognitive decline following traumatic brain injury (CNSAflame) – ERA NET NEURON funded network.
Each year about 1.5 million people are affected by traumatic brain injury (TBI) in the EU, a disorder caused by an external force to the head typically during a road traffic, sport, or domestic accident. 70,000 of these patients die and 100,000 become disabled. Since these are mostly children and young adults, TBI is the most frequent cause of death and disability in the population younger than 45 years of age. While many lives were saved in recent years due to improved emergency and hospital care, it has become evident that surviving patients often suffer from various chronic neurological disorders such as epilepsy, depression and progressive dementia for their entire remaining life.

Currently, we lack treatments that could tackle these chronic complications induced by TBI (chronic TBI). CNSAflame aims to investigate whether the brain stays inflamed long-term - possibly for years - after the initial injury and whether chronic neuroinflammation is involved in loss of memory and cognitive decline induced by TBI. The ultimate aim of the project is to understand the underlying causes of chronic TBI as a basis for the development of an effective cure. In order to achieve this goal, the CNSAflame consortium composed of six research groups from Israel, France, Latvia, Sweden, and Germany will use animal models of TBI and investigate TBI patients with innovative state-of-the-art histological and imaging technologies. We will first monitor inflammation and degeneration of the brain over months in animal models (corresponding to years in humans). In parallel, we will investigate how chronic inflammation affects the human brain. Finally, we will use a bias-reducing multi-center approach to test whether inhibition of chronic inflammation is able to reduce post-traumatic cognitive decline.
Coordinators: Nikolaus Plesnila and Ali Ertürk
For more information see **http://cnsaflame.isd-muc.de/**

CVgenes@target (Exploitation of genomic variants affecting coronary artery disease and stroke risk for therapeutic intervention, funded by EU FP7)
Atherosclerosis and its most disabling sequelae, stroke and coronary artery disease (CAD), are leading causes of death in Europe. Until now, preventive and therapeutic interventions for these diseases aim at ameliorating the effects of established cardiovascular risk factors. More recently, results of genome-wide association (GWA) studies added to our perception of mechanisms leading to atherosclerosis. Collectively, over 50 genetic loci with a role in CAD and stroke have been identified. Some genes at these loci work through known risk factors such as lipids and, in fact, are already established or evolving treatment targets. However, this is not true for the majority of risk variants, which implies that key pathways leading to atherosclerosis are yet to be exploited for therapeutic intervention.

The EU network CVgenes@target utilizes genomic variants affecting atherosclerosis risk for identification of both underlying genes and affected pathways in order to identify, characterize, and validate novel therapeutically relevant targets for prevention and treatment of CAD and stroke. Three interconnected programmes pave the way from discovery of CAD/stroke risk loci to therapeutically modifiable targets. Martin Dichgans is a leader of WP4 on In vivo/ex vivo studies for target validation, and compound characterization and contributes to WP 3 on characterization of candidate genes and risk variants and WP5 on assay development.
For more information see **http://cvgenesattarget.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*	2017	2018
Personnel costs	2,834,038 €	2,707,763 €
Material costs	555,079 €	733,033 €
Travel expenses	52,589 €	90,882 €
Investments	1,350,902 €	213,772 €
Total	4,792,608 €	3,745,450 €

Third party funds (spent) / Source	Number of projects 2017	Funds spent 2017	Number of projects 2018	Funds spent 2018
DFG	63	4,370,782 €	93	2,340,691 €
BMBF, EU	28	431,283 €	36	649,405 €
Foundations (Fondation Leducq, Corona Stiftung…)	13	208,062 €	25	210,368 €
External third party funding spent		5,010,128 €		3,200,464 €
Others	40	1,296,112 €	79	785,942 €
Vascular Dementia Research Foundation*		4,792,608 €		3,745,450 €
Amount of further third party funding		6,088,720 €		4,531,392 €
Total third party funding spent		11,098,848 €		7,731,856 €

** (without outpatient clinic)*

Project	*Funding Institution*	*Role (PI=Principal Investigator)*	*Period*
SyNergy **Munich Cluster for Systems Neurology** *Period I: 01/2013 to 06/2015* *Period II: 07/2015 to 10/2017* *Bridge Funding: 11/2017 to 12/2018*	DFG (German Research Foundation)	PI, Tandem projects B3, B6: M. Dichgans	01/2013 to 12/2018
		PI, Tandem projects B5, B9, B10: N. Plesnila	
		Associated Investigator, Tandem project B9, Core 9: A. Ertürk	
		W3-Professur "Vaskuläre Biologie", Core 13: J. Bernhagen	
		SyNergy Professor: J. Bernhagen	
		SyNergy Professor: D. Paquet	
		Tandem project B12: A. Liesz	
		Clinical Scientist Group: A. Liesz	
		Clinical Scientist Program: S. Tiedt	
		Clinical Studies Hub: M. Dichgans	
		Tissue Clearing Hub: A. Ertürk	
		SyNergy "Racks für Tierhaltung ISD": M. Dichgans	
		SyNergy Kleintier PET/MR: M. Dichgans	
		Light Sheet Microscope: A. Ertürk	
Emmy-Noether Research Award on „Brain-released alarmins as mediators of immunological comorbidities after stroke"	DFG	PI: A. Liesz	Jan 2016 to Jan 2021
Supporting funds for 3T MRI	DFG	PI: M. Dichgans	-
SVDs@target – Small vessel diseases in a mechanistic perspective: Targets for Intervention – Affected pathways and mechanistic exploitation for prevention of stroke and dementia.	EU/Horizon 2020	Coordinator: M. Dichgans	Jan 2016 to Dec 2020
Fondation Leducq – Transatlantic Network of Excellence in Cardiovascular and Neurovascular Research	Fondation Leducq	PI: M. Dichgans	Aug 2012 to Jul 2018

