

# Emerging Trajectories for Next Generation Tissue Engineers

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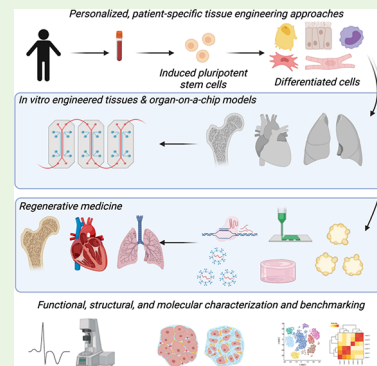
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**ABSTRACT:** The field of tissue engineering has evolved from its early days of engineering tissue substitutes to current efforts at building human tissues for regenerative medicine and mechanistic studies of tissue disease, injury, and regeneration. Advances in bioengineering, material science, and stem cell biology have enabled major developments in the field. In this perspective, we reflect on the September 2021 virtual Next Generation Tissue Engineering symposium and trainee workshop, as well as our projections for the field over the next 15 years.



**KEYWORDS:** tissue engineering, bioengineering, regenerative medicine, biomaterials

## ■ TISSUE ENGINEERING: THE NEXT GENERATION (2005)

In May 2005, the first Tissue Engineering: The Next Generation meeting was held in Boston, with cochairs Profs. Gordana Vunjak-Novakovic and David Kaplan bringing together the current and emerging leaders in the then newly developing field.<sup>1,2</sup> From its early beginnings in the 1980s and 1990s, tissue engineering as a field was primarily focused on the use of cells as materials for replacement and regeneration of damaged organs in the body. In 2005, the majority of investigators were focused on exploiting developmental biology to control stem and progenitor cell fate and engineering functional replacements for a few key tissues, including cartilage, bone and heart muscle. In addition, emphasis was placed on advancing from monolithic and static biomaterials to more complex and dynamic biomaterials. The meeting highlighted the need for cross-disciplinary approaches to advance and inform the design of tissue systems.

## ■ TISSUE ENGINEERING: THE NEXT GENERATION (2021)

Just over 15 years and a global pandemic later, the second major gathering was held in September 2021 virtually over Zoom, co-organized again by Profs. Gordana Vunjak-Novakovic and David Kaplan, with the goal to further explore the foundations of tissue engineering and its clinical translation, well past the expectations envisioned in the inaugural meeting. Since 2005, there have been major developments in related fields, including stem cell biology, molecular biology,

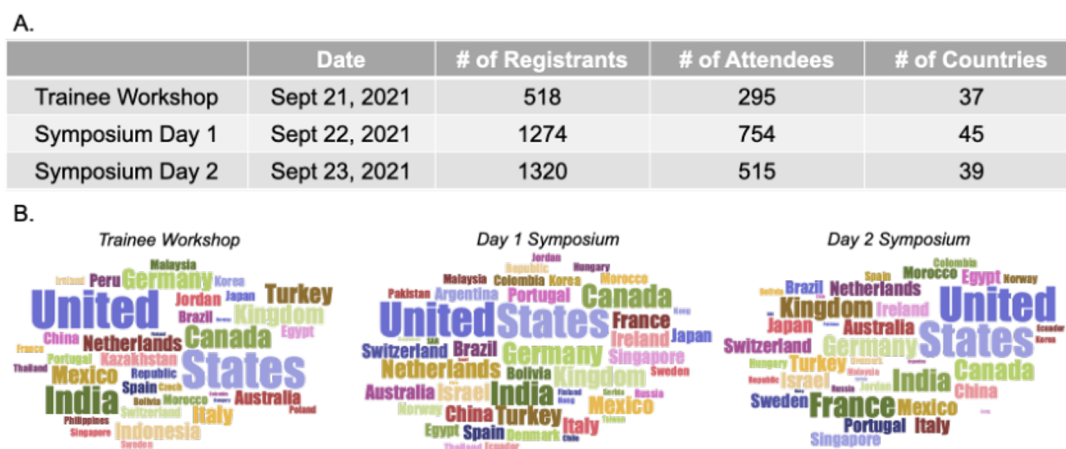
and materials science. The advent of critical new tools to manipulate cells, including induced pluripotent stem cells (iPSCs) and gene editing technologies, has provided an increased motivation for designing personalized approaches to tissue engineering, further facilitating clinical translation of patient-specific treatments.<sup>3</sup> To that end, the field has expanded from a focus solely on engineered tissues for replacement or regeneration of human organs, to human tissue models to better understand biology, disease, and toxicity in vitro.<sup>4,5</sup> Leaders of the field in academia, industry, and government agencies gathered together to discuss biological principles, enabling technologies, and scientific barriers for translating engineered tissues of increasing biological fidelity into products benefiting the patients.

