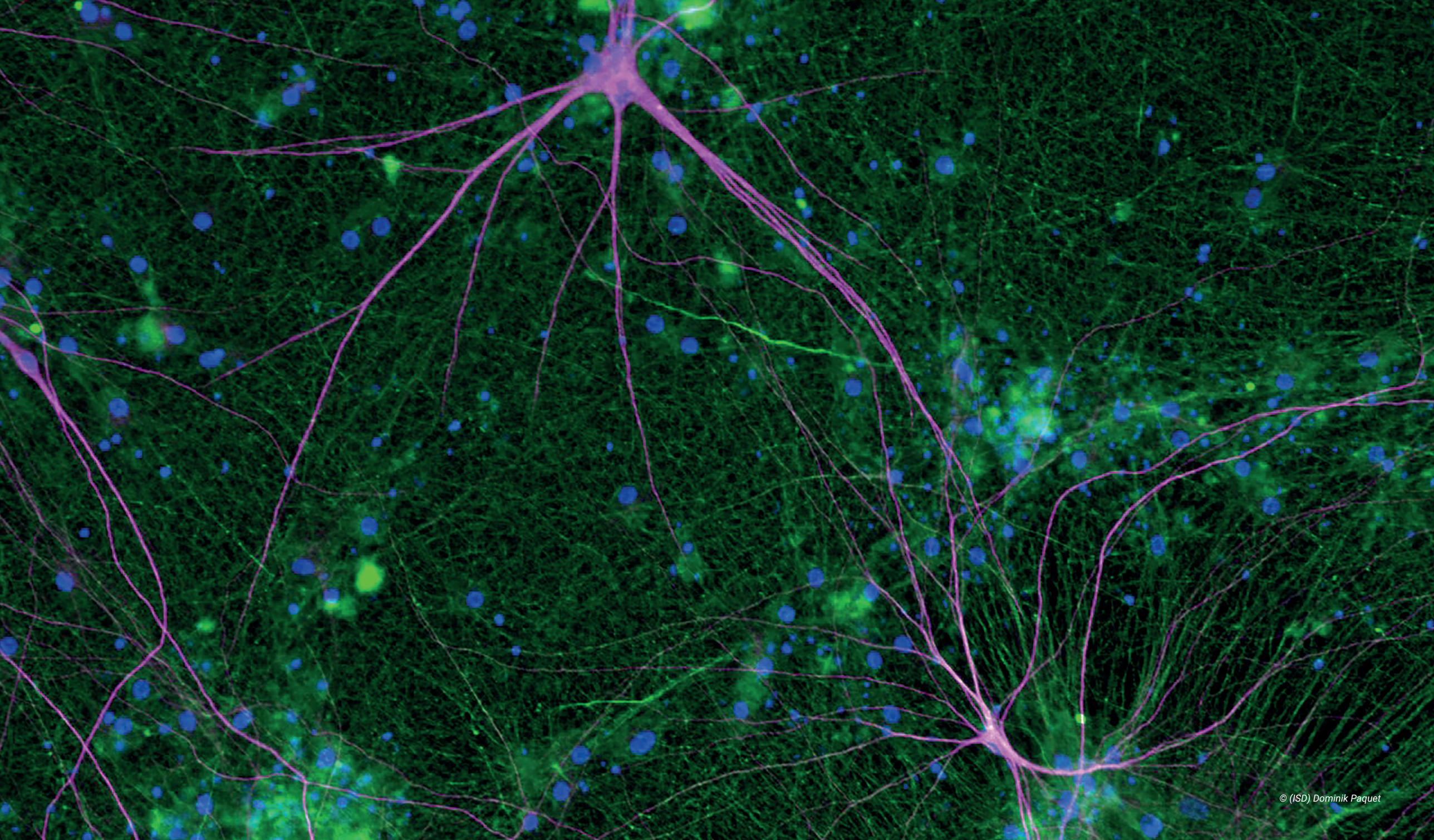
# Annual Report 2019/2020

Institute for Stroke and Dementia Research
LMU Klinikum
Ludwig-Maximilians-Universität München



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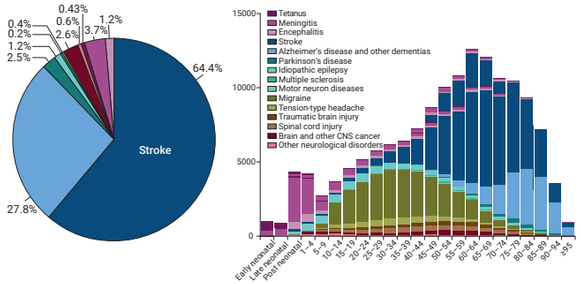
# Foreword

## *The Institute for Stroke and Dementia Research*

Stroke and Dementia rank among the most common diseases worldwide and the most pressing health problems in ageing societies.




*Left: Proportion (%) of disability-adjusted life years.*
*Right: Stratified for age*

Stroke remains 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 clinician and medical 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.

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 125 people, including 88 scientific staff ranging from master and PhD students to full professors. Currently, the ISD hosts 8 senior and 3 junior 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, as well as a memory clinic. Within the new CSD building, the ISD closely collaborates with its partnering institution – the German Center for Neurodegenerative Diseases (DZNE).

Scientists from the ISD recently received prestigious research awards, including the Rolf-Becker award (to Ali Ertürk), several Young Investigator awards, and a Chan Zuckerberg Initiative (CZI) award (to Ozgun Gokce and Mikael Simons). Ali Ertürk obtained an ERC consolidator grant and meanwhile moved to the Helmholtz Zentrum München (HMGU) as the director of a new research institute, while continuing to maintain an operation at the ISD.

Arthur Liesz was appointed W2 professor for Stroke Immunology and will lead the new DFG funded research unit ImmunoStroke (FOR 2879) into its next application phase. Our investigators are acquiring increasing amounts of third party funding with 3.8 million Euro spent in 2019, and more than 3.9 million Euro spent in 2020. Within this period, ISD investigators published more than 170 papers in peer-reviewed international journals, including leading journals in the fields of Genetics, Neuroscience, Cardiovascular Research, and Science in general.

Among the most recent accomplishments in terms of infrastructure are the installment of a FEMTOSmart Galvo 3-Photon microscope (expanding options for noninvasive structural and functional imaging in living systems) and a Genomics unit equipped with nanoliter liquid handling robots for miniaturized molecular biology reactions. Together, these further add to the technology hubs of the DFG-funded excellence cluster for systems neurology (SyNergy).

The ISD is part of an ever-growing neuroscience community in Munich, and is heavily involved in the SyNergy cluster. SyNergy began its 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 successfully applied for continuation of funding with an even more developed strategic plan. The ISD further entertains close links with various collaborative research centers, such as the CRC1123 on atherosclerosis and CRC TR274 on checkpoints in CNS recovery, 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. The ISD is further actively engaged in the newly-funded Hertie Network of Excellence in Clinical Neuroscience.

Among the plans for 2021/22 is the installment of two new Junior Research Groups. Starting on January 1st, Nicolai Franzmeier, who has a focus on neuroimaging in dementia and excelled at the ISD over the last years, will establish his own research group. On March 1st, Sarah Jäkel, an expert on oligodendrocyte biology who recently was awarded an Emmy Noether Grant from the DFG, will join the institute to set up her own program. We further hope to expand on our infrastructure for clinical trials, and will make an even stronger push towards the 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 2019/2020.

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 cutting-edge 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 LMU Klinikum 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 team** embedded into an outpatient clinic specialized on the diagnosis and treatment of stroke, cerebrovascular disease, and neurodegenerative diseases that cause cognitive decline.
- **biobank**
- state-of-the-art **human MRI** research scanner
- state-of-the-art **micro MRI/PET scanner**
- **light-sheet microscopy** (Ultramicroscope II and Blaze): fluorescent microscope scan of whole mouse body/organs and of large human organs
- in vivo **2-photon microscope**
- in vivo **3-photon microscope**
- **facility for** induced pluripotent stem cell (**iPSC**) culture, CRISPR genome editing, and differentiation
- **electron microscopy** (DZNE)
- **multi-photon microscopy** with 1300 nm pulsed IR laser and FLIM-FRET
- **Cell sorter** for single cell isolation
- **Nanoliter liquid handling robots** for miniaturized molecular biology reactions
- Cytek NorthernLights spectral flow cytometer
- advanced flow cytometry (2x **BD FACSVerse**; 1x **Cytek Spectral Analyzer**)
- **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
- high-content screening
- **isotope labs**
- **SPF facility**
- zebrafish facility (DZNE)
- seminar rooms
- wet labs

# Organisation

## *Board of Directors*

Director of the Institute for Stroke
and Dementia Research and Chairman
Prof. Dr. med. Martin Dichgans

Chair Vascular Biology
Prof. Dr. rer. nat. Jürgen Bernhagen

Managing Director
Markus A. Frühauf

## *Board of Trustees*

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Vascular Dementia Research Foundation

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Vascular Dementia Research Foundation

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Vascular Dementia Research Foundation

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Disorders

Thomas Szelag
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(to be officially appointed in 2021)

Prof. Dr. med. Dr. h.c. Karl-Walter Jauch
Prof. Dr. Markus M. Lerch (since January 2021)
Director, LMU Klinikum

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

Bernd Sibler
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Wissenschaft, Forschung und Kunst

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Chief Executive Director
of the Center for Stroke Research Berlin
Charité Hospital
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Professor of Neuroscience
Head of the Department of Molecular Neuroscience
Chair of Molecular Biology of Neurological Disease
at the UCL Institute of Neurology
University College London, UK

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

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

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

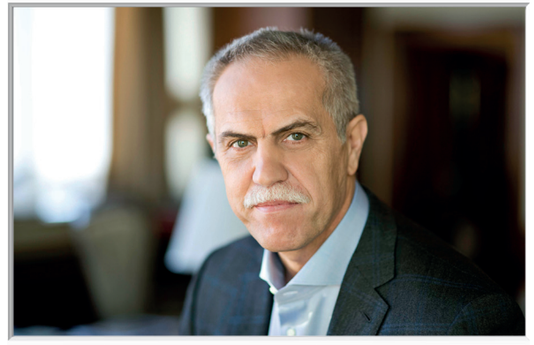
## *Founders*

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

LMU Klinikum

Ludwig-Maximilians-Universität München

Bayerisches Staatsministerium für Wissenschaft,
Forschung und Kunst



*Zygmunt Solorz-Żak*

## 12/2020

### Bayer Early Excellence in Science Award for Nicolai Franzmeier

Nicolai Franzmeier is being recognized with the 2020 Bayer Early Excellence in Science Award in Medical Sciences, which is awarded by the Bayer foundation to excellent young scientists and physicians in the early stages of their academic and clinical research careers. He received the award for developing novel neuroimaging tools to investigate Alzheimer's disease progression, showing that tau pathology, i.e. the key driver of cognitive decline, spreads across brain networks.

## 10/2020

### Alzheimer's Strategic Fund award for Dominik Paquet

Dominik Paquet received an Alzheimer's Strategic Fund: Neuroimmune Project award grant by the Alzheimer's Association. Together with Christian Haass, Dominik Paquet is part of a research consortium investigating neuron-microglia crosstalk in FTD. The consortium was awarded 2.5 million USD for the funding period.

## 08/2020

### Junior Research Group Award for Steffen Tiedt

Steffen Tiedt, a clinician-scientist at the ISD, was awarded 1.0 million Euro by the Corona-Foundation for a research program on "Precision Medicine in Stroke (PROMISE)". The support will enable him to establish a Junior Research Group that will focus on identifying circulating molecular signatures by profiling samples both from stroke patients and mouse models. Such signatures could aid stroke diagnostics and enhance our understanding of stroke pathophysiology.

## 08/2020

### Rolf-Becker Prize 2020 awarded to ISD scientist

Ali Ertürk was awarded with the "Rolf-Becker"-Prize for one of the best scientific outputs in 2019/2020 by the Medical Faculty of LMU Munich. He received this prestigious award for his work on Deep Learning revealing therapeutic antibody targeting in the entire body published in CELL.

## 06/2020

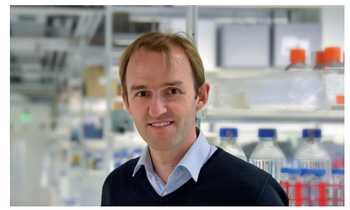
### Martin Dichgans to serve ESO as its President

The European Stroke Organisation (ESO) has rapidly grown to become a driving force in convening stroke researchers around the globe, promoting research and educational events and optimising stroke care in Europe and beyond. Starting in May 2020, Martin Dichgans currently serves ESO as its new President. His focus will be on promoting the development of the ESO Guidelines and further strengthening ESO's role within the community.


## 06/2020

### Sanofi iAward 2020 for PaquetLab

As the only awardee in Germany, Dominik Paquet received the iAward of the Sanofi Innovation Awards Europe Program 2020 to support the lab's work on iPSC models of Tauopathies. The prestigious iAward is awarded annually to 15-20 European research groups to foster preclinical work and translational collaborations with Sanofi.



# News

# News

## 12/2019

### ERC Consolidator Grant for Ali Ertürk

Ali Ertürk received a prestigious ERC Consolidator Grant for his research project CALVARIA 'Translational Aspects of the Discovery of Skull Meninges Connections' (SMC). Recently discovered by Ali Ertürk and others, SMCs enable immune cells to migrate into the brain, suggesting they could play a role in brain disorders, including stroke and dementia.

European Research Council

## 11/2019

### Hertie Network of Excellence in Clinical Neuroscience

Neuroscientists at LMU and TUM have been awarded members of the Hertie Network of Excellence in Clinical Neuroscience. The program provides support to junior scientists and facilitates collaborations across participating sites. The scientific focus of the Munich site (Speakers: M. Dichgans and Thomas Korn) is on neurovascular, neurodegenerative, and neuroinflammatory diseases and their underlying mechanisms.

HERTIE NETWORK OF EXCELLENCE IN CLINICAL NEUROSCIENCE

## 07/2019

### ISD Research Retreat at Lake Ammersee

July 10th and 11th ISD research teams met for the yearly scientific retreat to present their projects and discuss the science. At the heart of this meeting were presentations from all Ph.D. students, including an evening poster session. The last year brought about important achievements, both scientifically and with regard to expertise and infrastructure. The meeting further served as an opportunity to familiarize people with the medium- and long-term strategy of ISD.

## 07/2019

### Research support from NCL Foundation for Paquet-Lab

The project led by Christian Grimm (Walther Straub Institute) and Dominik Paquet (ISD) is supported with 86.000 Euros by the German Neuronal Ceroid Lipofuscinosis Foundation (NCL) and aims to develop novel treatment strategies for childhood dementia.

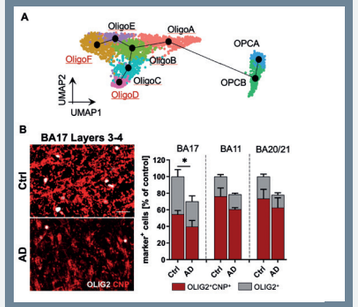


# Preview

*New Lab: "Oligodendrocyte Pathology" PI: Sarah Jäkel*

Emmy Noether-Programm DFG Deutsche Forschungsgemeinschaft

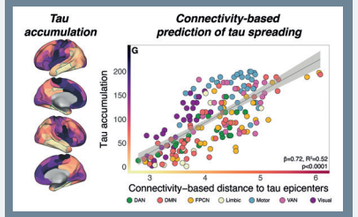
As an Emmy-Noether junior group leader, I am studying the role of oligodendrocytes – the myelin forming cells in the central nervous system – in the pathogenesis of Alzheimer's disease. Using a combination of cutting-edge transcriptomic approaches such as single-nuclei RNA-sequencing on post-mortem human brain tissue, as well as two and three-dimensional human stem cell-derived oligodendrocyte cultures as model systems, I aim to characterize the functional oligodendrocyte cell states that I have recently described and unravel their individual contribution to disease.



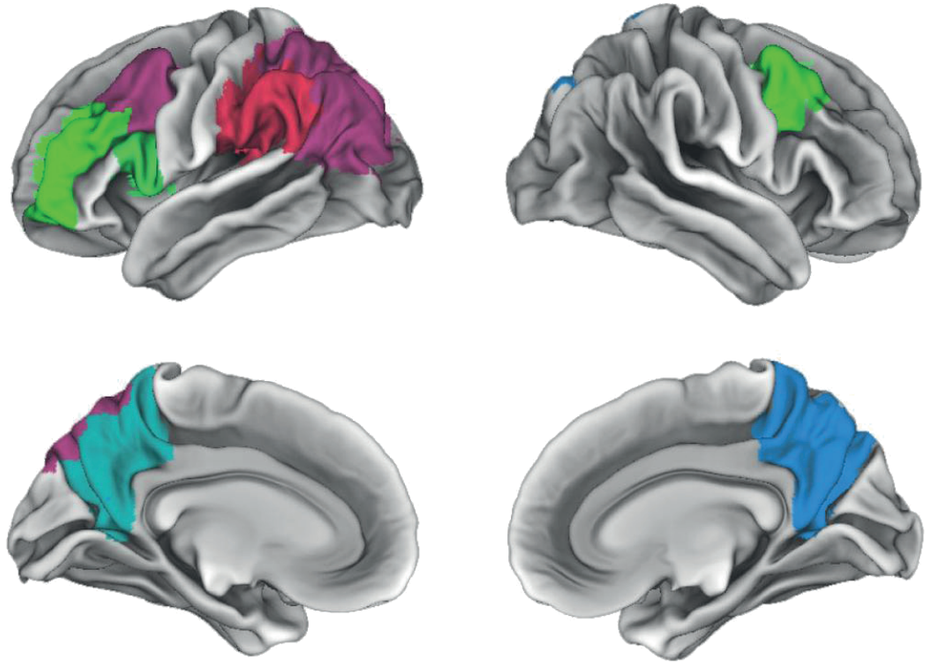

*Oligodendrocytes in the human brain are heterogeneous (A) and lost in AD in a region-specific manner (B).*

*New Junior Research Group: "AD Neuroimaging" PI: Nico Franzmeier*

We are interested in understanding the mechanisms that promote the development and progression of Alzheimer's disease. To this end, we combine multimodal neuroimaging (i.e. PET and MRI), genetics and clinical data in large-scale patient cohorts.
A major research focus is the network-based prediction of trans-neuronal tau pathology spread, i.e. the major driver of neurodegeneration and cognitive decline, which we have recently established by combining MRI-based connectomics and tau-PET. Our overall aim is to develop clinically applicable models for predicting patient-specific disease trajectories, which can be utilized for disease prognosis and to determine patient-specific endpoints in clinical trials.




*Connectivity-based models for predicting tau spreading in Alzheimer's disease, Franzmeier et al. Sci Adv. 2020.*





# 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 into investigator-initiated clinical studies and trials. We further collaborate with industry through participation into industry-driven multi-center studies.*

Major aims and topics of our clinical studies include:

- 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*

Prof. Dr. med. Martin Dichgans / director
PD Dr. med. Katharina Bürger / senior physician
PD Dr. med. Konstantinos Dimitriadis / senior physician
Prof. Dr. med. Arthur Liesz / senior physician

Christine Brauneis / study nurse
Angelika Dörr / study nurse
Esther D'Andrade / study nurse
Daniela Dettling, B.Sc. / neuropsychologist
Ulrike Flohr, M.Sc. / neuropsychologist
Veronique Handfest / social worker
Sandra Hein / study nurse
Dr. med. Juliana Inacio Maiostre / physician
Daniel Janowitz / physician
Dr. med. Anna Kopczak / physician
Dr. med. Bettina Küster / physician
Merima Mehmedovic / reception
Valentina Schöftenhuber / reception
Sandra Schreiner / reception
Dr. Dr. med. Steffen Tiedt / physician
Adelgunde Zollver / study nurse

## *Contact*

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Tel.: +49-89-4400-46046

*"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."*

| Clinical staff \| outpatient clinic | |
|---|---|
| function | total number |
| physicians | 6 |
| neuropsychologists | 3 |
| study nurses | 5 |
| social workers | 1 |
| technical assistants | 1 |
| outpatient office | 3 |
| clinical data manager | 2 |
| total | 21 |

| Costs \| outpatient clinic | |
|---|---|
| In 2020, the total costs for the outpatient clinic amounted to 720,532 €. 80% of these costs were covered by the Vascular Dementia Research Foundation. | |
| personnel | 676,184 € |
| material | 23,482 € |
| travel expenses | 1,540 € |
| investments | 1,315 € |
| miscellaneous | 18,011 € |
| total | 720,532 € |



## *Statistics | Outpatient Clinic*

The number of appointments in 2019 and 2020 amounted to 2,672 and 1,605. This 40% reduction in patient traffic is predominantly attributed to the effects of the corona pandemic. The total number of clinical appointments was 1,975 (2019) and 1,210 (2020). The total number of research visits was 697 (2019) and 395 (2020), which corresponds to an decrease of 56,7% percent.

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, or 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.

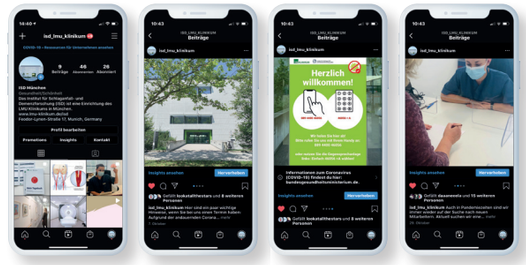
Patients presenting to the memory clinic usually had one of the following diagnoses: subjective cognitive disorder, mild cognitive impairment (MCI, including both amnestic MCI and non-amnestic MCI, both single- and multiple-domain), vascular dementia (VaD), Alzheimer's disease (AD), other neurodegenerative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


## *Website Outpatient Clinic*

https://www.lmu-klinikum.de/isd

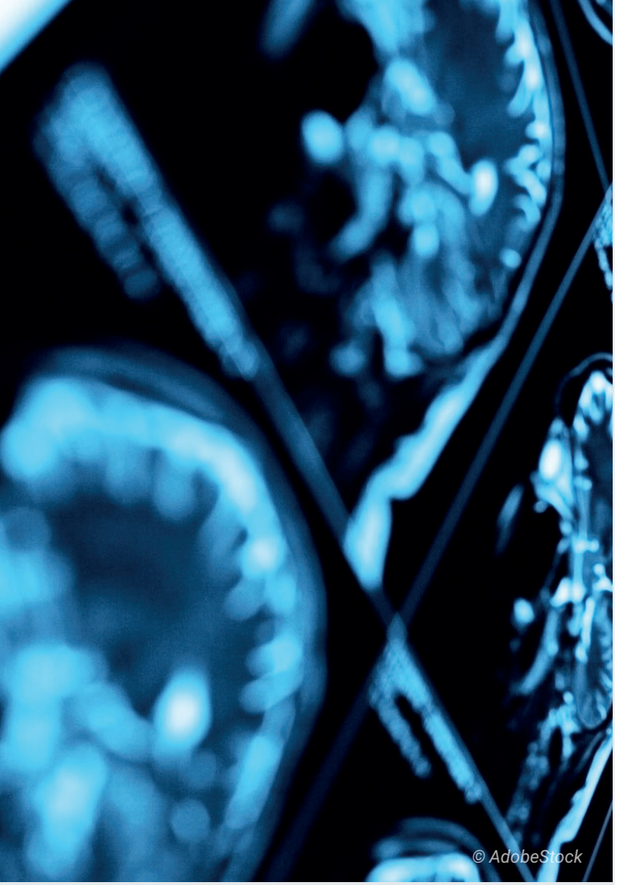
## *Follow us on Instagram*

https://www.instagram.com/isd_lmu_klinikum/




## *Information by print products*

For public outreach, the ISD is regularily producing flyers and products to inform patients about its work and prevention programs.