Third Party Funding

Project	*Funding Institution*	*Role (PI=Principal Investigator)*	*Period*
SFB 1123 Atherosclerosis – Mechanisms and networks of novel therapeutic targets	DFG German Research Foundation	**Role of HDAC9 in Atherosclerosis.** PIs: M. Dichgans, C. Haffner, Y. Asare	Jul 2014 to Jun 2018
		Mechanisms of atherogenic recruitment by MIF family proteins and peptide-based therapeutic leads. PIs: J. Bernhagen, A. Kapurniotu (TUM)	Jul 2014 to Jun 2018
DEMDAS – DZNE Mechanisms of Dementia after Stroke.	DZNE	Coordinator and PI: M. Dichgans	Period I: Jan 2013 to Dec 2016 Period II: Jan 2017 to Dec 2021
CoSTREAM – Common mechanisms and pathways in Stroke and Alzheimer's disease.	EU/Horizon 2020	PI: M. Dichgans	Mar 2012 to Nov 2020
Neuroinflammatory mechanisms of chronic neurodegeneration and cognitive decline following traumatic brain injury	ERA-Net Neuron	PIs: A. Ertürk, N. Plesnila	Apr 2015 to Mar 2018
Protektion vor kardiovaskulären Veränderungen im Alter durch S-Nitrosierung des Zytokins Macrophage Migration Inhibitory Factor	Else-Kröner-Fresenius-Stiftung (EKFS)	T. Rassaf (Essen University Hospital), J. Bernhagen	Jan 2016 to Dec 2018
Molecular mechanisms of recessive and dominant mutations in the small vessel disease-related high temperature requirement protease HTRA1	DFG German Research Foundation	PI: M. Dichgans PI: N. Beaufort	Jan 2017 to Dec 2019
Structural and functional connectivity in cerebral small vessel disease	DFG German Research Foundation	PI: M. Düring	Jan 2017 to Dec 2019
Bedeutung von Perizyten für die Störung der zerebralen Mikrozirkulation nach Subarachnoidalblutung	Else-Kröner-Fresenius-Stiftung (EKFS)	PI: N. Plesnila	Mar 2014 to Jul 2019
Leukocyte-Interaction with immunological brain barriers	DFG German Research Foundation	PI: A. Liesz	Oct 2014 to Sep 2017
Assessing neurodegeneration throughout the entire brain at a single cell resolution in mice	DFG German Research Foundation	PI: A. Ertürk	Feb 2017 to Jan 2020
Usage of tissue clearing technology to investigate brain regions that are involved in diabetics	Member of Helmholtz Alliance ICEMED	PI: A. Ertürk	Nov 2016 to Oct 2018
VASCAMY – Interaction beween vascular and amyloid brain pathology in Alzheimer's disease	EU/Marie Curie	PI: M. Ewers	Jun 2013 to Jun 2017
FöFoLe funding MD thesis/Sabrina Reichl („The atypical chemokine MIF and B lymphocytes in atherosclerosis: emerging molecular and cellular links")	FöFoLe funding, LMU/KUM	PI: J. Bernhagen	Jan 2018 to Dez 2019
FöFoLe funding MD thesis/Christine Heisen („Microglial activity in neurol. dysfunction")	FöFoLe funding, LMU/KUM	PI: O. Gokce	Jan 2018 to Dez 2019
A novel oxidized MIF form; DZHK project PR.2-C	Deut. Zentrum für Herz-/Kreislauferkrankungen (DZHK)	PI: J. Bernhagen (T. Rassaf, Essen)	Jan 2018 to Jun 2019

