6th ForTra Workshop for Translational Research:

Valuable lessons in the language of technology transfer

It is the dream of every clinician-scientist to successfully take their project from bench to bedside. However, this is not possible without building strong bridges. Building these bridges is similar to the process of translation. All the words written in the preclinical language must be translated into a clinical context. What was valid in the test tube, in cell culture, and in the animal model must prove its validity first in healthy humans and then in patients. This is an arduous task for anyone who is just an excellent scientist. It takes much more than scientific excellence to build and cross the bridge from the laboratory to the clinic. It requires knowledge of regulatory requirements, of how to get access to funding, and mastery of good manufacturing practices. These skills are not typically taught in medical schools or biotech programs. They are taught by ForTra gGmbH, the non-profit subsidiary of EKFS, a teacher who is not only knowledgeable but also has deep pockets. Since the start of the translational research program in 2017, funding of 31 projects by ForTra had been completed until September 2023, when a first success evaluation was initiated. Since then, 16 of these projects (which had received €12,403,000 funding from ForTra) have obtained follow-on funding from other sources totaling €123,624,533, a tenfold leverage of the original ForTra money. Three of these formely ForTra-funded projects were presented at the workshop and are described in the attached fact sheets. The educational qualities of ForTra in "teaching the language of technology transfer and all you need to know when your project leaves the bench", as its managing director Martin Zörnig put it, were once again demonstrated at the 6th Workshop for Translational Research held at the Goethe University in Frankfurt am Main on September 9 and 10, 2024, which was attended by 230 participants.

Its overarching theme was:
Financing and manufacturing – important things to consider to propel your project from lab to clinic.

Beyond that theme, and in addition, speakers from Fresenius and Sartorius provided insights into the innovation strategies of larger companies, and Bio Spring, founded in Frankfurt in 1997 by Ph.D. students from Goethe University, presented its success story. Once a small manufacturer of oligonucleotides, the company is now a "hidden champion" and world leader in the production of guide RNAs for genome editing. Klaus Cichutek, longtime president of the Paul Ehrlich Institute, explained how his agency supports the development of vaccines and biomedicines. A prominent patent attorney shared his knowledge on intellectual property due diligence, and a professor from Munich spoke about the effects of a ketogenic diet on chronic inflammatory processes.

Farewell to a wasteland of unmet medical needs
According to its overarching theme, presentations and panels dealing with financing and manufacturing were at the forefront of the workshop. But it was the keynote address by Dirk Jäger, managing director of the National Center for Tumor Diseases (NCT) in Heidelberg, Germany, that set the tone, providing an exemplary panoramic view of a wasteland of unmet medical needs and sketching a vision of a promised land of effective treatments and cures. "We are still limited in oncology," Jäger said. In most cases,

diagnoses were based on minimal morphological information and a few molecular markers. Worse, building on the results of large, randomized trials, oncologists tended to treat their patients as statistical entities, assuming that each should respond similarly or at least comparably to a predefined chemotherapy regimen. "We know that cancer patients are not really comparable to each other," said Jäger. "And in some centers, we look deeply at the profile of the individual tumor. But this is highly experimental and has not yet become part of daily routine." Presenting exciting concepts and data from his current research, he raised hopes that this might change in the not-too-distant future - based on individualized cell therapies.

Help from the private funding sector

Cell and gene therapies - advanced therapy medicinal products (ATMPs) in general - not only hold great promise, but they have also already proven their potential in recent years. In a pharmaceutical industry hungry for innovation to replenish its product pipelines, interest in ATMPs is growing, even if they are turning the traditional blockbuster business model upside-down. At the same time, interest in novel small molecules or monoclonal antibodies, for example, remains high as long as they offer a chance for sustainable medical innovation. This is a great opportunity for academic researchers to take their own ATMPs or other approaches into the clinic and then attract larger companies or start their own. But where will they get the money to do this? After public funding runs out, any bench-to-bedside translation will need the help of the private funding sector. This became clear in the discussions of a high-caliber panel with representatives of several funds and business angels dedicated to investing in the life sciences. Even in Germany, the chances of getting funding are not as bad as they sometimes seem.

