Gerd Gründer

The department's work program for the next five to seven years is to evaluate the efficacy and safety of existing therapies, especially drug-based therapies, to improve their use in clinical practice, and to develop new therapies with improved efficacy and (especially long-term) tolerability. This clinically focused research is accompanied by studies on the mechanisms of action of these treatments. The department not only uses molecular imaging by means of positron emission tomography (PET), but also the entire range of methods available at the ZI.

After a two-year planning and application phase, in the summer of 2021 I began the largest science-initiated clinical trial of a psychedelic ever conducted anywhere in the world. In the EPIsoDE (“Efficacy and Safety of Psilocybin in Treatment-Resistant Depression”) study, 144 patients with treatment-resistant depression are being treated with either a high (25 mg) or low (5 mg) dose of psilocybin or an active placebo (100 mg nicotinamide). By mid-August 2022, almost half of the planned patients have been randomized. The study, which has attracted a great deal of attention far beyond Germany and has been extensively reported on in the press, has already led to an enormous increase in knowledge in the Mannheim and Berlin study teams. These findings are currently being incorporated into the planning of a much larger phase III study, which could begin in 2024 if the appropriate funding can be secured. In fact, I believe that psychedelic-assisted psychotherapy represents a paradigm shift in psychiatric (pharmaceutical) therapy. Unlike classic psychopharmacotherapy, which aims to correct neuronal dysfunction and neurochemical imbalances, psychedelic-assisted psychotherapy has salutogenic potential: it initiates change processes, promotes resilience and develops resources. My goal in the next ten years is the implementation of psychedelic-assisted psychotherapies in psychiatric care not only in Germany but in Europe. For this purpose, a further training curriculum for psychedelic therapists is being developed in cooperation with the MIND Foundation, Berlin. The first groups of therapists have been trained in Berlin since November 2021. The need for specially trained therapists will increase significantly in the coming years. At the same time, specialized clinics will emerge that not only have trained therapists, but also have the special architecture that must be regarded as the effective factor of these special treatments. Setting factors such as room, ward and building architecture are still given too little consideration in current psychiatry. So it will take an interdisciplinary effort to develop psychedelic medicine to its fullest potential. In order to embed this process in a broad public discourse, the INSIGHT 2023 Conference in Berlin (the largest European congress on the subject of psychedelics) will be co-designed in 2023, and a "citizens' forum" is planned in Berlin, the purpose of which is public discussion of the implementation of psychedelic medicine in culture and society. In addition to citizens, lawyers, ethicists, politicians, philosophers and journalists should also be involved.

The therapy research is accompanied by an extensive program to research the psychological and biological mechanisms of action of psychedelic- assisted psychotherapy. The currently largest fMRT study on the biological mechanisms of action of psychedelic therapies is already running as a supplement to the EPIsoDE study. Each patient is subjected to a concise fMRI battery at three time points (baseline, one and six weeks after the first dose of the substance). The special feature of this study is that all investigations are randomized and double-blind. Also from a methodological point of view, this study should therefore represent a milestone. An extensive program for examining biomarkers (microbiome, genetics,

epigenetics, inflammation markers, hormones, etc.), which are preserved at several points in the course of the study, supplements the study program.

For the future characterization of the binding behavior of psychedelics to 5-HT_{2A} serotonin receptors, a pair of radioligands is now being developed in a collaborative project at the Institute for Nuclear Chemistry at the University of Mainz (Prof. Patrick Riß). Based on the starting molecule M100,907, both an agonist and an antagonist at 5-HT_{2A} receptors are to be developed. So that the tracers can also be used at the ZI Mannheim (and other external institutions), they are provided with a fluorine-18 label. Such permits use on humans within a radius of 200 km and more around the place of manufacture.

The question of whether long-term pharmacological treament, which we have been carrying out as the clinical standard for decades, leads to adaptive brain changes that may negatively affect the clinical course of their disease in many patients has occupied me for a long time. In my opinion, such questions are still not discussed enough in our field. That was also the main motive for publishing a small textbook on the subject (in German; English "Stopping psychotropic drugs? Why, when and how?"; Elsevier 2021). In a PET/MR study with the radioligand [^{18}F]fallypride, I investigate the hypothesis that antipsychotic (long-term) therapy leads to the development of supersensitive dopamine receptors. The hybrid technology allows us on the one hand to quantify the availability of D_2-type dopamine receptors and on the other hand - in one session - to investigate the sensitivity of the receptor to dopaminergic stimulation by applying the dopamine agonist apomorphine. For the first time, the study will allow a definitive statement to be made as to whether long-term antipsychotic therapy may negatively affect the long-term course of the disease, at least in individual patients. The public reaction to dealing with the topic is so significant (e.g. numerous inquiries from those affected who find their psychiatrists neither listen to such questions nor support them in stopping their medication) that I will also deal more clinically with the topic in the future and would like to set up a special outpatient clinic for these questions.

