Marcus Meinhardt

Academic Profile:

"From Mechanisms to Rigorous Efficacy Studies"

The core vison of my research is to promote preclinical research **data quality and integrity** in order to develop **novel therapeutic approaches** in the field of substance disorders (SUD), ultimately providing go/no-go decisions for clinical development. Techniques that I apply range from classical molecular & biochemical methods, innovative transgenic *in vivo* manipulations to state-of-the-art neuroimaging approaches (Positron Emission Tomography and Magnetic Resonance Imaging) in preclinical animal models for addiction and associated comorbidities. Since 2021, I am head of the newly established research group ***Translational Psychopharmacology,*** bridging preclinical research (Institute for Psychopharmacology) to clinical work (Department of Molecular Neuroimaging) at the Central Institute of Mental Health in Mannheim (CIMH). I have a background in biotechnology and neuroscience with particular expertise in the field of preclinical behavioral neuroscience, molecular biology, and neuroimaging research methods. Additionally, I have intensive pharmaceutical industry experience, including pre-clinical target development, CNS pharmacokinetics and quality management.

The current focus of my research can be divided into three pillars:

1. The identification of innovative new treatments as well as mechanisms of action for SUDs.
2. Improving ethics for the use of animals towards narrowing the translational gap in psychiatry
3. Preclinical efficacy studies under highest scientific standards

Current pharmacological treatments have limited efficacy, thus better treatments that can be easily translated into the clinical situation are warranted. My recent preclinical research has identified the **metabotropic glutamate receptor 2** (mGluR2) as a potential treatment target for SUDs. However, further detailed characterization of the receptor in alcohol dependence is needed in order to understand its role in alcohol relapse and to generate treatment strategies. Additionally, current pharmacological compounds directly targeting the mGluR2 generate severe side effects, meaning that the receptor dysregulation has to be tackled from other angles in order to meet clinical needs. Therefore, I am conducting research in the **first research pillar**, to i) manifest the role of prefrontal mGluR2 in **alcohol relapse** ii) investigate the **(epigenetic) mechanisms** of downregulated receptor function and iii) **develop treatment** opportunities that restore mGluR2 function and have **a high translational value**, which is all supported by a personal DFG grant (ME 5279/3-1). This work is closely related to a project of the collaborate research center *Transregio* 265-B08 project, since alcohol-dependent patients commonly show impairments in executive functions that facilitate craving and can lead to relapse. Within the TRR265-B08, I explore impairments in executive functions in rodent discounting tasks, investigate common molecular mechanisms for **cognitive impairments**, and increased craving in alcoholism. The TRR265-B08 is a highly translational project and involves close collaboration with the division for Clinical Psychology at the Central Institute of

Mental Health (Prof Dr. Kirsch) and the Department of Theoretical Neuroscience & Clinic for Psychiatry and Psychotherapy (Dr. Georgia Koppe). In addition, I am a project leader for two further translational TRR265 sub-projects, investigating longitudinal dynamical state transitions (A05: Prof. Spanagel; Dr. Noori, both CIMH) as well as sex hormone variations (A08: Dr. Lenz, CIMH) on trajectories of losing and regaining control over alcohol use. Here, I am using a DSM-5 based model for alcohol addiction with a high predictive power, which enables to uniquely monitor disease trajectories in a prospective manner under precisely controlled conditions.

The **second pillar** focusses on data integrity and research rigor in preclinical research. This pillar is based on the fact that I believe that good animal welfare is linked to the quality of research data generated from laboratory animals, their validity as models of human disease and the reproducibility of animal studies. Therefore, I promote that an improvement of the ethics and practices in the use of animals through the implementation of a quality system is essential to close the translational gap in psychiatric research. A key component in this concept was the establishment of the **3R-Center Rhine-Neckar @ CIMH in 2021** (funded by the Ministry of Science, Research and Arts Baden-Württemberg) for animal experimentation in psychiatry. The center is dedicated to the 3R animal welfare principles (3R: reduce, refine, replace whenever possible) and to strengthen the validity, robustness, and rigor of preclinical data to enable a smoother, faster and safer transition from preclinical to clinical testing and drug approval (see www.3r-rn.de). Prof. Rainer Spanagel and I are both founders of the center and have partners from the two medical and the biosciences faculties of the Heidelberg University. Several movements in the field, e.g. from 3 to 6Rs (by adding robustness, registration and reporting) are already picking up speed, however, I want to go a step further and suggest the use of a preclinical quality system, called **EQIPD** (European Quality in Preclinical Research). This quality system ensures that robust and reliable preclinical data are generated, while being lean and effective, thus overall promoting and accelerating the **development of new innovations and treatments**. It is also optimally adapted to the unique needs of non-regulated biomedical research.

