LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Annual Report 2013/2014

Institute for Stroke and Dementia Research (ISD)

www.isd-muc.de

Content

04 The Institute for Stroke and Dementia Research (ISD)

06 Foreword
08 New Building
10 Organisation
12 Highlights 2013/2014
16 Outpatient Clinic

22 Research

25 Research Groups
25 Department of Translational Stroke and Dementia Research
28 Laboratory of Experimental Stroke Research
30 Brain Imaging and Biomarker Research
32 Vascular Cognitive Impairment
34 Acute Brain Injury Research
36 Stroke-Immunology
38 Small Vessel Disease

40 Research Highlights 2013/2014
44 Investigator Initiated Clinical Studies
49 Participation in Multicenter Trials (Selection)
50 Ongoing Research Projects

58 Numbers and Facts

60 Research Alliances and Project Fundings
63 Third Party Funding
66 Teaching
68 Habilitations & Theses
69 Honours & Awards
70 Conferences, Trainings and Events
73 Participation in Graduate Schools
74 Publications
83 Staff
84 Local Partners
85 Imprint
86 How to get to the ISD

The Center for Stroke and Dementia Research
hosting the Institute for Stroke and Dementia Research (ISD)
and the German Center for Neurodegenerative Diseases (DZNE)

The Institute for Stroke and Dementia Research

Stroke and Dementia rank among the ten most frequent diseases worldwide and are two of the most pressing health problems in ageing societies (WHO Report 2002). Stroke is the second most common cause of death and the third most common cause of permanent physical or mental impairment. 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 being the leading causes.

The Institute for Stroke and Dementia Research (ISD) is designed as a novel type of research facility bridging the traditional barriers between academic medicine and basic science.

By bringing together a critical mass of excellent scientists and academic clinicians the ISD facilitates the transfer of basic research findings into clinical applications (bench to bedside) while focusing basic research on clinically relevant questions (bedside to bench). At the same time, the ISD seeks to provide the highest quality in patient care by concentrating on the prevention, diagnosis and treatment of stroke and cognitive decline.

The ISD was founded in 2009 and launched in 2010 through the extraordinary generosity and vision of Zygmunt Solorz Żak. Mr Solorz Żak recognized the promise of integrating patient care with clinical and basic research to change medicine and saw the need to empower physicians and scientists from different fields to work together to realize that promise. His founding gift was intended to provide the resources necessary to allow the institute to maintain a high degree of flexibility within a rapidly moving field.

Munich's pre-eminent University Hospital, the University of Munich, and the State of Bavaria shared Mr. Solorz-Żak's vision and joined together with him as the founding partner of the Institute for Stroke and Dementia Research.

Since its inauguration in 2010, the ISD has grown to more than 85 people including 62 scientists of all levels, from Ph.D. students to full professors. It is home to a growing number of junior and senior research groups and departments. In 2013 the ISD was visited by its advisory board with a first formal evaluation to come in 2020.

Scientists at ISD obtain increasing amounts of third party funding with 0.8 million Euro spent in 2014 and more than 1.5. million Euro spent in 2014. In 2014 ISD investigators published more than 60 papers in peer-reviewed journals including leading journals in the fields of Genetics, Neuroscience, and Clinical Neurology.

The new clinician scientists group on Stroke Immunology has started operations in July 2013 and has quickly become a visible component of the ISD. The group strengthens ISD's expertise in experimental stroke research while also extending its focus to aspects of neuroinflammation – a major theme of the Munich Cluster for Systems Neurology (SyNergy). Strong linkages with SyNergy are further seen with a new research group on Acute Brain Injury that started its work in July 2014. The ISD is part of a still growing neuroscience community in Munich. Together with other researchers ISD investigators recently initiated the DFG-funded cluster of excellence (SyNergy – Munich cluster of excellence for Systems of Neurology). SyNergy has started operations in early 2013 and will provide significant structural and financial support for collaborative research in Munich.

After 4 years of construction the new Center for Stroke and Dementia Research (CSD) building has now gone into operation.

The new building hosts the ISD and the German Center for Neurodegenerative Diseases DZNE (page 8 and 9).

We are grateful for the opportunities provided to us and wish to report on our activies.

In the following we highlight major activities and developments in 2013/2014.

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

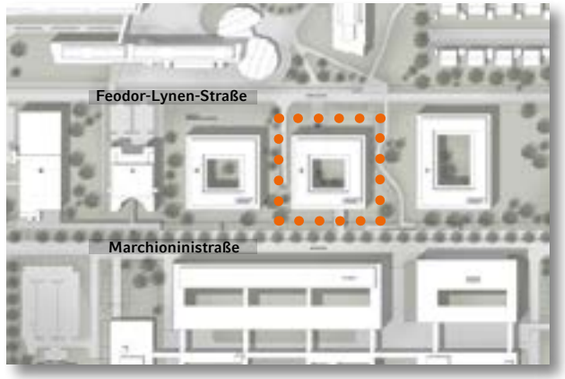
Center for Stroke and Dementia Research

Laboratory before move-in

Entrance Feodor-Lynen-Straße

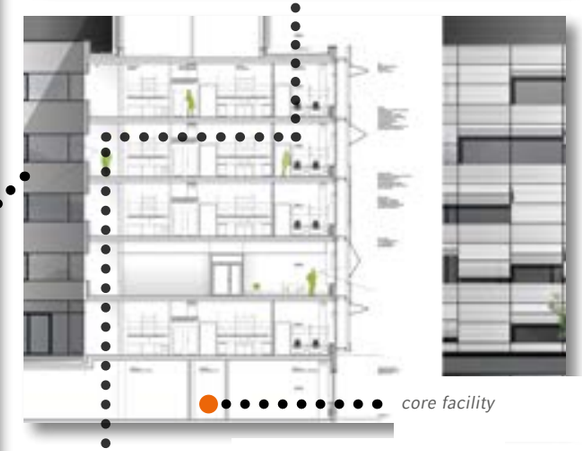
Social room before move-in

Center for Stroke and Dementia Research CSD



Facts: sponsored by the research ministry of the state of Bavaria; 8.311 sqm of occupancy space; hosts scientists from both Munich universities and the Helmholtz association; architects: Nickl & partners; in operation since winter 2014

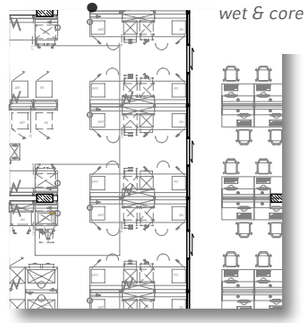
... located on biomedical research campus LMU the new building hosts the Institute for Stroke and Dementia Research (ISD) and the German Center for Neurodegenerative Diseases (DZNE)...

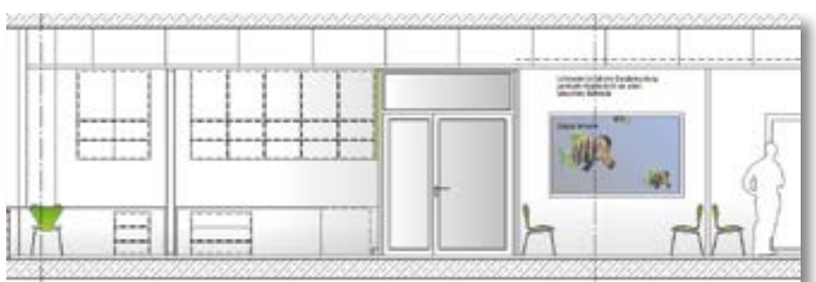


core facility

...there is a dedicated outpatient clinic & clinical trials unit for cerebro-vascular disorders and patients with dementia...

wet & core lab units





... lecture halls, seminar rooms, and discussion corners offer ample opportunities for teaching and exchange ...

...the new building provides home to more than 200 basic and clinician scientists, technical and support staff.

Organisation

Board of Directors

Director and Chairman
Prof. Dr. med. Martin Dichgans

Managing Director
Markus A. Frühauf

Scientific Advisory Board

Prof. Dr. med. Ulrich Dirnagl
Director, Experimental Neurology
Charite Hospital, Humboldt University, Berlin, Germany

Prof. Dr. med. Dr. h.c. Dipl. Psych. Werner Hacke
Director, Dept. of Neurology, University of Heidelberg, Heidelberg, Germany

Prof. John Hardy, Ph.D., MD (Hon) Umea, FMedSci,
Professor of Neuroscience
Department of Molecular Neuroscience and Reta Lila Weston Laboratories
Institute of Neurology, University College London, London, UK

Prof. David M. Holtzman, MD (currently on hold)
Professor and Chairman, Dept. of Neurology
Washington University School of Medicine , St. Louis, MO USA

Prof. Costantino Iadecola, MD
Cotzias Distinguished Professor of Neurology and Neuroscience
Chief, Division of Neurobiology, Weill Medical College of Cornell University, New York, NY USA

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

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

Board of Trustees

Zygmunt Solorz-Żak (Chairman)
Vascular Dementia Research Foundation

RA Erich Steinsdörfer (Vice Chairman)
Vascular Dementia Research Foundation

RA Josef Birka
Vascular Dementia Research Foundation

Prof. Dr. med. Dr. h.c. Thomas Brandt, FRCP
Chairman, Integrated Center for Research and
Treatment of Vertigo, Balance and Ocular Motor Disorders

Prof. Dr. med. Dr. h.c. Karl-Walter Jauch
Director, Klinikum der Universität München

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

Dr. Maximilian Lang
Bayerisches Staatsministerium für Wissenschaft, Forschung und Kunst

Founders

Zygmunt & Malgorzata Solorz-Żak (Benefactors)

Klinikum der Universität München

Ludwig-Maximilians-Universität München

State of Bavaria

Highlights 2013/2014

February 2015
Hannelore Kohl Foundation

Dr. Nicole Terpolilli, a clinician scientist working in the Laboratory of Experimental Stroke Research (Prof. N. Plesnila) received the prestigious 2014 Hannelore Kohl Foundation Award for her publication on the use of inhaled nitric oxide (iNO) for the treatment of traumatic brain injury (Terpolilli et al., J Neurotrauma 2013), a concept she proved to be also efficacious following ischemic stroke, cerebral hemorrhage (Terpolilli et al., Circulation Research 2012), and - in collaboration with Prof. W. Kuebler, Univ. Toronto - after cardiac ischemia (Neye et al. Intensive Care Med. 2012). These results suggest that iNO can represent a general therapeutic concept for protection of ischemic tissue.

November 2014
ISD moves into new building

Architects: Nickl & Partner; Construction: Staatl. Bauamt München II; Construction time: 10/2010-11/2014; Total occupancy space: 8,311 sqm; Laboratories: 5,592 sqm; Core facilities: 1,594 sqm; Outpatient clinic: 478 sqm; Art: Martin Wöhrl.

October 2014
Multi-national EU grant awarded to ISD

Ali Ertürk and Nikolaus Plesnila received a multi-national grant from the Era-Net Neuron program of the European Commission. The consortium (CnsAflame) coordinated by them involves partners from Germany, Sweden, France, and Israel. CnsAflame will investigate the contribution of neuroinflammation in secondary (chronic) neurodegeneration and cognitive decline after traumatic brain injury. The consortium will utilize state-of-the art technologies including 3D imaging by light-sheet microscopy, in vivo 2-photon microscopy and ultra-high field MRI to examine post-traumatic neuroinflammation in animal models and in patients. Hence a unique translational research platform will be created to generate novel therapeutic concepts.

September 2014
"The Ego" by Martin Wöhrl

A 4m cast bronze sculpture of a broken vase called "The Ego" by artist Martin Wöhrl has been placed in front of the new CSD building. Martin Wöhrl, Munich 2014: *"[...] for one the sculpture – an overdimensional archaeological object - reflects the largest possible contrast between the technocratic architecture of the research building and its surrounding. It further reflects the beauty of age, a human ideal that goes back to the antiquity. As it happens, this work, which seems to have aged in dignity, shows cracks, tears, and restored parts. Was it for the purpose of restoring or for preventing its further destruction? The idea of physical decline might be irritating but the slow loss of our mind - and hence of our personality - is a shock. An object as a symbol for mind, that is my idea." Martin Wöhrl, Munich 2014.*

July 2014
New recruit: Ali Ertürk

Dr. Ali Ertürk joins ISD as an independent junior research group leader. After completing his Ph.D. at the Max-Planck-Institute of Neurobiology in Munich, he worked at Genentech, Inc. in San Francisco as a postdoctoral fellow with Dr. Morgan Sheng. Dr. Ertürk's group focuses on neurodegenerative mechanisms after acute brain injuries (stroke and trauma) and aims to develop breakthrough therapeutic approaches. In particular, they investigate the role of caspase-3 signaling pathway in synapse degeneration, which may take place well before the actual neuronal cell death in the secondary phase of acute brain lesions. His group routinely uses leading-edge imaging technologies including 3D imaging of entire, transparent brains.

July 2014
Scientific retreat at Kardinal-Wendel-Haus, Munich

July 8th and 9th ISD research teams met for a scientific retreat to present their projects and discuss the science. At the heart of this meeting were presentations from all Ph.D. students, which were connected to a 'best presentation award'. The last year brought about important achievements both scientifically and with regard to expertise and infrastructure. The meeting further served as an opportunity to familiarize people with the medium and long-term strategy of ISD.

Februar 2014
Role of HDAC9 in atherosclerosis SFB 1123 project funded by DFG

The HDAC9 gene region on 7p21.1 was identified as a major risk locus for carotid atherosclerosis and stroke. HDAC9 has previously been shown to control the maturation and function of FOXP3+ regulatory T (Treg) cells, which in turn have atheroprotective function. The inhibitory effect of HDAC9 on Treg cells renders these cells a promising candidate for targeted analyses. The main aims of the current project therefore are (1) to study the effects of HDAC9 deficiency on atherogenesis and atherothrombosis in mouse models, (2) to examine allele-specific effects on Treg cell function in humans, and (3) to determine allele-specific effects on plaque characteristics and HDAC9 expression in human atherosclerotic plaques.

January 2014
Young Scientist Award for Marco Duering

A paper by Marco Düring and colleagues received the 2013 young scientist award of the Competence Network Stroke. The prize is awarded for an outstanding scientific work of a young scientist in the field of clinical or experimental stroke research. The award-winning study, published in Brain, investigated the mechanisms underlying incident lacunes, a prominent feature of small vessel disease. The prize was conferred at the ANIM congress 2014 in Hannover.

Januar 2014
2nd MESCOG investigator meeting

Zuers (Austria): Starting in February 2012 investigators from Munich, Paris, and Graz engaged in a collaborative network to tackle the mechanisms of cerebral small vessel disease and how small vessel-related brain lesions cause cognitive decline. The network centers on studies in humans with a methodological focus on MR imaging and image post-processing. 1/2014 saw the 2nd investigator meeting, which included both senior and young investigators from all participating teams. The program is well on track and has already resulted in considerable output. The project is funded by the EU FP6, ERA-NET NEURON scheme (Coordinator: M. Dichgans) and will continue until mid 2016. For more information see www.mescog.eu.

August 2013
Arthur Liesz joins ISD

On August 1st Arthur Liesz and team joined the ISD. Arthur Liesz established a Clinician-Scientist Group working on Stroke-Immunology. Their research focus is on interactions between the brain and the immune system after acute stroke and their impact on remote organ function. An acute lesion of the brain disturbs the well-balanced cross-talk between both systems. Hence, the scientific focuses of the newly established research group is on both directions of brain-immune interaction: 1) The impact of immune mechanisms on neuronal damage and recovery after stroke and 2) systemic immunomodulation and infectious complications after acute brain injury.

July 2013
SyNergy Grand Rounds series started

July 2013 marks the start of the SyNergy Grand Rounds series, which brings basic research and clinical neurology closer together. Clinicians present instructive patient cases and researchers then provide pathogenetic background on the diseases and symptoms discussed. Topics are centered around neurovascular, neuroinflammatory, and neurodegenerative disease The SyNergy rounds provide clinical exposure to basic scientists and insights into current research for clinicians. Grand rounds are already extremely popular among students, post-docs and clinicians.

May 2013
EU FP7 and BMBF research networks approved for funding

ISD has expanded its focus on atherosclerotic stroke and mechanisms of atherosclerosis. Starting with discoveries on common genetic variants shown to be associated with large artery stroke ISD investigators recently engaged in follow-up mechanistic studies. Using proteome wide analyses and an array of in vitro and in vivo models the group currently explores how sequence variants in and around HDAC9 and other candidate genes mediate atherogenesis and progression. The projects will be supported by an EU FP7 collaborative research grant (cvgenes@target) and a second collaborative grant from the BMBF (e:AtheroSysMed). Both pursue a systems medicine approach that involves investigators from multiple fields, including cardiology and -omics techniques. *(see also page 62)*

Outpatient Clinic

Opened in June 2010, the outpatient clinic was successfully established as a platform for both optimized treatment and the conduct of investigator-initiated and industry-driven trials. The clinic 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.

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

Outpatient clinic

Institute for Stroke and Dementia Research (ISD)
Klinikum der Universität München
Feodor-Lynen-Straße 17
81377 München
Internet: www.isd-muc.de

Contact
E-Mail: ambulanz.isd@med.uni-muenchen.de
Tel.: +49-89-4400-46046
Fax: +49-89-4400-46040

Outpatient clinic staff

Rupert Aigner
Dr. med. Anna Bayer-Karpinska
PD Dr. med. Katharina Bürger
Dr. med. Cihan Catak
Margit Deschner
Prof. Dr. med. Martin Dichgans
Angelika Dörr
PD Dr. med. Marco Düring
Maria Gissler
Timo Hasselwander
Brigitte Huber
Dipl. Psych. Manuel Jooßens
Eva Markov
Dr. med. Claudia Müller
Dorothea Reinartz
Viktoria Sokol
Dipl. Soz.-Päd. Irene von Tiesenhausen
Steffen Tiedt
Dipl. Psych. Elisabeth Unterauer
Kristina Vincent
Dr. med. Frank Wollenweber
Dr. rer. nat. Vera Zietemann, M.P.H.
Adelgunde Zollver

Neurovascular & Stroke Prevention Unit

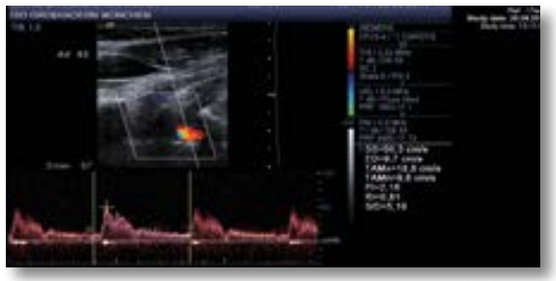
As a tertiary referral center our outpatient clinic takes care of the whole spectrum of neurovascular diseases with a special focus on primary and secondary prevention of stroke. The risk of a first or recurrent stroke can be efficiently reduced through preventive actions. To be successful preventive interventions require early recognition of risk factors and their targeted treatment.
The neurovascular outpatient clinic offers comprehensive diagnostic assessment, counselling and personalized treatment to patients and subjects at risk for developing a stroke or cardiovascular events. The neurovascular clinic is an integrative part of the Interdisciplinary Stroke Center Munich (www.iszm.de). It closely collaborates with neighboring disciplines such as neuroradiology, neurosurgery, vascular surgery and the Cyberknife-Center Munich. The neurovascular clinic is also a platform for the planning, conduct and coordination of investigator initiated trials (e.g. DEMDAS, CAPIAS, PROSCIS, BM3N, SuSPect-CAA, see page 44-48). It further participates as a recruiting center in multicenter trials (IITs and industry-sponsored). A major focus of our own IITs is to achieve a better understanding of post-stroke dementia in order to identify novel diagnostic markers and targets for preventive therapies.

Publications:

Wollenweber FA, **Zietemann V**, Gschwendtner A, Opherk C, **Dichgans M**. *Subclinical hyperthyroidism is a risk factor for poor functional outcome after ischemic stroke*. **Stroke**. 2013 May;44(5):1446-8. PMID 23482604

Wollenweber FA,**Zietemann V**, Rominger A, Opherk C, **Bayer-Karpinska A**, Gschwendtner A, **Coloma Andrews L**, **Bürger K**, **Duering M**, **Dichgans M**. *The Determinants of Dementia After Stroke (DEDEMAS) Study: protocol and pilot data*. **Int J Stroke**. 2014 Apr;9(3):387-92. PMID 23834337

Wollenweber FA, **Buerger K**, **Mueller C**, Ertl-Wagner B, **Malik R**, **Dichgans M**, Linn J, Opherk C. *Prevalence of cortical superficial siderosis in patients with cognitive impairment.* **J Neurol.** 2014 Feb;261(2):277-82. doi: 10.1007/s00415-013-7181-y. PMID:24221645



Ultrasound examination demonstrating a normal right vertebral artery

Retina scan with automated detection of retinal vessels

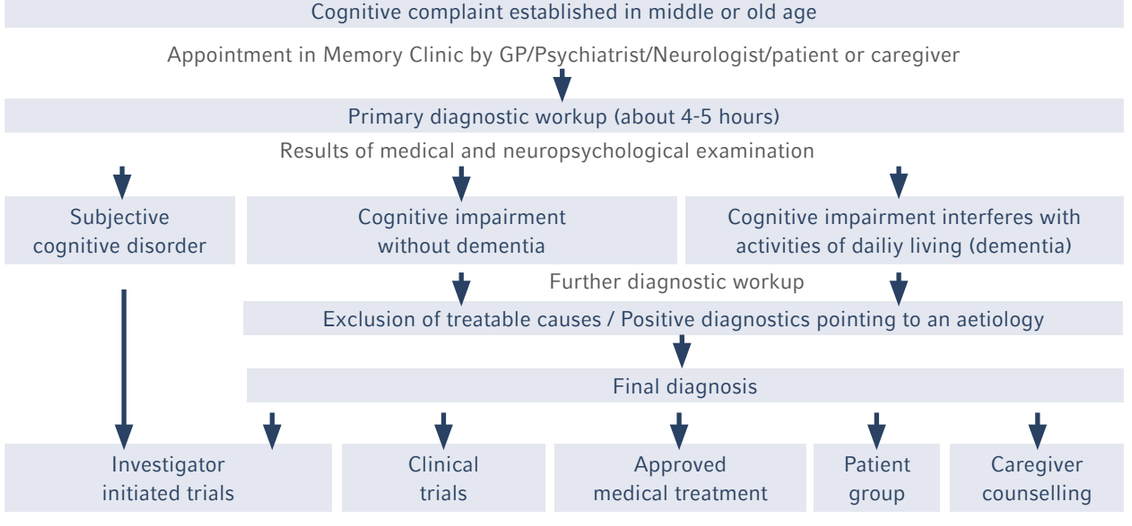
Memory Clinic

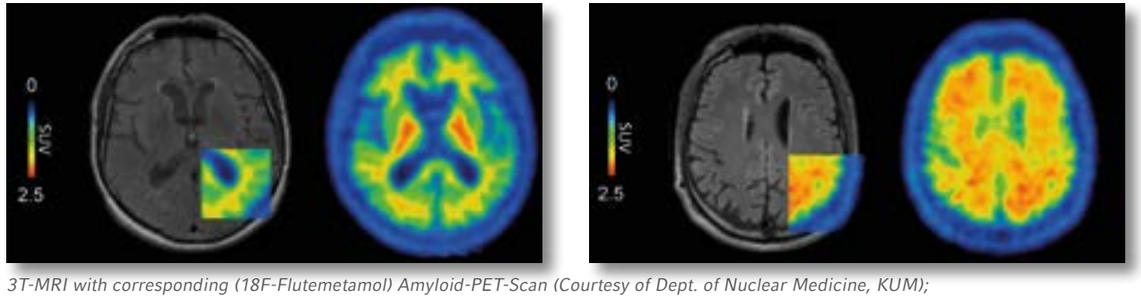
A decline of cognitive skills such as memory or attention may be normal and age-related or attributable to disease processes such as vascular disease, depression, metabolic malfunction and potentially to neurodegenerative dementia including Alzheimer's disease (AD). Early recognition of cognitive decline is critical as in many instances the clinical course can be modified by preventive means and targeted treatments. In our Memory Clinic cognitively impaired subjects and individuals at risk receive comprehensive diagnostic workup, counselling and treatment.

The ISD is dedicated to identify possible causes of cognitive decline by diagnostic processes that are streamlined according to latest scientific results. To improve our diagnostic work-up, we have opened a day clinic in January 2015.

We also offer talks and presentations to the public to inform about AD and other dementia disorders; we closely cooperate with other health system players like the Munich Alzheimer's Association, service centers for the elderly living at home, day care institutions, and charity organizations.

