Annual Report
2021/2022

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

About the ISD

Funding

Outpatient Clinic

Education

Research

Miscellaneous

Foreword

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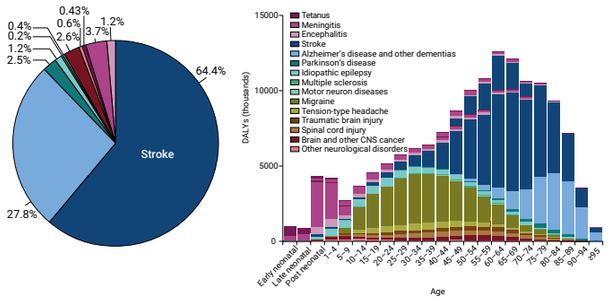
The Institute for Stroke and Dementia Research

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 (Source: Feigin, ..., Dichgans et al. Lancet Neurol 2019)

Stroke remains the leading cause of permanent disability and the second leading cause of death worldwide (Global Burden of Disease Study 2019). 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).

ISD investigators are listed among the most Highly Cited Researchers world-wide (Clarivate statistics, 2022). Once more, scientists from the ISD received prestigious research awards, including an Emmy Noether Award from the DFG (to Marios Georgakis), a Chan Zuckerberg Initiative (CZI) award (to Ozgun Gokce and Mikael Simons), the Leon Senior Scientist Prize (to Michael Ewers), and several Young Investigator awards. Ali Ertürk was appointed W3 professor for 'Systems Biology and Technology Transfer' (LMU). Mika Simons, who holds a W3 professorship at the Technical University Munich and is affiliated to the DZNE now also is affiliated to the Institute for Stroke and Dementia Research (ISD). Ozgun Gokce received a call for a W2 professorship in Bonn and will transition on April 1st 2023. The DFG funded research unit ImmunoStroke (FOR 2879; speaker: Arthur Liesz) recently was approved a second funding period. In addition, CRC 1123 (vice speaker: Jürgen Bernhagen) started the third funding period.

Our investigators are acquiring increasing amounts of third-party funding with 4.7 million Euro spent in 2021, and more than 4.1 million Euro spent in 2022. Within this period, ISD investigators published more than 145 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 collaborative grants are an international Network of Excellence on the Brain Endothelium (funded by the Leducq Foundation), ImmunoStroke (DFG FOR 2879), and several ERA-NET Neuron grants (funded by the European Commission).

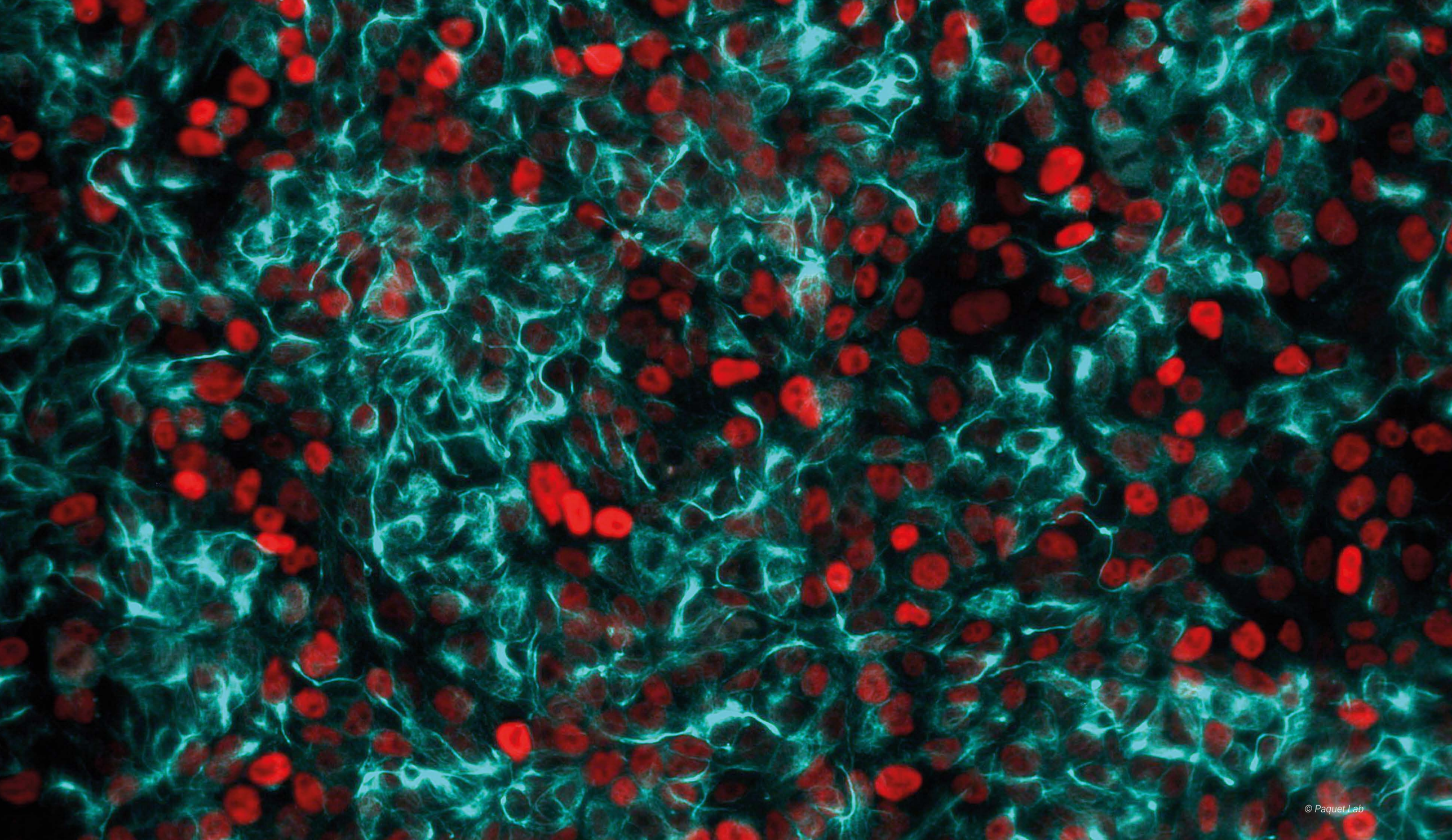
Relevant new infrastructure includes the instalment of a Zeiss LSM980 confocal microscope, a FEMTOSmart Galvo 3-Photon microscope, and a Genomics unit equipped with nanoliter liquid handling robots for miniaturized molecular biology reactions. The new instrumentation further adds to the technology hubs 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 excellence cluster. SyNergy began its operations in early 2013 and has generated a major momentum with unprecedented opportunities for 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, the CRC TR274 on checkpoints in CNS recovery, and ImmunoStroke, and is involved in multiple national, and international research hubs including networks funded by the Leducq Foundation, EU (FP7, Horizon2020, ERA-NET NEURON), and NIH, several of which are coordinated by the ISD. The ISD is further actively engaged in the Hertie Network of Excellence in Clinical Neuroscience, which is about to move into its second funding phase.

Among the plans for 2021/22 is the installment of a new Junior Research Group on Data Science for computational genomics, single-cell and spatial omics. Starting on November 1st, 2022, Marios Georgakis, who has a focus on stroke epidemiology and bioinformatics, established his own research group. On December 1st, Anna-Sophie Wahl, an expert on experimental stroke research, who recently transitioned from the ETH Zurich, Switzerland, joined the ISD to set up her lab. 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 2021/2022.

Prof. Martin Dichgans, MD
Director, Institute for Stroke and Dementia Research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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. one every 3 seconds. 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 55 million worldwide in 2020 to 139 million by 2050 (World Alzheimner Report 2020).

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 (selection)**:**

- **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 sorters** for single cell isolation
- **nanoliter liquid handling robots** for miniaturized molecular biology reactions
- Cytek Northern Lights spectral flow cytometer
- **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

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Zygmunt Solorz

Founders

Zygmunt Solorz (Benefactor)
Warsaw, Poland

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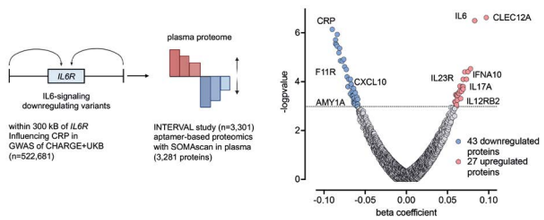
News

New Junior Research Group: "Epidemiology and Bioinformatics – Stroke Precision Lab" PI: Marios Georgakis

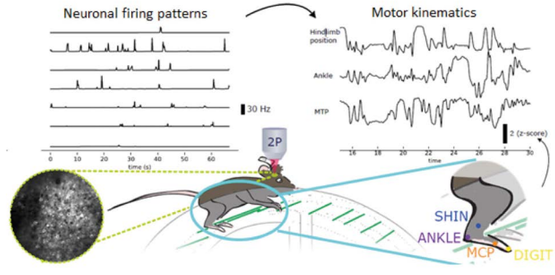
In our group, we aim to address a pressing need to optimize brain health with the development of precise and personalized preventive strategies oriented towards cerebrovascular pathologies. We analyze large-scale multi-dimensional data with the goal to detect novel disease-modifying drug targets, improve the molecular phenotyping of cerebrovascular disease, discover in vivo biomarkers of cerebrovascular pathologies, and develop patient-oriented risk stratification tools.

New Lab: „Neuronal repair and rewiring" PI: Anna-Sophia Wahl

With my team I aim at revealing fundamental principles of brain repair to deal with chronic impairment after stroke and to identify novel targets to enhance functional recovery. We examine how surviving nerve cells participate in repair processes, how new connections are formed and old connections are strengthened using a combination of chronic multiphoton imaging in vivo, optogenetics and deep learning paradigms to explore causal relationships between neuronal computation and the behavioral phenotype.



The DFG awarded an Emmy Noether Award to Marios Georgakis for establishing an independent junior research group.



We record the activity of individual neurons in health and after stroke over several weeks in relation to the behavior.

Hertie Network of Excellence in Clinical Neuroscience approved for prolongation

January 2023 The Hertie Foundation will continue funding for its Network of Excellence in Clinical Neuroscience. The program provides support to junior scientists (4 from LMU and TUM) and facilitates collaborations across participating sites. The scientific focus of the Munich site (Speakers: Martin Dichgans and Thomas Korn) is on neurovascular, neurodegenerative, and neuroinflammatory diseases and their underlying mechanisms.

ERA-NET Collaborative grants on cerebrovascular diseases (CVD)

December 2022 The European Commission will fund 14 Transnational Research Projects on CVD – among them 4 Networks with participation of ISD researchers: BiotaBB (Coordinator: Corinne Benakis), VasOx (Coordinator: Nick Plesnila), MeniSPYs (PI: Arthur Liesz), and MatriSVDs (PI: Martin Dichgans). These networks focus on the role of microbiota and the blood brain-barrier, oxidative stress, the meninges, and the microvascular matrisome in stroke and neurovascular disease.

Martin Dichgans among „Highly Cited Researchers 2022"

November 2022 Of the world's population of scientists and social scientists, Highly Cited Researchers™ are 1 in 1,000. The current list from Clarivate identifies researchers who demonstrated significant influence in their chosen field or fields through the publication of multiple highly cited papers during the last decade. Their names are drawn from publications that rank in the top 1% by citations for field and publication year in the Web of Science™ citation index.

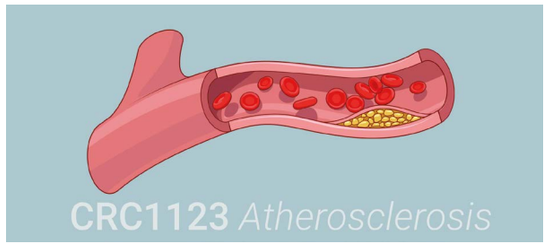
Leducq grant on Brain Endothelium in Cerebral Small Vessel Disease

September 2022 The Leducq Foundation has chosen to fund an International Network of Excellence on Brain Endothelium: A Nexus for Cerebral Small Vessel Disease (BRENDA) with 7.5 M USD over five years. The Network is coordinated by Martin Dichgans and Frank Faraci (University of Iowa, USA) and involves further investigators from Germany, Sweden, France, and the USA.

2nd funding period for ImmunoStroke granted

October 2022 The German Research Foundation (DFG) has decided to fund the DFG Research Unit „ImmunoStroke: From Immune Cells to Stroke Recovery" with 4.6 Million € for a second funding period of 3 years. The consortium is coordinated by Arthur Liesz and spans across 4 German universities, bringing together researchers in Munich, Hamburg, Essen and Münster. Find more information on https://immunostroke.de.

CRC1123 approved for another 4 years



June 2022 The Collaborative Research Center CRC1123 "Atherosclerosis – Mechanisms & Networks of Novel Therapeutic Targets" was awarded a 3rd period until 2026. The cluster encompasses 20 projects. ISD scientists participate in projects A2, A3, B3, and B11. Jürgen Bernhagen is the Vice-Spokesperson. CRC1123 aims to elucidate the mechanisms and molecular networks driving atherosclerosis and further the identification of therapeutic target candidates.

Leducq grant on circadian mechanisms in stroke

Fondation Leducq

November 2021 The Leducq Foundation awarded a new trans-atlantic network of excellence on circadian effects in stroke (coordinators: Eng Lo, Boston, & Alastair Buchan, Oxford). Together with basic, translational, and clinical scientists in the USA, UK, and Spain, the ISD (PI: Steffen Tiedt) now seeks to understand how circadian biology affects stroke pathophysiology with the ultimate aim to identify novel therapeutic targets for stroke.

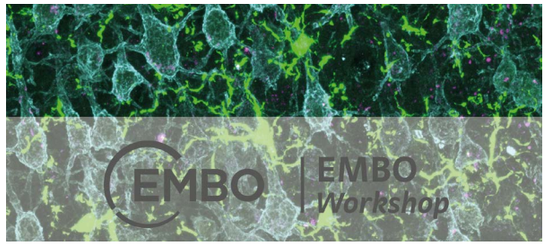
de Leon Senior Scientist Prize for Michael Ewers

July 2021 Michael Ewers received the prestigious 2021 de Leon Prize for Neuroimaging awarded at the Alzheimer Association International Conference in Denver. The de Leon Prize in Neuroimaging recognizes senior scientists and is shared with Dr. Juan Fortea, Spain.

ISD Research Retreat

July 2022 ISD research teams met for the annual scientific retreat to present their projects and discuss the science. At the heart of this meeting were presentations from PhD students, including an evening poster session, a guest talk by Nobel price laureate Reinhard Genzel, and focused workshops. The meeting further served as an opportunity to familiarize people with the medium- and long-term strategy of the ISD.

EMBO Workshop – Stroke-Immunology



February 2022 The EMBO Workshop on Stroke-Immunology running 9 – 12 March in Munich, Germany, will provide a platform for uniting experts in the field with leading scientists from related research areas, including immunology, neuroscience, and advanced research tools. This shall facilitate close interactions and lasting relationships between established scientists in this emerging research area with leaders in related fields, accelerating further developments in stroke-immunology.

m4 Award for Bernhagen Lab

m⁴ Award

October 2021 The Bernhagen (ISD) and Kapurniotu (TUM) labs are among the awardees of this year's m4 competition for innovative biomedical projects by the Bavarian State Ministry of Economic Affairs. Despite significant progress, atherosclerotic disease (stroke and myocardial infarction) remains the leading cause of death. Tackling residual inflammatory risk has evolved as a promising preventive strategy. The m4 award will enable the team to develop chemokine receptor mimics as drug leads to selectively inhibit key atherosclerosis-causing chemokine

Sarah Jäkel joins ISD as a Junior Group Leader

March 2021 As an **Emmy Noether awardee,** Sarah Jäkel explores the role of oligodendrocytes – the myelin forming cells in the central nervous system – in the pathogenesis of Alzheimer's disease. Applying cutting-edge transcriptomic approaches such as single-nuclei RNA-sequencing to post-mortem human brain tissue as well as two and three-dimensional human stem cell-derived oligodendrocyte cultures as model systems, she aims to characterize the functional oligodendrocyte cell states that she recently described and unravel their individual contribution to disease.

Outpatient Clinic

Outpatient clinic staff

Prof. Dr. med. Martin Dichgans / Clinical Director
PD Dr. med. Katharina Bürger / Senior Physician
PD Dr. med. Konstantinos Dimitriadis / Senior Physician
Prof. Dr. med. Arthur Liesz / Senior Physician

Regina Altmann / Documentalist
Imaine Ben Jeema / Study Nurse
Brigitte Faschinger / Study Nurse
Veronique Handfest / Social Worker
Sarina Heimmerer / Reception
Fabian Hirsch / Psychologist
Jonas Jäger / Student Worker
Daniel Janowitz / Physician
Dr. Maria Kaffe / Physician
Wiete Kaulbach / Reception
Nada Khalifeh / Student Worker
Barbara Klapacz / Documentalist
Dr. med. Anna Kopczak/ Physician
Dr. med. Bettina Küster / Physician
Adelina Maier / Student Worker
Michaela Müller / Psychologist
Markus Proksch / Student Worker
Janina Schneider / Trainee
Martina Schnoor-Mayr / Reception
Dr. med. Arnulf Ignaz Steiger / Physician
Konstanze Strohm / Psychologist
Marie Susanne Suttmann / Study Nurse
Saskia Wernsdorf / Physician
Adelgunde Zollver / Study Nurse

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 multicenter 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).

Contact
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Tel.: +49-89-4400-46046

"More than ten years ago, my perception of subtle cognitive impairment and my mother's dementia were the reason for a first appointment at the ISD outpatient clinic.

Even though I have been taking part in an observational study since then, the first time that someone mentioned there could be signs of a starting dementia was not before 2021. Then, finally I got the diagnosis of Alzheimer's disease. Despite our earlier suspects, my husband's and my life changed completely.

From now on the participation in the ISD prevention program together with the professional and encouraging assistance of the ISD staff as well as the vivid exchange with other patients helped us to get along with the situation. In patient seminars and art lessons offered by the ISD, we learn to deal with feelings such as fear and helplessness. Over the years, I have come to value the unique atmosphere, professionalism, and empathy of the team.

My husband and I, we think that the ISD team and the therapeutic options offered to us are crucial to live at best with the disease focussing on priorities that really matter."

Clinical staff | outpatient clinic	
function	total number
physicians	7
neuropsychologists	3
study nurses	6
social workers	1
technical assistants	2
outpatient office	3
clinical data manager	2
total	24

Costs | outpatient clinic	
In 2022, the total costs for the outpatient clinic amounted to 943,971 €. 83% of these costs were covered by the Vascular Dementia Research Foundation.	
personnel	884,896 €
material	54,215 €
investments	4,860 €
total	943,971 €

Statistics | Outpatient Clinic

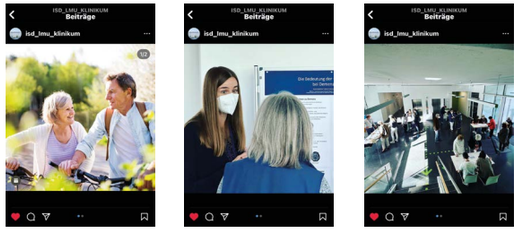
The number of appointments in 2021 and 2022 amounted to 1,871 and 2,107. While this is an increase of 13%, the numbers are still below pre-pandemic levels (2019: 2,632). The total number of clinical appointments was 1,373 (2021) and 1,564 (2022). The total number of research visits was 498 (2021) and 543 (2022), which corresponds to an increase of 9% 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.

Public outreach events: open house / prevention day



Follow us on Instagram
https://www.instagram.com/isd_lmu_klinikum/

Information by print products

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

Website Outpatient Clinic
https://www.lmu-klinikum.de/isd

Stroke Prevention Unit

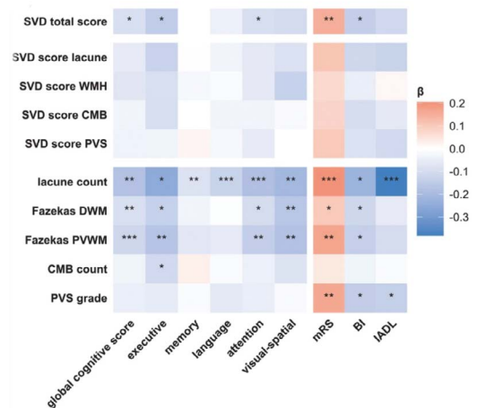
Senior Physician:
Konstantinos Dimitriadis

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.