Project	*Funding Institution*	*Role (PI=Principal Investigator)*	*Period*
Strukturelle und funktionelle Konnektivität als Biomarker der vaskulären kognitiven Störung	Else-Kröner-Fresenius-Stiftung (EKFS)	PI: M. Düring	Feb 2015 to Jan 2017
Elucidating the role of Tau isoform expression in human iPSC-derived Tauopathy models	VERUM Foundation	PI: D. Paquet	Dec 2018 to Nov 2020
HDAC9-mediated mechanisms underlying vascular inflammation	Medical Faculty, FöFoLe	PI: Y. Asare	Dec 2015 to May 2017
Characterization of neurodegeneration in the entire brain after TBI using novel 3D imaging approach	Medical Faculty, FöFoLe	PI: A. Ertürk	Sep 2016 to Mar 2018
An iPSC-derived human brain tissue model to investigate neurodegenerative and -vascular disorders	LMUexcellent	PI: D. Paquet	Dec 2018 to Nov 2019
The gut microbiota in post-stroke neuronal plasticity	LMU, LMUexcellent initiative	PI: A. Liesz	Mar 2016 to Feb 2017
Disentangling brain damage due to Alzheimer's and vasc. disease using DTI	Alzheimer Forschung Initiative e.V.	PI: M. Düring	Nov 2016 to Oct 2018
Strategic Partnership LMU/Singapore within LMUexc ("Mechanisms of cardiovascular protection: from preconditioning to endothelial memory")	LMUexc / DFG	PI: J. Bernhagen	Oct 2017 to Sept 2019
Usage of tissue clearing in metabolic disorders	Helmholtz	PI: A. Ertürk	Jun 2018 to Apr 2019
Structural and functional features of skull-meninges connections (SMCs)	LMU	PI: A. Ertürk	Jan 2018 to Dec 2019
Age and AD related bottlenecks in glymphatic-lymphatic waste transport	NIH	PI: A. Ertürk	Sep 2017 to Aug 2022
sTREM2. PGRN and GRN as CSF markers	Association for Frontotemporal Degeneration (AFTD)	PI: M. Ewers	Jan 2016 to Jan 2018
NEURON-Verbund TRAINS: Zeitabhängige Fernwirkungen nach Schädigung des Zentral-Nervensystems	BMBF NEURON	PI: N. Plesnila	Aug 2017 to May 2020
MISST- Ebenen-spezifische Untersuchung der synaptischen Fehlfunktion nach Schlaganfall	DLR Projektträger	PI: N. Plesnila	Aug 2018 to Aug 2021
Die Rolle von MIF innerhalb der kardialen ischämischen Präkonditionierung	DFG	PI: J. Bernhagen	Nov 2015 to Oct 2018
X-KINGDOM-MIF - Vergleichende Analyse der Funktion von Macrophage Migration Inhibitory Factor (MIF)-Proteinen in Tier- und Pflanzenreichen	DFG	PI: J. Bernhagen	Jan 2017 to Dec 2019
Indikation von Inhibitoren der pathologischen Notch3-Aggregation	DFG	PI: C. Haffner	Nov 2017 to Nov 2020
Entwicklung genetisch kodierter K+ Fluoreszenzsensoren	DFG	PI: N. Plesnila	Feb 2018 to Feb 2021
Förderung Investitionsfond	LMUexcellent	PI: M. Dichgans	Jun 2018 to May 2019
Role of MIF-2 in wound healing	DFG	PI: J. Bernhagen	May 2018 to Apr 2021
Förderung Investitionsfond	LMU Excellent	PI: O. Gökce	Jul 2018 to Jul 2019
Nachwuchsförderungsfonds	LMU Excellent	PI: D. Paquet	Dec 2018 to Nov 2019
Ersteinrichtungs-/Investitionsmittel für Geräte der LMU	LMU Excellent	PI: J. Bernhagen	Nov 2015 to Nov 2020
Förderung Investitionsfond	LMUexcellent	PI: A. Ertürk	Jul 2017 to Jun 2018
DigiMed Bayern P4 Medizin von Carotis Stenose und Schlaganfall	Projektträger Bayern	PI: M. Dichgans	Okt 2018 to Nov 2023
Young Investigator Grant Agreement (Transfer)	Brain & Behavoir Research Foundation	PI: O. Gökce	Jan 2015 to Dec 2017
Young Investigator Grant Agreement	Brain & Behavoir Res. Foundation	PI: O. Gökce	Jan 2017 to Jan 2019
Conference funding 9th International MIF Symposium	DFG	PI: J. Bernhagen	Jul 2018 to Dec 2018
German-Israeli Minerva Workshop	Minerva Foundation	PI: J. Bernhagen (I. Shachar, Israel)	Oct 2017
Molecular mechanisms causing spine loss in chronic traumatic brain injury	Fritz Thyssen Stiftung	PI: A. Ertürk	Feb 2017 to Aug 2019
Dichotome Rolle von MIF-Zytokinen als Tumorpromotor und -suppressor in der Pathogenese chemisch- und UV-induzierter Plattenepithelkarzinome	Wilhelm-Sander-Stiftung	PI: J. Bernhagen	Apr 2017 to Mrz 2019
Genetics of Early-Onset Stroke Consortium	NIH	PI: M. Dichgans	Jan 2018 to Dec 2022
Crosstalk between microbiota metabolites and immune cells, the missing link to brain damage "MetaBiota"	EU/Horizon 2020	PI: A. Liesz	May 2017 to Apr 2019
ERC Starting Grant - RecoverInFlame	EU/Horizon 2020	PI: A. Liesz	Nov 2017 to Oct 2023
Meta Biota	EU/Horizon 2020	PI: A. Liesz	May 2017 to Apr 2019
Neurotarget	EU/Horizon 2020	PI: N. Plesnila	Dec 2018 to Nov 2020
Effects of HDAC9 deficiency on pro-atherogenic NF-kB responses	Friedrich-Baur-Stiftung	PI: Y. Asare	Jul 2017 to Dec 2018
Poly-SNP-Genotypisierung bei Patienten mit cerebraler Amyloidangiopathie	Friedrich-Baur-Stiftung	PI: F. Wollenweber	Jul 2017 to Dec 2018
Inflammatorische Mechanismen in der Erholung motorischer Defizite nach Schlaganfall	Friedrich-Baur-Stiftung	PI: A. Liesz	Jul 2018 to Dec 2019
Mechanism of microvascular inquiry in FoxF2	Friedrich-Baur-Stiftung	PI: K. Völgyi	Jul 2018 to Dec 2019
Development of single cell sequencing approach to reveal in vivo RNA dynamics	Friedrich-Baur-Stiftung	PI: O. Gökce	Jul 2018 to Dec 2019