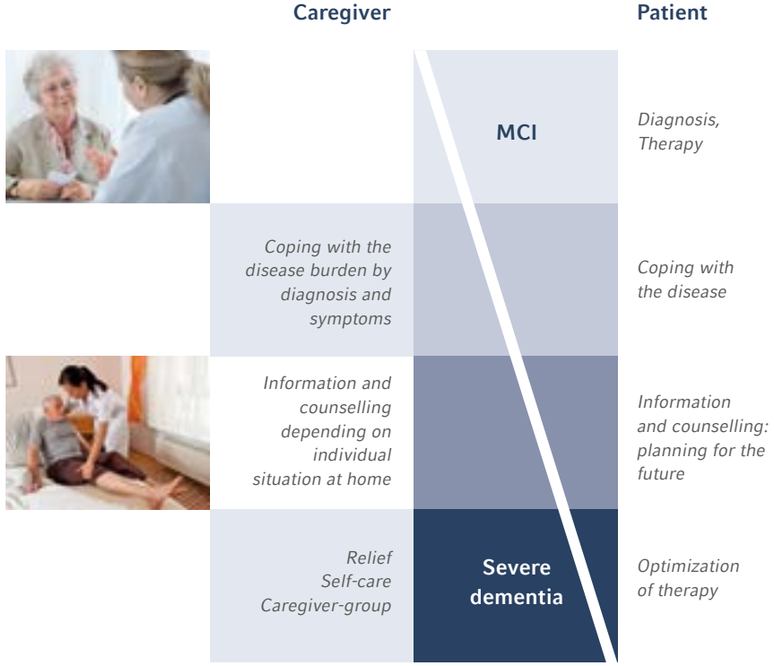
Algorithm for the management of patients with cognitive problems





3T-MRI with corresponding (18F-Flutemetamol) Amyloid-PET-Scan (Courtesy of Dept. of Nuclear Medicine, KUM);
left panel: Amyloid negative imaging of a cognitively healthy patient; right panel: Amyloid positive imaging of patient with AD.

As disease progresses, caregiver counselling and support becomes increasingly important. Our Memory Clinic establishes strong linkages with other partners in the health care system.



Clinical performance / facts & numbers

January-December 2014 (2013)
Overall 2,647 (2,358) patients visited the outpatient clinic reaching full capacity in 2014. With more space available in the new building we expect that numbers will rise in 2015.

Clinical Patient Appointments: 1,609 (1,471)
Scientific Patient Appointments: 1,038 (887)

Patients presenting to the stroke prevention unit usually had one of the following diagnoses: Previous stroke or transient ischemic attack, risk factors for stroke such as carotid artery stenosis, cerebral small vessel disease including rare genetic forms such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), previous hemorrhage, superficial siderosis, migraine.

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), Alzheimer's disease (AD), mixed dementia, vascular dementia, and other neurodegenerative dementia disorders like FTLD and DLB.

Age distribution of patients

age	percentage
11 - 20	0.3%
21 - 30	1.5%
31 - 40	3.6%
41 - 50	7.5%
51 - 60	14.4%
61 - 70	21.4%
71 - 80	39.0%
81 - 90	12.0%
91 - 100	0.3%

gender distribution: 48% male, 52% female

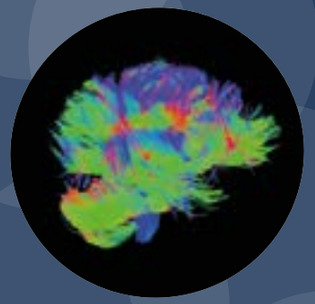
Clinical staff | outpatient clinic

function	total
chief physician	1
senior physicians	2
physicians	3
neuropsychologists	2
study nurses	5
social workers	1
technical assistants	1
outpatient office	3
total	**18**

Costs | outpatient clinic

In 2014 the total costs for the outpatient clinic amounted to 841,007 €. 79% of these costs were covered by the Vascular Dementia Research Foundation.

personnel	655,544 €
material	41,123 €
travel expenses	4,706 €
investments	9,102 €
miscellaneous	130,532 €
total	**841,007 €**



Research

Scope of research
The focus of ISD research is on the following project areas:

- Small vessel disease | Microvessels
- Vascular cognitive impairment | Post-stroke dementia
- Interactions between vascular and neurodegenerative disease
- Investigator-initiated clinical studies and trials
- Brain imaging
- Genetics & New targets
- Molecular mechanisms
- Animal models | Vascular mechanisms

Additional areas currently moving into focus include:

- Second generation "-omics" approaches
- Neurodegenerative mechanisms following stroke
- Atherosclerotic stroke
- Stroke-Immunology

Contact
Institute for Stroke and Dementia Research (ISD)
Klinikum der Universität München
Feodor-Lynen-Straße 17
81377 München
Web: www.isd-muc.de

Kathrin Gehring
E-Mail: kathrin.gehring@med.uni-muenchen.de
Tel.: +49-89-4400-46220

Jasmin Sirin Gezgin
E-Mail: jasmin.gezgin@med.uni-muenchen.de
Tel.: +49-89-4400-46242

Dr. Karin Waegemann
E-Mail: karin.waegemann@med.uni-muenchen.de
Tel.: +49-89-4400-46016

	Number of projects 2013	Funds spent 2013	Number of projects 2014	Funds spent 2014
DFG	7	414,476 €	11	654,165 €
BMBF, EU	4	126,657 €	7	304,093 €
Foundations (Fondation Leducq, Corona Stiftung…)	2	166,576 €	4	352,684 €
External third party funding spent		707,709 €		1,310,942 €
Vascular Dementia Research Foundation	1	2,683,378 € *	1	3,649,418 € *
Others	13	88,721 €	22	182,724 €
Total third party funding spent		3,479,808 €		5,143,084 €

**not including costs for outpatient clinic*

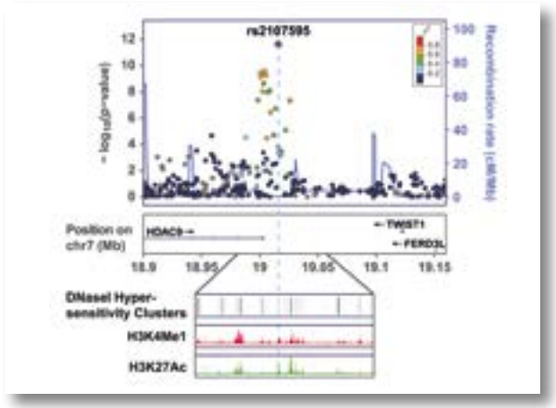
Research Groups

Translational Stroke and Dementia Research
Prof. Dr. med. Martin Dichgans

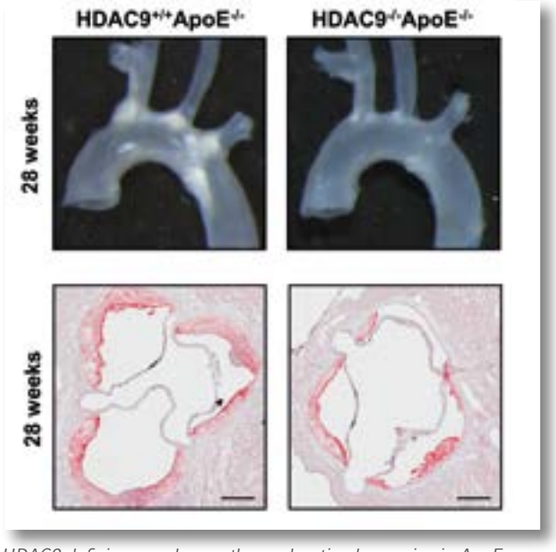
The department is committed to improve options in early recognition, prevention, diagnosis and treatment of stroke and dementia. Our focus is on disease mechanisms and prevention while integrating basic and patient-oriented research.

Genetics and novel targets: A major research interest of the department is the identification of novel targets for stroke and dementia. The group is involved in ongoing international efforts to identify common and rare genetic variants for stroke through genome-wide approaches. Following the identification of susceptibility loci for atherosclerotic stroke (Gschwendtner A et al. Ann Neurol 2009, Bellenguez C et al. Nat Genet. 2012, Holliday EG et al. Nat Genet 2012) the group is now moving to exome chip analyses and whole exome sequencing. We are further interested in the mechanisms linking disease-associated variants with stroke risk as well as with specific vascular pathologies including atherosclerosis. Approaches include proteomic tools (e.g. PWAS), genome editing of cells and animals, and mouse models including single and double knock-out animals. (Azghandi et al. Stroke 2015).

A second major focus of our work is **small vessel disease** (SVD). For one, we are interested in the molecular and cellular mechanisms underlying SVD. Thus, for example, we are exploring the mechanisms by which mutations in HTRA1 and NOTCH3, the genes implicated in CARASIL and CADASIL, respectively, induce microvascular pathology (Beaufort et al. Proc Natl Acad Sci USA 2014). We further aim to understand how structural and dynamic changes in small arteries and microvessels contribute to the occurrence of brain lesions and are studying this in animal models of CADASIL and



Regional association plot of the HDAC9 gene region showing association signals around rs2107595 for atherosclerotic stroke (Azghandi et al. Stroke 2015; Traylor et al. Lancet Neurol 2012) rs21707585 localizes to a region with regulatory properties.

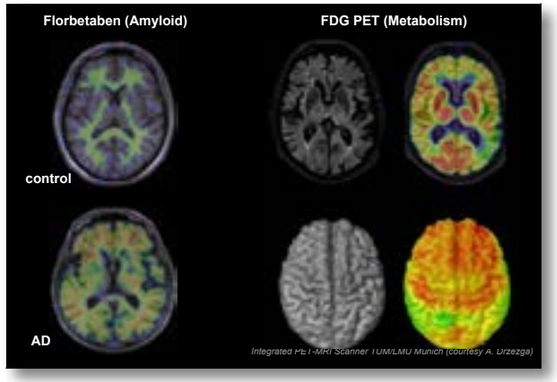


HDAC9 deficiency reduces atherosclerotic plaque size in ApoE deficient mice (Azghandi et al. Stroke 2015)

CARASIL. This work integrates into a Leducq Transatlantic Network of Excellence in Cardiovascular and Neurovascular Research.

A third research area is **vascular cognitive impairment** (VCI). Using new imaging techniques such as tract-based spatial statistics and voxel based morphometry the group aims to understand how vascular lesions in single or multiple brain regions contribute to deficits in distinct cognitive domains (www.mescog.eu) and how vascular and neurodegenerative pathology intersect in causing cognitive decline. (e.g. see Duering et al. Neurology, in press; Wardlaw JM, Smith C, Dichgans M. Lancet Neurol 2013; Wardlaw JM, Smith E, ... , Dichgans M. Lancet Neurol 2013). To study these aspects the group has set up a number of prospective studies including a multicenter study on Post-Stroke Dementia funded by the DZNE/BMBF (ClinicalTrials.gov-ID: NCT01334749).

Patient-oriented and translational research is greatly facilitated by ISD's outpatient clinic. The group has established a state of the art biobank with streamlined quality-controlled sample management (acquisition, processing, storage, retrieval, etc.) and a continuously expanding collection of samples from subjects with presymptomatic and symptomatic stages of stroke and dementia.



left: Amlyoid imaging using the novel PET tracer [F18] Florbetaben; right: merged [F18] FDG PET / MR images from our integrated PET/MR scanner (LMU/TUM)

Key Publications

Azghandi S, **Prell C**, ..., **Schneider M**, **Malik R**, ..., **Haffner C**, **Dichgans M**. *Deficiency of the Stroke Relevant HDAC9 Gene Attenuates Atherosclerosis in Accord With Allele-Specific Effects at 7p21.1.* **Stroke**. 2015 Jan;46(1):197-202.

Beaufort N, **Scharrer E**, ..., **Haffner C**, **Dichgans M**. *Cerebral small vessel disease-related protease HtrA1 processes latent TGF-β binding protein 1 and facilitates TGF-β signaling.* **Proc Natl Acad Sci USA**. 2014 Nov 18;111(46):16496-501.

Dichgans M, **Malik R**, ..., Farrall M, Schunkert H; ... *Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants.* **Stroke.** 2014 Jan;45(1):24-36.

Malik R, ..., Mitchell BD, Rosand J, Meschia JF, Levi C, Rothwell PM, ..., Dichgans M; Wellcome Trust Case Control Consortium 2. *Multilocus genetic risk score associates with ischemic stroke in case-control and prospective cohort studies.* **Stroke.** 2014 Feb;45(2):394-402.

Opherk C, **Gonik M**, **Duering M**, **Malik R**, ..., **Dichgans M**. *Genome-wide genotyping demonstrates a polygenic risk score associated with white matter hyperintensity volume in CADASIL.* **Stroke**. 2014 Apr;45(4):968-72.

Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, ..., **Duering M**, ... **Dichgans M**; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). *Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration.* **Lancet Neurol.** 2013 Aug;12(8):822-38.

Wardlaw JM, Smith C, **Dichgans M**. *Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging.* **Lancet Neurol.** 2013 May;12(5):483-97.

Team: Department of Translational Stroke and Dementia Research

Group Members

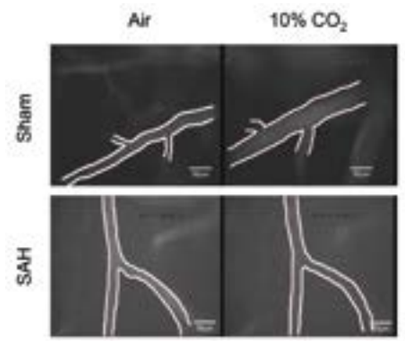
Prof. Dr. med. Martin Dichgans
Dr. rer. nat. Yaw Asare
Dr. rer. nat. Nathalie Beaufort
Dr. rer. nat. Mariya Gonik
PD Dr. rer. nat. Christof Haffner
Dr. rer. nat. Jessica Kast
Dr. rer. nat. Rainer Malik
Dr. rer. nat. Caroline Prell-Schicker
Dr. rer. nat. Matthias Prestel
Dr. rer. nat. Eva Scharrer
Dr. rer. nat. Karin Waegemann
Sepiede Azghandi, B.Sc.
Patrizia Hanecker, M.Sc.
Veronika Kautzky
Timon Landinger
Manuel Lehm
Natalie Leistner
Barbara Lindner
Melanie Schneider
Steffen Tiedt
Guangyao Yan

Laboratory of Experimental Stroke Research

Prof. Dr. med. Nikolaus Plesnila

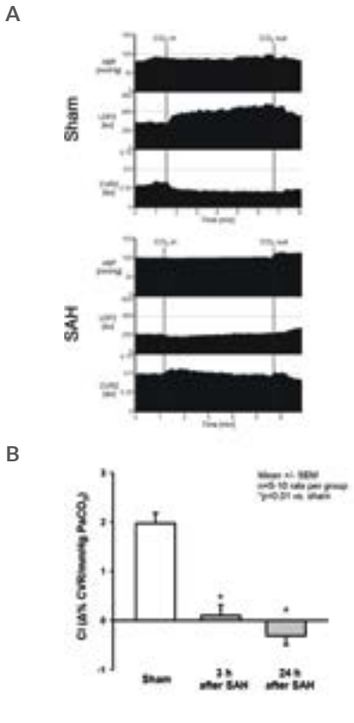
Our aim is to uncover the pathophysiology of ischemic and hemorrhagic stroke. This knowledge should be used as the basis for the development of novel therapeutic options for stroke patients. The main expertise of the laboratory gathers around experimental stroke models (transient & permanent focal cerebral ischemia, global ischemia, subarachnoid hemorrhage) and methods for the investigation of the cerebral microcirculation (intravital microscopy using conventional and 2-photon excitation). Combining these two technologies members of the laboratory study the role of the cerebral microcirculation in ischemic and hemorrhagic stroke, in murine models of small vessel disease, and in other brain injury paradigms.

Fig.1



Cerebral arterioles do not respond to elevated arterial pCO2 after experimental subarachnoid hemorrhage (SAH), a subtype of stroke with a particularly unfavorable outcome. This suggests severely impaired nitric oxide signaling in the vascular wall or in adjacent nerve terminals. Hence, replacing NO may be a viable therapeutic option to prevent vascular dysfunction after SAH.

Fig.2



Key Publications

Prades R, Oller-Salvia B, **Schwarzmaier SM**, Selva J, Moros M, **Balbi M**, ..., **Plesnila N**, Teixidó M, Giralt E. *Applying the Retro-Enantio Approach to Obtain a Peptide Capable of Overcoming the Blood-Brain Barrier.* **Angew Chem Int Ed Engl.** 2015 (accepted for publication)

Bühler D, **Azghandi S**, **Schüller K**, **Plesnila N.** *Effect of Decompressive Craniectomy on Outcome Following Subarachnoid Hemorrhage in Mice.* **Stroke.** 2015 Mar;46(3):819-26.

D'Orsi B, Kilbride SM, ..., Bonner HP, **Plesnila N**, Engel T, Henshall DC, Düssmann H, Prehn JHM. *Bax acutely regulates neuronal Ca2+ homeostasis* **J Neuroscience** (Accepted for publication)

Schwarzmaier SM, Terpolilli NA, Dienel A, Gallozzi M, Schinzel R, Tegtmeier F, **Plesnila N.** *Endothelial nitric oxide synthase mediates arteriolar vasodilatation after traumatic brain injury in mice.* **J Neurotrauma** (accepted for publication)

Gröger M**, Plesnila N.** *The neuroprotective effect of 17β-estradiol is independent of its antioxidantive properties* **Brain Research.** 2014, 1589C:61-67.

Krieg S, Sonanini S**, Plesnila N,** Trabold R *Effect of small molecule vasopressin V1a and V2 receptor antagonists on brain edema formation and secondary brain damage following traumatic brain injury in mice* **J Neurotrauma** (Accepted for publication)

Friedrich B, ..., Kozniewska E, **Plesnila N.** *CO2 has no therapeutic effect on early microvasospasm after experimental subarachnoid hemorrhage.* **J Cereb Blood Flow Metab.** 2014 Aug;34(8):e1-6.

Team: Laboratory of Experimental Stroke Research

Group Members

Prof. Dr. med. Nikolaus Plesnila
Dr. rer. nat. Athanasios Lourbopoulos
Dr. rer. nat. Mitrajit Ghosh
Dr. rer. nat. Farida Hellal
Dr. med. Susanne Schwarzmaier
Dr. med. Nicole Terpolilli
Matilde Balbi, M.Sc.
Dominik Bühler
Carina Exner
Kathrin Gehring
Nicole Heumos
Sabrina Katzdobler
Maximilian Knarr
Uta Mamrak
Iga Rynarzewska
Pierre Scheffler
Kathrin Schüller
Charlotte Schwicht
Irina Westermayer
Katherina Werchoturov

Brain Imaging and Biomarker Research
Prof. Dr. Michael Ewers

The major focus of our research is to better understand the brain changes that underlie the initial development of cognitive impairment in the course of Alzheimer's disease (AD). Elderly subjects who are cognitively normal may show substantial brain pathologies (beta-aymloid, vascular pathology, inflammation), i.e. abnormalities that are typically observed in patients with full-blown AD dementia. We use combined MRI and molecular PET imaging to understand how these primary brain pathologies affect functional neuronal networks underlying the emergence of dementia symptoms.

In a first line of investigations, we showed in elderly cognitive healthy subjects that reduced glucose metabolism assessed by FDG-PET is predictive of the likelihood to develop mild cognitive impairment and AD type dementia within 2-3 years (Ewers M et al. Neuroimage (Clinical), 2014). The spatio-temporal dynamics of the spreading of glucose hypometabolism and grey matter atrophy follows a specific sequence within boundaries of functional networks (Thal, Attems, & Ewers, J Alz Dis, 2014; Araque-Caballero et al., under review). We are currently probing functional connectivity changes within such neural networks by fMRI to better predict and track the impairment of cognitive abilities in non-demented subjects at risk of AD. Importantly, we found that at the same level of glucose hypometabolism, some elderly subjects show better cognitive performance when compared to others. Part of that difference can be attributed to early life experience, such as education, believed to reflect cognitive reserve (Ewers et al. Neurology 2013)

We are currently investigating what functional network mechanisms may underlie cognitive reserve and how to train and stimulate such networks of cognitive reserve in clinical interventions.

A second major focus of our research, funded by the EU, is the investigation of the interaction between early key pathologies of AD (e.g. Aß and tau) and small vessel disease. In collaboration with the North American Alzheimer's Disease Neuroimaging Initiative (ADNI, PI Michael Weiner), we recently observed that white matter hyperintensities (WMH) within specific fiber tracts (measured by DTI) are associated with reduced functional connectivity between brain areas connected by these tracts (Taylor et al, under review). These results suggest that pathologies related to small vessel disease (SVD) are an important factor, independent from Aß pathology, to explain functional network damage that underlies cognitive impairment in AD. We now apply episodic-memory task related fMRI and structural DTI methods in subjects with AD or CADASIL (PI: Dr. Düring) to investigate the SVD-related perfusion changes in neural networks. Understanding the contribution of SVD to brain dysfunction is of great clinical importance since the vascular pathology can be targeted by interventions such as risk factor control and physical activity, thus offering a possibility to slow down cognitive decline in aging and AD.

In a third approach we apply statistical data mining methods to MRI, PET, and EEG images to extract key brain changes for the prediction of AD dementia. Specifically, we are testing novel image clustering methods and multivariate machine learning statistics for establishing neuroimaging-based case-by-case diagnostics in a cost-effective and clinically feasible way. These methods are being developed in collaboration with the Institute of Informatics at the LMU and Helmholtz Center Munich.

Key Publications

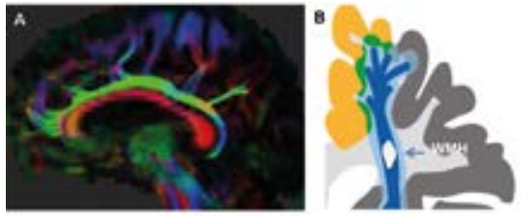
Ewers M, Mattson MP, Minthon L, Molinuevo JL, Antonell A, Popp J, Jessen F, Herukka SK, Soininen H, Maetzler W, Leyhe T, Taniguchi M, **Buerger K,** Urakami K, Lista S, Dubois B, Blennow K, Hampel H. *CSF biomarkers for the differential diagnosis of Alzheimer's disease. A large-scale international multi-center study.* **Alzheimers Dement.** (in press).

Thal DR, Attems J, **Ewers M.** *Spreading of amyloid, tau, and microvascular pathology in Alzheimer's disease: findings from neuropathological and neuroimaging studies.* **J Alzheimers Dis.** 2014;42 Suppl 4:S421-9.

Ewers M, Brendel M, Rizk-Jackson A, Romminger A, Bartenstein P, Schuff N, Weiner MW. *Reduced FDG-PET brain metabolism and executive function predict clinical progression in elderly healthy subjects.* **Neuroimage Clin.** 2013 Nov; (5):311-20.

Grothe MJ, **Ewers M,** Krause B, Heinsen H, Teipel SJ, Alzheimer's Disease Neuroimaging I. *Basal forebrain atrophy and cortical amyloid deposition in nondemented elderly subjects.* **Alzheimers Dement.** 2014 Oct;10(5 Suppl):S344-53.

Ewers M, Insel P, Stern Y, Weiner M. *Cognitive Reserve Associated with FDG-PET in Preclinical Alzheimer's Disease.* **Neurology.** 2013 Mar; 80(13):1194-201.



Using DTI based fiber tracking (A), we locate WMH within fiber bundles to assess their impact on brain activity in connected tissue (B).

Teams: Brain Imaging and Biomarker Research and Vascular Cognitive Impairment

Group Members

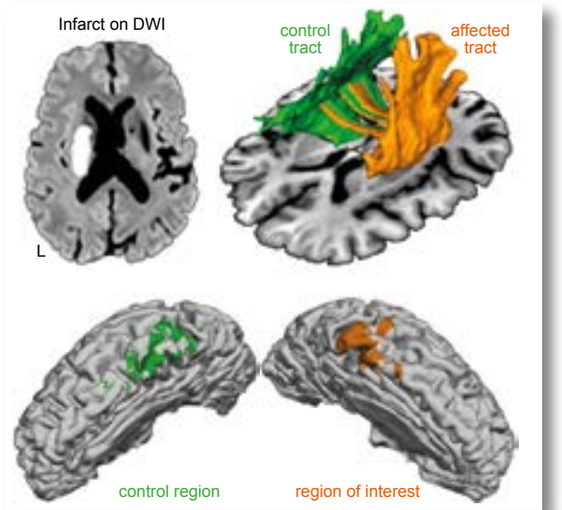
Prof. Dr. Michael Ewers
Dr. rer. nat. Miguel Araque Caballero
Nicolai Franzmeier
Alexander Taylor, M.Sc.
Jinyi Ren
Lee Simon-Vermot, M.Sc.
Yifei Zhang, M.Sc.
Kathrin Gehring

Vascular Cognitive Impairment
(Junior Research Group)
PD Dr. med. 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 several 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. In an EU funded project (ERA-NET Neuron, MESCOG) scientists from Paris, Graz and Munich have teamed up to investigate the mechanisms of SVD in CADASIL as well as age-related sporadic SVD.