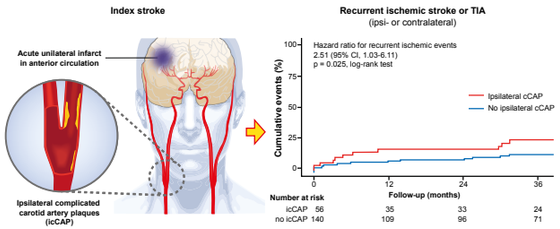
The SPU offers comprehensive diagnostic assessment, counselling and personalized treatment to patients and individuals at risk. The clinic is part of the Interdisciplinary Stroke Center Munich (www.iszm.de). It closely collaborates with neighboring disciplines, such as neuroradiology, neurosurgery, and 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

Patient appointment at the ISD



Cerebral small vessel disease features on brain MRI of stroke patients are associated with worse cognitive and functional outcomes in the first year after stroke.



Complicated nonstenosing carotid artery plaques (CAPs) are an under-recognized cause of stroke.

Selected Publications

Markus HS, van Der Flier WM, Smith EE, Bath P, Biessels GJ, Briceno E, Brodtman A, Chabriat H, Chen C, de Leeuw FE, Egle M, Ganesh A, Georgakis MK, Gottesman RF, Kwon S, Launer L, Mok V, O'Brien J, Ottenhoff L, Pendlebury S, Richard E, Sachdev P, Schmidt R, Springer M, Tiedt S, Wardlaw JM, Verdelho A, Webb A, Werring D, Duering M, Levine D, Dichgans M. *Framework for Clinical Trials in Cerebral Small Vessel Disease (FINESSE): A Review.* **JAMA Neurol**. 2022 Nov 1;79(11):1187-1198. doi: 10.1001/jamaneurol.2022.2262.

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Georgakis MK, Fang R, Düring M, Wollenweber FA, Bode FJ, Stösser S, Kindlein C, Hermann P, Liman TG, Nolte CH, Kerti L, Ikenberg B, Bernkopf K, Poppert H, Glanz W, Perosa V, Janowitz D, Wagner M, Neumann K, Speck O, Dobisch L, Düzel E, Gesierich B, Dewenter A, Spottke A, Waegemann K, Görtler M, Wunderlich S, Endres M, Zerr I, Petzold G, Dichgans M; DEMDAS Investigators. *Cerebral small vessel disease burden and cognitive and functional outcomes after stroke: A multicenter prospective cohort study.* **Alzheimers Dement.** 2022 Jul 25. doi: 10.1002/alz.12744. Epub ahead of print.

Memory Clinic

Senior Physician:
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).

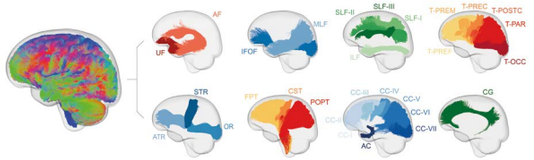
Recent clinical trials have emphasized the potential of preventive treatment, particularly, when initiated in the pre-dementia phase. Hence, there is a growing interest in improved options for early diagnosis. Our memory clinic offers comprehensive diagnostic workup, counselling, and treatment to individuals 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 and have now started again.

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)

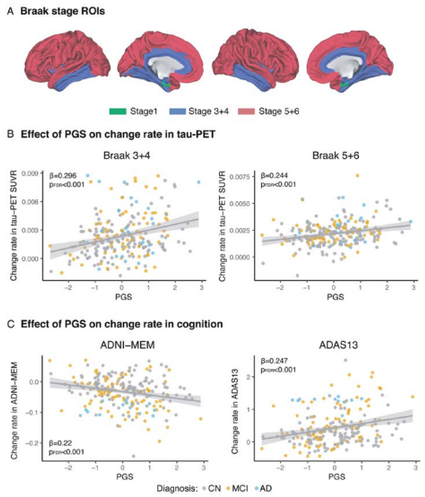

Das Tagesthema
MEDIZIN
+ Eine gesunde Lebensweise senkt das Risiko um bis zu 35 Prozent +
Alzheimer: So können Sie vorbeugen!
„Für uns zählt der Augenblick"
Ein Ehepaar (74, 78) berichtet: Unser Alltag mit der Krankheit
8 REPORT
Silvia kommt als Patienten-Botschafterin nach München
Alzheimer: So hilft die Königin
Rückschläge bei neuen Medikamenten

Media coverage of the ISD outpatient clinic by local newspapers. Topic on prevention and diagnosis of Alzheimer's disease

White matter tissue alterations of major fibre tracts are a characteristic hallmark of both Alzheimer's and cerebral small vessel disease. Using advanced MRI techniques, ISD investigators found that fibre density captures the effects of cerebral small vessel disease, while fibre-bundle cross-section is largely determined by neurodegeneration following AD (Dewenter et al., 2022).



Polygenic variation accounts for a substantial portion of the risk of Alzheimer's disease, but its effect on the rate of fibrillar-tau accumulation as a key driver of dementia symptoms is unclear. Rubinski et al. showed that the rate of tau progression assessed via longitudinal molecular PET over 2 years can be predicted by a set of genetic variants derived from the to-date largest GWAS on AD. They found that a polygenic risk score has utility for risk enrichment in clinical trials targeting tau pathology in AD.



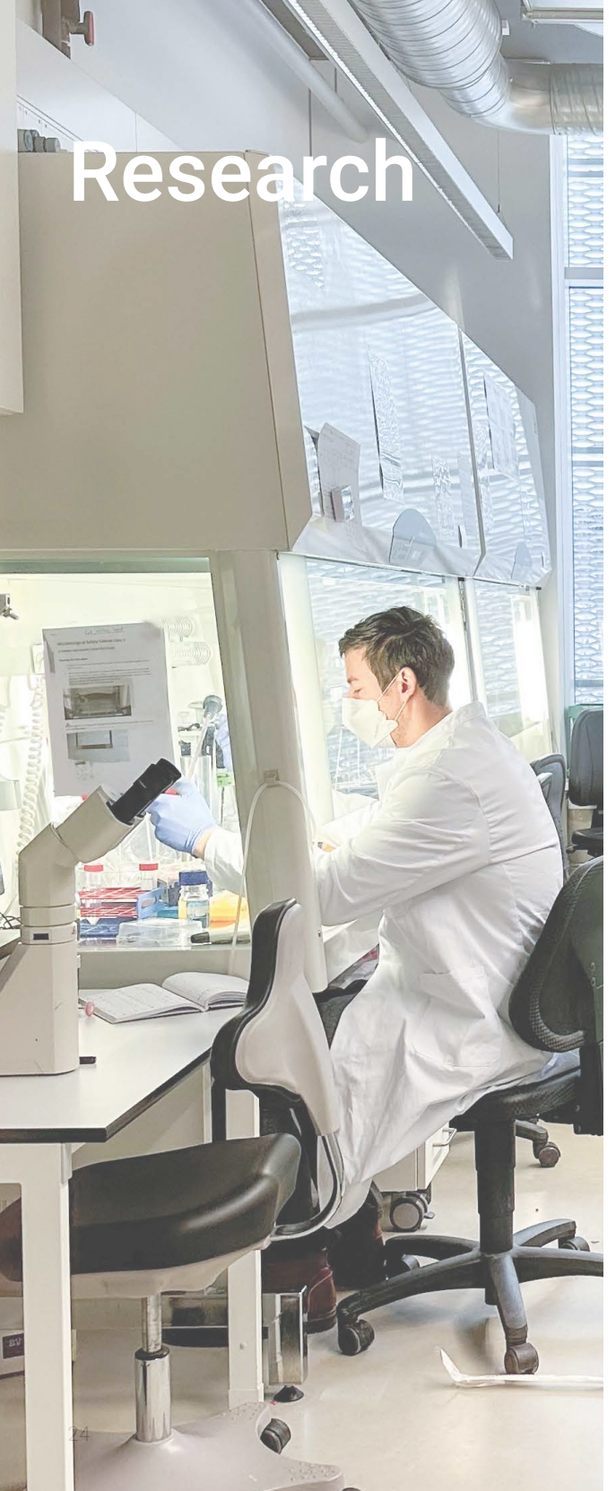
Selected Publications

Rubinski A, Frerich S, Malik R, Franzmeier N, Ramirez A, Dichgans M, Ewers M; *Alzheimer's Disease Neuroimaging Initiative (ADNI). Polygenic Effect on Tau Pathology Progression in Alzheimer's Disease*. **Ann Neurol**. 2022 Dec 26. doi: 10.1002/ana.26588. Epub ahead of print.

Dewenter A, Jacob MA, Cai M, Gesierich B, Hager P, Kopczak A, Biel D, Ewers M, Tuladhar AM, de Leeuw FE, Dichgans M, Franzmeier N, Duering M; SVDs@target Consortium and Alzheimer's Disease Neuroimaging Initiative (ADNI). *Disentangling the effects of Alzheimer's and small vessel disease on white matter fibre tracts*. **Brain**. 2022 Jul 21:awac265. doi: 10.1093/brain/awac265. Epub ahead of print.

Frimmer D, Buerger K. *Kognitive Interventionen bei der Alzheimer-Krankheit.* **Fortschr Neurol Psychiatr.** 2022 Jul;90(7-08):344-351. German. doi: 10.1055/a-1869-4377. Epub 2022 Jul 20.

Patient appointment at the ISD



Research

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)
- Biology of Glia and Neuroinflammation
- Neuronal Repair and Rewiring
- Epidemiology
- Human iPSC-based disease models

Methodological approaches include
- Prospective investigator-initiated observational and interventional studies in patients
- Interventional clinical trials (IITs)
- 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
- Spatial transcriptomics
- Proteomics or brain microvessels, and defined cell-types

Research Groups

Translational Research Martin Dichgans
Vascular Biology Jürgen Bernhagen
Biology of Glia and Neuroinflammation Mikael Simons
Stroke-Immunology Arthur Liesz
Brain Imaging and Biomarker Michael Ewers
iPSC-Models of Brain Diseases Dominik Paquet
Experimental Stroke Research Nikolaus Plesnila
Acute Brain Injury Ali Ertürk
Vascular Cognitive Impairment Marco Düring

Junior Research Groups

Systems Neuroscience Ozgun Gokce
Microbiome-Gut-Brain Interactions Corinne Benakis
Alzheimer's Disease Neuroimaging Nicolai Franzmeier
Oligodendrocyte Pathology Sarah Jäkel
Molecular Biomarkers Steffen Tiedt
Epidemiology and Bioinformatics Marios Georgakis

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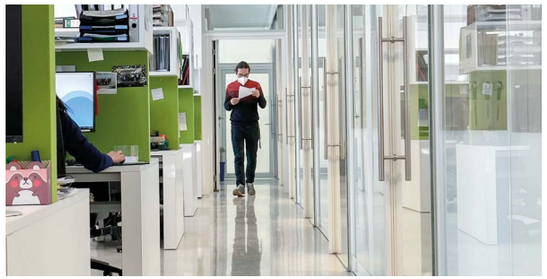


ISD Lab

Translational Stroke and Dementia Research

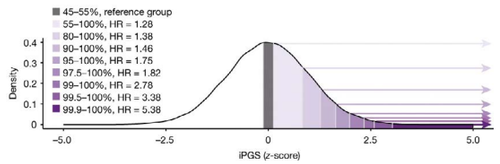
Principal Investigator:
Martin Dichgans

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.



Risk prediction for ischemic stroke in a trial setting using an integrated polygenic score. Compared to individuals in the middle decile (45-55%, gray area) individuals in the upper 0.1 percentile of the score distribution have a hazard ratio of 5.38 of experiencing an incident stroke (Mishra et al. Nature, 2022)

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Dr. Marios Georgakis / Postdoc
Dr. med. Anna Kopczak / Clinician Scientist
Dr. med. Maria Kaffe / Clinician Scientist
Barbara Lindner / Technical Assistant
Dr. Rainer Malik / Postdoc
Melanie Schneider / Technical Assistant
Dr. Katalin Todorov-Völgyi / Postdoc
Dr. Karin Waegemann / Research Coordinator
Jenni Alt / Team Assistant
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Judit Gonzalez Gallego / PhD Student
Christina Schlegl / MD Student
Luise Schröger / PhD Student
Federica Tosato / PhD Student
Luka Zivkovic / MD Student

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Key Publications

Mishra A*, Malik R*, (...), Dichgans M ✉, Debette S ✉. *Stroke genetics informs drug discovery and risk prediction across ancestries.* **Nature**. Nov;611(7934):115-123. doi: 10.1038/s41586-022-05165-3. Epub 2022 Sep 30.

Georgakis MK, (...), Dichgans M; DEMDAS Investigators. *Cerebral small vessel disease burden and cognitive and functional outcomes after stroke: A multicenter prospective cohort study.* **Alzheimers Dement.** 2022 Jul 25. doi: 10.1002/alz.12744. Epub ahead of print.

Kopczak A, (...), Dichgans M. *Complicated Carotid Artery Plaques and Risk of Recurrent Ischemic Stroke or TIA.* **J Am Coll Cardiol.** 2022 Apr 27:S0735-1097(22)04687-3. doi: 10.1016/j.jacc.2022.03.376. Epub ahead of print.

Rost NS, Brodtmann A, Pase MP, van Veluw SJ, Biffi A, Duering M, Hinman JD, Dichgans M. *Post-Stroke Cognitive Impairment and Dementia.* **Circ Res.** 2022 Apr 15;130(8):1252-1271. doi: 10.1161/CIRCRESAHA.122.319951. Epub 2022 Apr 14.

Georgakis MK, (...), Dichgans M. *Targeting the CCL2-CCR2 axis for atheroprotection.* **Eur Heart J.** 2022 Mar 7:ehac094. doi: 10.1093/eurheartj/ehac094. Epub ahead of print.

Malik R, Georgakis MK, Neitzel J, Rannikmäe K, Ewers M, Seshadri S, Sudlow CLM, Dichgans M. *Midlife vascular risk factors and risk of incident dementia: Longitudinal cohort and Mendelian randomization analyses in the UK Biobank.* **Alzheimers Dement.** 2021 Sep;17(9):1422-1431. doi: 10.1002/alz.12320. Epub 2021 Mar 22.

Georgakis MK, Malik R, Li X, Gill D, Levin MG, Vy HMT, Judy R, Ritchie M, Verma SS; Regeneron Genetics Center, Nadkarni GN, Damrauer SM, Theodoratou E, Dichgans M. *Genetically Downregulated Interleukin-6 Signaling Is Associated With a Favorable Cardiometabolic Profile: A Phenome-Wide Association Study.* **Circulation.** 2021 Mar 16;143(11):1177-1180. doi: 10.1161/CIRCULATIONAHA.120.052604. Epub 2021 Mar 15.

Vascular Biology

Principal Investigator:
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, novel MIFs) and related chemokines in atherosclerosis, ischemic stroke, and myocardial infarction (e.g. Merk et al., PNAS 2011; Lüdike et al., Circulation 2012; Stoppe et al., Sci Transl Med 2018; Kontos et al., Nat Commun 2020; Tilstam et al., J Clin Invest 2021). 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, 2021; Brandhofer et al., Cell Mol Life Sci 2022). 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 multi-protein signaling complexes such as the COP9 signalosome (CSN) atherogenesis and neuroinflammation, as well as NFκB/HDAC9 and the NLRP3 inflammasome in cooperation with the Asare/Dichgans lab (Asare et al., Circ Res 2020; Asare et al., Signal Transduct Target Ther. 2022). The CSN is regulates CRL E3 ligase NEDDylation, controlling degradation of various proteins. Based on our initial discovery linking the CSN to inflammation (Kleemann et al., Nature 2000), we identified an atheroprotective effect of CSN5 (Asare et al., PNAS 2017). Current 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 (e.g. Taş et al., Nat Commun 2022).

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Dr. med. Adrian Hoffmann / LMUexc Clinician Scientist
Simona Gerra / Technical Assistant
Maida Avdic / Technical Assistant
Dr. rer. nat. Markus Brandhofer / Postdoctoral Investigator
Yuan Tian, PhD / Postdoctoral Investigator
Ying Gao, MD / PhD Student
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Kobra Moradzadeh Gavbazeh / PhD Student
Simon Ebert / PhD Student
Noor Ismail, cand. med. / MD Student
Michael Kobina Otabil / PhD Student
Elena Siminkovic, cand. med. / MD Student
Lukas Spiller, cand. med. / MD Student
Dario Ponto, cand. med. / MD Student

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Key Publications

Kapurniotu A, Bernhagen J. *Lasso-grafted designer cytokines*. **Nat Biomed Eng**. 2022 Nov 24. doi: 10.1038/s41551-022-00974-3. Epub ahead of print.

Brandhofer M, Hoffmann A, (...), Kapurniotu A, Weber C, von Hundelshausen P, Bernhagen J. *Heterocomplexes between the atypical chemokine MIF and the CXC-motif chemokine CXCL4L1 regulate inflammation and thrombus formation.* **Cell Mol Life Sci**. 2022 Sep 12;79(10):512. doi: 10.1007/s00018-022-04539-0.

Asare Y, Shnipova M, Živković L, Schlegl C, Tosato F, Aronova A, Brandhofer M, Strohm L, Beaufort N, Malik R, Weber C, Bernhagen J, Dichgans M. *IKKβ binds NLRP3 providing a shortcut to inflammasome activation for rapid immune responses.* **Signal Transduct Target Ther**. 2022 Oct 19;7(1):355. doi: 10.1038/s41392-022-01189-3.

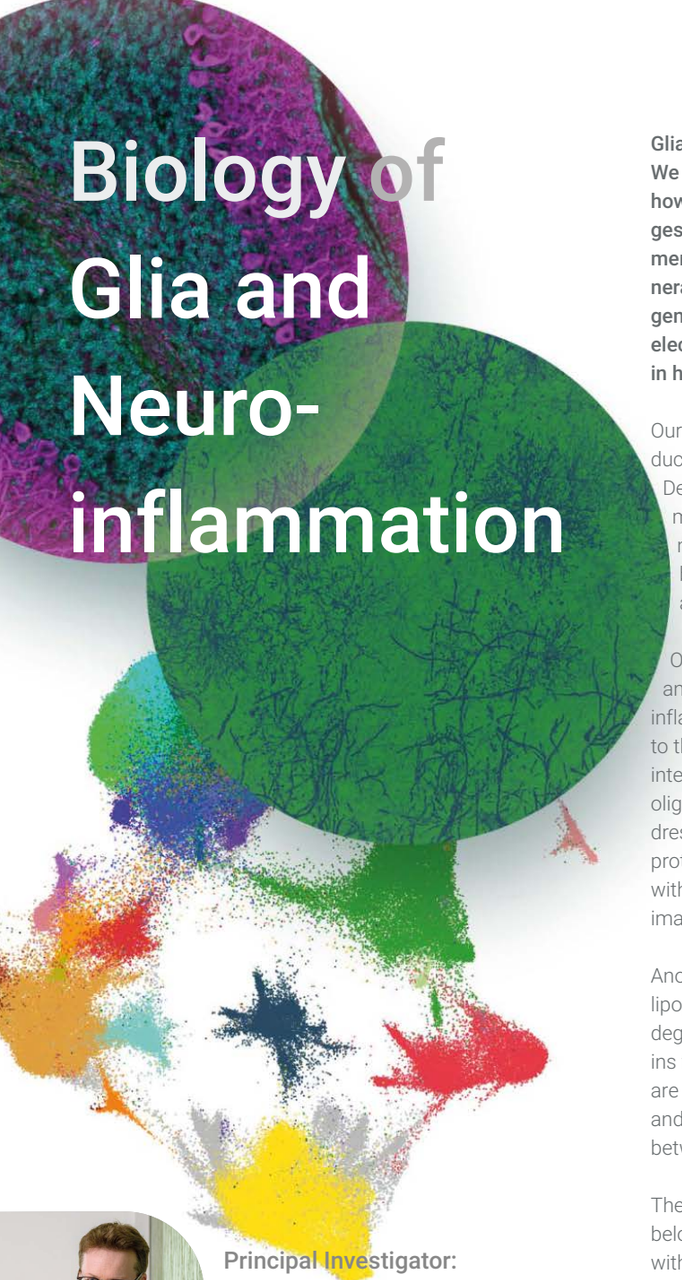
Taş K, Volta BD, Lindner C, El Bounkari O, Hille K, Tian Y, (...), Weber C, Megens RTA, Bernhagen J, Kapurniotu A. *Designed peptides as nanomolar cross-amyloid inhibitors acting via supramolecular nanofiber co-assembly*. **Nat Commun**. 2022 Aug 25;13(1):5004. doi: 10.1038/s41467-022-32688-0.