On day 1 of the symposium (September 22, 2021), the program began with a keynote lecture from MIT's Dr. Robert Langer on technologies that enabled the development of tissue engineering as a field, from early antiangiogenic controlled therapeutics, biomaterials, and controlled delivery systems. Day 1 continued with sessions on (i) Biological Principles, featuring speakers Sharon Gerech (Johns Hopkins), Kristi Anseth (University of Colorado), Tejal Desai (University of

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**Figure 1.** Symposium demographics, including (A) table of registrants and (B) word map of participating countries during the entirety of the meeting.

California at San Francisco), Milica Radisic (University of Toronto), Celeste Nelson (Princeton University), and Joseph Wu (Stanford University); (ii) Enabling Technologies, featuring Jason Burdick (University of Pennsylvania), Samira Musah (Duke University), Andrés García (Georgia Institute of Technology), Elizabeth Cosgriff-Hernandez (University of Texas at Austin), Peter Loskill (University of Tübingen), and David Mooney (Harvard University); and (iii) a closing roundtable discussion on Scientific Barriers with Sheila Chari (*Cell Stem Cell*), Sergiu Pasca (Stanford University), Pep Pàmies (*Nature Biomedical Engineering*), and moderator Kara Spiller (Drexel University).

On day 2 of the symposium (September 23, 2021), National Institute of Biomedical Imaging and Bioengineering (NIBIB) Director Dr. Bruce Tromberg opened with a keynote lecture on the role of the NIBIB and governmental funding agencies on accelerating technology development in tissue engineering. This lecture was followed by sessions on (i) Engineering Complexity, featuring speakers Jennifer Elisseff (Johns Hopkins University), Christopher Chen (Boston University), Warren Grayson (Johns Hopkins University), Christine Mummery (Leiden University Medical Center), Dan Huh (University of Pennsylvania), and Shulamit Levenberg (Israel Institute of Technology); (ii) Translation, featuring Laura Niklason (Yale University, Humacyte), Karen Christman (University of California San Diego), Donald Ingber (Harvard University), Lucie Low (National Institutes of Health), Guillermo Ameer (Northwestern University), and Molly Stevens (Imperial College London); and (iii) a concluding roundtable discussion on Commercialization with Cato Laurencin (University of Connecticut), Nina Tandon (Epi-Bone), Orin Herskowitz (Columbia Technology Ventures), and moderator John Fisher (University of Maryland).

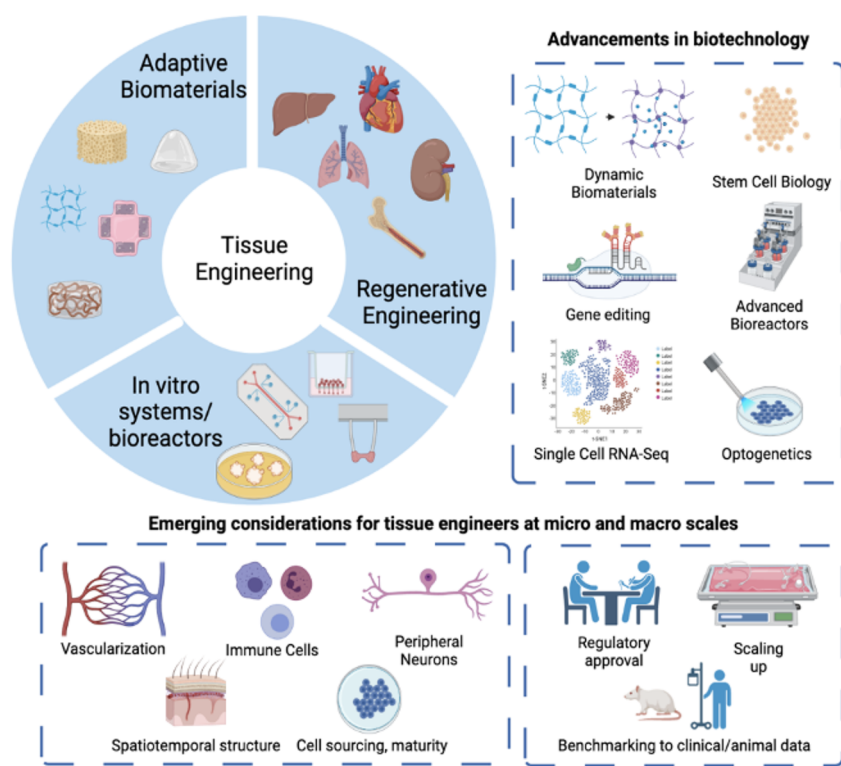
Unlike the 2005 meeting, the speakers in this meeting largely focused on the considerations of highly complex tissues with increasing biological fidelity, including in vitro models with patient-centric designs (i.e., all cells derived from single iPSC donors), systemic considerations (i.e., multi-organ-on-a-chip, immune cells, vascularization), and highly complex architectures (i.e., advancements in cell-instructive organization, responsive and dynamic biomaterials, 3D bioprinting). Furthermore, the emphasis on translating biotechnological tools to accelerate patient benefits was far greater.