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



Analysis of changes in tract integrity and cortical morphology in connected regions after stroke. The hemisphere affected by an ischemic infarct is compared to the contralateral hemisphere (control).

Key Publications

Duering M, Righart R, Wollenweber FA, Zietemann V, Gesierich B, Dichgans M. *Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts.* **Neurology.** (in press)

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

Duering M, Csanadi E, **Gesierich B,** Jouvent E, Hervé D, Seiler S, Belaroussi B, Ropele S, Schmidt R, Chabriat H, **Dichgans M.** *Incident lacunes preferentially localize to the edge of white matter hyperintensities: insights into the pathophysiology of cerebral small vessel disease.* **Brain.** 2013 Feb; 34(2):400-72013.

Duering M, Righart R, Csanadi E, Jouvent E, Hervé D, Chabriat H, **Dichgans M.** *Incident subcortical infarcts induce focal thinning in connected cortical regions.* **Neurology.** 2012 Nov; 79:20.2025-2028.

Duering M, Zieren N, Hervé D, Jouvent E, Reyes R, Peters N, Pachai C, **Opherk C,** Chabriat H**, Dichgans M.** *Strategic role of frontal white matter tracts in vascular cognitive impairment: a voxel-based lesion-symptom mapping study in CADASIL.* **Brain.** 2011 Aug; 134:Pt 8.2366-2375.

Group Members

Ruth Adam, Ph.D.
Ebru Baykara, M.Sc.
PD Dr. med. Marco Düring
Benno Gesierich, Ph.D.
Jasmin Sirin Gezgin

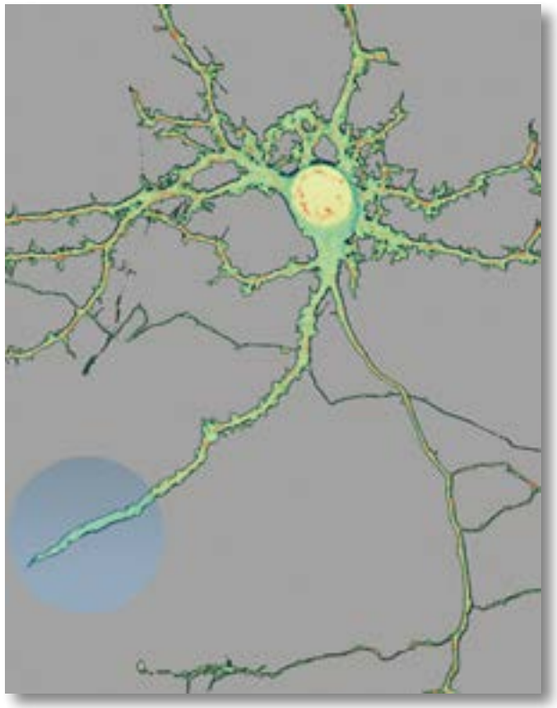
Acute Brain Injury Research
(Junior Research Group)
Dr. rer. nat. Ali Erturk

My laboratory is interested in understanding key mechanisms leading to neurodegeneration after acute brain injuries: stroke and trauma. We use the cutting-edge technologies to investigate the causes of degeneration in the neuronal circuitry.

Patients with acute brain injury often develop chronic complications including early onset dementia, epilepsy and neuropsychiatric disorders. While these complications are suggestive of continuous alterations in the injured brain circuitry, virtually nothing is known about how the initial injury alters the brain structure and ultimately its function. We recently demonstrated that a focal caspase-3 activation in dendrites leads to deterioration of the spines/synapses at the site of caspase-3 activity, while the rest of neuron remains completely intact. We now investigate whether a similar caspase-3 activity may underlie dendritic spine/synapse degeneration in the secondary phase of acute brain lesion.

One of the main struggles in neuroscience in general is the difficulty to accurately analyze long neuronal connections in the brain. We use a novel approach aiming at mapping acute and chronic changes in the entire brain caused by small, well-defined brain lesions. To this end, we utilize cutting-edge imaging techniques including high-resolution 3D imaging of the entire brain that we recently developed (Figure). This is followed by screening for novel molecular players that are altered in chronically affected brain regions to halt secondary neurological problems.

In parallel, we continue to develop and apply new imaging technologies to improve our ability to visualize and analyze anatomical connections in the brain. We believe that a global appreciation of cellular changes in the entire brain should lead to a deeper understanding of the morphological substrate affecting brain function in disease and deliver useful prognostic and therapeutic information.



Optogenetic activation of caspase-3 locally (blue region) causes spine loss in cultured hippocampal neurons

Key Publications

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

Chen Y, Wang Y, **Ertürk A**, Kallop D, Jiang J, Weimer RM, Kaminker J, Sheng M. *Activity-induced nr4a1 regulates spine density and distribution pattern of excitatory synapses in pyramidal neurons.* **Neuron.** 2014 Jul 16;83(2):431-43.

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

Ertürk A, Mauch CP, Hellal F, Förstner F, Keck T, Becker K, Jährling N, Steffens H, Richter M, Hübener M, Kramer E, Kirchhoff F, Dodt HU, Bradke F. *Three-dimensional imaging of the unsectioned adult spinal cord to assess axon regeneration and glial responses after injury.* **Nat Med.** 2011 Dec 25;18(1):166-71. (Cover article of the 2012 January Nature Medicine issue).

Ylera B*, **Ertürk A***, Hellal F, Nadrigny F, Hurtado A, Tahirovic S, Oudega M, Kirchhoff F, Bradke F. *Chronically CNS-injured adult sensory neurons gain regenerative competence upon a lesion of their peripheral axon.* **Curr Biol.** 2009 Jun 9;19(11):930-6. *Co-first author.

Group Members

Dr. Ali Erturk
Dr. Lamia'a Bahnassawy
Ruiyao Marika Cai
Chenchen Pan
Leone Njaramba
Alireza Ghasemi
Jasmin Sirin Gezgin

3D imaging of unsectioned spinal cord axons imaged by light-sheet microscope

Stroke-Immunology
(Clinician Scientist Group)
Dr. Arthur Liesz

Our group is interested in the interplay between the brain and the immune system after an acute stroke. An acute lesion of the brain disturbs the well-balanced interconnection between both systems. Hence our research focuses on both directions of brain-immune interaction: 1) The impact of immune mechanisms on neuronal damage and recovery after stroke and 2) systemic immunomodulation and infectious complications after acute brain injury. Our group has a strong translational interest with the ultimate goal of developing new concepts and potential therapies for the benefit of stroke patients.

Our methodical spectrum covers diverse brain ischemia models, transgenic animal models, a broad spectrum of cutting-edge immunological techniques as well as histological, biomolecular and behavioral analysis tools. Because of our inter-disciplinary research approach we are highly connected with local and international collaborators.

In one of our projects, we investigated the control of the inflammatory reaction after ischemic brain injury by active regulatory mechanisms. We have previously identified an important neuroprotective role of endogenous regulatory T cells in stroke (Liesz et al., Nature Medicine, 2009). Use of this potent endogenous mechanism by directly augmenting their immunosuppressive capacities or their downstream signalling pathways is being tested as promising therapeutic targets at the center of post-ischemic neuroinflammation (Liesz et al., J Neuroscience, 2013).

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

A third main project investigates the mechanisms of peripheral immune alterations after brain ischemia. Acute brain lesions induce profound alterations in the systemic immune homeostasis. We aim to characterize humoral mediators which are released by the necrotic brain tissue (so called danger-associated molecular patterns, "DAMPs") as strong modulators of the systemic immune system resulting in lymphocyte apoptosis and functional perturbance (Liesz et al., J Neurosci, 2015)

Key Publications

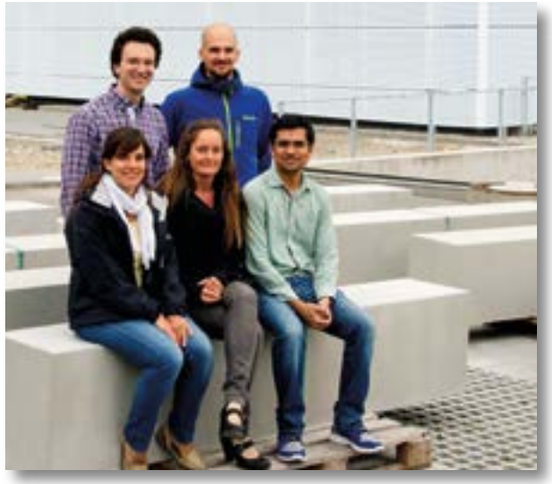
Liesz A, Suri-Payer E, Veltkamp C, Dörr H, Sommer C, Rivest S, Giese T, Veltkamp R. *Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke* **Nature Medicine.** 2009 Feb;15(2):192-9. doi: 10.1038/nm.1927.

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

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

Liesz A, Dalpke A, Mracsko E, Antoine DJ, Roth S, [...] Veltkamp R. *DAMP signaling is a key pathway inducing immune modulation after brain injury* **The Journal of Neuroscience.** 2015 Jan 14;35(2):583-98.

Liesz A, Hagmann S, Zschoche C, Adamek J, Zhou W, Sun L, Dalpke A, Nawroth P, Veltkamp R. *The spectrum of systemic immune alterations after murine focal ischemia: Immunodepression versus immunomodulation* **Stroke**. 2009 Aug;40(8):2849-58.



Team: Clinician Scientist Group on Stroke-Immunology

Group Members

Dr. med. Arthur Liesz
Vikramjeet Singh, Ph.D.
Gemma Llovera Garcia, M.Sc.
Stefan Roth, M.Sc.
Rebecca Sadler, B.Sc.
Kerstin Hofmann
Kathrin Gehring

Small Vessel Disease (molecular and cellular mechanisms)

PD Dr. rer. nat. Christof Haffner

A substantial portion of cerebral small vessel disease (SVD) risk is attributed to genetic factors. We are focusing on NOTCH3, which is affected in CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), the most common monogenic cause of SVD and vascular dementia, and HTRA1, the susceptibility gene for the related recessive disorder CARASIL. We aim at the identification of molecular targets and mechanisms likely to contribute to the pathology of sporadic SVD.

NOTCH3: The accumulation and deposition of the NOTCH3 extracellular domain (NOTCH3-ECD), early manifestation and hallmark of CADASIL, is considered the starting point of a chain of pathological events eventually causing brain vessel dysfunction and disease. We use molecular and cellular approaches to identify factors mediating NOTCH3-ECD toxicity. We further apply scanning for intensely fluorescent targets (SIFT), a confocal technology developed for monitoring protein multimerization *in vitro*, to identify disease-relevant co-aggregating factors and to screen for NOTCH3-ECD aggregation inhibitors.

HTRA1: CARASIL results from loss-of-function mutations in the HTRA1 gene encoding a highly conserved serine protease with incompletely defined substrate specificity and a putative role in TGF-β signaling. We use biochemical and proteomic approaches to identify CARASIL-relevant HTRA1 substrates. In addition, we currently establish HTRA1-/- mice as disease model and will use them in combination with cellular systems including human fibroblasts to explore the role of HTRA1 and TGF-β signaling in the pathogenesis of SVD.

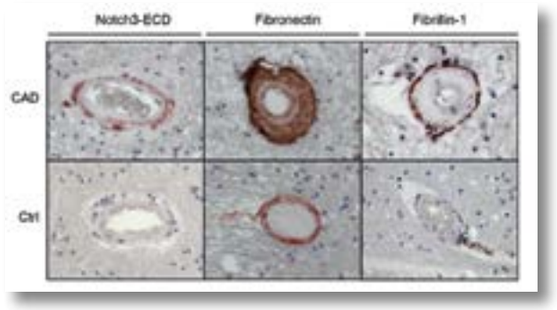


Figure: Brain vessels of CADASIL patients (CAD) are characterized by the deposition of the NOTCH3 extracellular domain (ECD) and the accumulation of the extracellular matrix proteins fibronectin and fibrilin-1.

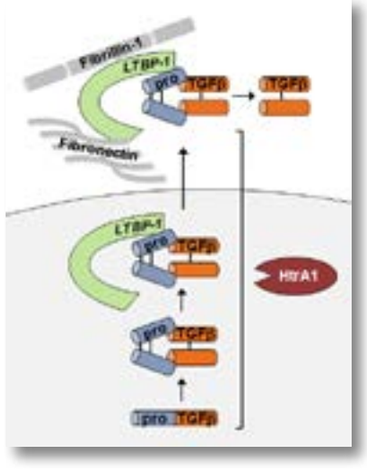


Figure: TGF-β is synthesized as proform and undergoes intracellular dimerization/proteolytic processing. It is secreted as an inactive complex containing latent TGF-β binding protein 1 (LTBP-1) which mediates its sequestration within the extracellular matrix. The HTRA1 protease regulates TGF-β production or activation from the latency complex by a poorly understood mechanism.

Key Publications

Kast J, Hanecker P, Beaufort N, Giese A, Joutel A, **Dichgans M,** Opherk C, **Haffner C.** *Sequestration of latent TGF-β binding protein 1 into CADASIL-related Notch3-ECD deposits.* **Acta Neuropathol Commun.** 2014 Aug 13;2(1):96-107.

Wollenweber FA, Hanecker P, Bayer-Karpinska A, Malik R, Bäzner H, Moreton F, Muir KW1, Müller S, Giese A, Opherk C, **Dichgans M, Haffner C, Duering M**. *Cysteine-Sparing CADASIL Mutations in NOTCH3 Show Proaggregatory Properties In Vitro.* **Stroke**. 2015 Mar;46(3):786-92.

Beaufort N, Scharrer E, ..., Haffner C, Dichgans M. *Cerebral small vessel disease-related protease HtrA1 processes latent TGF-β binding protein 1 and facilitates TGF-β signaling.* **Proc Natl Acad Sci U S A.** 2014 Nov 18;111(46):16496-501.

Azghandi S, Prell C, ..., Schneider M, Malik R, ..., Haffner C, Dichgans M. *Deficiency of the Stroke Relevant HDAC9 Gene Attenuates Atherosclerosis in Accord With Allele-Specific Effects at 7p21.1.* **Stroke.** 2015 Jan;46(1):197-202.

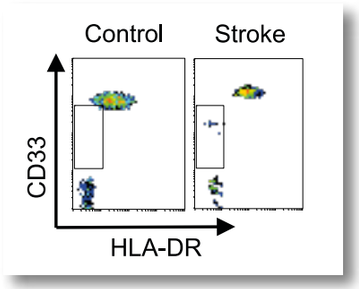
Team: Small Vessel Disease

Group Members

PD Dr. rer. nat. Christof Haffner
Dr. rer. nat Nathalie Beaufort
Dr. rer. nat. Caroline Prell-Schicker
Dr. rer. nat. Eva Scharrer
Sepiede Azghandi, B.Sc.
Kathrin Gehring
Timon Landinger
Natalie Leistner
Barbara Lindner
Melanie Schneider
Andreas Zellner, M.Sc.

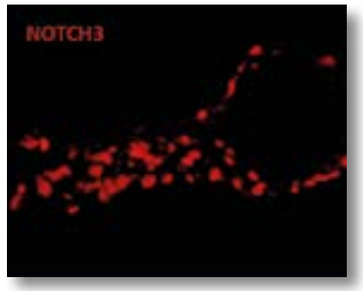
Research Highlights 2013/2014

Alarmins in brain-immune communication



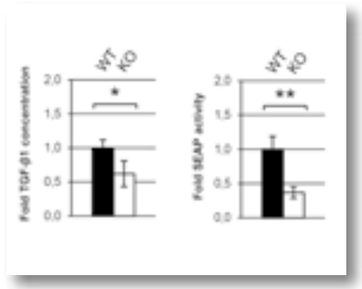
A new study by A. Liesz and colleagues identifies alarmins, in particular HMGB1, as key mediators of the complex peripheral immune alterations after stroke. HMGB1 is released from the ischemic brain in the hyperacute phase of stroke in mice and patients. Cytokines secreted in the periphery in response to brain injury induced sickness behavior, which could be abrogated by inhibition of the HMGB1-RAGE pathway or direct cytokine neutralization. Subsequently, HMGB1-release induced bone marrow egress and splenic proliferation of bone marrow-derived suppressor cells (MDSCs), inhibiting the adaptive immune responses in vivo and vitro. *(Liesz A et al. The Journal of Neuroscience 2015)*

New insights into CADASIL pathogenesis



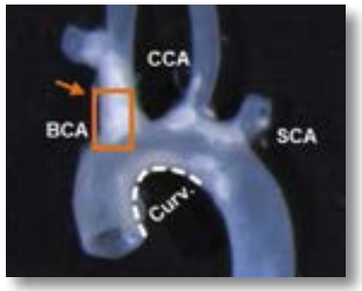
Two new studies in Stroke and Acta Neuropathologica Communications provide new insights into the genetics and pathomechanisms of CADASIL. Wollenweber et al. report on a CADASIL family with a rare cysteine-sparing NOTCH3 mutation and demonstrate enhanced aggregation of this mutant in vitro using single-particle analysis. The study challenges the current view of cysteine mutations as exclusive disease cause. Kast et al. identify latent TGF-β binding protein 1 (LTBP-1), a regulator of the TGF-β signaling pathway, as component of the disease-specific NOTCH3 deposits highlighting the importance of the extracellular matrix in small vessel disease. *(Wollenweber FA et al., Stroke 2015, Kast et al., Acta Neuropathol. Commun. 2014)*

Cerebral SVD and TGF-β signaling



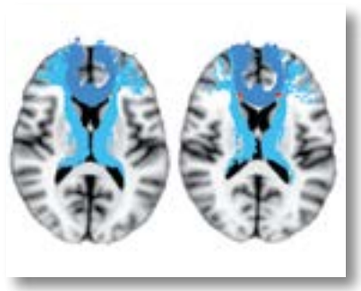
A study published in the Proceedings of the National Academy of Sciences links a reduction of TGF-β signaling to the hereditary small vessel disease CARASIL. The condition is caused by loss-of-function mutations in the high temperature requirement protease HtrA1. We found LTBP-1, an extracellular matrix protein and major regulator of TGF-β bioavailability to be a substrate for HtrA1. Findings are supported by analyses of brain tissue and embryonic cells from HtrA1-deficient mice, as well as skin fibroblasts from a CARASIL patient. Our findings suggest an attenuation of TGF-β signalling caused by a lack of HtrA1-mediated LTBP-1 processing as a key molecular mechanism underlying CARASIL pathogenesis. *(Beaufort N et al. Proc Natl Acad Sci USA. 2014)*

HDAC9 and atherosclerosis



A new study by ISD investigators published in the STROKE journal shows that HDAC9 represents the disease-relevant gene at the stroke risk locus on 7p21.1. Our findings offer novel mechanistic insights and have implications for the development of novel preventive strategies *(Azghandi S et al. Stroke 2015)*

Strategic white matter tracts in vascular cognitive impairment

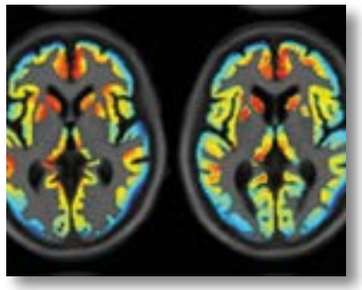


The impact of lesion location in age-related small vessel disease was studied within the EU-funded MESCOG-project. 584 community-dwelling elderly, recruited through the Austrian Stroke Prevention Study (Graz), underwent MRI and neuropsychological testing. Voxel-based lesion-symptom mapping and Bayesian network analysis identified the anterior thalamic radiation and the forceps minor as strategic locations. The findings highlight damage to frontal interhemispheric tracts and thalamic projection fiber tracts harboring frontal-subcortical neuronal circuits as a predictor for processing speed performance in age-related small vessel disease. *(Duering M et al. Neurology 2014)*

Stroke risk prediction through genetic risk functions

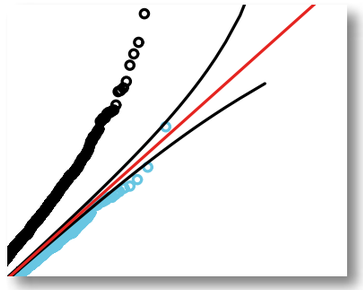
Two separate but complementing studies from the ISD in collaboration with the CHARGE consortium published in Stroke show that composite genetic risk scores based on known common genetic variants for vascular risk factors of stroke (e.g. blood pressure or atrial fibrillation) can discriminate between ischemic stroke cases and controls in both case-control and prospective cohort studies. This again confirms the polygenic nature of ischemic stroke and highlights the potential importance of genetic testing in clinical practice. *(Malik R et al. Stroke 2014, Ibrahim-Verbaas CA et al. Stroke 2014)*

Detection of preclinical Alzheimer's disease



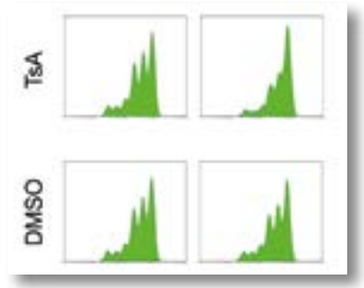
Results of a study by Ewers & colleagues suggest that reduced FDG-PET and subtle changes in the mental ability of cognitively normal elderlies predict the future development of dementia symptoms. Because the detection of AD in the asymptomatic stage is inherently difficult due to the subtle severity of symptoms, these findings on combined neuroimaging and neuropsychological testing represent a major step forward towards early detection of AD. Since major treatment approaches such as amyloid immunization are focusing on such an early time window of the course of the disease, biomarkers tests of preclinical AD are urgently needed. *(Ewers M et al. NeuroImage Clinical 2013)*

Shared genetic susceptibility to stroke and CAD



By analyzing genome-wide data from the METASTROKE and CARDIoGRAM consortia ISD investigators showed that common variants at a substantial number of genetic loci influence risk of both ischemic stroke, and here especially large artery stroke (LAS), and coronary artery disease (CAD). The pattern of association for the two phenotypes is strikingly similar for a substantial number of investigated genomic regions, suggesting shared genetic risk at these loci. The study also pinpoints novel genetic risk loci that are expected to emerge as independent risk factors for LAS in future studies. *(Dichgans M et al. Stroke 2014).*

Regulatory T cells limit neuroinflammation in experimental stroke

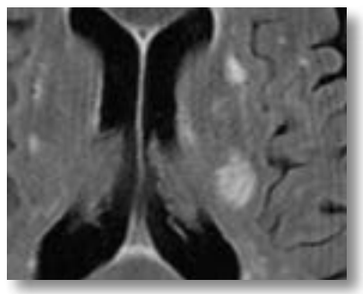


A study by Arthur Liesz and colleagues, published in the October issue of The Journal of Neuroscience, describes the use of histone deacetylase inhibitors (HDACi) to boost the number and function of regulatory T cells (Treg), a specialised cell population orchestrating the immune reaction after ischemic brain injury. In vivo treatment reduced infarct volumes and behavioral deficits after cortical brain ischemia, attenuated cerebral proinflammatory cytokine expression, and increased numbers of brain-invading Tregs. A similar effect was obtained using tubastatin, a specific inhibitor of HDAC6 and a key HDAC in Treg regulation. These results suggest that modulation of Treg function by HDACi is a novel and potent target to intervene at the center of neuroinflammation. *(Liesz A et al. The Journal of Neuroscience 2013)*

Cognitive reserve may have protective effects in Alzheimer's disease

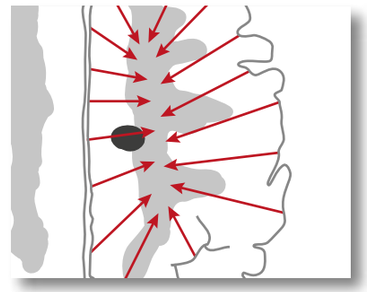
Epidemiological studies suggest that higher levels of education (a measure of cognitive reserve) are associated with lower risk of Alzheimer's disease (AD) dementia. However, it is unclear whether higher education protects against the impact of AD related brain damage. Using FDG-PET imaging to assess neurodegeneration M. Ewers and colleagues demonstrated that elderly at-risk AD subjects exhibited more pronounced FDG-PET hypometabolism when they had higher levels of education – yet these subjects remained cognitively normal. Thus cognitive reserve (education) may have a protective effect against the impact of AD pathology on cognition early in the course of the disease *(Ewers M et al. Neurology 2013).*

STandards for ReportIng Vascular changes on nEuroimaging (STRIVE)



In a united approach specialists in vascular imaging established neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. The results are published in the August issue of Lancet Neurology. *(Wardlaw JM, Smith E, …, Dichgans M. The Lancet Neurology 2013)*

Incident lacunes and the WMH penumbra



The traditional view holds that lacunes and white matter hyperintensities (WMH), two hallmarks of small vessel disease (SVD), have distinct pathomechanisms. A study on incident lacunes and their topology with WMH challenges this view. The analysis identifies the edge of WMH as a predilection site for lacunes: 91% of incident lacunes developed in contact or overlap with WMH. Together with information from vascular anatomy and the progression pattern of WMH over disease stages, these observations offer insights into the mechanisms underlying WMH and lacunes and refine the concept of the WMH penumbra. *(Duering M et al. Brain, 2013).*

Investigator Initiated Studies (Selection)

In 2013 and 2014 ISD investigators conducted a number of investigator initiated clinical studies including epidemiological and interventional studies. Most of them are registered at www.clinicaltrials.gov.

