HHS Public Access

Author manuscript

Cell Stem Cell. Author manuscript; available in PMC 2018 May 29.

Published in final edited form as:

Cell Stem Cell. 2014 February 06; 14(2): 146–148. doi:10.1016/j.stem.2014.01.004.

Translational Research: The Path for Bringing Discovery to Patients

Leonard Zon[1,*]

[1]Stem Cell Program and Hematology/Oncology, Children's Hospital and Dana-Farber Cancer Institute, HHMI, Harvard Stem Cell Institute, Harvard Medical School, Boston, MA 02115, USA

Abstract

Translating basic research findings into therapeutic settings presents many scientific, logistic, and financial challenges for academic researchers. Here, I highlight some key insights for navigating such challenges based on recent clinical trials initiated by basic research from my lab.

Introduction

A lot of people are talking about translational research. It can be defined in many ways, but a simple rendition would be the discovery of a new therapeutic in your own lab and the subsequent clinical trial to test its activity in humans. This event is likely to happen only a few times in a career as a researcher. I trained as a hematologist/oncologist and intrinsically want to see translation from the bench to the bedside. As a physician scientist, my career has focused on the developmental biology of hematopoiesis, using the zebrafish as a model system. As the zebrafish model developed into an excellent chemical genetics system, my laboratory began attempting to discover new therapies and translating the findings to curing patients. We brought two therapies from the tank to the bedside, and here, I will highlight lessons that are critical for success in translational research based on my personal experience.

Our Story

My experience with translational research using the zebrafish involves a project in which we were trying to improve the safety and efficacy of blood stem cell transplantation by discovering drugs that could increase their number or their potency. In 2007, we undertook a chemical screen in the zebrafish model in which a library of small molecules of 2,500 chemicals of known action were screened for their ability to induce expression of the hematopoietic stem cell genes *runx1* and *c-myb* in the developing zebrafish aorta (North et al., 2007). This screen identified 35 chemicals capable of inducing an increased hematopoietic expression pattern in the aorta, suggesting the production of more stem cells. One of those chemicals was a strong inducer called 16,16-dimethyl prostaglandin E2 (dmPGE2). This chemical represented the first small molecule discovered that can amplify a stem cell population from an organ. In an effort to see if this could be therapeutically useful,

*Correspondence: zon@enders.tch.harvard.edu.

we undertook competitive repopulation experiments in the mouse. dmPGE2 led to a 4-fold increase in the number of stem cells that engrafted, suggesting that the addition of prostaglandin could lead to enhanced engraftment. This work was confirmed by the Pelus laboratory (Hoggatt et al., 2009) and further suggested that treatment of dmPGE2 ex vivo could become a therapy. The process described here may therefore be applicable to both cell therapy applications and more traditional screening efforts.

We next undertook preclinical modeling using cord blood. To test the efficacy of dmPGE2 on cord blood units, with the idea of developing a new therapy to enhance engraftment, single cord blood samples were split in half; half was treated with prostaglandin, while the other half was left untreated (Goessling et al., 2011). These were transplanted into immunodeficient irradiated mice. The study showed that there was more human blood in the peripheral blood of the mice, and they exhibited higher chimerism in their blood and bone marrow 3 months later. This was the preclinical data that allowed us to go to the FDA.

To develop an FDA application, there were many meetings with the Center for Human Cell Therapy at the Harvard Medical School. This group helped us develop standard operating procedures for the treatment of the cord blood units with dmPGE2. dmPGE2 was given to patients in the early 1980s for the treatment of stomach ulcers. These studies demonstrated safety of the drug and allowed our team to predict that toxicity in the cord blood trial would be unlikely. An IND submission occurred in May, 2008 with an FDA response in June of that year. The FDA, interestingly, did not open the previous files on dmPGE2 and relied on the published literature and our preclinical data. We provided toxicity data in mice. We generated a clinical protocol that required vetting through a Scientific Review Committee at the hospitals at which the trial was to be done, the Dana-Farber Cancer Institute, and Massachusetts General Hospital, as well as IRB approval. The contents of the IND application itself, when stacked and placed on the ground, totaled about 1 foot tall. The FDA process was amended and approved in 2009. Any alterations in the manipulation of the cells or changes to the protocol would have to be reviewed by the FDA.

As we were ready to proceed with the clinical trial, we dealt with issues of manufacturing. We custom ordered a lot of dmPGE2 that was sufficient for the entire clinical trial. The academic discovery path to the bedside was efficient, but as translational costs and standard procedures became issues, it became clear that having a company involved would be an advantage. I had filed the patent for the use of dmPGE2 for transplantation and was approached to start a company based on the technology. FATE Therapeutics was formed.