# Stroke Prevention Unit

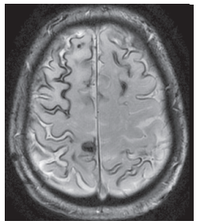
Senior Physician:
PD Dr. med. Konstantinos Dimitriadis

*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.*

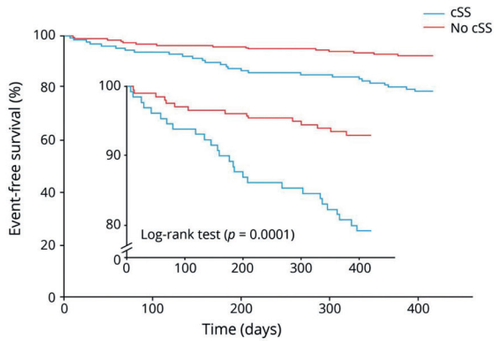
The SPU offers comprehensive diagnostic assessment, counselling and personalized treatment to patients and individuals at risk. The clinic is part of the Interdisciplinary Stroke Center Munich (www.iszm.de). It closely collaborates with neighboring disciplines, such as neuroradiology, neurosurgery, and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

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

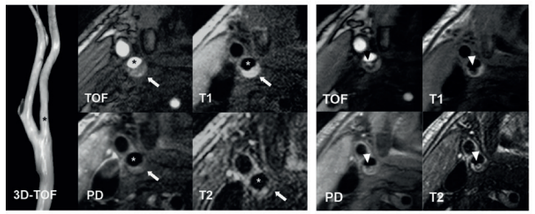
*Regular blood pressure measurements continue to be critically important during the COVID-19 pandemic. Some patients receive telemetric blood pressure monitoring as part of a study protocol.*



***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*




*Kaplan-Meier analyses in patients with suspected CAA stratified for the presence of cSS. Shown is the time to the composite endpoint stroke or death.*




***Rupture of a vulnerable carotid artery plaque.*** *Left: Baseline carotid MRI demonstrating a complicated AHA type-VI plaque of the right internal carotid artery (*). Right: repeat MRI following a new ischemic event. Note that the plaque exhibits a new ulceration with parts of the former lipid/necrotic core missing (arrowhead).*

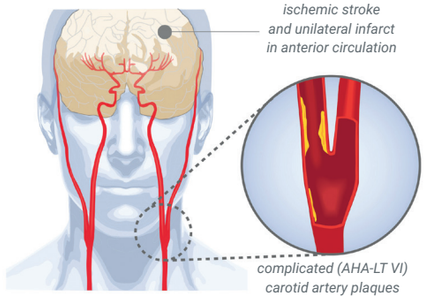
## *Selected Publications:*

Kopczak A, Schindler A, Bayer-Karpinska A, Koch ML, Sepp D, Zeller J, Strecker C, Hempel JM, Yuan C, Malik R, Wollenweber FA, Boeckh-Behrens T, Cyran CC, Helck A, Harloff A, Ziemann U, Poli S, Poppert H, Saam T[$], Dichgans M[$]* (*corresponding authors; [$]equally contributing). *Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke.* **J Am Coll Cardiol.** 2020 Nov 10;76(19):2212-2222.

Kopczak A, Schindler A, Saam T, Dichgans M. *Comparison of Different Plaque Imaging Techniques to Detect Complicated Carotid Artery Plaques*. **J Am Coll Cardiol.** (Letter in press).

Iadecola C, Duering M, Hachinski V, Joutel A, Pendlebury ST, Schneider JA, Dichgans M. *Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel.* **J Am Coll Cardiol**. 2019 Jul 2;73(25):3326-3344.

Tiedt S, Brandmaier S, Kollmeier H, Duering M, Artati A, Adamski J, Klein M, Liebig T, Holdt LM, Teupser D, Wang-Sattler R, Schwedhelm E, Gieger C, Dichgans M. *Circulating Metabolites Differentiate Acute Ischemic Stroke from Stroke Mimics.* **Ann Neurol.** 2020 Oct;88(4):736-746.




***Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke.*** *Modified from Kopzcak et al. J Am Coll Cardiol. 2020*

# Memory Clinic

Senior Physician:
PD Dr. med Katharina Bürger

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

Recent clinical trials have emphasized the potential of preventive treatment, particularly, when initiated in the pre-dementia phase. Hence, there is a growing interest in 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 subjects with mild cognitive impairment and patients suffering from early or moderate stages of dementia. Also, patient and caregiver-directed interventions are provided (patient and caregiver support group, music and art therapy). Group interventions had to be suspended during the pandemic.

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-dementia stages through combining extensive neuropsychological tests and advanced markers of brain alterations based on biofluids and cutting-edge PET ligands (i.e. amyloid-PET, tau-PET). In our research studies, we investigate brain mechanisms underlying cognitive resilience *(Neitzel et al. Neurology 2019, Figure 1)* and immunity *(Ewers et al. EMBO Mol Med. 2020)* as well as prognostic algorithms to understand disease progression *(Franzmeier et al. Nat Commun. 2020, Sci Adv. 2020, Figures 2 & 3)*.

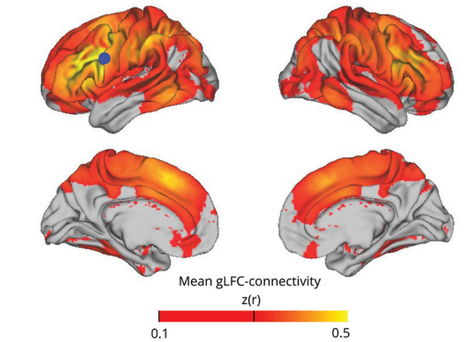



*Figure 1: Cognitive Resilience network against tau pathology (Neitzel et al. Neurology 2019)*

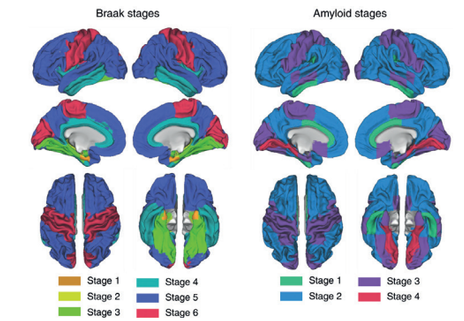



*Figure 2: PET-based staging of Alzheimer's disease pathology. (Franzmeier et al. Nat Commun. 2019)*

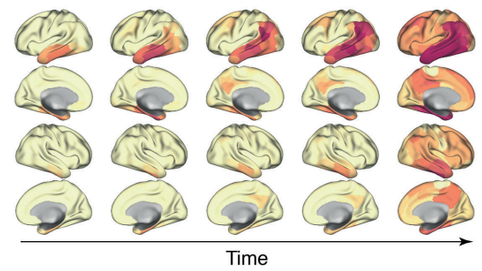



*Figure 3: Spreading of tau pathology in Alzheimer's disease as assessed via tau-PET imaging (Franzmeier et al., Sci Adv. 2020)*

## *Selected Publications:*


Franzmeier N, Dewenter A, Frontzkowski L, Dichgans M, Rubinski A, Neitzel J, ..., Buerger K, Duering M, Hansson O, Ewers M. *Patient-centered connectivity-based prediction of tau pathology spread in Alzheimer's disease.* **Sci Adv.** 2020 Nov 27;6(48):eabd1327.

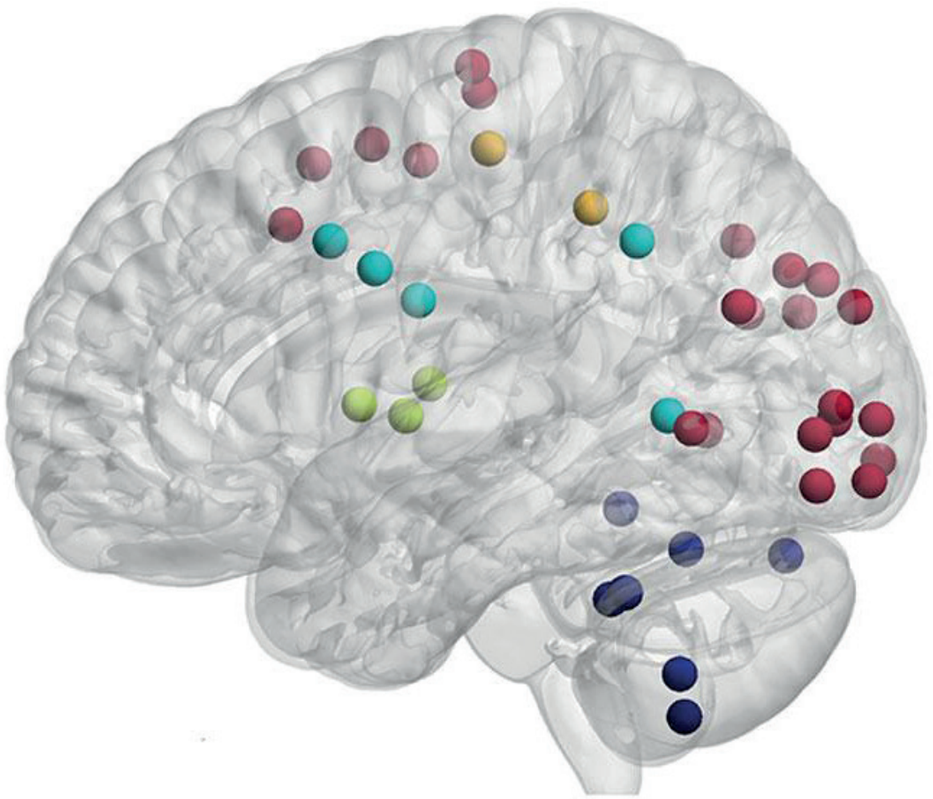
Finsterwalder S, Vlegels N, Gesierich B, Araque Caballero MÁ, Weaver NA, Franzmeier N, Georgakis MK, Konieczny MJ, ..., DELCODE study group, Buerger K, Janowitz D, Teipel SJ, ..., Ewers M, Levin J, Schmidt R, Pasternak O, Dichgans M, Biessels GJ, Duering M. *Small vessel disease more than Alzheimer's disease determines diffusion MRI alterations in memory clinic patients.* **Alzheimers Dement.** 2020 Nov;16(11):1504-1514.

Ewers M, Franzmeier N, ..., Dichgans M, Trojanowski JQ, Shaw LM, Weiner MW, Haass C; Alzheimer's Disease Neuroimaging Initiative. *Increased soluble TREM2 in cerebrospinal fluid is associated with reduced cognitive and clinical decline in Alzheimer's disease.* **Sci Transl Med.** 2019 Aug 28;11(507):eaav6221.

Neitzel J, Franzmeier N, Rubinski A, Ewers M; Alzheimer's Disease Neuroimaging Initiative (ADNI). *Left frontal connectivity attenuates the adverse effect of entorhinal tau pathology on memory.* **Neurology**. 2019 Jul 23;93(4):e347-e357.

Franzmeier N, ..., Duering M, Dichgans M, Levin J, ...; Alzheimer's disease neuroimaging initiative (ADNI); Dominantly Inherited Alzheimer Network (DIAN), Ewers M. *Predicting sporadic Alzheimer's disease progression via inherited Alzheimer's disease-informed machine-learning.* **Alzheimers Dement.** 2020 Mar;16(3):501-511.

Ewers M, ..., Herms J, Dichgans M; Alzheimer's Disease Neuroimaging Initiative (ADNI), Brendel M, Haass C, Franzmeier N. *Higher CSF sTREM2 and microglia activation are associated with slower rates of beta-amyloid accumulation.* **EMBO Mol Med.** 2020 Sep 7;12(9):e12308.



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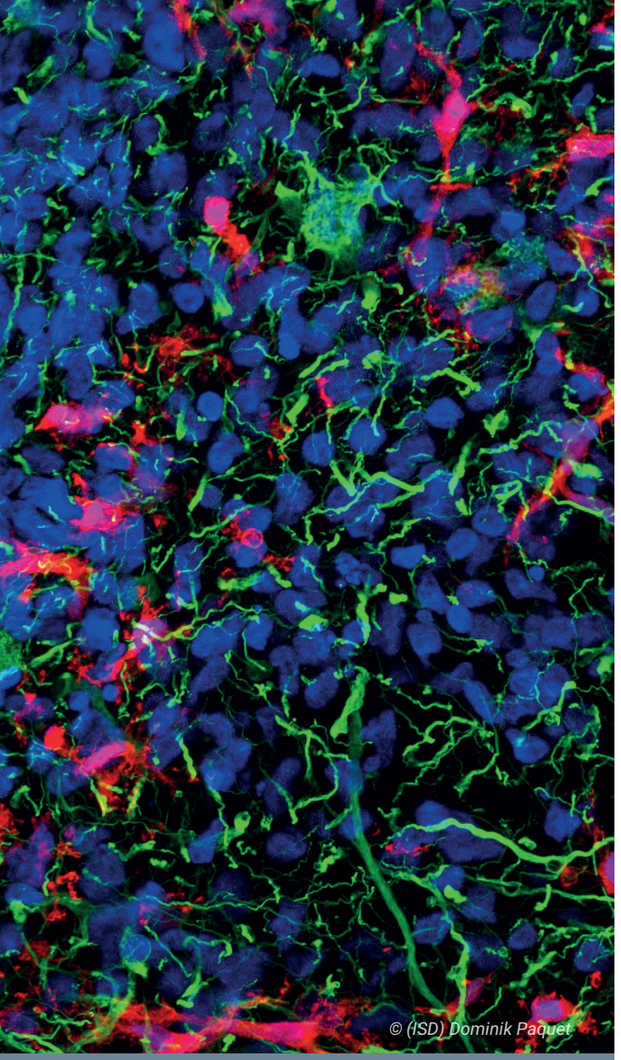
# Research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# Research Groups

**Translational Research**
Martin Dichgans

**Vascular Biology**
Jürgen Bernhagen

**Vascular Cognitive Impairment**
Marco Düring

**Brain Imaging and Biomarker**
Michael Ewers

**Acute Brain Injury**
Ali Ertürk

**Stroke-Immunology**
Arthur Liesz

**iPSC-Models of Brain Diseases**
Dominik Paquet

**Experimental Stroke Research**
Nikolaus Plesnila

**Microbiome-Gut-Brain Interactions**
Corinne Benakis (Junior Research Group)

**Systems Neuroscience**
Ozgun Gokce (Junior Research Group)

**Molecular Biomarkers**
Steffen Tiedt (Junior Research Group)



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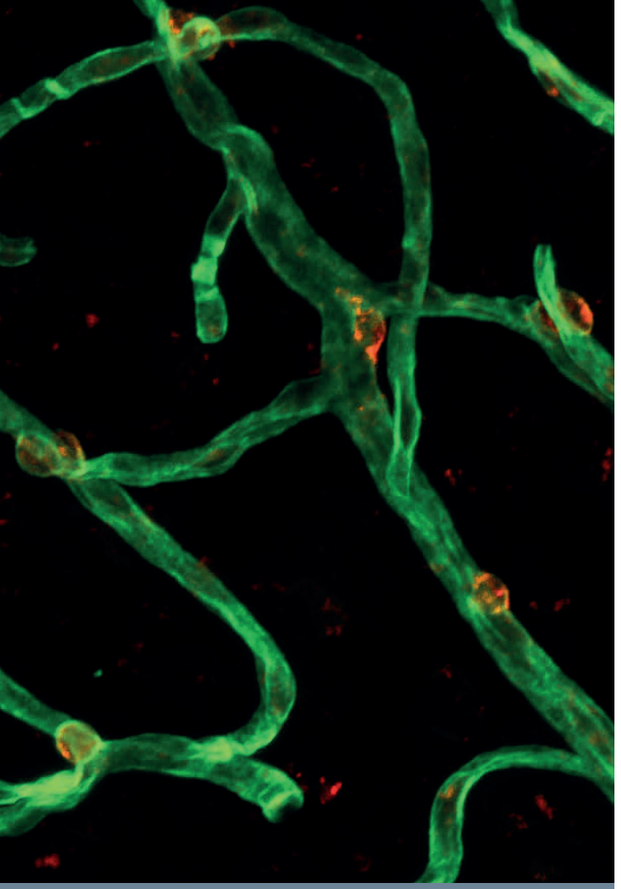
## *Scope of research*

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

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. HtrA1, Col4A1, 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 (in particular 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.

***Team***

*Prof. Dr. med. Martin Dichgans / PI*
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*Dr. Nathalie Beaufort / postdoc*
*Alexandra Fekete / team assistant*
*Simon Frerich / PhD student*
*Dr. Marios Georgakis / postdoc*
*Judit Gonzalez Gallego / PhD student*
*Vanessa Granja Burbano / PhD student*
*Dr. rer. nat. Christof Haffner / postdoc*
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*Dr. med. Anna Kopczak / clinician scientist*
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*Dr. rer. nat. Rainer Malik / postdoc*
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*Luka Zivkovic / MD student*

**https://www.isd-research.de/dichgans-lab**
**@ISD_Research**

**Key Publications** (2019 & 2020)


Georgakis MK, Malik R, Li X, ..., Theodoratou E, Dichgans M. *Genetically downregulated interleukin-6 signaling is associated with a favorable cardiometabolic profile: a phenome-wide association study.* **Circulation.** (in press).

Georgakis MK, de Lemos JA, Ayers C, Wang B, Björkbacka H, Pana TA, Thorand B, Sun C, Fani L, Malik R, ..., Nilsson J, Benjamin EJ, Dichgans M. *Association of Circulating Monocyte Chemoattractant Protein-1 Levels With Cardiovascular Mortality: A Meta-analysis of Population-Based Studies.* **JAMA Cardiol.** 2020 Nov 4. doi: 10.1001/jamacardio.2020.5392.

Asare Y, Campbell-James TA, Bokov Y, Yu LL, Prestel M, El Bounkari O, Roth S, Megens RT, Straub T, Thomas K, Yan G, Schneider M, Ziesch N, Tiedt S, Silvestre-Roig C, Braster Q, Huang Y, Schneider M, Malik R, Haffner C, Liesz A, Soehnlein O, Bernhagen J, Dichgans M. *Histone Deacetylase 9 Activates IKK to Regulate Atherosclerotic Plaque Vulnerability.* **Circ Res.** 2020 Aug 28;127(6):811-823.

Georgakis MK, Malik R, Anderson CD, Parhofer KG, Hopewell JC, Dichgans M. *Genetic determinants of blood lipids and cerebral small vessel disease: role of high-density lipoprotein cholesterol.* **Brain.** 2020 Feb 1;143(2):597-610.

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Dichgans M, Pulit SL, Rosand J. *Stroke genetics: discovery, biology, and clinical applications.* **Lancet Neurol.** 2019 Jun;18(6):587-599.

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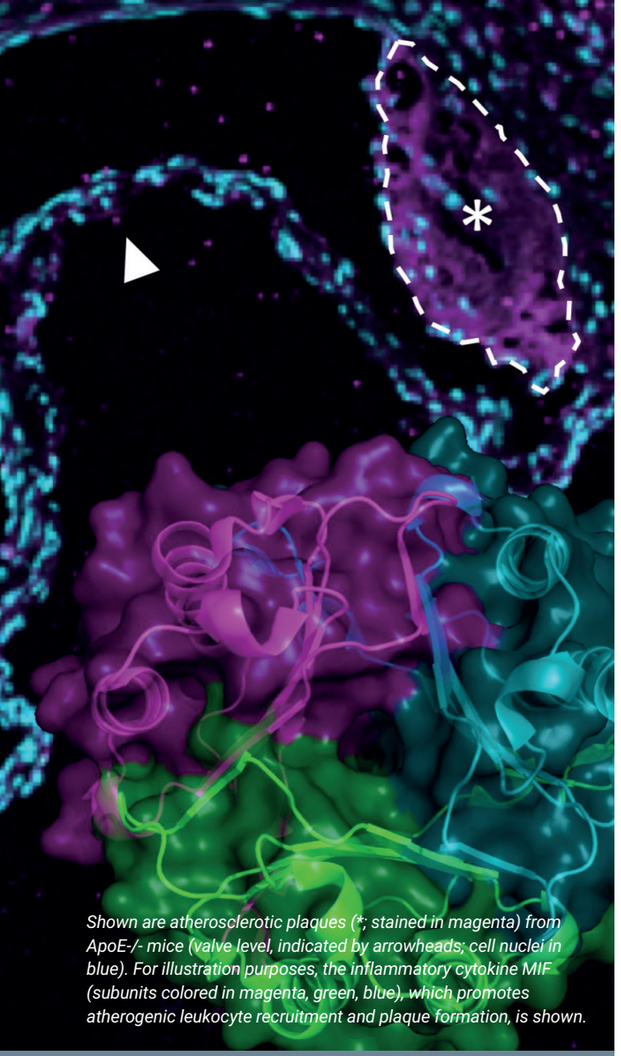

*Shown are atherosclerotic plaques (*; stained in magenta) from ApoE-/- mice (valve level, indicated by arrowheads; cell nuclei in blue). For illustration purposes, the inflammatory cytokine MIF (subunits colored in magenta, green, blue), which promotes atherogenic leukocyte recruitment and plaque formation,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

# Vascular Biology

Research Group – PI: Jürgen Bernhagen



**We are interested in mechanisms of cardiovascular disease and inflammation. The main focus is on atypical chemokines, inflammatory signaling-pathways, and leukocyte recruitment 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 the design of therapeutic strategies and clinical translation.**

We discovered the cytokine MIF and characterized it as a key atypical chemokine (Bernhagen et al., Nature 1993; Bernhagen et al., Nat. Med. 2007). Relying on biochemical/vascular biology methods in combination with multi-photon-microscopy, scRNAseq, proteomics, transgenic mouse models and clinical approaches, we study the entire MIF family (MIF, MIF-2, CXCR2, CXCR4, CXCR7, CD74, sCD74, novel MIFs) and related chemokines in atherosclerosis, ischemic stroke, and myocardial infarction (e.g. Merk et al., PNAS 2011; Lüdike et al., Circulation 2012; Schmitz et al., FASEB J 2018; Stoppe et al., Sci Transl Med 2018; Kontos, El Bounkari, Krammer et al., Nat Commun 2020). Capitalizing on collaborations at ISD, SFB1123, and DZHK, this involves deciphering ligand/receptor pathways, interactions between atypical and classical chemokines driving leukocyte recruitment, mechanisms of oxidation, ischemia/reperfusion and alarmins such as HMG-proteins (Schindler et al., Redox Biol 2018; Roth et al., Sci Transl Med 2018; Dobersch et al., Nat Commun, in press). Together with the Gokce Lab, we elucidate links between MIF proteins, microglial inflammation and Alzheimer's (AD) pathogenesis.
Another focus is on pathways mediated by the COP9 signalosome (CSN) and NFκB/HDAC9 in atherogenesis and neuroinflammation. The CSN is a multi-protein complex that regulates CRL E3 ligase NEDDylation, controlling degradation of various proteins. Based on our discovery linking the CSN to inflammation (Kleemann et al., Nature 2000), we identified an atheroprotective effect of CSN5 (Asare et al., PNAS 2017). Recent work focuses on the CSN holocomplex and plaque destabilization and CSN-based pharmacological strategies. Capitalizing on local and international collaborations, we pursue links to other inflammatory conditions and neurodegeneration in AD and ALS.

***Team***

*Prof. Dr. rer. nat. Jürgen Bernhagen / PI*
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*Sabrina Lukanovic, LL.M. / team assistant*
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*Leon Zwißler, cand. med. / MD doctoral student*
*Elena Siminkovic, cand. med. / MD doctoral student*
*Eva Preuner, cand. med. / MD doctoral student*
*Mathias Holzner, cand. med. / MD doctoral student*
*Lukas Spiller, cand. med. / MD doctoral student*
*Iris Woltering, cand. med. / MD doctoral student*
*Vanessa Rohde, BSc / master student*
*Sofia Leistl / bachelor student*

**http://BernhagenLab.isd-muc.de**
**@BernhagenLab**

**Key Publications**


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.* (*corresponding authors). *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.

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* (*corresponding authors). *The protective role of macrophage migration inhibitory factor in acute kidney injury after cardiac surgery.* **Sci Transl Med.** 2018 May 16;10(441):eaan4886. doi: 10.1126/scitranslmed.aan4886.

