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MINERVA

Microglia/neuron crosstalk in autism spectrum disorder: Role of early inflammatory activation

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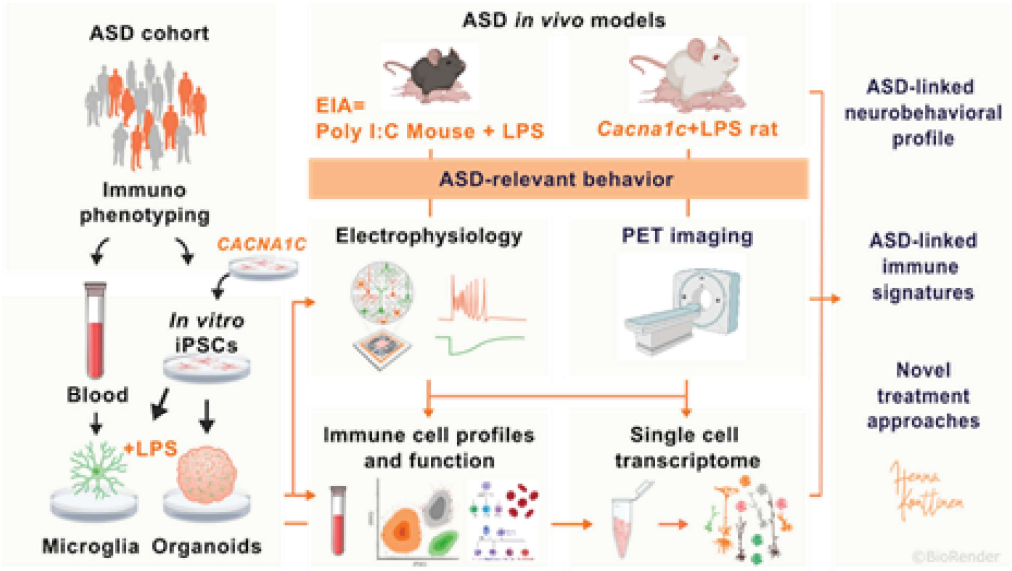
The goal of MINERVA is to understand how the immune system and genetic risk factors influence the activity of immune cells in the brain, the microglia, and their communication with neurons, and how these processes modulate neurodevelopmental alterations and the severity of autism spectrum disorder (ASD). The results of these studies will help to better understand the mechanisms of the immune system that are associated with ASD development and behavioral impairment. In addition, based on these results, innovative therapeutic approaches may be developed that target neuro-immune and behavioral deficits in ASD. In particular, we apply 3D-organoid cultures containing neurons and microglia, which are obtained from patient-derived stem cells, to investigate the close interplay between the immune cells and the neurons for development of a human neuronal network in a dish. Further, we investigate the effects of immune stimulation on early brain development and behavioral alterations in rodent models relevant to ASD. Comparing immune and metabolic signatures in the animal and cell models with ASD-patient samples, will allow evaluation of the potential translation of the data obtained in the experimental settings to the clinic, including potential therapeutic approaches.

We hypothesize that genetic risk factors, especially Cacna1 mutations, accelerate bioenergetic dysfunction and persistent pro-inflammatory activation of microglia and peripheral immune cells, which further drive malfunction in the microglia-neuron interaction and propagate the impact of maternal infections on E/I imbalance in the developing brain. This leads to sustained, lifelong consequences in modulating ASD phenotype and disease severity. We utilize samples, cells and clinical data from individuals with ASD and state-of-the-art human-based in vitro and in vivo models

to discover the molecular underpinnings of ASD and test potential treatment approaches. Combination of in vivo models, human cells and human-based 3D cerebral organoids provide an innovative international collaboration platform to discover disease mechanisms and test novel therapeutics that translate back to the clinic.



Impact : Novel therapeutic mechanisms // validation of novel innovative and translational models // Promotion of meaningful ASD patient involvement //Dissemination and communication