The research line I pursue in the **third pillar** is highly interconnected to the principles and research of the two upper pillars. Identified drug candidates are tested further in a confirmatory mode in preclinical phase II multi-site efficacy studies under highest quality standards. Currently, I am project leader/PI of three ongoing multi-site trials. The **AhEAD project** (www.ahead-study.de, funded by the BMBF) pursues the aim of testing the long-lasting efficacy and safety of intranasal, anti-inflammatory exosome treatment in male and female rats in models on alcohol drinking and relapse behavior. This project is in collaboration with the Charité Berlin (Prof. Christine Winter) and the University of Erlangen (Prof. Christian Müller). With the same collaborators, preclinical phase II multi-site efficacy studies are performed to explore the efficacy of Oxytocin as innovative new treatment option for alcohol dependence in the **Target-OXY project** (funded by the BMBF). This project is build up as tandem project and has a clinical partner at the Clinic for Addictive Behavior and Addiction Medicine at the CIMH (Prof. Falk Kiefer). The third ongoing multi-center trial within the **PsiAlc project** (www.psialc.org, funded by the BMBF) investigates the efficacy and safety of psilocybin in male and female rats in models on alcohol drinking and relapse behavior. This project is in collaboration with partners from INSERM Amiens (Prof. Mickael Naassila) and the University of Camerino (Prof. Roberto Ciccocioppo).

Key Output of the Years 2020-now

Key outputs of my work has focused on applying innovative neuroscientific research methods on the above outlined three research pillars. The basis for the mechanistic studies and target validation was set in my work back in 2013 (Meinhardt et al., 2013). Here, we could show that the **mGluR2 loss** in the rodent and human corticoaccumbal neurocircuitry is a **major consequence of alcohol dependence** and a key pathophysiological mechanism mediating increased propensity to relapse and that normalization of mGluR2 function within this brain circuit may be of therapeutic value. In the following years, we could demonstrate a causal link between reduced prefrontal mGluR2 function and both impaired executive control and alcohol craving, using a bidirectional neuromodulation approach. In this context, a neuron-specific prefrontal mGluR2 knockdown in rats generated a phenotype of reduced cognitive flexibility and excessive alcohol seeking. Conversely, virally restoring prefrontal mGluR2 levels in alcohol-dependent rats rescued these pathological behaviors. With this in mind, I searched for a pharmacological intervention with high translational potential. **Psilocybin, the active ingredient of magic mushrooms,** was a substance capable of restoring mGluR2 expression and reducing relapse behavior (Meinhardt et al., 2021). Psilocybin is now evaluated further in multi-center studies, as mentioned above. Moreover, we recently investigate mechanistic effects of psilocybin on brain networks in AUD (Reinwald et al., 2022).

Additionally, I evaluated several new mechanisms of action for SUDs. I could show that beta-arrestin 2 expression is differentially regulated in alcohol dependence, which has direct implication on the rewarding properties of alcohol via the μ-opioid receptors (Meinhardt et al., 2022). **Beta-arrestin 2** expression also showed a daily rhythmicity linked to an inverse pattern of μ-opioid receptors, suggesting an involvement for beta-arrestin 2 on circadian regulation of G-protein coupled receptors in alcohol dependence. Therefore, these data may explain different treatment efficacies in human alcoholics, and thus suggesting the development of novel bArr2-related treatment targets. In another mechanistic research project, we investigated epigenetic alterations in alcohol dependence and found that dysregulation of the histone demethylase "**KDM6B**" in alcohol dependence is associated with epigenetic regulation of inflammatory signaling pathways (Johnstone et al., 2021). These findings implicate a novel KDM6B-mediated epigenetic signaling pathway integrated with inflammatory signaling pathways that are known to underlie the development of alcohol addiction. Based on these results, we initiated a program to evaluate anti-inflammatory substances for AUD within the AhEAD project

Within the 3R Center Rhine-Neckar, I was able to build up a 3R/6R infrastructure, developed 3R/6R tools, trainings and dissemination strategies and provide them on the website (www.3r-rn.de). Furthermore, I integrated the 3R Center Rhine-Neckar into 3R-networks accross Europe @ **norecopa** (https://norecopa.no/3r-guide/3r-center-rhein-neckar) and the **EU3Rnet**. Together with all partners of EU3Rnet, we started a publication series; the first manuscript was released in May 2022 (Neuhaus et al., 2022).

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