The Helmholtz Virtual Institute „RNA dysmetabolism in ALS and FTD”

The Helmholtz Virtual Institute “RNA dysmetabolism in Amyotrophic Lateral Sclerosis” is one of over 100 Virtual Institutes that are funded by the Helmholtz Association. These institutes bring together the expertise of Helmholtz Centers with German universities and additional associated national and international partners on significant fields of research. The institutes are funded over a period of three to five years with up to 600,000 Euro yearly.

The German Center for Neurodegenerative Diseases (DZNE) regards ALS and FTD as neurodegenerative diseases with substantial medical and scientific significance with respect to the mission of the DZNE. Research in this field has been successfully expanded; currently, research on ALS and FTD is carried out in Dresden, Munich at the DZNE was brought together with the internationally recognized competence in the area of ALS and FTD of the Strasbourg (France) and Umeå (Sweden). The University Ulm is one of the most significant clinical research institutes in ALS and FTD, whose expertise ranges from basic research to highly specialized care for patients. Its neurobiobank comprises about 4000 patient-specific cell lines and 1000 blood and liquor samples. Together with the associated partners in Umeå and Strasbourg, one of the worldwide largest biobanks is available for research on ALS and FTD.

Research objective

Our scientific goal is to clarify the role of dysfunctional RNA metabolism in ALS and FTD with respect to the underlying mechanisms and the consequences for function and survival of nerve cells. In more detail, we want to investigate the pathomechanism of ALS and FTD linked mutations in FUS and C9ORF72 as well as the fundamental cell biological functions of these genes under physiological conditions, in particular with regard to cell metabolism and synapse formation.

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease with a prevalence of 6-8 in 100,000 people and occurs between the age of 40 and 80.
is characterized by the degeneration of upper motor neurons within the fibers. Their degeneration leads to a progressive muscle weakness and cases) onset. Most ALS patients die within 3 to 5 years after symptom contrast to sporadic ALS (SALS).

**Frontotemporal dementia (FTD)** is a neurodegenerative disease characterized by a progressive atrophy of the frontal and temporal lobes of the forebrain. FTD accounts for up to 15% of all dementia cases and thus is the third most common form of Lewy bodies. FTD occurs between the mid 40s and mid 60s of age and awareness, blunted emotionality and/or language impairment. 30-40% of all FTD cases are hereditary, thus called familial FTD.

Fuelled by new findings, the idea strengthened that pure forms of ALS and FTD can have FTD and vice versa (ALS-FTD) and patients which have primarily other disease.

Neuropathological hallmarks of the overlapping diseases represent ubiquitin-positive neuronal cytoplasmic inclusions (NCIs) composed of protein aggregates that contain TDP-43 (FTD/ALS-TDP) or FUS (ALS/FTD-FUS), tau aggregates can be found in non-overlapping FTD: FTD-tau. These pathologies appear in conjunction with distinct gene mutations: while mutations in genes for C9ORF72, GRN (Progranulin), TARDBP (TDP-43), and VCP cause TDP pathology, only FUS gene mutations lead to FUS bearing NCIs. Most recently discovered mutations in ALS and FTD are linked to RNA metabolism, either in form of mutated RNA binding proteins (TDP-43, FUS) or in form of a potential toxic RNA product (hexanucleotide repeat expansions of C9ORF72). This suggests that a disturbed RNA metabolism is involved in the etiology of ALS and FTD.

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**Scientific program**

**1. Cellular models of FUS and C9ORF72 in neurodegeneration**

- Tobias Böckers (Ulm University)
- Andreas Hermann, Alexander Storch (DZNE Dresden)
- Gerd Kempermann (DZNE Dresden)
- Peter Andersen (University of Umeå)

Here, the aim is to use stem cells to elucidate fundamental biological functions of the FUS and C9ORF72 in RNA metabolism and the consequences of their disease-related mutations in motoneuron degeneration and dementia. Somatic stem cell models of FUS and C9ORF72 in stem cell function, neurogenesis, motoneuron development and degeneration, and the potential usefulness of these genes as targets for therapeutic or preventive intervention.
2. Effect of RNA-related ALS gene mutations on energy metabolism

