Teaching translation – ForTra's second mission

If you don't know how to translate, you're likely to get lost in translation. This holds true for the ferryman and for the interpreter as well as for the biomedical researcher who strives to cross the bridge between the scientific promise of her findings and clinical practice. Yet while ferrymen and interpreters are trained in well-defined apprenticeships, translation from bench to bedside is rarely taught at medical schools and science faculties. Fortunately, however, the Else Kröner Fresenius Foundation (EKFS) has begun to fill this gap by offering comprehensive and complimentary workshops on biomedical translation. While these workshops involve all stakeholders in biomedical translation, the primary target audience is early-career researchers and clinician scientists from academia. The 5th such Workshop for Translational Research – organized by EKFS's non-profit subsidiary ForTra gGmbH – was held at Goethe University in Frankfurt am Main on 11th and 12th July 2023. Its overarching question was:

How can we improve the benefit of biomedical research for the patient?

In two key notes, 19 talks and one panel discussion – all embedded in lively discussions – the participants were provided with seven well-reasoned possible answers:

…by conducting excellent research
Excellent research and a thorough preclinical development of its findings are the preconditions for any successful translation of a biomedical project to its clinical application. This goes without saying, but it should be kept in mind. Five of such outstanding projects – introduced on the attached factsheets (page 4 and onwards) – were presented at the workshop. Their translation is financially supported by ForTra.

…by adhering to regulatory requirements early on
Biomedical researchers have to navigate an almost unfathomable variety of regulatory requirements in order to move their project forward to the patient. These requirements need to be met already during preclinical development shortly after lead optimization. It is not sufficient to design an assay only for publication. In parallel it should be validated according to the current regulatory rules in terms of bioanalytical methods and product characterization, for example. In the EU, these rules have only recently changed. They now follow the Clinical Trials Regulation (536/2014), which is in action since February 2022 and has become mandatory in March 2023. The audience of the ForTra Workshop learned to understand what this new regulation means: It allows for an authorization application via one single EU portal and thus fully harmonizes the procedure between the member states. This makes it easier to conduct multinational clinical trials, corresponding to the expectations of the pharmaceutical industry. Yet it substantially increases the workload both for the agency and the applicant – a challenge for academic research and development. A similar daunting challenge is posed by the new European Medical Device Regulation (45/2017), which entered into application in May 2021 (with several transitional provisions). In comparison to the previous legislation, it comprises three times more text. This makes it even for experts difficult to oversee. Academic scientists who want to succeed in letting the patients benefit from their research, therefore have no other choice than to either dig themselves deeply into the complex regulatory matter or involve experts who understand it early on.

…by knowing where to find appropriate funding opportunities

Today, academic research depends to a considerable degree on third-party funds, all the more if it is as costly as biomedical translation. For this reason, ForTra offers substantial funding opportunities. In 2022, it spent almost five million euros to fund six promising projects, which are close to entering the clinic. The importance of funding biomedical translation is increasingly recognized by other institutions, too. Five of them showcased their respective portfolio to the audience of the workshop and explained how to apply in some detail: The German Research Foundation, traditionally focused on basic research, recently has introduced a clinical trial program to support patient-oriented clinical research. The German Ministry of Education and Research provides funding measures for early clinical trials, and – in a European framework – for translational cancer research. To financially support both structures and projects in translational oncology is the mission of the German Cancer Aid, which also grants clinician-scientist fellowships. From the relatively small Wilhelm Sander-Stiftung, cancer researchers can expect quick and effective support. Last but not least, the Federal Agency for Disruptive Innovation emphasized its interest in biomedical breakthroughs, when it presented itself to the audience as a "newish kid on the innovation block".

…by partnering with clinical research institutions

Underfunding, misleading expectations of one's own product, developmental delays due to insufficient project management or unawareness of the patient recruitment funnel – these are major causes for translational projects to starve in the proverbial valley of death. Translationally oriented publicly funded or supported clinical research institutions associated with university medicine can help to mitigate those risks. Other than conventional contract research organizations, these institutions bring academic competence to the table and are eager to be part of shaping the medicine of tomorrow. Two of these institutions introduced themselves and their potential services to the audience of the ForTra Workshop: The Early Clinical Trial Unit (ECTU) of Hannover Medical School (MHH) and the Division Clinical Research of the Frankfurt-based Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP). The ECTU comprises 20 beds for conducting clinical studies from phase I to IIa, including infrastructure from special diagnostics to quality control. While it primarily serves to translate MHH-derived projects, it is open for partnerships with external investigators. The Fraunhofer ITMP, with its focus on inflammation and pain, has comparable in-house phase I to IIa-units and shows a similar receptiveness for external partners.