Founding a company is an interesting process. I was approached by Randy Moon, a long-term colleague who works on Wnt signaling. Randy, Sheng Ding, and Phil Beachy were interested in forming a company to work on stem cells and were approached by several venture capital companies, Polaris, ARCH, and Venrock. These venture groups felt that this new stem cell company would benefit from including physician-scientists as founders. David Scadden also joined the consortium. Lastly, Rudy Jaenisch had interesting technology on iPSCs and was included. FATE Therapeutics had six initial founders and the venture firms were able to raise millions of dollars. The process of forming a startup is very efficient. Early decisions include defining the leadership of the company, particularly choosing a CEO

and their staff. Eventually certain projects were chosen and dmPGE2 was one of the lead programs.

We validated our standard operating procedures by independent use of several cord bloods, and the first patient was treated in May 2009. We were able to obtain NIH funding for the clinical trial, but a number of presentations and meetings were required to secure this funding. I was able to transfer the physician IND to FATE Therapeutics, and they participated in the clinical trial.

The company was instrumental in bringing the product to the clinic and deciphering key differences between the preclinical and clinical processes. An initial set of patients was treated with dmPGE2 that was maintained at a specific temperature based on our *Nature* paper that employed mouse stem cells, but the temperature was too cold for activation of cyclic AMP in the human cells. This discrepancy represented a fundamental difference between the preclinical work in our laboratory and the clinical work done in the standard operating procedures in which temperature was greatly monitored. The company recognized that the chemical was not active, went back to the lab to find the optimal conditions, and then came forward with a change in the processing protocol. This example demonstrates how a company can have a great impact on the product by researching difficulties early on and evaluating the process later.

The clinical trial, which was recently published, involved 12 new patients who had leukemia (Cutler et al., 2013). They lacked matched adult marrow but had umbilical cord units that were matched. The patients were between 18 and 65 years of age. In this Phase I trial, the patients undertook a competitive repopulation in which one of the cord blood units was treated with dmPGE2 for 120 min. The trial results demonstrated that in 10 out of the 12 patients, the treated cord blood preferentially engrafted and the neutrophils and platelets from the treated cord blood grafted roughly 4.5 days earlier than the untreated graft. This small number of patients demonstrated the safety of the product and also allowed the company involved, FATE Therapeutics, for which I am a stockholder, to move to a Phase II clinical trial. The translational application of zebrafish was a significant breakthrough in which a chemical moved from an embryonic phenotype in zebrafish through work in mice to human cord blood samples into immunodeficient mice. The timeline was a 36 month period of time from tank to bedside.

A significant number of people were involved to get the chemical to become a product. This included the Principal Clinical Investigator, Corey Cutler, who was involved in protocol design and taking care of the patients. There were coinvestigators who are oncologists who donated their time and helped with the development of the scientific protocol. In addition, two postdoctoral fellows from my own laboratory, Trista North, Ph.D., and Wolfram Goessling, M.D.-Ph.D., were in every meeting weekly for over a year and a half. The directors of the CHCT, Les Silberstein and Jerry Ritz, also participated in these meetings, and there was great help from their secretarial staff. At the Dana-Farber Cancer Institute, the Cell Manipulation Facility was involved, including a significant number of statisticians. At Boston Children’s Hospital it was important for the General Council and the VP of Research to help with some of the regulatory events. We had great help during the IND application

from Regulatory Affairs at the hospital. There were many discussions from the Intellectual Property Office at Boston Children's Hospital, and ultimately, when the clinical trial was accomplished, a company was formed, FATE Therapeutics, that included the medical director as well as senior investigators in the company who participated in research.

Some General Tips

Getting Through the Thought Process of Moving a Drug to the Clinic

As one is beginning their scientific pursuits as a researcher, it is important to have the clinic in mind. In every NIH grant, there is a justification on how the work will translate into issues of health. My suggestion is to look at those sentences and evaluate if the work in your lab could directly help patients. It is vital to involve M.D.s in discussions to think about translation. It is wonderful to have a mentor who is an M.D. with a laboratory, who can think through how the current technology could be applied in a clinical setting. Departments may benefit from the development of a mentoring system. At Harvard, we have recently started educational sessions for translation to the members of academic departments, sharing success stories.

Evaluate the Clinical Scenario

An important discovery in the laboratory may have many applications; however, it is very important to pick the best application to show activity of the agent or device in humans. There should be a consultation with disease experts. One method is to organize a lecture at a hospital or medical school to the relevant clinical audience. Picking the right disease to test a drug is critical, and you want to get independent feedback on the best clinical path forward.