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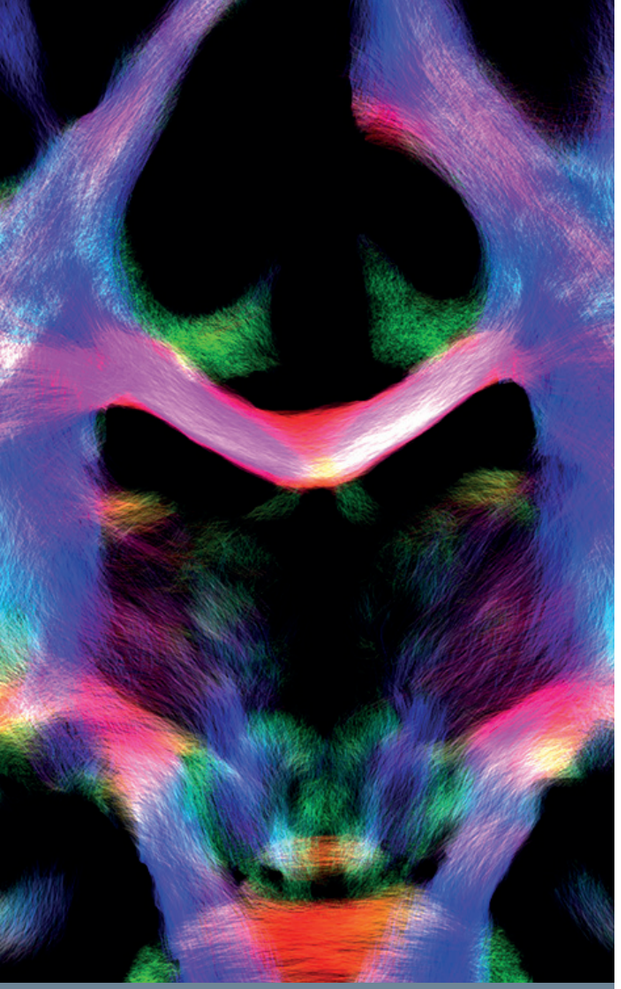
Sinitski D, Gruner K, Brandhofer M, Kontos C, Winkler P, Reinstädler A, Bourilhon P, Xiao Z, Cool R, Kapurniotu A, Dekker FJ, Panstruga R*, Bernhagen J* (*corresponding authors). *Cross-kingdom mimicry of the receptor signaling and leukocyte recruitment activity of a human cytokine by its plant orthologs.* **J Biol Chem.** 2020 Jan 17;295(3):850-867.

Asare Y, Campbell-James TA, Bokov Y, Yu LL, Prestel M, El Bounkari O, Roth S, Megens RTA, Straub T, Thomas K, Yan G, Schneider M, Ziesch N, Tiedt S, ..., Malik R, Haffner C, Liesz A, Soehnlein O, Bernhagen J, Dichgans M. *Histone Deacetylase 9 Activates IKK to Regulate Atherosclerotic Plaque Vulnerability.* **Circ Res.** 2020 Aug 28;127(6):811-823.

Kontos C, El Bounkari O, Krammer C, Sinitski D, Hille K, Zan C, Yan G, Wang S, Gao Y, Brandhofer M, Megens RTA, Hoffmann A, Pauli J, Asare Y, Gerra S, Bourilhon P, Leng L, Eckstein HH, Kempf WE, Pelisek J, Gokce O, Maegdefessel L, Bucala R, Dichgans M, Weber C, Kapurniotu A*, Bernhagen J* (*corresponding authors). *Designed CXCR4 mimic acts as a soluble chemokine receptor that blocks atherogenic inflammation by agonist-specific targeting.* **Nat Commun.** 2020 Nov 25;11(1):5981. doi: 10.1038/s41467-020-19764-z.



# 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.**

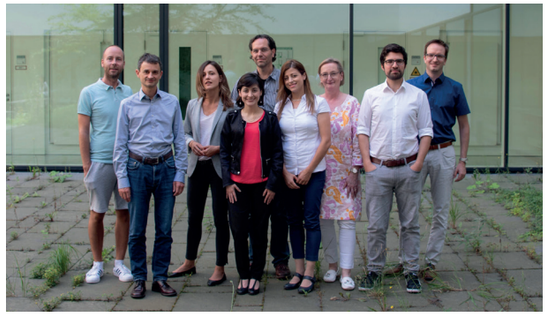
Our methodological expertise is in structural and functional neuroimaging in humans using advanced analytical and statistical techniques.

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.





***Team***

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*Prof. Dr. med. Marco Düring / PI*
*Rong Fang / PhD student MMRS*
*Sofia Finsterwalder, PhD / GSN graduate*
*Benno Gesierich, PhD / postdoc*
*Susan Habash / radiographer (MTRA)*
*Mathias Hübner / research assistant*
*Marek Konieczny, MSc / PhD student MMRS*
*Hedwig Pietsch / team assistant*
*Dr. med. vet. Ulrike Schillinger / veterinary physician*

**https://www.isd-research.de/duering-lab**
**@ISDneuroimaging**

***Marco Düring** has been instrumental in establishing neuroimaging research infrastructure at the ISD. He recently moved to become the Head of Research at MIAC AG, Basel Switzerland and continues his academic research at the Department of Biomedical Engineering, University of Basel. He remains affiliated with the ISD.*

**Key Publications**


Konieczny MJ, Dewenter A, Telgte AT, Gesierich B, Wiegertjes K, Finsterwalder S, Kopczak A, Hübner M, Malik R, Tuladhar AM, Marques JP, Norris DG, Koch A, Dietrich O, Ewers M, Schmidt R, de Leeuw FE, Duering M. *Multi-shell diffusion MRI models for white matter characterization in cerebral small vessel disease.* **Neurology**. 2020 Nov 16;10.1212/WNL.0000000000011213.

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Ter Telgte A, Wiegertjes K, Gesierich B, Marques JP, Huebner M, de Klerk JJ, Schreuder FHBM, Araque Caballero MA, Kuijf HJ, Norris DG, Klijn CJM, Dichgans M, Tuladhar AM, Duering M*, de Leeuw FE*. *Contribution of acute infarcts to cerebral small vessel disease progression.* **Ann Neurol.** 2019 Oct;86(4):582-592.

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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.

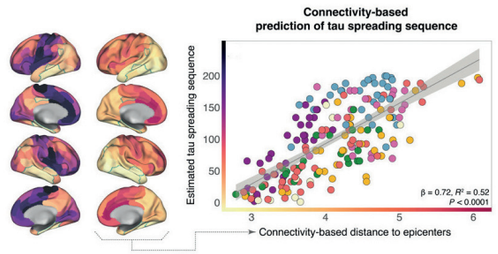
# Brain Imaging & Biomarker Research

Research Group – PI: Michael Ewers



**Our research focuses on the spreading of key pathologies in Alzheimer's disease (AD) and the improvement of prediction tools. Specifically, we combine functional connectomics, myelin imaging and advanced molecular PET markers to model the spatiotemporal evolution of fibrillar tau and beta-amyloid. Our prediction models are tailored to enable precision-medicine guided patient-level prognosis of disease progression. Another research focus of our team centers on brain mechanisms underlying cognitive resilience in AD. Specifically, we examine the protective factors of the brain's innate immune system along with functional network changes that alleviate cognitive decline.**

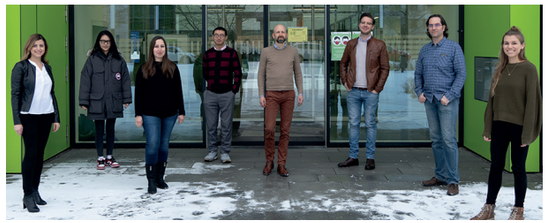
**Functional connectome & progression of tau pathology**
Neurofibrillar tangles are the single most important drivers of neurodegeneration and cognitive decline in AD. The tau-bearing tangle deposits progress in spatiotemporally distinct patterns in the brain, but which factors shape that spatial distribution is unclear. Based on joined resting-state fMRI connectivity and tau PET analysis, we found that fibrillar tau accumulation progresses from initial epicenters of high tau to those brain areas that are most closely connected to the epicenter. Our approach allows to predict the progression of tau accumulation at the patient-level, thus providing an important step towards precision medicine.




**Functional networks supporting cognitive resilience**
Cognitive resilience designates the ability to show disproportional high levels of cognitive function despite substantial brain pathology. Cognitive resilience is an important factor slowing down the development of dementia in AD, but the underlying mechanism are not well understood.

To address that question, we focus on the topological characteristics of the functional connectome of the brain that underly resilience. Using graph theoretical analyses, we identified hub connectivity in the fronto-parietal control network *(Neitzel et al. 2019)* as well as higher segregation of functional networks *(Franzmeier et al. Brain, in press)* as key neural substrates supporting cognitive resilience against pathologic tau.

**The role of TREM2-related microglia activation in AD**
Rare loss-of-function mutations in the gene encoding TREM2, i.e. a receptor molecular expressed by microglia, are associated with a dramatic increase in the risk of AD. Together with our collaborator Prof. Christian Haass (DZNE, Munich), we found changes in biofluid levels of soluble TREM2 protein occur up to 5 years before the onset of AD dementia *(Suarez-Calvet, Science Trans Med, 2016)*, consistent with a microglia response triggered by AD pathology. Importantly, higher biomarker levels of sTREM2 at a given level of beta-amyloid and tau pathology were associated with slower subsequent cognitive decline *(Ewers et al. Sci Transl Med. 2019)*, reduced detrimental effects of ApoE e3 genotype *(Franzmeier et al. Mol Neurodeg. 2020)* and slower rate of increase in amyloid PET *(Ewers et al. EMBO Mol Med. 2020)*.



***Team***
*Dr. Davina Biel / postdoc*
*Prof. Dr. Michael Ewers / PI*
*Dr. Nicolai Franzmeier / postdoc*
*Dr. Julia Neitzel / postdoc*
*Susan Habash / radiographer MTRA*
*Hübner, Mathias / research assistant*
*Lukas Frontzkowski / MD student*
*Paul Hager / MSc student*
*Yin Luan / PhD student*
*Jinyi Ren / PhD student*
*Anna Rubinski / PhD student*
*Lukai Zheng / MD student*
*Hedwig Pietsch / team assistant*

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**Key Publications** (2019 & 2020)

Franzmeier N, Dewenter A, Frontzkowski L, Dichgans M, Rubinski A, Neitzel J, Smith R, Strandberg O, Ossenkoppele R, Buerger K, Duering M, Hansson O, Ewers M. *Patient-centered connectivity-based prediction of tau pathology spread in Alzheimer's disease*. **Sci Adv.** 2020 Nov 27;6(48):eabd1327.

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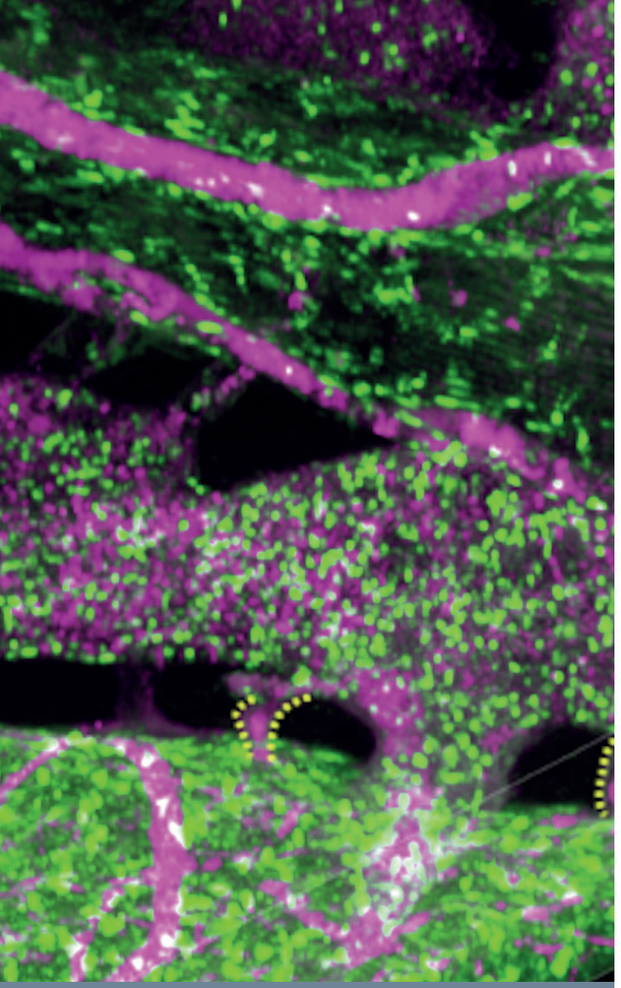

# Acute Brain Injury Research

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 unbiased technologies including single cell RNAseq, Mass Spec-based proteomics, 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 Nature Neuroscience, 2019). 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.

***Team***

*Dr. Ali Ertürk / PI*
*Mayar Ali / PhD student*
*Rami Al-Maskari / PhD student*
*Dr. Harsharan S. Bhatia / postdoc*
*Karen Biniossek / team assistant*
*Marin Bralo / technical assistant*
*Dr. Suheda Erener / science manager*
*Dr. Farida Hellal / postdoc*
*Izabela Horvath / PhD student*
*Louiza Ignatiou / Master's student*
*Dr. Doris Kaltenecker / Postdoc*
*Ilgin Kolabas / PhD student*
*Louis Kümmerle / PhD student*
*Hongcheng Mai / PhD student*
*Muge Molbay / PhD student*
*Dr. Tzu-Lun Ohn / postdoc*
*Furkan Ozturk / PhD student*
*Johannes Paetzold / PhD student*
*Dr. Chenchen Pan / postdoc*
*Zhouyi Rong / PhD student*
*Oliver Schoppe, M.Sc. / PhD student*
*Mihail Todorov / PhD*
*Ana Toman Fabjan / team assistant*
*Dr. Alison Wright / postdoc*
*Shan Zhao / PhD*

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**Key Publications**


Todorov MI, Paetzold JC, Schoppe O, Tetteh G, Shit S, Efremov V, Todorov-Völgyi K, Düring M, Dichgans M, Piraud M, Menze B, Ertürk A. *Machine learning analysis of whole mouse brain vasculature.* **Nat Methods.** 2020 Apr;17(4):442-449.

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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.** 2019 Feb;22(2):317-327. (Cover)

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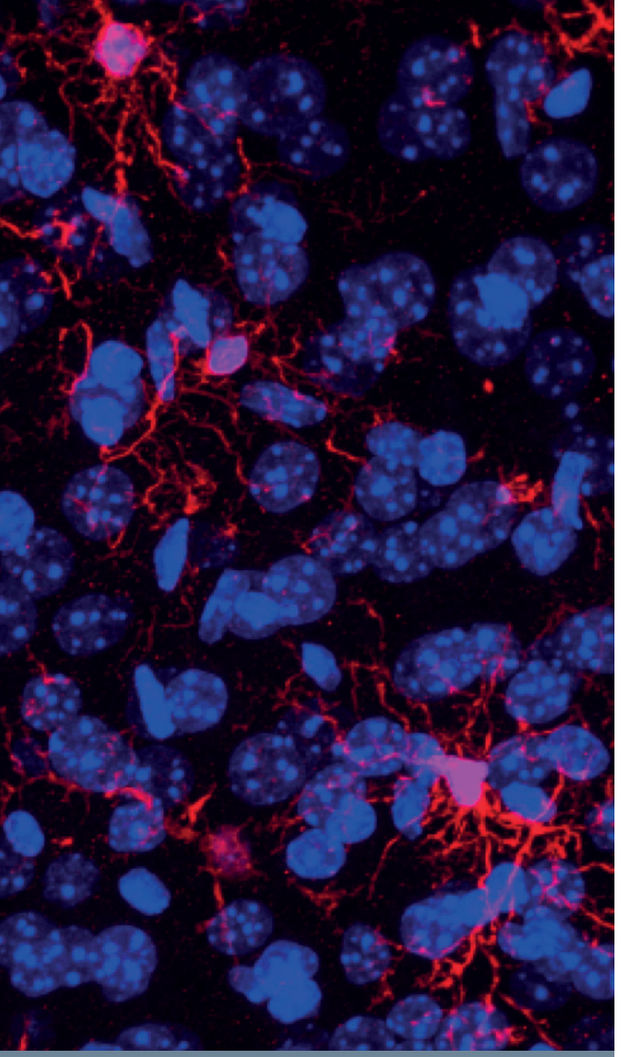

# Stroke-Immunology

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.**

The lab has a strong translational research focus with the ultimate goal to develop novel diagnostic tools, therapies and mechanistic insights on the highly complex disease which stroke represents. Currently, the laboratory focuses on the following main research topics within the area of brain-immune interaction:

**Cerebral lymphocyte invasion: beyond the vasculature**
One focus of our research is the migration of pro-inflammatory leukocytes to the ischemic brain. We are investigating pathophysiological mechanisms of leukocyte-endothelial interaction and novel therapeutic approaches for translational use (Science Translational Medicine, 2015). We have previously identified the choroid plexus as a previously unrecognized invasion pathways (Acta Neuropathologica, 2017) and are further striving to understand the differential role of alternative invasion routes to the injured brain.

**The systemic immune effects of stroke**
We aim to expand our knowledge on the multicellular interaction in the systemic immune compartment after stroke and the role of circulating blood factors in modulating immune homeostasis. We previously described alarmins as key mediators leading to the exacerbation of vascular inflammation (Science Translational Medicine, 2018) and currently study the mechanisms contributing to sustained systemic immune changes after stroke.

**Chronic neuroinflammation: friend or foe in post-stroke recovery?**
We have recently identified that acute brain ischemia not only induces acute inflammation but results in long-lasting and profound neuroinflammation. These findings suggest either a deficiency in endogenous resolution mechanisms or a preponderance of currently unknown mechanisms driving chronic immune activation after stroke. We try to elucidate the underlying mechanism and study how chronic neuroinflammation affect the chronic recovery after stroke.

**From mouse to patient … and back**
A premise of our work is to address key unmet needs of stroke patients and make use of translationally relevant tools. Access to stroke patients allows us to identify clinically relevant questions and utilize patient biosamples and clinical data together with our experimental models to answer these questions.

***Team***

*Prof. Dr. med. Arthur Liesz / PI*
*Dr. Stefan Roth / postdoctoral fellow*
*Dr. Gemma Llovera / postdoctoral fellow*
*Dr. Alba Simats / postdoctoral fellow*
*Dr. Dániel Varga / postdoctoral fellow*
*Dr. Tanima Bose / postdoctoral fellow*
*Alessio Ricci / PhD student*
*Jie Zhu / PhD student*
*Steffanie Heindl / PhD student*
*Jiayu Cao / PhD student*
*Philip Melton / MD Student*
*Kelsey Pinkham / PhD student*
*Sijia Zhang / PhD student*
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*Yasemin Aydin / team assistant*

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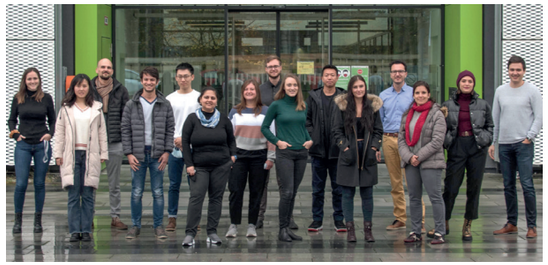

**Key Publications**


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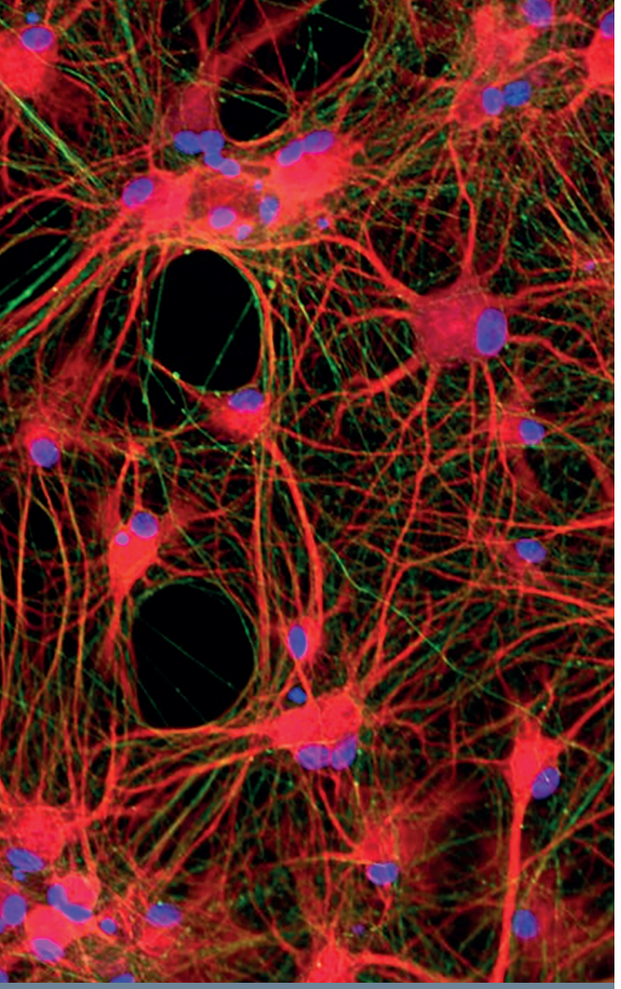

# iPSC-Models of Brain Diseases

Research Group – PI: Dominik Paquet

**The PaquetLab aims to build human tissue models recapitulating major brain diseases. To establish these models, we apply and combine cutting-edge technologies, such as CRISPR/Cas genome editing, induced pluripotent stem cells (iPSCs), differentiation of iPSCs into human brain cells, and brain tissue engineering. Using these models, we aim to understand the molecular and cellular mechanisms leading to nerve cell damage and death, and subsequent cognitive decline in patients with neuropsychiatric disorders and neurovascular impairments.**

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.



***Team***

*Prof. Dr. Dominik Paquet / PI*
*Merle Bublitz / master student*
*Carolina Cardoso Goncalves / graduate student (GSN)*
*Dennis Crusius / technical assistant*
*Angelika Dannert / graduate student (GSN)*
*Judit Gonzalez-Gallego / graduate student (GSN) – co-supervised with Martin Dichgans*
*Bérénice Horlacher / master student*
*Julien Klimmt / graduate student (GSN)*
*Joseph Kroeger / graduate student (GSN)*
*Einar Krogsaeter / graduate student – co-supervised with Christian Grimm /LMU*
*Liliana Pedro-Domingues / graduate student (GSN) – co-supervised with Mika Simons / DZNE*
*Marvin Reich / graduate student (GSN) – co-supervised with Christian Haass / DZNE*
*Sophie Robinson / graduate student (GSN) – co-supervised with Christian Haass / DZNE*
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*Isabel Weisheit / graduate student (GSN)*
*Jennifer Yilmaz / lab manager*

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**Key Publications**


Weisheit I, Kroeger JA, Malik R, Wefers B, Lichtner P, Wurst W, Dichgans M, Paquet D. *Simple and reliable detection of CRISPR-induced on-target effects by qgPCR and SNP genotyping.* **Nat Protoc** 2021 (in press).

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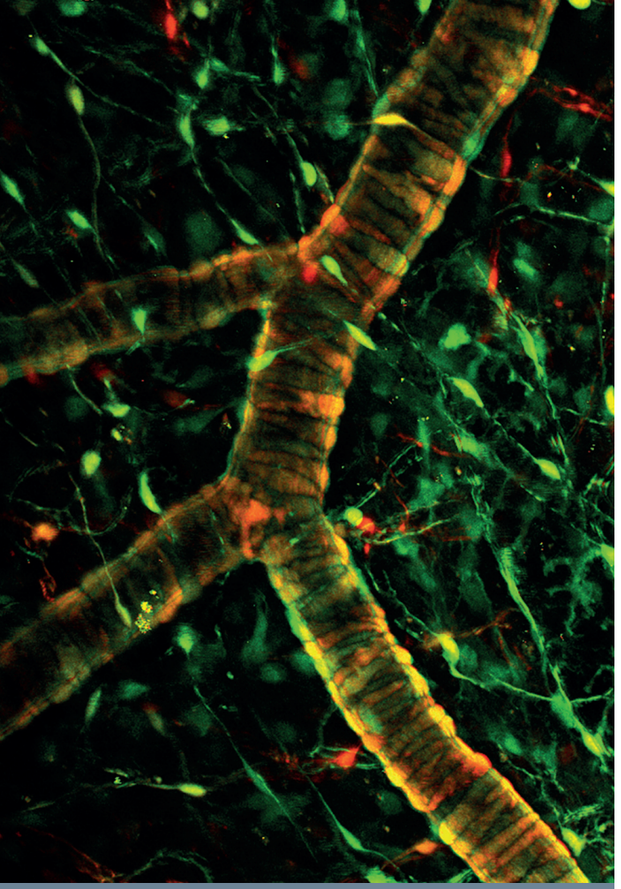

# Laboratory of Experimental Stroke Research

Research Group – PI: Nikolaus Plesnila



**The main interest of the laboratory is to understand the role of cerebral blood vessels in the pathophysiology of CNS disorders as a basis for the development of novel therapeutic strategies.**

In the past two years the laboratory worked, among others, on two topics: 1) the mechanisms causing cerebral microvasospasms after subarachnoid hemorrhage (SAH), and 2) the development of novel imaging tools for the visualization of neurovascular pathologies.

