Julia Ladewig

After I completing my studies in biology at the university of Bielefeld, Germany (with distinction; 1,0*) in 2003 I spend one year abroad at the Imperial College in London where I obtained a Master of Science degree in Medical Ethics (funded by a scholarship of the German Academic Exchange Service (DAAD)). Following my studies I joined the Institute of Reconstructive Neurobiology, University of Bonn, Germany by the end of 2004 as junior research fellow. Finalizing my doctoral degree (Dr. rer. nat., magna cum laude) in 2009 I continued my scientific career in Bonn as a Postdoc. In 2014 I was awarded with an independent junior research group. In 2018 I received a Group Leader position at the Hector Institute of Translational Brain Research (HITBR) at the ZI in Mannheim.

Throughout my past and present research works, I was using human pluripotent stem cells (PSCs) as a tool to generate specific cell populations of the human brain and to exploit neuronal physiology, stem cell-based brain regeneration as well as neurodevelopmental, degenerative and psychiatric disorders. This fact demonstrates my strong interest in the application of PSC-based model systems to study human brain development and function. During my early time in this area, I developed a lineage selection protocol for the isolation of young PSC-derived human neurons. This work was published with me as first author in 'Stem Cells' in 2008. I also establish a highly efficient protocol to generate human neurons directly from somatic cells (iNs). This work was published with me as first author in 'Nature Methods' in 2012. Next to this focus, I was involved in several studies concentrating on different neurodegenerative diseases such as Alzheimer's Disease and ataxia which led to multiped co-author publications in renowned journals including 'Nature, 'Proceedings of the National Academy of Sciences' (PNAS) and 'Molecular Therapy'. I got then interested in neuronal behavior and used PSC-derived neurons to study neuronal migration and integration. This work was published in 2014 in 'Nature Neuroscience' with me as first author. These studies turned my attention to more developmental aspects of neuronal migration: the migration of neurons during cortical development. Consequently, I applied for and secured my first independent funding in 2011 (Young Investigator Start Up Funding, 2011-2012, 'Modeling cortical migration defects using patient-specific induced neurons') to follow my distinct research interest within the Institute. I continued on this research and extended into the field of human brain development with an additional funding from BONFOR (University of Bonn BONFOR Program, 2012-2013). In 2014, I secured my own independent Junior Research Group and established my own lab. Since then, I focused on the understanding of human cortical development in health and disease. I exploited the self-organizing capacity of PSCs into brain organoids and started to study neurodevelopmental disorders using this cellular model. Specifically, I developed the organoid technique further to generate homogeneous forebrain specific organotypic structures *in vitro.* With this system I was equipped with a reliable *in vitro* model for studying the mechanisms controlling cell diversity and positioning in the developing human cerebral cortex in health and changes associated with developmental malformations. In 2017, I could place my first corresponding author publication in 'Cell Reports' describing our developed organoid-based model and its application to model a severe malformation of cortical development, the Miller-Dieker Syndrom. Here we identified for the first time that a non-cell autonomous defect in ß-catenin signaling contributes to the phenotypic changes described in our in vitro disease model. During this early times as principle investigator I received the young investigator award of the German Society of Stem Cell Research and secured my first European consortium funding: 'Stem cells and mechanisms contributing to human cortical malformations', funded by the

Neuron Network of European Funding for Neuroscience Research. This funding was the start of a serious of fruitful interactions with renowned national and international researcher in the field. Since 2018 I am group leader at the Hector Institute for Translational Brain Research in Mannheim focusing on applying brain organoids to study human brain development and associated psychiatric disorders. I use the opportunity at the ZI to unravel molecular mechanism leading to psychiatric disorders and to develop therapeutic approaches for them. My credo is that you first need to understand the disease mechanism before you can develop effective therapies. In this context I am also asking the question whether human specific aspects of brain development might be associated not only with higher brain function but also with psychiatric disorders. To further exploit the organoid technology to study- and interfere with psychiatric disorders we are also developing organoid models mirroring complex circuitries of the human brain such as the dopaminergic and serotonergic pathway. Here we are generating organoids representing distinct brain regions and aim to fuse them in the order found in vivo. We are applying these systems to study reward and depression. Besides studying molecular bases of psychiatric disease, I am applying the organoid technology for therapeutic approaches. In this context I could successfully raise third-party funds as part of the European funding measure E-Rare/ European Joint Program on Rare Diseases (EJP-RF), to apply our organoid model to Rett Syndrome, an early childhood brain disorder. I started the project in March 2021 together with leading scientists from Italy, Spain and France, which aims to use the CRISPR/Cas9 technology coupled with AAV-mediated delivery to develop a personalized MECP2 gene therapy. My contribution is to use patient-specific forebrain organoids to test the efficiency of the gene-therapy tool kit. In addition, I could secure DFG funding since I started at the ZI, including one focusing on using cortical forebrain organoids to decipher molecular mechanisms involved in EML1-induced ribbon-like subcortical heterotopia, a malformation of cortical development associated with mental retardation and epilepsy. The output of this project involves a publication in ‘EMBO Reports’ in 2022 with me as corresponding author.
Overall, I have published during my research career 21 peer reviewed research articles with an h-index of 18 and an i10-index of 19 which were cited more than 2916 times in total (according to google scholar). I am experienced in teaching and supervising PhD, MD, Bachelor and Master theses and in leading an independent research group currently consisting of 2 Postdocs, 4 PhD Students, 2 Master Students and a Technician.

Key output of the years 2020-now

Major achievements in the last 2 years include several publications: one on a human cerebral organoid-based model for EML1-linked human cortical malformation entitled: ‘iPSC-derived cerebral organoids reveal progenitor pathology in EML1-linked cortical malformation’ (EMBO Reports, 23;5:e54027), another work focusing on human brain development association to a gene connected to bipolar disorders which is entitled: “Human-specific ARHGAP11B ensures human-like basal progenitor levels in hominid cerebral organoids” (accepted at EMBO Reports), as well as a review article entitled: ‘Cerebral organoids to unravel the mechanisms underlying malformations of human cortical development’ (Semin Cell Dev Biol. doi:10.1016/j.semcdb.2020.06.001). All three articles were created in my research group with me as corresponding author. They show that the experimental tool I am using is capable to recapitulate certain aspects of human brain development and associated disorders. In addition, I, as well as members of my team, contributed as co-author(s) to a voltametric approach for characterizing the biophysical and chemical functionality of human induced pluripotent stem

cell-derived serotonin neurons (Anal Chem. 28:94(25):8856) and to a study investigating asymmetric Notch activity in human neural stem cell (Science advances, eabl5792). These co-author publications show the fruitful interaction between the working group of Professor Koch (Head of the HITBR) and my team. Due to the different publications, I am well known in the field and are accordingly invited to present my work in talks including a talk at the annual meeting of the German Stem Cell Network in 2022. Further, I received with my team several travel awards for scientific excellence from the International Society of Stem Cell Research as well as from the German Stem Cell Network showing that our work is appreciated in the scientific community. In this context I would like to mention, that out of 5 available travel awards for the annual meeting of the German Stem Cell Network 3 were given to members of my team. In addition, I like to highlight the very good team spirit and enthusiasm of the members of my group for their work which suggests that I am capable of motivating young scientists. This good team spirit is for instanced reflected by an outreach project of the members of my group where they got involved in the Color Squared project and redesigned a junction box in K5, Mannheim. Here they show their fascination for their work at the HITBR and want to bring it closer to the public (https://www.zi-mannheim.de/institut/news-detail/zi-forscherinnen-bringen-farbe-in-die-nachbarschaft.html).