## ■ NEXT GENERATION TISSUE ENGINEERS: TRAINEE WORKSHOP (2021)

In the early days of the COVID-19 pandemic, the number of opportunities for trainees to present at national or international meetings was limited, leading to an introduction of “trainee-for-trainee” meetings. These not only enabled rising scientists to present their research and network but also provided opportunities for trainees to conceptualize, organize, and implement scientific gatherings with an international reach. The Next Generation Tissue Engineers Trainee Workshop was organized by trainees from Columbia University (Dr. Pamela Graney, Dr. Sharon Fleischer, and Naveed Tavakol), and Tufts University (Thomas Falcucci). The goal of the workshop was to promote tissue engineering through dissemination of research and establish a community for continued exchange of ideas and collaborations among emerging bioengineers.

Speakers were chosen from a global and diverse pool of applicants, with limited overlap among similar institutions, based on developments in critical areas of (i) Responsive Biomaterials, featuring Kiet Tran (Rowan University), TianBai Wang (Boston University), Max Yavitt (University of Colorado Boulder), and Laura Alderfer (University of Notre Dame); (ii) In Vitro Systems and Bioreactors, featuring Miryam Adelfio (University of Massachusetts-Lowell), Daniella Fodera (Columbia University), Vivek Yadav (University of Notre Dame), and QingHua Wu (University of Toronto); and (iii) Regenerative Engineering, featuring Katherine Leiby (Yale University), Kelsey Collins (Washington University of St. Louis), Christopher Anderson (Yale University), and Bo Ri Seo (Harvard University). The featured presenters took novel approaches to assess and control cellular phenotype and tissue function, like real-time imaging, biophysical stimulation, and single-cell characterization, to apply these new technologies to existing or new scientific barriers, like COVID-19, for example.

Uniquely, the trainee meeting featured a vibrant “career conversations” discussion featuring panelists from various bioengineering career disciplines including Brendon Baker (academia, University of Michigan), Caitlin Czajka (scientific publishing, *Science Translational Medicine*), Misti Ushio (industry, TARA Biosystems), and Seila Selimović (governmental funding, BARDA, U.S. Department of Health and Human Services), highlighting the breadth of opportunities available to bioengineers. The symposium concluded with an



**Figure 2.** State of the field of tissue engineering. Innovations in biomaterials, regenerative engineering strategies, in vitro systems, and biotechnology have propelled the advancement of tissue engineering over the last 20 years. Emerging considerations for continued acceleration focus on building complexity into existing models and enabling translation to patients. Created with Biorender.com.

informal happy hour, where a number of international participants exchanged thoughts on bridging the geographical and interdisciplinary distances in collaborative research for future impact on the field.