We previously demonstrated that within a few hours after SAH pial arterioles show pearl-string like constrictions and cerebral perfusion is reduced by more than 60%. Investigating conventional targets of vasoconstriction after hemorrhage, e.g. endothelin receptors, we could not improve microvasospasm formation. However, having a closer look at blood-derived factors revealed that free iron is an important driver of microvascular spasms. Our future aim is to elucidate the molecular mechanisms by which free iron elicits damage and vasoconstriction in pial and intraparenchymal microvessels.

The investigation of cerebrovascular pathologies in vivo is restricted by the relatively low tissue penetration of currently available microscopic technologies and by the lack of sufficiently bright cellular tracers. In order to overcome these obstacles, we joined forces with a microscopy manufacturer and used third party funding to develop a 3-photon microscope optimized for in vivo imaging of awake mice. This system, which was recently installed in our laboratory, allows imaging of brain structures with subcellular resolution up to 1.5 cm below the cortical surface, e.g. the corpus callosum and possibly the hippocampus, structures which could so far not be investigated in vivo. Further, we developed ultra-bright nanoparticles to investigate the permeability of meningeal, pial, and intraparenchymal vessels following ischemic stroke (Khalin et al., ACS Nano 2020) and visualized BBB opening in a mouse stroke model. In the future, we will use these novel tools to investigate microvascular dysfunction after cerebral ischemia.

***Team***

*(from left to right):*
*Igor Khalin, MD, PhD / senior postdoc*
*Xiangjiang Lin / MD student*
*Ziyu Fan / MD student*
*Joshua Shrouder / PhD student*
*Dr. Farida Hellal / senior postdoc*
*Dr. Severin Filser / postdoc*
*Yue Hu / MD student*
*Hedwig Pietsch / team assistant*
*Anna-Lena Müller / trainee*
*Janina Biller / technical assistant*
*Bernhard Groschup / PhD student*
*Susana Valero-Freitag / PhD student*
*Antonia Wehn / MD student*
*Rebecca Sienel / PhD student*
*Cara Ardela / MD student*
*Uta Mamrak / technical assistant*
*Prof. Dr. med. Nikolaus Plesnila / PI*
*Dr. Burcu Şeker / postdoc*

*Not on picture:*
*Gian Marco Calandra / PhD student*
*Shiqi Cheng / MD student*
*Christian Corvin / MD student*
*Carina Exner, MD*
*Dr. Malo Gaubert / postdoc*
*Katharina Kamm / clinician scientist*
*Yuko Kondo, MD / visiting scientist*
*Hanhan Liu, MD / PhD student*
*Xiang Mao / MD student*
*Constanze Raitmayr / Erasmus student*
*Dr. med. Katrin Rauen / postdoc*
*Stefan Saicic / MD student*
*Julian Schwarting / clinician scientist*
*Dr. med. Susanne Schwarzmaier / clinician scientist*
*PD Dr. med. Nicole Terpolilli / clinician scientist*
*Umeasalugo, Kosisochukwu Emmanuel / PhD student*

**https://www.isd-research.de/plesnila-lab**

**Key Publications**


Khalin I, Heimburger D, Melnychuk N, Collot M, Groschup B, Hellal F, Reisch A, Plesnila N, Klymchenko AS. *Ultrabright Fluorescent Polymeric Nanoparticles with a Stealth Pluronic Shell for Live Tracking in the Mouse Brain.* **ACS Nano.** 2020 Aug 25;14(8):9755-9770.

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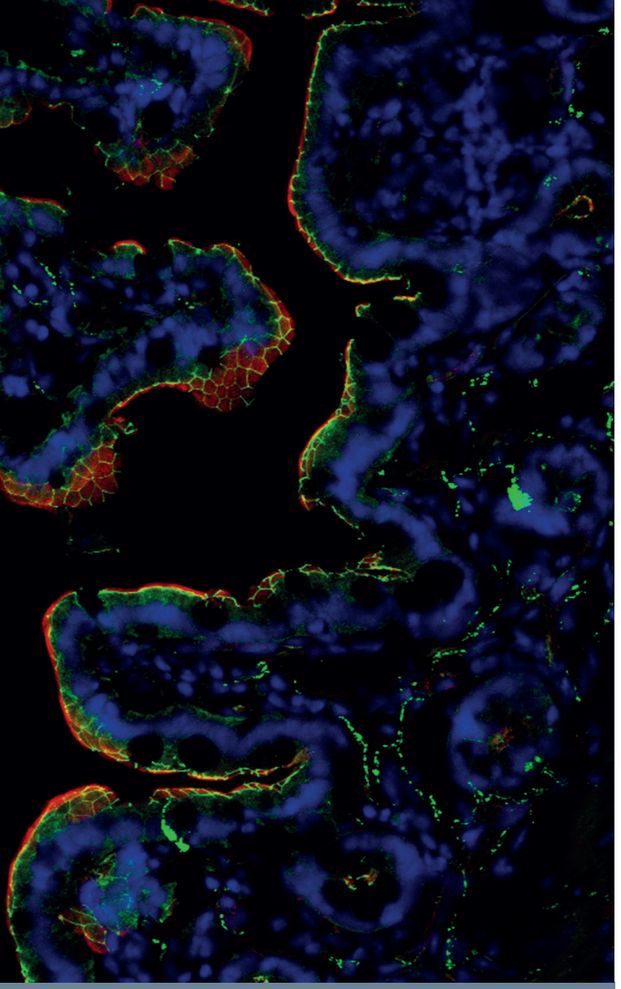


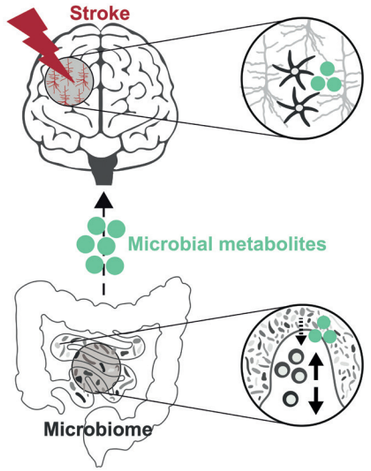
# Gut-Brain Axis Research Group

Junior Research Group – PI: Corinne Benakis

**The research focus of our lab is to understand the bidirectional link between the gut microbiome and the brain after stroke. In particular, we aim to investigate how bacteria regulate the intestinal immune system in the context of cerebral ischemia.**

Important advances in sequencing techniques within the microbial community and untargeted metabolomics have allowed us to search for specific bacteria and their metabolites responsible in microbiome-host interactions, which have a great influence in a range of fields, from neurodevelopment to brain diseases. However, in stroke, it is still unknown how gut bacteria communicate with immune cells and impact both the neuroinflammation and neurological function.

Thus, our goal is to understand the functional role of bacteria derived metabolites on the host intestinal immune response and how microbial cues impact stroke recovery. To tackle this research question, we use a combination of metabolomics, metagenomics, flow cytometry analysis, single-cell sorting, and in-vitro immune cell culture, as well as mouse models (photo-convertible transgenic mice, probiotics/postbiotics treatment) and integrative meta-analysis to elucidate the mechanisms involved in microbiome-gut-brain interactions. Ultimately, this innovative research paradigm will enable the development of novel therapeutic strategies to improve recovery in stroke patients.




***Team***

*Dr. Corinne Benakis / PI*
*Dr. med. vet. Monica Weiler / lab technician*
*Rosa Delgado / PhD candidate*
*Diana Fink / Master's student*
*Isha Yogesh / Master's student*
*Alexander Beer / internship's student*

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**Key Publications**


Delgado Jiménez R, Benakis C. *The Gut Ecosystem: A Critical Player in Stroke.* **Neuromolecular Med.** 2020 Nov 18. Epub ahead of print.

Benakis C, Poon C, Lane D, Brea D, Sita G, Moore J, Murphy M, Racchumi G, Iadecola C, Anrather J. *Distinct Commensal Bacterial Signature in the Gut Is Associated With Acute and Long-Term Protection From Ischemic Stroke.* **Stroke.** 2020 Jun;51(6):1844-1854.

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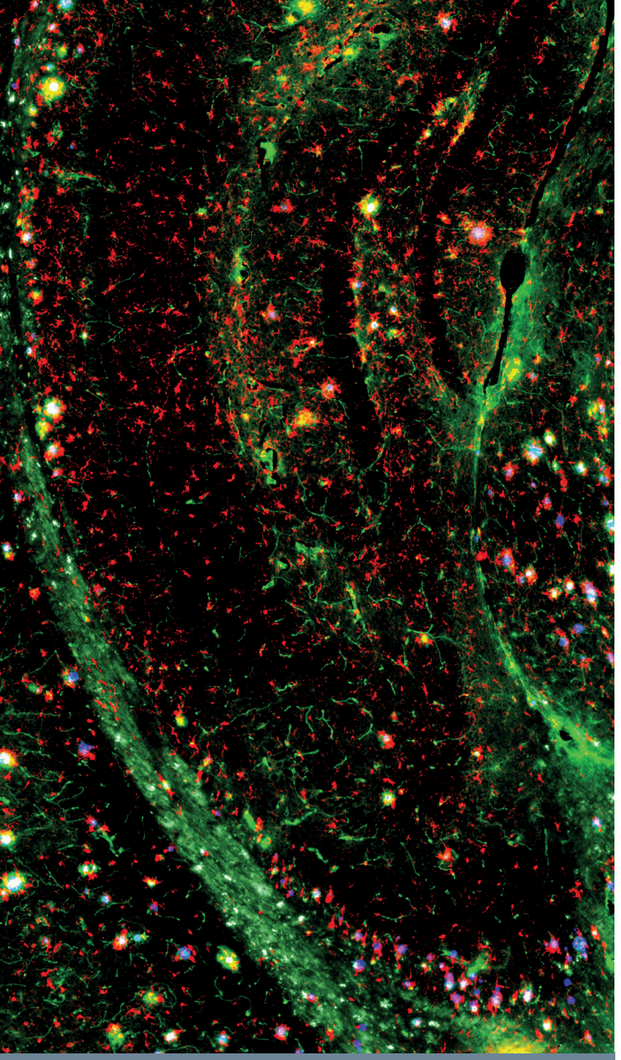

# Systems Neuroscience

Junior Research Group – PI: Ozgun Gokce



**The immune and the nervous system evolved to respond to changes in the environment. Both systems recognize the outer world (by antibodies or sensory organs), learn (pathogens or food sources), and remember them. Back in 1967, Hood, Gray, & Dreyer proposed a genetic learning and memory mechanism for the immune and the nervous systems. Since then, site-specific somatic recombination and hypermutation in T and B cells have been well established as a genetic mechanism for learning and memory in the immune system but how the nervous system achieves learning and memory is still unclear. In the last ten years, revolutionary developments in high-throughput "-omics" measurements allowed us to characterize interactions between immune and nervous systems, which revealed surprising roles of immune mechanisms in shaping the nervous system in health and disease. Our group focuses on identifying shared mechanisms regulating nervous and immune systems and how these two systems regulate each other during aging and diseases.**

**1. Role of white matter and cerebrovascular aging in neurodegeneration**

White matter volume starts to decrease gradually from 50 years of age onwards. Electron microscopy studies performed in non-human primates have shown that the major changes observed during normal aging are not a loss of neurons, but rather changes in myelinated nerve fiber morphology. Our single-cell RNA-seq work showed that aging results in microglial activation in the white matter. We propose that age-related gliovascular changes induce myelin damage, which in turn affects microglia function in the white matter. Our group focuses on understanding how age-related gliovascular changes form and lead to the development neurodegenerative diseases.

**2. Emerging Roles of cytokines in neurological diseases**

The highest expressed chemokine in neurons is macrophage migration inhibitory factor (MIF), which is also a newly identified nuclease. In collaboration with Prof. Bernhagen, we are studying MIF functions in the brain. We are testing if targeting MIF functions is a viable therapeutic strategy for neurodegenerative disorders.

***Team***

*Peter Androvič, PhD / postdoc*
*Simon Besson-Girard, MSc / GSN PhD student*
*Buket Bulut, MSc / PhD student*
*Katrin Gehring / Master-PhD student*
*Ozgun Gokce, PhD / PI*
*Jona Golemi / MD student*
*Christine Heisen / MD student*
*Hao Ji, MD / MMRS PhD student*
*Lu Liu, MD / MMRS PhD student*
*Tuğberk Kaya, MSc / GSN PhD student*
*Fumere Usifo, MSc / lab manager*
*Yijing Wang, MD / PhD student*
*Sabrina Lukanovic / team assistant*

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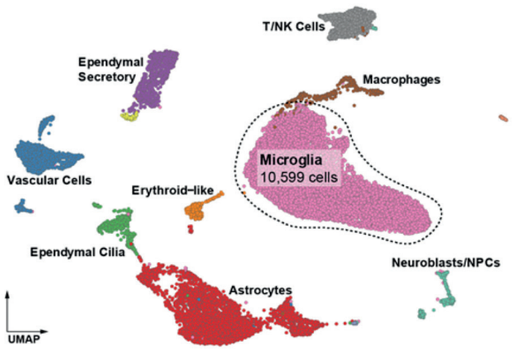


**Key Publications**

Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, van der Meer F, Kallio K, Kaya T, Anastasina M, Smura T, Levanov L, Szirovicza L, Tobi A, Kallio-Kokko H, Österlund P, Joensuu M, Meunier FA, Butcher SJ, Winkler MS, Mollenhauer B, Helenius A, Gokce O, Teesalu T, Hepojoki J, Vapalahti O, Stadelmann C, Balistreri G, Simons M. *Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity.* **Science**. 2020 Nov 13;370(6518):856-860.

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# Molecular Biomarkers – from Omics to Mechanisms

Junior Research Group – PI: Steffen Tiedt

**We aim to identify circulating signatures that inform on the local and systemic effects of stroke and to explore the underlying molecular and pathophysiological mechanisms. Events in most organs including the local and systemic events (e.g. stress) related to acute stroke are captured by the circulating proteome and metabolome. In a bedside-to-bench-approach we apply profiling technologies on human samples to identify differentially regulated molecules and study their functional role in vitro and in vivo using experimental stroke models, transgenic animal models, different imaging modalities, and a broad range of biomolecular tools.**

Our work is motivated by the heterogeneity of ischemic stroke, which poses a challenge for assigning patients to optimal treatment strategies and is a major reason for the large number of failed clinical trials. Current diagnostic algorithms are insufficient to capture both the mechanisms leading to and following stroke. The number of circulating proteins (3.500) and metabolites (25.000) exceeds the number of proteins and metabolites currently assessed in clinical practice (≈ 20) by several orders of magnitude thus illustrating the potential of profiling studies to inform beyond established diagnostic algorithms. Our ultimate goal is to implement meaningful circulating biomarkers in clinical stroke care.

To achieve this, we have recruited more than 2,000 patients with acute stroke or stroke-like diseases into our CIRCULAting biomarkers after Stroke (CIRCULAS) study, which focuses on early and serial biosampling in the acute phase of stroke. In a precision medicine approach, combining deep clinical phenotyping with profiling technologies, such as RNA sequencing, proteomics, and metabolomics, as well as ultrasensitive single-molecule and point-of-care technologies, we have identified novel markers for stroke on different molecular levels

***Team***

*Dr. Dr. med. Steffen Tiedt / PI*
*Sonja Ametsbichler / MD student*
*Vanessa Granja Burbano / GSN graduate student*
*Sabrina Helm / MD student*
*Michael Karg / MD student*
*Melanie Kaufmann / MD student*
*Evan Hunter Stanton / GSN graduate student*
*Teresa Allegra Wölfer / MD student*
*Alexandra Fekete / team assistant*

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**@SteffenTiedt**

**Key Publications**


Tiedt S, Brandmaier S, Kollmeier H, Duering M, Artati A, Adamski J, Klein M, Liebig T, Holdt LM, Teupser D, Wang-Sattler R, Schwedhelm E, Gieger C, Dichgans M. *Circulating Metabolites Differentiate Acute Ischemic Stroke from Stroke Mimics.* **Ann Neurol.** 2020 Oct;88(4):736-746.

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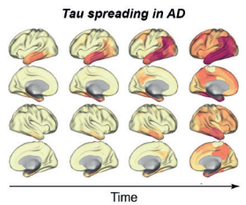
## 12/2020

### Patient-centered prediction of tau spreading in Alzheimer's (AD)

The spreading of tau pathology throughout the brain is the major driver of cognitive decline in AD. ISD researchers developed a new functional connectivity-based prediction model for the forecasting of future tau PET spreading patterns in AD patients. This patient-centered prediction model provides a precision-medicine tool for predicting disease progression and defining a patient-tailored outcome measure to boost power in clinical trials targeting tau pathology...

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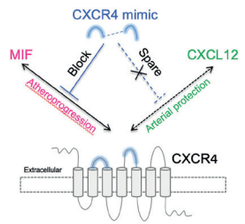
# News

## 11/2020

### Chemokine receptor mimic blocks atherosclerosis by chemokine-specific targeting

Atherosclerosis is an inflammatory disease and the main cause of stroke and myocardial infarction, but the development of anti-atherosclerotic cytokine/chemokine-targeting therapeutics has remained challenging. A research team led by the Bernhagen Lab at ISD and the Kapurniotu Lab at TUM designed peptide-based mimics of the chemokine receptor CXCR4 that block experimental atherosclerosis. The new compounds selectively target pro-atherogenic chemokine pathways, while homeostatic ones are spared.

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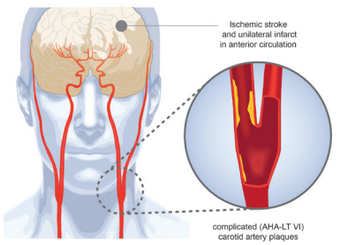
## 11/2020

### Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke

In up to 30% of patients the aetiology of stroke remains unknown. Applying high-resolution contrast-enhanced carotid MRI to patients with acute ischemic stroke ISD investigators identified nonstenosing complicated carotid artery plaques (cCAP) as an underrecognized cause of stroke. The most frequent feature of ipsilateral cCAP was intraplaque haemorrhage (89%), which can be reliably detected by conventional MRI sequences. Whether integrating carotid MRI into the diagnostic workflow would add clinical decision-making remains to be explored.

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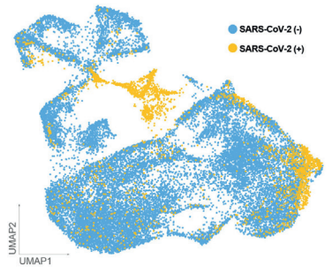
## 10/2020

### Neuropilin-1 opens the door to SARS-CoV-2 cell entry and infectivity

An international research team, coordinated by Mikael Simons (DZNE) with participation of the Gokce Lab identified neuropilin-1 as a factor that facilitates SARS-CoV-2 entry into cells including of the central nervous system.

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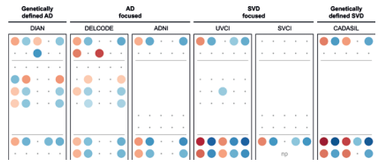
## 08/2020

### Diffusion MRI alterations in the elderly are predominantly of vascular origin

Diffusion tensor imaging is widely used to study the brain microstructure, especially in memory clinic patients. The determinants of diffusion alterations are, however, largely unknown. A large-scale study led by ISD investigators addresses this important question by identifying cerebral small vessel disease as the main determinant of diffusion alterations.

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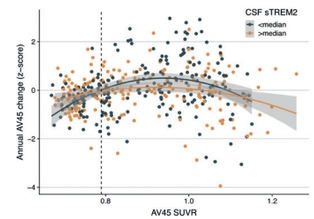
## 08/2020

### Higher sTREM2 and microglia PET associated with lower amyloid accumulation.

Alterations in the brain's immune response are associated with higher risk of Alzheimer's dementia, but the effect of microglia activation on amyloid-plaque deposition is elusive. ISD and DZNE investigators found higher CSF sTREM2 and TSPO PET, i.e. biomarkers of microglia activation, to be associated with lower amyloid accumulation in both mouse models of amyloid deposition and elderly individuals, suggesting a protective effect of TREM2-related microglia activity against a key Alzheimer's pathology...

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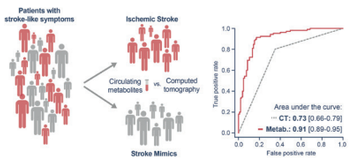
## 08/2020

### Metabolic signature differentiates ischemic stroke from stroke mimics

Early discrimination of patients with ischemic stroke (IS) from stroke mimics (SM) is important to allocate treatments, but poses a diagnostic challenge. Applying untargeted metabolomics to serum samples from > 800 patients with stroke-like symptoms, ISD investigators identified a signature of circulating metabolites that differentiates IS from SM with higher accuracy than multimodal cranial computed tomography upon hospital admission...

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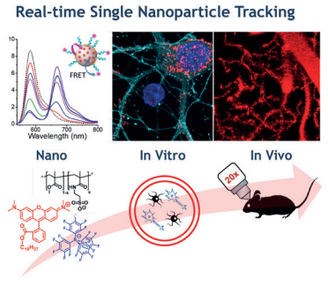
## 07/2020

### Visualization of biocompatible nanoparticles

Biocompatible nanoparticles have huge therapeutic potential, but could so far not be visualized. In a collaboration with investigators from Strasbourg, Igor Khalin (Plesnila Lab) now demonstrates that specifically designed ultra-bright nanoparticles can be traced in vivo by 2-photon microscopy. This technological breakthrough greatly improves our understanding how to target therapeutic compounds to the CNS...

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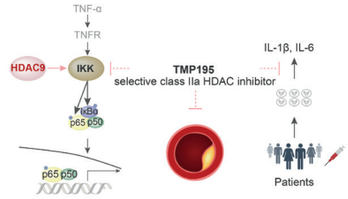
## 06/2020

### HDAC9 – from GWAS discovery to mechanisms and therapeutic targeting

Drug targets with support from human genetics have a higher probability of reaching phase III clinical trials and regulatory approval. Following their GWAS-based discovery of HDAC9 as a major risk locus for human atherosclerosis, ISD investigators identified a detailed mechanism linking HDAC9 to vascular inflammation. They further demonstrate that therapeutic inhibition of this HDAC9-dependent pathway confers plaque stability on top of atheroprotection...

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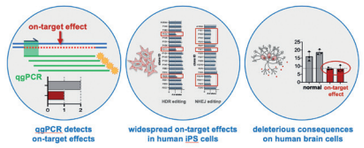
## 05/2020

### Taming widespread collateral damage of CRISPR editing

CRISPR-Cas9 has revolutionized disease-research, as it greatly simplifies targeted genome editing. However, CRISPR systems are not entirely accurate and can introduce potentially harmful additional mutations, called on-target effects. In a collaborative study with the Dichgans Lab, the PaquetLab identified widespread prevalence of on-target effects in clinically relevant CRISPR-edited iPS cells and describes broadly applicable tools to detect these unintended alterations. The new method improves the reliability of CRISPR editing...

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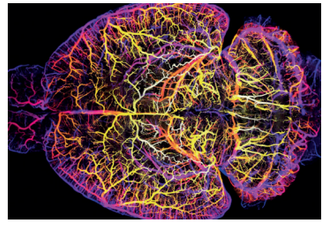
## 03/2020

### Machine learning analysis of whole mouse brain vasculature

The Ertürk Lab in collaboration with others (ISD, Helmholtz Munich and TUM) developed an artifical intelligence aided tool to study the vasculature in complete transparent mouse brains. Using 3D microscopy, they visualized the underlying complex network of all brain vessels at the capillary level. Their new tool can generate reference maps of the adult mouse brain vasculature, which could be used to model synthetic cerebrovascular networks. On this basis, unknown vascular properties can be discovered and biological models can be confirmed...



