INSTALZ
Genomic Instability in Alzheimer's Disease and Related Disorders: a Single-Cell Approach

Increasing evidence suggests that the genetic information in our brains varies from cell to cell. Aims: the INSTALZ consortium aims at understanding how cellular subtypes in the brain and altered stability of the neuronal genome and transcriptome in the developing and adult brain determine the risk of developing these chronic disorders in late adulthood.

We have used single-nuclei genome and transcriptome sequencing (snG&T-seq) technology, spatial transcriptomics and cell biological assays to address these questions in mouse models, *Drosophila* models and human AD and tauopathy brains. Societal challenge: INSTALZ addresses the need to precisely understand the mechanisms leading to neuronal degeneration at the single-cell level in order to develop more specific preventive and therapeutic strategies. (Expected) outcomes: We have used single-nuclei genome and transcriptome sequencing (snG&T-seq) technology, spatial transcriptomics and cell biological assays to address these questions in mouse models, *Drosophila* models and human AD and tauopathy brains.

Outcomes: Work is still ongoing but studies in the INSTALZ consortium have revealed the importance of (1) A□ plaque-related microglia-astroglia spatiotemporal crosstalk, (2) neuronal oligomeric tau-induced mitochondrial and DNA repair pro-survival pathways, (3) direct links between tau, DNA and the occurrence of single neuron aneuploidies/copy number variants. Successes and challenges: INSTALZ succesfully brought together partners that have never collaborated before. Budget problems represented the main challenges, in particular for the expensive snG&T-seq experiments in order to reach sufficient statistical power. Dissemination: The target group of INSTALZ has been the scientific community. INSTALZ and the JPND program were acknowledged in 6 published and 2 submitted research articles. At least six articles are ready for submission or in preparation. Results have been presented at several international scientific meetings.