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PERSPECTIVE

Translational neural engineering: multiple perspectives on bringing benchtop research into the clinical domain

Patrick Rousche[1], David M Schneeweis[2], Eric J Perreault[3] and Winnie Jensen[4]

[1] Department of Bioengineering, University of Illinois at Chicago, Science and Engineering Offices (SEO), Room 218, M/C 063, 851 South Morgan Street, Chicago, IL 60607, USA
[2] Interdepartmental Neuroscience Program, Northwestern University, 2205 Tech Drive 2-095 Hogan Hall, Evanston, IL 60208-3520, USA
[3] Department of Biomedical Engineering and Department of Physical Medicine and Rehabilitation, Northwestern University, 345 E Superior St, Chicago, IL 60611, USA
[4] Center for Sensory–Motor Interaction, Deparment of Health Technology and Science, Aalborg University, Fredrik Bajers Vej 7, Room A2-204, 9220 Aalborg, Denmark

E-mail: rousche@uic.edu

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Abstract
A half-day forum to address a wide range of issues related to translational neural engineering was conducted at the annual meeting of the Biomedical Engineering Society. Successful practitioners of translational neural engineering from academics, clinical medicine and industry were invited to share a diversity of perspectives and experiences on the translational process. The forum was targeted towards traditional academic researchers who may be interested in the expanded funding opportunities available for translational research that emphasizes product commercialization and clinical implementation. The seminar was funded by the NIH with support from the Rehabilitation Institute of Chicago. We report here a summary of the speaker viewpoints with particular focus on extracting successful strategies for engaging in or conducting translational neural engineering research. *Daryl Kipke*, *PhD*, (Department of Biomedical Engineering at the University of Michigan) and *Molly Shoichet*, *PhD*, (Department of Chemical Engineering at the University of Toronto) gave details of their extensive experience with product commercialization while holding primary appointments in academic departments. They both encouraged strong clinical input at very early stages of research. Neurosurgeon *Fady Charbel*, *MD*, (Department of Neurosurgery at the University of Illinois at Chicago) discussed his role in product commercialization as a clinician. *Todd Kuiken*, *MD*, *PhD*, (Director of the Neural Engineering for Artificial Limbs at the Rehabilitation Institute of Chicago, affiliated with Northwestern University) also a clinician, described a model of translational engineering that emphasized the development of clinically relevant technology, without a strong commercialization imperative. The clinicians emphasized the importance of communicating effectively with engineers. Representing commercial neural engineering was *Doug Sheffield*, *PhD*, (Director of New Technology at Vertis Neuroscience, Inc.) who strongly encouraged open industrial–academic partnerships as an efficient path forward in the translational process. *Joe Pancrazio*, *PhD*, a Program Director at NIH's National Institute of Neurological Disorders and Stroke, emphasized that NIH

funding for translational research was aimed at breaking down scientific barriers to clinic entrance. *Vivian Weil*, *PhD*, (Director of Center for the Study of Ethics in the Professions at the Illinois Institute of Technology) a specialist on ethics in science and engineering, spoke of the usefulness of developing a code of ethics for addressing ethical aspects of translation from the bench to clinical implementation and of translation across disciplines in multi-disciplinary projects. Finally, the patient perspective was represented by *Mr Jesse Sullivan*. A double-arm amputee and patient of Dr Kuiken's, Mr Sullivan demonstrated the critically important role of the patient in successful translational neural engineering research.

Introduction

Among institutions that fund biomedical engineering research there has been a recent trend to encourage and support work that is 'translational' in nature. For many researchers engaged in more traditional 'basic' research, this trend represents both an opportunity and a challenge: an opportunity to more directly impact clinically relevant problems, but a challenge to adapt from more traditional ways of practicing academic science and engineering. This shift is problematic for several reasons, but for many, the most fundamental challenge is to understand what exactly qualifies as translational research, and to figure out how to leverage existing expertise, knowledge, experience and resources into a translational model. A standard academic researcher wishing to become engaged in translational research is likely to ask her or himself many questions: Where on the bench-to-bedside continuum must my research be to be considered 'translational'? Must it involve human subjects? Do I need to engage clinicians, and if so, at what level of involvement? Should I look to partner with a company? Should I form my own company? How should I handle intellectual property—(especially if I have never worried much about it before)? How do my students fit into all of this? How do I balance my other research (and academic) activities with translational ventures?