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

Risk of dementia is high after stroke but the mechanisms of post stroke dementia (PSD) are insufficiently understood. Specifically, there are few data on how vascular and neurodegenerative mechanisms interact in determining cognitive decline after stroke. The primary aim of the DEMDAS study is to identify predictors of PSD. A particular focus is on biological markers (neuroimaging, biochemical markers derived from blood) and on interactions between vascular and neurodegenerative mechanisms. 600 patients with an acute stroke and without prior dementia will be followed for 5 years with assessments at baseline (< 72 h after onset of stroke), and at 3, 6, 12, 24, 36, 48, and 60 months. Baseline assessments include variables previously demonstrated to be associated with PSD as well as novel variables. Brain MRI (structural MRI and resting state fMRI) in combination with detailed neuropsychological testing and blood draws will be done at 6, 12, 36, and 60 months. Patients developing cognitive impairment (with or without dementia) and a subgroup of matched individuals without cognitive decline will be examined by brain FDG-PET and Amyloid-PET scanning. Efforts will be made to classify demented patients into diagnostic categories (Vascular Dementia, Mixed Dementia, Alzheimer's disease, other categories). Predictive factors for PSD will be identified using multiple Cox-proportional hazards models. Apart from providing insights into the mechanisms of PSD this study holds the potential to identify novel diagnostic markers and novel targets for preventive therapies. The study was initially started as a monocentric study (DEDEMAS [Determinants of Dementia After Stroke]) and subsequently extended as a multicenter study through funding from the DZNE (additional: sites Bonn, Berlin, Göttingen, Magdeburg, Munich).
Planned sample size: 600
Started May 2011
Current enrollment: 226
(195 at ISD + 31 from additional study centres)
Estimated date for study completion: 2022
Principle investigator: M. Dichgans
Project management: F. Wollenweber, K. Waegemann
Funding: Munich Cluster for Systems Neurology (SyNergy) & DZNE.

Publications:
Wollenweber FA, Zietemann V, Rominger A, Opherk C, **Bayer-Karpinska A**, Gschwendtner A, **Coloma Andrews L, Bürger K, Duering M, Dichgans M**,... *The Determinants of Dementia After Stroke (DEDEMAS) Study: protocol and pilot data.* **Int J Stroke.** 2014 Apr;9(3):387-92.

Duering M, Righart R, **Wollenweber FA, Zietemann V, Gesierich B, Dichgans M**. *Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts.* **Neurology**; in press.

PROSCIS (Prospective stroke cohort with incident stroke NCT01364168)

The primary aim of this study is to derive and validate risk scores for vascular endpoints (recurrent stroke, myocardial infarction, and other complications of stroke) and death following an incident stroke. 850 patients with an incident stroke will be followed for 36 months with additional assessments at 3, 12, and 24 months.
Planned sample size: 850
Started February 2011
Current enrollment: 450
We estimate to complete the study in 2018
Principle investigators: M. Dichgans, V. Zietemann

Publications:
Liman T, **Zietemann V**, Wiedmann S, Jungehuelsing GJ, Endres M, **Wollenweber FA**, Wellwood I, **Dichgans M**, Heuschmann PU. *Prediction of vascular risk after stroke – protocol and pilot data of the Prospective Cohort with Incident Stroke (PROSCIS).* **Int J Stroke.** 2013 Aug;8(6):484-90.

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

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

Publications:
Wollenweber FA, **Zietemann V**, Gschwendtner A, Opherk C, **Dichgans M.** *Subclinical hyperthyroidism is a risk factor for poor functional outcome after ischemic stroke.* **Stroke.** 2013 May;44(5):1446-8.

CAPIAS (Carotid Plaque Imaging in Acute Stroke NCT01284933)

Even with extensive diagnostic workup the underlying etiology remains unidentified in about 25% of patients with acute ischemic stroke or transient ischemic attack (TIA). Current stroke classification schemes consider atherosclerotic lesions only as causative if associated with substantial luminal narrowing. However, the degree of luminal stenosis is an insufficient measure of plaque vulnerability. The aim of CAPIAS is to determine the frequency, characteristics, and consequences of complicated AHA lesion type VI carotid artery plaques in patients with cryptogenic stroke. For plaque characterization all patients undergo high resolution black-blood carotid MRI at 3.0-Tesla (hr-bb-MRI) and contrast enhanced ultrasound. The hypotheses driving this study are that i) a substantial proportion of cryptogenic strokes in the anterior circulation are caused by AHA-LT VI plaques; ii) these patients are at high risk of developing a recurrent stroke, TIA, or clinically silent lesion detectable by brain MRI; and iii) AHA-LT VI plaques are associated with specific infarct patterns. Furthermore we will search for biomarkers associated with AHA-LT VI plaques. CAPIAS will provide valuable insights into stroke mechanisms, may have important implications for diagnostic decision making, and provide the basis for the planning of targeted interventional studies. The study was started in 2011 and subsequently extended as a multicenter study with additional sites in Munich (Technical University), Freiburg and Tübingen.
Planned sample size: 300
Started February 2011
Current enrollment: 184
Principle investigator: M. Dichgans, T. Saam
Project management: A. Bayer-Karpinska

Publications:
Bayer-Karpinska A, Schwarz F, **Wollenweber FA**, Poppert H, Boeckh-Behrens T, Becker A, Clevert DA, Nikolaou K, Opherk C, **Dichgans M**, Saam T. *The carotid plaque imaging in acute stroke (CAPIAS) study: protocol and initial baseline data*. **BMC Neurol**. 2013 Dec 13;13:201.

Schwarz F, **Bayer-Karpinska A**, Poppert H, Buchholz M, Cyran C, Grimm J, Helck A, Nikolaou K, Opherk C, **Dichgans M**, Saam T. *Serial carotid MRI identifies rupture of a vulnerable plaque resulting in amaurosis fugax*. **Neurology**. 2013 Mar 19;80(12):1171-2.

OutPreC MCI (Outcome Predictors of a Cognitive Intervention in aMCI NCT01525368)

Cognitive training has been shown to be effective in patients with amnestic mild cognitive impairment (aMCI), a group at high-risk for Alzheimer's disease (AD). Our previous results showed stable hypometabolism in FDG-PET in the intervention group, whereas in an active control group hypometabolism increased on follow-up in regions typically affected by AD. However, not all patients respond equally well to a cognitive intervention. Identifying factors that predict response to treatment could help selecting patients for a targeted intervention. 160 patients were screened for the study, 122 fulfilled inclusion and exclusion criteria. 100 patients completed the study (6-month cognitive intervention group, n=69; active control group, n = 31).
We found modest intervention effects in terms of the primary outcome variables when comparing the intervention versus the active control condition. Age, aMCI subtype, APOE genotype, cognitive reserve, and hippocampal volume as a surrogate for AD pathology were studied as potential predictors for intervention effects in the intervention group only. Our results suggest better treatment effects in younger patients, APOE E4 non-carriers and patients with higher hippocampal volume. Further analyses in particular of the imaging data are under way.
Publication in preparation.
Completed
Started November 2011
Enrollment: 100
Principle investigator: K. Bürger

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

Non-traumatic cortical superficial siderosis (cSS) is a common finding in patients with cerebral amyloid angiopathy (CAA) and can be its sole imaging sign. The clinical features and course as well as the prognostic significance of cSS in CAA patients remain unclear. In a retrospective study we previously showed that cSS may be an important predictor for future intracranial hemorrhage. However, prospective data are missing. The SuSPect-CAA study is designed as a prospective observational multi-center cohort study. Primary objective of the study is to evaluate if cSS is a predictor for future stroke and mortality (primary endpoint: combined rate of stroke and death after 36 months). Secondary objectives of the study include 1) to evaluate if cSS represents a marker of future intracranial hemorrhage, especially at the site of initial siderosis, 2) to describe the clinical presentation and course of cSS, 3) to assess associated imaging findings, 4) to determine the differential diagnoses of cSS. All subjects presenting to the study center (out- or inpatient treatment with neuroimaging) will be screened. The study population will consist of two patient groups: Study group: Patients meeting the modified Boston criteria for probable or possible CAA. Patients meeting the classical Boston criteria for possible or probable CAA but without any cSS will be assigned to the control group. A total of 100 patients per group will be enrolled. Baseline and follow-up assessment at 6, 12, 24, and 36 months will be performed by visits in the respective neurological outpatient clinic including a structured interview and neurological exam, neuropsychological tests, EEG and MRI. Currently the study has been rolled out successfully to Amsterdam, Barcelona, Porto and Reggio Emilia. As additional sites are currently Boston Dresden, Graz and London preparing for participation.
Planned sample size: 200
Started May 2013
Current enrollment: 87
Principle investigator: C. Opherk
Publications:
Linn J, **Wollenweber FA**, Lummel N, Bochmann K, Pfefferkorn T, Gschwendtner A, Bruckmann H, **Dichgans M, Opherk C**. *Superficial siderosis is a warning sign for future intracranial hemorrhage*. **J Neurol.** 2013 Jan;260(1):176-81.

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

In Alzheimer's disease (AD), cerebrovascular disease frequently co-occurs with ß-amyloid (Aß). However, the specific roles of Aß and vascular pathologies in the development of neurodegeneration early in the course of AD are poorly understood. The overall aim of this study is to disentangle the specific contribution of Aß pathology and cerebrovascular disease to neuronal network impairment and cognitive decline in the early stage of AD. To this end, we have set up a prospective 5-year longitudinal neuroimaging study, which will include 80 non-demented subjects with mild cognitive impairment (MCI) of episodic memory or executive function and 60 elderly cognitively healthy subjects (HC). The deposition of Aß (as measured by amyloid PET) and ischemic brain damage (as measured by MRI and DTI) will be tested as predictors of neuronal network changes (DTI, fMRI) and cognitive decline during annual follow-up. In addition, we will include 50 subjects with CADASIL, an inherited small vessel disease and model for pure vascular cognitive impairment, to study the same parameters in patients with pure vascular disease. We expect that the results of this study will allow determining the specific impact of brain Aß and cerebrovascular pathology on neuronal network dysfunction and cognitive decline.
Planned sample size: 190
Started: July 2013
Current enrollment: 106
Principle investigators: M. Ewers, M. Düring, K. Bürger

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

Early-onset Alzheimer's disease (EOAD) accounts for 1-6% of AD cases and is highly genetically determined but only a minority of cases is autosomal-dominantly inherited. The amyloid-hypothesis is thought to be valid for early- and late onset AD (EOAD and LOAD). There is evidence, however, that production and degradation of beta-amyloid are differentially affected. The study will examine potential differences in beta-amyloid metabolism between EOAD and LOAD. Age-matched healthy individuals will serve as controls. Primary objective: To compare markers of beta-amyloid production and degradation in blood and cerebrospinal fluid between EOAD and LOAD. Secondary objectives: (1) To compare disease expression in EOAD compared to LOAD using

neuropsychological and neurological examinations, and MRI. (2) To examine whether markers of beta-amyloid metabolism correlate to clinical disease expression. Recruitment goal: 75 EOAD and 75 LOAD patients as well as 50 control subjects within two years. The study is implemented in the DZNE's Clinical Register.
Started: July 2013
Current enrollment: 42
Principle investigator: K. Bürger

DELCODE (Longitudinal Cognitive Impairment and Dementia Study)

DELCODE capitalizes on the preclinical stage of AD with the aim to characterize the neuronal networks mechanisms of cognitive adaptation and decompensation. The focus of DELCODE is on episodic memory and working memory as potential indicators of preclinical AD. Effects on neuronal networks (e.g. topology, connections strength, consistencies) will be analyzed cross-sectionally and longitudinally and will be used as predictors for cognitive decline. DELCODE will also aim at the refined description of earliest cognitive alterations with neuropsychological tasks beyond the standard assessments. These will be also assessed longitudinally. Markers of disease pathology (amyloid and brain volume loss) as well as genetic and non-genetic risk factors and indicators of cognitive reserve will serve as independent variables, and their effect on neuronal network alterations in the presence of disease will be assessed.
Planned sample size: 1000
Started: February 2014
Current enrollment: 137 (all DZNE centres)
Principle investigator: K. Bürger

eMIRgency (microRNAs in the acute stroke setting)

Recent work suggests a potential role of microRNAs as diagnostic and prognostic markers in cardiovascular disease. microRNAs are small non-coding RNAs that regulate protein expression intracellularly, but can also be released from lesion sites and circulate in the peripheral blood. The overall goal of this case-control study is to identify differences in microRNA patterns of acute stroke patients compared to healthy controls. Patients presenting within 24 hours of symptom onset are included and subjected to sequential blood draws during hospitalization. To characterize circulating microRNAs RNA will be isolated from cell-free plasma. Individual microRNA profiles will be characterized using state of the art technology such as RNA sequencing and qPCR. To control for potential confounders past medical history, medication, neuroimaging and clinical laboratory parameter are recorded. In addition to their potential diagnostic and prognostic value, functional analyses of stroke-relevant microRNAs will provide insights into stroke mechanisms.
Planned sample size: 150 patients and 150 controls
Started: February 2014
Current enrollment: 101 patients and 56 controls
Principle investigator: M. Dichgans
Project management: S. Tiedt, M. Prestel

Participation in Multicenter Trials (Selection)

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

STARSHINE
A randomized, double-blind, parallel-group, placebo-controlled study of a Lundbeck compound in patients with mild-moderate AD treated with donepezil.
Local principle investigator: K. Bürger
Status: started January 2015, recruiting

GN28525
A multcenter, open-label, long-term safety extension of phase II ABE 4869g and ABE 4955g in patients with mild to moderate Alzheimer's Disease
Study drug: Crenezumab (MABT5102A)
Local principle investigator: K. Bürger
Status: started June 2013, recruiting
Recruitment completed

ARUBA
A Randomized Multicenter Trial of Unruptured Brain AVMs
Local principle investigator: F. Wollenweber
Terminated prematurely by DSMB.
(Mohr et al. Lancet. 2014)

Sifap II
Stroke in young Fabry patients: Characterisation of the stroke rehabilitation in young patients with Fabry diseases.
Local principle investigator: M. Dichgans
Status: completed

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

WAKE UP
Efficacy and safety of MRI-based thrombolysis in wake-up stroke: a randomized, double-blind, placebo-controlled trial
Local principle investigator: M. Dichgans
Status: started April 2013, recruiting

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

StrokeUnit plus
Developing new concepts for detecting, managing and preventing earlycomplications after acute stroke - the "Stroke Unit Plus" Consortium
Observational study
IIT: Charite Berlin
Local principle investigator: M. Dichgans
Status: started August 2014, recruiting

DESCRIBE
DZNE Clinical Register Study of Neurodegenerative Disorders
Local principle investigator: K. Bürger
Status: upcoming

Ongoing Research Projects (Selection)

Large scale genetic studies in ischemic stroke

Investigators: R. Malik, A. Gschwendtner, C. Opherk, M. Dichgans

ISD investigators are involved in a number of genome-wide association (GWAS) and follow-up genetic studies conducted within the International Stroke Genetics Consortium ISGC. These collaborative efforts have resulted in the identification of two novel loci for atherosclerotic stroke (Bellenguez C et al. Nat Genet 2012; Holliday EG et al. Nat Genet 2012) and confirmation of these and other loci in the METASTROKE consortium (Traylor M et al, Lancet Neurology, 2012; Debette et al. Nat Genet 2015). Additional projects recently completed include a GWAS on quantitative trait loci for white matter hyperintensities in patients with cerebral small vessel disease (C. Opherk et al. Stroke 2014) and clinical risk prediction through genetic risk scores (Malik et al. Stroke 2014; Ibrahim et al. Stroke 2014). Current projects led by the Munich group include an exome chip analysis in >4000 patients with large artery atherosclerotic stroke (ECLAS), that will elicit the role of common exome variants in this stroke subtype. Using GWAS data from METASTROKE and the CARDIoGRAMplusC4D consortium we could recently demonstrate shared genetic susceptibility to large artery stroke and coronary artery disease/myocardial infarction (Dichgans M et al, Stroke 2014) and are now focusing on several of these loci for further functional follow up (see below). Current efforts are directed towards a larger meta-analysis based on data imputed to 1000G also integrating data from the RACE, COMPASS, and NINDS-SIGN studies (Malik et al., manuscript in preparation) and studies on shared genetic susceptibility with migraine (Malik et al. Neurology, in press) and Alzheimer's disease.

Publications:

Malik R, ..., Mitchell BD, Rosand J, Meschia JF, Levi C, Rothwell PM, ..., **Dichgans M**; Wellcome Trust Case Control Consortium 2. *Multilocus genetic risk score associates with ischemic stroke in case-control and prospective cohort studies.* **Stroke.** 2014 Feb;45(2):394-402.

Ibrahim-Verbaas CA, ..., **Malik R**, **Dichgans M**, Schmidt H, ..., van Duijn CM, Launer LJ. *Predicting stroke through genetic risk functions: the CHARGE Risk Score Project.* **Stroke.** 2014 Feb;45(2):403-12.

Dichgans M, **Malik R**, ..., Farrall M, Schunkert H; ... *Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants.* **Stroke.** 2014 Jan;45(1):24-36.

Debette S, ..., **Dichgans M**, Gschwendtner A, ..., International Stroke Genetics Consortium, Ringelstein EB, ... *Common variation in PHACTR1 is associated with susceptibility to cervical artery dissection.* **Nat Genet.** 2015 Jan;47(1):78-83.

Traylor M, ..., Fornage M, ..., **Dichgans M**, Markus HS. *Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies.* **Lancet Neurol.** 2012 Nov;11(11):951-62

Molecular mechanisms associated with a new susceptibility locus for large artery stroke in the chromosome 7p21.1 region

Investigators: C. Prell, M. Prestel, R. Malik, C. Haffner, M. Dichgans

The newly identified susceptibility locus for large artery (atherosclerotic) stroke in the 7p21.1 region encompasses the tail end of the histone deacetylase (HDAC) 9 gene and the downstream intergenic region. The association with atherosclerosis was confirmed in AtheroExpress, a large collection of endarterectomy biomaterial (collaboration: S. van der Laan, G. Pasterkamp, Utrecht). Disease-associated genetic variants within this locus including the lead variant rs2107595 affect non-coding residues and might influence gene transcription. We could demonstrate an association of the rs2107595 risk allele with elevated HDAC9 mRNA levels in peripheral blood mononuclear cells of healthy donors indicating a role of this gene in disease development. To identify causative variants genetic, proteomic and cell biological approaches are applied. We are currently performing targeted resequencing of the 7p21.1 region including the complete HDAC9 gene in patient and control samples to search for unknown risk variants. Furthermore, a DNA-protein interaction approach in combination with mass spectrometry revealed specific interaction of the E2F3/Rb1 trancriptional complex with the rs2107595 common allele (collaboration: M. Mann, Martinsried). A regulation of HDAC9 transcription by this complex is suggested by data from transcriptional reporter assays, gene expression analysis and chromatin immunoprecipitation (ChIP).

Publications:

..., Spencer CC, ..., **Malik R**, Pera J, ..., **Dichgans M**, Donnelly P, Markus HS. *Genome-wide association study identifies a variant in HDAC9 associated with large vessel ischemic stroke.* **Nat Genet.** 2012 Mar;44(3):328-33

Targeted resequencing of the HDAC9 locus in large-artery atherosclerotic stroke

Investigators: C. Haffner, R. Malik, N. Leistner, M. Dichgans

The HDAC9 gene region has been identified as strong risk locus for large-artery atherosclerotic stroke (LAS) and coronary artery disease (CAD) thus suggesting a role in atherosclerosis. Our data indicate that the increased risk is caused by processes occurring at the transcriptional level but the causative genetic variants are currently unknown. To obtain detailed information on the genetic architecture of the HDAC9 /TWIST1 / FERD3L locus and map disease causating single nucleotide polymorphisms (SNPs) we have started a targeted resequencing project using next generation sequencing (NGS). Our approach includes the enrichment of a ~1Mb region (encountering the complete HDAC9 gene and the two downstream genes TWIST1 and FERD3L) from 192 patient and 192 matched control samples and determination of the complete genomic sequence by high-throughput sequencing on a Applied Biosystems SOLiD platform (collaboration Max-Planck-Institute for Psychiatry, Munich). After completion of this project we will have a complete overview of the genetic architecture of the HDAC9 locus, which will deepen our understanding of the genetic mechanisms contributing to the development of atherosclerosis.

Role of the stroke-relevant HDAC9 gene in protein deacetylation and gene regulation

Investigators: M. Prestel, A. Ladurner, M. Dichgans

HDAC9 is implicated in large artery stroke but the molecular mechanisms linking HDAC9 to large artery disease and stroke are not understood. HDAC9 deacetylates lysine residues of histones as well as non-histone proteins. Deacetylation of histones favors chromatin compaction and attenuates gene transcription, whereas deacetylation of non-histone proteins reduces protein stability and acts as a molecular switch in signaling pathways. In this project we aim at identifying novel targets of HDAC9 to better understand its function in genome regulation and stroke-relevant signaling pathways. To address

HDAC9 function globally we will screen for HDAC9 chromatin binding sites using genome-wide chromatin immunoprecipitation (CHIP) assays (Prestel M et al., 2010). Analysis of epigenetic histone marks and DNA features at HDAC9 binding sites will provide insight into the role of HDAC9 in chromatin biology. This approach will be paralleled by a comparison of the proteome of HDAC9 knockout and wild-type mice. By establishing the acetylome of non-histone proteins (Masri S et al., 2013) we will further identify key substrates of HDAC9, which will direct us to the signaling pathways triggered by HDAC9.

Publications:

Masri S, Patel VR, Eckel-Mahan KL, Peleg S, Forne I, Ladurner AG, Baldi P, Imhof A, and Sassone-Corsi P *Circadian acetylome reveals regulation of mitochondrial metabolic pathways.* PNAS. 2013 110, 3339-3344.

Prestel M, Feller C, Straub T, Mitlohner H, and Becker PB *The Activation Potential of MOF Is Constrained for Dosage Compensation.* **Molecular cell.** 2010; 38, 815-826.

Follow-up of disease-associated SNPs implicated in atherosclerotic phenotypes

Investigators: M. Lehm, M. Prestel, M. Gonik, R. Malik, R. Jox, M. Dichgans, M. Mann

Recent genome-wide association studies (GWAS) have identified shared genetic susceptibility to large artery (atherosclerotic) stroke and coronary artery disease (CAD) (Deloukas P et al. Nat Genet 2012; Dichgans M et al. Stroke 2014). Most lead SNPs are located in non-coding regions and bioinformatic analyses suggest that many of them affect regulatory regions. We are currently applying proteome-wide analyses (PWA) (Butter et al., 2012) to identify and functionally characterize causative SNPs for CAD and atherosclerotic stroke. Specifically, we use a staged design with I) pre-selection of SNPs; II) proteome-wide analysis of SNPs (PWAS); and III) functional characterization of the most promising allele-specific interactors. Selection of SNPs with putative effects on the proteome will be based on i) data already generated by fine-mapping and ii) data generated by in silico and bioinformatics analyses. Functional characterization of SNPs and allele-specific interactors identified by PWAS will involve reporter gene assays, gain- and loss-of-function approaches in cultured cells, and techniques targeted at the respective interactors (goal: identification of causative SNPs and interactors) (collaboration with Matthias Mann, MPI for Biochemistry).