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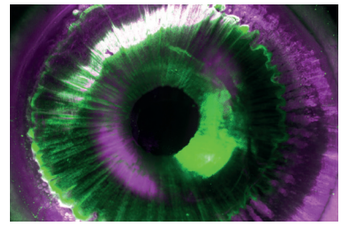
## 03/2020

### Transparent human organs – 3D maps at cellular level

The Ertürk Lab (ISD and Helmholtz Munich) managed to make intact human organs transparent. Using microscopic imaging they visualized underlying complex structures of see-through organs at the cellular level. Resulting organ maps could serve as templates for 3D-bioprinting technologies. This eventually could contribute to the creation of on demand artificial organs for patients in need...



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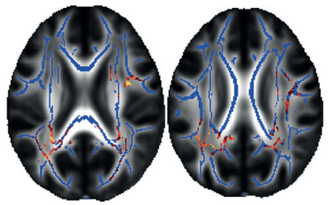
# News

## 03/2020

### Aβ deposition associated with white matter alterations in cognitive normal people

In an international collaboration, ISD researchers report increased amyloid PET uptake to be associated with higher age-related fiber tract alterations and white matter hyperintensities in cognitively asymptomatic people...

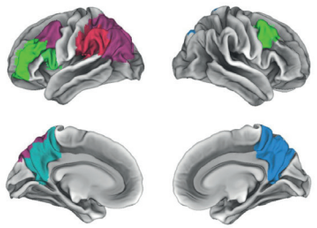


*Caballero MÁA, Song Z, Rubinski A, Duering M, Dichgans M, Park DC, Ewers M. Age-dependent amyloid deposition is associated with white matter alterations in cognitively normal adults during the adult life span. **Alzheimers Dement.** 2020 Apr;16(4):651-661.*

## 02/2020

### Digital medicine model of cognitive worsening in Alzheimer's disease

In a large collaborative study with the North American DIAN and ADNI studies, ISD researchers developed a fully automated and cross-validated machine-learning algorithm for the prediction of disease progression in Alzheimer's disease. The biofluid and neuroimaging derived model allows to predict the rate of cognitive decline over a clinically relevant time window of 4 years....



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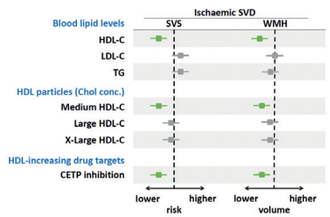
## 02/2020

### Role of HDL-C in cerebral Small Vessel Disease

Using Mendelian Randomization, ISD investigators showed that genetic predisposition to higher HDL-C, specifically to cholesterol in medium-sized HDL, is associated with small vessel stroke and white matter injury. Their analyses indicate that HDL-C-raising strategies could be considered for the prevention of ischemic small vessel disease, but the net benefit of such an approach needs to be tested in a randomized controlled trial...

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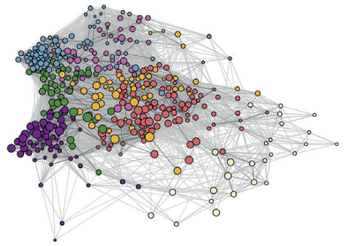
## 01/2020

### Tau spreading associated with functional connectivity in Alzheimer's disease

A multinational study led by the Ewers Lab and first author Nicolai Franzmeier shows that functional brain architecture predicts the spatial patterns of the gradual spreading of tau pathology in Alzheimer's disease, supporting in-vitro findings of trans-neuronal tau propagation...



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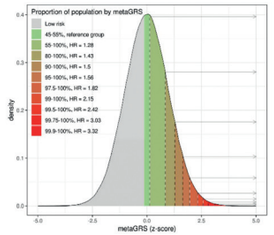
## 12/2019

### *Improved Genomic Risk Score (GRS) for Stroke*

ISD researchers developed a metaGRS for ischaemic stroke (IS) that outperforms previous GRS and identifies a subset of individuals at monogenic levels of risk. Individuals in the top 0.25% of the metaGRS have a threefold increased risk of IS. The results suggest that, for individuals with a high metaGRS, achieving risk factor levels recommended by current guidelines may be insufficient to mitigate risk...

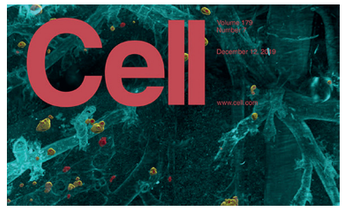



*Abraham G, Malik R, Yonova-Doing E, Salim A, Wang T, Danesh J, Butterworth AS, Howson JMM, Inouye M, Dichgans M. Genomic risk score offers predictive performance comparable to clinical risk factors for ischaemic stroke**. Nat Commun.** 2019 Dec 20;10(1):5819. doi: 10.1038/s41467-019-13848-1.*

## 12/2019

### Deep Learning Reveals Therapeutic Antibody Targeting in the Entire Body

Combining clearing technology with deep learning algorithms, ISD investigators developed an integrated pipeline for automated quantification of cancer metastases and therapeutic antibody targeting (DeepMACT) that enables analysing the size, shape, and spatial distribution of metastases, and the degree to which metastases are targeted by therapeutic monoclonal antibodies in entire mice...



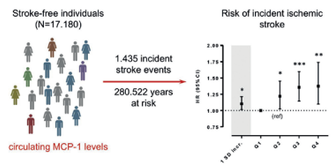

*Pan C, Schoppe O, Parra-Damas A, Cai R, Todorov MI, ..., Ertürk A. Deep Learning Reveals Cancer Metastasis and Therapeutic Antibody Targeting in the Entire Body. **Cell.** 2019 Dec 12;179(7):1661-1676.e19.*

# News

## 09/2019

### Circulating MCP-1 levels associate with stroke risk

Expanding on their previous Mendelian Randomisation study (CIRCULATION 2019) ISD researchers now provide further evidence for a causal role of MCP-1 in stroke. In a meta-analysis of observational data from 17,180 stroke-free individuals they found higher circulating MCP-1 levels to be associated with long-term risk of incident ischemic stroke...

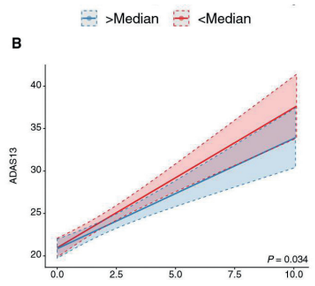



*Georgakis MK, Malik R, ..., Dichgans M. Circulating Monocyte Chemoattractant Protein-1 and Risk of Stroke: Meta-Analysis of Population-Based Studies Involving 17 180 Individuals. **Circ Res.** 2019 Sep 27;125(8):773-782.*

## 08/2019

### Protective effects of TREM2 in Alzheimer's Disease

The teams of M. Ewers and C. Haass found higher cerebrospinal fluid comcentrations of TREM2, a biomarker of microglia activation, to slow down cognitive decline in Alzheimer's Disaease...

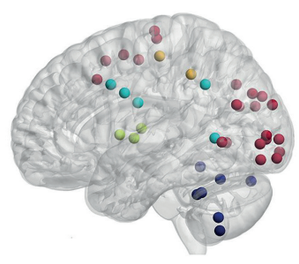



*Ewers M, Franzmeier N, ..., Dichgans M, Trojanowski JQ, Shaw LM, Weiner MW, Haass C; Alzheimer's Disease Neuroimaging Initiative. Increased soluble TREM2 in cerebrospinal fluid is associated with reduced cognitive and clinical decline in Alzheimer's disease. **Sci Transl Med.** 2019 Aug 28;11(507):eaav6221.*

## 07/2019

### Novel insights into small vessel disease progression

Using a prospective, high-frequency serial imaging study, a team of researchers at ISD and Radboudumc Nijmegen identified acute infarcts as the cause of incident lacunes and almost a third of incident microbleeds. In contrast, the progression of white matter hyperintensities was independent from acute infarcts. These new insights were enabled through a unique study design with monthly MRI exams...

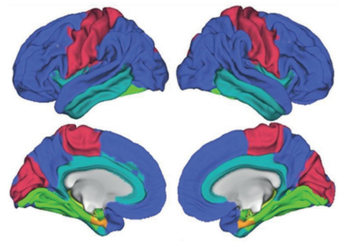


*Ter Telgte A, Wiegertjes K, Gesierich B, Marques JP, Huebner M, de Klerk JJ, Schreuder FHBM, Araque Caballero MA, Kuijf HJ, Norris DG, Klijn CJM, Dichgans M, Tuladhar AM, Duering M, de Leeuw FE. Contribution of acute infarcts to cerebral small vessel disease progression. **Ann Neurol.** 2019 Oct;86(4):582-592.*

## 04/2019

### BIN1 SNP associated with tau deposition in Alzheimer's

A multinational study led by Michael Ewers and his team suggests that enhanced tau pathology may underlie the increased risk of Alzheimer's conferred by the BIN1 single nucleotide polymorphism – the second most important genetic risk factor of AD...

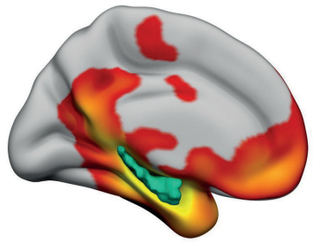


*Franzmeier N, Rubinski A, Neitzel J, Ewers M; Alzheimer's Disease Neuroimaging Initiative (ADNI). The BIN1 rs744373 SNP is associated with increased tau-PET levels and impaired memory. **Nat Commun.** 2019 Apr 16;10(1):1766. doi: 10.1038/s41467-019-09564-5.*

## 04/2019

### *BDNF*$_{Val66Met}$ SNP modulates hippocampus disconnection in Alzheimer's

ISD researchers found a common variant in the BDNF gene to modulate the impact of amyloid pathology on hippocampal network connectivity and memory in Alzheimer's disease...

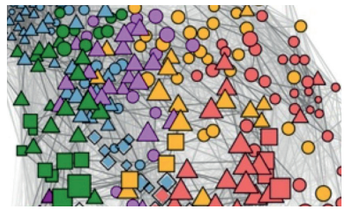


*Franzmeier N, Ren J,..., Ewers M. The BDNFVal66Met SNP modulates the association between beta-amyloid and hippocampal disconnection in Alzheimer's disease. **Mol Psychiatry.** 2019 Mar 21:10.1038/s41380-019-0404-6.*

## 02/2019

### Functional connectivity associated with tau pathology

A combined fMRI and tau PET study in Alzheimer's disease by Michael Ewers and team shows that the spatial pattern of tau pathology is predicted by functional network connectivity, suggesting that cross-talk between brain regions is conducive to tau spreading...



*Franzmeier N, Rubinski A, Neitzel J, Kim Y, Damm A, Na DL, Kim HJ, Lyoo CH, Cho H, Finsterwalder S, Duering M, Seo SW, Ewers M; Alzheimer's Disease Neuroimaging Initiative. Functional connectivity associated with tau levels in ageing, Alzheimer's, and small vessel disease. **Brain.** 2019 Apr 1;142(4):1093-1107.*

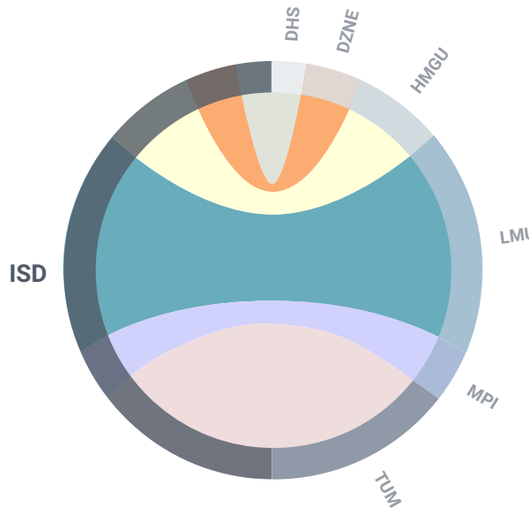
# News

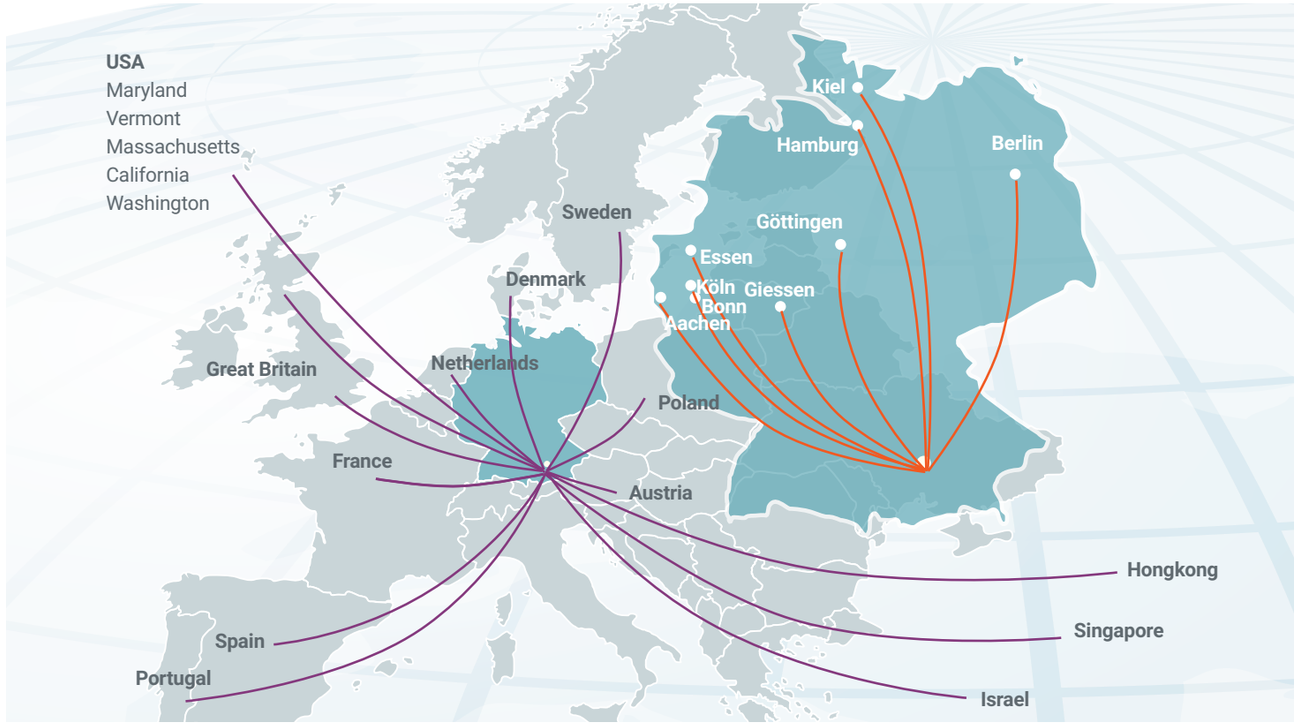
# Collaborations

**Local Collaborations**

Over the past years, the ISD has established strong partnerships: locally, nationally, and internationally – through third party funded networks including CRCs, EU-funded projects, and from private foundations such as the Cure Alzheimer's fund. Locally, we are most strongly connected to institutions at the LMU and TUM, the German Center for Neurodegenerative Diseases (DZNE) and the Max Planck Institutes. Nationally, our collaborators are spread across Germany, while internationally we are mostly connected within Europe, but also to the US and Asia.

| | |
|---|---|
| **LMU** (Ludwig-Maximilians-Universität) | **37 %** |
| **TUM** (Technische Universität München) | **28 %** |
| **HMGU** (Helmholtz Zentrum München) | **14 %** |
| **DZNE** (German Center for Neurodegenerative Diseases) | **9 %** |
| **MPI** (Max-Planck-Institutes) | **9 %** |
| **DHS** (Deutsches Herzzentrum) | **3 %** |



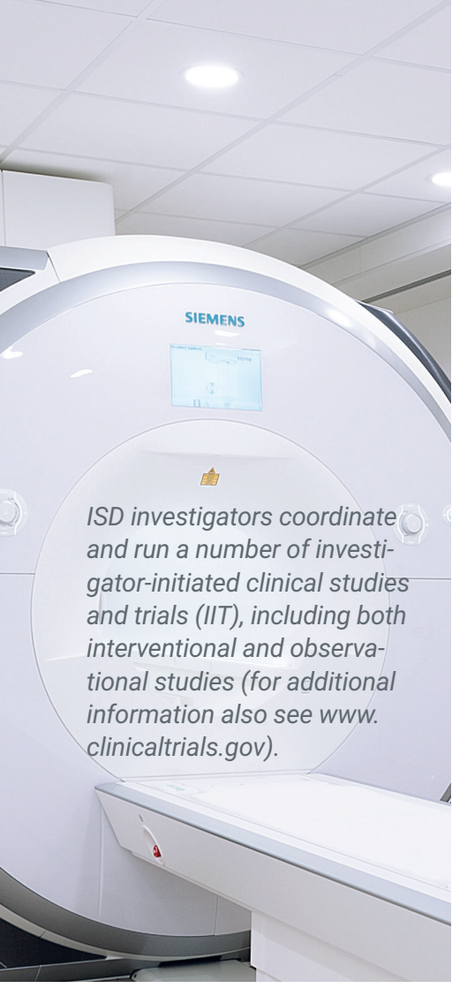




**Selection of Collaborations with other German Sites**

- RWTH Aachen University
- DZNE Bonn
- University of Bonn
- University of Cologne
- University of Duisburg
- University of Essen
- University of Gießen
- University Göttingen
- Universitätsklinikum Hamburg-Eppendorf
- Forschungszentrum Jülich
- Univ. Schleswig-Holstein
- Universität Kiel

**Selection of International Collaborations**

- Medical University Graz, Austria
- European Institute for Biomedical Imaging Research, Vienna, Austria
- University of Copenhagen, Denmark
- A.I. Virtanen Inst. for Molecular Sciences, Kuopio, Finland
- University of Bordeaux, France
- Insitut Pasteur de Lille, France
- Sophia Antipolis, Nice, France
- Univ. Paris, France
- Radboudumc, Nijmegen, Netherlands
- UMC Utrecht, Netherlands
- Duke NUS and National Heart Center, Singapore




*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
(NCT01334749)

*The **DZNE M**echanism of **D**ementia after **A**fter **S**troke Study*

DEMDAS is a hospital-based longitudinal prospective multicenter study in patients suffering from acute stroke. Patients are recruited up to 120 hours after stroke and followed over 5 years to identify predictors for Post Stroke Cognitive Impairment (PS-CI) and Post Stroke Dementia (PSD) and to derive and validate a risk score for PS-D and PS-CI. Meanwhile recruitment is completed. Initial results have been obtained in respect to infarct characterization on MRI and we recently performed a first calculation on the statistical power for analysis of the study endpoints. We further identified a biomarker, which has utility as a predictor for stroke outcome.

Sample size DEDEMAS (ISD): 141
Sample size DEMDAS (multicenter): 600
Current enrollment: 741 (completed)
Study sites: Munich (ISD, TUM), Berlin, Bonn, Göttingen, Magdeburg
Started May 2013
Estimated date for study completion: 2023
Funding: German Center for Neurodegenerative Diseases (DZNE)
**Coordinator: M. Dichgans**

*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.*

*Duering M, Adam R, Wollenweber FA, Bayer-Karpinska A, Baykara E, Cubillos-Pinilla LY, Gesierich B, Araque Caballero MÁ, Stoecklein S, Ewers M, Pasternak O, Dichgans M. Within-lesion heterogeneity of subcortical DWI lesion evolution, and stroke outcome: A voxel-based analysis. **J Cereb Blood Flow Metab.** 2020 Jul;40(7):1482-1491.*


## PROSCIS
(NCT01364168)

***PRO**spective **S**troke **C**ohort with **I**ncident **S**troke*

The primary aim of this observational 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.

Sample size: 850
Current enrollment: 438
Study sites: Munich (ISD, TUM), Berlin
Started: February 2011
Estimated date for study completion: 2024
Funding: Vascular Dementia Research Foundation
**Coordinator: M. Dichgans**

## 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.

Sample size: 3000
Current enrollment: 459
Study sites: Munich
Started: February 2011
Funding: Vascular Dementia Research Foundation
**Coordinator: M. Dichgans**

## CAPIAS
(NCT01284933)

***CA**rotid **P**laque **I**maging in **A**cute **S**troke*

CAPIAS is an observational multicenter study with the aim to determine the prevalence of complicated (American Heart Association-lesion type VI) nonstenosing carotid artery plaques in cryptogenic stroke by carotid MRI. 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.

Sample size: 300
Current enrollment: 234 (completed)
Study sites: Munich (ISD, TUM), Freiburg
Started: February 2011
Estimated date for study completion: 07/2021
Funding: Vascular Dementia Research Foundation
**Coordinator: M. Dichgans**

*Kopczak A, Schindler A, Bayer-Karpinska A, Koch ML, Sepp D, Zeller J, Strecker C, Hempel JM, Yuan C, Malik R, Wollenweber FA, Boeckh-Behrens T, Cyran CC, Helck A, Harloff A, Ziemann U, Poli S, Poppert H, Dichgans M, Saam T. Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke. **J Am Coll Cardiol.** 2020 Nov 10;76(19):2212-2222.*

## TREAT-SVDs
(NCT03082014)

*Effec**T**s of Amlodipine and other Blood P**RE**ssure Lowering **A**gents on Microvascular Func**T**ion in **S**mall **V**essel Disease**S***

TREAT-SVDs is a prospective, multicentre, international, 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. TREAT@SVDs compares the effect of different antihypertensive drug classes on microvascular function, assessed by cerebrovascular reactivity in response to a CO2 stimulus and blood pressure variability, in SVDs.

Sample size: 105 (30 genetic SVDs + 75 sporadic SVDs)
Current enrolment: 84 (21 genetic SVDs + 63 sporadic SVDs)
Study sites: Munich, Oxford, Edinburgh, Maastricht, Utrecht
Started: February 2018
Estimated date for study completion: 2021
Funding: EU Horizon2020 research and innovation programme, (SVDs@target)
**Coordinator: M. Dichgans**

## INVESTIGATE-SVDs
(ISRCTN10514229)

***I**maging **N**euro**V**ascular, **E**ndothelial and **ST**ructural **I**nte**G**rity in Prep**A**ration to **T**rEat **S**mall **V**essel Disease**S***

INVESTIGATE-SVDs is an international, multicentre observational study including an interventional study paradigm. The study has included patients with lacunar ischemic stroke, representing sporadic SVD and with CADASIL, representing genetic SVD. The main objective is to determine blood brain barrier integrity and the interplay with microvessel function including perivascular spaces and cerebrovascular reactivity in response to CO2 stimulus.

Sample size: 75 (30 genetic SVDs + 45 sporadic SVDs)
Current enrollment: 75 (completed)
Study sites: Edinburgh, Maastricht, Munich
Started: February 2017
Funding: EU Horizon2020 research and innovation programme, (SVDs@target)
**Local PI: M. Dichgans**


## Zoom@SVDs
(NTR6265)

***Zoom**ing in at microvascular malfunction in **S**mall **V**essel Disease**S** with 7T MRI*

Zoom@SVDs is an international observational study with 7T MRI in two subsets of patients: patients with sporadic SVDs and healthy controls and patients with CADASIL as a hereditary form of SVDs and matched healthy controls. In ZOOM@SVDs we are, for the first time, zooming in on the small vessel function itself with 7T MRI. The study aims to determine novel MRI markers of microvascular malfunction in patients with SVDs and to explore the relation between microvascular function and parenchymal lesion presence at baseline and lesion progression after 24 months.

Sample size: 120 (20 genetic SVDs + 10 healthy controls; 60 sporadic SVDs + 30 healthy controls)
Current enrollment: 114
Study sites: Utrecht, Munich
Started: March 2017
Estimated date for study completion: 2022
Funding: EU Horizon2020 research and innovation programme, (SVDs@target)
**Local PI: M. Dichgans**

## CIRCULAS

***CIRCUL**ating biomarkers **A**fter **S**troke)*

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. CIRCULAS is a case-control study with longitudinal biosampling aimed at identifying novel blood-based biomarkers to support decision-making in the acute phase of stroke.

