

Commentary

Translating Mechanobiology to the Clinic: A Panel Discussion from the 2018 CMBE Conference

ALISA MORSS CLYNE,¹ MICHELE MARCOLONGO,¹ ERIC M. DARLING,² and NADEEN O. CHAHINE³

¹Drexel University, Philadelphia, PA, USA; ²Brown University, Providence, RI, USA; and ³Columbia University, New York, NY, USA

(Received 14 September 2018; accepted 17 September 2018)

Associate Editor Michael R. King oversaw the review of this article.

Abstract—The 2018 BMES Cellular and Molecular Bioengineering (CMBE) Conference was organized around the theme of Discovering the Keys: Transformative and Translational Mechanobiology. The conference programming included a panel discussion on Translating Mechanobiology to the Clinic. The goal of the panel was to initiate a dialogue and share pearls of wisdom from participants' successes and failures in academia and in industry toward translating scientific discoveries in mechanobiology to technology products in the market or toward devices or drugs that impact clinical care. This commentary reviews the major themes and questions discussed during the panel, including defining translational research and how it applies to mechanobiology, the current landscape in translational mechanobiology, the process for translating mechanobiology research, challenges in translating mechanobiology research, and unique opportunities in translating mechanobiology research.

Keywords—Mechanobiology, Biomedical engineering, Translation, Technology transfer, Commercialization.

INTRODUCTION AND BACKGROUND

The 2018 BMES Cellular and Molecular Bioengineering Conference co-chairs, Nadeen O. Chahine, PhD of Columbia University, Alisa Morss Clyne, PhD of Drexel University and Eric M. Darling, PhD of Brown University, organized a panel discussion on Translating Mechanobiology to the Clinic during the January 2018 event. The conference goal was to push the boundaries of mechanobiology in fundamental research, novel techniques, biological models, and technology development. It is now well accepted that both the mechanical properties of biological systems and mechanical forces applied to biological systems

play critical roles in pathology and pathophysiology. Important challenges remain in creating new technologies to probe and manipulate biomechanics *in vitro* and *in vivo* and use these discoveries to enhance technology for serving humanity and health. We organized a conference integrating engineers and biologists with clinical and technology development experience, each of whom has been encouraged to bridge the gap between fundamental research and translation. Our choice of theme was intended to address the key challenge in how mechanobiology can continue to advance transformative research at the interface of engineering and biomedical science for improved human health.

One way in which we addressed this need is by organizing a panel discussion on translating mechanobiology. The goal of the panel was to initiate a dialogue and share pearls of wisdom from participant's successes and failures in academia and in industry toward translating scientific discoveries to technologies that impact clinical care or technology in the market. The moderator was Michele Marcolongo, PhD, Department Head and Professor, Material Science and Engineering, Drexel University. The panel also consisted of five principal investigators from academia and one from industry. The academic participants were: Bianxiao Cui, PhD, Associate Professor of Chemistry at Stanford University; Delphine Dean, PhD, Gregg-Graniteville Associate Professor of Bioengineering at Clemson University; Dennis Discher, PhD, Robert D. Bent Professor of Chemical and Biomolecular Engineering at the University of Pennsylvania; Farshid Guilak, PhD, Professor of Orthopaedic Surgery at Washington University, St. Louis and Director of Research for the Shriners Hospitals for Children; and Robert Mauck, PhD, Mary Black Ralston Professor of Orthopaedic Surgery at the Univer-

Address correspondence to Alisa Morss Clyne, Drexel University, Philadelphia, PA, USA. Electronic mail: asm67@drexel.edu

sity of Pennsylvania. The industry participant was Nicholas Geisse, PhD, Chief Science Officer, NanoSurface Biomedical, Inc.

WHAT IS TRANSLATIONAL RESEARCH AND HOW DOES IT APPLY TO MECHANOBIOLOGY?

The NIH National Center for Advancing Translational Sciences (NCATS) defines the term translation as, “the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public”.¹ The definition purposely uses broad and inclusive terminology without specifying directionality, and it also includes the community as the actual end user for translational interventions. From the view of Dennis Discher, translational research is the process of taking new ideas developed in laboratory research and moving them to a broader community outside of the original laboratory, including other laboratories, companies, and the clinic. This process can be led by the principal investigator who made the original discovery, or it can be picked up by someone else who was able to read a scientific paper, understand how the technology works, and move it forward. While the principal investigator does not necessarily have to be involved, Delphine Dean emphasized that the translation must enable someone or some entity to make money for that entity to be incentivized to invest time and resources into the translation of technology to the marketplace.