Publications:

Deloukas P et al. *Large-scale association analysis identifies new risk loci for coronary artery disease.* Nature Genetics. 2012 45, 25–33

Dichgans M, Malik R, König I et al. *Shared genetic susceptibility to ischemic stroke and coronary artery disease – a genome-wide analysis of common variants (submitted).* **Stroke.** 2014 *Jan;45(1):24-36.*

Free radicals: novel signalling molecules involved in vascular and neuronal dysfunction following cerebral ischemia

Investigators: M. Schneider, W. Wurst, J. Schick, M. Conrad, N. Plesnila

Acutely or chronically increased levels of reactive oxygen species (ROS) are major hallmarks of many neurological disorders including stroke and cerebral hemorrhage. Contrary to earlier assumptions about the indiscriminate detrimental cellular effects of ROS, recent reports indicate that oxidative stress-dependent cell death may occur in a programmed fashion. In this context, the selenoenzyme glutathione peroxidase 4 (Gpx4) is emerging as one of the most significant members of the mammalian ROS regulating antioxidant network by efficiently sensing GSH levels and controlling the abundance of cellular LOOH. Gpx4 knock-out is embryonically lethal and neuron-specific ablation of all selenoproteins or Gpx4 alone leads to widespread neurodegeneration thereby demonstrating the over all importance of this enzyme for proper brain function. Currently, we use a conditional and tissue-specific Gpx4 ablation strategy to investigate the biological relevance of Gpx4 regulation in distinct cellular compartments of the neurovascular unit and to uncover the role of Gpx4 in acute neurovascular diseases, e.g. ischemic and hemorrhagic stroke.

Publications:

Seiler A, **Schneider M**, Förster H, Roth S, Wirth EK, Culmsee C, Plesnila N, Kremmer E, Rådmark O, Wurst W, Bornkamm GW, Schweizer U, Conrad M. *Glutathione peroxidase 4 senses and translates oxidative stress into 12/15-lipoxygenase dependent- and AIF-mediated cell death.* **Cell Metab.** 2008 8(3):237-48

Wortmann M, **Schneider M**, Pircher J, Hellfritsch J, Aichler M, Vegi N, Kölle P, Kuhlencordt P, Walch A, Pohl U, Bornkamm GW, Conrad M, Beck H. *Combined Deficiency in Glutathione Peroxidase 4 (Gpx4) and Vitamin E Causes Multi-Organ Thrombus Formation and Early Death in Mice.* **Circ Res.** 2013 113(4):408-17

Friedmann Angeli JP, **Schneider M** et al. *Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice.* **Nat Cell Biol.** 2014;16(12):1180-91

Mitochondrial dynamics in ischemic neuronal cell death

Investigators: L. Meissner, U. Mamrak, H. Zischka, C. Culmsee, N. Plesnila

Mitochondria play a crucial role in neuronal cell death after stroke. Over the last decade several key players such as the BLC-2 proteins Bid, Bax and Bak have been identified to associate with mitochondria in order to initiate mitochondrial cell death signalling and the release of pro-apoptotic executers such as AIF and cytochrome C. Recently, mitochondrial dynamics have been associated with neuronal cell death. Bid and Bax were found to interact with Drp1, the regulator of mitochondrial fission and inhibition of mitochondrial fission was neuroprotective following cerebral ischemia in vivo. However the exact mechanisms how mitochondrial cell death signalling and mitochondrial dynamics play together in vivo to execute cell death are not fully understood. In order to identify novel mitochondrial proteins involved in neuronal cell death we isolated mitochondria from the cortical penumbra of mice subjected to 60 min middle cerebral artery occlusion (MCAo), an experimental model of ischemic stroke. Mitochondria of ischemic and sham operated mice were isolated 1, 6, 12, and 24 h after MCAo using a novel mouse specific immuno-magnetic bead isolation method. Proteomic profiles of these highly purified penumbral mitochondria were generated using a comparative iTraq-based LC-MS approach in order to obtain relative quantification of mitochondrial proteins between sham and MCAo animals. The proteomic screen identified up to 600 proteins per mitochondrial fraction. Interestingly the most significant increase in protein levels over time was observed in proteins of the cytoskeletal mitochondrial transport machinery which will be further investigated in follow up experiments. These findings suggest that mitochondrial mobility is an important component of neuronal mitochon-

drial cell death signaling in the ischemic brain and may represent a novel target for neuroprotective strategies.

Publications:
Dolga AM, ..., **Plesnila N**, Höglinger GU, Culmsee C. *Subcellular expression and neuroprotective effects of SK channels in human dopaminergic neurons.* **Cell Death Dis**. *2014; 16;5:e999*

Doti N, Reuther C, Scognamiglio PL, Dolga AM, **Plesnila N**, Ruvo M, Culmsee C. I*nhibition of the AIF/CypA complex protects against intrinsic death pathways induced by oxidative stress.* **Cell Death Dis**. *2014 Jan 16;5:e993*

Dolga AM, Netter MF, Perocchi F, Doti N, Meissner L, Tobaben S, Grohm J, Zischka H, **Plesnila N**, Decher N, Culmsee C. *Mitochondrial small conductance SK2 channels prevent glutamate-induced oxytosis and mitochondrial dysfunction.* **J Biol Chem**. *2013; 12;288(15):10792-804*

Strategic brain regions in vascular cognitive impairment

Investigators: M. Duering, B. Gesierich, M. Gonik, M. Dichgans

The mechanisms of cognitive impairment in patients with small vessel disease are still debated. MR imaging studies have demonstrated an impact of the total burden of lacunar infarcts and white matter hyperintensities on cognitive performance. In general however, correlations between volumetric measures and cognitive performance have been modest leaving much of the clinical variance unexplained. By applying voxel-based lesion-symptom mapping to CADASIL patients (collaboration: H. Chabriat, Paris), we previously showed that the location of lesions within distinct white matter tracts (anterior thalamic radiation [ATR] and forceps minor [Fmin]) critically influences cognitive performance in specific cognitive domains (Duering et al., Brain 2011). We subsequently confirmed the strategic role of frontal-subcortical neuronal circuits using graph-based statistical models (Duering et al., NeuroImage 2012). Analyzing 580 subjects from the Austrian Stroke Prevention Study (Collaboration: R. Schmidt, Graz,) we further confirmed a strategic role of frontal-subcortical neuronal circuits (specifically the ATR and Fmin) in age-related small vessel disease (Duering et al., Neurology 2014). We recently extended this project towards functional analyses. We now investigate strategic brain locations and networks by assessing connectivity between brain regions on resting-state functional MRI.

Publications:
Duering M, Zieren N, Kern A, **Gonik M**, Hervé D, Jouvent E, Peters N, Pachai C, Opherk C, Chabriat HC, **Dichgans M**. *Strategic Role of Frontal White Matter Tracts in Vascular Cognitive Impairment: A Voxel-Based Lesion-Symptom Mapping Study in CADASIL.* **Brain.** 2011 Aug;134(Pt 8):2366-75

Duering M, Gonik M, Malik R, Zieren N, Reyes S, Jouvent E, Hervé D, Gschwendtner A, Opherk C, Chabriat H, **Dichgans M**. I*dentification of a strategic brain network underlying processing speed deficits in vascular cognitive impairment.* **NeuroImage.** 2012 66:177–183

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

Impact of subcortical ischemic lesions on cortical morphology

Investigators: M. Düring, R. Adam, M. Dichgans

While brain atrophy has been recognized as a clinically important predictor of cognitive decline, little is known about the mechanisms underlying brain atrophy in small vessel disease. One possible mechanism is secondary neurodegeneration in the cortex due to subcortical lesions. To address this question we examined the effect of incident lacunar lesions on cortical morphology in a longitudinal data fromset of CADASIL patients (collaboration: H. Chabriat, Paris). Incident lacunear lesions were systematically identified using difference imaging. Connected cortical regions were delineated on scans prior to lesion occurrence using DTI-based probabilistic tractography. We found thinning over time to be more pronounced in the connected cortical region compared with non-connected areas (Duering et al., Neurology 2012). This is the first study providing direct evidence for focal changes of cortical morphology following lacunar infarcts in connected subcortical tissue. This implies a role for secondary neurodegeneration within the cortical grey matter following axonal damage in the white matter. In a recent study, we were able to reproduce these findings in patients from with acute ischemic stroke recruited through the DEDEMAS study, thus demonstrating the importance of this finding mechanism for in other stroke subtypes (Duering et al, Neurology 2015). Furthermore, we were able to relate the secondary alterations of the cortex with to the microstructural damage of connecting fiber tracts as measured by diffusion tensor imaging.

Publications:
Duering M, Righart R, Csanadi E, Jouvent E, Hervé D, Chabriat H, **Dichgans M**. *Incident subcortical infarcts induce focal thinning in connected cortical regions.* **Neurology** 2012; 79(20), 2016–7.

Righart R, **Duering M, Gonik M**, Jouvent E, Reyes S. *Impact of regional cortical and subcortical changes on processing speed in cerebral small vessel disease.* **NeuroImage: Clinical**. 2013. Jun 19;2:854-61

Duering M, Righart R, **Wollenweber FA, Zietemann V, Gesierich B, Dichgans M**. *Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts.* **Neurology. 2015** (in press)

Molecular mechanisms associated with HTRA1 mutations and role of the TGF-β signalling pathway in CARASIL

Investigators: N. Beaufort, E. Scharrer, C. Haffner, M. Dichgans

CARASIL (Cerebral autosomal-recessive arteriopathy with subcortical infarcts and leucoencephalopathy), a rare inherited form of SVD, is caused by loss-of-function mutations in the high temperature requirement A1 (HTRA1) gene encoding an evolutionary conserved serine protease. We recently identified a role of the transforming growth factor-β (TGFβ) signaling pathway in CARASIL (Beaufort et al. Proc Natl Acad Sci USA 2014) and are currently exploring the consequences of HtrA1 deficiency on vascular smooth muscle and endothelial cell function. We are further examining the molecular mechanism by which mutations in functionally distinct domains of the HtrA1 protease become pathogenic. HtrA1 forms heterotrimers and the spectrum of mutations associated with CARASIL has recently been extended to residues outside the protease domains. This raises the possibility that some mutations affect protease activity by interfering with multimerization of the HtrA1 protein. The project is embedded in a Transatlantic

Network of Excellence funded by the Leducq Foundation.

Publications:

Beaufort N, **Scharrer E**, Kremmer E, Lux V, Ehrmann M, Huber R, Houlden H, Werring D, **Haffner C**, **Dichgans M**. *Cerebral small vessel disease-related protease HtrA1 processes latent TGF-β binding protein 1 and facilitates TGF-β signaling.* **Proc Natl Acad Sci U S A.** 2014 Nov 18;111(46):16496-501. PMID 25369932

Molecular mechanisms and consequences of NOTCH3 receptor aggregation in CADASIL

Investigators: A. Zellner, M. Dichgans, C. Haffner,

CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is the most common monogenic cause of stroke and vascular dementia. Accumulation and deposition of the NOTCH3 extracellular domain in blood vessels is a central feature of the disease. To dissect the mechanisms of NOTCH3 multimerization in vitro we recently developed a robust aggregation assay based on recombinant NOTCH3 fragments. Using single-molecule analysis techniques we could recapitulate NOTCH3 aggregation in vitro. NOTCH3 multimerization requires no co-factor and is facilitated by sulfhydryl groups. Although wild-type NOTCH3 does not exhibit multimerization itself, it can participate in aggregates of mutant NOTCH3. Using this quantitative assay, we analyzed the effect of a number of synthetic and natural compounds and identified several substances with anti-aggregatory potential. Ongoing experiments aim to validate these compounds in cellular and mouse models with the goal to identify potential candidates for a therapeutic approach. We have further identified latent TGF-β binding protein 1 (LTBP-1), a regulator of the TGF-β signaling pathway, as component of NOTCH3 deposits and demonstrated its co-localization with NOTCH3 in CADASIL patient vessel walls, highlighting the importance of the extracellular matrix in small vessel disease. Currently, the role of the TGF-β signaling pathway in CADASIL pathogenesis is investigated.

Publications:

Wollenweber FA, **Hanecker P**, **Bayer-Karpinska A**, **Malik R**, Bäzner H, Moreton F, Muir KW, Müller S, Giese A, **Opherk C**, **Dichgans M**, **Haffner C**, **Duering M**. *Cysteine-Sparing CADASIL Mutations in NOTCH3 Show Proaggregatory Properties In Vitro.* **Stroke.** 2015 Mar;46(3):786-92

Kast J, **Hanecker P**, **Beaufort N**, Giese A, Joutel A, **Dichgans M**, **Opherk C**, **Haffner C**. *Sequestration of latent TGF-ß binding protein 1 into CADASIL-related Notch3-ECD deposits.* **Acta Neuropathol Commun.** 2014 Aug 13;2(1):96.

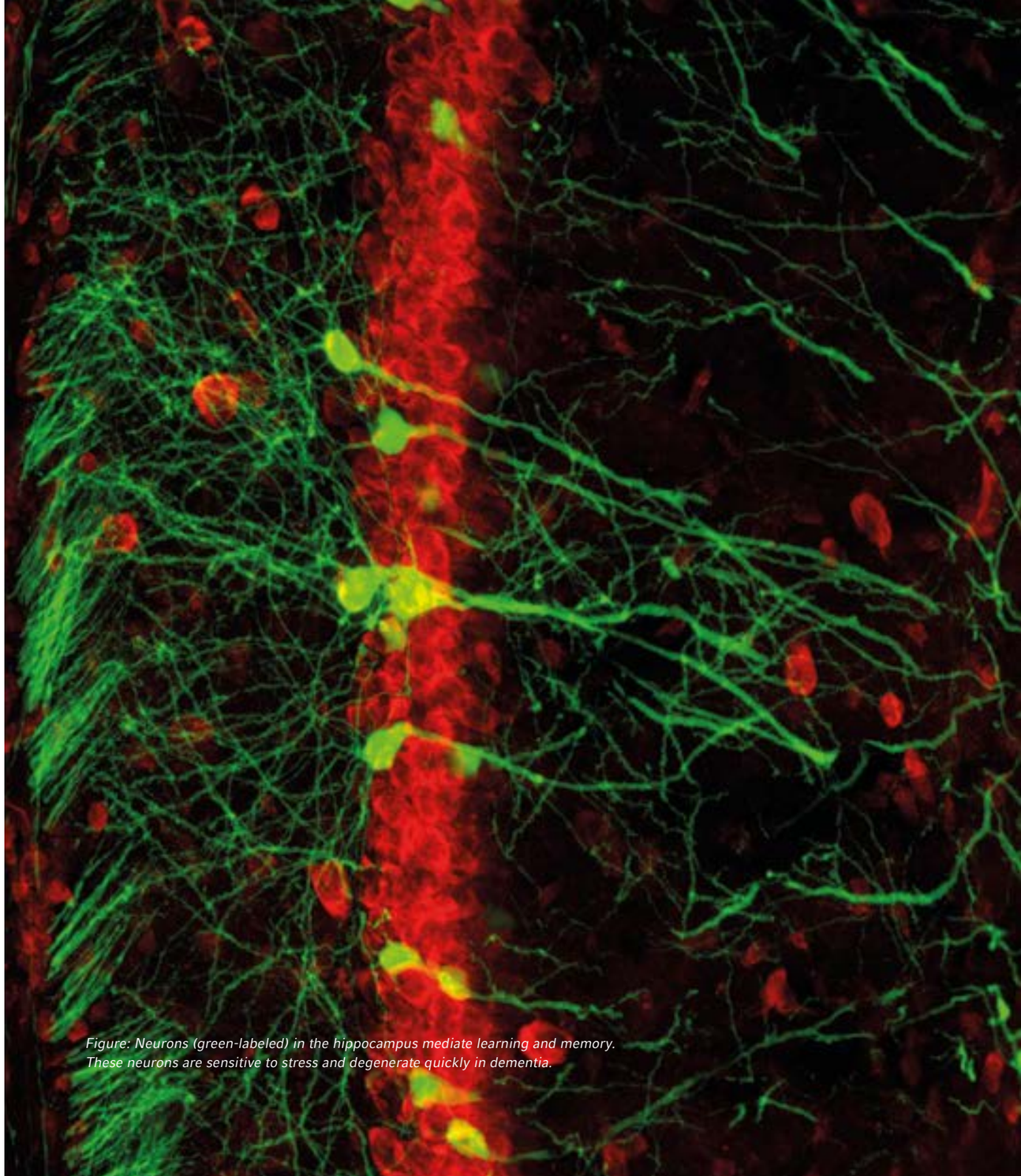
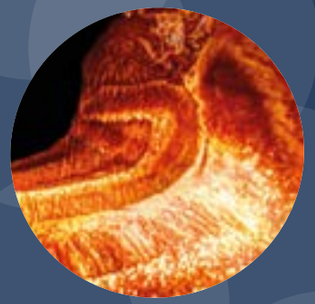


Figure: Neurons (green-labeled) in the hippocampus mediate learning and memory. These neurons are sensitive to stress and degenerate quickly in dementia.



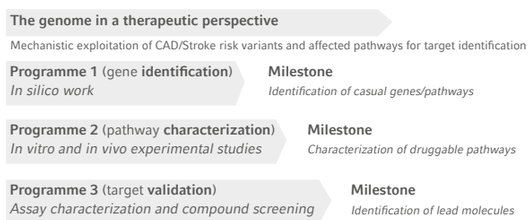
Research Alliances and Project Fundings

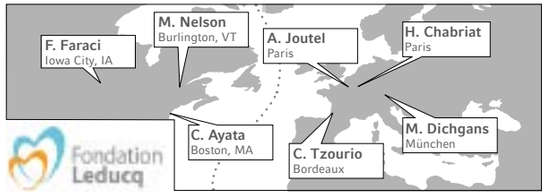
SyNergy
Munich Cluster for Systems Neurology

www.synergy-munich.de

Munich Cluster for Systems Neurology (SyNergy) funded by the DFG Excellence initiative promotes integrative research major neurological diseases (neurovascular, neurodegenerative, neurinflammatory), with the aim to improve pathomechanistic understanding and eventually therapeutic options. The central focus is to foster intense collaboration across the traditional boundaries of neurodegenerative, -inflammatory and –vascular diseases. SyNergy research projects are organized into 3 **Research Areas,** each targeted at one specific pathomechanistic "nexus". **Core-Projects** bundle systems neurology-specific expertise to make it accessible to all SyNergy projects. **Tandem Projects** are highly collaborative research projects. The projects combine expertise across traditional pathomechanisms, as well as systems biology and systems neuroscience tools. Many projects involve both basic scientists and academic clinicians.
ISD participates in the following Projects:
Tandem Projects:
B 1: Contribution of pericytes in vascular insufficiency in CADASIL (PI: Prof. Plesnila)
B 3: Transcriptional regulation of HDAC9 (PI: Prof. Dichgans)
B 6: Role of the stroke-relevant HDAC9 gene in the cellular proteome & acetylome (PI: Prof. Dichgans)
Core-Projects:
Core 6: Development of novel methodology for the joint analysis of -omics data (PI: Prof. Dichgans)
Core 9: Non-apoptotic caspase activity in synapse loss and neuronal differentiation (PI: Dr. Ertürk)
Clinical Scientist Program (PI: Dr. Liesz)
Clinical Studies Hub (PI: Prof. Dichgans)
SyNergy Board: Prof. Dichgans

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





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

The ISD participates in a network: **Pathogenesis of Small vessel Disease of the Brain.** Small vessel diseases (SVD) account for 25% to 30% of ischemic strokes and are a leading cause of cognitive decline and disability worldwide. Very little is known about the underlying causes of SVDs. The identification of genes involved in two genetic forms of non-hypertensive adult-onset SVD marks an important advance in the understanding of SVD. CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is an archetypal SVD that emerges as the most common heritable cause of stroke and vascular dementia worldwide. It is caused by missense mutations in NOTCH3 coding for a cell surface receptor. CARASIL (Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), predominantly reported in Japanese families, is a rare SVD with a more complex phenotype. It is caused by loss-of-function mutations of the high temperature requirement protease HTRA1. Mouse models of CADASIL and CARASIL are used to explore common forms of SVDs, and to identify potential therapeutic targets.

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

CRC 1123: Atherosclerosis - Mechanisms and Networks of Novel Therapeutic Targets
Vascular disease including coronary artery disease (CAD) and stroke remains the leading cause of death and morbidity worldwide. The underlying factor common to most of these conditions is atherosclerosis. In order to develop more effective strategies for the prevention and treatment of arterial disease, a better understanding of the p athogenesis and progression of atherosclerosis is crucial. It is the mission of the CRC 1123 to improve the in-depth understanding of molecular networks in atherogenesis, atheroprogression and atherothrombosis as the pathological sequence of CAD, leading to the identification of worthwhile targets for treating atherosclerosis.
ISD participates in the Project **B 03 Role of HDAC9 in Atherosclerosis:** The HDAC9 gene region on 7p21.1 was identified as a major risk locus for carotid atherosclerosis and stroke. HDAC9 has previously been shown to control the maturation and function of FOXP3+ regulatory T (Treg) cells, which in turn have atheroprotective function. The inhibitory effect of HDAC9 on Treg cells renders these cells a promising candidate for targeted analyses. The main aims of the current project therefore are (1) to study the effects of HDAC9 deficiency on *atherogenesis and atherothrombosis* in mouse models, (2) to examine allele-specific effects on Treg cell function in humans, and (3) to determine allele-specific effects on plaque characteristics and HDAC9 expression in human atherosclerotic plaques.
For further information see
http://www.sfb1123.med.uni-muenchen.de/index.html

Mechanisms of Small Vessel Related Brain Damage and Cognitive Impairment: Integrating Imaging Findings from Genetic and Sporadic Disease (EU FP7 funded ERANET-NEURON). Cerebral small vessel disease (SVD) is a major cause of stroke and the leading cause of vascular cognitive impairment (VCI). It also contributes to other disabling symptoms such as gait disturbance and late-life depression and its prevalence strongly increases with age. Neuroimaging in combination with detailed neuropsychological testing has been by far the most fruitful approach to uncover the pleiotropic effects of cerebral SVD on the brain and on cognition. This approach has recently been combined with genetics. We hypothesise that CADASIL, a hereditary SVD, and common sporadic forms of SVD have shared mechanisms and that integrating imaging data from both conditions will allow defining key mechanisms of small-vessel related brain damage and associated cognitive impairment. To tackle this question we will use our combined patient, family and population-based resources and apply state of the art image post-processing and analytical tools.
Coordinator: M. Dichgans.
For more information see *http://www.mescog.eu/*

Systems medicine of myocardial infarction and stroke e:AtheroSysMed
Atherosclerosis is a leading cause of death in Europe. Until now, prevention and therapy of its most disabling sequelae, i.e. coronary artery disease (CAD) and stroke, aim at ameliorating traditional risk factors. Recently, over 50 chromosomal loci as well as novel lifestyle factors have been identified affecting CAD or stroke risk. Surprisingly, only a few of these disease markers mediate their effects via traditional risk factors. Thus, current treatment does not address all principle disease mechanisms. Future efforts should be directed at a multi-scale, patient-centered approach applying -omics technologies including methyl-omics, transcriptomics, and metabolomics for quantifying the downstream impact of both genetic and life-style mediated risks. e:AtheroSysMed will use computational and mathematical modeling approaches to move beyond current state-of-the-art towards a holistic understanding of mechanisms and treatment options for CAD and stroke.