Sample size: 2000
Current enrollment: 1.346 patients
Study site: Munich
Started: February 2014
Estimated completion: 2024
Funding: Vascular Dementia Research Foundation, FöFoLe, FBI
**PI: M. Dichgans**
**Project management: S. Tiedt**

*Tiedt S, ..., Dichgans M. Circulating Metabolites Differentiate Acute Ischemic Stroke from Stroke Mimics. **Ann Neurol.** 2020 Oct;88(4):736-746.*

*Tiedt S, ..., 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.*

## ICARUS
(NCT04412187)

***I**nflammatory fa**C**tors **A**fte**R** ac**U**te ischemic **S**troke*

ICARUS is an interventional single-centre hospital-based study in patients with an acute ischemic stroke. ICARUS involves serial TSPO-PET imaging along with serial MRI and immune cell profiling in blood. The study aims to define the characteristics and determinants of microglial activation after stroke and to assess the correlation of microglial activation with circulating inflammatory markers, structural brain changes, and neurological outcomes. ICARUS comes along with a substudy to evaluate, if MRI ASL sequences can be used for brain perfusion measurement with the aim to reduce the burden of dynamic PET for patients.

Sample size: 36 (main study); 10 (Substudy)
Current enrolment: 7 (substudy)
Study site: Munich
Started: July 2020
Estimated date for study completion: 2024
Funding: German Research Foundation (DFG), (ImmunoStroke)
**PI: M. Dichgans**

## HIFI-CAA

***HI**gh **F**requency **I**maging in patients with **C**erebral **A**myloid **A**ngiopathy*

HIFI-CAA is an observational single-centre study with serial, monthly MR imaging to evaluate the development and temporal evolution of incident and prevalent focal subarachnoid hemorrhages (fSAH) and cortical superficial siderosis (cSS) in CAA patients and to compare with lobar ICH survivors. Furthermore the monthly incident of acute ischemic lesions is assessed and the interrelationship between these types of hemorrhagic lesions and acute ischemic lesions in relation to the functional status.

Sample size: 75 (50 patients with cSS or fSAH; 25 patients with lobar haemorrhage)
Current enrolment: 20
Study site: Munich
Started: March 2019
Estimated completion: 2023
Funding: Vascular Dementia Research Foundation
**PI: M. Düring**

## APICES
(NCT04057690)

***A**utomatic **P**red**IC**tion of **E**dema After **S**troke*

APICES is an observational, retrospective study that aims to use machine learning for comprehensive analysis of CT images as well as clinical data from 1500 patients with large ischemic MCA strokes in order to develop a model for early prediction of malignant brain edema.

Sample size: 1500 (retrospective datasets)
Current enrollment: 63
Study site: Tübingen (Sponsor), Berlin, Munich, Hamburg, Heidelberg
Started: April 2019
Estimated date for study completion: 2022
Funding: Innovationsfond des gemeinsamen Bundesausschuss
**PI: K. Dimitriadis**

## CONVINCE
(NCT02898610)

*(German Extension) **CO**lchicine for Preventio**N** of **V**ascular **I**nflammation in **N**on-**C**ardio**E**mbolic Stroke*

CONVINCE is a randomized open label trial to compare low-dose colchicine plus usual care, to usual care alone, to prevent non-fatal recurrent ischaemic stroke and coronary events and vascular death after non-severe, non-cardioembolic stroke.

Sample size: 3154 plus 524
Study sites: 17 European sites, Canada, United Arab Emirates, plus 26 sites in Germany
Started: not yet, in preparation
Funding: German Research Foundation (DFG)
**PI: M. Dichgans, K. Dimitriadis**

## ESCAPE-NEXT

*Biomarker Sub-study of the Efficacy and Safety of Nerinetide in Subjects with Acute Ischemic Stroke Undergoing Endovascular Thrombectomy Excluding Thrombolysis (ESCAPE-NEXT) trial.*

This is an observational Sub-study of ESCAPE-NEXT to Collect, Store, and Analyze Blood Samples for the Evaluation of Circulating Surrogate Markers of Clinical Outcome

Sample size: up to 1020
Current enrollment: 0
Study site: global multicentre
Started: December 2020
Estimated date for study completion: 2023
Funding: CIHR
**PI: M. Dichgans**

## 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: 102 (ISD)
Funding: DZNE
**PI: K. Bürger**

## EGO

*EGO is an observational single-centre study in patients with mild cognitive impairment and cognitively normal controls.*

EGO involves Alzheimer's disease biomarker assessments and MRI scanning together with extensive neuropsychological testing as well as lifestyle assessments. The goal of EGO is to identify functional brain network mechanisms that confer resilience against the impact of Alzheimer's disease related brain changes on cognitive performance.
**PI: N. Franzmeier**

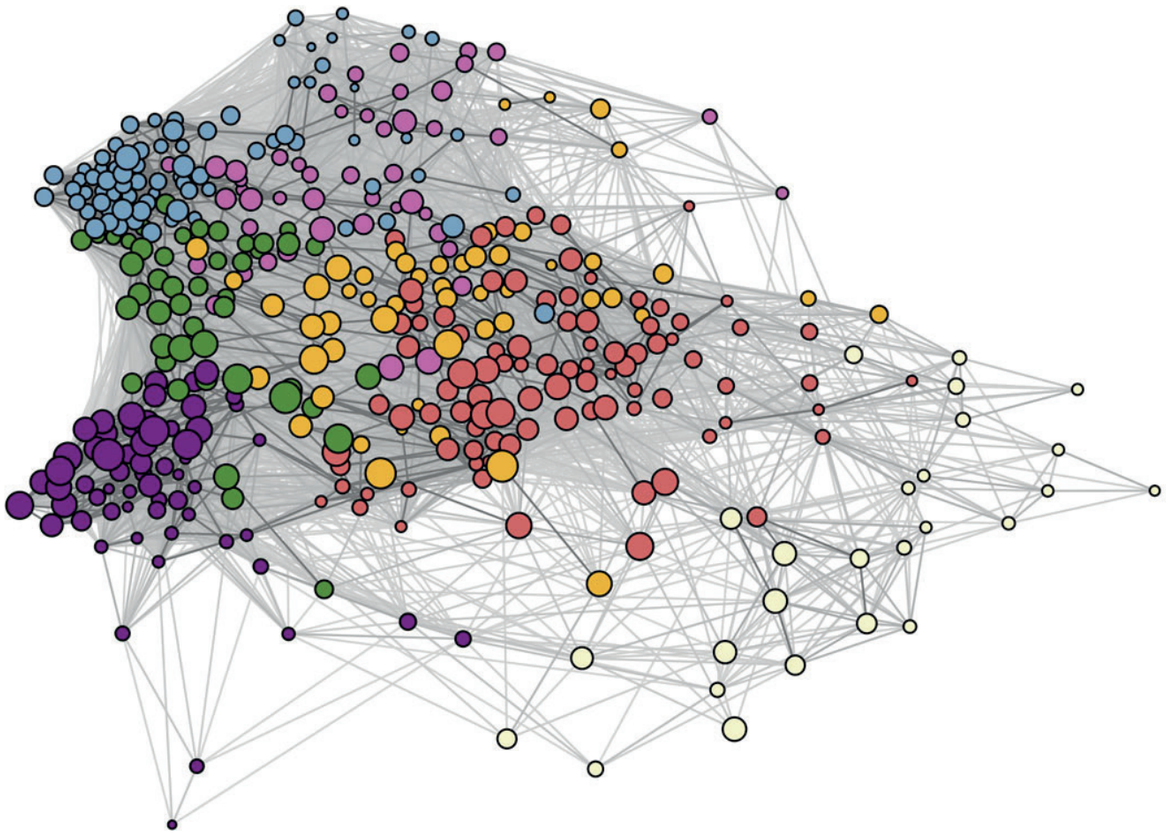
## *Industry-sponsored Trials*

**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 AD.
Protocol number 251AD201
Sponsor: Biogen USA/UK
Status: ongoing
**PI: K. Bürger**

**SIMaMCI**
Randomized Controlled Trial of Simvastatin in Amnestic MCI Patients.
**PI: K. Bürger**
Status: completed

**ANNEXA-I**
A Randomized Clinical Trial of Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor
Sponsor: Portola Pharmaceuticals
Status: ongoing
**PI: K. Dimitriadis**

**ESCAPE-NEXT** (NCT04462536)
ESCAPE-NEXT is a multicenter, randomized double-blinded trial to determine the efficacy of the neuroprotectant nerinetide in reducing global disability in patients with acute ischemic stroke undergoing endovascular thrombectomy excluding thrombolysis.
Sponsor: NoNO Inc.
Status: in preparation
**PI: M. Dichgans**
**Coordinator: K. Dimitriadis**

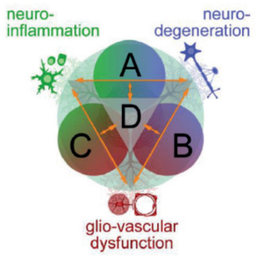




# Funding

# Project Funding

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




SyNergy defines Systems Neurology as a new research field where systems-level biology and systems neuroscience meet clinical neurology to generate an integrative understanding of the interplay of the different pathomechanisms, neurodegeneration, inflammation and vascular dysfunction, in a broad range of neurological diseases.

SyNergy Munich Cluster for Systems Neurology

DFG

ISD investigators participate in the following:

**Tandem Projects**

**Research Area A: Immune Pathology & Neurodegeneration**

A4 *Microglia heterogeneity in neurological disorders of neurodegenerative, inflammatory and vascular origin.*
**M. Dichgans,** Tandem contributor

**Research Area B: Glio-Vascular Dysfunction and Neurodegeneration**

B1 *System neurology of cell-type specific mitochondrial pathology in neurodegeneration and ischemic models.*
**A. Liesz**, Tandem contributor

B2 *Identifying key regulators of neuronal replacement after neurodegeration and stroke.*
**A. Liesz**, coordinating PI;
**M. Dichgans**, Tandem contributor;
**N. Plesnila**, AI

B3 *Small vessel disease (SVD) – multiscale imaging from models to patients.*
**A. Liesz**, coordinating PI;
**M. Dichgans**, Tandem contributor;
**N. Plesnila**, AI

**Research Area C: Glio-Vascular Dysfunction and Immune Pathology**

C3 *Exploring disorders of the neuro-glio-vascular unit in isogenic human iPSC-derived in vitro models.*
**M. Dichgans**, coordinating PI;
**D. Paquet**, coordinating PI;
**N. Plesnila**, AI

**Research Area D: From Pathomechanisms towards Clinical Impact**
**M. Dichgans**, Coordinator

D1 *Microglial activity markers: from mouse models to humans.*
**M. Dichgans**, Tandem contributor

D2 *Pharmacological inhibition of HDAC9 for artheroprotection and its effect on neuroprotection.*
**M. Dichgans**, coordinating PI;
**J. Bernhagen**, AI; **A. Liesz**, AI

**Technology hubs**

**Mesoscale Hub**
Provides two central techniques, virus-based trans-synaptic tracing and tissue clearing to view the entire nervouse system. **A. Ertürk**, AI

**Macroscale Hub**
Provides two streams of multi-modal imaging, small animal MRI/PET and human MRI/PET for in vivo macroscale imaging. **M. Düring**, AI

**Genome Hub**
Provides expertise in optimal design and application of genome editing to generate novel models mimicking human disease conditions.
**D. Paquet**, coordinator

**M. Dichgans**, Member of the SyNergy Board

*For further information, see www.synergy-munich.de*

## CRC 1123: Atherosclerosis – Mechanisms and Networks of Novel Therapeutic Targets

Cardiovascular disease remains the major cause of death in the Western world. It is mainly caused by atherosclerosis. This network aims to decipher the molecular and cellular determinants of atherosclerosis, giving rise to novel links between genetic, inflammatory and metabolic factors. It will provide targets for future therapeutic options and interventions to treat atherosclerosis with minimal side effects on immune response and homeostatic metabolic activities.

*ISD participates with two projects in this CRC:*

**Research Area A: Signal Proteins and Cytokines**

A03 The MIF protein/receptor network in atherosclerosis: mechanisms, novel members, and specific therapeutic strategies.
**PI: J. Bernhagen**

**Research Area B: Nucleic Acids and Lipid Mediators**

B03 Mechanisms underlying the role of HDAC9 in atherosclerosis.
**PI: Y. Asare**, **M. Dichgans**

*For further information, see www.sfb1123.med.uni-muenchen.de*

CRC 1123

## Molecular mechanisms of recessive and dominant mutations in the small vessel disease-related high temperature requirement protease HTRA1

CARASIL is a familial cerebral small vessel disease caused by loss-of-function mutations in the HTRA1 gene. In addition, HTRA1 mutations have been identified as a major cause of autosomal dominant SVD. This project aims to identify the molecular mechanisms through which HTRA1 plays a role in CARASIL and other cerebral microangiopathies. We could already show that a set of pathogenic mutations result in oligomeric assembly defects of the proteolytically active complex and we are developing a repair strategy to rescue the function.

**PI: M. Dichgans, N. Beaufort**

DFG Deutsche Forschungsgemeinschaft

## FOR 2879: From Immune Cells to Stroke Recovery

While cerebral ischemia is traditionally not regarded as a classical neuroinflammatory disorder, stroke triggers a plethora of immune responses well comparable to those occurring in other autoimmune brain diseases. The reciprocal interaction of local and systemic immunological responses to brain injury are barely understood and particularly for stroke recovery the underlying mechanisms have not been uncovered.

The ImmunoStroke consortium aims to answer the selected questions how immunity modulates stroke recovery, dissect the impact of neuroinflammation in human stroke patients and reveal novel surrogate markers of human post-stroke neuroinflammation. The consortium consists of 12 projects at 4 sites including two clinical observational studies.

**PI: A. Liesz, M. Dichgans, G. Llovera**

*For further information, see https://immunostroke.de*

IMMUNOSTROKE

## Small Vessel Diseases in a Mechanistic Perspective:

*Targets for Intervention - Affected pathways and mechanistic exploitation for prevention of stroke and dementia.*

The SVDs@target consortium tackles one of the most pressing health issues in ageing societies. The ambition is to decipher the underlying pathologies of small vessel disease with the ultimate goal to reduce the burden of stroke and dementia. Our preliminary results already provide a better understanding of the disease pathways leading from basic risk factors to functional deficits. They provide new directions for clinical research, such as the importance of early life blood pressure and blood pressure variability for stroke and dementia risk and the role of microglia for cognitive impairment. In addition, two novel MRI markers for microvascular dysfunction were established. So far, SVDs@target has published > 70 papers.

*The project includes three clinical 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 trial to determine the effects of different blood pressure lowering agents on microvascular function in patients with distinct SVDs

Coordinator: **M. Dichgans**

*For further information, see www.svds-at-target.eu/*

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

Stroke and Alzheimer's (AD) are on the rise and often co-occur in the same patient. Both diseases have long been considered "partners in crime", with overlapping mechanisms causing the diseases. The CoSTREAM is improving the understanding of the relationship between these diseases by a multidisciplinary approach. The network already could identify specific genomic regions that mediate risk to stroke or AD and created a polygenic risk score based on genes implicated in stroke that predicts AD. ISD is the leader of WP1 "Genetics". So far, CoSTREAM has published > 90 papers.

**PI: M. Dichgans**

*For further information, see www.costream.eu*

## DigiMed Bayern for the Medicine of the Future

The lighthouse P4-medicine project DigiMed Bayern was launched at the end of 2018 with over 20 million € funding by the Bavarian State Ministry of Health and Care. DigiMed Bayern combines comprehensive datasets of patients diagnosed with atherosclerotic diseases, such as coronary heart disease and stroke, or with genetic risk factors. This dataset will be further enriched with state-of-the-art multi-dimensional molecular characterization (-omics technologies) of associated sample material.

The ISD is involved in WP2 "*P4 medicine for carotid stenosis and stroke*" with the aim to connect human biobanks from different partners with clinical studies to identify novel markers and therapeutic targets for stroke prevention and therapy.

**PI: M. Dichgans**

*Funded by Bayerisches Staatsministerium für Gesundheit und Pflege (StMGP)*

## Clinical Mass Spectrometry Center Munich CINSPECT-M

The overall goal of this joint large-scale project, funded by the Federal Ministry of Education and Research (BMBF) with 6 million euros, is to establish a clinical mass spectrometry center for molecular brain research in Munich. CLINSPECT-M combines medical information and data from mass spectrometry using bioinformatics to gain a better understanding of the complex interrelationships between severe neurological disorders, to understand their molecular causes and to monitor the course of therapy.

The ISD is involved in WP03 "*Neurovascular dieseases*" with the aim to define circulating blood biomarkers for a better therapeutic decision-making in acute stroke.

**PI: M. Dichgans**


## Genetics of Early-Onset Ischemic Stroke Consortium

The overall goal of this study is to assemble an international consortium to to decipher genetic determinants, both single gene and complex inheritance of early-onset stroke and cerebrovascular disease and search for the pathways through which they alter stroke susceptibility. The proposed study assembles the largest study of early-onset stroke to date, with over 13,000 ischemic stroke patients under age 60 and over 73,000 controls. We expect that this effort will lead to better treatments for Mendelian forms of stroke and will identify novel biological mechanisms that are also relevant to older-onset stroke.

**PI: M. Dichgans**

Funded by NINDS (National Institute of Neurological Disorders)

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

| | 2019 | 2020 |
|---|---|---|
| Personnel costs | 3,030,657 € | 3,011,665 € |
| Consumables | 897,859 € | 1,060,773 € |
| Travel expenses | 44,315 € | 6,134 € |
| Investments | 81,511 € | 163,798 € |
| Total | 4,054,342 € | 4,242,370 € |

**not including costs for outpatient clinic*

# Third Party Funding

**Third party funds (spent)**

| Source | Number of projects 2019 | Funds spent 2019 |
|---|---|---|
| BMBF/DLR | 3 | 711,488 € |
| DFG | 37 | 1,483,225 € |
| EU | 7 | 771,177 € |
| Others | 29 | 606,953 € |
| LMU | 15 | 296,470 € |
| Total third party funding spent | | 3,869,313 € |

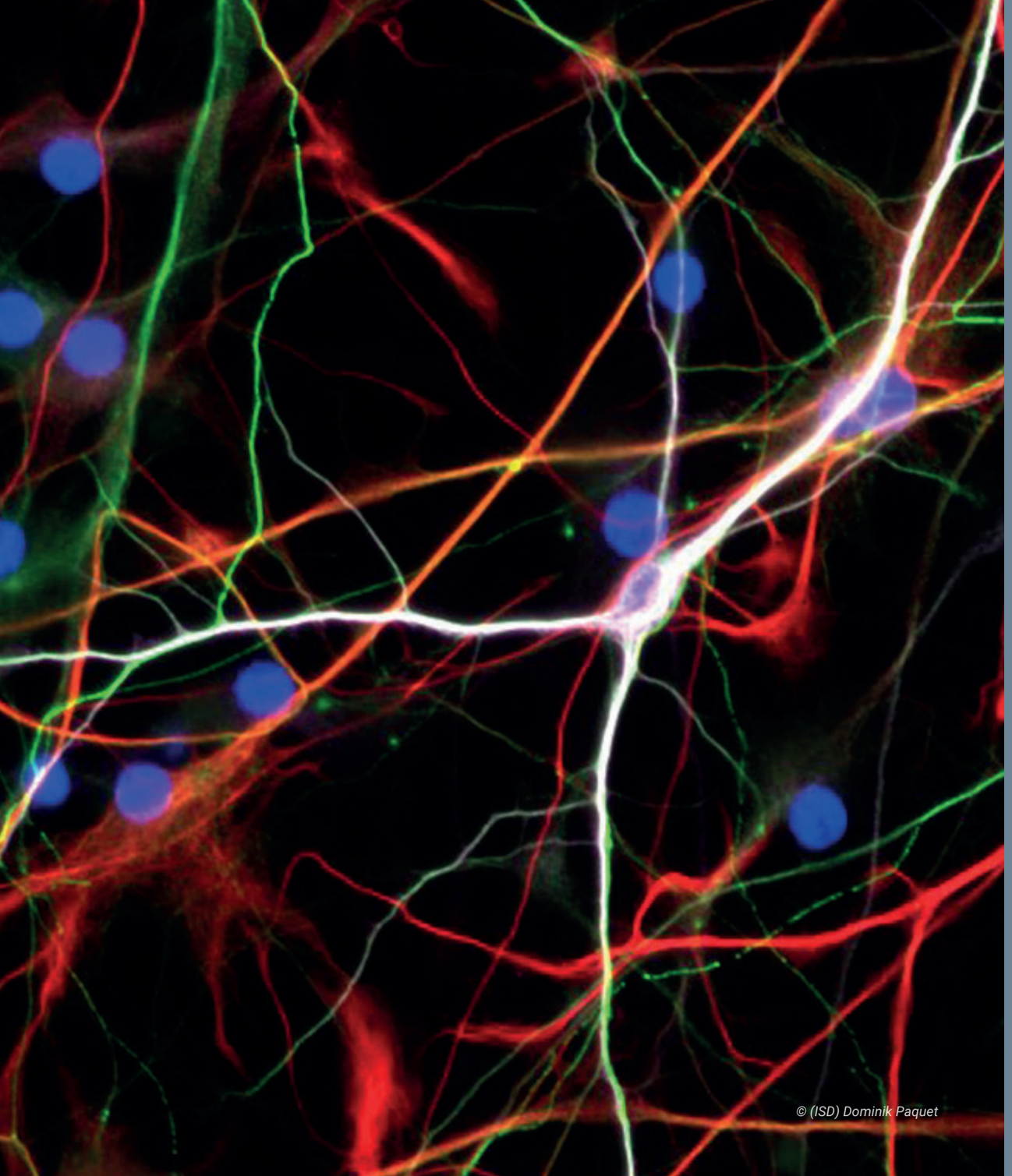
| Source | Number of projects 2020 | Funds spent 2020 |
|---|---|---|
| BMBF/DLR | 6 | 334,215 € |
| DFG | 44 | 2,250,137 € |
| EU | 7 | 508,540 € |
| Others | 26 | 639,391 € |
| LMU | 16 | 197,015 € |
| Total third party funding spent | | 3,929,298 € |

| Funding Institution | Project | Role (PI=Principal Investigator) | Period |
|---|---|---|---|
| DFG | Die MIF-Proteinfamilie bei ischämischer Herzerkrankung und Herzinsuffizienz: molekulare Mechanismen und Translationswege | J. Bernhagen (PI) | 4/2020 – 4/2023 |
| | SFB/TRR: Checkpoints of Central Nervous System Recovery | O. Gökce (PI)<br>A. Liesz (PI) | 1/2020 – 12/2023 |
| | DFG-FOR: Immunostroke - From immune cells to stroke recovery | A. Liesz (Coordinator, PI)<br>M. Dichgans (PI)<br>G. Llovera (PI) | 7/2019 – 7/2022 |
| | Clinician Scientist PRogram In Vascular MEdicine: PRIME | S. Tiedt (PI) | 4/2019 – 3/2022 |
| | SyNergy | M. Dichgans (PI)<br>J. Bernhagen (PI)<br>M. Düring (AI)<br>A. Liesz (PI)<br>D. Paquet (PI)<br>N. Plesnila (AI)<br>O. Gökce (AI)<br>A. Ertürk (AI) | 1/2019 – 6/2022 |
| | T-Zellen als Regulatoren der Mikroglia-Funktion in Schlaganfall | C. Benakis (PI) | 5/2019 – 4/2022 |
| | Role of MIF-2 in wound healing | J. Bernhagen (PI) | 5/2018 – 4/2021 |
| | Entwicklung genetsch kodierter K+ Fluoreszenzsensoren | N. Plesnila (PI) | 2/2018 – 2/2021 |
| | Indikation von Inhibitoren der pathologischen Notch3-Aggregation | C. Haffner (PI) | 11/2017 – 12/2021 |
| | Strukturelle und funktionelle Konnektivität bei der cerebralen Mikroangiopathie: Pathomechanistische Einblicke durch die Untersuchung genetischer und sporadischer Fälle | M. Düring (PI) | 4/2017 – 12/2020 |
| | X-KINGDOM-MIF - Vergleichende Analyse der Funktion von Macrophage Migration Inhibitory Factor (MIF)-Proteinen in Tier- und Pflanzenreichen | J. Bernhagen (PI) | 1/2017 – 6/2021 |
| | Molekulare Mechanismen rezessiver und dominanteer Mutationen in HTRA1 - einer Protease mit Krankheitsrelevanz bei zerebralen Mikroangiopathien | M. Dichgans (PI)<br>N. Beaufort (PI) | 1/2017 – 7/2021 |
| | Beurteilung der Neurodegeneration im gesamten Gehirm nach SHT in Mäusen auf Einzelzellebene \| TBI-map | A. Ertürk (PI) | 9/2016 – 6/2020 |
| | SFB1123: Atherosclerosis - Mechanisms and Networks of Novel Therapeutic Targets | M. Dichgans (PI)<br>Y. Asare (PI)<br>J. Bernhagen (PI) | 10/2014 – 6/2022 |

| Funding Institution | Project | Role (PI=Principal Investigator) | Period |
|---|---|---|---|
| BMBF | **iBioStroke-Identifikation und klinische Validierung von Biomarkern für den langfristigen Krankheitsverlauf nach zerebraler Ischämie** | N. Plesnila (PI) | 4/2020 – 3/2023 |
| | **Clinspect-M-Klinisches Massenspektronomiezentrum München** | M. Dichgans (PI) | 3/2020 – 2/2023 |
| | **Astrozytärer Metabolismus nach ischämischem Stress** | N. Plesnila (PI) | 12/2019 – 11/2022 |
| | **Treat-ION-Neue Therapien für neurologische Ionenkanal- und Transporterstörungen - Teilprojekt 7 Pathophysiologische Mechanismen** | N. Plesnila (PI) | 5/2019 – 4/2022 |
| | **MISST- Ebenenen-spezifische Untersuchung der synaptischen Fehlfunktion nach Schlaganfall** | N. Plesnila (PI) | 8/2018 – 8/2021 |
| | **NEURON-Verbund TRAINS: Zeitabhängige Fernwirkungen nach Schädigung des Zentral-Nervensystems** | N. Plesnila (PI) | 8/2017 – 5/2020 |
| | **DEMDAS-Intersite Project: Targeting Microvessels and the Neurovascular Unit** | M. Dichgans (Coordinator) | 1/2017 – 12/2021 |
| EU | **VasoRecovery – Immunological mechanisms of post-stroke dysfunction and recovery of neurovascular coupling** | A. Liesz (PI) | 5/2020 – 4/2022 |
| | **Neurotarget – Treatment of traumatic brain injury using dye-loaded polymeric nanoparticles** | N. Plesnila (PI) | 12/2018 – 11/2020 |
| | **RecoverInFlame – T-cell-driven inflammatory mechanisms promote recovery after acute brain injury** | A. Liesz (PI) | 11/2018 – 10/2023 |
| | **MetaBiota – Crosstalk between microbiota metabolites and immune cells, the missing link to brain damage** | A. Liesz (PI) | 5/2017 – 4/2019 |
| | **SVDs@target – Small Vessel Diseases in a mechanistic perspective: Targets for Intervention** | M. Dichgans (Coordinator) | 1/2016 – 12/2021 |
| | **CoSTREAM – Common mechanisms and pathways in Stroke and Alzheimer's disease** | M. Dichgans (PI) | 12/2015 – 5/2021 |

