Platform 2: Preclinical developmental model platform – 5 year plan

Driven by newly identified predictors and modulators from the cohort platform our unique preclinical model platform will provide an integrative framework to study mechanisms of somatic and mental health trajectories. It will be central to the translational and transdiagnostic approach of CHILDHealth and the complimentarity to DZKJ partner institutions. The work packages (P) are: I) generation of models, II) multimodal phenotyping, target identification, preclinical interventions III) mechanism-based human translation.

P I will (i) define a sustainable resource of innovative models to investigate disease mechanisms, (ii) address genetic susceptibility using induced pluripotent stem cell (iPSC) models from patients with defined monogenic disease (e.g. Shank mutations) or low/high polygenic risk scores (e.g. ADHS) and (iii) assess the complex gene-environment interaction using scalable 2D/3D cell models [neurons, immune cells, blood-brain-barrier (BBB), blood-cerebrospinal-fluid-barrier (BCSFB), gut cells] and assembloids (organoids of different regional identities fused and functionally connected). Environmental factors include psychosocial stress (leading to changes in neurotransmitters and hormones such as cortisol or norepinephrine), activation of the immune system (cytokines, immune modulators), toxins or mediators originating from other organs (inflammatory signals, RNA, microbiome-induced metabolite alterations). Read-out parameters include structural changes and cellular morphologies, cellular function (biochemical assays, physiology including calcium imaging or multi electron arrays) and deep phenotyping by genomic approaches such as bulk and single cell transcriptomics, epigenomics, proteomics and lipidomics.

P II will use vertebrate models with increasing complexity (zebrafish, mouse, rat) and (i) disentangle the impact of genetic risk and adverse environmental factors in analogy to P 1 for complex phenotype dimensions (e.g. behavior, weight gain). (ii) We will pursue a transdiagnostic approach to study social processes (e.g. social interaction, social choice, trust, social reward and preference) in various animal models related to ADHD. For doing so rats will be examined in a 24/7 automated monitoring system for socially grouped animals in their home-cages to model dynamic disease trajectories, risk and resilience patterns. (iii) We will identify specific targets and modify those by pharmacological interventions (i.e. drugs, programmable RNA) or by standardized environmental changes. For example, we hypothesize that ADHD patients who are especially impaired in social behavior have a dysfunctional oxytocin system and that oxytocin as a co-treatment to classical methylphenidate and amphetamine, respectively, may improve the deficits in the social domain.

P III will (i) define molecular biotypes of patients with mental or somatic diseases/comorbidities and (ii) inform platform III with individualized biotype-specific intervention strategies to restore protective patterns.

Use case: As an example how mediators from the periphery impact on the multitude of models integrated in platform 2 we will analyze the gut microbiome – brain axis, as dysbiosis is a risk factor for sustained inflammation and contributes to adverse neurodevelopmental outcome in risk cohorts such as preterm infants. The entry of the different metabolites originating from the microbiome to the brain will be studied by our unique blood CSF models. Neuronal cultures and brain organoids will be exposed to these metabolites at different time points of development and maturity, morphological and functional changes will be assessed in parallel to transcriptional programs and potential epigenetic alterations and scars. The endeavor is paralleled by animal models. Additionally, gut microbiota from children with risk profiles can be transplanted in germ-free animals to study the influence of the microbiome and metabolome on somatic and mental health outcomes and to investigate whether potentially beneficial modulators could rescue the phenotype. Positive results of those preclinical treatment trials could provide a basis for future clinical studies along the translational chain.

Gantt Chart Platform 2

	GANTT Chart	Year 1	Year 2	Year 3	Year 4	Year 5
P1	**Generation of models for transdiagnostic developmental trajectories**					
MS1.1	Define essential models					
MS1.2	Build infrastructure for core facilities (3R, robotics, scRNA seq)					
MS1.3	Generate models from iPSC to address genetic susceptibility					
MS1.4	Generate 2D/3D models to address gene-environment interaction					
P2	**Multimodal phenotyping in models of increasing complexity**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
MS2.1	Multimodal phenotyping and gene-environment interaction					
MS2.2	Longitudinal assessment of specific targets, risk and resilience markers					
MS2.3	Pre-clinical interventions by drugs, programmable RNA etc.					
P3	**Back translation into humans**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
MS3.1	Define molecular biotypes of disease phenotypes in human cohorts					
MS3.2	Restoration of protective patterns by biotype-individualized intervention					