Teaching

2018 | Faculty of Medicine

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

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

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

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

Malik R | Genetische Analysen komplexer Erkrankungen (7C0157)

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

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

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

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

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

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

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

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

Dichgans M I Ewers M I Diskussion aktueller Forschungsbefunde zur Alzheimer Demenz (7C4046)

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

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

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

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

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

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

Bernhagen J, Besson-Girard S, Brandhofer M, El Bounkari O, Gökce Ö, Krammer C, Schindler L, Sinitski D, Wang S | Current developments in vascular biology: mechanisms and pathologies (7C0375)

Bernhagen J, Besson-Girard S, Brandhofer M, El Bounkari O, Gökce Ö, Krammer C, Schindler L, Sinitski D, Wang S | Current topics in molecular atherosclerosis research (7C4047)

Dichgans M, Bernhagen J, El Bounkari O, Gökce Ö, Sinitski D, Wang S | Doktorandenkolloqium: (kardio)vaskuläre Pathologien - von den Grundlagen der vaskulären und Neurobiologie zur Pathogenese (7C0376)

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

Bernhagen J, El Bounkari O, Gökce Ö, Hoffmann A | Practical Course Molecular and Cellular Cardiovascular Medicine (7C0480)

Bernhagen J, Besson-Girard S, Brandhofer M, El Bounkari O, Gökce Ö, Krammer C, Schindler L, Sinitski D, Wang S | Current developments in vascular biology: mechanisms and pathologies (7C0375)

Bernhagen J, Besson-Girard S, Brandhofer M, El Bounkari O, Gökce Ö, Krammer C, Schindler L, Sinitski D, Wang S | Current topics in molecular atherosclerosis research (7C4047)

Dichgans M, Bernhagen J, El Bounkari O, Gökce Ö, Sinitski D, Wang S | Doktorandenkolloqium: (kardio)vaskuläre Pathologien - von den Grundlagen der vaskulären und Neurobiologie zur Pathogenese (7C0376)

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

2018 | Faculty of Biology

Ewers M, Adam, R, Flanagin V, Düring M I Seminar Functional Connectomics in Disease: Applied Resting State Imaging – (19341)

Ewers M, Adam R, Düring M, Caballero M, Malik, R I Seminar Structural connectomics in disease: Applied diffusion tensor imaging (DTI) and fiber tracking (19340)

Ewers M, Düring M, Adam R, , Caballero M, Malik R, Franzmeier N, Stöcklein S I Seminar Structural and Functional Connectomics in Neuroimaging (19300)

Dichgans M, Haffner C, Plesnila N, Beaufort N, Liesz A, Bernhagen J, Gökce Ö, El Bounkari O, Prestel M, Paquet D | P 2.5 Practical Course Molecular Neurogenetics and Experimental Stroke Research (19025)

Bernhagen J, El Bounkari O, Gökce Ö, Hoffmann A | Practical Course Molecular and Cellular Cardiovascular Medicine (7C0480)

Gokce O, | Molecular biology and –omics approaches in the biomedical neurosciences master program. Lecture & practical lab course

2018 | Faculty of Chemistry and Pharmacology / Gene Center

Bernhagen J | Innate Immunity and Inflammation – Lecture, Elective Module Master of Biochemistry (T1QC-M)

Bernhagen J | Innate Immunity and Inflammation – Seminar, Elective Module Master of Biochemistry (T1WS-P)

Bernhagen J, El Bounkari O | Innate Immunity and Inflammation – Practical Course, Elective Module Master of Biochemistry (T1HJ-M)

2017 | Faculty of Medicine

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

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

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

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

Malik R | Genetische Analysen komplexer Erkrankungen (7C0157)

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

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

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

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

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

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

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

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

Dichgans M, Ewers M I Diskussion aktueller Forschungsbefunde zur Alzheimer Demenz (7C4046)

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

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

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

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

Bernhagen J, Brandhofer M, Chen H, El Bounkari O, Gökce Ö, Nguyen P, Krammer C, Schindler L, Sinitski D, Tursch M | Current developments in vascular biology: mechanisms and pathologies (7C0375)

Bernhagen J, Brandhofer M, Chen H, El Bounkari O, Gökce Ö, Nguyen P, Krammer C, Schindler L, Sinitski D, Tursch M | Current topics in molecular atherosclerosis research (7C4047)

Bernhagen J, El Bounkari O, Gökce Ö, Sinitski D I Doktorandenkolloqium: (kardio)vaskuläre Pathologien - von den Grundlagen der vaskulären und Neurobiologie zur Pathogenese (7C0376)

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

2017 | Faculty of Biology

Ewers M, Adam, R, Flanagin V, Düring M I Seminar Functional Connectomics in Disease: Applied Resting State Imaging (19341)

Ewers M, Adam R, Düring M, Caballero M, Malik, R I Seminar Structural connectomics in disease: Applied diffusion tensor imaging (DTI) and fiber tracking (19340)

Ewers M, Düring M, Adam R, , Caballero M, Malik R, Franzmeier N, Stöcklein S I Seminar Structural and Functional Connectomics in Neuroimaging (19300)

2017 | Faculty of Chemistry and Pharmacology / Gene Center

Bernhagen J | Innate Immunity and Inflammation – Lecture, Elective Module Master of Biochemistry (T1QC-M)

Bernhagen J | Innate Immunity and Inflammation – Seminar, Elective Module Master of Biochemistry (T1WS-P)

Education

Clinician Scientist Program PRIME
Starting from January 2019 the DFG-funded clinician scientist PRrogram In vascular Medicine (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) connect these measures with an advanced scientist program to establish a sustained pipeline for independency of highly qualified early career researchers; and 5) 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 postdocs (see www.mcn.lmu.de).

