Philipp Koch
*11.11.1974
Head of the Department for Translational Brain Research

Academic profile

I was appointed as Professor for Stem Cell Research in Psychiatry and Head of the Department of Translational Brain Research at the CIMH in October 2017 when I started to build up a research team focusing on driving stem cell research towards translation and application in psychiatry. Originally, I am educated as a medical doctor and was in the process of specializing for neuropathology at the University of Bonn, Germany, when I first came in contact with human pluripotent stem cells (that time human embryonic stem cells) in 2003 right after the German parliament approved the first import of this newly available and fascinating cell type in Germany. From that moment, I have been working at the forefront of human pluripotent stem cell research in Germany with several seminal contributions covering enabling techniques and application (e.g. Koch et al., PNAS, 2009, doi: 10.1073/pnas.0808387106; Ladewig et al and Koch, Nature Methods 2012, doi: 10.1038/nmeth.1972; Ladewig*, Koch* et al, Nature Neuroscience 2014, doi: 10.1038/nn.3583). As a group leader at the Institute of Reconstructive Neurobiology in Bonn, Germany and with the advent of human induced pluripotent stem cells (iPS cells), I focused on investigating and modeling neurodegenerative disease applying cell generated from patients (e.g. Koch et al., Nature 2011, doi: 10.1038/nature10671; Mertens et al., and Koch, 2013, 2014, doi: 10.1016/j.stemcr.2013.10.011, doi: 10.1016/j.ajpath.2013.01.043; Doerr et al. and Koch 2014, doi: 10.1038/mt.2015.106). While in the context of neurodegenerative disorders, my work was mostly based on defined genetic alterations with clear genotype – phenotype relationships, my work at the CIMH started to tackle the challenge of how to address cellular phenotypes from much less defined patient cohorts. In psychiatry we are confronted with patients showing diverse and overlapping clinical presentations of different spectra of psychiatric disorders, with complex polygenic etiologies and often unclear environmental priming. With the generous support of the Hector Stiftung II which is funding my group and position, as well as the junior group of developmental brain pathologies in my department, I set up and equipped a modern cell phenotyping laboratory at the CIMH with a core platform for iPS cell generation and quality control and a platform for the phenotypic characterization of cellular phenotypes including morphometric parameters and functionality.

'The vision behind my work is to use stem cell-based unbiased molecular phenotyping as a basis for patient stratification, personalized drug discovery and treatment.'

In iPS cell derived cultures, phenotypes are solely based on genetics as epigenetic engrams of the patients are deleted during the process of iPS cell generation and the environment is under complete experimental control. In our work, we perform detailed molecular phenotyping of disease-associated cells including neurons of different neurotransmitter phenotype or regional identity, glia and/or microglia, both as pure cultures and in interaction paradigms. Our phenotyping is based on a complex multiparametric assessment of patients' cells including morphometric parameters, functional parameters and multi-OMICs profiles. This endeavor aims at stratifying patients into defined molecular biotypes and to identify subgroup-specific molecular targets for drug discovery.

Once identified such targets we aim setting up automated, paralleled and standardized assays for drug discovery by high content screening. Performing drug discovery directly in iPS cell-

derived neural cultures from such biotype-stratified individuals should minimize artefacts due to molecular heterogeneity and an inadequate cellular physiology, and should at the same time provide information about toxicology of a certain compound to predict the insurgence of side effects in authentic human brain cells. Secondary screens based on complex cellular models such as cerebral organoids should further reduce the number of false-positive hits processed into the subsequent steps of drug discovery. Thus, in such a refined pipeline, iPS cell-based systems will streamline drug development by biotype stratification, target identification and validation eventually leading to precise “mechanistic” pharmacological intervention and accordingly to the development of the so-called “precision psychiatry.”

We dedicated the first 5 years of our research to set up patient repositories, and deep phenotyping of cells originating from multiple neuropsychiatric disorders. In collaboration with the translation platform KSILINK in Strasbourg, France we set up a proof of principle screen in 384 well plates on human neurons, defined assessment and readout parameters and developed a multiparametric classification combining several molecular features by AI-based discrimination. We are currently in the phase of translating the molecular phenotypes identified in our research of the first years to high content formats. Our vision for the upcoming years is supported by the Hector Stiftung II by financing a completely automated high content screening platform at the CIMH which we plan to set up mid of 2023. In this in-house facility, we will concentrate on repurposing drugs and compounds for fast clinical translation and develop assays further for industrial partnerships. I am participating principle investigator in the newly forming German Center for Mental Health where we aim to harmonize and connect stem cell research in psychiatry across the participating German centers. Next to the funding of the Hector foundation the department secured substantial third-party funding (> 3 Mio Euros in the last 5 years), including several BMBF and DFG grants.

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Key Output 2020-today

1.)

