Frontotemporal lobar degeneration – from basic mechanisms and target identification to translational and clinical approaches

NOMIS / DZNE Project

The DZNE laid a superb groundwork to start a large interdisciplinary project, connecting basic research with clinical approaches. We will use Frontotemporal Lobar Degeneration (FTLD) as a prototype syndrome for which we want to provide mechanism-based therapy by combining our strength in basic and clinical research.

While all clinical approaches to slow memory decline of Alzheimer's disease patients have failed because treatment started too late at a time when the disease is already manifested or major side effects occurred because physiologically relevant functions of secretases were blocked, FTLD may provide a rather unique opportunity for treatment strategies. This especially holds true for gene mutation carriers.

Within our current studies several disease causing gene mutations have been identified and establishment of larger patient cohorts with individual mutations appears to be reasonable. Moreover, several of these gene products are not only obvious biomarkers such as Progranulin (PGRN), TREM2 (Triggering receptor on myeloid cells 2), or Dipeptide Repeat Proteins (DPRs) but may also serve as drug targets. With seven DZNE-sites, a virtual Helmholtz-Institute, a collaborating University Center in Ulm and more than 30 principal investigators involved we have set up a strong interdisciplinary network, which allows:

1. patient identification,
2. stratification,
3. genetic screening,
4. mechanistic research,
5. screening for disease modifying small molecules and
6. finally small prove of principle clinical trials.
Modelling frontotemporal lobar degeneration using patient-specific iPSC and iPSC-derived cortical neurons
PD Dr. Dr. Andreas Hermann
DZNE Dresden

PGRN: a therapeutic target and biomarker
Dr. Anja Capell / Prof. Dr. Dr. h.c. Christian Haass
DZNE Munich

Targeting DPR aggregation and seeding – from peptides to patients
Prof. Dr. Dieter Edbauer
DZNE Munich

Extracellular Tau Transmission
Prof. Dr. Günter Höglinger
DZNE Munich

TDP-43 posttranslational modifications with focus on phosphorylation
Prof. Dr. Manuela Neumann
DZNE Tübingen

TDP-43 posttranslational modifications with focus on ubiquitinylation
Prof. Dr. Philipp Kahle
DZNE Tübingen

**Epigenetics**
> Prof. Dr. Peter Heutink
DZNE Tübingen

**Core unit FTLD-TDP mouse models/ Role of TDP-43 in neurotrophic**
> Prof. Dr. Manuela Neumann / > Prof. Dr. Dieter Edbauer
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