Although the need to shift towards a translational emphasis affects nearly all areas of biomedical research, the field of neural engineering (NE) is uniquely impacted by virtue of the special status of the brain and nervous system—special not only because of the many unique scientific challenges, but because of unique ethical and philosophic challenges as well. In short, transitioning a traditional academic research approach to a new 'translational' model may be a particularly daunting task for standard academic practitioners of neural engineering.

This symposium, organized at the annual meeting of the Biomedical Engineering Society, was conceived as a forum to address some of the questions above, and identify what it really means to do translational neural engineering (TNE)—and to do it successfully. In order to provide a multifaceted view of TNE, a program was created that featured presenters who could provide a diversity of perspectives and experiences. *Nitish Thakor*, *PhD*, (Department of Biomedical Engineering at Johns Hopkins University) was the symposium moderator. Representing the 'academic researcher' were *Daryl Kipke, PhD,* and *Molly Shoichet, PhD*, both of whom have extensive experience with product commercialization while holding primary appointments in academic departments—Biomedical Engineering (at the University of Michigan) and Chemical Engineering (at the University of Toronto), respectively. *Fady Charbel, MD*, also has extensive experience with product commercialization, but as head of the Department of Neurosurgery (at the University of Illinois at Chicago)—and a practicing neurosurgeon—discussed how he sees biomedical product development first from the clinical point of view. *Todd Kuiken, MD, PhD*, also a clinician/researcher (at The Rehabilitation Institute of Chicago, affiliated with Northwestern University), described his brand of TNE that represents a somewhat different model from that of the others: one that emphasizes the development of clinically relevant technology, but without strong commercialization imperative. Representing the view from a NE company was *Doug Sheffield, PhD*, a scientist (most recently at Northstar Neuroscience) with many years experience in the biomedical product development industry. *Joe Pancrazio, PhD*, currently a Program Director at NIH's National Institute of Neurological Disorders and Stroke, spoke from the perspective of one involved in funding TNE projects. Speaking to some of the ethical and philosophical issues surrounding TNE, was *Vivian Weil, PhD*, a specialist on ethics in science and engineering, who has worked closely with neural engineers. Finally, a vital, but too often neglected, perspective—that of the patient—was represented by *Jesse Sullivan*. A double-arm amputee and patient of Dr Kuiken's, Mr Sullivan demonstrated the critically important role of the patient in successful TNE.

Why translational neural engineering?

Translational research is one of the sub-initiatives of the NIH Roadmap, falling under Re-engineering the Clinical Research Enterprise, one of NIH's three primary themes. This initiative is being supported through the establishment of large centre-type awards, and through the establishment of core services intended to catalyze certain types of clinically-relevant research. While it has always been the mission of the NIH to support research that leads to medical advances for improved human health, this new initiative is a tacit recognition of the NIH's desire and need to shepherd ideas from the discovery phase through to early clinical testing. Improvements in the funding or implementation of translational research necessarily focus on improvement of the bench to bedside path. The trend towards translational research is echoed in other funding agencies. For example, the W M Coulter Foundation has an explicit mission to fund

translational research in Bioengineering. It comes as no surprise that research scientists will inevitably pursue research opportunities that are well funded.

In this current climate, (as stated by Dr Kipke): translational research is a *win*, *win*, *win* proposition. A *win* for principal investigators (PIs) who enjoy the traditional scholarly benefits of publishing, research, and training students; a *win* for funding agencies and a win for the public (taxpayers and patients) who may see and/or enjoy the direct benefits of successful translational research.

Varied perspectives on translational neural engineering research

The symposium opened with two researchers from engineering academia who have had extensive experience with commercialization: Daryl Kipke, PhD from the University of Michigan, and Molly Shoichet, PhD from the University of Toronto. Kipke and Shoichet have primary appointments in academic departments—Biomedical Engineering and Chemical Engineering, respectively. They recounted their personal experiences in moving from traditional engineering academic research models to translational research models via start-up companies.

Kipke is an unabashed (and successful) proponent of TNE, but he was careful to highlight its possible pitfalls for the academic researcher. In his view, a rigid template that will ensure TNE success is generally unavailable and it would be unreasonable to create one. The process is not easy yet there are some factors under a researcher's control that can help improve one's probability of success. Primary among these is investment in the right scientific and/or clinical collaborators. Success for him was primarily due to building a team of hand-picked individuals with the necessary skills and compatible attitudes towards the TNE process. Flexibility was essential for every stage of his product development and close interactions among the biomedical engineers and the medical professionals ensured that the research output/final product remained clinically feasible. Furthermore, Kipke stressed that his TNE success also hinged on a laborious and extensive search for investors.