Georgakis MK*, Bernhagen J*, Heitman LH, Weber C, Dichgans M. *Targeting the CCL2-CCR2 axis for atheroprotection.* **Eur Heart J**. 2022 May 14;43(19):1799-1808. doi: 10.1093/eurheartj/ehac094.

Mohanta SK, (...), Michel JB, Bernhagen J, Dichgans M, D'Agostino G, Guzik TJ, Olofsson PS, Yin C, Weber C, Lembo G, Carnevale D, Habenicht AJR. *Neuroimmune cardiovascular interfaces control atherosclerosis.* **Nature**. 2022 May;605(7908):152-159. doi: 10.1038/s41586-022-04673-6. Epub 2022 Apr 27.

Schindler L, Smyth LCD, Bernhagen J*, Hampton MB, Dickerhof N*. *Macrophage migration inhibitory factor (MIF) enhances hypochlorous acid production in phagocytic neutrophils.* **Redox Biol**. 2021 Mar 30;41:101946. doi: 10.1016/j.redox.2021.101946. Epub ahead of print.

Biology of Glia and Neuro-inflammation



Principal Investigator:
Mikael Simons

Glia are essential for the function of the nervous system. We study how glial cells contribute to brain function and how their dysfunction leads to diseases. Our research ranges from functions of glia during nervous system development and maintenance to their role in aging, neurodegenerative and inflammatory diseases. Our lab combines genetic, molecular, biochemical and advanced light and electron microscopy techniques to study how glia operate in health and disease.

Our focus is on myelin, an insulating membrane sheath produced by oligodendrocytes in the central nervous system. Destruction of myelin leads is a pathological hallmark of multiple sclerosis, but is also associated with several neurodegenerative disorders. Another focus is on the biology of microglia, and their functions in regenerative and degenerative processes.

One current research project is on white matter aging and on the question of how myelin aging drives chronic inflammatory responses, and how inflammation is linked to the pathogenesis of age-related diseases. We are also interested in the neuroprotective role of glia, in particular oligodendrocytes, in aging and neurodegeneration. To address these questions, we make use of single cell genomics, proteomics and lipidomics, and combine these analyses with functional studies in vivo by employing genetics and imaging techniques.

Another important area of research is on the functions of lipoproteins in development, regeneration, aging and neurodegeneration with the CNS. We are analyzing how lipoproteins function as vehicles in intercellular communication, and are exploring their functions as an extracellular surveillance and delivery system that connects lipid metabolic pathways between the different cells.

The lab is part of the Institute of Neuronal Cell Biology, belongs to the TUM Faculty of Medicine, and is affiliated with the German Center for Neurodegenerative Diseases and the Institute for Stroke and Dementia Research. Our lab is located at the Center of Stroke and Dementia Research at Campus Grosshadern in Munich.

Prof. Dr. med. Mikael Simons / PI
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Dr. Ludovico Cantuti-Castelvetri / Postdoc
Dr. med. Minou Djannatian / Clinician Scientist
Dr. Seiji Kaji / Postdoc
Dr. med Johanna Knoeferle / Postdoc
Dr. Lena Spieth / Postdoc
Alkmini Damkou / PhD Student
Liliana Pedro Domingues / PhD Student
Garyfallia Gouna / PhD Student
Tugberk Kaya / PhD Student
Shreeya Kedia / PhD Student
Swathi Radha / PhD Student
Lennart Schlaphoff / PhD Student
Vini Tiwari / PhD Student
Martin Zirngibl / PhD Student
Jianping Wu / PhD Student
Agata Rhomberg / Technician
Tommaso Di Genio / Master Student
Simona Vitale / Master Student

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Key Publications

Kaya T, Mattugini N, Liu L, Ji H, Cantuti-Castelvetri L, Wu J, Schifferer M, Groh J, Martini R, Besson-Girard S, Kaji S, Liesz A, Gokce O*, Simons M*. *CD8+ T cells induce interferon-responsive oligodendrocytes and microglia in white matter aging*. **Nat Neurosci.** 2022 Nov;25(11):1446-1457. doi: 10.1038/s41593-022-01183-6. Epub 2022 Oct 24.

Franklin RJM, Simons M. *CNS remyelination and inflammation: From basic mechanisms to therapeutic opportunities* **Neuron** 2022 Nov 2;110(21):3549-3565

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Bosch-Queralt M, Cantuti-Castelvetri L, Damkou A, Schifferer M, Schlepckow K, Alexopoulos I, Lütjohann D, Klose C, Vaculčiaková L, Masuda T, Prinz M, Monroe KM, Di Paolo G, Lewcock JW, Haass C, Simons M. *Diet-dependent regulation of TGFβ impairs reparative innate immune responses after demyelination*. **Nat Metab**. 2021 Feb;3(2):211-227. doi: 10.1038/s42255-021-00341-7. Epub 2021 Feb 18.

Mukherjee C*, Kling T*, Russo B, Miebach K, Kess E, Schifferer M, Pedro LD, Weikert U, Fard MK, Kannaiyan N, Rossner M, Aicher ML, Goebbels S, Nave KA, Krämer-Albers EM, Schneider A*, Simons M*. *Oligodendrocytes Provide Antioxidant Defense Function for Neurons by Secreting Ferritin Heavy Chain*. **Cell Metab**. 2020 Aug 4;32(2):259-272.e10. doi: 10.1016/j.cmet.2020.05.019. Epub 2020 Jun 11.

Stroke-Immunology

Principal Investigator:
Arthur Liesz

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

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

1. Chronic neuroinflammation and neurological recovery: Ischemic brain lesions not only induce an acute inflammatory response to the tissue injury but result in chronic neuroinflammation which is insufficiently resolved. We are interested in the mechanisms contributing to chronic neuroinflammation and ist impact on neurological recovery.

2. The systemic inflammatory response to stroke Stroke induces a multi-phasic sterile inflammatory response in the systemic immune compartment. We investigate immunological mechanisms regulating the systemic immune response and aim to identify novel immunological drug targets.

3. Immune-mediated comorbidities of stroke patients
The morbidity of stroke patients depends largely on non-neurological comorbidities such as post-stroke infections, metabolic disorders and vascular inflammation (atherosclerosis). We analyze the contribution of post-stroke inflammation to induction and exacerbation of such comorbidities.

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Dr. Gemma Llovera / Postdoctoral fellow
Dr. Alba Simats / Postdoctoral fellow
Dr. Steffanie Heindl / Postdoctoral fellow
Dr. Dániel Varga / Postdoctoral fellow
Saskia Wernsdorf / Clinical Research Fellow
Alessio Ricci / PhD Student
Olga Carofiglio / PhD Student
Jie Zhu / PhD Student
Jiayu Cao / PhD Student
Kelsey Pinkham / PhD Student
Sijia Zhang / PhD Student
Philip Melton / MD Student
Kerstin Thuß-Silczak / Lab Technician
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Stefanie Hentze / Team Assistant

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Key Publications

Benakis C, Simats A, Tritschler S, Heindl S, Besson-Girard S, Llovera G, Pinkham K, Kolz A, Ricci A, Theis FJ, Bittner S, Gökce Ö, Peters A, Liesz A. *T cells modulate the microglial response to brain ischemia*. **Elife**. 2022 Dec 13;11:e82031. doi: 10.7554/eLife.82031.

Simats A, Liesz A. *Systemic inflammation after stroke: implications for post-stroke comorbidities*. **EMBO Mol Med**. 2022 Sep 7;14(9):e16269. doi: 10.15252/emmm.202216269. Epub 2022 Aug 15.

Heindl S, Ricci A, Carofiglio O, Zhou Q, Arzberger T, Lenart N, Franzmeier N, Hortobagyi T, Nelson PT, Stowe AM, Denes A, Edbauer D, Liesz A. *Chronic T cell proliferation in brains after stroke could interfere with the efficacy of immunotherapies*. **J Exp Med**. 2021 Aug 2;218(8):e20202411. doi: 10.1084/jem.20202411. Epub 2021 May 26.

Colombo AV, Sadler RK, Llovera G, Singh V, Roth S, Heindl S, Sebastian Monasor L, Verhoeven A, Peters F, Parhizkar S, Kamp F, Gomez de Aguero M, MacPherson AJ, Winkler E, Herms J, Benakis C, Dichgans M, Steiner H, Giera M, Haass C, Tahirovic S, Liesz A. *Microbiota-derived short chain fatty acids modulate microglia and promote Aβ plaque deposition.* **Elife**. 2021 Apr 13;10:e59826. doi: 10.7554/eLife.59826.

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.** 2021 Jan;91:668-672. doi: 10.1016/j.bbi.2020.11.016. Epub 2020 Nov 14.

Roth S, Cao J, Singh V, Tiedt S, Hundeshagen G, Li T, Boehme JD, Chauhan D, Zhu J, Ricci A, Gorka O, Asare Y, Yang J, Lopez MS, Rehberg M, Bruder D, Zhang S, Groß O, Dichgans M, Hornung V, Liesz A. *Post-injury immunosuppression and secondary infections are caused by an AIM2 inflammasome-driven signaling cascade.* **Immunity**. 2021 Apr 13;54(4):648-659.e8. doi: 10.1016/j.immuni.2021.02.004. Epub 2021 Mar 4.

Brain Imaging & Biomarker

Principal Investigator:
Michael Ewers

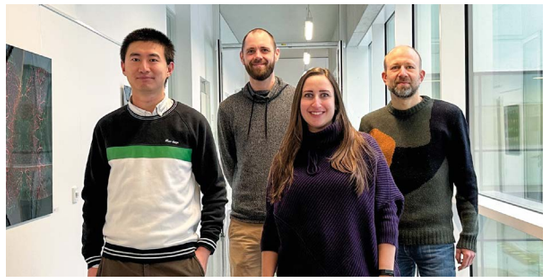
Our research focuses on the spreading of key pathologies in Alzheimer's disease (AD) and the improvement of prediction tools. Specifically, we combine functional connectomics, genetics and advanced molecular PET markers to model the spatiotemporal evolution of fibrillar tau and beta-amyloid. Our prediction 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 in AD. We recently extended these findings on connectivity-based prediction of tau to 4R primary tauopathies, combining PET and histopathologically detected tau. Therefore, our approach allows to predict the progression of tau accumulation across different tauopathies.

Modulating factors of beta-amyloid fibrillar tau
Another research interest is to discovery those factors that modulate the susceptibility to develop tau pathology in AD. One focus centers on identifying genetic risk for the prediction of beta-amyloid and tau accumulation. We demonstrated worsening effects of AD-risk variants in BIN1 (Franzmeier et al. Alzheimer's dementia, 2022) are associated with faster tau pathology, but SNPs in Klotho were protective against both Aß and fibrillar tau (Neitzel et al. Nat Commun 2019). In addition, we developed a polygenic risk score to combine the effect of multiple SNPs for the prediction of tau-PET accumulation, which could be utilized for risk enrichment in clinical trials (Rubinski et al. Annals Neurology, 2022).

A second focus centers on myelin, i.e. the membrane protein which ensheats the axons in the brain. We revealed that ontogenetically lower myelinated brain regions are those that exhibit highest susceptibility to tau pathology in AD (Rubinski et al. Alz Res Ther, 2022). In patients with AD, myelin is reduced and a decrease of myelin was associated with faster tau accumulation (Rubinski et al. in progress). These findings suggest that myelin alterations may contribute to the etiology of AD and are a potential treatment target.

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 as well as higher segregation of functional works (Ewers et al. Brain, 2021) as key neural substrates supporting cognitive resilience against pathologic tau.



Prof. Dr. Michael Ewers / PI
Dr. Anna Rubinski / PhD
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Lukai Zheng / PhD Student
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Key Publications

Rubinski A, Frerich S, Malik R, Franzmeier N, Ramirez A, Dichgans M, Ewers M; Alzheimer's Disease Neuroimaging Initiative (ADNI). *Polygenic Effect on Tau Pathology Progression in Alzheimer's Disease.* **Ann Neurol.** 2022 Dec 26. doi: 10.1002/ana.26588. Epub ahead of print. .

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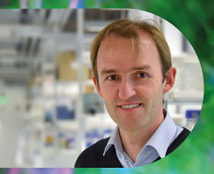
iPSC-Models of Brain Diseases



Principal Investigator:
Dominik Paquet

The Paquet Lab 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 iPSC-based model systems, which allow 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 human brain cell types, developed efficient technologies to introduce and remove patient mutations using CRISPR/Cas genome editing, and set up technologies to generate multicellular human tissues from stem cells modeling brain parenchyma and the neurovascular unit (NVU).

By engineering synergistic combinations of familial mutations causing Alzheimer's disease (AD) or Frontotemporal dementia (FTD) into our models, we can elicit typical phenotypes, such as Abeta accumulation in the extracellular matrix of the AD model, or formation of Tau seeds, misfolding and aggregation in the FTD model. By showing these late-stage phenotypes, our models allow novel studies on disease mechanisms that were so far out of reach in existing models.

Our in vitro human NVU model not only displays brain-typical features, such as tight and adherens junctions, barrier formation, and perfusability, but loss of a gene associated with neurovascular diseases also causes characteristic disease phenotypes, such a barrier loss and increase of transport, both affecting BBB function.

Prof. Dr. Dominik Paquet / PI
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Julien Klimmt / Postdoc
Patricia Yuste / Postdoc
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Judit Gonzalez Gallego / GSN Graduate Student
Liliana Pedro / GSN Graduate Student
Joseph Kroeger / GSN Graduate Student
Marvin Reich / GSN Graduate Student
Sophie Robinson / GSN Graduate Student
Carolina Cardoso Goncalves / GSN Graduate Student
Einar Krogsaeter / Graduate Student
Merle Bublitz / GSN Graduate Student
Melanie Falke / Master Student
Lea Knez / Master Student
Elizabeth Bader / Master Student

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Key Publications

Pantazis CB, (...), Crusius D, Paquet D, Raulin AC, (...), Erlebach L, Welzer M, Kronenberg-Versteeg D, Lyu G, Arenas E, Coccia E, Sarrafha L, Ahfeldt T, Marioni JC, Skarnes WC, Cookson MR, Ward ME, Merkle FT. *A reference human induced pluripotent stem cell line for large-scale collaborative studies*. **Cell Stem Cell**. 2022 Dec 1;29(12):1685-1702.e22. doi: 10.1016/j.stem.2022.11.004.

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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*. **Nature Protocols** 16, 2021: 1714–1739.

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Laboratory of Experimental Stroke Research

Principal Investigator:
Nikolaus Plesnila

The main interest of the laboratory is to study cerebral microvessels in health and disease and to use the evolving knowledge to develop novel therapeutic strategies for patients. For this purpose, we use in vitro and in vivo models for acute and chronic brain disorders, e.g., ischemic and hemorrhagic stroke or brain trauma, and investigate neuro-vascular morphology and function by using AAV- and nanoparticle-based labeling and genetically encoded sensor technology together with in vivo multi-photon microscopy.

Current investigations focus around two main topics: 1) the role of the cerebral microcirculation for brain injury after subarachnoid hemorrhage (SAH) and 2) the function of cerebral microvessels following cerebral ischemia.

Experiments on the cerebral microcirculation of the ischemic penumbra using nanoparticle tracing, transgenic reporter mice, and in vivo microscopy revealed that pericytes, the contractile cellular elements of cerebral capillaries, constrict during and long-term after cerebral ischemia. Thus, pericytes may be involved in the no-reflow phenomenon after ischemic stroke. Post-ischemic microvascular constrictions may also mediate leukocyte plugging, however, we observed such changes only in the infarct core. In the ischemic penumbra leukocytes adhered mainly to post-capillary venules, a process which was blunted by inhalation of NO. Our most recent results suggest that post-ischemic tissue perfusion may be critically limited by the secondary formation of microvascular clots. Delayed micro-clot formation induces significant changes in the surrounding brain parenchyma and may thus contribute to neuroinflammation and additional tissue damage beyond its effects on tissue perfusion.

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Dr. Katharina Kamm / Clinician Scientist
Dr. Igor Khalin / Postdoctoral Fellow
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Dr. Katrin Rauen / Clinician Scientist
Dr. Burcu Şeker / Postdoctoral Fellow
Dr. Susanne Schwarzmaier / Clinician Scientist
Dr. Julian Schwarting / Clinician Scientist
Dr. Joshua Shrouder / Postdoctoral Fellow
Dr. Rebecca Sienel / Postdoctoral Fellow
Dr. Nicole Terpolilli / Clinician Scientist
Kosisochukwu Umeasalugo / PhD Student
Antonia Wehn / Clinical Scientist
Dr. Sodai Yoshimura / Visiting Researcher

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

Key Publications

Khalin I, Adarsh N, Schifferer M, Wehn A, Groschup B, Misgeld T, Klymchenko A, Plesnila N. *Size-Selective Transfer of Lipid Nanoparticle-Based Drug Carriers Across the Blood Brain Barrier Via Vascular Occlusions Following Traumatic Brain Injury*. **Small**. 2022 May;18(18):e2200302.

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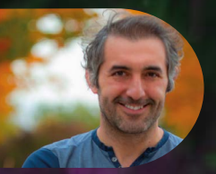
Acute Brain Injury



Principal Investigator:
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.

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Rami Al-Maskari / PhD Student
Dr. Harsharan S. Bhatia / Postdoc
Marin Bralo / Technical Assistant
Dr. Markus Elsner / Co-deputy
Dr. Farida Hellal / Co-deputy
Izabela Horvath / PhD Student
Luciano Höher / Intern
Dr. Saketh Kapoor / Postdoc
Dr. Doris Kaltenecker / Postdoc
Karoline Kadletz / PhD Student
Ilgin Kolabas / PhD Student
Louis Kümmerle / PhD Student
Dr. Jie Luo / Postdoc
Hongcheng Mai / PhD Student
Muge Molbay / PhD Student
Furkan Ozturk / PhD Student
Johannes Paetzold / PhD Student
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Selin Ulukaya / Master Student
Zihua Huang / CSC PhD Student
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Key Publications

Bhatia…Ertürk A. *Spatial proteomics in optically cleared preclinical & clinical specimens* **Cell** (in press) (cover)

Cai M…Ertürk A. *Cellular level whole mouse imaging with vDISCO*. **Nat. Protocols** (in press)

Mohanta SK, Peng L, Li Y, Lu S, Sun T, Carnevale L, Perrotta M, Ma Z, Förstera B, Stanic K, Zhang C, Zhang X, Szczepaniak P, Bianchini M, Saeed BR, Carnevale R, Hu D, Nosalski R, Pallante F, Beer M, Santovito D, Ertürk A, Mettenleiter TC, Klupp BG, Megens RTA, Steffens S, Pelisek J, Eckstein HH, Kleemann R, Habenicht L, Mallat Z, Michel JB, Bernhagen J, Dichgans M, D'Agostino G, Guzik TJ, Olofsson PS, Yin C, Weber C, Lembo G, Carnevale D, Habenicht AJR. *Neuroimmune cardiovascular interfaces control atherosclerosis*. **Nature**. 2022 May;605(7908):152-159. doi: 10.1038/s41586-022-04673-6. Epub 2022 Apr 27.

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Vascular Cognitive Impairment

Principal Investigator:
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 established a fully automated and robust biomarker based on diffusion tensor imaging. The marker is available publicly (www.psmd-marker.com) and already implemented in many studies world-wide. Building on this work, we are currently evaluating more advanced diffusion models for an improved characterization of tissue alterations.

Another focus of our work is on the interplay between vascular and neurodegenerative pathology. Our group established the link between subcortical pathology and changes of cortical morphology implying a role for remote, secondary neurodegeneration in stroke and VCI. Recently, we were able to disentangle the effects of vascular and neurodegenerative pathology on white matter tracts by using the fixel-based analysis framework (Dewenter et al., Brain 2022).

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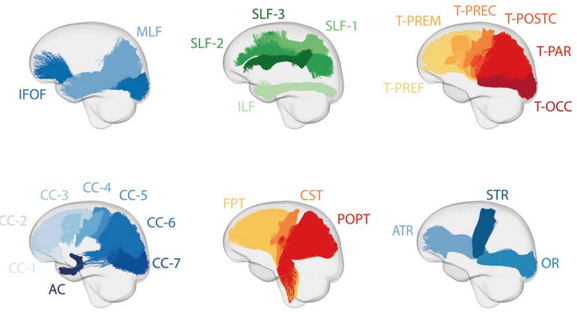

Fixel-based analysis of diffusion MRI allows to untangle white matter alterations in major fiber tracts due to Alzheimer's disease and cerebral small vessel disease (Dewenter et al., Brain 2023)

Key Publications

Dewenter A, Jacob MA, Cai M, Gesierich B, Hager P, Kopczak A, Biel D, Ewers M, Tuladhar AM, de Leeuw FE, Dichgans M, Franzmeier N, Duering M; SVDs@target Consortium and Alzheimer's Disease Neuroimaging Initiative (ADNI). *Disentangling the effects of Alzheimer's and small vessel disease on white matter fibre tracts*. **Brain**. 2022 Jul 21:awac265. doi: 10.1093/brain/awac265. Epub ahead of print.