…by meeting the expectations of potential investors

The further a project proceeds, the more money it will burn and the less likely it is that normal research funding will cope with these demands. Investors with deeper pockets are needed. But how should clinician-scientists interact with the financial world? This issue was addressed in a panel discussion with four representatives of this world, namely life sciences analysts and investors. Asked what they expected from an applicant with whom they'd be interested to meet a second time, they consistently agreed on the following: An outstanding idea. Intellectual property in that idea, i.e., the implemented transformation of that idea into a patented invention. A clear definition of the unmet medical need that shall be satisfied by the realization of that idea. A dedicated project team with a shared commitment. A well reflected consciousness and communication of

the unique selling point of that project. The ability to understandably explain the underlying biology and to supply convincing proof of concept data, ideally endorsed by some external validation from opinion leaders in the respective field. Such expectations raise the bar high, but don't make it insurmountable.

…by using best-practice examples as a guide

This is well illustrated by the story of Vivlion. The business plan of the company was based on a brilliant idea of how to improve the craft of genome editing. This idea was developed by a young scientist at a research institute of Goethe University. The head of this institute fostered innovation wherever he could. He gave his team the freedom to pursue high risk-high gain projects. He made sure to value the differences by bringing people of different expertise together. Thus, the initial idea could be optimally explored and brought to fruition as a proprietary technology – guided by the advice of the university's technology transfer company. When Vivlion was spun out of Goethe University in December 2018, the university remained to be both a shareholder and customer, while a private equity company agreed to secure seed funding. With its genome editing reagents and consultancy services, Vivlion in the meantime has become a widely respected solution provider in a fast-growing niche of the global R&D market.

…by keeping the bigger picture in mind

From time to time, creativity needs to be spurred by a look to the horizon and beyond. How inspiring this can be, was illuminated in the key notes of the ForTra Workshop, one given from a scientific, the other from a business perspective. The myc-Protein is a decisive downstream effector of confluent oncogenic pathways in almost all types of cancer. Why does it instruct so many diverse tumor phenotypes? Professor Gerard Evan of the Francis Crick Institute in London asked and suggested a thought-provoking answer. As an activator of mitogenesis, the expression of myc is switched on when tissues have to be repaired after injury. In this process of regeneration, those tissues look very much like cancer. Could the onset of cancer generally be explained by an overshooting regeneration process, in which myc isn't switched off again? Yet if so, how could one succeed in targeting this protein? Solving this question would certainly lead over the bridge of hope, whose necessity for a successful translation of a good idea over the island of indifference to the land of innovation Dr. Sean Fielding of the University of Exeter emphasized in his talk. It is hard stuff, he said, to create something new for a market that's reachable and willing to pay the prize before you run out of money. Yet you can succeed if you really understand your motivations and decide whether you'd rather be an entrepreneurial academic or an academic entrepreneur.

"Great to be offered such an opportunity", a young scientist acclaimed the ForTra workshop. As a member of a team that is just in the process of seeking the best way to translate its project, she learned a lot here, she said, and made some important acquaintances. And a speaker from a funding foundation admitted: "Good to get an update on the latest regulatory requirements here." There was the genome and the proteome and so many more -omes in current biomedical research, another participant commented, but equally important for the latter's success was certainly the connectome as a mutual learning process between stakeholders from so many different walks of translational research, as enabled by this workshop.

(*Joachim Pietzsch, "wissenswort")*

Precision immunotherapy: Mutation-specific TCR-T cell therapy

PD Dr. Antonia Busse (Charité – Universitätsmedizin Berlin)

Medical need

Diffuse large B-cell lymphoma (DLBCL) is the most frequent high-grade B-cell malignancy. Its prognosis remains to be poor. 40% of newly diagnosed patients are refractory to primary therapy or suffer a relapse after it. Most of them are not fit enough to tolerate a salvage chemotherapy followed by autologous stem cell transplantation. Fortunately, however, half of these patients respond to Chimeric Antigen Receptor (CAR)-T cell therapy against the B-cell antigen CD19. Yet by for example modulating the surface expression of CD19, tumor cells can escape this therapy. Furthermore, this therapy can lead to severe side effects because CD19 is not only expressed by malignant, but also by normal B cells.

