

## 4.1 Executive summary

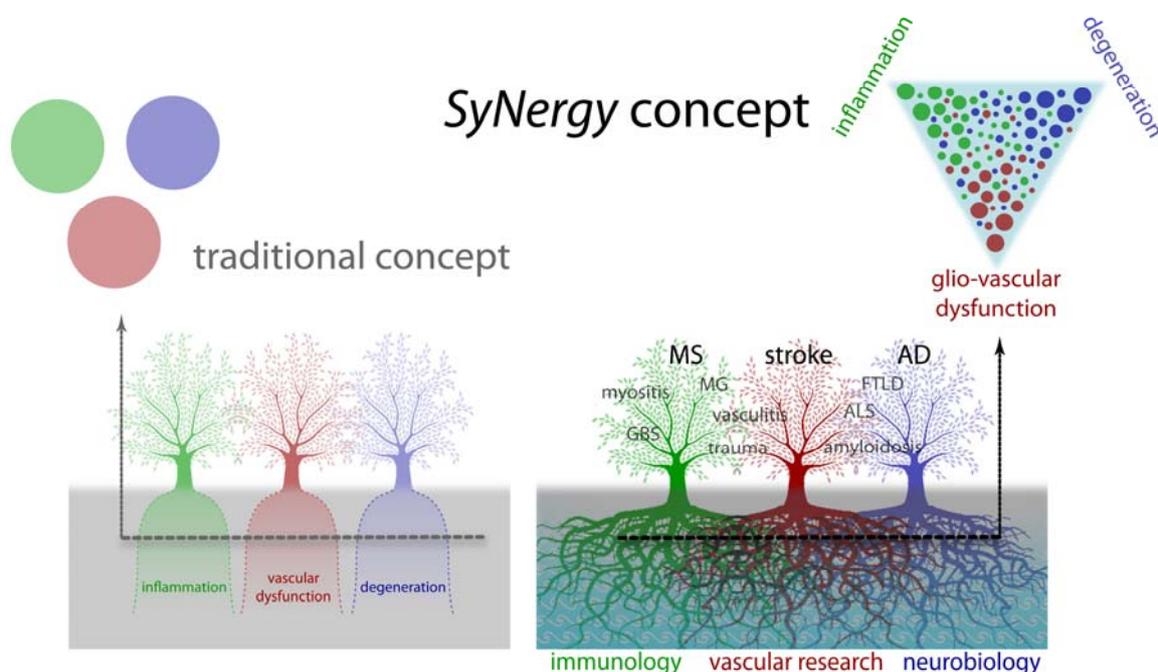
### Our mission and goals

Traditional nosology holds that neurological diseases can be separated

into mechanistically distinct families, including neurodegenerative, inflammatory and vascular conditions. Underlying this classification is the assumption that disease manifestations relate in a categorical fashion to a discernable mechanism. As a result, research efforts have traditionally reflected this categorization, and are mostly focussed on one or another of these mechanisms. However, recent insights have revealed a more complex relationship between different disease mechanisms and prompt a rethinking of the relationship between disease entities and their underlying mechanisms. **Such reassessment suggests that distinct disease manifestations can not be explained in isolation but instead all root in an intricate network of shared pathomechanisms (Figure 1).**