Preclinical Testing

The experiments should establish the proof of principle. In our case, the preclinical testing should support transplantation efficacy in the preclinical model. Advisory groups can be involved in clinical translation to facilitate these projects. We had monthly meetings with the Center for Human Cell Therapy and this was quite important to success. Funding is required to do the preclinical testing. There are many institutions that want to facilitate translational research and some funding might be available.

Find Interactive Conversations

Find a mentor. This is absolutely critical to move to a clinical IND. The mentor should be someone who has done translational work before and has gone to the point of filing an IND with the FDA. Regulatory help from an institution or hospital will be needed. There are many forms to complete and there is a need for administrative help. Work with the Technology Transfer Office, as they are critical to investigate any intellectual property that may be involved in this process, and involve the legal team, because there will be regulatory issues and conflicts of interest based on your own institutional policies. Having administrative help, such as secretarial work, is also very important. Probably one of the most rewarding approaches I had was to involve the scientists in my own laboratory who made the original discovery with the clinical translation. This facilitates the work and helps develop the preclinical work necessary at the FDA.

Protocol

It is very helpful to have the medical team involved very early on. Developing a protocol for dmPGE2-treated cells required a significant number of conversations. There were about six independent meetings on defining the best approach to use for the chemical. We involved statisticians to determine the optimal number of patients that would be treated. Stopping rules needed to be established if toxicity occurred, and there would be an evaluation whether or not to proceed.

Continue the Lab Work

There are a number of studies that are needed for the preclinical work. Once an IND application has been filed, it is important to continue that work. There is plenty of time between submitting the IND application and when the actual clinical protocol is set. The work that we did in the last year before the IND application was finally approved was critical to the success of the program. Establish statistics within your own experiments and collect all samples of tissue that have been treated for drugs or cells, since these count as toxicology reports for the FDA. We did many studies in the mice to establish the safety of dmPGE2, and the toxicologic reports were used for the FDA application.

A Second Shot at Translation

My laboratory has recently put a second chemical from a zebrafish into a patient. This involved the treatment of melanoma, which is a devastating disease, and 50% of the patients have an activating BRAF mutation. There is a BRAF inhibitor on the market called vemurafenib that leads to a substantial response, but unfortunately, at 6 months the patients relapse. We undertook a chemical screen to look for small molecules that block neural crest development. In the process, we found that an inhibitor of dihydrooratate dehydrogenase (DHODH) that affects pyrimidine biosynthesis led to a block in transcription elongation, and this affected the expression of neural crest genes as well as melanoma formation. We undertook xenograft studies of human melanoma into nude mice, and we treated the mice using the DHODH inhibitor leflunomide, a drug that is in clinical practice for arthritis. This led to a substantial response in tumor growth. A combination of leflunomide and a BRAF inhibitor led to a substantial decrease in tumor volume. We are currently undertaking a clinical trial at Massachusetts General Hospital and the Dana Farber Cancer Institute using the combination with an end point to increase the progression-free survival from 7 months to 10.5 months. We hope to treat 43 patients and to date, 3 patients have been treated. These two examples of bringing chemicals from an animal model into the clinic have been greatly instructive to understand the process of translational research.

Acknowledgments

L.Z. is a founder and stockholder of FATE, Inc., a founder and stockholder of Scholar Rock, and a scientific advisor for Stemgent.

References

Cutler C, Multani P, Robbins D, Kim HT, Le T, Hoggatt J, Pelus LM, Desponts C, Chen YB, Rezner B, et al. Prostaglandin-modulated umbilical cord blood hematopoietic stem cell transplantation. Blood. 2013; 122:3074–3081. [PubMed: 23996087]

Goessling W, Allen RS, Guan X, Jin P, Uchida N, Dovey M, Harris JM, Metzger ME, Bonifacino AC, Stroncek D, et al. Prostaglandin E2 enhances human cord blood stem cell xenotransplants and shows long-term safety in preclinical nonhuman primate transplant models. Cell Stem Cell. 2011; 8:445–458. [PubMed: 21474107]

Hoggatt J, Singh P, Sampath J, Pelus LM. Blood. 2009; 113:5444–5455. [PubMed: 19324903]

North TE, Goessling W, Walkley CR, Lengerke C, Kopani KR, Lord AM, Weber GJ, Bowman TV, Jang IH, Grosser T, et al. Nature. 2007; 447:1007–1011. [PubMed: 17581586]