# Third Party Funding

| Funding Institution | Project | Role (PI=Principal Investigator) | Period |
|---|---|---|---|
| StMGP | **DigiMed Bayern P4 Medizin von Carotis Stenose und Schlaganfall** | M. Dichgans (PI) | 10/2019 – 11/2023 |
| NIH | **Genetics of Early-Onset Stroke Consortium** | M. Dichgans (PI) | 01/2018 – 12/2022 |
| DZHK | **Link between DAMPs and MIF proteins in cardio remodeling after I/R injury and relevance for heart failure** | J. Bernhagen (PI) | 1/2020 – 12/2020 |
| Emmy-Noether | **Die Rolle Hirn-sezernierter Alarmine als Mediatoren immunologischer Komorbitditäten nach Schlaganfall** | A. Liesz (PI) | 2/2019 – 1/2021 |
| Else Kröner-Fresenius-Stiftung | **Harnessing Reward Circuitry for Stroke Recovery** | O. Gökce (PI) | 5/2020 – 5/2023 |
| | **Bedeutung von Perisyten für die Störung der zerebralen Mikrozirkulation nach Subarachnoidalblutung** | N. Plesnila (PI) | 5/2014 – 7/2019 |
| Corona Stiftung | **Precision Medicine in Stroke (PREMISE): integrating deep phenotyping from 1000stroke patientes and experimental stroke models** | S. Tiedt (PI) | 7/2020 – 7/2025 |
| Hertie Stiftung | **Hertie Network of Excellence in Clinical Neuroscience** | N. Franzmeier (PI) | 1/2020 – 12/2022 |
| | **Hertie Academy 2020** | N. Franzmeier (PI) | 5/2020 – 12/2023 |
| Dr. Helmut Legerlotz-Stiftung | **Effekte von stimulierenden Umweltfaktoren auf die Immunabwehr des Gehirns bei der Alzheimer Erkrankung** | M. Ewers (PI) | 11/2020 – 12/2021 |
| BrightFocus Foundation | **An iPSC-derived human brain tissue model for Alzheimers disease** | D. Paquet (PI) | 7/2019 – 6/2022 |
| Wilhelm Vaillant Stiftung | **Elucidating the role of Tau isoform expression in human iPSC-derived Tauopathy models** | D. Paquet (PI) | 1/2019 – 12/2020 |
| NCL Stiftung | **Novel therapeutic strategies for rare diseases with endolysosomal dysfunction** | D. Paquet (PI) | 1/2019 – 12/2021 |
| Verum Stiftung | **Elucidating the role of Tau isoform expression in human iPSC-derived Tauopathy models** | D. Paquet (PI) | 11/2018 – 11/2020 |
| Fritz Thyssen Stiftung | **Molecular mechanisms causing spine loss in chronic traumatic brain injury** | A. Ertürk (PI) | 2/2017 – 2/2021 |
| Sanofi Innovation Award 2020 | **A human iPSC-derived model of Tauopathies** | D. Paquet (PI) | 10/2020 – 9/2021 |
| Minerva Stiftung | **Arches Award – Functional dissection of the Insula-reward system connectivity in control of immunity** | O. Gökce (PI) | 4/2019 – 4/2023 |




# Education

### 2020 | Faculty of Medicine

*Bartenstein P, Bürger K, Dichgans M, ...| Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (7C0233) und (7P0602)*

*Beaufort N, ... | Demenzen: Molekulare Grundlagen und pathophysiologische Konzepte (7C0019)*

*Bernhagen J, ... | Current developments in vascular biology: mechanisms and pathologies (7C0375)*

*Bernhagen J, ... | Current topics in molecular atherosclerosis research (7C4047)*

*Bernhagen J, ... | Interdisziplinäre Vorlesung: Promotionsstudium Molekulare Medizin und Systembiologische Medizin (7C0422)*

*Bernhagen J, ... | Practical Course Molecular and Cellular Cardiovascular Medicine (7C0485)*

*Bernhagen J, ... | Doktorandenkolloqium: (kardio)vaskuläre Pathologien - von den Grundlagen der vaskulären und Neurobiologie zur Pathogenese (7C0376)*

*Bürger K | Blockpraktikum Psychiatrie und Psychotherapie 1 (7M1463)*

*Bürger K, ... I Strukturelle Magnetresonanztomographie in der Demenzforschung (7C0248)*

*Bürger K, ... | Interdisziplinäre Therapie von Demenzen (7P0607)*

*Caballero M, ... | Stroke and Dementia Research - News and Views (7C0124)*

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

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

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

*Dichgans M, ... I Experimentelle Schlaganfallforschung (7C0123)*

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

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

*Dichgans M, Liesz A I Developments and trends in neuroimmunological research (7C0155)*

# Teaching

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

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

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

*Düring M, ... | Structural and Functional Connectomics in Neuroimaging (7C0170)*

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

*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)*

*Paquet D, … | Biomedical Neuroscience, Lecture, Seminar and Course - Molecular Biology (TUM)*

### 2020 | Faculty of Biology

*Dichgans M, ..., Paquet D | Molecular Neurogenetics and Experimental Stroke Research (19025)*

*Dichgans M, Malik R, Prestel M I Methods in Clinical Neuroscience (19309)*

*Liesz A, Roth S, Dichgans M I Neuroimmunological methods in experimental stroke research (19399)*

*Ewers M, ... I Structural and Functional Connectomics in Neuroimaging (19217)*

*Schneider M, Dichgans M I Experimental stroke research – Introduction to laboratory animal science (19229)*

*Paquet D, … I Special Methods in Systemic, Cellular and Molecular Neuroscience for Experts - Lecture (19188)*

*Paquet D, … I Special Methods in Systemic, Cellular and Molecular Neuroscience for Experts - Seminar (19189)*

*Paquet D, … I Special Methods in Systemic, Cellular and Molecular Neuroscience for Experts - Course (19190)*

### 2020 | Faculty of Chemistry&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)*

*Paquet D, … | Model organisms (T1YE-MN)*

### 2019 | Faculty of Medicine

*Bartenstein P, Bürger K, Dichgans M, ... | Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (7C0233) und (7P0602)*

*Beaufort N, ... | Demenzen: Molekulare Grundlagen und pathophysiologische Konzepte (7C0019)*

*Bernhagen J, ... | Current developments in vascular biology: mechanisms and pathologies (7C0375)*

*Bernhagen J, ... | Current topics in molecular atherosclerosis research (7C4047)*

*Bernhagen J, ... | Interdisziplinäre Vorlesung: Promotionsstudium Molekulare Medizin und Systembiologische Medizin (7C0422)*

*Bernhagen J, ... | Practical Course Molecular and Cellular Cardiovascular Medicine (7C0485)*

*Bernhagen J, ... | Doktorandenkolloqium: (kardio)vaskuläre Pathologien - von den Grundlagen der vaskulären und Neurobiologie zur Pathogenese (7C0376)*

*Bürger K, ... I Strukturelle Magnetresonanztomographie in der Demenzforschung (7C0248)*

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

*Bürger K | Seminar Psychiatrie und Psychotherapie 1 (7M1463)*

*Caballero M, Beaufort N, Dichgans M, Düring M, ... | Stroke and Dementia Research – News and Views (7C0124)*

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

*Caballero M, Düring M, ... | Structural and Functional Connectomics in Neuroimaging (7C0170)*

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

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

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

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

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

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

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

*Dichgans M, ... | Interdisziplinäre Behandlung des Schlaganfalls (7C0014)*

*Dichgans M, ... | Interdisziplinäre Behandlung des Schlaganfalls (7P0610)*

*Dichgans M, Paquet D | Experimental research on neurodegenerative and neurovascular disorders (7C0189)*

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

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

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

*Paquet D, … | Biomedical Neuroscience, Lecture, Seminar and Course – Molecular Biology (TUM)*

### 2019 | Faculty of Biology

*Caballero M, ... | Structural and Functional Connectomics in Neuroimaging (19321)*

*Dichgans M, ... | Molecular Neurogenetics and Experimental Stroke Research (19028)*

*Dichgans M, Liesz A, ... | Practical course - Neuroimmunological methods in experimental stroke research (19362)*

*Dichgans M, Malik R, Prestel M | Methods in Clinical Neuroscience (19309)*

*Schneider M, Dichgans M | Experimental stroke research – Introduction to laboratory animal science (19355)*

*Paquet D, … | Special Methods in Systemic, Cellular and Molecular Neuroscience for Experts - Lecture (19310)*

*Paquet D, … | Special Methods in Systemic, Cellular and Molecular Neuroscience for Experts - Seminar (19311)*

*Paquet D, … | Special Methods in Systemic, Cellular and Molecular Neuroscience for Experts - Course (19312)*

### 2019 | Faculty of Chemistry&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)*

*Paquet D, … | Model organisms (T1YE-MN)*

# Education

Participation in Graduate Schools:

**Graduate School of Systemic Neurosciences (GSN)**
Under the umbrella of the Munich Center of Neurosciences – Brain & Mind (MCN), the GSN coordinates high-quality and integrated master and doctoral research programs in the neurosciences. ISD staff actively participates in this ambitious program. The program offers: 1) structured, student-centered training in English; 2) comprehensive state of-the-art training within the exceptionally broad scope of neuroscience topics and technologies in Munich; 3) ECTS-based grading; 4) personal career planning and coaching for scientific and related careers; 5) lab rotations within the MCN/GSN, with collaborating institutions at LMU, TUM, the Max-Planck-Institutes, the Helmholtz Center Munich, and their international partners; and 6) an international network for careers in academia and RTD projects (see www.mcn.lmu.de). Martin Dichgans and Judit Gonzalez-Gallego (PhD student) are on the scientific board of the GSN.

**MMRS and IRTG1123**
The Munich Medical Research School (MMRS) is an umbrella organization at LMU that coordinates doctoral degrees at LMU Medical School. IRTG1123 is the Integrated graduate program of the CRC 1123 “Atherosclerosis” and offers a dedicated PhD program for doctoral researchers in athero-sclerosis and cardiovascular medicine. IRTG1123 students obtain a doctoral degree according to the umbrella guidelines of MMRS. Depending on the student’s/supervisor’s academic background, the following doctoral degrees can be obtained: PhD in Medical Research with international compatibility; the German Dr. rer. nat.; the Dr. hum. biol. (Human Biology); and the Dr. med. (Human Medicine). Doctoral researchers enrolled in IRTG1123 typically undergo a 3-year structured PhD program, allowing the students to collect necessary ECTS points and engage in cutting-edge atherosclerosis research. MD thesis students can join the program for the duration of their protected research time. The structured program encompasses: 1) Basic science seminars focusing on atherosclerosis, inflammation, and immunology; 2) Advanced methods courses with an emphasis on in vivo animal models and state-of-the-art imaging; 3) Soft skill seminars on communication, presentation and topics relevant for an academic and non-academia science career; 4) Scientific education provided by lecture series (by renowned national¬/international speakers), annual retreats, workshops and summer schools. Every PhD student is assigned a thesis advisory committee, which supervises the work, its feasibility and milestones and advises the student regarding career planning.
ISD staff participates in IRTG1123 with currently 6 PhD/MD students in training; J. Milic (PhD student at ISD) is the Student Spokesperson of IRTG1123.

**MMRS / FöFoLe-MD doctoral studies in Molecular and Clinical-Translational Medicine**
The FöFoLe-MD doctoral study program in Molecular and Clinical-Translational Medicine aims at a comprehensive and structured training of MD students in medical research. The program was installed at LMU Medical School in 2011 and fosters the research training of the most talented and motivated 40 MD students of LMU as part of a structured 18 months doctoral thesis program, in which the MD students spend full-time in the lab in a dedicated manner protected from curricular duties, and accompanied by a tailored theoretical training program. In a competitive procedure, professors and PIs of the Medical School propose MD thesis projects and the best students are matched with suitable labs and projects. The program is funded by both an 18-month fellowship for the MD students and a bench fee for the thesis project and conference participation.
Several ISD labs have successfully competed in this program and hosted a total of 10 FöFoLe MD thesis students in 2019-2020.

**Clinician Scientist Program PRIME**
Starting in 2019, the DFG-funded clinician scientist PRrogram In vascular MEdicine (PRIME; coordinator: S. Massberg) promotes clinical and scientific careers of clinician scientists with a vascular research focus. PRIME is integrated into the interdisciplinary Munich Clinician Scientist Program (MCSP) framework to pursue the following aims: 1) establish an institutionalized vascular clinician scientist program for talented early career researchers as a track integrated into the respective resident programs; 2) provide flexible models of protected research time adapted to the specific needs of clinical training within the participating disciplines, while minimizing delay in board certification; 3) provide a scientific qualification program that addresses the needs of clinician scientists with a vascular focus; 4) connect this with an advanced scientist program to establish a sustained pipeline for independency of highly qualified early career researchers; and 5) expand the mentoring/role model program to the needs of PRIME to enhance visibility and appeal of the program. PRIME convenes groups of disciplines with a vascular focus. Specific measures are implemented to grant equal opportunity of clinician scientists. Independent experts on governance and performance management in academic research institutions evaluate PRIME and provide applicants and PIs with feedback. The ISD has a coordinating role in the PRIME Neurovascular Medicine Cluster.

**Hertie Academy of Clinical Neuroscience**
The Hertie Academy of Clinical Neuroscience enrolls highly talented young medical and clinician scientist from five German universities that form the Hertie Network of Excellence in Clinical Neuroscience. All fellows undergo a mentored 3-year structured training program, that is intended to provide the fellows with key leadership skills required for an independent scientific career path.

# PhD and MD Theses

**PhD Theses**

**Advanced diffusion models in cerebral small vessel disease.** M. Konieczny, PhD (MMRS), submitted Oct 2020

**Influence of the circadian rhythm on infarct volume and the metabolic response after experimental stroke.** V. G. Burbano, PhD (GSN), started Mar 2020

**Temporal profile and determinants of the systemic catabolic response in the acute phase of ischemic stroke.** E. H. Stanton, PhD (GSN), started Mar 2020

**Neuroprotection by sex hormones.** K. Umeasalugo, PhD, started Jan 2020

**The role of common genetic variants in stroke and cardiovascular disease.** S. Frerich, PhD, started July 2020

**Predicting the effects of progressive grey matter atrophy in tauopathies.** L. Zheng, PhD, started Jan 2020

**Investigating genomic damage during brain aging via single cell genomic technologies.** K. Gehring, Master & PhD, started Sep 2020

**Metabolic signaling in neurons.** B.Groschup, PhD, started Jan 2019

**Investigating molecular signatures of brain aging via single cell genomic technologies.** T. Kaya, PhD (GSN), started Sep 2019

**Investigating the physiological and pathological role of Col4A1 in human iPSCs-derived neurovascular unit model.** J. Kroeger, PhD (GSN), started Jan 2019

**A human 3D brain tissue models for Alzheimer's disease.** C. Cardoso Goncalves, PhD (GSN), started Oct 2019

**Modulating and comparing activation states of GRN- and TREM2-mutant human iPSC-derived microglia.** S. Robinson, PhD (GSN), started Jan 2019

**Symptom-network mapping of tau pathology in Alzheimer's disease.** Y. Luan, PhD, started Jan 2019

**Novel MIF and D-DT proteins in atherosclerosis.** B. Yang, PhD (IRTG1123), started Oct 2019

**Digital biomarkers of cerebral small vessel disease.** A. Dewenter, PhD (GSN), started Oct 2019

**MIF-2/D-DT in atherosclerosis and stroke.** C. Zan, Dr. med., started Sep 2018

**Peptide-based inhibition strategies to block chemokine pathways in cardio-vascular disease.** Y. Gao, PhD (MMRS), started Apr 2019

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

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

**Post-stroke sterile inflammation in atherosclerotic plaque rupture and secondary infarctions.** J. Cao, PhD, started Sep 2018

**Investigating protein aggregation role in vasc. dementia and neuro-degeneration via genomics.** H. Ji, PhD (MMRS), started Sep 2018

**Investigating MIF-family nuclease functions.** B. Bulut, PhD (MMRS), started May 2018

**Investigating MIF-family role in vascular dementia and neuro-degeneration via genomics**. L. Lui, PhD (MMRS), started June 2018

**Effects of Amyloid and Tau pathology on brain function and cognition in AD.** A. Rubinski, Dr. hum. biol, started Jan 2018

**Fate of pericytes after ischemic stroke.** J. Shrouder, PhD, started Jan 2018

**Vascular inflammation after ischemic stroke.** R. Sienel, Dr. rer. nat., started Apr 2018

**Human iPSC-derived brain tissue models for Alzheimer's disease**. J. Klimmt, PhD (GSN), started Apr 2017

**Detection of Deleterious On-Target Effects after HDR-Mediated CRISPR Editing.** I. Weisheit, PhD (GSN), started Apr 2017

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

**Role of the COP9 signalosome in neuroinflammation and ischemic stroke.** Y. Tian, PhD (MMRS), started Oct 2017

**Role of the COP9 signalosome in atherosclerosis.** J. Milic, PhD (IRTG1123), started May 2017

**Investigating the nervous and immune system at the single cell resolution.** S. Besson-Girard, PhD (GSN), started Jan 2017

**MIF proteins in atherogenesis: structure-activity relationship studies and novel cellular routes.** C. Krammer, Dr. rer. nat. (IRTG1123), started Mar 2017

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

**Interactions between MIF-family proteins and the classical chemokine ligand/receptor network.** M. Brandhofer, Dr. rer. nat., started in Apr 2016

**Medical Theses**

**CSD propagation in FHM3 mice after ischemic stroke.** S. Saicic, Dr. med. submitted Nov 2020

**Bedeutung der Topographie bei subkortikalen Hirninfarkten**. M. Achmüller, Dr. med., submitted 2020

**Protein composition distinguishes cardioembolic and large-artery atherosclerotic thrombi.** T. Wölfer, Dr. med., started Nov 2020

**Utilization of routine laboratory results to determine the prevalence of systemic complications and to predict thrombectomy success, interventional complications, and functional outcome after thrombectomy.** M. Karg, Dr. med., started Oct 2020

**Investigating the role of CD74 in CD4+ T-cell regulation.** I. Woltering, Dr. med., May 2020

**Elucidation of the molecular mechanisms of atypical chemokines in acute and chronic inflammation.** E. Siminkovitch, Dr. med., started Feb 2020

**NO-signaling after SAH**, C. Corvin, Dr. med. (FöFoLe), started Aug 2020

**In-vitro aggregation studies of the CADASIL-relevant Notch3 protein.** G. Wagenstetter, Dr. med., started Jul 2019

**The role of system segregation and hub connectivity in cognitive resilience.** L. Frontzkowski, Dr. med., started Apr 2019

**Characterization of novel NEDDylation inhibitors in models of atherogenic inflammation.** E. Preuner, Dr. med., started Sep 2019

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

**Mechanism and functional consequences of chemokine/cytokine oxidation by neutrophils.** L. Zwißler, Dr. med. (IRTG1123), started Mar 2018

**Link between MIF and aging in atherosclerosis.** S. Reichl, Dr. med., (FöFoLe), started in Mar 2018

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

**Assessment of neuro-vascular coupling in vivo.** Z. Fan, Dr. med., started Jan 2018

**Iron-induced necroptotic signaling.** A. When, Dr. med. (FöFoLe), started Oct 2018

**Analysis of a novel CARASIL mouse model.** A. Gerhard, Dr. med., started Jan

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

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

**Completed**

**MIF proteins and their role in mediating neutrophil activity and survival.** L. Schindler, Dr. rer. nat., completed Dec 2020

**Systematic Analysis of Whole Mouse Brain Vasculature and Intact Human Organs Using Machine Learning**. M. Todorov, PhD, completed Dec 2020

**Holistic Three-dimensional Cellular Mapping of Mammalian Organs by Tissue Clearing Technologies**. S Zhao, Ph.D, completed Dec 2020

**The role of MIF proteins in ischemic stroke.** S. Wang, Dr. med., completed Dec 2020

**Diaschisis after ischemic stroke.** S. Valero-Freitag, PhD (GSN), completed Oct 2020

**Quantitative measurement of blood-brain barrier leakage.** Y. Hu, Dr. hum. biol., completed Oct 2020

**Functional characterization of the conserved cis-regulatory element at the HDAC9 locus – a major risk locus for atherosclerosis.** G. Yan, Dr. rer. nat., completed Jun 2020

**Proteomic approach to study molecular pathomechanisms in hereditary small vessels disease.** A. Zellner, Dr. rer. nat., completed Jun 2020

**Using Genetics to Explore Novel Risk Factors and Drug Targets for Cerebrovascular Disease.** M. Georgakis, PhD, completed Apr 2020

