MyRIAD: (Micro)RNA and informatics approaches for diagnosis, prognosis and treatment of Alzheimer's disease and Dementia

Neurodegenerative disorders are associated with genetic causes that manifest with changes in core cellular mechanisms and changes in the expression of specific genes, resulting in milder to a very severe phenotype. Research results suggest that genes, with pathogenic variants associated with early-onset neurodegeneration, are dysregulated in neurodegenerative conditions, such as Alzheimer's disease (AD). The advent of omics approaches highlighted multiple novel pathways likely involved in AD, however functional approaches are lacking. There is an urgent need for a better understanding of the mechanisms underlying AD and the spectrum of undiagnosed neurodegenerative diseases.

Early detection is a key factor in modifying disease course. To date, definitive diagnosis often requires post-mortem examination of brain tissue. While a number of biomarkers are available (e.g. PET, MRI, CSF markers), their utility is limited by costs, limited patient acceptability or poor scalability. Circulating and extracellular vesicles- (EV-) enriched microRNAs, small non-coding RNAs, hold a promising potential as diagnostic and prognostic non-invasive biomarkers of AD and other neurodegenerative conditions. One of the earliest reported events during disease initiation in cells is redox imbalance, and by-products of RNA oxidation have been detected in patients with AD. Our data support microRNA oxidation, a newly discovered phenomenon, in neurodegeneration and their potential as specific biomarkers of early pathology.

This project will enhance current understanding of AD and neurodegenerative conditions through the discovery and validation of novel biomarkers and therapeutic targets. Systems biology approach based on existing and generated in this project omics datasets from different stages of neurodegeneration in AD will generate *in silico* model of neurodegeneration which will be further validated in human neuronal progenitors. Through RNA-based approaches (miR and ASOs), we will demonstrate the functional effect of modulating newly proposed candidate genes (including V-ATPase) on pathways related to neurodegeneration.

IBCH leads WP4: Harnessing the potential of RNA approaches to validate novel players in neurodegeneration and provide proof of principle for RNA therapies to ameliorate neurodegeneration in AD and beyond

Specific tasks lead by the IBCH PAS:

1. Design of novel approaches based on oligonucleotides for selected therapeutic targets related to neurodegeneration
2. Validation of the effectiveness of therapeutic approaches in advanced neuronal cell cultures
3. Identification of desirable and non-specific effects of tested oligonucleotides in neuronal cell lines derived from patients