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I am genuinely interested in the process of translating scientific knowledge into clinical applications. While my primary curiosity in neuroscience was sparked by the molecular biologist's idea that genes can directly influence behavior, guided by my experiences as a psychiatrist I also have a keen mind for potential clinical applications. Along my way I developed an interest in addictive behaviors and the consequences of heavy alcohol use, which are the focus of my working groups for Molecular Psychopharmacology and Translational Addiction Research at the IoP. My research brings together diverse experimental approaches to assess addiction on multiple levels ranging from molecular, cellular and circuit level to behavior and clinical outcomes. I have a special interest in finding brain processes that can be objectively compared between humans and experimental animals (mostly rodents) and may comprise potential biomarkers for therapy development in AUD.
My professional carrier led me through several top-level research institutes and I was fortunate to work with eminent scientists in the fields of neuroscience and addiction which enabled me with a very broad view on research and clinical praxis to understand and combat AUD. These experiences brought me into the position to develop two highly integrative European research initiatives on alcohol research and to lead these consortia. As a testimony to the breath of my scientific approach, besides scientific publications, my work was awarded by very different organizations both in terms of standing and different philosophies (e.g. Lundbeck and German Alliance for Addiction Support). In the following, I will provide some highlights of my career as a translational researcher.

Studies and doctoral thesis (1981-1992)
Already during my medical studies, I became fascinated by the rapidly developing possibilities for genetic engineering. Thus, after receiving the license to practice I turned to molecular biology and started a thesis project on mRNA based viral vectors for gene therapy at the Central Institute for Molecular Biology in Berlin-Buch. Over the German reunification I graduated, left with the experience of how science can offer a place of comfort in times of turmoil, for better and worse.

Postdoc and residency at the Karolinska Institute (1992 - 2004).
Coming from East Germany, a postdoc abroad was a must. I met Prof. Kjell Fuxe of the Karolinska Institute in Stockholm and he quickly inspired me with his enthusiasm for

neuroscience. We began studies of targeted *in vivo* gene regulation in the brains of laboratory animals and were the first to show that behavior can be manipulated by local changes in gene expression using antisense techniques against the transcription factor cFos (*PNAS 1996*). Seeing how animals turned their path to the tune of these molecules and studying the underlying mechanisms was highly fascinating. These results continue to influence my research activities to this day. Two stays in the US and Canada gave me further important impulses. At the invitation of Prof. Donald Pfaff at Rockefeller Institute, I could gain insight into the fundamentals of viral gene transfer into the brain. With HFSPO support I visited the lab of Prof. Harry Robertson at Dalhousie University in Halifax, a leading researcher on the role of the c-Fos in the brain and the emerging field of transcriptome-wide analysis. These visits allowed me to be the first to introduce such procedures into animal addiction research (*Mol. Psychiatry 2000*), for which I received Lundbeck awards of the Scandinavian Society for Neuropsychopharmacology in 2000 and 2003.
Although I am strongly fascinated by basic neurobiological research, I increasingly lacked a connection to medical problems. At this stage, I met a like-minded Swedish physician-scientist, Dr. Markus Heilig, who introduced me to the clinical and scientific problems of addictive disorders, and who became my mentor and collegial friend for many years. The scientific fruits of this collaboration were the development of a new animal model for alcohol dependence (*Faseb J 2002*) that became the gold standard in the field for many years and a translational research approach to explore new pharmacological mechanisms of action for the treatment of alcohol addiction. In parallel from 1995 to 2001, I was a resident at the Psychiatric Clinic at Karolinska Hospital, and then worked as a consulting senior physician mainly in the field of addiction treatment. In 2003, I was appointed as a lecturer in psychiatry at the Karolinska Institute (equivalent to German habilitation).

Unit Director at NIAAA (2004-2008)
In 2004, I received an offer from Dr. Heilig who had been appointed as the clinical director of the National Institute on Alcohol Abuse and Alcoholism to continue our medication development program together at NIAAA. The decision to leave the Karolinska Institute and with it the prospect of an independent research group was not easy for me. In the end, and I saw the prospects at the NIH as the greater and more exciting challenge. At the NIAAA, I took over the establishment of the Molecular Pathology Unit. This new lab, which I led until 2008, was involved in a variety of studies ranging from animal experimental work in rodents and monkeys, genetic and neuroimaging studies, to drug testing, and encompassing a wide range of methods. As my main work from this period, I would like to mention the functional validation of the CRH system as a pharmacological target for relapse-preventive drugs (*Biol. Psychiatry 2008*), which was instrumental in initiating clinical trials of CRH1 receptor antagonists by NIAAA. The trivial outcome of these trials was an intellectual shock for the field and profoundly altered my thinking whether and how findings from animal models can be translated to the human condition.