I consider therapeutic drug monitoring (TDM) to be an important tool for improving the effectiveness and safety of psychiatric pharmacotherapy. To date, TDM is the only real tool for personalizing drug therapy in psychiatry. In clinical practice, it is often not yet accepted as a routine method because the relationships between blood levels and effects and side effects are considered to be insufficiently documented. In the last few years, my co-workers have submitted important papers that address the question of how a therapeutic reference range can be found and defined. Systematic reviews and meta-analyses have been presented for several of the world's most commonly used psychotropic drugs (aripiprazole, escitalopram, olanzapine, venlafaxine), which place pharmacotherapy with these substances on a more rational basis.

Finally, one of my particular concerns is the training and support of young scientists. I would also particularly like to support the training of "Clinician Scientists", i.e. the training of physicians who, in addition to clinical training as specialists, are also striving for a scientific career. In my department, I employ four half-time physicians who are training to become specialists with a further 50% in the Department of Psychiatry and Psychotherapy, as well as another half-time physician who is aiming for specialist training at a later date. In my department, more than 15 people from a wide variety of educational backgrounds (physicians, psychologists, pharmacists) are currently doing their doctorate, striving for either an Dr. med. or a Dr. sc. hum.

Key output of the years 2020-now

Since 2021 I have also started to establish myself in the field of psychedelics-assisted psychotherapy as an author. As editor of "Pharmacopsychiatry" I designed a “Special Issue” on "Psychedelics in Psychiatry" in 2021. In addition to an editorial (Gründer: Psychedelics: A New Treatment Paradigm in Psychiatry? Pharmacopsychiatry 2021; 54: 149-150), with which I introduce the issue, I have explained in my own contribution together with H. Jungaberle which special features of the therapy with psychedelics must be considered if these substances are to be included in clinical psychiatric routine (Gründer & Jungaberle, The Potential Role of Psychedelic Drugs in Mental Health Care of the Future. Pharmacopsychiatry 2021; 54: 191-199). The methodological considerations that led to the design of our EPIsoDE study have now also been published (Mertens et al., Methodological challenges in psychedelic drug trials: Efficacy and safety of psilocybin in treatment-resistant major depression (EPIsoDE) - Rational and study design Neuroscience Applied 2022; https://doi.org/10.1016/j.nsa.2022.100104). In it we also included some critical thoughts that we had published as a letter in the New England Journal of Medicine (Gründer & Mertens, N Engl J Med 2021; 385: 863). In a paper that has already been widely cited, we deal with the psychological mechanisms of action of psychedelic-assisted psychotherapy (Wolff et al., Learning to Let Go: A Cognitive-Behavioral Model of How Psychedelic Therapy Promotes Acceptance. Front Psychiatry 2020; 11: 5. doi: 10.3389/fpsyt.2020.00005), and in a German-language review we bring the topic closer to the German specialist public (Gründer et al., Sind Psychedelika schnellwirksame Antidepressiva? Nervenarzt 2022; 93: 254-262).

In more than 20 papers published since 2020, we have published our results on therapeutic drug monitoring (TDM) and the pharmacokinetics of psychotropic drugs. The two most significant among them are a consensus paper on the TDM of antipsychotics that was published in cooperation with the American Society of Clinical Psychopharmacology (Schoretsanitis et al., Blood Levels to Optimize Antipsychotic Treatment in Clinical Practice: A Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (J Clin Psychiatry 2020; 81: 19cs13169. doi: 10.4088/JCP.19cs13169), and the result of an international working group of the World Federation of Societies Biological Psychiatry (WFSBP), which I now lead, in which all currently available methods for personalizing therapy with antidepressants (TDM; pharmacogenetics, molecular neuroimaging) are comprehensively presented (Eap et al., Tools for optimizing pharmacotherapy in psychiatry (therapeutic drug monitoring, molecular brain imaging and pharmacogenetic tests): focus on antidepressants. World J Biol Psychiatry. 2021; 22:561-628. doi: 10.1080/15622975.2021.1878427). A paper first-authored by my graduate student, X. Hart, may be of fundamental importance for the development of TDM beyond psychiatry, as we set forth how future therapeutic reference ranges for drugs will be determined (Hart et al., Therapeutic Reference Ranges for Psychotropic Drugs: A Protocol for Systematic Reviews Front Psychiatry 2021;12:787043.doi:10.3389/fpsyt.2021.787043).

Finally, we participate in classic clinical trials. These are trials in which the pharmaceutical industry acts as a sponsor, but also publicly funded Investigator Initiated Trials. The most significant was recently published in the Lancet Psychiatry (Schmidt-Kraepelin et al.,

Amisulpride and olanzapine combination treatment versus each monotherapy in acutely ill patients with schizophrenia in Germany (COMBINE): a double-blind randomized controlled trial. Lancet Psychiatry 2022; 9 : 291-306).