Schoichet echoed many of Kipke's sentiments in her discussions of moving her research work from the basic science of academics to a translational realm via her start-up company. She cautioned that researchers with an idea for translational research need to very carefully identify the market that the idea is intended to support. In some cases, the research idea must be expanded in order to successfully accommodate a given market—like Kipke, Schoichet agreed that flexibility and adaptability are essentials in helping the basic research move into the translational domain. Furthermore, Schoichet cautioned that industry and academia must work closely together on the same goal—maximal success can only be achieved if both sides agree on the exact 'question' that needs to be answered. She suggested that tackling easy projects first allowed for traditional researchers to forge a working path in the area.

The middle portion of the symposium presented two clinicians holding academic appointments from which they have segued into translational neural engineering research. They detailed interesting and somewhat contrasting models of physician-instigated translational research. Fady Charbel MD heads the Neurosurgery Department at the University of Illinois at Chicago and outlined his role in translational research via start-up companies, detailing his involvement and approach from device conception to final commercially available products for neurosurgery. Todd Kuiken, MD/PhD, is a clinician in Physical Medicine and Rehabilitation at Northwestern University and the Rehabilitation Institute of Chicago. Kuiken's work represents a somewhat different translational model—one that emphasizes the development of clinically relevant technology for amputee rehabilitation, but without strong commercialization imperative.

Charbel recounted his experiences in developing two different products for neurosurgical use. His product ideas arose out of a direct and obvious personal need to help a patient. A strong motivating factor was the desire to actually use the product and not have to wait for someone else to develop it. Such observations are almost by necessity limited to clinicians. Yet, product design and testing required engineers. Charbel suggested clinicians and engineers meet weekly to work on continuous dialogue. He talked of language and operational differences between the two fields that required a large amount of energy to overcome. He summed up these differences with the following statement: 'Engineers want the perfect product, doctors want a product that works'. Charbel sees success as being best obtainable only through synergistic activities between the clinicians and engineers. Independent observations and developments will not suffice.

Todd Kuiken MD, PhD is also a clinician involved at the patient level in bringing new technologies to bear on existing problems. He described how his TNE success is characterized by substantial fundamental research which, coupled with advanced robotic engineering, has enabled the creation of the most advanced prototype upper arm prostheses available anywhere in the world. Kuiken stressed that while the constituent technologies may have some form of enabling potential, concept devices such as his are not likely to be commercializeable for some time in the future. Like Charbel, Kuiken found an intensely personal motivation in developing tools that would be useful in treating his patients. Kuiken also talked at length about the inevitable collaboration involved in any successful TNE research model. He compared collaboration to marriage—partners must first meet several times to determine the likelihood of a long-term and successful bond. Kuiken's presentation was capped with a demonstration of his enabling technology allowing for biological control of an artificial arm system. He introduced Mr Jesse Sullivan, a former electrical lineman who became a double amputee after an on-the-job accident. Mr Sullivan elegantly demonstrated the capabilities of his unique system. His presence was a strong and motivating reminder of the end-user's role in the translational research process.

Doug Sheffield, DVM, PhD spoke at the symposium on behalf of industry. At the time, Dr Sheffield was serving as

Director of New Technologies at NorthStar Neuroscience, a start-up company that had recently gone public. He supported the contention that one successful TNE model was based on accurate assessment of market needs and establishment of appropriate collaborators. Sheffield argued for a TNE research model heavily based on direct (and well-chosen) collaborations between industry and academics. His company favoured a hands-off approach on the experimental design and methods implemented by the academic collaborators but a hands-on approach in data review and company/academic lab interaction. He emphasized the importance of mutual trust between the two factions. He also emphasized the importance of clinicians in the research loop and like Schoichet, encouraged a strategy of starting small.