Konieczny MJ, Dewenter A, Ter Telgte A, 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**. 2021 Feb 2;96(5):e698-e708. doi: 10.1212/WNL.0000000000011213. Epub 2020 Nov 16.

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Verburgt E, Janssen E, Jacob M, Cai M, Ter Telgte A, Wiegertjes K, Kessels RPC, Norris DG, Marques J, Duering M, Tuladhar AM, De Leeuw FE. *Role of small acute hyperintense lesions in long-term progression of cerebral small vessel disease and clinical outcome: a 14-year follow-up study*. **J Neurol Neurosurg Psychiatry.** 2022 Oct 21:jnnp-2022-330091. doi: 10.1136/jnnp-2022-330091. Epub ahead of print.

van den Brink H, Kopczak A, Arts T, Onkenhout L, Siero JCW, Zwanenburg JJM, Hein S, Hübner M, Gesierich B, Duering M, Stringer MS, Hendrikse J, Wardlaw JM, Joutel A, Dichgans M, Biessels GJ; SVDs@target group. *CADASIL Affects Multiple Aspects of Cerebral Small Vessel Function on 7T-MRI.* **Ann Neurol.** 2022 Oct 12. doi: 10.1002/ana.26527. Epub ahead of print.

Systems Neuroscience

Principal Investigator:
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.

Peter Androvič, PhD / postdoc
Simon Besson-Girard, MSc / GSN PhD student
Buket Bulut / PhD student
Elena Ernst / Master student
Katrin Gehring / Master-PhD student
Ozgun Gokce, PhD / PI
Hao Ji, MD / MMRS PhD student
Lu Liu, MD / MMRS PhD student
Tuğberk Kaya / GSN PhD student
Yijing Wang, MD / PhD student

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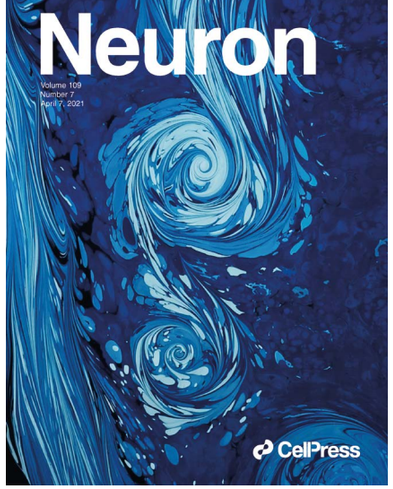


Key Publications

Kaya T, Mattugini N, Liu L, Ji H, Cantuti-Castelvetri L, Wu J, Schifferer M, Groh J, Martini R, Besson-Girard S, Kaji S, Liesz A, Gokce O, Simons M. *CD8+ T cells induce interferon-responsive oligodendrocytes and microglia in white matter aging.* **Nat Neurosci.** 2022 Nov;25(11):1446-1457. doi: 10.1038/s41593-022-01183-6. Epub 2022 Oct 24.

Besson-Girard S, Ji H, Gehring K, Bulut B, Kaya T, Usifo F, Simons M, Gokce O. *Dissociation of microdissected mouse brain tissue for artifact free single-cell RNA sequencing.* **STAR Protoc.** 2021 Apr https://doi.org/10.1016/j.xpro.2021.100590

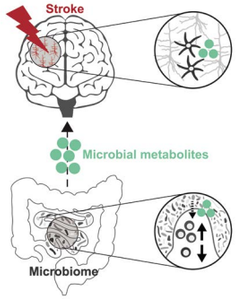
Safaiyan S, Besson-Girard S, Kaya T, Cantuti-Castelvetri L, Liu L, Ji H, Schifferer M, Gouna G, Usifo F, Kannaiyan N, Fitzner D, Xiang X, Rossner MJ, Brendel M, Gokce O, Simons M. *White matter aging drives microglial diversity.* **Neuron**. 2021 Feb 11:S0896-6273(21)00073-8. doi: 10.1016/j.neuron.2021.01.027. Epub ahead of print.

Ozgun Gokce accepted a call to become an Associate Professorship at the University of Bonn. He will be leaving the ISD on April 1st 2023.

Microbiome-Gut-Brain Axis

Principal Investigator:
Corinne Benakis

The gut microbiome has been reproducibly demonstrated to play a pivotal role in brain health and brain disease. Recent experimental and clinical studies suggest that stroke out-come is substantially impacted by the composition of the gut microbiome, which acts as a key modulator of immunity and metabolism (Benakis et al., Curr. Opin. Neurobiol. 2020; Benakis et al., Nat. Med. 2016). The research focus of our lab is to understand the bidirectional link between the gut microbiome and the brain after stroke. This research paradigm will enable the development of novel therapeutic strategies to improve recovery in stroke patients.



Gut-to-brain communication may occur via the production of metabolites from gut-resident bacteria. Indeed, there is accumulating evidence showing that metabolites derived from the microbiome influence brain diseases by regulating intestinal immune-cell function.

Here, we have a multi-target strategy by looking at the specific role of the gut metabolites on the brain function directly as well as on gut immune cells. In particular, we are investigating whether these microbiota-derived factors can restore the compromised brain barrier function (blood brain barrier and meningeal compartment) in cerebral ischemia. In an other project, we are testing whether microbial metabolites can polarize regulatory T cells in the gut and promote stroke recovery.

In addition to our interest in better deciphering the biological mechanism behind the gut-brain axis interaction in mouse stroke models, we aim to better understand the changes and function of the microbiota in stroke patients. Indeed, specific associations between microbiota and stroke outcome remain unclear, and stroke patients are often elderly and present with comorbidities, confounding stroke-mediated microbiota alterations. Using bioinformatic tools to analyse bacterial sequencing meta-data across several studies and countries, we are looking at interaction between host variables and microbial associations with stroke and determine whether controlling for these factors can identify robust signatures.

The key objective of our research group is to investigate whether metabolites produced by gut bacteria can influence stroke-induced neuroinflammation in mice and patients, as well as post-stroke comorbidities such as chronic neuroinflammation, cognitive decline and depression.

To reach this goal, we use a combination of metabolomics, metagenomics, bioinformatic pipelines, flow cytometry analysis, scRNAseq, and in-vitro immune cell culture, as well as mouse models (photo-convertible transgenic mice, humanized-fecal microbiota transplantation mice, probiotics/postbiotics) to elucidate the mechanisms involved in microbiome-gut-brain interactions.

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Minnah Irfan / Master Student
Alexandria Ruggles / Master Student

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Key Publications

Sorbie A, Delgado Jiménez R, Benakis C. *Increasing transparency and reproducibility in stroke-microbiota research: A toolbox for microbiota analysis*. **iScience**. 2022 Feb 26;25(4):103998. doi: 10.1016/j.isci.2022.103998.

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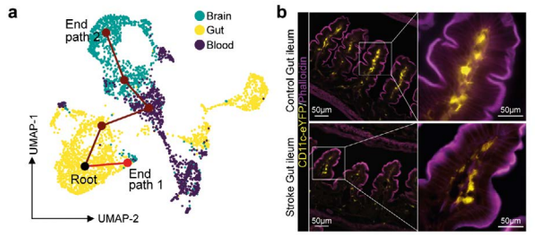
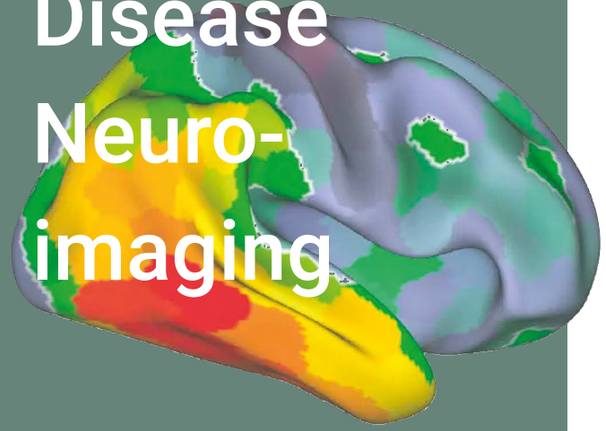


Intestinal cell mobilization after stroke. (a) *Pseudotime analysis of the differentially expressed genes in CD11c cells isolated from the gut, brain and blood after stroke in WT mice reveals two paths from the gut to the brain.* ***(b)*** *Immunohistochemistry images and magnification of the ileum small intestine in sham (top row) and stroke (bottom row) of CD11c-eYFP mice (yellow) counterstained with phalloidin (magenta) to visualize the villi.*

Alzheimer's Disease Neuro-imaging

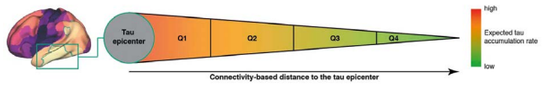


Principal Investigator:
Nicolai Franzmeier

Alzheimer's disease is characterized by the accumulation of cerebral beta-amyloid (Aβ) and tau pathology, which together cause progressive neurodegeneration and cognitive decline.

Our overarching goal is to better understand the mechanisms that promote the development and progression of Alzheimer's disease in order to develop clinically applicable personalized medicine models for predicting patient-specific disease trajectories (e.g. Franzmeier et al., Alzheimers Dement, 2020; Biel et al., Alz Res Ther, 2022). To this end, we combine multi-modal neuroimaging methods including positron-emission tomography (PET) and magnetic resonance imaging (MRI) with clinical assessments and genetics in large-scale patient data.

A major research focus is the prediction of trans-neuronal tau pathology spread, i.e. the major driver of neurodegeneration and cognitive decline in Alzheimer's disease. In a translational approach, we combine tau-PET imaging with MRI-based connectomics for modeling connectivity-based tau spreading patterns (e.g. Franzmeier et al., Brain, 2019; Nat Commun, 2020; Sci Adv, 2020; Steward et al., Alzheimers Dement, 2022). We have recently established connectivity-based tau spreading models, which allow accurate prediction of future tau spreading patterns on the patient level (Franzmeier et al., Sci Adv, 2020; Pichet Binette, Franzmeier et al., Nat Commun, 2022). These prediction models have high clinical utility, as they can be utilized to determine patient-specific endpoints in tau targeting trials which can drastically enhance the sensitivity for detecting treatment effects
In ongoing collaborative work, we are extensively validating these tau spreading models across atypical Alzheimer's disease variants and other neurodegenerative tauopathies.



For our second major interest, we study mechanisms by which life-style factors and genetic variants (i.e. SNPs) modulate Alzheimer's disease risk. Here, we found recently that key risk SNPs in the BIN1 gene drive specifically the development of tau pathology (Franzmeier et al., Nat Commun, 2019, Alzheimers Dement, 2021), whereas carriage of SNPs related to neuronal plasticity (i.e. BDNFVal66Met) can be beneficial and attenuate the effect of Alzheimer's disease pathology on neurodegeneration and cognitive decline (Franzmeier et al., Mol Neurodeg, 2020). In addition, we have identified protective brain mechanisms that are related to life-style factors (e.g. education) and buffer the effect of Alzheimer's disease related brain changes on cognitive decline (e.g. Franzmeier et al., Neurology, 2017; Brain, 2018; Alz Res Ther, 2018).

In summary, our research is motivated by the understanding of brain mechanisms that 1) promote the progression of AD pathology and 2) mechanisms that may help protect individuals from developing dementia despite the presence and progression of AD pathology. As an outlook, we aim to bring together these different lines of research to determine how protective mechanisms, genetics and functional brain networks may modulate the spread and progression of AD pathology and the development of AD-related cognitive impairment.

Dr. Nicolai Franzmeier / PI
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Key Publications

Biel D, Suárez-Calvet M, Hager P, Rubinski A, Dewenter A, Steward A, Roemer S, Ewers M, Haass C, Brendel M, Franzmeier N; ADNI. *sTREM2 is associated with amyloid-related p-tau increases and glucose hypermetabolism in Alzheimer's disease*. **EMBO Mol Med**. 2023 Jan 9:e16987. doi: 10.15252/emmm.202216987. Epub ahead of print. .

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Oligo-dendrocyte Pathology

Principal Investigator:
Sarah Jäkel

We aim at understanding the role of oligodendrocytes – the myelin forming cells in the central nervous system – in Alzheimer's disease. For decades, the pathology in Alzheimer's has been considered purely neuronal, however, recent advances have clearly demonstrated glial involvement, initiating a shift in scientific focus. Oligodendrocytes have been shown to be the first cell type to transcriptionally change in the earliest stages of the disease, while the functional importance of these changes still remains unknown. With an expertise in human oligodendrocyte biology, our work focusses on describing changes in the cellular distribution of oligodendrocytes in the human brain and to unravel how their functional changes contribute to the pathogenesis of Alzheimer's disease.

Our work is based on the observation that developmental cortical myelination does not happen all at once and late myelinated regions are affected earlier by Alzheimer's disease than early myelinated ones. My previous work revealed oligodendrocytes in the human brain are heterogeneous, representing different states that might exhibit different functions. In the context of Alzheimer's disease, this could in turn influence the vulnerability of neurons to degenerate within different brain areas. Hence, by understanding the distribution and the function of different oligodendrocyte states we aim to explain why some brain regions are more affected by Alzheimer's than others.

We use 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 in which we recreate and characterize the functional oligodendrocyte cell states, giving our research a highly translational character.

Our long-term vision is to compare oligodendrocyte pathology in different neurodevelopmental and neurovascular disorders that can ultimately lead to the discovery of novel therapeutic targets.

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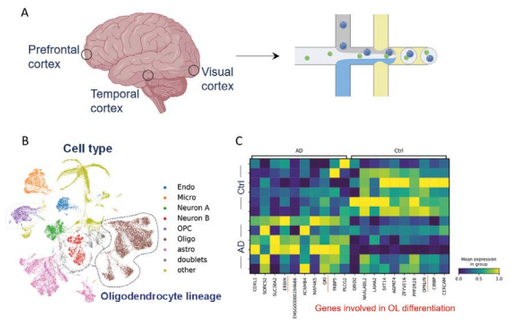
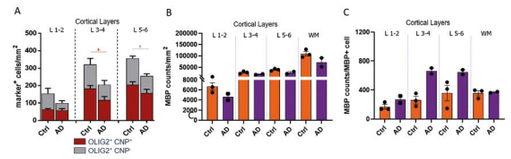


Transcriptional analysis of oligodendrocytes.
A *Scheme of experimental setup for single nuclei RNA-sequencing experiment on post-mortem human brain tissue.* ***B*** *UMAP plot of all recovered cell types.* ***C*** *Differential gene expression of oligodendrocytes between Ctrl and AD suggest impaired differentiation in AD patients.*



Oligodendrocytes in the visual cortex of control and AD patients. A *quantifications of oligodendrocyte lineage (OLIG2) cells and mature oligodendrocytes (CNP) across different cortical layers show a significant reduction of oligodendrocytes in AD patients.* ***B*** *Quantifications of MBP mRNA across different cortical layers show no significant transcriptional changes in AD patients.* ***C*** *Quantification of MBP mRNA normalized to the number of oligodendrocytes show an increase in AD patients, indicating that oligodendrocytes in AD patients are compensating for the loss of cells.*

Key Publications

Macnair W, Calini D, Agirre E, Bryois J, Jäkel S, Kukanja P, Stokar-Regenscheit N, Ott V, Foo LC, Collin L, Schippling S, Urich E, Nutma E, Marzin M, Amor S, Magliozzi R, Heidari E, Robinson MD, Castelo-Branco G, Williams A, Malhotra D. *Single nuclei RNAseq stratifies multiple sclerosis patients into three distinct white matter glia responses*. **bioRxiv**. 2022.

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Molecular Biomarkers – from Omics to Mechanisms

Principal Investigator:
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 3,000 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 ultra-sensitive single-molecule and point-of-care technologies, we have identified novel markers for stroke on different molecular levels.

Dr. Dr. med. Steffen Tiedt / PI
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Vanessa Granja Burbano / PhD student
Evan Hunter Stanton / PhD student
Linjie Zhang / PhD student
Yasin Eshraghi / PhD student
Teresa Allegra Wölfer / MD student
Nada Khalifeh / MD student
Michael Karg / MD student
Charlotte Forster / MD student
Walter Viegener / Master student
Jenny Alt / Team Assistant

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Key Publications

Tiedt S, Buchan AM, Dichgans M, Lizasoain I, Moro MA, Lo EH. *The neurovascular unit and systemic biology in stroke - implications for translation and treatment*. **Nat Rev Neurol.** 2022 Sep 9. doi: 10.1038/s41582-022-00703-z. Epub ahead of print.

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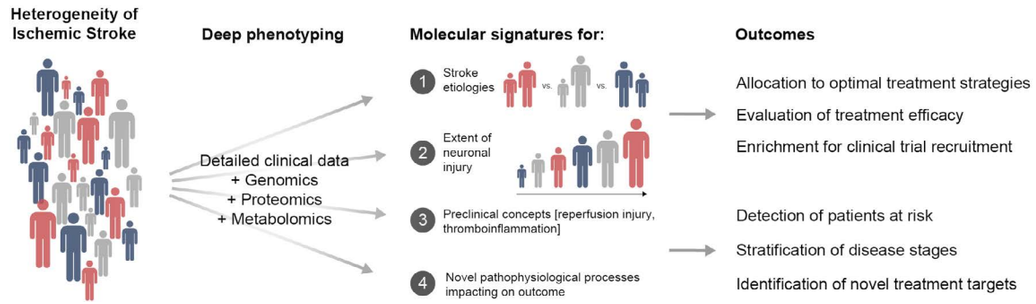
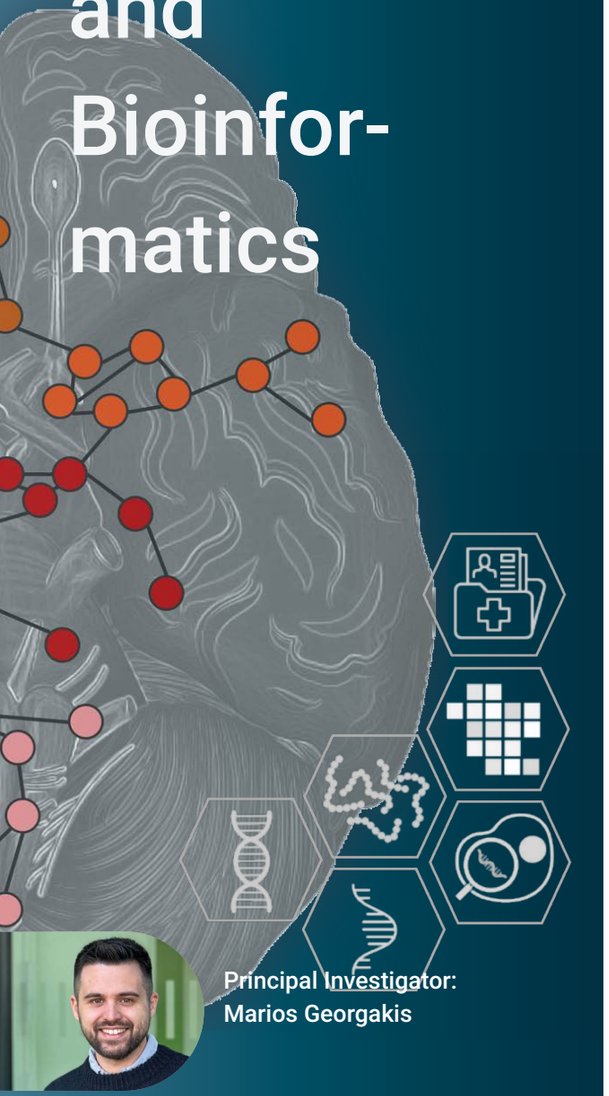


Epidemiology and Bioinformatics



Principal Investigator:
Marios Georgakis

Cerebrovascular diseases represent a leading cause of death and disability worldwide. Our work is motivated by a pressing need to optimize cerebrovascular health with the development of precise and personalized preventive and therapeutic strategies. To this end, we use large-scale and multi-dimensional data from epidemiological studies and human biobanks (genomics, transcriptomics, proteomics, imaging) and apply bioinformatic tools to inform such strategies. We have a special focus on extra- and intracranial atherosclerosis, one of the most common causes of stroke.

