In the human brain there are more than a hundred billion nerve cells. They are connected to each other through an infinitely complex network of nerve processes. While it has been a common belief that only neurons could be considered the building blocks of nervous data exchange, neuroscientists recently uncovered that also glial cells do affect certain physiological processes like synaptic connectivity. An understanding the complexity of the mammalian brain, its ability to multilayer data processing and storing as well as its dysfunctions, is not possible without gaining insights into the heterogeneity of cell types and subtypes residing the brain, their interactions and molecular functioning.

Less than 3% of the human genome generates protein-coding transcripts; however, the majority is dynamically transcribed into noncoding RNAs (ncRNAs). ncRNAs are emerging as key regulators that can orchestrate different aspects of gene expression and molecular functions. This applies to neurons, extremely structurally complex cells, where transport of RNA, local translation and precise spatially and temporarily orchestrated regulation of gene expression are essential to functionalize different cellular compartments. It has been discovered only recently that the nervous system is a hotspot for circular RNA (circRNA) expression. Interestingly, in the brain the overall enrichment for this newly discovered class of ncRNAs was observed in synaptic terminals. Yet, the functions of the vast majority of circRNAs, including brain- and synapse-enriched circRNAs, remain unknown to date.

The central hypothesis of this proposal is that circRNAs are a functionally relevant class of ncRNAs in the brain. Essentially, it is supported by the most recent insights on circRNA Cdr1as, which deficiency in the mouse brain caused a physiological (altered excitatory neurotransmission) and behavioral phenotype, reflected in deficits in sensorimotor gating associated with neuropsychiatric disorders [Piwecka et al. 2017]. **The main objective of the proposal is to study and gain more insights into circRNA biology in mammalian neurons and the brain.** I propose to use a mouse model and mouse primary neuronal and astrocyte cultures to study in-depth circRNA expression patterns across neural cell types residing the brain, their subcellular localization, interactions with proteins and other noncoding RNAs such as microRNAs. Additionally, we will perform circRNA loss-of-function studies and analyze the effects of circRNA deficiency on synaptic transmission. To this end, we will apply cutting-edge new technologies like single-cell RNA sequencing (scRNA-seq) and imaging of circRNA at single molecule resolution, along with developing new methods for studying circRNA interactions, circRNA knockdowns and electrophysiological recordings.

The ambition of this project is to take advantage of interdisciplinary efforts of molecular, cellular and systems biology as well as neurobiology to address the question of how circRNA shape the regulatory networks in neurons and other neural cell types. This novel approach holds promise to bring a substantial and beyond state-of-the-art advance in the understanding of RNA regulatory mechanisms in the brain and brain disorders.