Suggested Solution

To target a surface antigen that only malignant B cells display by a human T-cell receptor (TCR). The Busse group has identified such an antigen, which stems from a characteristic point mutation of lymphoid malignancies. In this mutation, position 265 of the MyD88 adaptor protein is changed from leucine to proline. A 10-mer peptide spanning the mutant sequence is presented by the MHC complex of malignant B-cells, which bear the HLA-B7 antigen. This is the case in about one-fifth of the European population.

Current Status

The Busse group succeeded in isolating a high-affinity TCR targeting this 10-mer peptide, which mediates a strong in vitro T-cell response against the tumor cells presenting it. Adoptive transfer of T cells transduced with this TCR induced a durable regression of human lymphoma xenografts in mice. A preliminary safety screening did not indicate any off-target activity. Based on these findings, the Busse group is preparing a prospective, single-arm multicenter phase I study of their individualized TCR-T cell therapy, which is planned to start in Q2/2024. The endorsement of this plan by the Paul-Ehrlich-Institut prompted the German Ministry of Education and Research to support the project.

Translational Gap (Fortra Funding)

To conduct this clinical trial, the viral vectors for the transfer of the tumor specific TCR into the patients' lymphocytes need to be produced according to the standards of Good Manufacturing Practice. This costly endeavor is funded by ForTra as well as the set-up of the manufacturing process of the TCR-T cell products.

Perspective

The translation of this precision immunotherapy into the clinic bears the potential for long-term remission of so far incurable B-cell lymphomas. By attacking only lymphoma cells but not normal tissue it is also hoped to considerably improve the tolerability of the treatment.

Reference

Çınar Ö, et al. High-affinity T-cell receptor specific for MyD88L265Pmutation for adoptive T-cell therapy of B-cell malignancies. J Immunother Cancer 2021;9:e002410. doi:10.1136/jitc-2021-002410

Link to further information

https://www.ekfs.de/en/scientific-funding/currently-funded-projects/precision-immunotherapy-mutation-specific-tcr-t-cell

Rapidly signal-enhanced metabolic magnetic resonance imaging

Dr. Stefan Glöggler (MPI für Multidisziplinäre Naturwissenschaften, Göttingen)

Medical need

Early diagnosis with cancer is key to surviving the disease. The overall survival rate in pancreatic cancer, for example, is only 12,5%, while it amounts to 44% in patients who have been diagnosed early. Yet the rate of early diagnostics in this indication is only 13%. It is therefore of utmost importance to increase the rate of early diagnostics by developing tools and technologies, which are both easy to handle, broadly accessible and reliably informative.

Suggested Solution

Most cancer cells are characterized by an altered energy production, i.e. their avoidance of the citric acid cycle and their preference for lactid acid fermentation (Warburg effect). An imaging technique that can detect this alteration indirectly due to glucose uptake by cancer cell, is positron emission tomography. It is associated with radioactivity, however, and therefore not broadly available. Magnetic resonance imaging (MRI), on the other hand, is widely used, yet rather insensitive for the diagnosis of cancer. To overcome this limitation, the Glöggler group has transformed the body-own metablolite pyruvate into a contrast-agent. For this purpose, pyruvate is first enrichened by an MRI-detectable ^{13}C isotope and its MRI-signal then enhanced by the highly energetic H_2 para-hydrogen. This boosts the MRI-signal by a factor of 10^4 to 10^5. This amplification allows to observe the conversion of pyruvate into lactate and to detect tumors that have been invisible for MRI imaging. The amplification also enables imaging in low magnetic fields and thus in small, inexpensive and portable tomographs. This could help giving more people access to MRIs in the future.

Current Status

A proof of concept has been provided by imaging human melanoma xenografts in mice (cf. reference). The required pyruvate blood concentration raised no toxicity concerns with regard to upscaling the production process of the contrast-agent to clinical quantities for application in humans. Before clinical trials can start, a device needs to be constructed, in which pyruvate is activated in the way described above. When placed adjacent to an MRI device, this activator delivers a syringe filled with contrast-agent, which can immediately be injected into the patient who shall be diagnosed – provided that regulatory authorities have approved the clinical application of this technology.