Our goals include: (i) the discovery of disease-modifying drug targets for novel therapeutic and preventive strategies against cerebrovascular disease, (ii) the deeper molecular and phenotyping of cerebrovascular pathologies, (iii) the discovery of in vivo biomarkers of cerebrovascular disease activity, and (iv) the development of personalized risk stratification tools for patients with or at risk for cerebrovascular disease.

Discovery of drug targets for cerebrovascular disease
Using human genetic data as our starting point, we bridge different multiomics levels with causal inference methods, such as Mendelian randomization, in order to dissect mechanisms leading to cerebrovascular disease. Our vision is to inform the development of disease-modifying treatments for cerebrovascular pathologies by triangulating the results from human genetics with data from epidemiological studies, human biobanks, and experimental models.

Deeper molecular phenotyping of cerebrovascular disease pathomechanisms
Using human samples, we apply novel high-throughput techniques, such as single-cell sequencing and spatial transcriptomics to deeper characterize cerebrovascular disease lesions at higher resolution. For this purpose, we recently developed the AtherOMICS biobank, which involves the collection of atherosclerotic plaque samples from patients undergoing carotid endarterectomy. Our vision is to detect disease processing signatures with diagnostic and therapeutic relevance.

Discovery of in vivo personalized biomarkers
The third key area of exploration involves the discovery of novel readouts of cerebrovascular disease presence and activity. We bridge data from high-throughput molecular technologies in human samples with imaging technologies, such as CT and MRI, as well as with multiomics analyses of peripheral blood samples, in order to detect in vivo phenotypes of disease activity. Our vision is to use such in vivo biomarkers as endpoints in clinical trials testing disease-modifying treatments.

Development of risk stratification tools
Cerebrovascular disease is highly heterogeneous, as is the predisposition of individuals to it depending on their genetic profiles and lifestyles. Over and over again, we see that the one-size fits all approaches we apply in the clinic do not equally work for all. We aim to develop efficient risk stratification tools by applying approaches that range from the development of polygenic risk scores in the general population to deploying deep learning methods in neuroimaging studies of stroke patients. Our vision is to identify individuals that might benefit from specific preventive or therapeutic approaches.

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Jana Mattar / MD Student
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Key Publications

Georgakis MK*, Bernhagen J*, Heitman L, Weber C, Dichgans M. *Targeting the CCL2-CCR2 Axis for Atheroprotection: Triangulation of Evidence and Steps Towards Clinical Translation*. **Eur Heart J**. 2022 May 14;43(19):1799-1808.

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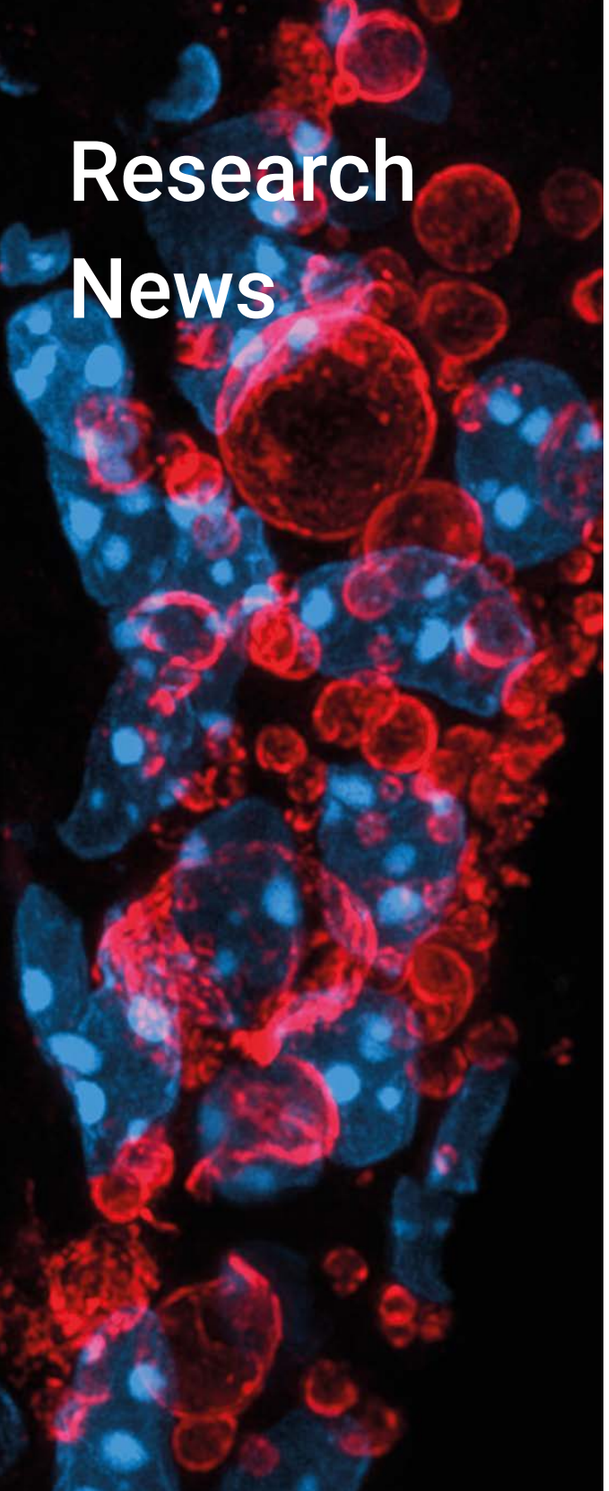
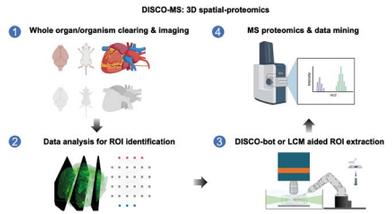


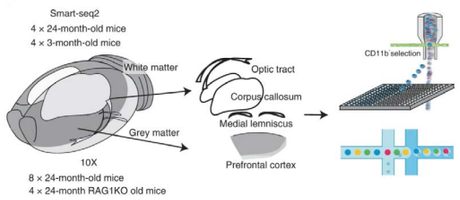
Research News

December 2022 3D spatial-omics technology to tackle complicated diseases



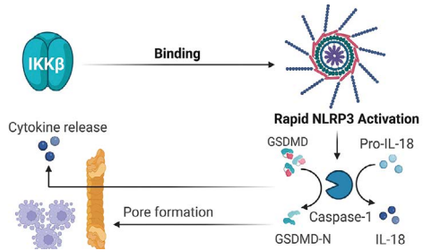
December 2022 Identifying subtle tissue changes at disease initiation or characterizing the molecular perturbations that trigger disease progression remains difficult in animal models or post-mortem human organs. To address this challenge, ISD investigators developed DISCO-MS, a 3D spatial-omics technology that combines methods of tissue clearing with cutting edge AI, robotics and proteomics technologies. They applied DISCO-MS to an Alzheimer's disease mouse model and to atherosclerotic plaques in the human heart to identify spatial-molecular maps. *Bhatia et al. Cell 2022.*

CD8+ T cells induce IFN-responsive oligodendrocytes & microglia in white matter aging



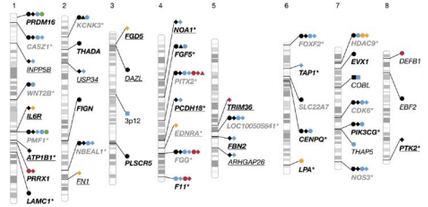
October 2022 Among the hallmarks of brain aging is a decline in white matter volume and function. Using scRNA-seq, the Gokce and Simons labs characterized age-related oligodendrocyte and microglial states. They identified a population of interferon-responsive oligodendrocytes (IRO) and microglia (IRM) that localize near CD8+ T cells in white matter. Lack of CD8+ T cells prevented age-related cell loss in white matter. Their findings unravel a so-far unknown role of the adaptive immune system during brain aging. *Kaya et al. Nat Neurosci. 2022*

A shortcut to inflammasome activation



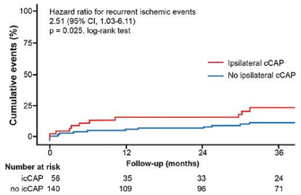
October 2022 A rapid immune response to signals released from pathogens and injuries is critical for maintaining tissue integrity and restoring homeostasis. This response is largely mediated by the concerted action of pattern recognition receptors. Such cooperativity has been described for Toll like receptors (TLRs) and the NLRP3 inflammasome, but the underlying molecular mechanisms remain elusive. ISD investigators now demonstrate that IKKβ binds NLRP3 providing a shortcut to inflammasome activation for rapid immune responses. *Asare et al. Signal Transduct Target Ther. 2022*

Stroke genetics informs drug discovery and risk prediction across ancestries



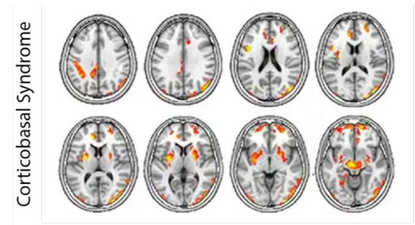
September 2022 A GWAS meta-analysis of >110,000 stroke patients and 1.5 Mio controls from five different ancestries identified multiple novel stroke risk loci. The study provides genetic evidence for putative drug effects with converging evidence for drugs targeting F11 and KLKB1 among others. Drugs targeting F11 and F11a are currently being examined in phase II trials for stroke prevention. A polygenic score predicted ischemic stroke across ancestries and in clinical-trial participants with cardiometabolic disease. *Mishra et al Nature. 2022*

Complicated carotid artery plaques and risk of recurrent ischemic stroke or TIA



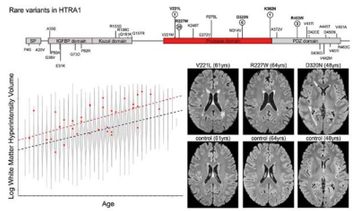
May 2022 Complicated nonstenosing carotid artery plaques (CAPs) are an under-recognized cause of stroke. Applying high-resolution contrast-enhanced carotid MRI to patients with acute ischemic stroke, ISD investigators found complicated CAP ipsilateral to acute ischemic anterior circulation stroke to be associated with an increased risk of recurrent ischemic stroke or TIA. Carotid plaque imaging identifies high-risk patients who might be suited for inclusion into future secondary prevention trials. *Kopczak et al. J Am Coll Cardiol. 2022*

Brain connectivity is associated with tau deposition in 4-repeat tauopathies



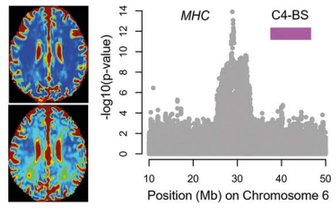
March 2022 Tau pathology drives neuronal dysfunction in 4-repeat tauopathies. Here, ISD researchers combined tau-PET, resting-state fMRI and histopathology data, to show that brain connectivity is associated with tau deposition patterns in patients with 4-repeat tauopathies. *Franzmeier et al. Nat Commun. 2022*

Role of HTRA1 in brain white matter hyperintensities



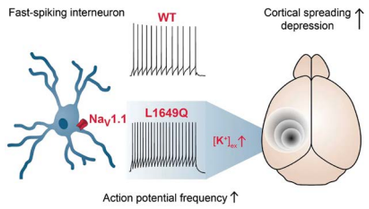
October 2022 In a whole-exome sequencing study on >16.000 individuals, ISD investigators found rare variants in the protease domain of HTRA1 to associate with brain WMH burden. The frequency of such variants in the general population was 1:450 and their presence corresponded to a larger effect than meeting the criteria for conventional vascular risk factors. Variants in EGFL8, which falls into a common pathway with HTRA1, also associated with WMH burden. *Malik et al. Brain 2021*

Role of complement component C4 in age-related white matter injury



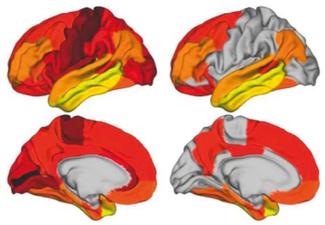
July 2021 Age-related loss of white matter integrity is a major determinant of cognitive decline and dementia. Analysing data from >30.000 UK Biobank participants, ISD investigators in collaboration with Matthew Traylor (London) found the complement component C4-BS variant to associate with age-related WM injury. These findings suggest a role of the complement systems and of gene-environment interactions in age-related loss of white matter microstructural integrity. *Traylor et al. Brain 2022*

Interneurons trigger cortical spreading depolarizations (CSDs)



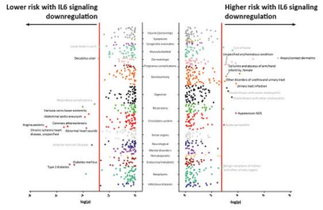
September 2021 CSDs are the electrophysiological correlate of migraine aura and involved in the propagation of brain damage after ischemic and traumatic brain injury. Using a novel migraine mouse model, the Plesnila Lab in collaboration with Tobias Freilinger, Holger Lerche (Tübingen, Germany), and Massimo Mantegazza (Nice, France) found that CSDs are triggered by inhibitory interneurons. This counterintuitive finding unravels the so far unknown cellular mechanism for the initiation of CSDs. *Auffenberg et al. J Clin Invest. 2021*

Common KLOTHO SNP protects against Tau pathology



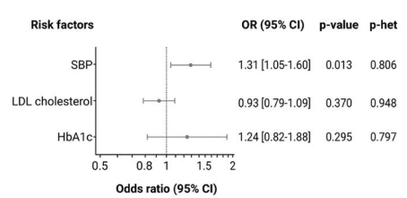
June 2021 ISD researchers found that a common variant in the anti-aging gene KLOTHO is associated with reduced fibrillar tau, a key pathology in Alzheimer's disease. *Neitzel et al. Nat Commun. 2021*

Genetic downregulation of IL-6 signaling leads to a favourable cardiometabolic profile



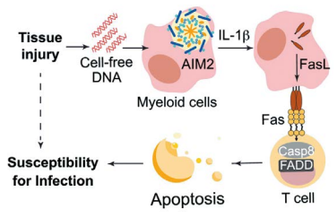
March 2021 Drugs targeting IL6 signaling have been approved for autoimmune diseases but the repurposing potential for other indications remains unknown. ISD researchers developed a genetic score predicting IL6 signaling activity over lifetime. In a phenome-wide association study they found genetically downregulated IL6 signaling to be associated with a favourable cardiometabolic profile including a lower risk of coronary artery disease and diabetes, and an increase in HDL cholesterol levels. Their results support repurposing of IL6R blockade as a strategy for lowering vascular risk. *Georgakis et al. Circulation 2021*

Life's simple 7 and incident dementia risk



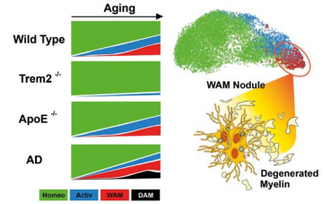
March 2021 Leveraging data from the UK Biobank (N=229,976 participants) ISD investigators examined whether cardiovascular health measured by the 'Life's simple 7' score is associated with incident all-cause dementia. They found that higher blood pressure was associated with higher risk of dementia both in longitudinal and Mendelian Randomization analyses. These findings underscore the importance of blood pressure control in midlife to mitigate dementia risk. *Malik et al. Alzheimers Dement. 2021*

AIM2-inflammasome signaling cascade causes post-stroke immunosuppression & secondary infections



March 2021 Stroke patients are predisposed to life-threatening infections after the initial ischemic event. This phenomenon is caused by a severe state of post-injury immunosuppression, which is characterized by a loss of T cells. Stefan Roth (Liesz Lab) in collaboration with others demonstrates that monocytes sense injury-released cell-free DNA via the AIM2 inflammasome inducing extrinsic T cell death. Uncovering this mechanism could open up new therapeutical approaches. *Roth et al. Immunity 2021*

White matter (WM) aging drives microglial diversity

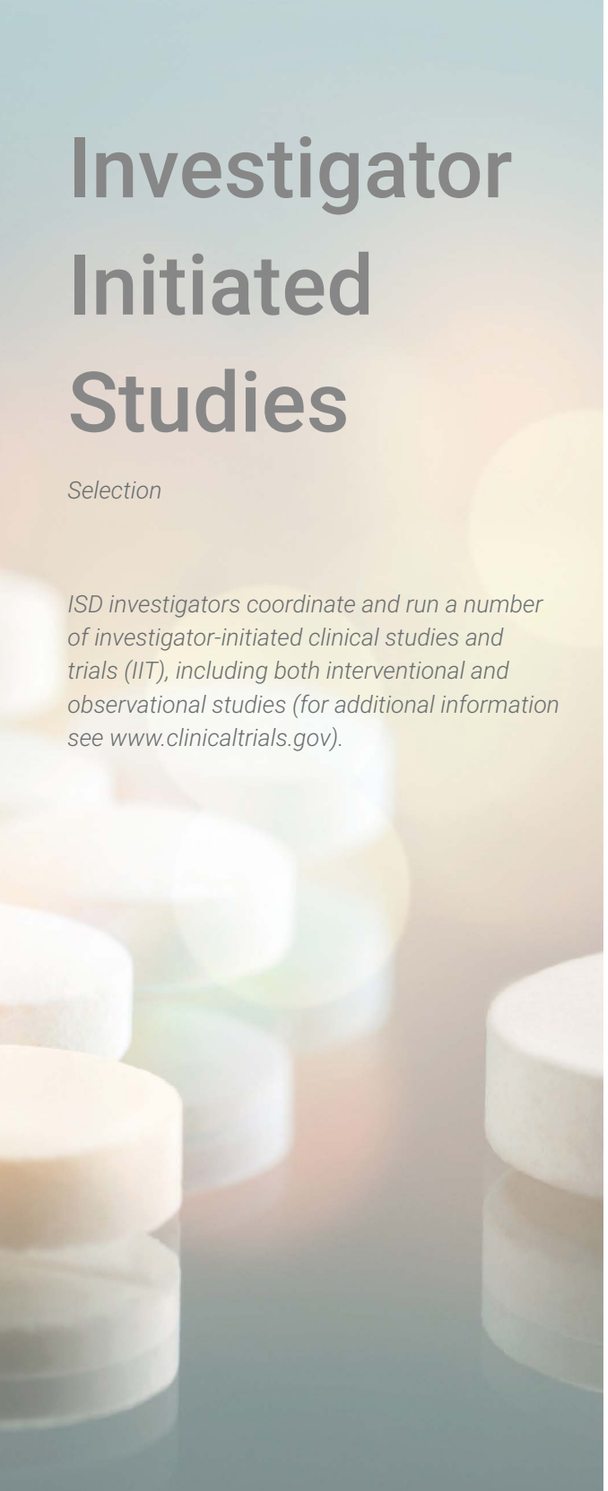


February 2021 Aging & vascular risk factors are associated with WM lesions and loss, but the role of microglia in aging WM has been elusive. Using single-cell RNA sequencing, ISD and DZNE investigators identified WM-associated microglia (WAMs), which form in a TREM2-dependent but APOE independent manner and are characterized by age-dependent activation of genes implicated in phagocytic activity and lipid metabolism. Thus, WAMs may represent a potentially protective response required to clear degenerated myelin accumulating during WM aging and disease. *Safaiyan et al. Neuron 2021*

Investigator Initiated Studies

Selection

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



Stroke Prevention Unit

Observational Studies

DEMDAS *(NCT01334749)*
*The **D**ZN**E** **M**echanism of **D**ementia after **A**fter **S**troke Study*
The DEMDAS (DZNE Mechanisms of Dementia After Stroke) study is a longitudinal prospective multicenter study of 600 stroke cases with follow-up assessments until 5 years. The aim of the study is to identify predictors of post-stroke dementia and mild cognitive impairment. A particular focus will be on biological markers (neuroimaging, biochemical markers derived from blood) and on interactions between vascular and neurodegenerative mechanisms.
Disease: Acute stroke
Funding: DZNE/Helmholtz
Coordinator: M Dichgans
Publications: Georgakis et al. Alzheimer's and Dementia 2022

PROSCIS *(NCT01364168)*
***PRO**spective **S**troke **C**ohort with Incident **S**troke*
The primary aim of the prospective observational study is to derive and validate risk scores for vascular endpoints (recurrent stroke, myocardial infarction, and other complications of stroke) and for death following an incident stroke. For this purpose patients with an incident stroke will be followed for 36 months
Disease: Acute stroke
Funding: Vascular Dementia Research Foundation
PI: M Dichgans
Publications: Mishra et al. Nature 2022