NCATS further defines translational research as “the endeavor to traverse a particular step of the translation process for a particular target or disease”.¹ While translational research is often viewed as a simple process, in fact the effort and new discoveries inherent in moving a concept from a defined setting in the laboratory to the complexities of the real world are often equal to if not greater than those involved in the initial discovery itself. Nicholas Geisse echoed this challenge in getting the research out of the laboratory as a product. Translational research comprises up to 95% of the effort in turning a great idea into a product that is exciting both to the company and to the consumers. Many companies in fact have multistage processes to whittle thousands of ideas into a commercializable product, with much of that process involving market validation with end users in the community.

Biomechanics research has in many ways always been inherently translational. From valve prostheses, stents, and ventricular assist devices in cardiology, to prosthetics, bone fixation devices, and replacement

joints in orthopedics, biomechanical engineers have successfully translated a wide variety of clinical observations into laboratory research and then back into medical products.² Mechanobiology, defined as the study of how biological systems sense, generate, and respond to physical forces, has not yet been translated in the same way as biomechanics research perhaps because mechanobiology grew out of fundamental *in vitro* cell and protein level experiments rather than from tissue and organ testing and pathology. However, Farshid Guilak describes translation as a huge untapped market for the mechanobiology research community because mechanobiology is relevant to every disease and organ system, some mechanobiology pathways already have drug targets, and the FDA is more prepared to regulate mechanobiology-derived devices and drugs compared to other systems with little precedent, such as tissue engineering products and stem cells. Thus, the translational pathway for mechanobiology may in fact be more straightforward than principal investigators currently believe.

CURRENT LANDSCAPE IN TRANSLATIONAL MECHANOBIOLOGY

While much of mechanobiology remains in the research laboratory, there are already several success stories in translating mechanobiological concepts. After Discher and colleagues showed that cells functioned differently on substrates of varied stiffness, the idea of culturing cells on gels that mimic tissue-specific stiffness caught on quickly. While Discher himself did not spin the idea into a company, new and existing companies picked up on his research and began to sell tissue culture substrates of varying stiffness. Today, most new cancer drugs are screened in cells grown on substrates with tumor specific stiffnesses.³ This is a profound example of how mechanobiology can have a widespread impact through translation from the research laboratory into standard practice for pharmaceutical development.

Regenerative rehabilitation, defined as the integration of principles and approaches from rehabilitation and regenerative medicine with the ultimate goal of developing innovative and effective methods that promote the restoration of function through tissue regeneration and repair, represents another burgeoning community in translational mechanobiology.⁵ Regenerative rehabilitation capitalizes on what is known about how mechanical stimuli can promote new tissue growth to create new rehabilitation programs that repair and even regenerate injured tissues. While challenges remain around what will be

patentable in regenerative rehabilitation, the translation of these ideas often goes directly to the patient through new algorithms and apps developed by health information technology companies.

Other potentially high impact areas include known intracellular signaling pathways which are newly shown to be mechanically driven. In this case, the mechanisms are already in place to create pharmaceutical targets through current FDA regulations. Guilak emphasized that mechanobiology as a field is at an inflection point for translation, with phenomenal potential for clinical impact. “We are at the point where we can start taking these fundamental discoveries about processes that have a mechanobiological basis, whether that’s tumor progression or kidney development, and figure out the pathways that drive the disease processes,” Guilak said.

THE PROCESS FOR TRANSLATING MECHANOBIOLOGY RESEARCH

The first stage in translating a laboratory discovery into a commercial product is patenting the idea through the institution’s technology transfer office. Once the patent has been filed, and perhaps a paper published and product made, a critical stage in translation is market research. It is essential to know who the customer is because the product must be sold for a profit in order to impact population health. Geisse noted that this “discovery” phase is an art and a skill at the same time. Many companies have formal programs designed to discover market needs and wants, which can be very different things. In fact, customer input is important throughout the process, and different techniques can be used for talking to customers when refining the idea as compared to when the product is just about to be released. While the process of translating an idea to a product is sometimes described in linear terms, in fact there are many feedback loops throughout the process that in the end create the successful product.

In some cases, the initial discovery turns out to fit a customer’s want differently than the investigator’s initial idea. This process of shifting the product purpose is called a pivot. It can result in a bigger, better, more impactful product; however, a successful pivot requires an open-minded inventor who can listen to and accept customer feedback and be willing to change the product. For example, Robert Mauck was surprised when orthopedic surgeons felt his initial concept of a spine therapy would not be appropriate for spines

but rather would be a better choice for the meniscus. With another of his innovations, the customers wanted the product for a cosmetic rather than a musculoskeletal application, so the company is now pursuing that route. Dean described an example in which her laboratory was creating a diabetic product for humans; however, through the publicity related to the discovery, she was contacted by potential customers who wanted to use the product to care for their pets. Since the regulatory process is simpler for animal care, the product debuted for pets rather than for people.