ISD is work package leader in **SP5 – PWAS for identification of functional SNPs (single nucleotide polymorphisms) and key molecules in arterial injury** with the following objectives:
- Proteome-wide analysis of disease associated SNPs
- Identification of key molecular targets and pathways in in vivo models of arterial injury

For further information see
http://www.gesundheitsforschung-bmbf.de/de/5111.php#AtheroSysMed

Third Party Funding

SyNergy – Munich Cluster for Systems Neurology. Coordinator Research Area B: M. Dichgans | Local budget (ISD): ~1.5 Mio €
Principal Investigator Tandem-Projects B3, B6, B5, Core 6: M. Dichgans | Budget: 300,000 € (Period I)
Principal Investigator Tandem-Project B1: N. Plesnila | Budget: 175,000 € (Period I)
Principal Investigator Clinical Studies Hub: M. Dichgans | Budget: 195,000 € (Period I)
Principal Investigator Clinician Scientist Group: A. Liesz | Budget: 783,000 € (Period I+II) | Funding Institution: DFG
Period I: Jan 2013 to Jun 2015 | Period II: Jul 2015 to Oct 2017

CVgenes-at-target – Exploitation of genomic variants affecting coronary artery disease and stroke risk for therapeutic intervention. Principal Investigator: M. Dichgans | Funding Institution: EU / FP7 | Period: Oct 2013 to Sep 2016 | Local budget: 547,000 €

e:AtheroSysMed – Systems medicine of myocardial infarction and stroke. Principal Investigator: M. Dichgans | Funding Institution: BMBF | Period: Dec 2013 to Nov 2018 | Local budget: 290,151 €

Fondation Leducq – Transatlantic Network of Excellence in Cardiovascular and Neurovascular Research "Pathogenesis of Small Vessel Disease of the Brain". Principal investigator: M. Dichgans | Funding institution: Fondation Leducq | Period: Aug 2012 to Jul 2017 | Funding: 590,150 €

MESCOG – Mechanism of Small Vessel Related Brain Damage and Cognitive Impairment, Integrating Imaging findings from Genetic and Sporadic Disease (01 EW1207). Coordinator/Principal investigator: M. Dichgans | Funding institution: EU | FP6 | ERA-NET NEURON | Period: Mar 2012 to Feb 2015 | Overall budget: 813,000 € | Local budget: 487,484 €

VaD MixD – Impact of Subcortical Ischemic Lesions on Regional Brain Atrophy and Response to a Cognitive Intervention | DZNE Intersite Project. Principal investigator: M. Düring, K, Bürger, M. Dichgans | Funding institution: German Center for Neurodegenerative Disease (DZNE) / BMBF | Period: Sep 2010 to Aug 2014 | Overall budget: 1,560,000 € | Local budget: 522,000 €

CoEN 017 – Standards for determining the vascular contribution to neurodegeneration (112010). Principal investigator: M. Dichgans | Funding institution: German Center for Neurodegenerative Disease (DZNE) / BMBF Period: Jan 2012 to Dec 2013 | Funding: 14,000 €

Molecular mechanisms of Notch3-aggregation in the pathogenesis of CADASIL (GZ:OP 212/1-1). Principal investigator: C. Opherk | Funding institution: DFG | Period: Oct 2010 to Sep 2013 | Funding: 270,000 €

Genome-wide search for Quantitative Trait Loci for radiographic white matter hyperintensities in CADASIL. Principal investigator: M. Dichgans | Funding institution: Corona-Foundation | Deutsches Stiftungszentrum Period: Jan 2011 to Dec 2016 | Funding: 600,000 €

Changes of the cerebral microcirculation after subarachnoidal hemorrhage: kinetics, significance and identification of mechanisms. Principal investigator: N. Plesnila | Funding institution: German Research Foundation (DFG)| Period: Oct 2010 to Oct 2013 | Funding: 240,000 €

MicroFlow – Molecular mechanisms of microvascular dysfunction following hemorrhagic stroke. Principal investigator: N. Plesnila | Funding institution: EU | Period: Jul 2012 to Jul 2016 | Funding: 100,000 €

VASCAMY – Interaction beween vascular and amyloid brain pathology in Alzheimer's disease. Principal investigator: M. Ewers | Funding Institution: EU | Period: Jun 2013 to Jun 2017 | Funding: 100,000 €

Role of astrocytic Glutathionperoxidase 4 following cerebral ischemia. Principal investigator: M. Schneider Funding institution: Friedrich-Baur-Stiftung | Period: Jun 2012 to Jun 2013 | Funding: 10,000 €

Functional connectivity in small vessel disease. Principal Investigator: M. Düring | Funding Institution: Medical Faculty, FöFoLe | Period: Aug 2013 to Jul 2014 | Funding: 45,000 €

Role of astrocytic Glutathionperoxidase 4 following cerebral ischemia. Principal investigator: M. Schneider Funding institution: Friedrich-Baur-Stiftung | Period: Jun 2013 to May 2014 | Funding: 10,000 €

The DZNE Early Onset Alzheimer's Disease Study – DEEARLY (additional funding for neurochemical analyses). Principal investigator: K. Bürger, D. Edbauer | Funding institution: Dr. Helmut Legerlotz-Stiftung | Period Jan 15 to Dec 15 | Funding: 12,000 €

DEMDAS – DZNE Mechanisms of Dementia after Stroke. Principal Investigators: M. Dichgans | Funding Institution: DZNE | Period: Jan 2013 to Sep 2016 | Overall budget: 1,770,000 € | Local budget: 381,000 €

Bedeutung von Perizyten für die Störung der zerebralen Mikrozirkulation nach Subarachnoidalblutung. Principal Investigators: N. Plesnila | Funding Institution: Else Kröner-Fresenius-Stiftung | Period: Mar 2014 to Feb 2017 | Funding: 244,000 €

StemForStroke – Secretome analysis of intrahecally applied bone marrow stromal cells in experimental stroke. Principal Investigators: N. Plesnila | Funding Institution: EU | Period: Mar 2014 to Feb 2016 | Funding: 169,000 €

Role of HDAC9 in Atherosclerosis – Project within the collaborative research programme SFB 1123 'Atherosclerosis – Mechanisms and networks of novel therapeutic targets' Principal Investigator: M. Dichgans, C. Haffner | Funding Institution: German Research Foundation (DFG) | Period: Oct 2013 to Jun 2018 | Funding: 364,100 €

Strukturelle und funktionelle Konnektivität als Biomarker der vaskulären kognitiven Störung. Principal Investigator: M. Düring | Funding Institution: Else Kröner-Fresenius-Stiftung | Period: Feb 2015 to Jan 2017 | Funding: 93,500 €

Leukocyte-Interaction with immunological brain barriers. Principal Investigator: A. Liesz | Funding Institution: German Research Foundation (DFG) | Period: Oct 2014 to Sep 2017 | Funding: 197,000 €

Mechanismen der Leukozyten-Endothel Interaktion. Principal Investigator: A. Liesz | Funding Institution: Medical Faculty, FöFoLe | Period: Jan 2014 to Jan 2015 | Funding: 52,000 €

Alarmin-mediated sterila inflammation. Principal Investigator: A. Liesz | Funding Institution: LMU, LMUexcellent initiative | Period: Mar 2015 to Feb 2016 | Funding: 50,000 €

Stressvermittelte Immunschwäche nach Schlaganfall. Principal Investigators: A. Liesz | Funding Institution: Daimler und Benz Stiftung | Period: Feb 2014 to Jan 2015 | Funding: 28,000 €

Neuroinflammatory mechanisms of chronic neurodegeneration and cognitive decline following traumatic brain injury. Principal Investigators: A. Erturk, N. Plesnila | Funding Institution: ERA-Net Neuron | Period: Apr 2015 to Mar 2018 | Overall budget: 1,203,143 € | Local budget: 299,880 €

Gaze behaviour during real spatial navigation | DSGZ Start-up Project. Principal investigator: F. Schöberl, A. Zwergal, K. Bürger | Funding institution: German Center for Vertigo and Balance Disorders (DSGZ) | Period: Nov 2014 to Apr 2016 | Overall budget: 110,394 € Euro.

Third party funds (spent) | Courtesy of Vascular Dementia Research Foundation*
(2014) personnel costs: 2,145,245 € / material costs: 688,024 € / travel expenses: 29,291 € / investments: 786,857 € total: 3,649,417 €
(2013) personnel costs: 1,964,281 € / material costs: 514,238 € / travel expenses: 51,889 € / investments: 152,971 € total: 2,683,379 €

**not including costs for outpatient clinic*

Teaching

2013

- Bürger K, Dichgans M, Opherk, C | Ringvorlesung mit Übungen im Modul IV Psychiatrie und Psychotherapie & Neurologie (7M1403)
- Opherk C, Düring M, Bayer-Karpinska A, Lehm M, Liesz A, Schmidt C, Tiedt S, Wollenweber F, Dichgans M | Blockpraktikum Neurologie und Neurochirurgie 1 (7M1407)
- Dichgans M, Opherk C, Düring M, Bayer-Karpinska A, Lehm M, Liesz A, Schmidt C, Tiedt S, Wollenweber F | Blockpraktikum Neurologie und Neurochirurgie 2 (7M1408)
- Bürger K, Wollenweber F | Blockpraktikum Psychiatrie und Psychotherapie 1 (7M1410)
- Bürger K, Wollenweber F | Blockpraktikum Psychiatrie und Psychotherapie 2 (7M1411)
- Dichgans M, Opherk C, Wollenweber F | Interdisziplinäre Behandlung des Schlaganfalls Einzelansicht (7C0014)
- Dichgans M, Opherk C | Experimentelle Ansätze in der Schlaganfalltherapie (7C0017)
- Beaufort N, Dichgans M, Haffner C, Malik R, Opherk C, Prestel M | Demenzen: Molekulare Grundlagen und pathophysiologische Konzepte (7C0019)
- Dichgans M, Opherk C | Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder (7C0025)
- Hellal F, Plesnila N, Schneider M | Experimentelle Schlaganfallforschung (7C0123) (extended)
- Bürger K, Dichgans M, Düring M, Ewers M, Haffner C, Hellal F, Malik R, Opherk C, Plesnila N, Prestel M | Stroke and Dementia Research – News and Views (7C0124) (extended)
- Bürger K, Dichgans M, Ewers M, Müller C, Opherk C | Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (7C0233)
- Bürger K, Dichgans M, Düring M, Ewers M, Gonik M | Strukturelle Magnetresonanztomographie in der Demenzforschung (7C0248)
- Ewers M, Düring M | Multimodale Bildgebung zu Gehirnveränderungen bei der Alzheimer Demenz (7C0263)
- Araque M, Düring M, Ewers M, Malik R | Neuroimaging of Brain Changes in Alzheimer's disease and Other Dementias (7C0146)
- Bürger K, Dichgans M, Opherk C | Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (7P0602)
- Dichgans M, Opherk C | Neurologische Notfall- und Intensivmedizin (7P0603)
- Bürger K, Dichgans M, Opherk C, Schmidt C, Wollenweber F | Interdisziplinäre Therapie von Demenzen (7P0607)
- Dichgans M, Opherk C | Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder (7P0609)
- Dichgans M, Opherk C, Wollenweber F | Interdisziplinäre Behandlung des Schlaganfalls (7P0610)
- Beaufort N, Dichgans M, Haffner C, Liesz A, Plesnila N | Practical Course Molecular Neurogenetics and Experimental Stroke Research (19012)
- Dichgans M, Liesz A | Practical course - Neuroimmunological methods in experimental stroke research (19302)

2014

- Bürger K, Dichgans M, Opherk C | Ringvorlesung mit Übungen im Modul IV Psychiatrie und Psychotherapie & Neurologie (7M1403)
- Opherk C, Düring M, Bayer-Karpinska A, Lehm M, Liesz A, Schmidt C, Tiedt S, Wollenweber F, Dichgans M | Blockpraktikum Neurologie und Neurochirurgie 1 (7M1407)
- Dichgans M, Opherk C, Düring M, BayerKarpinska A, Lehm M, Liesz A, Schmidt C, Tiedt S, Wollenweber F | Blockpraktikum Neurologie und Neurochirurgie 2 (7M1408)
- Bürger K, Wollenweber F | Blockpraktikum Psychiatrie und Psychotherapie 1 (7M1410)
- Bürger K, Wollenweber F | Blockpraktikum Psychiatrie und Psychotherapie 2 (7M1411)
- Dichgans M, Opherk C | Experimentelle Ansätze in der Schlaganfalltherapie (7C0017)
- Beaufort N, Dichgans M, Haffner C, Malik R, Opherk C, Prestel M | Demenzen: Molekulare Grundlagen und pathophysiologische Konzepte (7C0019)
- Dichgans M, Opherk C | Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder (7C0025)
- Hellal F, Liesz A, Plesnila N, Schneider M | Experimentelle Schlaganfallforschung (7C0123)
- Araque M, Beaufort N, Dichgans M, Düring M, Ewers M, Haffner C, Hellal F, Liesz A, Malik R, Plesnila N, Prestel M, Schneider M, Taylor A | Stroke and Dementia Research – News and Views (7C0124)
- Araque M, Düring M, Ewers M, Malik R | Neuroimaging of Brain Changes in Alzheimer's disease and Other Dementias (7C0146)
- Liesz A | Developments and trends in neuroimmunological research (7C0155)
- Plesnila N | Tutorial on good scientific practice in experimental stroke research (7C0156)
- Malik R | Genetische Analysen komplexer Erkrankungen (7C0157)
- Bürger K, Dichgans M, Ewers, M, Müller C | Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (7C0233)
- Bürger K, Dichgans M, Düring M, Ewers M, Gonik M | Strukturelle Magnetresonanztomographie in der Demenzforschung (7C0248)
- Araque M, Ewers M, Düring M, Taylor A | Multimodale Bildgebung zu Gehirnveränderungen bei der Alzheimer Demenz (7C0263)
- Bürger K, Dichgans M, Ewers M, Müller, C | Demonstration nuklearmedizinischer Befunde im Rahmen der Demenzdiagnostik (7P0602)
- Dichgans M, Opherk C | Neurologische Notfall- und Intensivmedizin (7P0603)
- Bürger K, Dichgans M, Müller C, Wollenweber F | Interdisziplinäre Therapie von Demenzen (7P0607)
- Dichgans M, Opherk C | Neurovaskuläre Intensivmedizin; Vorstellung ausgewählter Krankheitsbilder (7P0609)
- Dichgans M, Opherk C, Wollenweber F | Interdisziplinäre Behandlung des Schlaganfalls (7P0610)
- Beaufort N, Dichgans M, Haffner C, Liesz A, Plesnila N | Practical Course Molecular Neurogenetics and Experimental Stroke Research (19012)
- Dichgans M, Liesz A | Practical course - Neuroimmunological methods in experimental stroke research (19302)

Habilitations & Theses

Habilitations

Mechanisms and structural correlates of vascular cognitive impairment, Duering M, Habilitation in Experimental Neurology, Dec 2014

Ph.D. students

Functional brain mechanism underlying cognitive reserve in Alzheimer's disease (Thesis), Franzmeier N, planned degree: Dr. rer. nat., started Oct 2014

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

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

Role of HDAC9 in atherosclerotic mouse models, Azghandi S, planned degree: Ph.D., started Oct 2012

Characterization and treatment of cerebrovascular dysfunction in CADASIL mutant mice, Balbi M, planned degree: Ph.D. (Graduate School of Systemic Neurosciences), started Oct 2011

Mechanism of microvasospasm following subarachnoid hemorrhage, Schüller K, planned degree: Ph.D. (Graduate School of Systemic Neurosciences), started Oct 2011

Molecular Characterization of Notch3 Aggregates (Thesis), Hanecker P, planned degree: Dr. rer. nat., started Oct 2010

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

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

Involvement of latent TGF-β binding protein 1 in CADASIL-relevant Notch3 aggregation (Thesis), Kast J, Dr. rer. nat., completed Nov 2014

Mechanisms of small vessel disease in vascular cognitive impairment (Thesis), Zieren N, Dr. hum. biol., completed Nov 2013

Medical theses

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

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

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

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

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

Comparison of performance changes in cognitive and noncognitive domains after a cognitive intervention in subjects with amnestic mild cognitive impairment, Neufend A, planned degree: Dr. med., completed Dec 2014

The influence of personality factors on the effect of a cognitive intervention in subjects with amnestic mild cognitive impairment. Kramer J, planned degree: Dr. med., started Oct 2012

Development of cognition in patients with amnestic mild cognitive impairment after a multimodal cognitive intervention. Perathoner M, planned degree: Dr. med., started Oct 2012

The influence of the degree of cognitive impairment on the effect of a cognitive intervention in subjects with amnestic mild cognitive impairment. Koo J, planned degree: Dr. med., started Dec 2011

Honours & Awards

- **M. Düring** | Young Scientist Award of the Competence Network Stroke 2013 | Hannover 2013
- **M. Lehm** | Selected for the Harvard-LMU Young Scientists' Forum (YSF) 2014 LMUexcellent
- **S. Azghandi** | Stipend by the Peters-Beer-Foundation
- **S. Tiedt** | Stipend by the Josef-Hackl-Stiftung
- **N. Terpolilli** | Hannelore Kohl Foundation Award 2014

Conferences, Trainings and Events

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

Scientific Conferences & Symposia (selection)

- Annual Conference 30th ANIM (Mannheim, 23-26 Jan 2013) "Kontroversen in der Intensivmedizin bei Schlaganfallpatienten" scientific chair
- Special Symposium of Vascular Biology (Munich, 14-15 Mar 2013) scientific organizer
- Annual Conference 57th Meeting of Thrombosis and Haemostasis Research (Munich, 20-23 Feb 2013) "From gene discovery to mechanism and novel therapeutic targets: Novel findings in cerebrovascular and cardiovascular disease" scientific chair
- Annual Conference 57th Meeting of Thrombosis and Haemostasis Research (Munich, 20-23 Feb 2013) "Mehr Möglichkeiten in der Antikoagulation: Patientenrelevant?" scientific chair
- Half year conference 13th Workshop, International Stroke Genetics Consortium 2013 (Charlottesville, 24-27 Apr 2013) program committee
- Annual Conference 6th Congress of The International Society for Vascular Behavioural and Cognitive Disorders (VAS COG) (Toronto, 25-27 Jun 2013) "Theme 3: Post Stroke Dementia" scientific chair
- Annual Conference 1st Asia Pacific Stroke Conference 2013 (APSC) (Hong Kong, 28 Aug – 2 Sep 2013) "Small Vessel Disease" scientific chair
- Annual Conference 86th DGN (Dresden, 18-21 Sep 2013) "Antikoagulation im Umbruch" scientific chair
- Annual Conference 86th DGN (Dresden, 18-21 Sep 2013) "Kontroversen in der Schlaganfallmedizin" scientific chair
- Annual Conference 13th Cellular Mechanisms of Neurodegeneration (Eibsee, 23-25 Oct 2013) "Amyloid, aggregation and secretases" scientific chair
- Half year conference 14th Workshop, International Stroke Genetics Consortium 2013 (Lund, 13-15 Nov) program committee and scientific chair
- Special Symposium Paul-Martini-Stiftung (Berlin 15 Nov 2013); "Neue Therapieansätze bei Schlaganfall und Epilepsie" scientific chair
- Annual Conference 2nd ISCN (Salzburg, 28-30 Nov 2013) program committee and scientific chair
- Annual Conference 31st ANIM (Hannover, 22-24 Jan 2014) program committee and scientific chair
- Annual Conference 31st ANIM (Hannover, 22-24 Jan 2014); "Freie Vorträge 2" scientific chair
- Annual Conference ISC 2014 (San Diego, 10-14 Feb 2014) "Session 143: Vascular Disconnection: Mechanisms of Small Vessel Disease-related Cognitive Impairment" scientific chair
- Annual Conference 30th ICCN (Berlin, 20-23 Mar 2014) "Joint Symposium DSG" scientific chair
- Annual Conference 3rd ECCN (Lille, 31 Mar - 01 Apr 2014) "Session 3 Cerebrovascular disease") scientific chair
- 15th Workshop, International Stroke Genetics Consortium 2014 (Salt Lake City, 03-04 Apr) program committee
- Annual Conference 23rd ESC (Nizza, 06-09 May 2014) "Update on Cerebral Small Vessel Disease – challenges and opportunities" scientific chair
- Annual Conference 87th DGN (Munich, 15-19 Sep) "Schlaganfall Aktuell: Vorhofflimmern im Fokus" scientific chair
- Annual Conference 9th World Stroke Congress (Istanbul, 22-25 Oct 2014) "Vascular cognitive disorders: Recent advances in concepts, imaging, predictors and treatment" scientific chair
- Annual Conference 14th Cellular Mechanisms of Neurodegeneration (Eibsee, 05-07 Nov 2014) "Vascular Dysfunction" scientific chair

Education (selection)

- Annual Conference 85th Neurowoche (Hamburg, 25-28 Sep 2013) "Schlaganfall | Modul 2: Ischämie" scientific chair
- Annual Conference 57th Meeting of Thrombosis and Haemostasis Research (Munich, 20-23 Feb 2013) "Neurologie" scientific chair
- Annual Conference 1st Asia Pacific Stroke Conference 2013 (APSC) (Hong Kong, 28 Aug - 02 Sep 2013; "Workshop 3: Stroke genetics" scientific chair
- AHA / ASA Webinar on Stroke Genetics (Munich, 05 Nov 2013) http://stroke.ahajournals.org/site/misc/Stroke_Webinars.xhtml
- Neuroscience School of Advanced Studies (Abbazie di Novacella, 30 Aug - 06 Sep 2014) "Vascular Dementia/amyloid" scientific chair
- Annual Conference 87th DGN (Munich, 15-19 Sep) "Zerebrale Mikroangiopathie: Schadensprozesse und Bildgebungskorrelate als Grundlage für therapeutische Interventionen" scientific chair
- Annual Conference 87th DGN (Munich, 15-19 Sep) HTK 2 Schlaganfall "Neues und Bewährtes" scientific chair
- Annual Conference 87th DGN (Munich, 15-19 Sep) "SyNergy Themenblock Neurovaskulär "Schlaganfall im Fokus" – Interdisziplinäre Strategien in München" scientific chair

Additional Events (selection)

- Schlaganfall Aktuell – Diagnostik und Therapie – an event of the Interdisciplinary Stroke Center Munich (ISZM) (Munich, Nov 2014, organization)
- "Geistig fit im Alter" information event | open door (Munich, Sep 2014 and Oct 2013, organization)
- Weltschlaganfalltag 2014 – information event (Munich, Oct 2014, organization)
- „Schlaganfall-Prävention und Rehabilitation" Dr. Anna Bayer-Karpinska, Information event (Saulgrub, Oct 2014) Seminar der Gruppe Ruhestand im Verein der Sehbehinderten und Blinden in Schule und Beruf e.V. in Saulgrub
- Advisory Board Meeting, ISD Review by Scientific Advisory Board (Munich, 06 Aug 2013)
- "Gedächtnismobil am Stachus" information event (Munich, Jun 2013, organization)
- Munich Memory Alliance, information event, (Munich, April 2013, organization)
- "Richtfest" Topping out Ceremony of the Center for Stroke and Dementia Research (CSD) (Munich, Feb 2013)

External Speakers in ISD Talks

Yves Agid, Paris, France / Dr. Goran Marinković, Amsterdam, Netherlands / Dr. Mathias Gelderblom, Hamburg, Germany / Dr. rer. physiol. Britta Engelhardt, Bern, Switzerland / Dr. Stefan Klöppel, Freiburg, Germany / Prof. Dr. med. Henryk Barthel, Leipzig, Germany / Dr. Andreas Fischer, Heidelberg, Germany / Prof. Jochen Prehn, Dublin, Ireland / Dr. Jens Minnerup, Münster, Germany / Dr. Christoph Jüschke, Wien, Austria / Dr. Oskar Hansson, MD, PhD, Malmö, Schweden / Prof. Joanna Wardlaw, Edinborough, GB / Dr. Gael Chetelat, Paris, France / Dr. Christian Sorg, München, Germany / Prof. Dr. Christian Stapf, Paris, France / Prof. Dr. Heinrich Mattle, Bern, Switzerland *(and more)*

Participation in Graduate Schools

Munich Center for Neurosciences – Brain and Mind: ISD staff actively participates into teaching programs offered within the graduate school of the MCN. The training concept of the Graduate School of Systemic Neurosciences (GSN) is designed to offer: 1) an optimally structured and student-centered teaching program in English; 2) comprehensive and state of-the-art scientific training regarding topics and methods - exceptionally broad scope of the Munich neuroscience research spectrum for neuroscience-related projects and theses (M.Sc., Ph.D.); 3) ECTS based grading, fully compatible with the Bologna System; 4) personal career planning and intensive individual coaching for scientific and related careers; 5) various options for lab rotations within the Munich Graduate Program, with collaborating institutions at Ludwig-Maximilians-Universität München, Technische Universität München, Max-Planck-Institutes, Helmholtz Center Munich, DLR, etc. and their international research partners; 6) an international network for future careers in academia and RTD projects for graduates, Ph.D. students and postdocs (see www.mcn.lmu.de). M. Balbi and K. Schüller joined the GSN in 2011. S. Azghandi, M. Lehm, E. Baykara, S. Tiedt and L. Simon-Vermot joined in 2012. M. Dichgans is a scientific board member of the GSN. ISD staff further participates in the graduate program molecular medicine (Promotionsstudiengang Molekulare Medizin).