HIFI-CAA *(ISRCTN10514229)*
***HI**gh **F**requency **I**maging in patients with **C**erebral **A**myloid **A**ngiopathy*
HIFI is an observational prospective study with serial, monthly MRI imaging. The aims are to i) evaluate the development and temporal evolution of incident and prevalent focal convexity subarachnoid hemorrhages (fSAH) and cortical superficial siderosis (cSS) in CAA patients and ii) assess the monthly incidence of acute ischemic lesions in CAA patients with cSS/fSAH and to compare the incidence with lobar ICH survivors.
Disease: Cerebral amyloid angiopathy (CAA)
Funding: Vascular Dementia Research Foundation
PI: M. Düring

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. Bloodbased 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 bloodbased biomarkers to support decisionmaking in the acute phase of stroke.
Funding: Corona-Stiftung
Disease: Stroke
Coordinator: S. Tiedt
Publications: Tiedt et al. Ann Neurol. 2020, Tiedt et al. Neurology 2018

Interventional Studies

ICARUS *(NCT04412187)*
***I**nflammatory fa**C**tors **A**fte**R** ac**U**te ischemic **S**troke*
ICARUS is an interventional single-centre hospital-based cohort study in patients with acute ischemic stroke. The aims of the study are to i) define the charaacteristics and determinants of microglial activation after human stroke, and ii) assess the correlation of microglial activation with circulating inflammatory markers, structural brain changes on neuroimaging, and neurological outcomes. ICARUS involves serial TSPO-PET imaging along with serial MRI, immune cell profiling in blood, and both clinical and laboratory assessments.
Disease: Acute ischemic stroke
Funding: DFG
PI: M. Dichgans

FIND-AF-2 *(NCT04371055)*
Intensive Rhythm Monitoring to Decrease Ischemic Stroke and Systemic Embolism
Find-AF 2 is an interventional multicentre randomised open parallel controlled trial with blinded endpoint assessment. The primary objective is to determine, whether enhanced, prolonged and intensified ECG-monitoring leads to a reduction of cardioembolism (recurrent ischemic stroke or systemic embolism) by increasing the detection and adequate anticoagulation of underlying paroxysmal atrial fibrillation.
Disease: Acute ischemic stroke
Funding: DFG
PI: M. Dichgans

Clinical Trials

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 **D**isease**S***
In the multicentre, multinational open-label randomized trial TREAT-SVDs, we investigate the effects of three common blood pressure lowering drugs, amlodipine (calcium channel blocker), atenolol (beta-blocker) and losartan (AT1-receptor blocker) on microvascular function in patients with sporadic SVDs and CADASIL. Our aim is to demonstrate a beneficial effect of specific antihypertensive drug-classes on microvascular function in human SVDs.
Disease: Cerebral Small Vessel Diseases, CADASIL
Funding: EU/Horizon 2020
Coordinator: M. Dichgans
Publications: Kopczak et al. Eur Stroke J 2022

PRISE
Effects of a probiotic dietary supplement on the gut microbiome of stroke patients.
We are conducting a single-center interventional study of the brain-gut axis in stroke patients using a commercially available probiotic product approved as a dietary supplement. While taking the supplement, we will perform a characterization of the gut microbiome and its intervention-dependent diversity in our study participants. Additionally, we will document the resulting changes in the functional profile of this microbiome. Based on these observations, we would like to investigate the validity of probiotics as modulators of the microbiome in the context of stroke.
Funding: ISD
PI: A. Liesz

ESCAPE-NEXT *Phase 3 (NCT04462536)*
Efficacy and Safety of Nerinetide in Participants With Acute Ischemic Stroke Undergoing Endovascular Thrombectomy Excluding Thrombolysis
ESCAPE-NEXT is a Phase 3, randomized, multicentre, blinded, placebo-controlled trial in which patients with acute stroke are included on an emergency basis. The primary purpose of this study is to determine if a single dose of nerinetide can reduce global disability in people who have had a stroke and are selected for endovascular therapy without the use of a tissue plasminogen activator.
Disease: Acute ischemic stroke
Sponsor: NoNO Inc.
Co-PI: M. Dichgans; Co-PI: K. Dimitriadis

ANNEXa-I *Phase 4 (NCT03661528)*
Trial of Andexanet Alfa in ICH Patients Receiving an Oral FXa Inhibitor
ANNEXa-I is a randomized, multicenter clinical trial designed to determine the efficacy and safety of andexanet alfa compared to usual care in patients presenting with acute intracranial hemorrhage within 6 hours of symptom onset to baseline scan and within 15 hours of taking an oral factor Xa inhibitor.
Disease: Acute Intracranial Hemorrhage
Sponsor: Alexion Pharmaceuticals, Inc.
PI: K. Dimitriadis

ENRICH-AF *Phase 4 (NCT03950076)*
E*doxaba****N*** *fo****R*** ***I****ntra****C****ranial* ***H****emorrhage Survivors With* ***A****trial* ***F****ibrillation*
This interventional, multicenter trial aims to assess whether Edoxaban compared to non-antithrombotic medical therapy (either no antithrombotic therapy or antiplatelet monotherapy) reduces the risk of stroke in high-risk atrial fibrillation patients with previous intracranial hemorrhage.
Disease: Intracranial Hemorrhages, Atrial Fibrillation
Sponsor: Hamilton Health Sciences, through its Population Health Research Institute
PI: M. Dichgans

ELAN *(NCT03148457)*
E*arly versus* ***L****ate initiation of direct oral* ***A****nticoagulants in post-ischaemic stroke patients with atrial fibrillatio****N***
The international, multicentre trial aims to estimate the net benefit of early versus late (current standard practice) initiation of direct oral anticoagulants in patients with acute ischaemic stroke related to atrial fibrillation.
Disease: Ischaemic Stroke
Funding: Inselspital (University Hospital) Bern
Co-PI: A. Liesz

CONVINCE *(NCT02898610)*
(German Extension) ***CO****lchicine for Prevention****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.
Disease: Ischaemic Stroke
Funding: German Research Foundation (DFG)
PI: M. Dichgans, K. Dimitriadis

ELAN *(NCT03148457)*
E*arly versus* ***L****ate initiation of direct oral* ***A****nticoagulants in post-ischaemic stroke patients with atrial fibrillatio****N***
The international, multicentre trial aims to estimate the net benefit of early versus late (current standard practice) initiation of direct oral anticoagulants in patients with acute ischaemic stroke related to atrial fibrillation.
Disease: Ischaemic Stroke
Funding: Inselspital (University Hospital) Bern
Co-PI: A. Liesz

Memory Clinic

Observational Studies

EGO
Emotional resilience as a protective factor in mild cognitive impairment
This observational study aims to identify functional brain network mechanisms that confer resilience against the impact of Alzheimer`s disease related brain changes on cognitive performance.
Disease: Alzheimer`s disease
Funding: LMU FöFoLe
PI: N. Franzmeier

DELCODE
(German Clinical Trials Register Nr: DRKS00007966)
DZNE – Longitudinal Cognitive Impairment and Dementia Study
This observational multicenter study investigates different risk groups and individuals in an early stage of Alzheimer's disease over a period of several years with the aim of a better understanding of early disease stages, improved prediction of disease progression and identification of new markers for early Alzheimer's dementia diagnosis
Disease: Alzheimer`s disease
Funding: DZNE/Helmholtz
PI: K. Bürger

DESCRIBE
A DZNE Clinical Registry Study of Neurodegenerative Diseases
The aim of the DESCRIBE study is to use the results obtained in the context of normal patient care, together with the results of studies on biomaterials (blood, nerve water, lacrimal fluid and urine) including genetic tests, for scientific purposes and thus to increase knowledge of neuro-degenerative diseases and thus create the conditions for better therapies.
Disease: Neurodegenerative Diseases
Funding: DZNE/Helmholtz
PI: K. Bürger

Clinical Trials

Embark Phase 3 *(NCT04241068)*
A Study to Evaluate Safety and Tolerability of Aducanumab in Participants With Alzheimer's Disease Who Had Previously Participated in the Aducanumab Studies 221AD103, 221AD301, 221AD302 and 221AD205
The primary objective of this clinical trial is to evaluate the safety and tolerability of aducanumab over 100 weeks of treatment after a wash-out period imposed by discontinuation of feeder studies in participants who had previously received aducanumab or who had previously received placebo.
Disease: Alzheimer`s disease
Sponsor: Biogen
PI: K. Bürger

INVOKE-2 Phase 2 *(NCT04592874)*
A Phase 2 Study to Evaluate Efficacy and Safety of AL002 in Participants With Early Alzheimer's Disease
This phase 2 randomized, double blind, placebo controlled study evaluates the efficacy and safety of AL002 in participants with Early Alzheimer's Disease.
Disease: Alzheimer`s disease
Sponsor: Alector Inc.
PI: K. Bürger

EVOKE Phase 3 *(NCT04777396)*
A Research Study Investigating Semaglutide in People With Early Alzheimer's Disease
This clinical trial aims to find out whether the medicine, semaglutide, has a positive effect on early Alzheimer's disease.
Disease: Early Alzheimer's Disease
Sponsor: Novo Nordisk A/S
PI: K. Bürger

Collaborative Research

Selection

IMMUNOSTROKE

FOR 2879: ImmunoStroke: From immune cells to stroke recovery

www.immunostroke.de/

The inflammatory response to ischemic brain injury has meanwhile been well established as a key pathomechanism contributing to stroke outcome. Stroke is traditionally not considered an inflammatory disease, yet it shares multiple features with (auto)immune brain disorders. While these neuroinflammatory mechanisms have been described in detail for the acute phase after ischemic brain injury, mechanisms of brain-immune interaction during recovery in the chronic phase after stroke still await clarification. Likewise, consequences of immunomodulatory interventions for post-stroke repair and neuroplasticity are barely understood. Therefore, this Research Unit focus on studying the role of neuroinflammation for tissue remodeling and long-term recovery following stroke.

Coordinator FOR 2879: A. Liesz
A2: Inflammasomes in post-stroke regeneration.
PI: A. Liesz
A3: The role of microglia in cortical connectivity during recovery after stroke. **PI: A. Liesz**
C2: Microglia-PET as a surrogate marker for post-stroke neuroinflammation. **PI: M. Dichgans**
Z2: Standardization of animal models and outcome parameters. **PI: A. Liesz, G. Lovera**

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

sfb1123.med.uni-muenchen.de

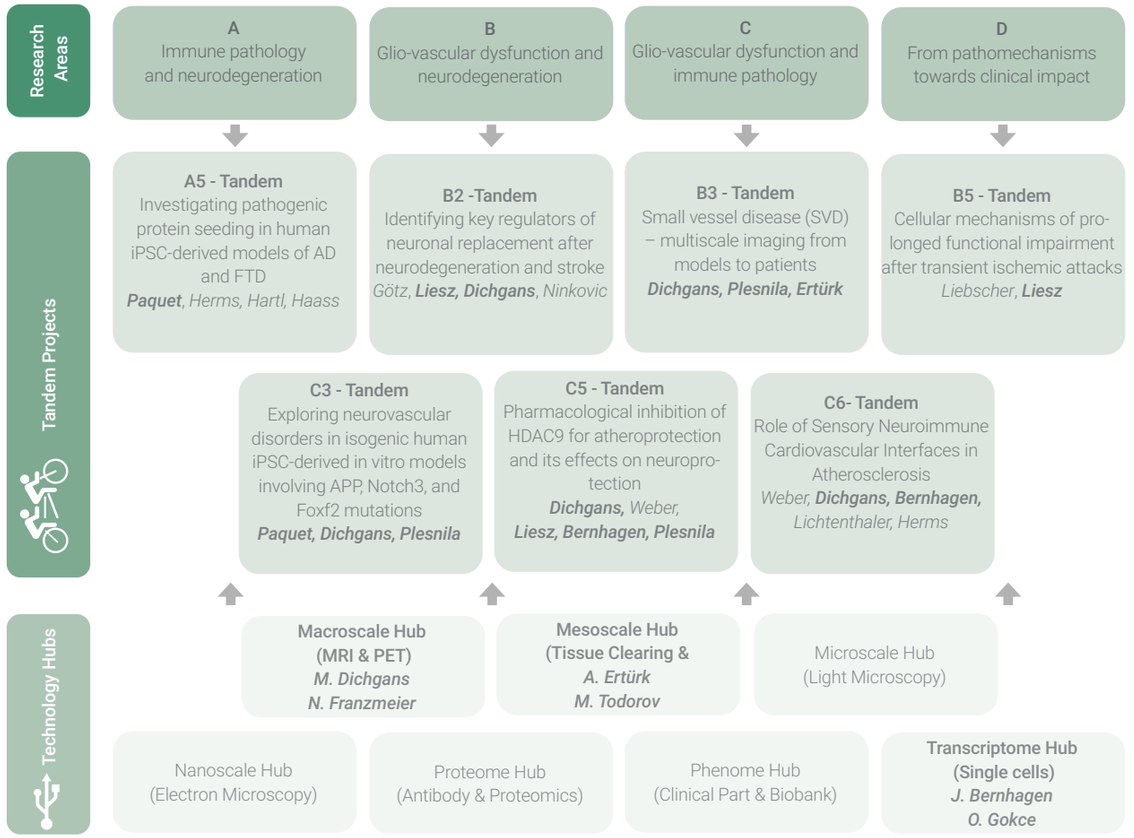
Vascular disease including coronary artery disease (CAD) and stroke is the leading cause of death and morbidity worldwide and imposes exorbitant socioeconomic costs.
This dilemma could be alleviated by improving vascular prevention and therapy based on a refined mechanistic pervasion of atherosclerosis as the underlying pathology. Beyond the emergence of PCSK9 inhibitors for efficient control of hyperlipidemia, the recent positive outcome of the CANTOS trial has lend convincing support to pursuing the concept that targeting inflammatory pathways has major impact in the pathogenesis and treatment of atherosclerosis. It remains the long-standing mission of the collaborative research center (CRC) 1123 in a third period to provide an in-depth mechanistic understanding of molecular networks in atherogenesis, atheroprogression and atherothrombosis and to improve the identification and validation of relevant therapeutic target candidates.

A02 Physical and functional interactions of chemokines with potent inflammatory effectors in atherosclerosis: focus on galectins : ***PI: J. Bernhagen***
A03 The MIF protein/receptor network in atherosclerosis: mechanisms, novel members, and specific therapeutic strategies: ***PI: J. Bernhagen***
B03 Mechanistic Role of HDAC9 in Atherosclerosis: ***PI: M. Dichgans, Y. Asare***
B11: Inflammation begets inflammation – impact of remote injuries on atherosclerosis progression: ***PI: A. LIesz***

SyNergy
Munich Cluster for Systems Neurology

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

www.synergy-munich.de/index.html



DFG Deutsche Forschungsgemeinschaft
German Research Foundation

ERA-NET Neuron:
ISD was successful in the lates ERA-Net call 2022 on *"Cerebrovascular Diseases including Small Vessel and Brain Barrier Dysfunction"* with the following 4 projects:

www.neuron-eranet.eu/

Role of oxidative stress for neuro-vascular function (VasOx)

Reactive oxygen species (ROS) play a detrimental role upon reperfusion from cerebral ischemia, the current standard therapy for ischemic stroke. The exact vascular and cellular mechanisms of this „reperfusion injury", however, remains largely unknown due to the lack of methodology to measure ROS in vivo and the lack of animal models. The current project will use novel multicistronic chemogenetic technology to measure and induce ROS in a cell specific manner in vivo. The results of VasOx will identify the temporal and cellular profile of ROS production after cerebral ischemia and decipher the underlying gene expression thereby defining novel molecular and cellular targets for future precision medicine therapeutics for stroke patients.

Coordinator: N. Plesnila

Multidimensional interrogation of microvascular matrisome abnormalities in cerebral small vessel diseases (MatriSVDs)

Cerebral small vessel diseases (cSVDs) are a leading cause of stroke and dementia with no mechanism-based treatments. We aim to provide novel insights into fundamental mechanisms underlying the loss of mural cells and remodeling of the microvascular extracellular matrix (ECM), the two major outcomes common to cSVDs. Our overarching hypothesis is that perturbations of the brain microvascular matrisome— the ensemble of ECM and associated proteins—are a convergent pathway in cSVDs.

PI: M. Dichgans

Modulation of brain barrier function by microbiota-derived factors in cerebral ischemia (BiotaBB)

Recent evidence identifies the gut microbiota as a modulator of brain function in health and diseases also by acting on the different brain barriers, the blood-brain barrier (BBB) and meninges. To date, it remains unclear whether gut metabolites affect the dysfunction of brain barriers in stroke. The aim of this project is to investigate the role of microbiota-derived factors in restoring compromised brain barrier function in cerebral ischemia.

Coordinator: C. Benakis

The meninges as a new player in post-stroke recovery (MeniSPYs)

The meninges have been described as an important cerebral invasion route in primary autoimmune diseases and important in regulating cerebral blood flow, antigen drainage to the systemic immune compartment and recirculation of leukocytes from brain to blood. However, little is known about the role of meninges in ischemic stroke. We will focus on meningeal gateways to understand the key mechanisms controlling meningeal inflammation and inflammatory cell recruitment with particular emphasis on the role of meningeal inflammatory actions on unfavourable outcomes after stroke that could be therapeutically targeted for the benefit of patients.

PI: A. Liesz

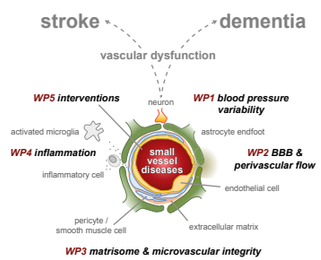
SVDs@target
Small vessel diseases in a mechanistic perspective

www.svds-at-target.eu/

Targets for Intervention: Affected pathways and mechanistic exploitation for prevention of stroke and dementia

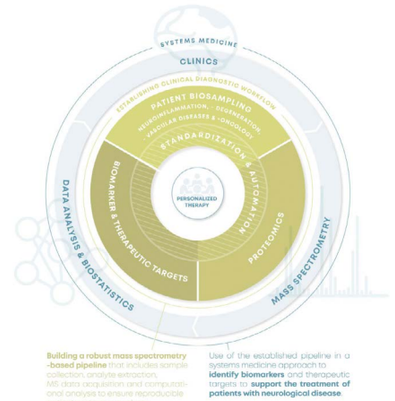
Cerebral small vessel disease (SVD) is a major cause of stroke, disability and dementia. It is caused by a dysfunction of the small arteries, which supply blood to the deep brain regions. Smooth muscle cells (SMC) that surround the vessels regulate blood flow and ensure a sufficient blood supply. Despite the consensus that SVDs are initiated by an endothelial dysfunction including blood-brain barrier (BBB) failure, the pathophysiology remain largely unknown. SVDs@target thus addressed one of the most pressing health issues in ageing societies. The project ended in Dec 2021 after six years. SVDs@target has discovered new pathomechanisms of SVDs and found promising key players which could serve as novel therapeutic targets. New MRI markers related to SVDs were identified and new MRI protocols were developed to assess vascular functions and to measure cardiac and respiration-induced brain deformations simultaneously.
The results of SVDs@target will improve the preventive treatment of the disease and will lead to a significant benefit at the individual and societal level.
https://www.svds-at-target.eu/

Coordinator: M. Dichgans



CLINSPECT-M
CLINICAL MASS SPECTROMETRY CENTER MUNICH

www.mscoresys.de/



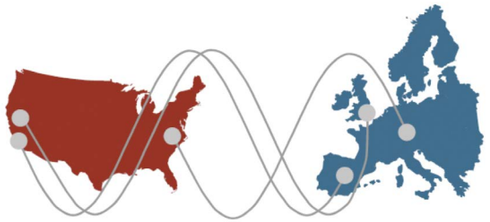
This project unites an outstanding team of Munich-based experts in proteomics, medicine and bioinformatics to translate mass spectrometry-based proteomics into clinical practice. With a biological-medical focus on diseases of the nervous system the overarching goals of CLINSPECT-M are to demonstrate that mass spectrometry in systems medicine i) is technically and logistically feasible ii) generates novel insights into disease biology iii) uncovers biomarkers for diagnosis, prognosis and treatment response and iv) provides short-, medium- and long-term clinical translation opportunities aiding clinical decision making for individual patients.

PI: M. Dichgans

Bundesministerium für Bildung und Forschung

Two new networks funded by Leducq Foundation in 2021 & 2022:

www.fondationleducq.org



Leducq Foundation: Trans-Atlantic Network of Excellence on Circadian Effects in Stroke (CIRCA)

Circadian rhythms affect almost all aspects of mammalian biology, so any pursuit of therapies for clinical disease may be meaningless without considering circadian mechanisms. This translational network aims to investigate in experimental models and human how circadian biology influences cerebrovascular disease, with the aim to reveal novel targets for effective therapies.