- Anke Witting, Patrick Weydt (Ulm University)
- Katrin Lindenberg (Ulm University)
- Philipp Kahle (DZNE Tübingen)
- Alexander Storch, Gerd Kempermann, Andreas Hermann (DZNE Dresden)
- Luc Dupuis, Jean-Philippe Loeffler (Inserm U692, Université Strasbourg)

Our goal is to study and compare effects of the mutations in FUS, TDP-43, and C9ORF72 on energy metabolism with the underlying hypothesis that defects in the pathways that control RNA metabolism will be critical for energy metabolism in ALS (and FTD) pathogenesis. Since effects of TDP-43 on mitochondrial morphology are known, we will focus on mitochondrial metabolism.

3. Synaptogenesis and synaptic plasticity

- Tobias Böckers (Ulm University)
- Alexander Storch, Andreas Hermann (DZNE Dresden)

Our aim is to further elucidate the extranuclear role and transport dynamics of FUS (including mutated FUS), with a focus on morphology and plasticity at excitatory synapses and neuromuscular junctions. We will investigate the interaction of FUS with Dynactin, an ALS-related protein that binds to microtubules and dynein. What is the functional role and importance of the interaction? Can mutations in Dynactin influence the functions or the subcellular localization of FUS or other RNA-binding proteins? In addition we pursue the initial characterization of C9ORF72 in primary neuronal cultures. Can a synaptic distribution of the protein be confirmed and what are the functional consequences?

4. Role of other protein deposits and co-aggregates in ALS and FTD

- Manuela Neumann (DZNE Tübingen)
- Christian Haass (DZNE München)
- Philipp Kahle (DZNE Tübingen)

The major aim here is to gain more insight into the full protein composition of inclusions among the various forms of FUSopathies and C9ORF72-linked TDPopathies. This will allow us to address the important question whether sequestration of other proteins and their subsequent functional depletion in neurons and glial cells is involved in FUS and C9ORF72-mediated neurodegeneration. Identificat
death in these conditions but might also lead to the identification of pror

Participants

- **DZNE Dresden:**
  - **Prof. Dr. Gerd Kempermann**
    Site Speaker
  - **Prof. Dr. Alexander Storch**
    Group Leader
  - **Dr. Dr. Andreas Hermann**
    Co-group leader & Senior neurologist at TU Dresden

- **DZNE Munich:**
  - **Prof. Dr. Dr. Christian Haass**
    Site Speaker

- **DZNE Tübingen:**
  - **Prof. Dr. Manuela Neumann**
    Group Leader
  - **Prof. Dr. Philipp Kahle**
    Group Leader at DZNE and Hertie Institute

- **German University Partner: University of Ulm**
  - **Prof. Dr. Albert C. Ludolph**
    Director and chair, Department of Neurology
  - **Dr. Katrin S. Lindenberg**
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Dr. Patrick Weydt
Neurologist, Department of Neurology

Dr. Anke Witting
Group Leader, Experimental Neurology, AG Neuroinflammation, Center

Prof. Dr. Tobias M. Böckers
Director of Institute, Institute for Anatomy & Cell Biology

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Prof. Dr. Peter M. Andersen
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News

- Munich, 31/8 - 2/9, 2016: Our Virtual Institute sponsors the "10th I

- Berlin, July 2015: Our Virtual Institute has very successfully passed
Ulm, May 29th, 2013: Tödliche Nervenkrankheit ALS: Stoffwechselfaktor PGC-1α beeinflusst Verlauf bei Männern

Ulm, January 11th, 2013: New Research Centres for Diseases of the Nervous System

Bonn/Ulm, June 29th, 2012: DZNE bekommt virtuelles Helmholtz-Institut

### Structure

**Steering Committee:**
- Gerd Kempermann, DZNE Dresden, Speaker of Virtual Institute
- Albert Ludolph, Ulm University, Vice-Speaker, Speaker of the University Partner
- Christian Haass, DZNE München
- Manuela Neumann, DZNE Tübingen

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