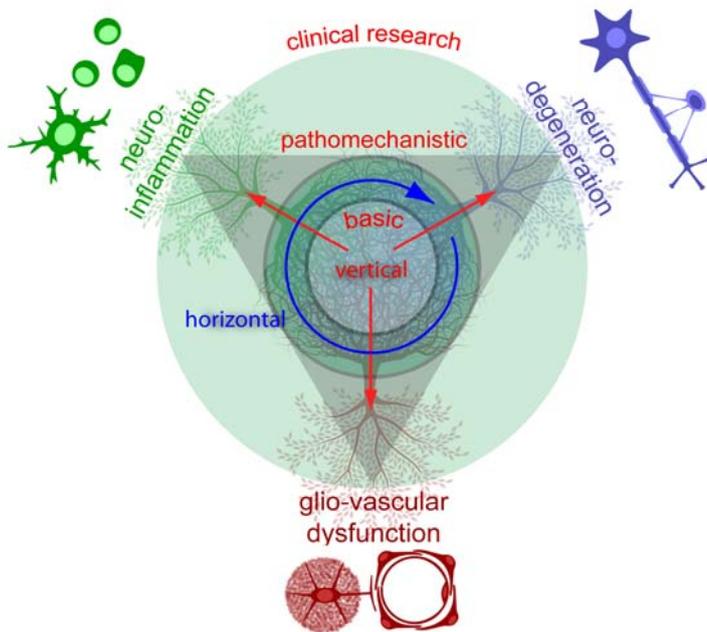
**Systems Neurology:** We define *systems neurology* as a new research field where systems biology and systems neuroscience meet with clinical neurology to generate an integrative understanding of how neurological diseases emerge from the interplay of degenerative, immune and vascular mechanisms.

To appropriately address these entangled “network” relationships, novel research tools and integrated approaches are needed. One approach that has been developed in basic life sciences to decipher such complex interactions and the resulting “emerging properties” is systems biology. Systems approaches have proven their power to analyse simple model organisms and the physiology of small neuronal networks, yet are only beginning to be applied to questions of immediate medical relevance. Neurological diseases meet the central theoretical tenet that motivates systems approaches: they affect one of the most complex biological systems, the



1 | Schematic comparison of the traditional nosological concept (left) and the SyNergy approach to neurological diseases (right).

human nervous system. While not all aspects of systems biology and systems neuroscience can be directly transferred into the realm of disease-oriented biomedical research, we believe that many of the tools that enable comprehensive quantitative study of dynamic systems are of direct relevance to the investigation of neurological disease. **The application of such tools and concepts to neurological diseases is currently emerging – a new field that we call “systems neurology”** (see definition on p.1).



2| Schematic representation of the transitional axes of the SyNergy approach and of the corresponding integrative role of the cluster.

The re-evaluation of how neurological diseases arise calls for new approaches on multiple levels. We therefore propose the establishment of the SyNergy cluster, a new research framework that will use an integrative approach to measure, model and modulate the emergence of neurological disease within intact organisms. **SyNergy aims to overcome the boundaries between traditional “pathomechanisms” by fostering close interdisciplinary collaboration (Figure 2).** This will be achieved (1) by establishing “**Tandem Projects**” that focus on links between

the pathomechanisms of degeneration, inflammation and glio-vascular dysfunction, ranging from basic to clinical research; and (2) by recruiting and promoting young “rising-star” scientists as “**SyNergy Professors**” to bridge the gaps between isolated pathomechanisms. With these instruments, the SyNergy cluster aims to establish an internationally recognized research center for systems neurology. Furthermore, SyNergy will establish dedicated programs to provide **early career researchers** with structured education and early independence, to aid and integrate **international scholars** and to promote **gender equality** and **young families**. As the combination of clinical and scientific skills is of particular importance for the success of SyNergy, we will install new measures to support **clinician-scientists**, including a clinical fast track program and independent research groups (“SyNergy Clinician-Scientist Groups”).