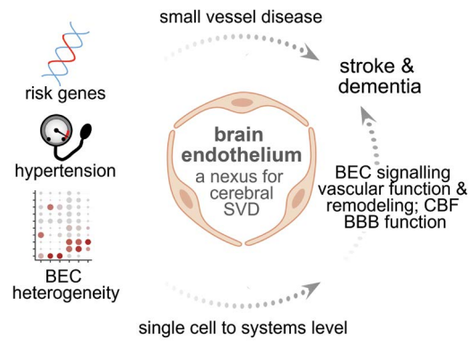
PI: S. Tiedt

Leducq Foundation: International Network of Excellence on Brain Endothelium: A Nexus for Cerebral Small Vessel Disease

Brain endothelial cells (BECs) have unique roles at the blood-brain barrier (BBB) and in controlling cerebral blood flow. This essential integrator function seems to be progressively degraded in SVD so BEC dysfunction serves as a nexus for the loss of brain health. The leading risk factor for SVD is hypertension. We propose a two-hit mechanism where hypertension synergizes with genetic predisposition to drive SVD. BRENDA will tackle these questions and significantly advance the understanding of BECs, their impact on brain health, and their potential as targets of novel therapies.

The international Network of Excellence BRENDA is supported by the Foundation Leducq with 7,5 Mio USD over five years and coordinated by Martin Dichgans and Frank Faraci (University of Iowa, USA).

Coordinator and PI: M. Dichgans
PI: D. Paquet



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 Leducq Foundation and 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.

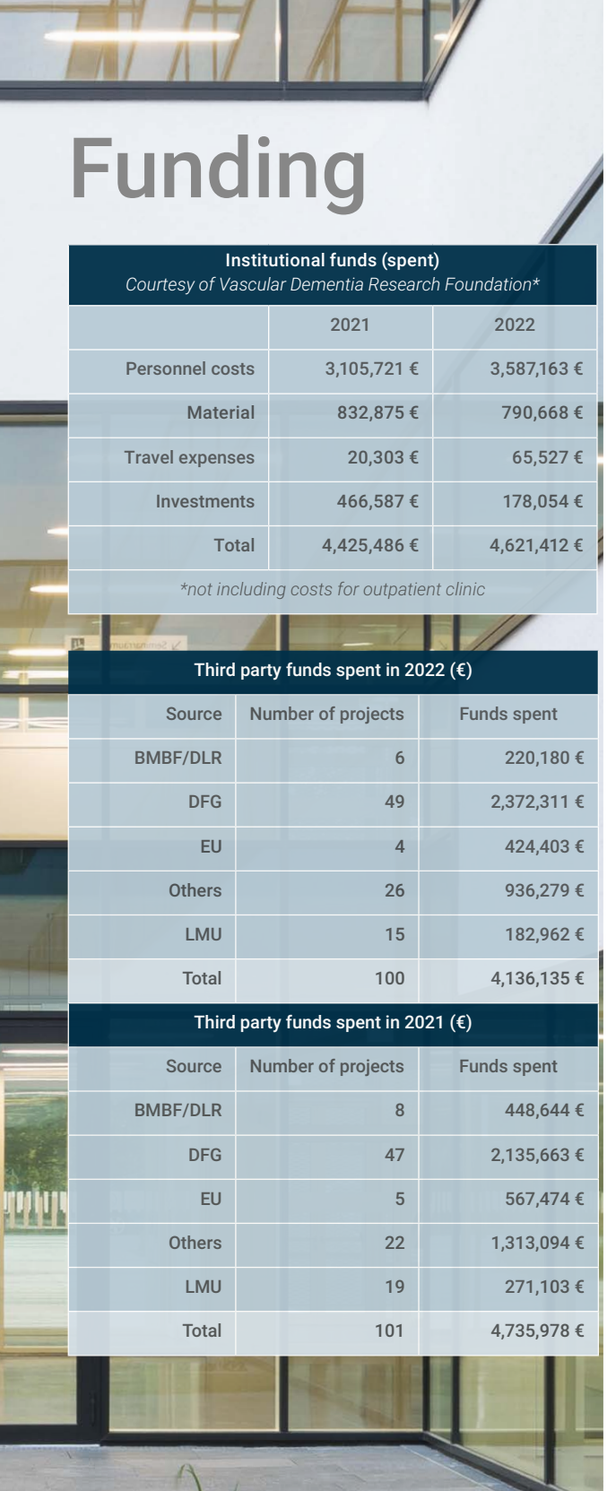
LMU (Ludwig-Maximilians-Universität)
TUM (Technische Universität München)
HMGU (Helmholtz Zentrum München)
DZNE (German Center for Neurodegenerative Diseases)
MPI (Max-Planck-Institutes)
DHS (Deutsches Herzzentrum)

Selection of Collaborations with other German Sites

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

Selection of International Collaborations

- Columbia University, New York, USA
- University of Vermont, Burlington, USA
- University of Iowa, Iowa, USA
- University of Edinburgh, UK
- University of Cambridge, UK
- University of Copenhagen, Denmark
- University of Uppsala, Sweden
- University of Gothenburg, Sweden
- University Paris Diderot, Paris, France
- Institut Pasteur de Lille, France
- University of Bordeaux, France
- Hungarian Academy of Sciences, Budapest, Hungary
- A.I. Virtanen Inst. for Molecular Sciences, Kuopio, Finland
- UMC Radboud, Nijmegen, The Netherlands
- UMC Utrecht, The Netherlands
- European Institute for Biomedical Imaging Research, Vienna, Austria
- Yale University, New Haven, USA
- Duke NUS and National Heart Center, Singapore



Funding

Institutional funds (spent) *Courtesy of Vascular Dementia Research Foundation**		
	2021	2022
Personnel costs	3,105,721 €	3,587,163 €
Material	832,875 €	790,668 €
Travel expenses	20,303 €	65,527 €
Investments	466,587 €	178,054 €
Total	4,425,486 €	4,621,412 €
*not including costs for outpatient clinic		

Third party funds spent in 2022 (€)		
Source	Number of projects	Funds spent
BMBF/DLR	6	220,180 €
DFG	49	2,372,311 €
EU	4	424,403 €
Others	26	936,279 €
LMU	15	182,962 €
Total	100	4,136,135 €

Third party funds spent in 2021 (€)		
Source	Number of projects	Funds spent
BMBF/DLR	8	448,644 €
DFG	47	2,135,663 €
EU	5	567,474 €
Others	22	1,313,094 €
LMU	19	271,103 €
Total	101	4,735,978 €

	Project	Role	Period
BMBF	**iBioStroke - Identifikation und klinische Validierung von Biomarkern für den langfristigen Krankheits-verlauf nach zerebraler IschämieSchlaganfall**	N. Plesnila	04/2020 - 03/2023
	CLINSPECT-M - Klinisches Massenspektrometrie Zent-rum München	M. Dichgans (PI)	03/2020 - 02/2023
	Role of Regnase-3 in viral myocarditis	M. Fischer (PI)	03/2020 - 02/2023
	Link between DAMPs and MIF proteins in cardiac re-modeling after I/R injury and relevance for heart failure	J. Bernhagen (PI)	12/2019 - 11/2022
	Astrozytärer Metabolismus nach ischämischem Stress	N. Plesnila	12/2019 - 11/2022
	Treat-ION - Pathophysiologi-sche Mechanismen	N. Plesnila (PI)	09/2019 - 08/2022
	MISST- Ebenen-spezifische Untersuchung der synap-tischen Fehlfunktion nach Schlaganfall	N. Plesnila	09/2018 - 08/2022

	Project	Role	Period
DFG Networks	**Munich Cluster for Systems Neurology (SyNergy) EXC 2145**		
	Basic funding	M. Dichgans A. Liesz D. Paquet	01/2019 - 12/2025
	Tandem-projects	J. Bernhagen (PI) M. Dichgans (PI) A. Liesz (PI) N. Plesnila (PI) D. Paquet (PI)	
	Technology hubs	A. Ertürk (PI) M. Dichgans (PI) N. Franzmeier (PI) O. Gokce (PI)	
	Clinician Scientist Program	M. Georgakis A. Kopczak	
	Early Excellence Academy	S. Jäkel (PI)	
	Confocal Microscope **Multispectral Flow Cytometer**	M. Dichgans S. Jäkel A. Liesz	
	Collaborative Research Centre, CRC1123: Atherosclerosis: Mechanisms and Networks of Novel Therapeutic Targets		
	TP A3: The MIF protein/receptor network in atherosclerosis: mechanisms, novel members, and specific therapeutic strategies	J. Bernhagen (PI)	10/2014 - 06/2026
	TP B3: Mechanistic Role of HDAC9 in Atherosclerosis	M. Dichgans (PI) Y. Asare (PI)	
	TP B11: Inflammation begets inflammation – impact of remote injuries on atherosclerosis progression	A. Liesz (PI)	
	Research Unit-FOR 2879: From immune cells to stroke recovery, A. Liesz (Coordinator)		
	TP-A2: Inflammasomes in post-stroke regeneration	A. Liesz (PI)	05/2018 - 10/2025
	TP-A3: The role of microglia in cortical connectivity during recovery after stroke	G. Llovera (PI) A. Liesz (PI)	
	TP-B4 „Priming von meningealen Immunzellen zur Regeneration nach Schlaganfall“	C. Benakis (PI)	
	TP-C2: Microglia-PET as a surrogate marker for post-stroke neuroinflammation	M. Dichgans (PI)	
	TP-Z2: Standardization of animal models and outcome parameters	G. Llovera (PI) A. Liesz (PI)	
	Transregio 274: Checkpoints of Central Nervous System Recovery		
	TP-A02: Targeting microglia for the resolution of chronic neuroinflammation after stroke	A. Liesz (PI)	01/2020 - 12/2023
	TP-A06: The role of lipid-sensing nucl. receptors as checkpoints in regul. phagocyte func-tion during recovery from **demyelinating injury**	M. Simons (PI)	
	TP-B01: The role of inflammatory cytokine signalling for efficient remyelination in MS	M. Simons (PI)	
	TP-Z02: Genomics and Bioinformatics Platform	O. Gokce (PI)	
	Transregio 128: Initiating/effector versus regulatory mechanisms in MS – progress towards tackling the disease		
	TP-B07: Association betw. cholesterol metabolism in myeloid cells and remyelination in mouse and human	M. Simons	01/2021 - 06/2024
	TP-B13: Can a disturbed iron metabolism in phagocytes contribute to the development of chronic inflammation in MS?	M. Simons	

	Project	Role	Period
DFG	**Emmy Noether**		
	Deciphering the role of oligodendricytes in the pathogenesis of Alzheimer's disease	S. Jäkel (PI)	3/2021 - 2/2023
	Die Rolle Hirn-sezernierter Alarmine als Mediatoren immunologischer Komorbiditäten nach Schlaganfall	A. Liesz (PI)	1/2020 - 6/2022
	Projects		
	Uncovering the role of rare and low-frequency mutations in stroke using a polygenic risk score informed approach – implications for risk prediction	M. Dichgans (PI) R. Malik (PI)	5/2022 - 4/2025
	Die Rolle von T-Zellen als Modulatoren der Mikroglia-Reaktivität bei der Alzheimer-Krankheit	A. Liesz (PI)	4/2022 - 4/2025
	Die Reevaluierung des "no-reflow" Phänomens: Verzögert auftretende Verschlüsse der zerebralen Mikrozirkulation als neue Therapieoption für den ischämischen Schlaganfall	N. Plesnila (PI) I. Khalin (PI)	3/2022 - 2/2025
	Deciphering the development and diversity of white and gray matter microglia in neurodegeneration and aging	O. Gokce (PI) M. Simons (PI)	2/2022 - 3/2024
	T-Zellen als Regulatoren der Mikroglia-Funktion in Schlaganfall	C. Benakis (PI)	4/2021 - 12/2022
	The MIF protein family in cardiac ischemia and heart failure: molecular mechanisms and translational avenues	J. Bernhagen (PI)	7/2020 - 6/2022
	Role of MIF-2 in wound healing	J. Bernhagen (PI)	7/2018 - 6/2022
	Clinician Scientist PRogram In Vascular MEdicine: PRIME	S. Tiedt	4/2019 - 3/2022
	X-KINGDOM-MIF: Comparative analysis of macrophage migration inhibitory factor (MIF) protein function in animal and plant kingdoms.	J. Bernhagen (PI)	2/2020 - 1/2022
	Die Langzeitfolgen eines Schlaganfalls auf die systemische Immunität	A. Simats (PI)	1/2021- 12/2021
	Entwicklung genetisch kodierter K+-Fluoreszenzsensoren	N. Plesnila (PI)	11/2017 - 9/2021
	Identifikation von Inhibitoren der pathologischen Notch3-Aggregation	C. Haffner (PI)	1/2017 - 7/2021
	Molecular mechanisms of recessive and dominant mutations in the small vessel disease-related high temperature requirement protease HTRA1	M. Dichgans (PI) N. Beaufort (PI)	11/2016 - 6/2021
	Strukturelle und funktionelle Konnektivität bei der cerebralen Mikroangiopathie: Pathomechanistische Einblicke durch die Untersuchung genetischer und sporadischer Fälle	M. Düring (PI)	4/2017 - 6/2021
EU	ERC: The biology of myelin and lipoproteins within a glial network	M. Simons (PI)	1/2022 - 12/2026
	ERC Starting Grant: -T-cell-driven inflammatory mechanisms promote recovery after acute brain injury (RecoverInFlame)	A. Liesz (PI)	11/2018 - 10/2023
	Marie Skłodowska-Curie: Immunological mechanisms of post-stroke dysfunction and recovery of neurovascular coupling (VasoRecovery)	A. Liesz (PI)	4/2020 - 4/2022
	Horizon 2020: Small Vessel Diseases in a mechanistic perspective: Targets for Intervention. Affected pathways and mechanistic exploitation for prevention of stroke & dementia (SVDs@ target)	M. Dichgans	1/2016 - 12/2021
	"Horizon 2020: Common mechanisms and pathways in Stroke and Alzheimer's disease (CoSTREAM)"	M. Dichgans (PI)	12/2015 - 5/2021

	Project	Role	Period
Foundations	**Foundation Leducq**		
	Leducq Trans-Atlantic Network of Excellence On Circadian Effects in Stroke (CIRCA)	S. Tiedt (PI)	1/2022 - 12/2026
	Adelson Foundation		
	Molecular pathways in Remyelination and Neuroprotecion	M. Simons (PI)	10/2022 - 9/2025
	Minerva Stiftung		
	Functional dissection of the Insula-reward system connectivity in control of immunity	O. Gokce (PI)	4/2019 - 4/2022
	BrightFocus Foundation		
	An iPSC-derived human brain tissue model for Alzheimers disease	D. Paquet (PI)	7/2019 - 6/2022
	Development of a human iPSC-based Tauopathy model showing advanced phenotypes	D. Paquet (PI)	1/2022 - 6/2025
	The role of brain connectivity as a mechanistic link between Amyloid and Tau pathology spread in Alzheimer´s disease	N. Franzmeier (PI)	7/2019 - 6/2022
	Dr. Helmut Legerlotz-Stiftung		
	Assoziation zwischen protektivem Klothoprotein und Tau-pathologie bei AD	Bürger/Ewers (PIs)	1/2022 - 12/2022
	Hertie Stiftung		
	Hertie Academy 2020	N. Franzmeier	5/2020 - 10/2023
	Else Kröner Fresenius Stiftung		
	Harnessing Reward Circuitry for Stroke Recovery	O. Gokce (PI)	5/2020- 5/2025
	Corona Stiftung		
	Precision Medicine in Stroke (PREMISE): integrating deep phenotyping from 1000 stroke patientes and experimental stroke models	S. Tiedt (PI)	7/2020 - 7/2025
	Fritz Thyssen Stiftung		
	Developing personalized biomarkers of subclinical arterial pathology with deep learning in carotid ultrasound images	M. Georgakis (PI)	7/2022 - 6/2024
	Friedrich-Baur-Stiftung		
	Nanoimmunotherapy targeting HDAC9 for vascular protection	Y. Asare (PI)	5/2020 - 11/2021
	The long-term consequences of stroke on systemic immunity	A. Simats (PI)	7/2021 - 7/2022
	Characterization of CNS potassium dynamics	S. Filser (PI)	7/2021 - 12/2022
	Gut Brain axis in stroke	C. Benakis (PI)	7/2022 - 12/2023
	Erweiterte Charakterisierung des MIF/CXCK4L1. (…)	M. Brandhofer (PI)	7/2022 - 12/2023
Other	**Bayerisches Staatsministereium für Gesundheit und Forschung**		
	DigiMed Bayern: P4 medicine for carotid stenosis and stroke	M. Dichgans	10/2018 - 11/2024
	M4-Award „SELECKREM"	J. Bernhagen	7/2022 - 6/2024
	NIH: Genetics of Early-Onset Stroke Consortium	M. Dichgans	1/2018 - 12/2023
	Alzheimer Association		
	Determing Cell Autonomous and Non-cell Autonomous Mechanisms (…)	D. Paquet	11/2022 - 12/2022
	Connectivity as a universal predictor of tau spreading in atypical AD	N. Franzmeier	1/2022 - 12/2023
	CSL Behring Innovation Identify novel alarmin molecules as therapeutic targets to prevent early recurrent cardiovascular events after stroke	A. Liesz	6/2020 - 6/2024
	Chan Zuckerberg Initiative DAF Role of white matter and cerebrovascular aging in neurodegeneration	Gokce/Simons (PIs)	1/2021 - 5/2022

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 5 PhD/MD students in training; A. Aronova (PhD student at ISD) is one of the Student Spokespersons 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 12 FöFoLe MD thesis students in 2021-2022.

Clinician Scientist Program PRIME
Starting in 2019, the DFG-funded clinician scientist PRogram 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.

