Rainer Spanagel, Ph.D. studied biology at the Universities of Tübingen and Munich and pursued his early training in behavioural pharmacology and neurochemistry at the Max Planck Institute (MPI) in Martinsried. In 1990, he moved to the MPI of Psychiatry in Munich and became head of the addiction research group and was awarded a lectureship in Pharmacology and Toxicology. In 2000, he relocated to Heidelberg University and the Central Institute of Mental Health (CIMH) in Mannheim, a leading European institution for biological psychiatry, to become scientific director of the Institute of Psychopharmacology. He is Editor-in-Chief of Addiction Biology. At the national level, he was spokesperson for the German Research Network Systems Medicine (e:Med) and is currently spokesperson for the German Network on Addiction (ReCoDe) (https://www.trr265.org/).

His academic career started at the Max Planck Institute (MPI) for Neurochemistry in Martinsried. Albert Herz and Toni Shippenberg became his mentors very early on and he was very fortunate to be in the right place at the right time – this was one of the three hot spots worldwide in opioid research at that time. He made a seminal discovery during his PhD, specifically the identification of the modulation of the reward pathway by the opposing actions of endogenous opioid systems. This discovery was crucial for understanding reward processes on a neurochemical level and laid the mechanistic foundation for the use of opioid antagonists to treat relapse in patients with alcohol use disorder.

In 1990, he moved to the MPI of Psychiatry in Munich (the Director at that time was Florian Holsboer). The main focus of the institute was corticotropin-releasing hormone (CRH) and stress-related disorders. Although the CRH-R1 receptor was already cloned, its *in vivo* function was not well characterized. Together with Wolfgang Wurst, he developed the first CRH-R1 knockout mouse model, which confirmed the role of the receptor in stress-responses and anxiety behavior. In follow-up studies, he made the very surprising discovery that the deletion of the CRH-R1 receptor resulted in enhanced stress-induced alcohol consumption, in stark contrast to the dogma that the lack or blockade of the receptor should diminish or even eliminate stress-induced effects. Despite the fact that this work was published in Science and was awarded the Sir Hans Krebs Award, the warning sign that CRH-R1 antagonists may not be clinically useful was ignored. At that time, there was no major pharmaceutical industry company that did not have a cost-intensive CRH-R1 program in place, and all clinical studies with promising CRH candidates eventually failed. Dr. Spanagel's work provided an early explanation of why this concept would fail, but more than $2 billion was invested for a largely negative clinical outcome. This should be seen as a prime example of how preclinical research can enrich human studies and that coordination between basic, preclinical and clinical researchers is needed to properly interpret results from animal studies.

In 2000, Dr. Spanagel moved to the ZI in Mannheim. There he researched the interaction between clock genes and psychiatric diseases. It was more than surprising to learn that clock genes not only control our day-night

rhythm, but also play a crucial role in stress- and drug-related diseases. This work made an important contribution to chronopharmacology.

Dr. Spanagel's main research efforts then focused on the clinical development of several anti-relapse agents. His research team has made exceptional translational contributions, as evidenced by the fact that they have developed DSM-based animal models to study addictive behavior. For example, his animal model of alcohol relapse has become the gold standard for the pharmaceutical industry. In collaboration with several pharmaceutical companies, his team has tested over 50 different putative anti-relapse agents in this model, some of which have been or are being further developed clinically.

Scientists working with laboratory animals are obliged to follow the so-called “3R principle”: refinement, reduction and replacement. For many years, the animal experiments at Dr. Spanagel research institute have been committed to the 3R principles. He established a 3R Center between the CIMH and the two medical and the biosciences faculties of the Heidelberg University – referred to as the now permanently funded 3R Center of the Rhine-Neckar Region. More recently he extended the 3R approach to 6R, to include robustness, registration and reporting, all of which aim to safeguard and increase the scientific value and reproducibility of animal research. For this, he developed guidelines to ensure the highest quality standards in preclinical research. In recognition of developing tools to increase ethical standards in animal research, he received the AREC Award from RSA in 2024.