Have the courage to share what you have

That's what the audience learned from the panelists, including the towering figure of Detlev Riesner, co-founder of Germany's largest biotech company Qiagen in 1985 and a tireless business angel ever since: More than a billion euros of venture capital (VC) is invested in German biotech every year, mainly by large funds such as Forbion or TVM Capital. However, every founder should be aware that VC is the most expensive capital they can get, due to the return requirements of the respective funds. Early-stage entrepreneurs should therefore try to get undiluted money. Although a billion euros is a relatively large amount of money, it is usually allocated to very few companies. A substantial funding gap exists in the translational seed stage before Series A. Business angels can only partially fill this gap. But what makes them indispensable is their combination of financial support and scientific advice. Their knowledge of both the project and the people (often their own PhD students) can mitigate the very high risk of outsourcing basic research. Spin-offs from university research, on the other hand, can receive early-stage funding from funds such as CARMA or Apollo Ventures (which specializes in age-related diseases). These funds are willing to take a risk and are often actively involved in the start-up process in collaboration with technology transfer offices. This help in building a company does not come for free. Commercial funds like Apollo take equity stakes beyond their investment. This reduces the founders' share. Since founders were usually excellent scientists but bad businessmen, they should have the character to share what they have, Detlev Riesner emphasized: "If you have two percent

of a well-run company, you are rich. If you have 50 percent of a company that is on the edge, you have sleepless nights."

Investors like that you asked and listened

No scientist seeking funding needs to approach an investor with a mature development package for his product. But even early-stage investors want to see at least an idea of how to get it into the clinic and how to structure its development there, not least to be able to estimate costs. This was confirmed by keynote speaker Jeff Skinner of London Business School, himself an experienced venture capitalist, when he spoke about "How not to waste seed funds". He reminded his audience that seed money is scarce and usually represents a one-time funding that must build a bridge to either positive operating cash flow, licensing or sale of the product, or a larger investment. He urged entrepreneurial scientists to be as specific as possible about what they want to do (product and business model), while writing a proposal that shows the big picture of why their project could be a promising opportunity. "Find investors and talk to them," Skinner said. "Investors like that you asked and listened. They invest in lines, not dots."

Investors are committed to excellent science

If investors are not presented with answers to some basic questions, such as a proven mode of action, pharmacokinetics, or early-stage toxicity, they will most likely not touch the product because they know pharma will not touch it. On the other hand, if they are convinced of the science behind the product, they will stick with it for a very long time and see it through thick and thin. For example, the bradykinin antagonist with the Hoechst AG laboratory code Hoe 140 was developed by former Hoechst scientists at their company Jerini under the name Icatibant for the treatment of hereditary angioedema. TVM Capital accompanied this development through several crises, including the crash of the Neuer Markt in Germany and a failed Phase III trial in the US, until Jerini was successfully sold to the British pharmaceutical company Shire for 500 million dollars. Subsequently, Icatibant, a product that was made in Germany and survived in Germany, achieved peak sales of $1.2 million annually for six years. However, some investors shy away from the binary risks of success or failure. Their funds can be attractive to academic spin-offs that seek to repurpose existing therapies or expand their indications. This is the case with the newly established Innovation Fund of the Fresenius group. Among other things, it is currently supporting the development of optimized equipment for the apheresis process in the production of CAR T cells.

How to navigate the regulatory waters

If it is difficult for a group of scientists to find a suitable investor for their promising project, it is almost intimidating to navigate the regulatory waters, especially when it comes to complying with Good Manufacturing Practice (GMP). However, this intimidation can be overcome, as several presentations by renowned experts in the field demonstrated. What is needed – besides money – is to understand regulatory science as a science in its own right, and to have a champion on your team who will work with the agencies as intelligently as possible. This means, above all, seeing them as partners in the development process and seeking their advice at least twice: once to integrate the CMC (Chemistry, Manufacturing and Controls) document into the target product profile at the beginning of preclinical development, and again before submitting the clinical trial application. It goes without saying that you should be well prepared for these meetings,

preferably with a briefing book. It is important to know that an agency will never answer open-ended questions such as "which development candidate is the best“ but will answer specific questions related to their agreement with a proposed development approach. The final stages of preclinical development, such as final toxicity and biodistribution studies, must be conducted with a GMP manufactured batch of product. It is advisable to book a slot with a contract manufacturer well in advance. The same is true for hiring a clinical research organization (CRO).