## Our infrastructure and expertise

Coordinated by LMU Munich, the SyNergy cluster is a **collaborative initiative of LMU and TUM**, joined in their commitment to strengthen neuroscience and clinical translation. Our initiative is based on the outstanding expertise and infrastructure in **pathomechanistic neurological research** at the two universities, and the numerous non-university institutions in Munich, as well as many current initiatives (see **box** to right). This expertise is flanked by **strong research efforts in systems neuroscience**, which will allow us to address the higher-level functional disturbances and plasticity (e.g., sensory or cognitive) involved in neurological disease. This neuroscience expertise is mirrored by a **focus on systems biology** both within the universities, as well as at the Max Planck Institutes and the Helmholtz Center Munich (HMGU). As a result of these initiatives, a superb infrastructure for establishing systems neurology research already exists. This infrastructure will serve as a basis for the SyNergy cluster, and is complemented by a **dense network of institutions dedicated to translational neurological research** in neurodegeneration (DZNE), neuroinflammation (INIM) and vascular dysfunction (ISD). Thus, new research findings can seamlessly be integrated into existing efforts aimed at clinical translation – aided by collaboration with the recently established industry partnership alliance, the BMBF-funded “**Munich Biotech Cluster m<sup>4</sup>** for personalized medicine”. **Major ongoing building initiatives**, namely the construction of the Biomedical Center (BMC) and the DZNE/ISD building (shared by LMU and TUM research groups) at the “HighTech Campus Großhadern”, will further strengthen the environment for basic, translational and clinical neuroscience research (**Figure 3**). These new buildings will provide dedicated lab space modules for Clinician-Scientist Groups and will house the new SyNergy professors. These construction projects and the subsequent relocation of existing research groups will result in a **unique clustering of SyNergy scientists**. The strong support by both Munich Excellence Universities and the State of Bavaria ensures the **quick launch and long-term sustainability** of our measures.

## Current infrastructural initiatives

### Systems Biology

- Control of Regulatory Networks (CoReNe) / H.-W. Mewes, W. Wurst
- European Conditional Mouse Mutagenesis Program (EUCOMM) / W. Wurst
- German Mouse Clinic / W. Wurst
- Helmholtz Association for Mental Health in an Aging Society (HelMA) / W. Wurst
- Systems Biology of Metabotypes (SysMBO) / T. Meitinger, H.-W. Mewes

### Pathomechanisms and Systems Neuroscience

- Bernstein Centred for Computational Neuroscience München (BCCN) / A. Herz
- ForNeuroCell II / J. Winkler, M. Götz
- Graduate School for Systemic Neurosciences (GSN<sup>LMU</sup>) / B. Grothe
- Munich Center for Neurosciences (MCN<sup>LMU</sup>) / B. Grothe
- Research Training Group 1373: Brain Signaling: from Neurons to Circuits / A. Konnerth
- SFB 571 Autoimmune Reactions: From Manifestations and Mechanisms to Therapy / R. Hohlfeld
- SFB 596 Molecular Mechanisms of Neurodegeneration / C. Haass
- SFB 870 Assembly and Function of Neuronal Circuits in Sensory Processing / B. Grothe

### Clinical Neurology and Translation

- Competence Network Multiple Sclerosis - Control-MS Consortium/ B. Hemmer
- German Center for Neurodegenerative Diseases München (DZNE) / C. Haass
- Institute of Clinical Neuroimmunology (INIM) / R. Hohlfeld
- Institute for Stroke and Dementia Research (ISD) / M. Dichgans
- Integrated Research and Treatment Center for Vertigo, Oculomotor and Movement Disorders (IFB) / T. Brandt
- m<sup>4</sup> Munich Biotech Cluster for Personalized Medicine / H. Domdev, P. Bartenstein

## Our measures

SyNergy will accomplish its aims as follows:

- **Tandem Projects:** These are highly collaborative research projects aimed at improving our understanding of degenerative, inflammatory and glio-vascular disease. The projects combine expertise across traditional pathomechanisms, as well as systems biology and systems neuroscience tools. Furthermore, in many projects research efforts of basic scientists and clinicians are bundled. This allows us to combine approaches that range from *in vitro* models to investigator-initiated trials. Three Research Areas have been specified (see *below*). Importantly, the portfolio of projects within the cluster is not static, but allows for addition of new projects and investigators as topics and techniques in systems neurology emerge.

- **SyNergy Professors:** We will recruit 5 new SyNergy Professors with expertise in disease-crossing research and systems neurology approaches. Two of these professorships have already been financed by LMU. Another three will be guaranteed by the host universities as part of the establishment of the cluster and will be integrated into the universities' tenure-track concepts.

- **Clinician-Scientist Groups:** To promote early career researchers and train clinician-scientists in the methods and concepts of systems neurology, we will offer attractive clinician-scientist packages that ensure full independence, while offering mentoring by senior scientists. The LMU and TUM neurology departments have agreed to implement a fast track towards board certification ("Facharzt") for these young neurologists.

