Abstract for project pitch

CrossSeeds - Mechanisms of pathogenic protein cross-seeding in neurodegenerative disorders

Authors: Stephan Schilling[1], Anja Schulze[1], Hans-Ulrich Demuth[1], Maike Hartlage-Ruebsamen[2], Steffen Rossner[2], Julia Sepulveda[3], Jaime Fuentealba[3], Stéphane Hunot[3], Fabio Canneva[4], Sandra Moceri[4], Johanna Habermeyer[4], Stephan von Hörsten[4], Maja Puchades[5], Jan G. Bjaalie[5]

[1] Fraunhofer Institute for Cell Therapy and Immunology IZI, Department for Drug Design and Target Validation, Halle (Saale), Germany

[2]University of Leipzig, Paul-Flechsig-Institute for Brain Research, Leipzig, Germany

[3]Experimental Therapeutics of Parkinson's Disease, Brain and Spine Institute (ICM), Inserm UMRS 1127, CNRS UMR 7225, Sorbonne University, Paris, France

[4] UKEr and FAU, Dept Experimental Therapy and Preclinical Center, Erlangen, Germany

[5]University of Oslo, Institute of Basic Medical Sciences, Oslo, Norway

A characteristic feature of neurodegenerative diseases is the misfolding and deposition of proteins or protein fragments in the brain of patients, which results in progressive tissue damage, destruction of nerve cells associated with neuropsychiatric symptoms, including but not limited to cognitive impairment and dementia. Our project was based on the hypothesis that a number of brain disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington disease (HD) share common pathogenic mechanisms leading to neurodegeneration. Here, we aimed at analysis of a potential cross-talk of peptides leading to neurodegeneration. Against this background, the CrossSeeds project addressed the question of whether the aggregation and toxicity of the various peptides influenced each other. All partners combined experimental approaches ranging from in vitro aggregation and toxicity studies, cross-breeding and evaluation of protein aggregates distribution in different animal models to the establishment of an open database for the characterization of the time-dependent development of amyloid deposits in model systems.
In summary, the following main results could be achieved within the framework of the project:

1. Identification of mechanisms of pathological protein co-aggregation (cross-seeding).
2. Documentation of brain maps of pathogenic protein aggregates in a database. The results are shared in an open database on rbwb.org.
3. We have developed new tools and a workflow for image-based quantification of protein aggregates. This workflow will enable large scale studies and allow a better integration of results from many studies in different laboratories.
4. New animal models for protein-cross-seeding in vivo were established and their phenotype analyzed.
5. Demonstration of the cell type-specific expression of pathological proteins in brain and development of (ELISA) tests for the detection of amyloid conglomerates in tissue.
6. Identification of novel pathogenic protein aggregates in brain of human subjects.

Taken together, the results indicate that it is very likely that various amyloid peptides affect their aggregation and may therefore be responsible for the symptoms of neurodegenerative processes. We provide further evidence for the hypothesis that defined disease processes and variants of pathological proteins characteristic for a certain neurodegenerative disorder may also contribute to the clinical course of other diseases and that co-aggregation of these peptides occurs specifically associated with the clinical course of transgenic mice and rats. The results provide the basis for further development of antibodies against disease-specific protein modifications.