The continuous challenge of implementation

While the principles of GMP are easy to understand, they are challenging to implement: Raw materials must be of the highest quality, or the final product will be flawed. Facilities and equipment must be properly designed, maintained, cleaned, and periodically validated to ensure that they are fit for their intended purpose. Personnel must be adequately trained to perform their duties effectively. This includes understanding procedures and adhering to hygiene requirements. All procedures must be reviewed periodically to ensure that they use the latest technology and science in pharmaceutical manufacturing. All manufacturing processes must be followed and documented to ensure consistency and quality.

When laws lag behind dynamic technologies

The production of cellular therapies for personalized medicine follows the same principles. The optimal cell line must be selected, a research cell bank established, and a GMP-compliant master cell bank built. This is necessary for both the cells to be used therapeutically and the viral vectors that will transduce them with the appropriate genetic information. However, the research and development of cellular therapies is so dynamic that guidelines and laws lag behind the latest technologies. This may require researchers to be creative in designing their regulatory path and position, and then discussing their plans with regulators as partners in breaking new ground. The agencies are very open to this. Cellular therapies are living medicines with a short shelf-life ex vivo and a long persistence in the body. Developers are expected, for example, to provide a potency assay that measures the amount of drug administered and predicts the drug's fate in vivo. However, their mode of action is often too complex to be fully elucidated, making the assessment of their quality parameters an enormously difficult task. Obviously, the classical concepts of pharmacokinetics and pharmacodynamics do not apply to cell therapies.

GMP Is expensive for a reason

Nevertheless, it is clear that both German and European law require that these and all other ATMPs be developed under GMP conditions. To meet this requirement, it is not enough to purchase a few sophisticated pieces of equipment. It "takes a village," as one expert put it. Not only for ATMPs, but especially for ATMPs, ensuring GMP involves many interlocking functions and expertise. It is expensive for a reason. In larger institutions or companies, it is a task for almost every department in the organization, from facility management to IT, legal, pharmacovigilance, purchasing, quality management, and regulatory affairs. In academic settings or start-ups, not all of these functions may be available. In this case, it is advisable to seek professional support early on.

A GMP-based hope from Heidelberg

The NCT in Heidelberg has also hired experts for the GMP-compliant production of cell-based cancer therapies and, with the support of the Dietmar Hopp Foundation, is investing in the construction of a GMP facility that will be able to produce enough cells for the clinical trials with individualized immunotherapeutic approaches that Dirk Jäger and his colleagues are currently preparing. One of the most promising trials in preparation is based on a combination of vaccine approaches and T-cell strategies. It is based on the knowledge that checkpoint inhibitors only boost an existing immune response and that patients with low immunity therefore need an infusion of potent tumor immunity. To this end, Jäger and his team identify a specific tumor antigen in a cancer patient and develop a vaccine against it. Typically, injection of the vaccine leads to a strong inflammatory response at the vaccination site, which attracts many lymphocytes. By biopsying this site after two or three vaccinations, the tumor-antigen-specific T cells can be isolated and expanded without genetic modification. Infusion of these so-called vaccination site-infiltrating lymphocytes (VIL) can induce a strong anti-tumor response. A refractory patient developed an almost complete response of his brain metastases and is still alive one year after treatment. Of course, this is only one case. But it represents an approach worth pursuing. Jäger and his team are planning a prospective clinical trial with VIL. "We know we have to go through a lot of regulatory steps before we can start," Jäger said. "I hope to be able to show you data from our first phase I/II trial in two or three years."