**ASIC1a channels after acute brain injury**. S. Cheng, Dr. med., completed May 2020

**GPX4 after cerebral ischemia**. I. Rynarzewska, Dr. med., completed Feb 2020

**GPX4 after SAH.** K. Ponnath, Dr. med., completed Jan 2020

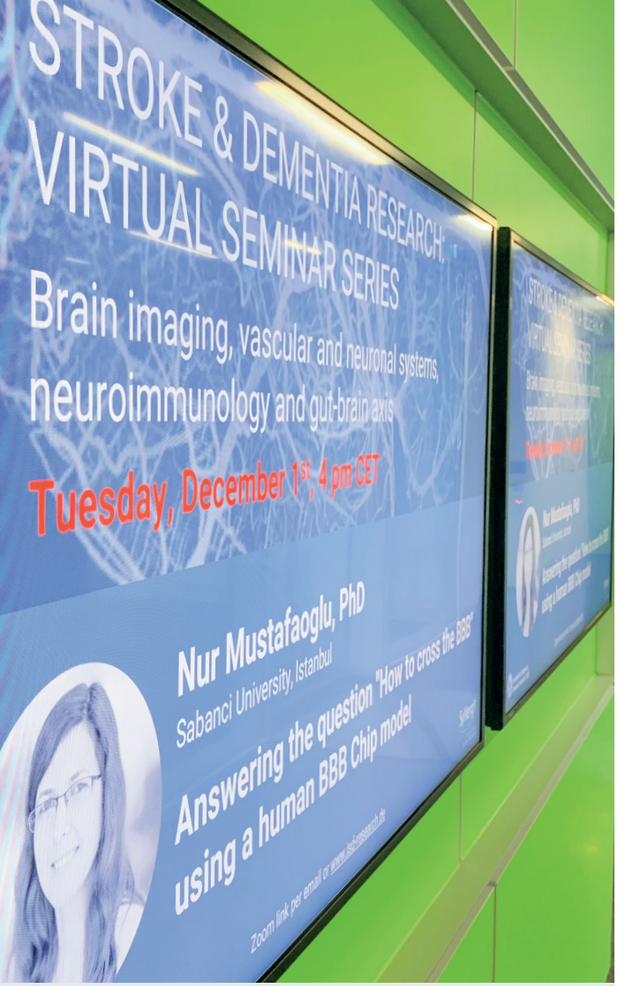
**eNOS after SAH.** I. Westermayer, Dr med., completed Feb 2020

**Neuroimaging markers for Alzheimer´s disease and cerebral small vessel disease.** S. Finsterwalder, PhD (GSN), graduated July 2020

**Wide-field calzium-imaging of neuronal activity for post-stroke connectivity.** J. Cramer, Dr. med., completed September 2019

**The lateral frontal cortex as a substrate of cognitive reserve**. J. Hartmann, MD, completed Aug 2019

**Microbiota-derived metabolites in modulating post-stroke recovery.** R. Sadler, PhD, completed Oct 2019




# Conferences, Trainings and Events

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

***ANIM 2019**, Arbeitstagung NeuroIntensiv Medizin*
*Berlin, Jan 2019 | M. Dichgans: speaker and scientific chair*

***ERA-NET NEURON***
*Riga, Latvia, May 2019 | M. Dichgans: scientific chair*

***ESOC, European Stroke Organisation Conference***
*Milan, Italy, May 2019 | M. Dichgans: scientific chair*

***92th DGN Congress,** Bayer Symposium*
*Stuttgart, Sep 2019, | M. Dichgans: speaker and scientific chair*

***International Stroke Genetics Consortium***
*St. Louis, Missouri, USA, Oct 2019 | M. Dichgans: scientific chair*

***Arbeitskreis Neurologie,** Sponsoring by Bayer Vital*
*Frankfurt, Nov 2019 | M. Dichgans: scientific chair*

***European Stroke Science Workshop***
*Garmisch, Dec 2019 | M. Dichgans: scientific chair*

***Heart & Brain Workshop***
*Düsseldorf, Sep 2020 | M. Dichgans: speaker and scientific chair*

***93th DGN Congress***
*Berlin, Nov 2020 | M. Dichgans: speaker and scientific chair*

***ESO-WSO Conference***
*Vienna, Austria, Nov 2020 | M. Dichgans: scientific chair*

***LMU Center for Advanced Studies***
*Research Focus Symposium Gut-Brain Axis,*
*Munich, Jun 2019 | A Liesz: organizer*

***ISCBFM Brain Meeting***
*Yokohama, Jul 2019 | A Liesz: scientific chair and speaker*

***SfN Neuroscience Meeting***
*Chicago, Oct 2019 | A. Liesz: scientific chair*

***SoCalSymposium on GLia-Nuron interactions***
*Riverside, USA, Jan 2020 | A Liesz: keynote speaker*

***Internation Stroke-Immunology Conference***
*Munich, Apr 2020 – postponed | A. Liesz: organizer*

***6th International Symposium Frontiers Cardiovascular Research***
*Stellenbosch, Apr 2019 | J. Bernhagen: speaker and scientific chair of the LMU/Singapore session*

***3rd Symposium on Platelets***
*Tübingen, Oct 2019 | J. Bernhagen: scientific chair in the Immunodefense session*

***9th Cardiac Regeneration and Vascular Biology conference***
*San Servolo, Jun 2020; moved to Jun 2021 |*
*J. Bernhagen: organizer, speaker and scientific chair*

***10th International MIF Symposium***
*Shanghai, Oct 2020 | J. Bernhagen: organizer, speaker and scientific chair*

***45. Annual Meeting of the Section ICP, CBF, and Hydrocephalus of the German Society of Neurosurgery***
*Mainz, Germany, 2019 | N. Plesnila: chair of the session "Intracranial pressure"*

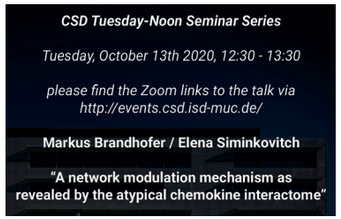
***International Subarachnoid Hemorrhage Conference***
*Amsterdam, The Netherlands, 2019 | N. Plesnila: chair of the session "Experimental SAH", 2019*

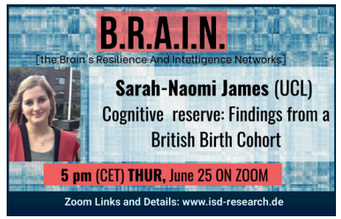
***AAIC 2019**, The Alzheimer's Association International Conference, Los Angeles, USA, Jul 2019 I M. Ewers: scientific chair*

***Cognitive Reserve Symposium 2019***
*Amsterdam, The Netherlands, Sep 2019 | M. Ewers: key note speaker*

***AAIC 2020,** The Alzheimer's Association International Conference Jul 2020 (Virtual Conference) I M. Ewers: scientific chair*




**External Speakers in ISD Live and virtual Talks** (Selection)

***Kaitlin Casaletto, PhD,** Assistant Professor, Weill Institute for Neurosciences, Memory and Aging Center, UCSF*

***Rachel Buckley, PhD,** Instructor in Neurology, Institution Massachusetts General Hospital*

***Tom Van Agtmael, PhD,** Ass. Professor, Institute of Cardiovascular and Medical Sciences, University of Glasgow*

***Prof. William Kremen**, Professor of Psychiatry, University of California San Diego*

***Susanne van Veluw, PhD,** Assistant Professor Harvard Medical School and Massachusetts General Hospital*

***Dr. Sarah-Naomi James**, University College London, UCL, Department of Primary Care and Population Health (PCPH)*

***Michael Belloy, PhD,** Postdoctoral Research Fellow, Neurology and Neurological Science, Stanford University, CA, USA*

***Tatjana Kleele, PhD,** Lab.of Experimental Biophysics Ecole, Polytechnique Federale de Lausanne (EPFL), Switzerland*

***Mattea Finelli, DPhil,** Department of Physiology, Anatomy and Genetics, University of Oxford, UK*

***Prof. Dr. Stefan Rose-John**, Institute of Biochemistry, Christian-Albrechts-Universität zu Kiel*

***Clement Cochain, PhD,** Deutsches Zentrum für Herzinsuffizienz Würzburg, Universitätsklinikum Würzburg*

***PD Dr. med. Joji B. Kuramatsu,** Oberarzt der Intensivstation, Neurologische Klinik, Universitätsklinikum Erlangen*

***Prof. Dr. Michael Ehrmann,** ZMB (Zentrum für Medizinische Biotechnologie), Universität Duisburg-Essen*

***Prof. Dr. med. Andreas Meisel,** Berlin, Klinik für Neurologie, Charité*

***Prof. Dr. Birgit Liss,** Institute of Applied Physiology, University of Ulm*

***Prof. Elizabeth M. C. Hillman**, Professor of Biomedical Engineering,Departments of Biomedical Engineering and Radiology, Columbia University, New York, USA*

***Dr. Jing Yang,** McGovern Institute for Brain Research, Center for Life Sciences, School of Life Sciences, Peking University, China*

***Prof. Dr. William A. Boisvert,** John A. Burns School of Medicine, University of Hawaii, USA*


| 2019 | |
|---|---|
| Number of publications | 71 |
| Impact factor: total / average | 860.1 / 12.3 |
| Number of publications with first and / or senior authorships | 30 |
| Impact factor: total / average | 420.2 / 14.0 |

| 2020 | |
|---|---|
| Number of publications | 110 |
| Impact factor: total / average | 979.9 / 9.4 |
| Number of publications with first and / or senior authorships | 54 |
| Impact factor: total / average | 479.7 / 9.6 |

# Publications


**2020**

Biechele G, Wind K, Blume T, Sacher C, Beyer L, Eckenweber F, Franzmeier N, Ewers M, Zott B, Lindner S, Gildehaus FJ, von Ungern-Sternberg B, Tahirovic S, Willem M, Bartenstein P, Cumming P, Rominger A, Herms J, Brendel M. *Microglial Activation in the Right Amygdala-Entorhinal-Hippocampal Complex is Associated with Preserved Spatial Learning in AppNL-G-F mice.* **Neuroimage**. 2020 Dec 29:117707.

Beyer L, Meyer-Wilmes J, Schönecker S, Schnabel J, Sauerbeck J, Scheifele M, Prix C, Unterrainer M, Catak C, Pogarell O, Palleis C, Perneczky R, Danek A, Buerger K, Bartenstein P, Levin J, Rominger A, Ewers M, Brendel M. *Cognitive reserve hypothesis in frontotemporal dementia: A FDG-PET study.* **Neuroimage Clin.** 2020 Dec 16;29:102535.

Küpper C, Feil K, Wollenweber FA, Tiedt S, Herzberg M, Dorn F, Liebig T, Dieterich M, Kellert L; GSR investigators. *Endovascular stroke treatment in orally anticoagulated patients: an analysis from the German Stroke Registry-Endovascular Treatment*. **J Neurol.** 2020 Dec 29. Epub ahead of print.

Lu Y, Wang Z, Georgakis MK, Lin H, Zheng L. *Genetic Liability to Depression and Risk of Coronary Artery Disease, Myocardial Infarction, and Other Cardiovascular Outcomes*. **J Am Heart Assoc**. 2020 Dec 29:e017986. Epub ahead of print.

Maners J, Gill D, Pankratz N, Laffan MA, Wolberg AS, de Maat MPM, Ligthart S, Tang W, Ward-Caviness CK, Fornage M, Debette S, Dichgans M, McKnight B, Boerwinkle E; CHARGE Inflammation Working Group; INVENT Consortium; MEGASTROKE consortium of the International Stroke Genetics Consortium (ISGC), Smith NL, Morrison AC, Dehghan A, de Vries PS. *A Mendelian randomization of γ' and total fibrinogen levels in relation to venous thromboembolism and ischemic stroke.* **Blood.** 2020 Dec 24;136(26):3062-3069.

Boltze J, Didwischus N, Merrow M, Dallmann R, Plesnila N. *Circadian effects on stroke outcome - Did we not wake up in time for neuroprotection?* **J Cereb Blood Flow Metab**. 2020 Dec 18:271678X20978711. Epub ahead of print.

Feil K, Küpper C, Tiedt S, Dimitriadis K, Herzberg M, Dorn F, Liebig T, Dieterich M, Kellert L; GSR investigators. *Safety and efficacy of mechanical thrombectomy in infective endocarditis: a matched case-control analysis from the German Stroke Registry-Endovascular Treatment (GSR-ET).* **Eur J Neurol.** 2020 Dec 16. Epub ahead of print.

Biechele G, Franzmeier N, Blume T, Ewers M, Luque JM, Eckenweber F, Sacher C, Beyer L, Ruch-Rubinstein F, Lindner S, Gildehaus FJ, von Ungern-Sternberg B, Cumming P, Bartenstein P, Rominger A, Höglinger GU, Herms J, Brendel M. *Glial activation is moderated by sex in response to amyloidosis but not to tau pathology in mouse models of neurodegenerative diseases.* **J Neuroinflammation.** 2020 Dec 14;17(1):374.

Lenz IJ, Plesnila N, Terpolilli NA. *Role of endothelial nitric oxide synthase for early brain injury after subarachnoid hemorrhage in mice.* **J Cereb Blood Flow Metab.** 2020 Nov 30:271678X20973787. Epub ahead of print.

Tiedt S, Bode FJ, Uphaus T, Alegiani A, Gröschel K, Petzold GC; GSR-ET investigators. *Impact of the COVID-19-pandemic on thrombectomy services in Germany.* **Neurol Res Pract.** 2020 Nov 23;2:44.

Franzmeier N, Dewenter A, Frontzkowski L, Dichgans M, Rubinski A, Neitzel J, Smith R, Strandberg O, Ossenkoppele R, Buerger K, Duering M, Hansson O, Ewers M. *Patient-centered connectivity-based prediction of tau pathology spread in Alzheimer's disease.* **Sci Adv.** 2020 Nov 27;6(48):eabd1327.

Kontos C, El Bounkari O, Krammer C, Sinitski D, Hille K, Zan C, Yan G, Wang S, Gao Y, Brandhofer M, Megens RTA, Hoffmann A, Pauli J, Asare Y, Gerra S, Bourilhon P, Leng L, Eckstein HH, Kempf WE, Pelisek J, Gokce O, Maegdefessel L, Bucala R, Dichgans M, Weber C, Kapurniotu A, Bernhagen J. *Designed CXCR4 mimic acts as a soluble chemokine receptor that blocks atherogenic inflammation by agonist-specific targeting.* **Nat Commun.** 2020 Nov 25;11(1):5981. doi: 10.1038/s41467-020-19764-z.

Delgado Jiménez R, Benakis C. *The Gut Ecosystem: A Critical Player in Stroke.* **Neuromolecular Med.** 2020 Nov 18.

Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, van der Meer F, Kallio K, Kaya T, Anastasina M, Smura T, Levanov L, Szirovicza L, Tobi A, Kallio-Kokko H, Österlund P, Joensuu M, Meunier FA, Butcher SJ, Winkler MS, Mollenhauer B, Helenius A, Gokce O, Teesalu T, Hepojoki J, Vapalahti O, Stadelmann C, Balistreri G, Simons M. *Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity.* **Science**. 2020 Nov 13;370(6518):856-860.

Bartrés-Faz D, Arenaza-Urquijo E, Ewers M, Belleville S, Chételat G, Franzmeier N, Gonneaud J, de Echevarri JMG, Okonkwo O, Schultz S, Valenzuela M, Stern Y, Vemuri P. *Theoretical frameworks and approaches used within the Reserve, Resilience and Protective Factors professional interest area of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment.* **Alzheimers Dement (Amst).** 2020 Nov 11;12(1):e12115.

Bakker MK,..., Malik R, Dichgans M, ..., Ruigrok YM.*Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors.* **Nat Genet.** 2020 Dec;52(12):1303-1313. Erratum in: Nat Genet. 2020 Dec 22

Ramírez-Fernández A, Urbina-Treviño L, Conte G, Alves M, Rissiek B, Durner A, Scalbert N, Zhang J, Magnus T, Koch-Nolte F, Plesnila N, Deussing JM, Engel T, Kopp R, Nicke A. *Deviant reporter expression and P2X4 passenger gene overexpression in the soluble EGFP BAC transgenic P2X7 reporter mouse model.* **Sci Rep.** 2020 Nov 16;10(1):19876.

Konieczny MJ, Dewenter A, Telgte AT, Gesierich B, Wiegertjes K, Finsterwalder S, Kopczak A, Hübner M, Malik R, Tuladhar AM, Marques JP, Norris DG, Koch A, Dietrich O, Ewers M, Schmidt R, de Leeuw FE, Duering M. *Multi-shell diffusion MRI models for white matter characterization in cerebral small vessel disease.* **Neurology.** 2020 Nov 16:10.1212/WNL.0000000000011213. Epub ahead of print.

Roth S, Yang J, Cramer JV, Malik R, Liesz A. *Detection of cytokine-induced sickness behavior after ischemic stroke by an optimized behavioral assessment battery.* **Brain Behav Immun.** 2020 Nov 14:S0889-1591(20)32392-8.

Kopczak A, Schindler A, Bayer-Karpinska A, Koch ML, Sepp D, Zeller J, Strecker C, Hempel JM, Yuan C, Malik R, Wollenweber FA, Boeckh-Behrens T, Cyran CC, Helck A, Harloff A, Ziemann U, Poli S, Poppert H, Saam T$^{\$}$, Dichgans M$* (*corresponding author; $^{\$}$equally contributing). *Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke.* **J Am Coll Cardiol.** 2020 Nov 10;76(19):2212-2222.

Georgakis MK, de Lemos JA, Ayers C, Wang B, Björkbacka H, Pana TA, Thorand B, Sun C, Fani L, Malik R, Dupuis J, Engström G, Orho-Melander M, Melander O, Boekholdt SM, Zierer A, Elhadad MA, Koenig W, Herder C, Hoogeveen RC, Kavousi M, Ballantyne CM, Peters A, Myint PK, Nilsson J, Benjamin EJ, Dichgans M. *Association of Circulating Monocyte Chemoattractant Protein-1 Levels With Cardiovascular Mortality: A Meta-analysis of Population-Based Studies.* **JAMA Cardiol.** 2020 Nov 4.

Schoppe O, Pan C, Coronel J, Mai H, Rong Z, Todorov MI, Müskes A, Navarro F, Li H, Ertürk A, Menze BH. *Deep learning-enabled multi-organ segmentation in whole-body mouse scans.* **Nat Commun**. 2020 Nov 6;11(1):5626. doi: 10.1038/s41467-020-19449-7

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Taş K, Sinitski D, Brandhofer M, Megens RTA, Weber C, Schultz JR, Bernhagen J, Kapurniotu A. *A MIF-Derived Cyclopeptide that Inhibits MIF Binding and Atherogenic Signaling via the Chemokine Receptor CXCR2.* **Chembiochem.** 2020 Oct 30.

Kappelmann N, Arloth J, Georgakis MK, Czamara D, Rost N, Ligthart S, Khandaker GM, Binder EB. *Dissecting the Association Between Inflammation, Metabolic Dysregulation, and Specific Depressive Symptoms: A Genetic Correlation and 2-Sample Mendelian Randomization Study.* **JAMA Psychiatry.** 2020 Oct 20:e203436.

Rubinski A, Franzmeier N, Neitzel J, Ewers M; Alzheimer's Disease Neuroimaging Initiative (ADNI). *FDG-PET hypermetabolism is associated with higher tau-PET in mild cognitive impairment at low amyloid-PET levels.* **Alzheimers Res Ther.** 2020 Oct 19;12(1):133.

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Ewers M, Ioannidis JPA, Plesnila N. *Access to data from clinical trials in the COVID-19 crisis: open, flexible, and time-sensitive.* **J Clin Epidemiol.** 2020 Oct 14:S0895-4356(20)31147-1.

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Franzmeier N, Suárez-Calvet M, Frontzkowski L, Moore A, Hohman TJ, Morenas-Rodriguez E, Nuscher B, Shaw L, Trojanowski JQ, Dichgans M, Kleinberger G, Haass C, Ewers M; Alzheimer's Disease Neuroimaging Initiative (ADNI). *Higher CSF sTREM2 attenuates ApoE4-related risk for cognitive decline and neurodegeneration.* **Mol Neurodegener.** 2020 Oct 8;15(1):57.

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## Honors & Awards (Selection)

C. Benakis | ImmunoStroke consortium award (DFG)

C. Benakis | SyNergy independent project award

C. Benakis | SyNergy travel grant 2019 International Stroke Conference 2019 Feb 6-8, Honolulu

D. Bühler | Fuchs-Preis 2019

M. Dichgans | Presidency, European Stroke Organisation (ESO)

N. Franzmeier | Alzheimer's Association – Conference travel fellowship

N. Franzmeier | Alzheimer Forschung Initiative – Travel fellowship

N. Franzmeier | German Academic Exchange Service – Travel fellowship

N. Franzmeier | LMU Excellence Travel Award

N. Franzmeier | Human Amyloid Imaging – Travel fellowship

N. Franzmeier | Tau2020 – Conference travel fellowship

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

O. Gokce | ARCHES award, Minerva Stiftung 2020-2023

O. Gokce | Chan Zuckerberg Neurodegeneration challenge award | The Chan Zuckerberg Initiative 2020-2022

K. Kamm | Wolffram Prize 2020

J. Milic | Gotthard Schettler Young Investigator Award at the Vascular Medicine and Atherosclerosis Conference (VMAC) 2020

D. Paquet | Sanofi iAward 2020

K. Salbaum | German Society for Biochemistry and Molecular Biology Best Master Thesis Award

R. Sienel | Synergy Travel Grant 2019 and 2020

N. Terpolilli | Chair of the Neurotrauma Section, German Society for Neurosurgery

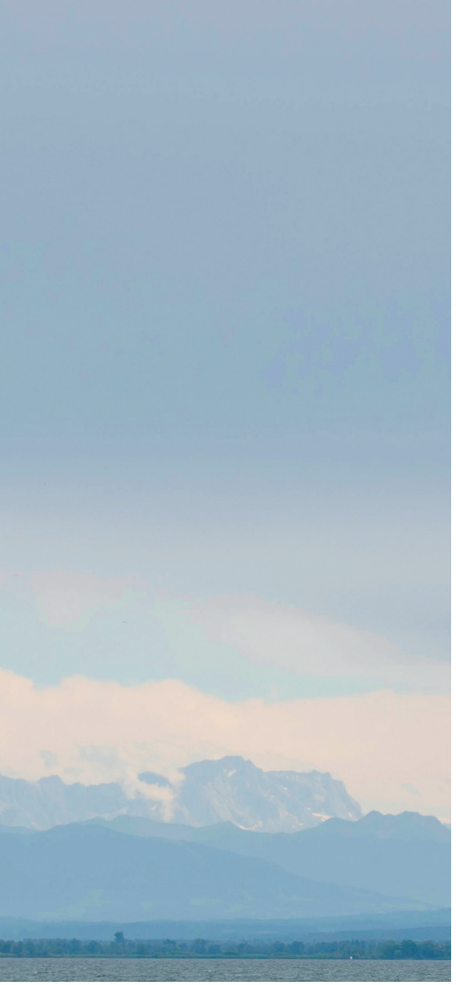
N. Terpolilli | Executive member of the Neurotrauma Committee, European Association of Neurosurgical Societies

S. Tiedt | 2019 Mentor of the Year (Medical faculty, LMU)

A. Wehn | Synergy Travel Grant 2019

S. Valero-Freitag | BRAIN & BRAIN PET Young Investigators Travel Award 2019

L. Schindler | German Academic Exchange Service, 1 year travel fellowhsip



*Altmann, Regina*
*Androvic, Peter, Dr.*
*Ametsbichler, Sonja*
*Aronova, Arailym, MSc*
*Asare, Yaw, Dr. rer. nat.*
*Aydin, Yasemin*
*Bahr, Jonas*
*Bay, Berkant*
*Beaufort, Nathalie, Dr. rer. nat.*
*Beer, Alexander*
*Benakis, Corinne, Dr. rer. nat.*
*Bernhagen, Jürgen, Prof. Dr.*
*Besson-Girard, Simon, MSc*
*Biel, Davina, Dr. rer. nat.*
*Biller, Janina*
*Boldoczki, Fanni, MSc*
*Bolini, Verena*
*Bose, Tanima, PhD*
*Bourilhon, Priscila*
*Brandhofer, Markus, MSc*
*Brauneis, Christine*
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*Bugar, Elina*
*Bulut, Buket, MSc*
*Bürger, Katharina, PD Dr. med.*
*Calandra, Gian Marco, MSc*
*Campbell-James, Thomas*
*Cao, Jiayu*
*Cara, Ardela*
*Cardoso Goncalves, Carolina, MSc*
*Coloma Andrews, Lisa, Dr. phil.*
*Corvin, Christian*
*Crusius, Dennis*
*D´Andrade, Esther*
*Dannert, Angelika, MSc*
*Delgado Jiménez, Rosa, M. Biom. Res.*
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