Publications

2015

Ruschel J, **Hellal F**, Flynn KC, Dupraz S, Elliott DA, Tedeschi A, Bates M, ... *Systemic administration of epothilone B promotes axon regeneration after spinal cord injury* **Science.** 2015 [Epub ahead of print] PMID 25765066

Duering M, Righart R, Wollenweber FA, Zietemann V, Gesierich B, Dichgans M. Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts. **Neurology**. 2015 (in press)

Prades R, Oller-Salvia B, Schwarzmaier SM, Selva J, Moros M, **Balbi M, ..., Plesnila N,** Teixidó M, Giralt E. *Applying the Retro-Enantio Approach to Obtain a Peptide Capable of Overcoming the Blood-Brain Barrier.* **Angew Chem Int Ed Engl.** 2015 (accepted for publication)

Liesz A, Dalpke A, Mracsko E, Antoine DJ, Roth S, Zhou W, Yang H, Na SY, Akhisaroglu M, Fleming T, Eigenbrod T, Nawroth PP, Tracey KJ, Veltkamp R. *DAMP Signaling is a Key Pathway Inducing Immune Modulation after Brain Injury.* **J Neurosci**. 2015 Jan 14;35(2):583-98. PMID 25589753

Veltkamp R, Na SY, **Liesz A**. *Response to letter regarding article, "amplification of regulatory T cells using a CD28 superagonist reduces brain damage after ischemic stroke in mice".* **Stroke**. 2015 Feb;46(2):e52. PMID 25586832

D'Orsi B, Kilbride SM, Chen G, Perez Alvarez S, Bonner HP, Pfeiffer S, **Plesnila N**, Engel T, Henshall DC, Düssmann H, Prehn JH. *Bax regulates neuronal Ca2+ homeostasis.* **J Neurosci.** 2015 Jan 28;35(4):1706-22. PMID 25632145

Bühler D, **Azghandi S**, **Schüller K**, **Plesnila N.** *Effect of Decompressive Craniectomy on Outcome Following Subarachnoid Hemorrhage in Mice.* **Stroke**. 2015 Mar;46(3):819-26. PMID 25593134

Schwarzmaier SM, Gallozzi M, **Plesnila N**. *Identification of the vascular source of vasogenic brain edema following traumatic brain injury using in vivo 2-photon microscopy in mice.* **J Neurotrauma**. 2015 Jan 13. [Epub ahead of print] PMID 25585052

Wollenweber FA, **Hanecker P**, **Bayer-Karpinska A**, **Malik R**, Bäzner H, Moreton F, Muir KW, Müller S, Giese A, Opherk C, **Dichgans M**, **Haffner C**, **Duering M**. *Cysteine-Sparing CADASIL Mutations in NOTCH3 Show Proaggregatory Properties In Vitro.* **Stroke.** 2015 Mar;46(3):786-92. PMID 25604251

de Vries B, ..., Göbel H, **Dichgans M**, Kubisch C, ... , on behalf of the International Headache Genetics Consortium. *Systematic re-evaluation of genes from candidate gene association studies in migraine using a large genome-wide association data set.* **Cephalalgia**. 2015 Jan 29. [Epub ahead of print] PMID 25633374

Holliday EG, Traylor M, **Malik R**, Bevan S, Falcone G, ..., **Dichgans M**, Markus HS, Levi C, Attia J, Wray NR; on behalf of the Australian Stroke Genetics Collaborative, the Wellcome Trust Case Control Consortium 2, and the International Stroke Genetics Consortium. *Genetic Overlap Between Diagnostic Subtypes of Ischemic Stroke.* **Stroke**. 2015 Mar;46(3):615-9. PMID 25613305

De Guio F, Mangin JF, **Duering M**, Ropele S, Chabriat H, Jouvent E. *White matter edema at the early stage of cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.* **Stroke**. 2015 Jan;46(1):258-61. PMID 25370582

Azghandi S, **Prell C**, van der Laan SW, **Schneider M**, **Malik R**, Berer K, Gerdes N, Pasterkamp G, Weber C, **Haffner C**, **Dichgans M**. *Deficiency of the Stroke Relevant HDAC9 Gene Attenuates Atherosclerosis in Accord With Allele-Specific Effects at 7p21.1.* **Stroke.** 2015 Jan;46(1):197-202. PMID 25388417

Debette S, ..., **Dichgans M**, Gschwendtner A, ..., International Stroke Genetics Consortium, Ringelstein EB, ... *Common variation in PHACTR1 is associated with susceptibility to cervical artery dissection.* **Nat Genet.** 2015 Jan;47(1):78-83. PMID 25420145

Na SY, Mracsko E, **Liesz A**, Hünig T, Veltkamp R. *Amplification of regulatory T cells using a CD28 superagonist reduces brain damage after ischemic stroke in mice.* **Stroke.** 2015 Jan;46(1):212-20. PMID 25378432

De Guio F, Mangin JF, **Duering M**, Ropele S, Chabriat H, Jouvent E. *White matter edema at the early stage of cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.* **Stroke**. 2015 Jan;46(1):258-61. PMID 25370582

2014 and 2013			
	n	IF total	IF average
Total	117	**885,4**	**7,6**
First-/Senior Authorship	44	**282,2**	**6,6**
Original Articles	112	**879,2**	**7,6**
First-/Senior Authorship	40	**213,9**	**5,5**

2014

Adib-Samii P, ..., **Dichgans M**, ..., Rost NS2, Markus HS2. *Genetic Architecture of White Matter Hyperintensities Differs in Hypertensive and Nonhypertensive Ischemic Stroke.* **Stroke.** 2014 Dec 30. PMID 25550368

Mracsko E, **Liesz A**, Stojanovic A, Lou WP, Osswald M, Zhou W, Karcher S, Winkler F, Martin-Villalba A, Cerwenka A, Veltkamp R. *Antigen dependently activated cluster of differentiation 8-positive T cells cause perforin-mediated neurotoxicity in experimental stroke.* **J Neurosci.** 2014 Dec 10;34(50):16784-95. PMID 25505331

Friedmann Angeli JP, **Schneider M**, Proneth B, ... Conrad M. *Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice.* **Nat Cell Biol.** 2014 Dec;16(12):1180-91. PMID 25402683

Ay H, ..., **Dichgans M**, E.., ..., **Lehm M**, Rosand J, Rothwell PM, ... *Pathogenic ischemic stroke phenotypes in the NINDS-stroke genetics network.* **Stroke**. 2014 Dec;45(12):3589-96. PMID 25378430

Belle M, Godefroy D, Dominici C, Heitz-Marchaland C, Zelina P, **Hellal F**, Bradke F, Chédotal A. *A simple method for 3D analysis of immunolabeled axonal tracts in a transparent nervous system.* **Cell Rep**. 2014 Nov 20;9(4):1191-201. PMID 25456121

Beyer SE, von Baumgarten L, Thierfelder KM, Rottenkolber M, Janssen H, **Dichgans M**, Johnson TR, Straube A, Ertl-Wagner B, Reiser MF, Sommer WH. *Predictive value of the velocity of collateral filling in patients with acute ischemic stroke.***J Cereb Blood Flow Metab**. 2014 Nov 5. PMID 25370859

Beaufort N, **Scharrer E**, Kremmer E, Lux V, Ehrmann M, Huber R, Houlden H, Werring D, **Haffner C**, **Dichgans M**. *Cerebral small vessel disease-related protease HtrA1 processes latent TGF-β binding protein 1 and facilitates TGF-β signaling.* **Proc Natl Acad Sci U S A.** 2014 Nov 18;111(46):16496-501. PMID 25369932

Schwarzmaier SM, **Plesnila N**. *Contributions of the immune system to the pathophysiology of traumatic brain injury - evidence by intravital microscopy.* **Front Cell Neurosci**. 2014 Nov 4;8:358. PMID 25408636

Schwarzmaier SM, Terpolilli NA, Dienel A, Gallozzi M, Schinzel R, Tegtmeier F, **Plesnila N**. *Endothelial nitric oxide synthase mediates arteriolar vasodilatation after traumatic brain injury in mice.* **J Neurotrauma.** 2014 Nov 3. [Epub ahead of print] PMID 25363688

Leong A, Rehman W, Dastani Z, Greenwood C, Timpson N, Langsetmo L, Berger C; METASTROKE, Fu L, Wong BY, Malik S, **Malik R**, Hanley DA, Cole DE, Goltzman D, Richards JB. *The causal effect of vitamin D binding protein (DBP) levels on calcemic and cardiometabolic diseases: a Mendelian randomization study.* **PLoS Med.** 2014 Oct 28;11(10):e1001751. PMID 25350643

Holliday EG, Traylor M, **Malik R**, ..., **Dichgans M**, ..., CKDGen Consortium and the International Stroke Genetics Consortium. *Polygenic overlap between kidney function and large artery atherosclerotic stroke.* **Stroke**. 2014 Dec;45(12):3508-13. PMID 25352485

McArdle PF, ..., **Dichgans M**, ..., Rosand J, Rost NS, Rothwell PM, ..., NINDS SiGN Study. *Agreement between TOAST and CCS ischemic*

stroke classification: the NINDS SiGN study. **Neurology**. 2014 Oct 28;83(18):1653-60. PMID 25261504

Seiler S, Pirpamer L, Hofer E, **Duering M**, Jouvent E, Fazekas F, Mangin JF, Chabriat H, **Dichgans M**, Ropele S, Schmidt R. *Magnetization transfer ratio relates to cognitive impairment in normal elderly.* **Front Aging Neurosci.** 2014 Sep 25;6:263. PMID 25309438

Ghadery C, ..., **Duering M**, Jouvent E, Schmidt H, Fazekas F, Mangin JF, Chabriat H, **Dichgans M**, Ropele S, Schmidt R. *R2* mapping for brain iron: associations with cognition in normal aging*. **Neurobiol Aging.** 2014 Sep 19. pii: S0197-4580(14)00618-6. PMID 25443291

Thal DR, Attems J, **Ewers M**. *Spreading of amyloid, tau, and microvascular pathology in Alzheimer's disease: findings from neuropathological and neuroimaging studies.* **J Alzheimers Dis**. 2014;42 Suppl 4:S421-9. PMID 25227313

Nyholt DR; for the International Headache Genetics Consortium:, Anttila V, ..., **Malik R**, ..., **Dichgans M**, ... *Concordance of genetic risk across migraine subgroups: Impact on current and future genetic association studies.* **Cephalalgia**. 2014 Sep 1. [Epub ahead of print] PMID 25179292

De Guio F, Reyes S, Vignaud A, **Duering M**, Ropele S, Duchesnay E, Chabriat H, Jouvent E. *In vivo high-resolution 7 Tesla MRI shows early and diffuse cortical alterations in CADASIL*. **PLoS One**. 2014 Aug 28;9(8):e106311. PMID 25165824

Lautner R, ..., Rujescu D, **Ewers M**, Landén M, ..., Alzheimer's Disease Neuroimaging Initiative. *Apolipoprotein E genotype and the diagnostic accuracy of cerebrospinal fluid biomarkers for Alzheimer disease.* **JAMA Psychiatry**. 2014 Oct;71(10):1183-91. PMID 25162367

Adam R, Noppeney U. *A phonologically congruent sound boosts a visual target into perceptual awareness.* **Front Integr Neurosci.** 2014 Sep 11;8:70. eCollection 2014

Gröger M, **Plesnila N**. *The neuroprotective effect of 17β-estradiol is independent of its antioxidative properties.* **Brain Res**. 2014 Aug 20;1589C:61-67. PMID 25148707

Bühler D, **Schüller K**, **Plesnila N**. *Protocol for the induction of subarachnoid hemorrhage in mice by perforation of the Circle of Willis with an endovascular filament.* **Transl Stroke Res**. 2014 Dec;5(6):653-9. PMID 25123204

Sinner MF, ..., **Malik R**, **Dichgans M**, Rosand J,..., Ellinor PT. *Integrating genetic, transcriptional, and functional analyses to identify 5 novel genes for atrial fibrillation.* **Circulation**. 2014 Oct 7;130(15):1225-35. PMID 25124494

Kast J, **Hanecker P**, **Beaufort N**, Giese A, Joutel A, **Dichgans M**, Opherk C, **Haffner C**. *Sequestration of latent TGF-β binding protein 1 into CADASIL-related Notch3-ECD deposits.* **Acta Neuropathol Commun.** 2014 Aug 13;2(1):96. [Epub ahead of print] PMID 25190493

Krieg SM, Sonanini S, **Plesnila N**, Trabold R. *Effect of Small Molecule Vasopressin V1a and V2 Receptor Antagonists on Brain Edema Formation and Secondary Brain Damage following Traumatic Brain Injury in Mice.* **J Neurotrauma**. 2015 Feb 15;32(4):221-7. Epub 2014 Dec 16. PMID 25111427

Traylor M, ..., **Malik R**, ..., METASTROKE, International Stroke Genetics Consortium, Wellcome Trust Case Consortium 2 (WTCCC2),..., **Dichgans M**, Lehtimäki T2, Lewis CM, Markus HS. *A novel MMP12 locus is associated with large artery atherosclerotic stroke using a genome-wide age-at-onset informed approach.* **PLoS Genet**. 2014 Jul 31;10(7):e1004469.PMID 25078452

Llovera G, Roth S, **Plesnila N**, Veltkamp R, **Liesz A**. *Modeling stroke in mice: permanent coagulation of the distal middle cerebral artery.* **J Vis Exp**. 2014 Jul 31;(89):e51729. PMID 25145316

Ye BS, Seo SW, ..., **Ewers M**,... *Amyloid burden, cerebrovascular disease, brain atrophy, and cognition in cognitively impaired patients.* **Alzheimers Dement**. 2014 Jul 19. pii: S1552-5260(14)02419-4. PMID 25048578

Kilarski LL, ..., **Malik R**, ..., **Dichgans M**, ..., GARNET Collaborative Research Group, Wellcome Trust Case Control Consortium 2, Australian Stroke Genetic Collaborative, the METASTROKE Consortium, and the International Stroke Genetics Consortium. *Meta-analysis in more than 17,900 cases of ischemic stroke reveals a novel association at 12q24.12.* **Neurology**. 2014 Aug 19;83(8):678-85. PMID 25031287

Liesz A, Bauer A, Hoheisel JD, Veltkamp R. *Intracerebral interleukin-10 injection modulates post-ischemic neuroinflammation: an experimental microarray study.* **Neurosci Lett.** 2014 Sep 5;579:18-23. PMID 25019688

Mracsko E, Javidi E, Na SY, Kahn A, **Liesz A**, Veltkamp R ... *Leukocyte invasion of the brain after experimental intracerebral hemorrhage in mice.* **Stroke.** 2014 Jul;45(7):2107-14, PMID 24916913

Mattle HP, Brainin M, Chamorro A, **Dichgans M**, Lees KR, Leys D, Michel P. *Second European Stroke Science Workshop.* **Stroke.** 2014 Jul;45(7):e113-22. PMID 24903983

Mracsko E, **Liesz A**, Karcher S, Zorn M, Bari F, Veltkamp R. *Differential effects of sympathetic nervous system and hypothalamic-pituitary-adrenal axis on systemic immune cells after severe experimental stroke.* **Brain Behav Immun.** 2014 Oct;41:200-9. PMID 24886966

Friedrich B, Michalik R, Oniszczuk A, Abubaker K, Kozniewska E, **Plesnila N.** *CO2 has no therapeutic effect on early microvasospasm after experimental subarachnoid hemorrhage.* **J Cereb Blood Flow Metab.** 2014 Aug;34(8):e1-6. PMID 24865999

Craggs LJ, Yamamoto Y, Ihara M, Fenwick R, Burke M, Oakley AE, Roeber S, **Duering M**, Kretzschmar H, Kalaria RN. *White matter pathology and disconnection in the frontal lobe in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).* **Neuropathol Appl Neurobiol**. 2014 Aug;40(5):591-602. PMID 23844775

De Guio F, Vignaud A, Ropele S, **Duering M**, Duchesnay E, Chabriat H, Jouvent E. *Loss of venous integrity in cerebral small vessel disease: a 7-T MRI study in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).* **Stroke**. 2014 Jul;45(7):2124-6. PMID 24867926

Cotlarciuc I, **Malik R,** Holliday EG, ..., Rosand J, ..., **Dichgans M**, Sharma P; METASTROKE and the International Stroke Genetics Consortium. *Effect of genetic variants associated with plasma homocysteine levels on stroke risk.* **Stroke**. 2014 Jul;45(7):1920-4. PMID 24846872

Gunda B, Porcher R, **Duering M**, Guichard JP, Mawet J, Jouvent E, **Dichgans M**, Chabriat H. *ADC histograms from routine DWI for longitudinal studies in cerebral small vessel disease: a field study in CADASIL.* **PLoS One.** 2014 May 12;9(5):e97173. PMID 24819368

Duering M, **Gesierich B**, Seiler S, Pirpamer L, **Gonik M**, Hofer E, Jouvent E, Duchesnay E, Chabriat H, Ropele S, Schmidt R, **Dichgans M**. *Strategic white matter tracts for processing speed deficits in age-related small vessel disease.* **Neurology.** 2014 Jun 3;82(22):1946-50. PMID 24793184

Kljajevic V, Grothe MJ, **Ewers M**, Teipel S; Alzheimer's Disease Neuroimaging Initiative. *Distinct pattern of hypometabolism and atrophy in preclinical and predementia Alzheimer's disease.* **Neurobiol Aging.** 2014 Sep;35(9):1973-81. PMID 24811241

Thierfelder KM, ..., Opherk C, ... *Vertebral artery hypoplasia: frequency and effect on cerebellar blood flow characteristics.* **Stroke**. 2014 May;45(5):1363-8. PMID 24699051

Thierfelder KM, ..., Opherk C, ... *Diagnostic accuracy of whole-brain computed tomographic perfusion imaging in small-volume infarctions.* **Invest Radiol.** 2014 Apr;49(4):236-42. PMID 24500091

Woo D, Falcone GJ, Devan WJ, ..., **Malik R**, **Dichgans M**, ..., International Stroke Genetics Consortium. *Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage.* **Am J Hum Genet.** 2014 Apr 3;94(4):511-21. PMID 24656865

Falcone GJ, **Malik R**, **Dichgans M**, Rosand J. *Current concepts and clinical applications of stroke genetics.* **Lancet Neurol.** 2014 Apr;13(4):405-18. PMID 24646874

Mäkelä KM, ..., **Dichgans M**, Wellcome Trust Case Control Consortium 2 (WTCCC2), ... *Association of the novel single-nucleotide polymorphism which increases oxidized low-density lipoprotein levels with cerebrovascular disease events.* **Atherosclerosis**. 2014 May;234(1):214-7. PMID 24681816

Lista S, Garaci FG, **Ewers M**, Teipel S, Zetterberg H, Blennow K, Hampel H. *CSF Aβ1-42 combined with neuroimaging biomarkers in the early detection, diagnosis and prediction of Alzheimer's disease.* **Alzheimers Dement**. 2014 May;10(3):381-92. PMID 23850330

Osterstock G, ..., **Plesnila N**, ... *Sustained alterations of hypothalamic tanycytes during posttraumatic hypopituitarism in male mice.* **Endocrinology.** 2014 May;155(5):1887-98. PMID 24601879

Wollenweber FA, **Zietemann V**, Rominger A, Opherk C, **Bayer-Karpinska A**, Gschwendtner A, **Coloma Andrews L**, **Bürger K**, **Duering M**, **Dichgans M**. *The Determinants of Dementia After Stroke (DEDEMAS) Study: protocol and pilot data.* **Int J Stroke**. 2014 Apr;9(3):387-92. PMID 23834337

Opherk C, **Gonik M**, **Duering M**, **Malik R,** Jouvent E, Hervé D, ..., Rosand J, Chabriat H, **Dichgans M**. *Genome-wide genotyping demonstrates a polygenic risk score associated with white matter hyperintensity volume in CADASIL.* **Stroke**. 2014 Apr;45(4):968-72. PMID 24578207

Noh Y, ..., **Ewers M**, ... *White matter hyperintensities are associated with amyloid burden in APOE4 non-carriers.* **J Alzheimers Dis.** 2014;40(4):877-86. PMID 24577457

Lee MJ, ..., **Ewers M**, ... *Synergistic effects of ischemia and β-amyloid burden on cognitive decline in patients with subcortical vascular mild cognitive impairment.* **JAMA Psychiatry**. 2014 Apr;71(4):412-22. PMID 24554306

Yao M, Hervé D, Jouvent E, **Duering M**, Reyes S, Godin O, Guichard JP, **Dichgans M**, Chabriat H. *Dilated perivascular spaces in small-vessel disease: a study in CADASIL.* **Cerebrovasc Dis**. 2014;37(3):155-63. PMID 24503815

Lee MJ, Park S, ..., **Ewers M**, ... *Differences in prefrontal, limbic, and white matter lesion volumes according to cognitive status in elderly patients with first-onset subsyndromal depression* **PLoS One.** 2014 Jan 31;9(1):e87747. PMID 24498184

Wijnands KA, Hoeksema MA, ..., J, **Ghosh M**, ..., Buurman WA, Lamers WH, Poeze M. *Arginase-1 deficiency regulates arginine concentrations and NOS2-mediated NO production during endotoxemia.* **PLoS One.** 2014 Jan 21;9(1):e86135. PMID 24465919

Malik R, ..., Mitchell BD, Rosand J, Meschia JF, Levi C, Rothwell PM, ..., **Dichgans M**; Wellcome Trust Case Control Consortium 2. *Multilocus genetic risk score associates with ischemic stroke in case-control and prospective cohort studies.* **Stroke.** 2014 Feb;45(2):394-402. PMID 24436234

Ibrahim-Verbaas CA, ..., **Malik R**, **Dichgans M**, Schmidt H, ..., van Duijn CM, Launer LJ. *Predicting stroke through genetic risk functions: the CHARGE Risk Score Project.* **Stroke.** 2014 Feb;45(2):403-12. PMID 24436238

Dolga AM, de Andrade A, Meissner L, Knaus HG, Höllerhage M, Christophersen P, Zischka H, **Plesnila N**, Höglinger GU, Culmsee C. *Subcellular expression and neuroprotective effects of SK channels in human dopaminergic neurons.* **Cell Death Dis.** 2014 Jan 16;5:e999. PMID 24434522

Doti N, Reuther C, Scognamiglio PL, Dolga AM, **Plesnila N**, Ruvo M, Culmsee C. *Inhibition of the AIF/CypA complex protects against intrinsic death pathways induced by oxidative stress.* **Cell Death Dis.** 2014 Jan 16;5:e993. PMID 24434516

Grothe MJ, **Ewers M**, Krause B, Heinsen H, Teipel SJ; Alzheimer's Disease Neuroimaging Initiative. *Basal forebrain atrophy and cortical amyloid deposition in nondemented elderly subjects.* **Alzheimers Dement.** 2014 Oct;10(5 Suppl):S344-53. PMID 24418052

Boltze J, Ayata C, Wagner DC, **Plesnila N.** *Preclinical phase III trials in translational stroke research: call for collective design of framework and guidelines.* **Stroke.** 2014 Feb;45(2):357. PMID 24407954

Lemmens KJ, van de Wier B, Vaes N, **Ghosh M**, van Zandvoort MA, van der Vijgh WJ, Bast A, Haenen GR. *The flavonoid 7-mono-O-(β-hydroxyethyl)-rutoside is able to protect endothelial cells by a direct antioxidant effect.* **Toxicol In Vitro**. 2014 Jun;28(4):538-43. PMID 24412621

Wollenweber FA, **Buerger K**, **Mueller C**, Ertl-Wagner B, **Malik R**, **Dichgans M**, Linn J, Opherk C. *Prevalence of cortical superficial siderosis in patients with cognitive impairment.* **J Neurol.** 2014 Feb;261(2):277-82. PMID 24221645

Andreasson U, ..., Helisalmi S, **Ewers M**, ..., Zetterberg H. *CSF biomarkers for Alzheimer's pathology and the effect size of APOE ε4.* **Mol Psychiatry**. 2014 Feb;19(2):148-9. PMID 23419830

Park JH, ..., **Ewers M**, ..., Na DL. *Effects of cerebrovascular disease and amyloid beta burden on cognition in subjects with subcortical vascular cognitive impairment.* **Neurobiol Aging**. 2014 Jan;35(1):254-60. PMID 23932881

De Guio F, Reyes S, **Duering M,** Pirpamer L, Chabriat H, Jouvent E. *Decreased T1 contrast between gray matter and normal-appearing white matter in CADASIL.* **AJNR Am J Neuroradiol**. 2014 Jan;35(1):72-6. PMID 23868154

Dichgans M, **Malik R**, ..., Farrall M, Schunkert H; ... *Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants.* **Stroke.** 2014 Jan;45(1):24-36. PMID 24262325

2013

Bayer-Karpinska A, Schwarz F, **Wollenweber FA**, Poppert H, Boeckh-Behrens T, Becker A, Clevert DA, Nikolaou K, Opherk C, **Dichgans M**, Saam T. *The carotid plaque imaging in acute stroke (CAPIAS) study: protocol and initial baseline data.* **BMC Neurol**. 2013 Dec 13;13:201. PMID 24330333

Schüller K, **Bühler D**, **Plesnila N**. *A murine model of subarachnoid hemorrhage.* **J Vis Exp**. 2013 Nov 21;(81):e50845. PMID 24300521