M. Dichgans and Judit Gonzalez-Gallego (PhD student) 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

Every PhD student is assigned a thesis advisory committee, which supervises the scientific work, its feasibility and milestones and advises the student in his/hers career planning and scientific network.

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

Theses & Awards *(Selection)*

PhD Theses

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

Functional exploration of Foxf2, a risk gene for cerebral small vessel disease. J González-Gallego, planned degree: PhD (GSN), started Oct 2018

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

MIF-2/D-DT in atherosclerosis and stroke. C. Zan, planned degree: PhD, started Sept 2018

The role of striatal circuit function and plasticity after stroke. H. Ji, planned degree: PhD, started Sep 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 Apr 2017

Investigating HDAC9 mediated dysfunction in CRISPR-edited iPSC-derived vascular in vitro models. I. Weisheit, planned degree: PhD (GSN), started Apr 2017

Neuroimaging markers for Alzheimer´s disease and cerebral small vessel disease, S. Finsterwalder, planned degree: PhD (GSN), started Apr 2017

The contribution of chronic neuroinflammation to post-stroke recovery. S. Heindl, planned degree: PhD, started Oct 2017

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

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-Girard, planned degree: PhD (GSN), started Jan 2017

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

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

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

The atypical chemokine interactome in inflammation. M. Brandhofer, planned degree: Dr. rer. nat., started in 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: Dr. rer. nat., started Apr 2015

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

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

Medical Theses

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

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

The role of oxidized species of the atypical chemokine MIF in early atherogenesis. L. Zwißler, 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., FöFoLe fellow for excellent structured MD thesis, started in Mar 2018

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

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

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

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

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

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

Completed:

The Functional Role of the Macrophage Migration Inhibitory Factor Protein Family in Myocardial Fibrosis. J. Soppert, Dr. rer. nat., completed April 2018

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

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

Association between resting-state functional connectivity, glucose metabolism and task-activation of neural networks. L. Simon-Vermot, PhD (GSN), completed Dec 2017

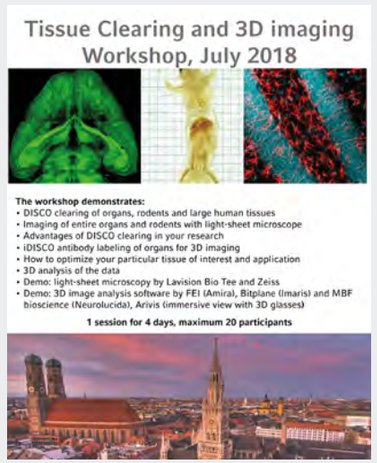
Imaging Markers of Cerebral Small Vessel Disease. E. Baykara, PhD (GSN), completed Aug 2018

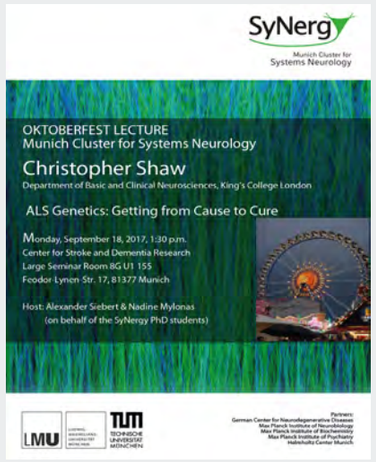
The protective role of MIF in acute kidney injury after cardiac surgery. L. Averdunk, MD, completed April 2018

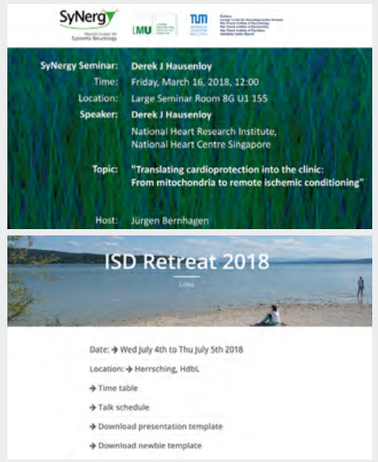
The role of brain-released alarmins in post-stroke atheroprogression. S. Roth, Dr. rer. nat., completed Oct 2018