At CIMH (since 2008).
Despite the excellent working conditions at NIH and good integration into US addiction research networks, my family and I did not want to stay in the US permanently. I was therefore excited to receive an offer by Prof. Rainer Spanagel (Head of IoP) to set up my own research group at CIMH which allowed me to return to Germany after 17 years abroad. The CIMH provided exciting new opportunities for me. I tried to approach the translational crisis by identifying objectively comparable responses in the brain of humans and rats. MRI seemed the right tool to do so, and we quickly succeeded in demonstrating surprisingly

similar increases in central glutamate levels during acute alcohol withdrawal (Biol. Psychiatry 2012). This was recognized as an exemplary study for translational research in psychiatry, and laid the foundation for a competitive concept resulting in two European network grants (ERA-Net TRANSALC, Horizon 2020 SyBil-AA). We also uncovered a novel pathophysiological mechanism for alcohol's damaging effects on the brain, that is reduction in signaling by the metabotrop glutamate receptor type 2 (mGluR2) in the prefrontal cortex of humans and rodents (J. Neuroscience 2013). Since then, the prefrontal cortex has kept me fascinated and triggered new research lines ranging from how alcohol-associated memory content is represented in the brain, to biased decision making in addicted humans and animals, and to the mechanistic underpinnings of psilocybin-assisted psychotherapy.
To conclude, I see myself as a highly integrative person and this is reflected in my research endeavors. To succeed with such an approach requires a truly collegial environment and collaborative spirit, which I have found at the CIMH thereby providing me with a scientific home.

Key output of the years 2020-now:

1. Meinhardt et al**.** 2021 *Sci Adv.* Psilocybin targets a common molecular mechanism for cognitive impairment and increased craving in alcoholism.

   This is a comprehensive follow-up of our previous discovery of a prefrontal mGluR2 deficit in alcohol dependent rats and humans (J. Neuroscience 2013). Here, we establish causality for the mGluR2 deficit to important behavioral shortcomings in addiction and presented a potential rescue strategy with psilocybin thereby suggesting a molecular mechanism for the drug's long-term anti-addictive effects observed in humans. The study received wide attention in the social media (Altimetric score 589) and we were invited to a *Neuropsychopharmacology Hot Topic* commentary (Meinhardt & Sommer in press)

2. De Santis et al. 2020 *Sci Adv*. Chronic alcohol consumption alters extracellular space geometry and transmitter diffusion in the brain.
   De Santis et al. 2019 *JAMA Psychiatry.* Microstructural White Matter Alterations in Men With Alcohol Use Disorder and Rats With Excessive Alcohol Consumption During Early Abstinence.

   These two companion papers represent a major output of the SyBil-AA collaboration. We report the main effects on grey and white matter microstructure caused by chronic excessive alcohol using diffusion tensor imaging in humans and rodents. We found astoundingly similar sensitivity and specificity, thus providing a strong basis for translational inference and potential biomarker development. We found that 1) chronic alcohol changes the diffusion properties in the extracellular space, a so far unrecognized mechanism of action of alcohol with likely implications for extra-synaptic neurotransmission; 2) cessation of alcohol drinking results in progressive white matter deterioration persisting for several weeks into abstinence, a so far unknown development that should be considered in rehabilitation programs; and 3) these effects are causally linked to a microglia response, which could be a potential therapeutic target. The studies received large attention in the public and social media (Altimetric score 416) and were awarded with two national prizes for clinical and basic

addiction research (Wolfram-Keup-Preis des Bundesverbands Suchthilfe 2020, Wilhelm-Feuerlein-Preis der DG Sucht 2021)

3. Sommer WH et al. 2022 *Neuropharmacology.* From a systems view to spotting a hidden island: A narrative review implicating insula function in alcoholism.

   This review describes our systems approach to AUD that was developed by the SyBil-AA collaboration and summarizes major findings. A full discovery cycle is illustrated starting from MRI in animals and clinical populations that converged on the insula as a major hub of a 'relapse-prone' brain network to translational intervention studies for target validation and treatment development.

4. Bordier et al. 2022 *Addict Biol.* Increased network centrality of the anterior insula in early abstinence from alcohol.

   As one output from our SyBil-AA collaboration we introduce a novel, graph theoretical approach to analyze resting state fMRI data. Our statistically robust systems level, non-local, and essentially unbiased analyses converged on a few well-defined brain regions and identified the anterior insula as a hub region for a 'relapse-prone' network state in AUD patients.

5. Wandres et al. 2021 *Neuropharmacology*. Alcohol and sweet reward are encoded by distinct meta-ensembles.

   Here, in a follow-up paper to a deep characterization of reward memory-activated neuronal ensembles *(J. Neuroscience* 2018) we further develop the ensemble concept. We demonstrate that encoding of reward specific memories may not solely depend on the activity of local groups of activated neurons – as widely posited and experimentally approached – but must involve communication between brain-wide distributed ensembles, i.e. meta-ensembles. Introducing a statistically robust graph theoretical framework to the analyses of cFos-based ensembles we found that reward-specific meta-ensembles are highly dynamic, formed on demand and differently configured according to the reward. Notably, the anterior insula emerged as a key node for network control in the alcohol condition, further supporting a role for this structure in AUD.

6. Bach et al. 2020 *Addict Biol.* Incubation of neural alcohol cue reactivity after withdrawal and its blockade by naltrexone.

   In this clinical trial we show that an in rodents well-established incubation phenomenon, i.e. progressively increased drug seeking after forced abstinence, translates to AUD patients on the level of neural cue reactivity and craving. Importantly, using this information for predicting the response to naltrexone, the most common. But low efficacious (NNT > 12) approved anti-relapse medication for AUD, can dramatically improve clinical outcomes.