Translational Gap (Fortra Funding)

ForTra finances the development and construction of the pyruvate-activator and the preclinical studies.

Perspective

Signal-enhanced MRI has the potential to improve early cancer diagnosis considerably.

Reference:

Hune T et al., Metabolic Tumor Imaging with Rapidly Signal-Enhanced 1-13C-Pyruvate-d3. ChemPhysChem 2023, 24. http://doi.org/10.1002/cphc.202200615

Link to further information

https://www.ekfs.de/wissenschaftliche-foerderung/aktuelle-foerderungen/signalverstaerkte-mrt-zur-demokratisierung-von

CC-1, a bispecific PSMAxCD3 antibody

Dr. Jonas Heitmann, Prof. Sr. Helmut Salih (Universitätsklinikum Tübingen)

Medical need

Globally, prostate cancer is the second-most frequent cancer in men, in Germany it is the most frequent one. The older the population gets, the more men are developing prostate cancer. Currently, more than 65,000 men in Germany are diagnosed with it annually. If the tumor has progressed into a metastatic stage, prostate cancer is not curable so far. Worldwide, 350,000 men die of the disease each year.

Suggested Solution

To treat prostate cancer with a bispecific antibody that binds both to the cancer cells and to the vessels nourishing the tumor to induce antitumor reactivity of T cells. The antibody CC-1 with PSMAxCD3 specificity displays such a dual mode of action. CC-1 leads to significantly less *off-target* effects compared to other immunotherapies. Beside prostate cancer, CC-1 can also be an option for patients with squamous cell carcinoma of the lung, especially in combination with checkpoint inhibition.

Current Status

Recruitment has been completed in the first human trial in patients with metastatic prostate carcinoma, which had started in late 2019. Preliminary results show very good tolerability. The target dose was reached without signs of significant toxicity, while already first evidence for efficacy was documented. A second clinical study with CC-1 in the lung cancer indication has been initiated. Based on the meanwhile available very favorable safety and preliminary efficacy data, recruitment for a phase I study in patients with biochemical recurrence of prostate cancer after curative therapy has started.

Translational Gap (Fortra Funding)

ForTra has already funded the production of additional CC-1 drug substance under GMP conditions that enables conduct of the clinical trials after the FIH trial. Additionally, ForTra is funding the phase I trial in patients with a biochemical relapse of prostate cancer after curative intended therapy.

Perspective

CC-1 holfs promise to become a new immunotherapy for the treatment of prostate cancer (and lung cancer) with high efficacy and moderate side effects.

References

Zekri L et al., An IgG-based bispecific antibody for improved dual targeting in PSMA-positive cancer. EMBO Molecular Medicine (2020). https://doi.org/10.15252/emmm.201911902

Heitmann J et al., Protocol of a prospective, multicentre phase I study to evaluate the safety, tolerability and preliminary efficacy of the bispecific PSMAxCD3 antibody CC-1 in patients with castration-resistant prostate carcinoma. BMJ Open (2020). https://bmjopen.bmj.com/content/10/10/e039639

Link to further information

https://www.ekfs.de/en/scientific-funding/currently-funded-projects/phase-i-trial-bispecific-psmaxcd3-antibody-cc-1

Corallopyronin A – a novel natural antibiotic

Prof. Dr. Achim Hoerauf (Universitätsklinikum Bonn)

Medical need

Filariasis is a group of parasitic diseases, which are caused by certain roundworms. They belong to the group of neglected tropical diseases. Prominent pathologic phenotypes of filariasis are elephantiasis and river blindness, respectively, which affect more than 72 million patients. Currently, no medical treatments are available to kill the long-lived adult worms causing these debilitating diseases.

Suggested solution

To administer Corallopyronin A (COR A), a natural antibiotic from soil bacteria. It was discovered in 1985 at the Helmholtz Centre for Infectious Dieease Research. Its preclinical development, however, did not start until almost 30 years later, when COR A had shown to exert high efficacy against *Wolbachia* bacteria. These bacteria are essential endosymbionts of most filariasis-causing roundworms. Consequently, their eradication could cure patients suffering from filariasis. Additionally, COR A is one of the rare DNA-dependent RNA polymerase inhibitors, a mode of action it shares with Rifampicin. Yet because it attacks the bacterial polymerase at a different site than the latter, the development of cross-resistance needs not be feared. This makes Corallopyronin A – in combination with other antibiotics – a potential reserve antibiotic against methicillin-resistant *S. aureus* (MRSA).