To advertise both the trainee workshop and the full symposium, we used a number of virtual resources generated throughout the COVID-19 pandemic period to advertise registration and abstract submissions. *Tissue Talks*, a seminar series that began during the early weeks of the pandemic to allow for dissemination of tissue engineering speakers to the international community, already had a consistent weekly following and email listserv, which was an easy method to advertise the upcoming symposium. Further, Twitter and LinkedIn allowed the co-organizers to post and advertise the symposium program, with reminders to trainees to submit abstracts for the oral presentations. Of note, these virtual symposia were free of charge to all registered attendees, allowing for anyone to participate. Further information on symposium programming, titles and individual sessions can be found at [nextgenterc.com/symposium](https://nextgenterc.com/symposium).

The trainee workshop attracted more than 500 registrants and 295 live Zoom attendees, whereas more than 1400 unique registrants and 500–800 attendees gathered virtually over the two-day symposium (Figure 1). With participants from approximately 45 countries, the virtual symposium format facilitated the international presence of the Next Generation meeting and the field as a whole. To that end, individuals from around the world were able to access the recordings of the symposium for up to 2 weeks after the event, with a number of individuals attending asynchronously from Asia and Oceania.

## STATE OF THE ART IN THE FIELD

In this perspective, we assess the state of the field and future directions in the areas of advanced biomaterials, regenerative engineering, and in vitro engineered tissues and offer our perspective guided by the speakers and discussions from the 2021 Next Generation Tissue Engineering meeting.

**Biomaterials.** Since the onset of the field of tissue engineering, research has strived to improve the properties, compatibility, and function of biomaterials. Over the years, a myriad of materials, both natural and synthetic, have been investigated for use in implantable materials, and in vitro models, to pioneer our understanding of mechanobiology, regenerative medicine, and developmental biology. The field of biomaterials continues to be rejuvenated as novel chemistries and practical synthetic approaches push the boundaries of what is capable at this time. Now, researchers are looking beyond the material used simply as a vessel for engineered tissue and toward developing dynamic and responsive materials for probing and manipulating the tissue environment (Figure 2).

The common goal among different applications of biomaterials is to recapitulate the features of native tissues from the nano to the macroscale and coerce cells into recognizing and interacting with the material as a tissue. This includes replicating the complex cell–matrix interactions during tissue development and disease, such as growth factor release and activation, pericellular mechanics, or matrix-mediated cell alignment or cross-talk. What were once early visions of reproducing these dynamic systems are now being realized with the advent of click chemistries, 3D printing, and optical technologies, ultimately improving our understanding



of the role that the extracellular matrix (ECM) plays in our tissues, both in vitro and in vivo.

This push to advance the features and utility of biomaterial designs has largely been driven by interdisciplinary collaborations at the interfaces of materials science, chemistry, biology, and engineering. Unfortunately, there remain large obstacles to capturing the complexity of the native microenvironment in engineered tissues. Biological time scales, tissue heterogeneity, and structural hierarchy are key features that will be critical for further advancing the field. Moreover, addressing constraints in translation from the lab bench to the clinic will be necessary to realize the therapeutic potential of these technologies. For example, complex material chemistries to achieve refined functions conflict with regulatory approval paths that trend toward simpler solutions, leaving creative materials systems at the bench because of hurdles that need to be navigated to get to the clinical level.

As we continue to develop more complex material systems, they remain limited by accessibility, reproducibility, and scaling. To provide material systems that are capable of resolving global biomedical challenges unbiasedly, availability must not be a bottleneck. For this reason, the development of materials that can be universally adapted to patient-specific parameters regardless of gender, race, or socio-economic status is an active area of pursuit and has recently been driven by the prospect of bioprinting and immunomodulatory materials. There also remains the need to standardize and validate materials for clinical trials. The process for starting clinical assessments and achieving Federal Drug Administration (FDA) approval is arduous and often fraught with failure, which is frequently a result of inability of model systems to assess the therapeutic potential of a drug or material in humans. Although in vitro models have proved auspicious toward replacing canonical animal studies for pharmaceuticals, biomaterials remain at an impasse. Entire organ systems are often needed to fully capture the complex and extensive response to an implanted material, thus restricting validation to animal models.<sup>5</sup> Only recently has research pivoted toward developing in vitro systems to replace animal studies in assessing the therapeutic potential of biomaterial platforms, as discussed later in this article.