The process of discovering customer wants and needs can be done by the inventor; however, it is usually better to have people with greater separation from the idea conduct the market research. The inventor can unintentionally bias questionnaires and interviews to get the desired answers or select customers with specific technical backgrounds who may reinforce desired answers or outcomes. Several panelists highlighted the academic entrepreneurs’ advantage of close proximity to business school students, who are often looking for market research opportunities as part of a class or business plan competition. Guilak had two teams of business school students do all the market research for his company as part of a class. These students then went on to win four business plan competitions and received the money needed to seed the company. This student-led process can also be formalized into “innovation slams,” for example those held at the NSF-funded Center for Engineering Mechanobiology (<https://cemb.upenn.edu/>). Students work together on ideation around a central idea, then interview one another to learn customer wants. The students then create a concept, get more feedback, and finally build the product out of craft materials or using basic prototyping. Throughout the process, students realize how their initial ideas were transformed by repetitive customer queries, resulting in a more refined product in the end.

Unfortunately, in some cases customer feedback results in the decision not to translate the idea. Bianxiao Cui attended customer week at the NSF ICORPS program. She had a great idea and a high impact paper to present. As she and her group talked to 100 different customers and companies, she realized that most of the people they thought would want the product were not interested in the new idea. This realization is common in the corporate world. Companies may spend a million dollars developing a product and then decide not to release it. While this process is painful, early customer feedback can help reduce how often this happens.

CHALLENGES IN TRANSLATING MECHANOBIOLOGY RESEARCH

The process of translating a discovery from an academic laboratory into a product is inherently different from the typical start-up model. Independent start-ups begin with a search phase, examining what customers want, and then create a product to satisfy the customer. Academic start-ups begin with a discovery, usually without the thought of creating a product, and as such there is a lag in translation. The investigator can get squeezed in a tug of war between their institution and start-up. Some of the challenges or impediments to translational research include the academic culture, shortage of translational investigators and business leaders, inadequate financial support, and the regulatory process.⁶

The academic culture in universities produces multiple impediments to translational work. First, there is the conflict for the principal investigator between the importance of publishing for one's academic career and the potential for patenting and licensing the same idea, which inevitably delays publication or presentation. Most institutions still do not give the same credit to translational activities in a tenure or promotion review as they do to high impact journal publications. However, this may be beginning to change, with tenure and promotion committees including innovation as part of a candidate's evaluation. In addition, there are opportunities to do both at the same time, for example by publishing in respectable journals that highlight translational work (e.g., *Science Translational Medicine*) and increased opportunities for government funding focused on translational research.

Another challenge in translating research out of an academic laboratory is the technology transfer process. Most technology transfer offices are relatively new, often understaffed, and still learning the best way to efficiently transfer ideas. Each institution has its own model for technology transfer, with some taking ownership of intellectual property developed by faculty, post-docs, and graduate students but not undergraduate students. Also, institutions offer different deals in licensing, which changes the potential financial benefit to the inventors. If there is a group of inventors, potentially from different institutions, they must also determine how to share inventorship among the varied inventors and their respective institutions. And while some institutions work to market a discovery for licensing, others expect the faculty member to do the marketing. The process is often complex, and faculty may find it difficult to push the process forward given their existing commitments to teaching, basic research, and service.

Large companies often find a technology more attractive for acquisition once it has been spun out into a company, since it may be complicated to license a technology directly from an academic institution. The existence of a start-up gives an interested company the impression that the discovery is not just a laboratory project. Academic laboratories can face challenges in conflict of interest once the investigator has started a company to translate the discovery. Different institutions take different approaches to manage the potential conflict. While some create a clear separation between the company and the laboratory, others have incubator space and core facilities for institution-based start-ups or allow the start-up to be located in the laboratory if there is specialized equipment that cannot be replicated. However, significant conflicts can arise when a graduate student working towards a PhD is doing experiments for a company created by their advisor. These conflicts are not show-stoppers, however, and can be worked through with guidance of institutional policy.

Another challenge in translational research is finding the right people to manage the translation. Many principal investigators do not have the experience, skills, time, or desire to translate a discovery into a product. In fact, the Coulter Foundation prefers to keep academics in the role of innovator, focused on seeding ideas, rather than developing those ideas as an entrepreneur. Faculty can still play an important role as a scientific advisor to the company, while leaving most of the scientific work to students or post-docs who have left the laboratory and the business work to a hired CEO. Finding the right CEO may be the hardest part of starting a company, since the number of business professionals who can successfully translate a scientific discovery to a successful product is small. Some universities provide support in this process by providing a pool of potential CEOs. While giving up decision-making control to the CEO is a challenge in itself, the company needs a person whose entire job is to initiate the company and keep it going for the 10+ years that it usually takes for an academic start-up to make a product or be sold to a larger company. The right CEO can take a mediocre technology and make it successful because they have the necessary knowledge and connections.