Honors & Awards

- C. Benakis | Marie Curie Individual Fellowship, 2017
- M. Düring | Adolf Wallenberg Award (DSG), 2017
- M. Düring | Radboud Excellence Initiative Fellowship 2018
- J. Milic | Dositej Oradovic Scholarship Serbia, 2017
- J. Milic | IRTG1123 Fellowship, 2018
- S. Wang | LMU-CSC Scholarship, 2017
- N. Franzmeier | Steinberg-Krupp Award 2018
- A. Hoffmann | Metiphys Scholarship, 2018
- C. Zan | LMU-CSC Scholarship, 2018
- Y. Gao | LMU-CSC Scholarship, 2018
- L. Zwißler | IRTG1123 Fellowship, 2018
- S. Roth | Rolf Becker Award, 2018
- M. Lopez | DAAD Fellowship 2018
- M. Georgakis | Research Grant for Doctoral Candidates and Young Academics and Scientists by (DAAD)| 2018-2019, Graduate Scholarship for Hellenes by Onassis Foundation | 2018-2020
- S. von Brauchitsch | Travel stipend for the congress of the Deutsche Gesellschaft für Neurologie (DGN), 2017 and 2018
- T. Campbell-James | Full scholarship for medical internship abroad, Beirut (Lebanon) (IFMSA) 2018, Full scholarship for Global Health Summer School, Katowice (Poland), (TUM), Faculty of Medicine, 2018, Kongress-Stipendium, DGN-Kongress, (DGN) 2018
- A. Gerhard | Congress scholarship, Neurowoche 2018 (DGN), MeCuM-StEP, Medical Faculty of LMU, 2018
- N.Schieferdecker | Scholarship for final year rotations for excellent students from the LMU
- L. Luya Yu | PROSA LMU, DAAD funded by Bundesministerium für Bildung und Forschung, 2018, Kongress-Stipendium, DGN-Kongress, Berlin, (DGN), 2017
- Y. Huang | Chinese Government Scholarship, Chinese scholarship council, 2018
- M. Dichgans | Honorary Member of the Austrian Stroke Society (ÖSG) 2017
- M. Dichgans | President-elect, European Stroke Organisation (ESO), 2018-present (Presidency to start in 2020)







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) I M. Dichgans: scientific chair

91th DGN Congress (Berlin, Nov 2018) DSG Symposium, Acute Stroke – Hot Topics, Bayer Symposium, Spotlight: Hilights of the Congress, Satellite Symposium, Mechanic Thrombectomy I M. Dichgans: scientific chair

Conferences, Trainings and Events *(Selection)*

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

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

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

AAIC 2018, The Alzheimer's Association International Conference 2018 (Chicago, USA, Jul 2018) I M. Ewers: session chair, speaker

DGNC Sektionstagung Vaskuläre Neurochirurgie (Aachen, Mar 2018) I N. Plesnila: keynote speaker

ANIM 2018, Arbeitstagung NeuroIntensiv Medizin (Würzburg, Feb 2018) I M. Dichgans: scientific chair

NTIM 2018, Jahrestagung der Sektion Intensivmedizin und Neurotraumatologie der DGNC (Würzburg, Jan 2018) I N. Plesnila: keynote speaker

5th Symposium of New Frontiers in Cardiovascular Research (Sapporo, June 2018**)** Session: Inflammation and Atherosclerosis I J. Bernhagen: speaker and co-organizer

9th International MIF Symposium Munich (Munich, Oct 2018) Session: "Session I – Cardiovascular Diseases and Session VII – Key note" I J. Bernhagen: speaker, chair and organizer; O. El Bounkari: speaker, co-organizer

International Stroke Genetics Consortium (Amsterdam, Niederlande, Nov 2017) I M. Dichgans: scientific chair

ResDem 2017, 1st International Conference on Cognitive Reserve in the Dementias (Munich Nov 2017) I M. Ewers: co-chair

DGN-Kongress (Leipzig, Sep 2017) I M. Dichgans: scientific chair

AAIC 2017, The Alzheimer's Association International Conference 2017 (London, UK, Jul 2017) I M. Ewers: session chair, speaker

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

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

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

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

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

4th Symposium of New Frontiers in Cardiovascular Research, (Havana, Cuba, March 2017) Session: „Inside – Outside Vessels" I J. Bernhagen: keynote speaker

First ANR-DFG MIF X-Kingdom Workshop, Institut Sophia Agrobiotech Sophia Antipolis France (Sophia Antipolis, March 2017) J. Bernhagen: speaker and co-organizer

Annual Conference 34th ANIM (Vienna, Jan 2017) Symposium DSG I M. Dichgans: scientific chair

4th ESO Stroke Science Workshop (Garmisch-Partenkirchen, Nov 2017) I 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

Karin Hochrainer, Weill Cornell Medical College

John Cryan, BSc Biochemistry, Nat.University of Ireland, Galway

Dominik Michalski, Klinik und Poliklinik für Neurologie, Universitätsklinikum Leipzig

Renaud Jolivet, CERN and University of Geneva

Willem Huijbers, Tilburg University, The Netherlands

Claudio D. Acuna Goycolea, Anatomy and Cell Biology, Heidelberg University

Karsten Ruscher, Wallenberg Neurosc. Center, Lund University

Tony Stöcker, DZNE Bonn

Paul G. Unschuld, 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 Szczygielski, Institute of Neuropathology, Saarland University Medical Center

Birgit Liss, Institut of Applied Physiology, Ulm University

Ana Martin-Villalba, German Cancer Research Center, DKFZ, Heidelberg

Publications

2018

Cai R, Pan C, Ghasemigharagoz A, Todorov MI, Förstera B, Zhao S, Bhatia HS, Parra-Damas A, Mrowka L, Theodorou D, Rempfler M, Xavier ALR, Kress BT, Benakis C, Steinke H, Liebscher S, Bechmann I, Liesz A, Menze B, Kerschensteiner M, Nedergaard M, Ertürk A. *Panoptic imaging of transparent mice reveals whole-body neuronal projections and skull-meninges connections.* **Nat Neurosci.** 2018 Dec 31.