Joe Pancrazio, PhD and Program Director in the Neural Prosthesis Program at NIH spoke on behalf of the NIH and outlined its approach towards funding TNE research with particular emphasis on the National Institutes for Neurological Disorders and Stroke (NINDS). He began by pointing out that up to eight different institutes at NIH support TNE research, not just NINDS. He outlined the well-known NIH structure for funding revolving around both intramural and extramural efforts and how both can contribute to support of TNE research projects. He cautioned investigators looking for funding to expand their scientific horizons and focus on the translational research questions that need to be answered (as opposed to the questions that individual investigators might like to be working on). Because the NINDS' mission includes 'the reduction of the burden of neurological disease and injury' he argued strongly for research ideas that will break barriers and help push ideas from the lab bench to the clinic. To date, neural-engineering-related research has not become translational because it has not yet broken significant barriers of access to the clinic. As an example, he cited the large body of work on implantable electrodes. Dr Pancrazio also strongly recommends that scientists/engineers enlist help from clinicians and from industry. The clinicians bring an urgency and realism to the clinical problems while the industrial partners help ensure an effective path to market. He outlined two vehicles for funding via NINDS. The first is the Translational Research Program designed to support therapy development products. Although these products can be drugs, biologics or devices, only 1 in 94 applications to date have been device-oriented, a traditional focus among neural engineering academic researchers. Secondly, he discussed the Cooperative Program in Translational Research at NINDS, intended to catalyze the development of partnerships between basic and clinical investigators, and to stimulate agreements between the academic and industrial sectors. He reminded attendees to frequently contact NIH program managers for guidance.

Finally Vivian Weil, PhD from the Illinois Institute of Technology, addressed some of the ethical and philosophical questions arising from TNE research, Dr Weil strongly argued that academics define and embrace appropriate terminology and definitions with respect to the idea of translational neural engineering. In her talk, she identified a dual meaning of the term 'translational' that incorporated the traditional process of carrying research from the laboratory bench to clinical implementation as well as a less-discussed use of the term to refer to the forging of a common language among specialists from different disciplines. She strongly argued that academics recognize and address ethical issues that arise in both sorts of translational enterprises. She identified key features that characterize the translational process: multi-disciplinary actors, differences in language and concepts among different specialists and areas (engineers versus physicians, for example), and a common motivating factor of addressing unmet market needs. This last factor plays a critical role in the way translational research intersects with governments and societies. In view of the considerable evidence of variation in norms and standards—including ethical standards—across disciplines, the risk of miscommunication and misunderstanding is too serious to ignore. Translation is not simply finding a dictionary equivalent. It requires an effort to forge a common language in collaborative research and development. Codes of ethics might help by addressing such issues as joint publication across disciplines. Translation in the usual sense demands that engineers and scientists be alert to ethical concerns at junctures along the way. For example, at the bench, they may have to anticipate worker safety issues in implementation. To avoid certain adverse outcomes, they may have to recognize the necessity of prompting researchers in outside specialties such as toxicology to initiate research. Such pressures from translation in both senses point to an expansion of the role of scientist and engineer. It comes with the indicated expansion of the sphere of responsibilities. Dr Weil summarized her talk with a look to the future for translational neural engineering research. She pointed to the usefulness of explicitly formulating or adding to codes of ethics to address the expanded role of scientists and engineers and to help develop a common level of understanding. She further encouraged scientists to better recognize their important roles in the intersection between science, technology and society. In that respect, she called for scientists to become more self-conscious agents in social interactions in which they are implicated, questioning, as policy makers do, for whom the research should be targeted.

Conclusion

Our symposium brought together a varied cast of experts in the nascent field of translational neural engineering in an attempt to compare and contrast ideas and expectations on the field from a wide range of disciplines. It is clear to us from the day's reports that translational research has certainly arrived in the broad research landscape that comprises neural engineering. It is also clear that the intersection between a diseased nervous system and potential therapeutic approaches is fraught with ethical, medical and scientific challenges. To date, in the academic research sector, this intersection is heavily weighted towards interface-type devices (electrodes for stimulation, nerve-growth conduits for regrowth, sensors for brain blood-flow monitoring etc). However, at NIH,

only 1 in 94 translational research applications has been device-based. Clearly, traditional academic researchers have been slow in identifying clinically-relevant opportunities and establishing the necessary clinical partnerships that are so vital to the translational research process. The translational research challenge thus continues to be demonstrating device safety and efficacy while ensuring/generating a viable commercial market. Because any number of different pathways might serve individual research teams, the speakers could offer no single effective formula for ensuring translational research success. In the most successful approaches, clinicians and engineers were inextricably linked, and this linking took place as early in the development process as possible. Likewise early commercial partner involvement was essential, particularly for academic researchers with limited experience. These observations from established experts in translational neural engineering research provide essential guidance for traditional academic researchers.