Translational research tends to be more expensive than basic research, since some discoveries are viewed as too high-risk until there are large animal or clinical data. Thus, funding is and remains a challenge for translational research. Traditional government funding mechanisms, such as SBIR and STTR from both NIH and NSF, can effectively support a small company for the time that it takes to de-risk the technology while potentially building value. These mechanisms

also enable collaboration or sub-contract with an academic laboratory, which can maintain the scientific link between the inventing laboratory and the company. New sources of support, including the NSF ICORPS program and the NIH NCATS, provide additional funding specifically for translational research. Investigators can also look outside traditional government funding to business competitions or investor and angel days, especially for larger pools of money needed for expensive animal or clinical trials. The technology transfer office or the business school may even provide assistance in pitching the idea. Another opportunity is to partner with a large company, which may raise money to more thoroughly test an idea. Several large companies have their own venture groups for just this purpose (corporate venture capital). If the inventor can prove that the discovery works, the large company may then license the technology. Finally, there are state-run economic development opportunities to seed early-stage start-ups. For example, Pennsylvania has a loan program for new start-ups that are located in the state. If the start-up is successful, then the loan must be paid back, but if the start-up is not successful, the loan is forgiven. The California Institute for Regenerative Medicine promised to bring therapies to the public, and to fulfill that promise, they are using their funds to support any clinical trial of a regenerative therapy with a site located in California.

A final challenge to translational research lies in the regulatory process ranging from human protections to FDA regulations. Many important and necessary changes focused on human protection and inclusion of traditionally underrepresented patients have been incorporated into the regulatory process over the past few decades. However, the increased regulation of clinical trials has also increased the burden on institutional review boards (IRBs), often without an increase in resources available to the IRB. In these cases, IRBs may pass this burden along to investigators, who may then feel that the regulatory burden of a clinical trial outweighs the potential benefits.⁶ IRBs could also find effective ways to enable scientists, engineers, and physicians to move forward with clinical trials even when there is financial interest in the outcome, often in the form of intellectual property. Another hurdle comes when the product is submitted for approval to the FDA. The FDA process is completely different for products that are already regulated (e.g., devices and drugs) than for products whose regulation has yet to be fully established (e.g., tissue engineered systems and stem cells). It remains much more complex to take a product with little precedent to market compared to a drug or device. It is therefore important to think about the regulatory pathway at the start of the translational process. Successful navigation of the FDA requires a multi-pronged approach, including both

deducing what the FDA wants and assisting them in making a determination on what they want. Regular communication with the FDA before, during, and after trials can help limit missteps. In the end, it is up to the researchers to help the FDA determine how to reduce risk yet maximize impact as they begin to regulate new types of products without significant precedent.

UNIQUE OPPORTUNITIES IN TRANSLATING MECHANOBIOLOGY RESEARCH

Despite these many challenges, the field of mechanobiology is emerging into a period that has rich potential for clinical translation. Academic institutions are doing more to encourage and support translation in innovative ways, and additional financial support is available from diverse sources ranging from government agencies to angel investors. In their parting words, the panelists agreed that academics have the opportunity to contribute to translational research in multiple ways. First, faculty are innovators in their fields, developing a multitude of new ideas and knowledge some of which may be easier to translate than others. Second, faculty educate undergraduate and graduate students as well as post-docs who will become the next generation of innovators and entrepreneurs. The opportunity for translational research and commercialization starts with process education. Resources now lay a pathway for “how-to” spin out a technology from an academic laboratory.⁴ Innovation ecosystems are advancing in many universities, providing education, a positive environment, and networks to make research translation part of the academic mission. The possibilities for mechanobiology to impact society in this important area are impressive.

REFERENCES

- ¹Austin, C. P. Translating translation. *Nat Rev Drug Discov* 17(7):455–456, 2018.
- ²Chien, S., *et al.* Engineering as a new frontier for translational medicine. *Sci Transl Med* 7(281):281fs13, 2015.
- ³Feng, J., *et al.* Substrate stiffness influences the outcome of antitumor drug screening in vitro. *Clin Hemorheol Microcirc* 55(1):121–131, 2013.
- ⁴Marcolongo, M. Academic Entrepreneurship: How to Bring Your Scientific Discovery to a Successful Commercial Product. Hoboken, NJ: Wiley, 2017.
- ⁵Perez-Terzic, C., and M. K. Childers. Regenerative rehabilitation: a new future? *Am J Phys Med Rehabil* 93(11 Suppl 3):S73–S78, 2014.
- ⁶Pober, J. S., C. S. Neuhauser, and J. M. Pober. Obstacles facing translational research in academic medical centers. *FASEB J* 15(13):2303–2313, 2001.