Emontzpohl C, Stoppe C, Theißen A, Beckers C, Neumann UP, Lurje G, Ju C, Bernhagen J, Tolba RH, Czigany Z. *The Role of Macrophage Migration Inhibitory Factor in Remote Ischemic Conditioning Induced Hepatoprotection in A Rodent Model of Liver Transplantation.* **Shock.** 2018 Dec 21.

von Neubeck B, Gondi G, Riganti C, Pan C, Parra Damas A, Scherb H, Ertürk A, Zeidler R. *An inhibitory antibody targeting carbonic anhydrase XII abrogates chemoresistance and significantly reduces lung metastases in an orthotopic breast cancer model in vivo.* **Int J Cancer.** 2018 Oct 15;143(8):2065-2075.

Ganjam GK, Terpolilli NA, Diemert S, Eisenbach I, Hoffmann L, Reuther C, Herden C, Roth J, Plesnila N, Culmsee C. *Cylindromatosis mediates neuronal cell death in vitro and in vivo.* **Cell Death Differ.** 2018 Aug;25(8):1394-1407.

Frik J, Merl-Pham J, Plesnila N, Mattugini N, Kjell J, Kraska J, Gómez RM, Hauck SM, Sirko S, Götz M. *Cross-talk between monocyte invasion and astrocyte proliferation regulates scarring in brain injury.* **EMBO Rep.** 2018 May;19(5). pii: e45294.

Liu H, Dienel A, Schöller K, Schwarzmaier SM, Nehrkorn K, Plesnila N, Terpolilli NA. *Microvasospasms After Experimental Subarachnoid Hemorrhage Do Not Depend on Endothelin A Receptors.* **Stroke.** 2018 Mar;49(3):693-699.

Anzabi M, Angleys H, Aamand R, Ardalan M, Mouridsen K, Rasmussen PM, Sørensen JCH, Plesnila N, Østergaard L, Iversen NK. *Capillary flow disturbances after experimental subarachnoid hemorrhage: a contributor to delayed cerebral ischemia?* **Microcirculation.** 2018 Nov 15:e12516.

Ling Y, De Guio F, Jouvent E, Duering M, Hervé D, Guichard JP, Godin O, Dichgans M, Chabriat H. *Clinical correlates of longitudinal MRI changes in CADASIL.* **J Cereb Blood Flow Metab.** 2018 Feb 5:271678X18757875.

Franzmeier N, Düzel E, Jessen F, Buerger K, Levin J, Duering M, Dichgans M, Haass C, Suárez-Calvet M, Fagan AM, Paumier K, ..., Araque Caballero MÁ, Metzger C, Bittner D, Weiner M, Lee JH, Salloway S, Danek A, Goate A, Schofield PR, Bateman RJ, Ewers M.*Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease.* **Brain.** 2018 Apr 1;141(4):1186-1200.

Duering M, Finsterwalder S, Baykara E, Tuladhar AM, Gesierich B, Konieczny MJ, Malik R, Franzmeier N, Ewers M, Jouvent E, Biessels GJ, Schmidt R, de Leeuw FE, Pasternak O, Dichgans M. *Free water determines diffusion alterations and clinical status in cerebral small vessel disease.* **Alzheimers Dement.** 2018 Jun;14(6):764-774.

Georgakis MK, Gill D, Rannikmäe K, Traylor M, Anderson CD, Lee JM, Kamatani Y, Hopewell JC, Worrall BB, Bernhagen J, Sudlow CLM, Malik R, Dichgans M. *Genetically Determined Levels of Circulating Cytokines and Risk of Stroke.* **Circulation.** 2019 Jan 8;139(2):256-268

Roth S, Singh V, Tiedt S, Schindler L, Huber G, Geerlof A, Antoine DJ, Anfray A, Orset C, Gauberti M, Fournier A, Holdt LM, Harris HE, Engelhardt B, Bianchi ME, Vivien D, Haffner C, Bernhagen J, Dichgans M, Liesz A. *Brain-released alarmins and stress response synergize in accelerating atherosclerosis progression after stroke.* **Sci Transl Med.** 2018 Mar 14;10(432).

Franzmeier N, Hartmann J, Taylor ANW, Araque-Caballero MÁ, Simon-Vermot L, Kambeitz-Ilankovic L, Bürger K, Catak C, Janowitz D, Müller C, Ertl-Wagner B, Stahl R, Dichgans M, Duering M, Ewers M. *The left frontal cortex supports reserve in aging by enhancing functional network efficiency.* **Alzheimers Res Ther.** 2018 Mar 6;10(1):28.

Malik R, Dichgans M. *Challenges and Opportunities in Stroke Genetics.* **Cardiovasc Res.** 2018 Jul 15;114(9):1226-1240.

Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese AK, van der Laan SW, Gretarsdottir S, ... Howson JMM, Kamatani Y, Debette S, Dichgans M,..., AFGen Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium; International Genomics of Blood Pressure (iGEN-BP) Consortium; INVENT Consortium; STARNET; BioBank Japan Cooperative Hospital Group; COMPASS Consortium; EPIC-CVD Consortium; EPIC-InterAct Consortium; International Stroke Genetics Consortium (ISGC); METASTROKE Consortium; Neurology Working Group of the CHARGE Consortium; NINDS Stroke Genetics Network (SiGN); UK Young Lacunar DNA Study; MEGASTROKE Consortium; MEGASTROKE Consortium: *Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes.* **Nat Genet.** 2018 Apr;50(4):524-537.

Bernhardt J, Zorowitz RD, Becker KJ, Keller E, Saposnik G, Strbian D, Dichgans M, Woo D, Reeves M, Thrift A, Kidwell CS, Olivot JM, Goyal M, Pierot L, Bennett DA, Howard G, Ford GA, Goldstein LB, Planas AM, Yenari MA, Greenberg SM, Pantoni L, Amin-Hanjani S, Tymianski M. *Advances in Stroke 2017.* **Stroke.** 2018 May;49(5):e174-e199.

Zellner A, Scharrer E, Arzberger T, Oka C, Domenga-Denier V, Joutel A, Lichtenthaler SF, Müller SA, Dichgans M, Haffner C. *CADASIL brain vessels show a HTRA1 loss-of-function profile.* **Acta Neuropathol.** 2018 Jul;136(1):111-125.

Brown R, Benveniste H, Black SE, Charpak S, Dichgans M, Joutel A, Nedergaard M, Smith KJ, Zlokovic BV, Wardlaw JM. *Understanding the role of the perivascular space in cerebral small vessel disease.* **Cardiovasc Res.** 2018 Sep 1;114(11):1462-1473.

Rutten-Jacobs LCA, Tozer DJ, Duering M, Malik R, Dichgans M, Markus HS, Traylor M. *Genetic Study of White Matter Integrity in UK Biobank (N=8448) and the Overlap With Stroke, Depression, and Dementia.* **Stroke.** 2018 Jun;49(6):1340-1347.

Roselli C, ..., Denny JC, Dichgans M, Dörr M, ..., Mahajan A, Malik R, Mansur AJ, ..., Ellinor PT. *Multi-ethnic genome-wide association study for atrial fibrillation.* **Nat Genet.** 50: 9. 1225-1233 Sep.

Duering M, Konieczny MJ, Tiedt S, Baykara E, Tuladhar AM, Leijsen EV, Lyrer P, Engelter ST, Gesierich B, Achmüller M, Barro C, Adam R, Ewers M, Dichgans M, Kuhle J, de Leeuw FE, Peters N. *Serum Neurofilament Light Chain Levels Are Related to Small Vessel Disease Burden.* **J Stroke.** 2018 May;20(2):228-238.

Duchesnay E, Hadj Selem F, De Guio F, Dubois M, Mangin JF, Duering M, Ropele S, Schmidt R, Dichgans M, Chabriat H, Jouvent E. *Different Types of White Matter Hyperintensities in CADASIL.* **Front Neurol.** 2018 Jul 10;9:526.

	2017		2018	
	number	IF total / IF Ø	number	IF total / IF Ø
Total Publications	57	455.2 / 8.0	72	629.7 / 9.7
First and/or Senior Authorship	26	181.4 / 7.0	20	204.3 / 10.2

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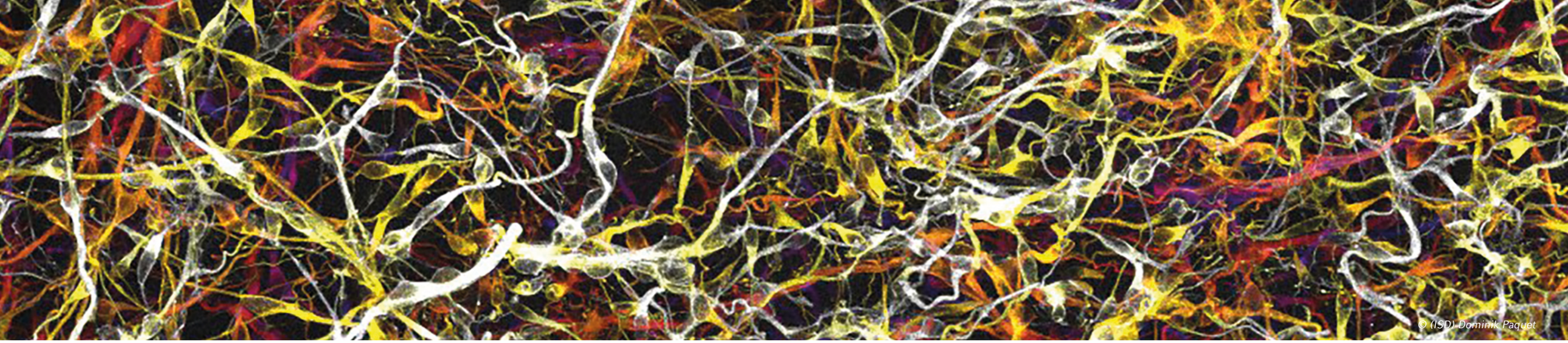

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