Voltammetric Appoarch for Characterizing the Biophysical and Chemical Functionality of Human Induced Pluripotent Stem Cell-Derived Serotonin Neurons

Holmes J, Lau T, Saylor R, Fernández-Novel N, Hersey M, Keen D, Hampel L, Horschitz S, Ladewig J, Parke B, Reed MC, Nijhout HF, Best J, **Koch P***, Hashemi P*. **Anal Chem.** 2022 Jun 28;94(25):8847-8856. doi: 10.1021/acs.analchem.1c05082. Epub 2022 Jun 17. (*corresponding authors)

Alterations in serotonin signaling are considered to contribute to the development of several psychiatric diseases including depression and autism spectrum disease. IPSCs provide an attractive new tool to address changes associated with such disorders but in particular to develop drugs which influence serotonin homeostasis and release. Together with Parastoo Hashemi, a biochemical engineer and pioneer in fast scan cyclic voltammetry working at the King’s College in London we provide the first detail biophysical and chemical characterization of serotonin neurons derived from pluripotent stem cell sources. I our work we were able to demonstrate real time serotonin release and analyzed kinetic properties induced by amino acids and antidepressive drugs. The publication is an important milestone demonstrating the applicability of specialized human brain cells for modern pharmacology and drug discovery.

Asymmetric Notch activity by differential inheritance of lysosomes in human neural stem cells

Bohl B, Jabali A, Ladewig J, **Koch P.** **Sci Adv.** 2022 Feb 11;8(6):eabl5792. doi: 10.1126/sciadv.abl5792. Epub 2022 Feb 11.

Understanding brain development using of human cell culture models as ever been a focus of our research. The investigation of human brain development is the basis for understanding pathologies and eventually targeting biological processes by drugs. In this publication, we were the first to demonstrate a so far unrecognized mechanism of how Notch signaling is distributed asymmetrically into dividing neural stem cell siblings via lysosomes. Our contribution greatly widens our knowledge about fundamental mechanisms of neural stemness, demonstrating the complexity of such processes in mammalian and especially human cells compared to simple model organisms such as flies of worms.
https://idw-online.de/de/news?print=1&id=788360

3.)
Human cerebral organoids reveal progenitor pathology in EML1-linked cortical malformation
Jabali A, Hoffrichter A, Uzquiano A, Marsoner F, Wilkens R, Siekmann M, Bohl B, Rossetti AC, Horschitz S, **Koch P**, Francis F, Ladewig J. **EMBO Rep.** 2022 May 4;23(5):e54027. doi: 10.15252/embr.202154027. Epub 2022 Mar 15. PMID: 35289477

One main focus of the department is the work on 3dimensional models of the brain (brain organoids). The work is mainly supervised by the research group leader Dr. Julia Ladewig who is leading the 'Developmental Pathologies' Team. In our work, we are addressing structural and molecular changes caused by developmental disorders leading to mental retardation, epilepsy and psychiatric disease.
https://idw-online.de/en/news790528

4.)
ALS-linked KIF5a deltaExon27 mutant causes neuronal toxicity through gain-of-function
Pant DC, Parameswaran J, Rao L, Loss I, Chilukuri G, Parlato R, Shi L, Glass JD, Bassell GJ, **Koch P**, Yilmaz R, Weishaupt JH, Gennerich A, Jiang J. **EMBO Rep.** 2022 Aug 3;23(8):e54234. doi: 10.15252/embr.202154234. Epub 2022 Jun 23. PMID: 35735139

hiPSC-Derived Schwan n Cells Influence Myogenic Differentiation in Neuromuscular Cocultures
Hörner SJ, Couturier N, Bruch R, **Koch P**, Hafner M, Rudolf R. **Cells**. 2021 Nov 24;10(12):3292. doi: 10.3390/cells10123292.

C9orf72-derived arginine-containing dipeptide repeats associate with axonal transport machinery and impede microtubule-based motility
Fumagalli L, Young FL, Boeynaems S, De Decker M, Mehta AR, Swijsen A, Fazal R, Guo W, Moisse M, Beckers J, Dedeene L, Selvaraj BT, Vandoorne T, Madan V, van Blitterswijk M, Raitcheva D, McCampbell A, Poesen K, Gitler AD, **Koch P**, Berghe PV, Thal DR, Verfaillie C, Chandran S, Van Den Bosch L, Bullock SL, Van Damme P. **Sci Adv.** 2021 Apr 9;7(15):eabg3013. doi: 10.1126/sciadv.abg3013. Print 2021 Apr.

The department is closely interacting with several preclinical and clinical research groups, both, locally and internationally. Here, we contribute with our deep and substantial knowledge

about iPS cell based brain models and disease. In all of the above-listed joined publications, researchers from partner groups were visiting scientists at our department and were trained in iPS cell enabling techniques. We consider interaction and knowledge transfer of such techniques as one of our research missions.