Teaching

2021 I Faculty of Medicine

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

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

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

Dichgans M, Filser S, Hallal F, Plesnila N, Seker B I Experimentelle Schlaganfallforschung (7C0123)

Beaufort N, (...) I Stroke and Dementia Research - News and Views (7C0124)

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

Dewenter A, Düring M, Ewers M, Franzmeier N, Malik R, Stöcklein S I Structural and Functional Connectomics in Neuroimaging (7C0170)

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

(...), Bürger K, (...)| Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (7C0233)

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

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

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

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

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

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

Sinitski D, Wang S, Yang B, Zan C I Current topics in molecular atherosclerosis research (7C4047)

Boulesteix A, (...) I MMRS lecture series “Good Scientific Practice” (7C4091)

Anders H, (...) I Interdisziplinäre Vorlesung: Promotionsstudium Molekulare Medizin und Systembiologische Medizin (7C0422)

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

(...), Bürger K, (...)I Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (7P0602)

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

(...), Bürger K, (...) I Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (790602)

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

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

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

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

Crispin A, Ewers M, (...) I Exercise: Advanced

Crispin A, Ewers M, (...) I Seminar: Advanced Methods in Clinical Epidemiology: Design, Evidence Synthesis, Safety and Quality (07565)

2021 I Faculty of Biology

Dichgans M, (...) I Molecular Neurogenetics and Experimental Stroke Research (19018)

Dichgans M, (...) I Molecular Neurogenetics and Experimental Stroke Research (19023)

Dichgans M, (...) I WP 10.1 Biomedical Neuroscience – Lecture (19257)

Dichgans M,(...) I Neuroimmunological methods in experimental stroke research (19280)

Dichgans M, Liesz A, Roth S, Benakis C I Neuroimmunological methods in experimental stroke research (19339)

Ewers M, Düring M, Franzmeier N, Malik R, Stöcklein S I Structural and Functional Connectomics in Neuroimaging (19356)

Schneider M, Dichgans M I Experimental stroke research – Introduction to laboratory animal science (19285)

2022 I Faculty of Medicine

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

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

Dichgans M I Demenzen: Molekulare Grundlagen und pathophysiologische Konzepte (7C0019)

Plesnila N, Filser S, Khalin I, Seker B I Experimentelle Schlaganfallforschung (7C0123)

Plesnila N, Dichgans M, Ewers M, Liesz A, Malik R, Paquet D I Stroke and Dementia Research - News and Views (7C0124)

Dichgans M, Klein M, Straube M I Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder (7C0025)

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

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

Biel D, Dewenter A, Ewers M, Franzmeier N, Malik R, Stöcklein S I Structural and Functional Connectomics in Neuroimaging (7C0170)

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

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

Filser S, (...) I Neurovascular Research Journal Club (7C01994)

Bartenstein P, (...)| Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (7C0233)

Biel D, (...) I Strukturelle Magnetresonanztomographie in der Demenzforschung (7C0248)

Biel D, (...) I Multimodale Bildgebung zu Gehirnveränderungen bei der Alzheimer Demenz (7C0263)

(...), Plesnila N, (...) I MMRS lecture series “Good Scientific Practice” (7C4091)

Anders H, Bernhagen J, (...) I Interdisziplinäre Vorlesung: Promotionsstudium Molekulare Medizin und Systembiologische Medizin (7C0422)

Androvic P, Bernhagen J, El Bounkari O, Gökce Ö I Practical Course Molecular and Cellular Cardiovascular Medicine (7C0485)

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

Androvic P, (...) I Doktorandenkolloqium: (kardio)vaskuläre Pathologien - von den Grundlagen der vaskulären und Neurobiologie zur Pathogenese (7C0376)

Bartenstein P, (...) I Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (7P0602)

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

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

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

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

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

2022I Faculty of Biology

Dichgans M, (...) I Molecular Neurogenetics and Experimental Stroke Research (19020)

Dichgans M, Liesz A, Roth S, Benakis C I Neuroimmunological methods in experimental stroke research (19359)

Ewers M, (...) I Structural and Functional Connectomics in Neuroimaging (19376)

Theses

Investigating the brain mechanisms that underlie cognitive resilience in neurodegenerative diseasese. Jannis Denecke, PhD (GSN) started 2022

Proteomics capturing the biology of thrombus formation. Yasin Eshraghi, PhD, started 2022

Temporal and spatial characterization of molecular outflow after stroke. Linjie Zhang, PhD, started 2022

Fabian Wagner: Understanding the role of Amyloid in Tau spreading, PhD, started 2022

Functional characterization of distinct oligodendrocyte states in Alzheimer's disease pathology. Nadia Dorosti, PhD (GSN), started 2022

Chemokine receptor ectodomain mimics as therapeutic tools in atherosclerosis. Simon Ebert, Dr. rer. nat., started 2022

Role of the ACK interactome in atherosclerosis. Michael Kobina Otabil, PhD (IRTG1123), started 2022

Mechanisms underlying atheroprotection by the COP9 signalosome. Yue Yuan, PhD, started 2022

Genomic, biochemical and functional characterization of novel MIF family proteins. Kobra Moradzadeh, PhD (IRTG1123), started 2022

Generation and Characterization of COL4A1 Small Vessel Disease. Joseph Kroeger (GSN), PhD, submitted Dec 2022

Biomarkers of inflammation in stroke patients and risk of stroke recurrence. Jana Mattar, MD, started 2022

Cell-type specific effects of HDAC9 in atherogenic inflammation. Federica Tosato, PhD, started 2021

Role of SCARF1 in atherosclerosis, Arailym Aronova, PhD (MMRS), started 2021

Predictors for cognitive impairment and dementia after stroke. Jule Marie Filler, PhD (GSN), started 2021

Using human iPSCs to study oligodendrocyte pathology in Alzheimer's disease. Courtney McQuade, PhD (GSN), started 2021

Functional adaptations of the contralateral neuronal network following stroke. Gian Marco Calandra, PhD (GSN), started 2021

Effect of DOCA-induced hypertension in genetic mouse models of cSVD - Exploring the 'second hit' hypothesis. Luise Sophia Klara Schröger, PhD (GSN), 2021.

Investigating modulators of Alzheimer's disease through multimodal neuroimaging biomarkers. Anna Steward, PhD (GSN), started 2021.

The neuro-immunomodulatory effect of gut microbiota-derived metabolites in experimental stroke. Rosa Delgado, PhD (MMRS), started 2020

Influence of the circadian rhythm on infarct volume and the metabolic response after experimental stroke. Vanessa Granja Burbano, PhD (GSN), started 2020

Temporal profile and determinants of the systemic catabolic response in the acute phase of ischemic stroke. Evan Hunter Stanton, PhD (GSN), started 2020

Cardiac dysfunction chronically after ischemic stroke. Sijia Zhang, PhD, started 2020

Functional genomic investigation of cerebrovascular disease. Simon Frerich, PhD (GSN), started 2020

Therapeutic potential of progesterone after traumatic brain injury. Kosisochukwu Umeasalugo, PhD (GSN), started Mar 2020

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

Prediction of cognitive and functional impairment after stroke using neuroimaging markers. Rong Fang, PhD (MMRS), started 2019

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

Cell autonomous effect of FOXF2 deficiency in mouse brain vasculature and a human BBB in vitro model. Judit González-Gallego, PhD, started 2018

The role of GABA in neuronal energy metabolism. Bernhard Groschup, PhD (GSN), started 2018

Single-cell approach on the modulation of immune cell identity in ageing and disease. Simon Besson-Girard, PhD (GSN), started 2018

The impact of post-stroke inflammation in atherosclerotic plaque rupture and recurrent stroke. Jiayu Cao, PhD (MMRS), started Oct 2018

Elucidating the role of Tau isoform expression in a human iPSC-derived Tauopathy model. Angelika Dannert, PhD, started 2018

Inflammatory pathways as drug targets for cardiovascular disease - insights from human genomics. Marek Konieczny, PhD, started 2018

Characterization of the novel MIF protein DDTL/MIF-3 in human atherosclerotic plaque tissue. Noor Ismail, Dr. med. (FöFoLe), started 2022

Characterizing the role of microglia in the formation of microvascular occlusions and the blood brain barrier integrity following the ischemic stroke. Eva Krestel, Dr. med., started 2021

Mapping the systemic response to stroke. Charlotte Forster, Dr. med., started 2021

Protein composition distinguishes cardioembolic and large-artery atherosclerotic thrombi. Teresa Wölfer, Dr. med., started 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. Michael Karg, Dr. med., started 2020

Molecular pathways in atherosclerotic vascular inflammation. Luka Zivkovic, Dr. med., started 2019

Role of HDAC9 in NF-kB driven pro-inflammatory responses. Thomas James-Campbell, Dr. med., started 2018

Effects of selective class IIa HDAC inhibition with TMP195 on proatherogenic mechanisms in endothelial cells and macrophages. Kyra Thomas, Dr. med., started 2018

Investigation of cytotoxic brain edema formation by in vivo 2-Photon Microscopy. Senbin Hu, MD, started 2021.

Role of inflammation on brain edema following acute brain injury. Yinghuimin Guo, MD, started 2021

The role of HDAC9 in NLRP3 inflammasome activity. Christina Schlegl, MD, started 2020

Investigating the role of CD74 in CD4+ T cell regulation. Iris Woltering, Dr. med., started 2020

Expanding the (atypical) chemokine interactome: network modulation through MIF-2/CCL20 heterooligomerization. Elena Siminkovitch, Dr. med. (FöFoLe), started 2020

DCN1-inhibitors: A new pharmacological strategy in atherosclerosis therapy. Dario Ponto, Dr. med. (FöFoLe), started 2020

Completed:

Modulation of Neuroinflammation and Stroke Outcome by the COP9 Signalosome. Yuan Tian, PhD (MMRS), 2022.

Effects of Hdac9 targeting on proinflammatory responses in vivo and in vitro in macrophages and monocytes. Lydia L. Yu, Dr. med, 2022

Role of large vessel stroke relevant gene HDAC9 in NF-κB activation + atherogenic processes in vascular cells. Yury Bokov, Dr. med., 2022

Left frontal hub connectivity enhances task related brain network segregation and cognition in aging – implications for cognitive reserve. Lukas Frontzkowski, Dr. med., 2022

Tau-network mapping of domain-specific cognitive impairment in AD. Ying Luan, PhD (Chinese Scholarship Council), 2022

Tractography-based diffusion MRI markers of cerebral small vessel disease. Anna Dewenter, PhD (GSN), 2022

Analysis of the brain vasculature in a novel mouse model of HTRA1-related cerebral small vessel disease. Ameli Gerhard, MD, Sep 2022.

The pericyte response to ischemic stroke. Josh Shrouder, PhD, 2021

Role of inhaled nitric oxide on vascular inflammation after experimental ischemic stroke. Rebecca Sienel, PhD, 2022

Detection of deleterious on-target effects after CRISPR-mediated genome editing in human induced pluripotent stem cells. Isabel Weisheit, PhD (GSN), 2021

A human stem-cell-derived cortical tissue model to investigate Alzheimer's disease. Julien Klimmt, PhD (GSN), 2022

Interactions between MIF-family proteins and the classical chemokine ligand/receptor network. Markus Brandhofer, Dr. rer. nat., 2022

The MIF homolog MIF-2/D-DT in atherosclerosis: Functional role and links to hepatic lipid metabolism. Chunfang Zan, PhD (IRTG1123), 2022

Role of the COP9 Signalosome in Atherogenic Inflammation. Jelena Milic, PhD (IRTG1123), 2022

MIF proteins and their receptors in atherogenesis: Structure-activity relationships and novel cellular routes. Christine Krammer, Dr. rer. nat. (IRTG1123), 2021

Effects of amyloid and tau pathology on brain function and cognition in Alzheimer's disease. Anna Rubinski, PhD, 2021

Conferences, Trainings and Events

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

International Neurotrauma Society (INTS) Meeting, Berlin, July 2022 | N. Plesnila: Conference Chair

ADPD Conference, Barcelona, March 2022 | D. Paquet: session chair and speaker

Lecture series about CRISPR genome editing at LMU Center for Advanced Studies (CAS), Munich, 2021-2022 | D. Paquet: scientific organizer and speaker

Cardiac Regeneration and Vascular Biology Conference, San Servolo, October 2021 | J. Bernhagen, co-organizer

2021 Virtual Conditioning Medicine Workshop Hearts and Brains: Conditioning medicine for cardiovascular and neurovascular disease | April 2021, J. Bernhagen, speaker

Virtual MIF Lecture Series 2021-2023 | Monthly , J. Bernhagen, organizer

Alzheimer's Association International Conference (AAIC), San Diego, 2022 | M. Ewers, session chair:

Alzheimer Imaging Conference, Amsterdam 2023 | M. Ewers, co-organizer

Japanese Society of Immunology Meeting 2022, Kumamoto, December 2022 | A. Liesz: keynote speaker

ESOC 2022, Lyon, May 2022 | A. Liesz: Program committee, scientific chair, speaker

Neuroscience School of Advanced Studies, Venice, April 2022 | A. Liesz: Convenor & Scientific Chair

EMBO Workshop „Stroke-Immunology", Munich, March 2022 | A. Liesz: organizer

Stroke-Immunology Conference 2021, Online, March 2021 | A. Liesz: organizer

7th European Stroke Conference Virtuell, September 2021 | M. Dichgans: scientific chair

ISGC Workshop, Bordeaux, September 2022 | M. Dichgans: scientific chair

Scientific Review Advisory Board ISD, Munich, September 2022 I M. Dichgans: organizer

External Speakers in ISD Live and virtual Talks

Dr. Bram Heijs, Assistant Professor, Leiden University Medical Center, Mass Spectrometry Imaging, Netherlands

Andy Shih, PhD, Seattle Children's Research Institute Seattle, WA, USA

Dr. Gregor-Alexander Pilz, Department for Cell Biology, BioMedizinisches Centrum, LMU, Munich

Simon Schäfer, Department of Psychiatry and Psychotherapy, TUM, Munich

Silvia Cappello, Developmental Neurobiology, Max Planck Institute of Psychiatry, Munich

Wouter Peelaerts, PhD, Laboratory of Neurobiology and Gene Therapy, KU Leuven, Belgium

Prof. Dr. Jerome Mertens, Institute of Molecular Biology, CMBI, Leopold-Franzens-University Innsbruck, Austria

Prof. Dame Pamela Shaw, Sheffield Institute for Translational Neuroscience, University of Sheffield, UK

Mathew Blurton-Jones, PhD, Department of Neurobiology and Behavior, University of California Irvine, USA

Ulf Dettmer, PhD, Ann Romney Center for Neurologic Diseases, Harvard Medical School, USA

Michael Ratz, PhD, Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden

Rory Koenen, PhD, Associate Professor Biochemie, School for Cardiovascular Diseases, Fac. Health, Medicine and Life Sciences, CARIM Maastricht University, Netherlands

Else Charlotte Sandset, MD, PhD, Oslo University Hospital, Stroke Unit, Dept of Neurology, Norwegen

Veronique Miron, PhD, UK Dementia Research Institute at The University of Edinburgh, UK

Michael Snyder, PhD, Stanford B. Ascherman Professor and Chair, Department of Genetics, Director, Stanford Center for Genomics and Personalized Medicine, School of Medicine, Stanford University, USA

Prof. Jürgen Cox, Max-Planck-Institut für Biochemie, Munich

Maren Büttner, PhD, LIMES Institute, University of Bonn ; German Center of Neurodegenerative Diseases (DZNE), Bonn; Department of Computational Health, Helmholtz Munich

Li Gan, PhD, Helen and Robert Appel Alzheimer's Disease Research Institute, Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, USA

Dr. Marius Wernig, Stanford University School of Medicine, California, USA

Dr. Jonas Neher, Experimental Neuroimmunology, DZNE Tübingen

Thomas Carmichael, MD, PhD, Department of Neurology, David Geffen School of Medicine at UCLA, USA

Publications

2022	Number of publications	113
	Impact factor: total / average	1756,18 / 15.54
	Number of publications with first and / or senior authorships	49
	Impact factor: total / average	774.33 / 16.47
2021	Number of publications	134
	Impact factor: total / average	1530.05 / 11.42
	Number of publications with first and / or senior authorships	40
	Impact factor: total / average	529.44 / 13.24

2022

Asare Y, Shnipova M, Živković L, Schlegl C, Tosato F, Aronova A, Brandhofer M, Strohm L, Beaufort N, Malik R, Weber C, Bernhagen J, Dichgans M. *IKKβ binds NLRP3 providing a shortcut to inflammasome activation for rapid immune responses.* **Signal Transduct Target Ther.** 2022 Oct 19;7(1):355. doi: 10.1038/s41392-022-01189-3.

Biel D, Luan Y, Brendel M, Hager P, Dewenter A, Moscoso A, Otero Svaldi D, Higgins IA, Pontecorvo M, Römer S, Steward A, Rubinski A, Zheng L, Schöll M, Shcherbinin S, Ewers M, Franzmeier N; Alzheimer's Disease Neuroimaging Initiative. *Combining tau-PET and fMRI meta-analyses for patient-centered prediction of cognitive decline in Alzheimer's disease.* **Alzheimers Res Ther.** 2022 Nov 7;14(1):166. doi: 10.1186/s13195-022-01105-5.

Benakis C, Liesz A. *The gut-brain axis in ischemic stroke: its relevance in pathology and as a therapeutic target.* **Neurol Res Pract.** 2022 Nov 14;4(1):57. doi: 10.1186/s42466-022-00222-8.

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Rubinski A, Frerich S, Malik R, Franzmeier N, Ramirez A, Dichgans M, Ewers M; Alzheimer's Disease Neuroimaging Initiative (ADNI). *Polygenic Effect on Tau Pathology Progression in Alzheimer's Disease.* **Ann Neurol.** 2022 Dec 26. doi: 10.1002/ana.26588. Epub ahead of print.

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Jaworek T, A, (...), Malik R, Dichgans M, Mitchell BD, Kittner SJ; Early Onset Stroke Genetics Consortium of the International Stroke Genetics Consortium (ISGC). *Contribution of Common Genetic Variants to Risk of Early Onset Ischemic Stroke*. **Neurology**. 2022 Aug 31;99(16):e1738–54. doi: 10.1212/WNL.0000000000201006. Epub ahead of print.

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Dichgans M, Meschia JF. *Advances in Stroke: Genetics, Genomics, Precision Medicine*. **Stroke**. 2022 Oct;53(10):3211-3213. doi: 10.1161/STROKEAHA.122.039305. Epub 2022 Sep 16.

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Honors & Awards

Corinne Benakis | 2022, Friedrich-Baur-Stiftung (Munich, Germany)

Markus Brandhofer | 2022, Friedrich-Baur-Stiftung (Munich, Germany)

Jürgen Bernhagen | 2021, m4 Award of the Bavarian State Ministry of Economic Affairs, State Development and Energy (2022-2024; together with A. Kapurniotu, TUM)

Angelika Dannert | 2022, Alzheimer Forschung Initiative e.V. Travel Grant for the AD/PD conference in Barcelona

Angelika Dannert | 2022, Tübingen Stem Cell Meeting Travel Stipend

Angelika Dannert | 2022, Tübingen Stem Cell Meeting Best Poster Award, 1st Place

Angelika Dannert | 2022, International Society for Neurochemistry Travel Award for the ISN-ASPN Meeting in Honolulu

Angelika Dannert | 2022, Otto Bayer Fellowship, Bayer Foundation

Angelika Dannert | 2021, SyNergy Travel Grant

Martin Dichgans | "Highly Cited Researchers 2022" Clarivate Award

Marco Düring | 2021, Honorary Clinical Professor, CUHK Hong Kong

Marco Düring | 2021, Executive Committee Member, VAS-COG society

Michael Ewers | 2021, ISTAART De Leon Prize in Neuroimaging Co-Senior Scientist

Michael Ewers | 2022, Alzheimer's Association – Conference travel fellowship

Michael Ewers | 2022, Elected senior scientist of the ISTAART Neuroimaging PIA

Nicolai Franzmeier | 2022, Alzheimer's Association Research Grant (AARG/AARG-D)

Marios Georgakis | 2022, Fritz-Thyssen Foundation Research Grant

Marios Georgakis | 2022, SyNergy Clinician-Scientist Programme

Marios Georgakis | 2021, "CHARGE" Meritorious Abstract Award

Marios Georgakis | 2021, DFG Walter-Benjamin Fellowship

Sarah Jäkel | 2022, September FöFoLe Research Grant (LMU)

Sarah Jäkel | 2021, March SyNergy Early Excellence Academy Startup grant

Julien Klimmt | 2022, ISN-APSN Meeting – Invitation and Travel Grant

Julien Klimmt | 2022, Stem Cell Meeting Tübingen – Travel Grant

Julien Klimmt | 2022, Alzheimer Forschung Initiative – Travel Grant

Julien Klimmt | 2021, Stichting Alzheimer Onderzoek (Belgian Alzheimer research foundation) – Travel Grant

Dominik Paquet | 2022, International Society for Molecular Neurodegeneration, best talk award

Dominik Paquet | 2022, Foundation Leducq Transatlantic Research Network Member

Dominik Paquet | 2022, FBRI Research Grant

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Dominik Paquet | 2022, Alzheimer's Association Research Grant

Dominik Paquet | 2021, Synergy ,scRNA-seq in neurodegenerative disease research grant

Isabel Weisheit | 2021, New York Academy of Sciences CRISPR M eeting – Invitation

Chunfang Zan | 2021, Best Junior Investigator Talk, Cardiac Regeneration & Vascular Biology Conference 2021

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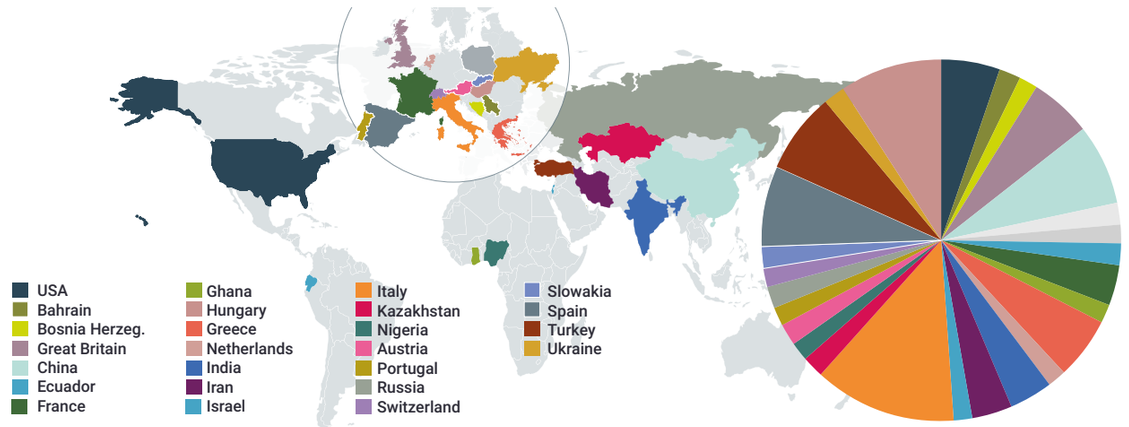

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