**Regenerative Engineering.** Notable advancements in stem cell biology and material science, together with insights from systems engineering and developmental biology, have propelled regenerative engineering forward, shifting the focus from engineering tissue replacements for the repair of single damaged or diseased tissues to regenerating native tissues and organ systems for treating a variety of clinical conditions (Figure 2). Today, most regenerative engineering approaches rely on the differentiation of iPSC-derived cells into cardiomyocytes, hepatocytes, and alveolar epithelial cells, among others. Though promising, this approach has been constrained by methods to drive cell maturation and differentiation into more specialized cell types. To address this need, emerging differentiation protocols focus on cell maturation by biochemical and physical cues and rely on insights from developmental biology to identify the cues required to generate cellular subpopulations. In addition, there is a strong emphasis on scaling-up differentiated cell production and for the development of more standardized protocols to meet clinical translation requirements.

The emergence of new experimental tools and techniques have greatly enhanced the translational potential of regener-

ative engineering. For example, CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9) gene editing enables researchers to modulate cells, imparting enhanced regenerative capabilities, such as improved proliferative capacity and secretion of regenerative factors in a tunable and controlled manner. Through gene editing, damaged cell populations can be genetically repaired in a patient-specific manner. When used in combination with cell delivery, in situ gene editing offers a promising therapeutic approach for targeting and selective replacement of diseased cells in patients. Other tools that have revolutionized regenerative engineering include single cell sequencing, which probes the cellular composition of the tissue being regenerated to provide a better picture of the specific cell populations in the tissue and study the efficacy of regenerative approaches for those cells.

As new technologies emerge to build higher fidelity tissues and manipulate damaged tissues in situ, the relationship between functionality and structural complexity will inform future designs. Spatiotemporal control of cell and tissue functions will remain crucial, and technologies that selectively control cell fate, like optogenetics and magnetic patterning, will garner support in generating structurally organized and biologically complex tissues. Another critical consideration that will continue to inform regenerative engineering approaches is the immune response to implanted tissues and therapeutic strategies. Understanding tissue functions at the organ and system levels will drive new approaches in regenerative medicine that will ultimately enable a patient's own body to be harnessed for directing tissue repair and regeneration.

**In Vitro Systems and Organs-on-a-Chip.** As discussed at the 2005 meeting and realized over the past decade, the tissue engineering community has placed a strong emphasis on the use of engineered systems to model human organ functions in vitro. Whether in the form of 3D multicellular models or organ-on-a-chip systems (OOC), these in vitro tissue mimics are designed to recapitulate one or just a few functions of individual organs, toward establishing human-relevant models of disease and drug toxicity.<sup>6</sup> Bioengineered systems can vary between simple 3D self-assembling aggregates, like organoids, and multicellular, spatially organized engineered human tissues, which in the latter often include microenvironmental factors to recapitulate the structural complexity of a given organ. Microfluidic OOC systems include biophysical stimuli to support fluid flow, migration, and interaction between individual engineered organs to multiorgan systems. To date, there have been engineered tissue models or OOC models for a variety of organs, including cardiac muscle, liver, lung, bone marrow, vasculature, brain, kidney, and cartilage, with an increasing number of new models each year.<sup>7–13</sup>

One of the key considerations for these new engineered tissue models is their utility for patient-centric models of organ functions. With the introduction of iPSCs, many engineered models have enabled recapitulation of select tissue functions with respect to an individual patient or diseased population. To that end, similar to how single-cell transcriptomics and CRISPR/Cas9 gene editing technologies have allowed for major developments in regenerative medicine endeavors, these tools have supported an increased understanding of mechanisms and potential therapeutic targets of diseased patient groups.<sup>14,15</sup> As human in vitro models increasingly gain popularity among basic and translational scientists, their

value only adds to—not replaces—the functions of animal models and other preclinical systems.

In the past five years, there has been a shift from single OOC models to multi-organ, “human-on-a-chip” models of systemic diseases and drug toxicity. By including multiple engineered organ components, studies of systemic diseases, like cancer and inflammation, may result in better recapitulation of human physiology than that of a single organ system. For studying drug efficacy and safety, multiorgan systems demonstrate utility for studying on-target effects (to an engineered tumor tissue or primary organoid sample) and off-target effects (to an engineered cardiac muscle or liver tissue).<sup>16–18</sup> Further, these models may incorporate engineered immune organs, like bone marrow or lymph nodes, which may allow for representative immune cells to infiltrate and respond during injury or regeneration.<sup>19,20</sup> For systemic diseases like cancer, envisioned uses of multiorgan systems can aim to recapitulate unpredictable phenomenon like metastasis entirely “in a dish.”