Current Status

As a natural compound, COR A cannot be chemically synthesized with reasonable effort. Its production has to be based on genetical engineering. To scale-up the required fermentation processes and to re-clone the synthesis cascade from its original bacterial species, which does not grow well, into another that allows cultivation up to 15,000 liters for an optimized yield has been a major challenge during the last decade. Having principally solved this, safety and non-toxicity recently have been successfully evaluated in preclinical studies. Based on these results, phase I clinical trials are now being planned while GLP-tox studies are being finalized.

Translational Gap (Fortra Funding)

To conduct clinical trials, it is necessary to both produce COR A on a kilogram scale and to formulate the substance (which freshly produced has a consistence like honey) in a bed of edible polymers so that it can be administered as a capsule. Both processes have to follow the standards of Good Manufacturing Practice. Their establishment is going be financed by ForTra.

Perspective

COR A has the potential to cure severe and widespread tropical diseases. In a secondary indication, its efficacy against *Neisseria gonorrhoeae* shall be tested. Generally, it also holds promise to be effective in the treatment of MRSA infections.

Reference

Krome AK et al., Corallopyronin A: antimicrobial discovery to preclinical development. Nat. Prod. Rep., 2022, 39, 1705. https://doi.org/10.1039/d2np00012a

Link to further information

https://www.microbiology-bonn.de/en

The microbiome as a source of and target for novel antibacterial strategies

Prof. Dr. Andreas Peschel and Dr. Meral Esen (Universität Tübingen and Universitätsklinikum Tübingen)

Medical need

Antimicrobial resistance is a fast-emerging global health problem of already almost pandemic nature. Six pathogens especially, summarized under the acronym ESKAPE (Details zu ESKAPE hier), are growing increasingly resistant to the effects of antibiotic treatment – with fatal consequences. It is estimated that they cause more than 1,2 million deaths per year. Methicillin-resistant *Staphylococcus aureus* (MRSA) belongs to the most prominent ESKAPE pathogens in nosocomial infections. Targeting it with reserve antibiotics, however, may further amplify resistance genes while also damaging the hosts´ microbiome.

Suggested Solution

To decolonize *S. aureus* from the nasal microbiome utilizing a "Live Biotherapeutic Product" (LBP) to produce a specific antimicrobial compound. Approximately one quarter of all humans carry *S. aureus* as a commensal and normally peaceful inhabitant in their nose. Yet this nasal carriage predisposes to invasive infection. *S. lugdunensis* is another commensal bacterium naturally occurring in human microbiomes. It produces lugdunin, a natural antimicrobial peptide that prohibits colonization by *S. aureus.* It is not prone to causing development of resistance in *S. aureus* and it is able to displace the latter in a selective, microbiome-preserving way.

Current Status

In animal models, lugdunin is effective against major pathogens. Moreover, it was shown that patients who carry *S. lugdunensis* in their nasal cavity had a six-fold lower risk of colonization with *S. aureus* compared to patients in whom this lugdunin producer could not be detected. In clinical studies with healthy volonteers the safety and efficacy of *S. lugdunensis* to avert long-term harmful *S. aureus* infections in high-risk patients shall now be explored.

Translational Gap (Fortra Funding)

In order to start clinical studies, *S. lugdunensis* needs to be developed into a LBP according to GMP standards. This process will be financially supported by ForTra, as well as the conduction of the first phase I/IIa trial with this product.

Perspective

S. lugdunensis could prevent severe MRSA infections by sustainably excluding S. aureus by a one-time treatment, while preserving the microbiome. Generally, the microbes constituting our microbiome (the microbiota) can be considered as a promising source for new antibiotics.

Reference

Tacconelli E, Autenrieth IB, Peschel A. Fighting the enemy within. Science 355: 689-690 (2017) https://doi.org/10.1126/science.aam6372

Zipperer A, Konnerth MC, Laux C et al. Human commensals producing a novel antibiotic impair pathogen colonization. Nature 535: 511-516 (2016) pubmed.ncbi.nlm.nih.gov/27466123/

Link to further information

https://www.dzif.de/en/project/new-strategies-specific-eradication-staphylococcus-aureus