- **Young scientists:** We will offer comprehensive training opportunities ranging from science exposure for high school pupils to promoting independence for post-docs. We will collaborate with 3 well-established Ph.D. programs (GSN, IMPRS-LS and TUM-Ph.D. program "*Medical Life Science and Technology*") to offer structured training and establish a "Systems Neurology Module" that will be integrated into the training programs of the collaborating schools. Post-docs will be given unique opportunities for early independence and international exchange.

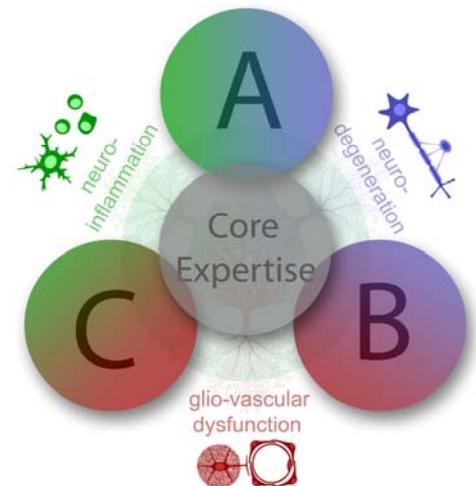
- **Gender equality, family and dual career support:** We will establish a career-stage specific gender and family support program that combines mentoring, financial help and gender mainstreaming to improve the career prospects of female and parent-scientist within SyNergy. Moreover, comprehensive dual career support will be provided by both universities.



3| Major construction projects are already underway and will create a unique concentration of SyNergy scientists at one site.

## Our research

SyNergy will invest about two thirds of its funding into research projects organized into **3 Research Areas (Figure 4)**, each targeted at one specific pathomechanistic “nexus”. These Research Areas will be complemented by a **Core Expertise**, which bundles systems neurology-specific expertise to make it accessible to all SyNergy projects. The Research Areas comprise up to three “**Nexus Complexes**” of projects, which are directed at related problems and bring together scientists with complementary pathomechanistic and core expertise:



4 | Research Areas and Core Expertise

## Research Area A – Inflammatory mechanisms of neurodegeneration

- A.I** **Shared cellular programs of neuroinflammation and neurodegeneration:** We plan to perform a comprehensive analysis of shared cell biological mechanisms of axon and synapse injury in degenerative and inflammatory conditions.
- A.II** **Determinants of inflammatory neurodegeneration:** We will identify molecular master regulators that act as brakes or accelerators of immune-mediated neural damage in MS.
- A.III** **Compensatory plasticity after neuroinflammatory and neurodegenerative injury:** We will investigate the compensatory response to inflammatory and degenerative damage at the neuronal network level.

## Research Area B – Bi-directional relationships between vascular dysfunction and degeneration

- B.I** **Targeting the interplay between vascular and neurodegenerative mechanisms in dementia:** We will explore the cross-talk between amyloid pathology and the neuro-vascular unit in animal models, but also a clinical study. In parallel, we will use a novel proteomics approaches to obtain an unbiased spectrum of proteins shed by A $\beta$ -generating proteases that need to be considered when modulating amyloid production.
- B.II** **Vascular dysfunction in ALS and FTLD:** This Nexus Complex is dedicated to testing the novel hypothesis that the functions of several proteins that are mutated in ALS/FTLD-U converge on neuro-vascular dysfunction.

## Research Area C – Glio-vascular response to inflammation

- C.I** **Bi-directional communication between the immune and vascular compartment:** Here we will determine how bi-directional interactions between T cells and glio-vascular components regulate immune cell entry into the CNS.
- C.II** **Systems biology of reactive glia in neuro-vascular, degenerative and inflammatory conditions:** We will perform a comprehensive analysis of the phenotypic spectrum of activated microglia and reactive astrocytes in inflammatory, ischemic and degenerative conditions of the nervous system.