Nevertheless, these promises are challenged by a critical need to benchmark findings to those of published human data in order to create robust systems that may inform therapeutic development and provide mechanistic insights into disease. In simple terms, it is important to identify both the utility or strengths of these systems, as well as the limitations. Notably, many existing models lack the systemic elements of the body in engineered in vitro systems, demonstrating the large need to incorporate immune elements, vascularization, and innervation into complex engineered tissues, as tissue function will change in response to higher biological fidelity.<sup>19,21–23</sup> Further, throughput of engineered models and OOC systems must increase for rapid widespread adoption of the technologies, especially for studying larger patient populations in biological studies.<sup>24</sup> These factors need to be balanced against overdesign and complexity, which may then limit utility, translation, and adaptability.

Although OOC and in vitro systems may still be in the developmental stages, they are already aiding in studies of disease and repurposing of drugs, such as in studying the changes associated with SARS-CoV-19.<sup>25–29</sup> Cases of rapid employment and use of engineered tissues may facilitate further governmental support of in vitro mimics to accelerate the FDA approval pipeline, potentially reducing the time from drug development to the market.

## ■ FUTURE PERSPECTIVES

The field of tissue engineering is reaching new frontiers as we continue to expand our biotechnological toolbox and gain a deeper understanding of human cell-, tissue-, organ- and system-level functions. In particular, the collective innovations in biomaterial designs, regenerative engineering, and in vitro model systems now enable large-scale, population-wide study of race, age, and sex-specific models of human health and disease. Sex-specific differences have often been overlooked when engineering biomaterials and tissues, despite obvious gaps in our understanding of how sex-specific factors contribute to patient health. Tissue engineering offers the potential to stratify these effects and identify factors that may be targeted for improved therapeutic intervention. These models can be applied to OOC systems, which can be further harnessed to inform regenerative engineering therapies. Similarly, questions of age, disease state, and other differences can be addressed with the technologies mentioned here, in

ways that have been either ignored or too challenging to address using animal models.

Bioengineering discoveries and their path to market will continue to depend on the regulatory infrastructure. We believe tissue engineering must pave the way for bringing the discovery from the bench to the clinic. As translation of regenerative technologies involves far more regulatory barriers for cellularized devices as compared to acellular implants, there is an increased emphasis on in vitro tools that can translate human drug testing and disease modeling in a shorter timeline. As tissue engineered technologies reach clinical eligibility, scale-up, and donor variability challenges will emerge as major considerations. Similarly, as limitations with the use of animal models due to regulations, ethics, or costs continue to increase, in vitro models will become more and more critical to scientific discovery and translation, in both academic and industrial settings. Further, the rapid development of these in vitro tools for tissue formation are already providing a foundation for other areas of technology impact, such as foods of the future via cellular agriculture, robotic designs for actuators, and more sustainable technologies into the future. We are just at the start of realizing this impact.

We could not discuss the future of tissue engineering without acknowledging the next generation of rising bioengineers. There is an increasing reliance on trainees as motivators in shaping the future of the field, with many trainee-focused opportunities helping build a cohort of leaders to address areas of improvement in the future. A common theme in the symposium discussions was the bridge between collaborative groups from related but distinct scientific fields. The aggregation of technological advancements in bioengineering, stem cell biology, developmental biology, synthetic biology, systems biology, materials science, chemistry, and medicine, aid in the translational efforts to see technology impact patients faster, with a myriad of tools being used in concert to either understand disease progression or treat the injury/disease itself.

International collaborations and networks are instrumental for the global impact of tissue engineering in finding solutions to unique problems in human health. To that end, funding mechanisms to support technological developments must emerge to provide the appropriate outlets for bioengineering advancements, including international synergies. With an increasing number of large pharmaceutical companies having an interest in OOC and bioengineering approaches to regeneration, there is a unique bridge between the academic and industrial worlds. These efforts can further support trainee career opportunities, allowing for scientists with diverse backgrounds to seek opportunities to lead tissue engineering efforts across academia and industry throughout the world. Aside from funding, exploiting online platforms, such as Twitter, for global networking and disseminating resources through open-access systems will remain critical to recruiting a diverse next generation of tissue engineers.

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## Notes

The authors declare no competing financial interest.

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