Engineering Tissues and Organs: The Road to the Clinic

With recent advances in both gene editing and stem cell biology, the promise of cellular therapies is now closer than ever. Clinical trials for the application of chimeric antigen receptor T cells has driven an enormous investment into the development of such cellular products and learnings from these emboldening investors and engaging regulators across the globe.

Making the Right Complex Tissue

Melissa Little
Murdoch Children's Research Institute
Royal Children's Hospital and the University of Melbourne

With recent advances in both gene editing and stem cell biology, the promise of cellular therapies is now closer than ever. Clinical trials for the application of chimeric antigen receptor T cells has driven an enormous investment into the development of such cellular products, and the learnings from these are emboldening investors and engaging regulators across the globe. There remains much to be learned for such high-risk and high-cost products, particularly because it is not a simple matter of shoehorning such products into the standard pharmaceutical development pipeline. The more challenging prospect, however, is with the recreation of structurally complex multicellular tissues and even replacement organs. As the push of the science and the pull of the patients grows, the constriction point in the middle sits with ensuring congruence between what is being built and what is genuinely needed. Both engineers and scientists need support to pivot their focus toward product development in the full understanding of the required endpoint. This will need the embedded involvement of clinicians and upskilling along the development pipeline, particularly around cellular manufacturing. In the pluripotent stem cell field, our capacity to use developmental biology principles to recapitulate the patterning of multicellular tissues *in vitro* is a very exciting advance. Here is the point at which engineering principles are essential to assist in both scale up and scale out but also in maturation and tissue viability with scale.

Aging and Tissue Regeneration

Guang-Hui Liu
Institute of Zoology, Chinese Academy of Sciences

Age is the major risk factor for most chronic human diseases. As a consequence, "anti-aging" strategies are being pursued as a way to prevent and treat age-related disorders.

As we age, our stem cells undergo functional decay and exhaustion. This decline leads to compromised tissue regeneration, which in turn promotes organismal aging. Therapeutic approaches that promote tissue regeneration and repair could therefore potentially mitigate aging and its deleterious effects.

Currently, there are three main methods to promote tissue regeneration: (1) supplement tissues with exogenous stem or progenitor cells; (2) chemically stimulate *in situ* stem cell expansion, differentiation, and/or somatic cell transdifferentiation; and (3) rejuvenate endogenous stem cell pools with specific biological factors. In animal models, these methods can alleviate diverse aging syndromes, including neurodegeneration, vascular degeneration, myocardial infarction, and osteoarthritis. Technological advances allow us to further improve these strategies to repair degenerating organs. For instance, genetically enhanced stem cells and vascular cells with improved efficacy and safety were recently generated by editing longevity genes and tumor suppressors. Approaches to activate tissue regeneration could also be optimized by targeting cellular senescence and regeneration pathways. Overall, engineering tissues and organs that resist aging would transform regenerative medicine, providing a potential "silver bullet" against chronic disease.

Brain-Computer Interfaces

Krishna V. Shenoy
Stanford University

Brain-computer interfaces (BCIs) have advanced considerably in recent years with tremendous new opportunities, and also challenges. The central idea of BCIs is that reading information out of a population of neurons in the brain to help people with paralysis communicate or to move prosthetic limbs; writing information into neural populations to help people see, feel, or both; and to address psychiatric and cognitive disorders, has been in the scientific dialog for decades. Progress on these next-generation BCIs has been inspired by the considerable recent success of cochlear implants, retinal prostheses, and brain stimulators for tremor and seizure control. Progress is rooted in fundamental new basic neuroscience discoveries in both pre-clinical animal models and in clinical trials, as well as rapidly evolving neurotechnology. Over the past 15 years there have been remarkable demonstrations in early clinical trials, including quickly and accurately moving prosthetic limbs and sensing their interactions with objects; quickly and accurately controlling numerous standard applications running on computers and tablets; and decoding intended speech. The past five years has also seen the creation of companies aiming to establish these new BCIs as standard of care. This is also an appropriate time to assure that neuroethics plays a central role in helping guide this increasing ability to read out and alter brain states that are central to our mental lives. If successful, important new treatments for neurological injury and disease might soon be at hand.

Your Disease on a Chip

Gordana Vunjak-Novakovic
Columbia University in the City of New York

The future of medicine is becoming increasingly focused on the individualized approach to the patient's genetics, the context of disease or injury, and the diversity of patients and their diseases. When a disease presents itself, the treatment should be tailored to the patient and the condition being treated, given that every individual could respond differently to a treatment because of their unique genetics, physiology, disease heterogeneity and interference with other medical conditions. Still, current treatments are largely based on population studies, which is at least in part due to the lack of predictive, patient-specific models of disease.

Once available, individualized models of "disease on a chip" could be routinely used for diagnosis, prognosis, and patient-tailored drug screening. Tissue engineering is responding to this need by building micro-sized human tissues from blood-derived pluripotent stem cells and connecting them into patho/physiologically relevant units. Microphysiological platforms, representing single or multiple organ systems, emerged less than ten years ago and are already used by the pharmaceutical industry for testing of drug safety and efficacy. Surprisingly and importantly, the predictive modeling of diseases and testing of drugs are becoming a fast-track application of tissue engineering by capitalizing on methods originally developed for regenerative medicine.

When Am I going to Have a New Heart?

Milica Radisic
University of Toronto

I still remember the day, 21 years ago, when I was mesmerized by a Langer and Vacanti article in *Scientific American*, which described the new discipline of tissue engineering (Langer and Vacanti, Scientific American 280, 86–89). We envisioned semi-bionic humans, whose organs would be replaced on demand, in 2020. Progress, however, has been more challenging than expected.

Despite notable successes such as living skin substitutes, larger vascularized organs such as the liver and heart still remain to be replaced. The growing impatience of both the scientists and the public with the slow translation process could be summarized with a question I received after one of my lectures: "Enough is enough. When am I going to have a new heart"?

This is a good opportunity to pause and remind ourselves that we should learn how to walk before we run. Large vital organs are made up of many sub-parts that often fulfill opposing functions, thus they have different design criteria. A heart is made of atria, ventricles, heart valves, blood vessels, and many different cell subtypes. It is necessary for us to learn how to make those sub-parts first, before putting the whole heart together.

Many cellular therapies have shown success in pre-clinical and small-scale clinical studies focused on niche applications, such as pediatric medicine. The classical tech-transfer approach, where new start-ups try to take giant leaps to translate these therapies into larger markets can often lead to failure. We would benefit from envisioning a new translation process—and funding mechanisms to support it—that would bring therapies for smaller subgroups of patients to the market. Simply stated, the field would move faster if we took many smaller steps, rather than one giant leap.

I remain convinced of the bright future of tissue engineering. Soon we might see tissue-engineered blood vessels in use and more complex organs to come.