Zietemann V, Schuster T, Duell TH. *[Time-Dependent Confounding in the Estimation of Treatment Effects in Randomised Trials with Multimodal Therapies - An Illustration of the Problem of Time-Dependent Confounding by Causal Graphs.]* **Gesundheitswesen**. 2015 Jan;77(1):62-6. Epub 2013 Nov 7. PMID 24203687

Ewers M, Brendel M, Rizk-Jackson A, Rominger A, Bartenstein P, Schuff N, Weiner MW; Alzheimer's Disease Neuroimaging Initiative (ADNI). *Reduced FDG-PET brain metabolism and executive function predict clinical progression in elderly healthy subjects.* **Neuroimage Clin**. 2013 Nov 4;4:45-52. PMID 24286024

Fazekas F, Enzinger C, Schmidt R, **Dichgans M**, ..., sifap1 Investigators. *MRI in acute cerebral ischemia of the young: the Stroke in Young Fabry Patients (sifap1) Study.* **Neurology**. 2013 Nov 26;81(22):1914-21. PMID 24186912

Liesz A, Zhou W, Na SY, Hämmerling GJ, Garbi N, Karcher S, Mracsko E, Backs J, Rivest S, Veltkamp R. *Boosting regulatory T cells limits neuroinflammation in permanent cortical stroke.* **J Neurosci**. 2013 Oct 30;33(44):17350-62. PMID 24174668

Dichgans M, Joutel A, Chabriat H. *Letter by Dichgans et al regarding article, „Peripheral artery disease as a manifestation of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and practical implications"* **Circulation**. 2013 Oct 22;128(17):e363. PMID 24146128

Liesz A, Rüger H, P..., Veltkamp R. *Stress mediators and immune dysfunction in patients with acute cerebrovascular diseases.* **PLoS One**. 2013 Sep 19;8(9):e74839. PMID 24069356

Ghosh M, van den Akker NM, ..., van Zandvoort MA. *Specific Visualization of Nitric Oxide in the Vasculature with Two-Photon Microscopy Using a Copper Based Fluorescent Probe* **PLoS One**. 2013 Sep 23;8(9):e75331. PMID 24086509

Meschia JF, ..., **Dichgans M**, ..., NINDS SiGN Study. *Stroke Genetics Network (SiGN) study: design and rationale for a genome-wide association study of ischemic stroke subtypes.* **Stroke**. 2013 Oct;44(10):2694-702. PMID 24021684

Sabater-Lleal M, Huang J, Chasman D, ..., **Dichgans M**, O'Donnell CJ. *Multiethnic meta-analysis of genome-wide association studies in >100 000 subjects identifies 23 fibrinogen-associated Loci but no strong evidence of a causal association between circulating fibrinogen and cardiovascular disease.* **Circulation**. 2013 Sep 17;128(12):1310-24. PMID 23969696

Schmitt S, ..., **Plesnila N**, ..., Zischka H. *A semi-automated method for isolating functionally intact mitochondria from cultured cells and tissue biopsies.* **Anal Biochem**. 2013 Dec 1;443(1):66-74. PMID 23969012

McFadden TM, ..., **Plesnila N**, ..., O'Brien FJ. *The delayed addition of human mesenchymal stem cells to pre-formed endothelial cell networks results in functional vascularization of a collagen-glycosaminoglycan scaffold in vivo.* **Acta Biomater**. 2013 Dec;9(12):9303-16. PMID 23958783

Yadav S, ..., **Malik R**, ..., **Dichgans M**, ...; International Stroke Genetics Consortium. *Genome-wide analysis of blood pressure variability and ischemic stroke.* **Stroke**. 2013 Oct;44(10):2703-9. PMID 23929743

Righart R, **Duering M**, **Gonik M**, Jouvent E, Reyes S, Hervé D, Chabriat H, **Dichgans M**. *Impact of regional cortical and subcortical changes on processing speed in cerebral small vessel disease.* **Neuroimage Clin.** 2013 Jun 19;2:854-61. PMID 24179837

Wardlaw J, Smith C, **Dichgans M**. *Microbleeds in cerebral small vessel disease - authors' reply.* **Lancet Neurol**. 2013 Aug;12(8):736-7. PMID 23867195

Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, ..., **Duering M**, ... **Dichgans M**; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). *Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration.* **Lancet Neurol.** 2013 Aug;12(8):822-38. PMID 23867200

Trelles M, Eberhardt KM, Buchholz M, Schindler A, **Bayer-Karpinska A**, **Dichgans M**, Reiser MF, Nikolaou K, Saam T. *CTA for screening of complicated atherosclerotic carotid plaque--American Heart Association type VI lesions as defined by MRI.* **AJNR Am J Neuroradiol**. 2013 Dec;34(12):2331-7. PMID 23868157

Duering M, Csanadi E, **Gesierich B**, Jouvent E, Hervé D, Seiler S, Belaroussi B, Ropele S, Schmidt R, Chabriat H, **Dichgans M**. *Incident lacunes preferentially localize to the edge of white matter hyperintensities: insights into the pathophysiology of cerebral small vessel disease.* **Brain**. 2013 Sep;136(Pt 9):2717-26. PMID 23864274

Saam T, Hetterich H, Hoffmann V, Yuan C, **Dichgans M**, Poppert H, Koeppel T, Hoffmann U, Reiser MF, Bamberg F. *Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging.* **J Am Coll Cardiol**. 2013 Sep 17;62(12):1081-91 PMID 23850912

Anttila V, ..., **Malik R**, ..., **Dichgans M**, ... *Genome-wide meta-analysis identifies new susceptibility loci for migraine.* **Nat Genet**. 2013 Aug;45(8):912-7. PMID 23793025

Wortmann M, **Schneider M**, Pircher J, ..., Beck H. *Combined deficiency in glutathione peroxidase 4 and vitamin E causes multiorgan thrombus formation and early death in mice.* **Circ Res**. 2013 Aug 2;113(4):408-17. PMID 23770613

Plesnila N. *Pathophysiological Role of Global Cerebral Ischemia following Subarachnoid Hemorrhage: The Current Experimental Evidence.* **Stroke Res Treat**. 2013;2013:651958 PMID 23844316

Kropp P, ..., **Dichgans M**, ... *Headache as a symptom at stroke onset in 4,431 young ischaemic stroke patients. Results from the „Stroke in Young Fabry Patients (SIFAP1) study".* **J Neural Transm**. 2013 Oct;120(10):1433-40. PMID 23748977

Coppenrath EM, Lummel N, Linn J, Lenz O, Habs M, Nikolaou K, Reiser MF, **Dichgans M**, Pfefferkorn T, Saam T. *Time-of-flight angiography: a viable alternative to contrast-enhanced MR angiography and fat-suppressed T1w images for the diagnosis of cervical artery dissection?* **Eur Radiol**. 2013 Oct;23(10):2784-92. PMID 23732685

Dyrba M, **Ewers M**, Wegrzyn M, ... *Robust automated detection of microstructural white matter degeneration in Alzheimer's disease using machine learning classification of multicenter DTI data.* **PLoS One**. 2013 May 31;8(5):e64925. PMID 23741425

Grimm JM, ..., Reiser MF, **Dichgans M**, Freilinger C, Nikolaou K, Saam T. *Comparison of symptomatic and asymptomatic atherosclerotic carotid plaques using parallel imaging and 3 T black-blood in vivo CMR.* **J Cardiovasc Magn Reson**. 2013 May 24;15:44. PMID 23705576

Adib-Samii P, ..., Gschwendtner A, **Malik R**, ..., Ciusani E, Holliday EG, Maguire J, Wardlaw J, Worrall B, ..., Rothwell PM, Meschia J, **Dichgans M**, ... *17q25 Locus is associated with white matter hyperintensity volume in ischemic stroke, but not with lacunar stroke status.* **Stroke**. 2013 Jun;44(6):1609-15. PMID 23674528

Traylor M, Bevan S, Rothwell PM, Sudlow C; Wellcome Trust Case Control Consortium 2 (WTCCC2), **Dichgans M**, Markus HS, Lewis CM. *Using phenotypic heterogeneity to increase the power of genome-wide association studies: application to age at onset of ischaemic stroke subphenotypes.* **Genet Epidemiol**. 2013 Jul;37(5):495-503. PMID 23674248

Misgeld T, Lichtenthaler SF, **Dichgans M**. *Between new genetic discoveries and large randomized trials--neurological research in the era of systems medicine.* **EMBO Rep**. 2013 Jun;14(6):489-92. PMID 23670197

Steiner T, Böhm M, **Dichgans M**, Diener HC, Ell C, Endres M, Epple C, Grond M, Laufs U, Nickenig G, Riess H, Röther J, Schellinger PD, Spannagl M, Veltkamp R. *Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (DOACs), apixaban, dabigatran and rivaroxaban.* **Clin Res Cardiol**. 2013 Jun;102(6):399-412. PMID 23669868

Sirko S, Behrendt G, Johansson PA, Tripathi P, Costa M, Bek S, Heinrich C, Tiedt S, Colak D, **Dichgans M**, Fischer IR, **Plesnila N**, Staufenbiel M, Haass C, Snapyan M, Saghatelyan A, Tsai LH, Fischer A, Grobe K, Dimou L, Götz M. *Reactive glia in the injured brain acquire stem cell properties in response to sonic hedgehog. [corrected].* **Cell Stem Cell**. 2013 Apr 4;12(4):426-39. PMID 23561443

Kunz M, Nussberger J, Holtmannspötter M, Bitterling H, **Plesnila N**, Zausinger S. *Bradykinin in blood and cerebrospinal fluid after acute cerebral lesions: correlations with cerebral edema and intracranial pressure.* **J Neurotrauma**. 2013 Oct 1;30(19):1638-44. PMID 23638655

Wardlaw JM, Smith C, **Dichgans M**. *Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging.* **Lancet Neurol.** 2013 May;12(5):483-97. PMID 23602162

Schwarz F, **Bayer-Karpinska A**, Poppert H, Buchholz M, Cyran C, Grimm J, Helck A, Nikolaou K, Opherk C, **Dichgans M**, Saam T. *Serial carotid MRI identifies rupture of a vulnerable plaque resulting in amaurosis fugax.* **Neurology**. 2013 Mar 19;80(12):1171-2.PMID 23509049

Ewers M, Insel PS, Stern Y, Weiner MW; Alzheimer's Disease Neuroimaging Initiative (ADNI). *Cognitive reserve associated with FDG-PET in preclinical Alzheimer disease.* **Neurology**. 2013 Mar 26;80(13):1194-201. PMID 23486873

Wollenweber FA, **Zietemann V**, Gschwendtner A, Opherk C, **Dichgans M**. *Subclinical hyperthyroidism is a risk factor for poor functional outcome after ischemic stroke.* **Stroke**. 2013 May;44(5):1446-8. PMID 23482604

Park JH, ..., **Ewers M**, ..., Na DL. *Pathogenesis of cerebral microbleeds: In vivo imaging of amyloid and subcortical ischemic small vessel disease in 226 individuals with cognitive impairment.* **Ann Neurol**. 2013 May;73(5):584-93. PMID 23495089

Bayer-Karpinska A, Patzig M, Adamczyk C, Dimitriadis K, **Wollenweber FA**, **Dichgans M**, Jahn K, Opherk C. *Reversible cerebral vasoconstriction syndrome with concurrent bilateral carotid artery dissection.* **Cephalalgia.** 2013 May;33(7):491-5. PMID 23475293

Schwarzmaier SM, Zimmermann R, McGarry NB, Trabold R, Kim SW, **Plesnila N**.*In vivo temporal and spatial profile of leukocyte adhesion and migration after experimental traumatic brain injury in mice.* **J Neuroinflammation**. 2013 Feb 28;10:32. PMID 23448240

Rauen K, Trabold R, Brem C, Terpolilli NA, **Plesnila N**. *Arginine vasopressin V1a receptor-deficient mice have reduced brain edema and secondary brain damage following traumatic brain injury.* **J Neurotrauma**. 2013 Aug 15;30(16):1442-8. PMID 23441636

Dolga AM, Netter MF, Perocchi F, Doti N, Meissner L, Tobaben S, Grohm J, Zischka H, **Plesnila N**, Decher N, Culmsee C. *Mitochondrial small conductance SK2 channels prevent glutamate-induced oxytosis and mitochondrial dysfunction.* **J Biol Chem**. 2013 Apr 12;288(15):10792-804. PMID 23430260

Vermeiren AP, ..., **Ewers M**, ..., Verhey FR. *The association between APOE ε4 and Alzheimer-type dementia among memory clinic patients is confined to those with a higher education. The DESCRIPA Study.***J Alzheimers Dis**. 2013;35(2):241-6. PMID 23380990

Dodel R, Rominger A, Bartenstein P, Barkhof F, Blennow K, Förster S, Winter Y, Bach JP, Popp J, Alferink J, Wiltfang J, **Buerger K**, Otto M, Antuono P, Jacoby M, Richter R, Stevens J, Melamed I, Goldstein J, Haag S, Wietek S, Farlow M, Jessen F. *Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial.* **Lancet Neurol**. 2013 Mar;12(3):233-43. PMID 23375965

Gschwendtner A, **Dichgans M**. *[Genetics of ischemic stroke].* **Nervenarzt**. 2013 Feb;84(2):166-72. PMID 23334453

Williams FM, ..., **Dichgans M**, Rothwell PM, ... *Ischemic stroke is associated with the ABO locus: the EuroCLOT study.* **Ann Neurol.** 2013 Jan;73(1):16-31. PMID 23381943

Rolfs A, ..., **Dichgans M**, Martus P, ... *Acute cerebrovascular disease in the young: the Stroke in Young Fabry Patients study* **Stroke**. 2013 Feb;44(2):340-9. PMID 23306324

Linn J, **Wollenweber FA**, Lummel N, Bochmann K, Pfefferkorn T, Gschwendtner A, Bruckmann H, **Dichgans M**, Opherk C. *Superficial siderosis is a warning sign for future intracranial hemorrhage*. **J Neurol.** 2013 Jan;260(1):176-81. PMID 22820723

Ganesh SK, ..., **Malik R,** ... *Loci influencing blood pressure identified using a cardiovascular gene-centric array.* **Hum Mol Genet**. 2013 Apr 15;22(8):1663-78. PMID 23303523

Zou F, ..., Wiltfang J, **Dichgans M**, Frölich L, ... *Linking protective GAB2 variants, increased cortical GAB2 expression and decreased* Alzheimer's *disease pathology.* **PLoS One**. 2013 May 28;8(5):e64802. Print 2013. PMID 23724096

Duering M, Gonik M, Malik R, Zieren N, Reyes S, Jouvent E, Hervé D, Gschwendtner A, Opherk C, Chabriat H, Dichgans M. *Identification of a strategic brain network underlying processing speed deficits in vascular cognitive impairment.* **Neuroimage.** 2013 Feb 1;66:177-83. PMID 23153965

Staff

Ruth Adam, Ph.D., postdoctoral researcher
Rupert Aigner, medical documentalist
Dr. rer. nat. Miguel Á. Araque Caballero, postdoctoral researcher
Dr. rer. nat. Yaw Asare, postdoctoral researcher
Sepiede Azghandi, B.Sc. postgraduate
Dr. rer. nat. Lamia'a, Bahnassawy, postdoctoral researcher
Matilde Balbi, M.Sc. Ph.D. student
Dr. med. Anna Bayer-Karpinska, clinical scientist, physician
Ebru Baykara, M.Sc. Ph.D. student
Dr. rer. nat. Nathalie Beaufort, postdoctoral researcher
Dominik Bühler, Ph.D. student
PD Dr. med. Katharina Bürger senior physician, psychiatrist
Ruiyao Marika Cai, Ph.D. student
Dr. med. Cihan Catak, physician, psychiatrist
Margit Deschner, study nurse
Prof. Dr. med. Martin Dichgans, director and chairman
Angelika Dörr, study nurse
PD Dr. med. Marco Düring, junior research group leader, physician
Dr. rer. nat. Ali Erturk, junior research group leader
Prof. Dr. Michael Ewers, PI
Carina Exner, Ph.D. student
Nicolai Franzmeier, M.Sc. psychologist / Ph.D. student
Daniel Friedrich, animal care taker
Markus A. Frühauf, managing director
Kathrin Gehring, research office
Benno Gesierich, Ph.D. postdoctoral researcher
Jasmin Sirin Gezgin, research assistant
Alireza Ghasemi, B.Sc. programmer
Mitrajit Ghosh, Ph.D. postdoctoral researcher
Maria Gissler, study nurse
Dr. rer. nat. Mariya Gonik, postdoctoral researcher
Claudia Günter, laboratory assistant
PD Dr. rer. nat. Christof Haffner, senior scientist
Timo Hasselwander, B.Sc. medical documentalist
Farida Hellal, Ph.D. postdoctoral researcher
Nicole Heumos, technical assistant
Kerstin Hofmann, technical assistant
Brigitte Huber, outpatient office
Dipl. Psych. Manuel Jooßens, psychologist
Sabrina Katzdobler, Ph.D. student
Veronika Kautzky, student assistant
Maximilian Knarr, Ph.D. student
Peggy Kunath, technical assistant
Dr. rer. nat. Tural Khudiyev, postdoctoral researcher
Timon Landinger, Ph.D. student
Manuel Lehm, clinician scientist, physician
Natalie Leistner, technical assistant
Dr. med. Arthur Liesz, scientist, group leader
Barbara Lindner, technical assistant
Gemma Llovera García, M.Sc. Ph.D. student
Daniel Loose, IT/IS
Dr. med. Athanasios Lourbopoulos, postdoctoral researcher
Dr. rer. nat. Rainer Malik, postdoctoral researcher
Uta Mamrak, technical assistant
Andreas Männer, object manager
Eva Markov, study nurse
Dr. med. Claudia Müller, physician, neurologist
Leone Njaramba, technical assistant
Chenchen Pan, M.Sc. Ph.D. student
Prof. Dr. med. Nikolaus Plesnila, PI
Dr. rer. nat. Caroline Prell-Schicker, postdoctoral researcher
Dr. rer. nat. Matthias Prestel, postdoctoral researcher
Katharina Rawnsley, student assistant
Dorothea Reinartz, outpatient office
Dipl. rer. nat. Stefan Roth, Ph.D. student
Iga Rynarzewska, Ph.D. student
Dr. rer. nat. Eva Scharrer, postdoctoral researcher
Pierre Scheffler, Ph.D. student
Dr. med. vet. Manuela Schneider, postdoctoral researcher
Melanie Schneider, technical assistant
Kathrin Schüller, veterinarian
Charlotte Schwicht, Ph.D. student
Lee Simon-Vermot, M.Sc. Ph.D. student
Vikramjeet Singh, postdoctoral researcher
Viktoria Sokol, technichal assistant
Flavia Söllner, Ph.D. student
Alissa Starkmann, student assistant
Alexander Taylor, M.Sc. postdoctoral researcher
Lilo Thomas, director's office
Steffen Tiedt, clinician scientist, physician
Dipl. Soz.päd. (FH) Irene von Tiesenhausen, social worker
Marlies Tursch, animal care taker
Dipl. Psych. Elisabeth Unterauer, psychologist
Kristina Vincent, outpatient office
Tamara Voß, animal care taker
Dr. rer. nat. Karin Waegemann, study coordinator
Antonia Weingart, communication & events
Katharina Werchoturov, Ph.D. student
Irina Westermayer, Ph.D. student
Dr. med. Frank Wollenweber, senior physician, neurologist
Stefanie Wurster, veterinary assistant
Guangyao Yan, Ph.D. student
Andreas Zellner, M.Sc. Ph.D. student
Yifei Zhang, M.Sc. Ph.D. student
Dr. rer. nat. M.P.H. Vera Zietemann, epidemiologist
Adelgunde Zollver, study nurse

Local Partners

Synergy
DFG funded Excellence Cluster for Systems Neurology
www.synergy-munich.de

ISZM
Interdisciplinary Stroke Center Munich (ISZM),
Klinikum der Universität München
www.iszm.de

DZNE
German Center for Neurodegenerative Diseases
www.dzne.de

Munich Memory Alliance
Alliance of university-based memory clinics in Munich
www.memoryalliance.de

Dept. of Neurology
Klinikum der Universität München
www.nefo.med.uni-muenchen.de

Imprint

Institute for Stroke and Dementia Research (ISD)
Klinikum der Universität München
Campus Großhadern
Feodor-Lynen-Straße 17
81377 Munich
Germany

Phone +49 (0)89 4400-46019
Fax: +49 (0)89 4400-46010

E-Mail: isd@med.uni-muenchen.de
Internet: www.isd-muc.de

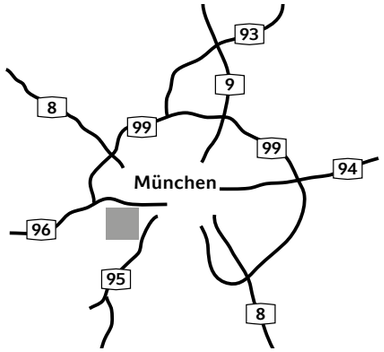
Responsible for contents:
Prof. Dr. med. Martin Dichgans, Director and Chairman | ISD
Markus A. Frühauf, Managing Director | ISD

Layout: Antonia Weingart | ISD
Photos: © Klinikum der Universität München, D. Lauffer, A. Weingart, A. Steeger, B. Woodward
© Firma BeluTec; shutterstock © Gina Sanders, © Alexander Raths

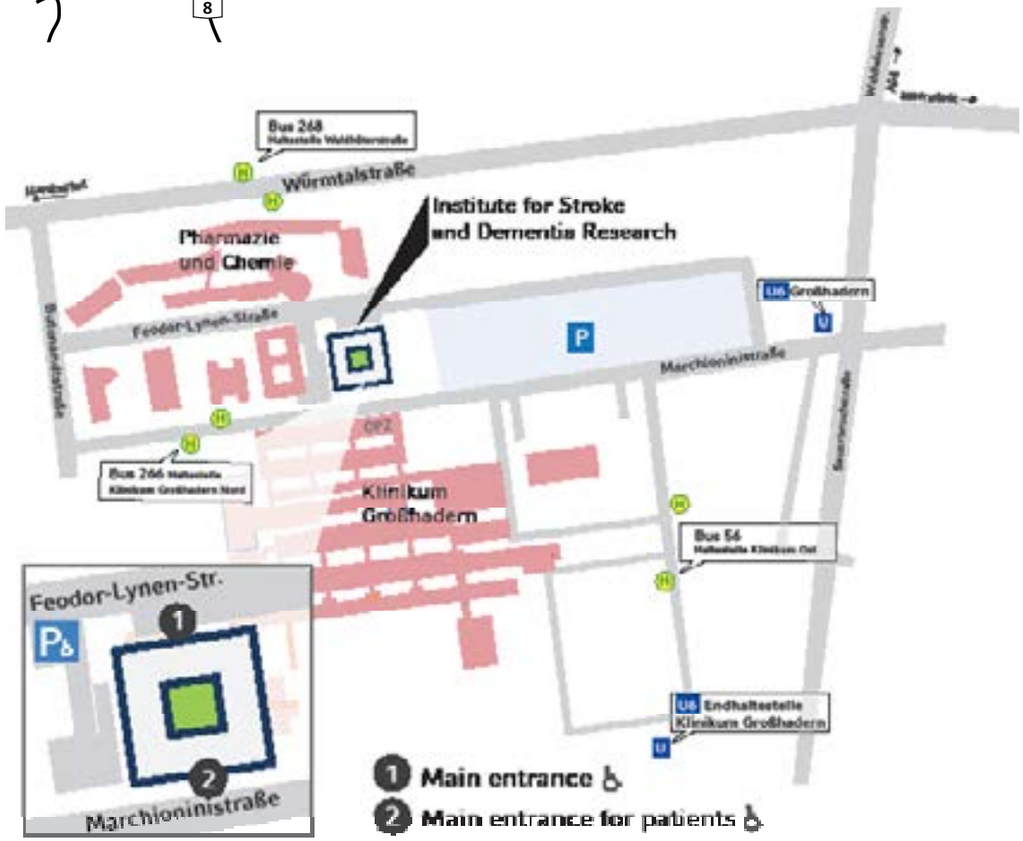
Printed by: PRINTello GmbH | www.printello.de

March 2015

How to get to the ISD



By public transport:
U-Bahn to “Großhadern”
Bus 56 to “Klinikum Ost” or
Bus 266 to “Marchioninistraße” or
Bus 268 “Waldhüterstraße”
By car:
From “Mittlerer Ring”,
take direction of “A95 Garmisch”,
follow signs to “Klinikum Großhadern”
Parking: see signs “Besucherparkplatz”



www.isd-muc.de