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Perspectives on Recent Developments and Directions in Tissue Engineering and Regenerative Medicine

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This perspective article draws on lessons learned at the 7th TERMIS World Congress held in Seattle, Washington in June 2024. This gathering of prominent researchers and translational scientists in tissue engineering and regenerative medicine (TERM) from around the world provided a forum to consider the impact of tissue engineering and its future directions. New frontiers are considered in the context of global challenges, including clinical translation and recent advances in pediatric tissue engineering, supercritical fluid technology for scaffold fabrication and sterilization, and learning from successful failures in tissue engineering and regenerative medicine. Bench-to-bedside translational strategies, inclusive research strategies, regulatory hurdles, and ethics linked to navigating responsibilities and innovations, are identified as important drivers in the field.

Keywords: tissue engineering, regenerative medicine, perspective, directions

Impact Statement

This perspective article draws on the 7th TERMIS World Congress to showcase how innovations in tissue engineering and regenerative medicine are continuing to address global challenges. By exploring the interplay of science, ethics, and translation, the article highlights strategies to accelerate clinical impact, foster interactions, and redefine success in advancing regenerative technologies for real-world applications.

Introduction

The theme of the 7th TERMIS World Congress (June 2024) was “Coming Together to Design Better Healthcare for All,” which set the stage for strategies to address the new frontiers in the field of tissue engineering and regenerative medicine (TERM) (see Supplementary Data S1). This international event brought leading experts from around the world to

discuss translational strategies to bring innovations from the lab to the clinic and how inclusive research practices are critical to ensure diverse perspectives are considered and therapies provide equitable outcomes for all patients. The ethical dimensions of TERM were also highlighted and thought leaders discussed guiding principles in navigating responsibilities and innovations of this rapidly evolving field. Herein, we provide a brief overview of these discussions and our perspectives on

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addressing the ethical, translational, and inclusive research challenges within the field of TERM.

New Frontiers in TERM

Global challenges on TERM research and its translation

The ultimate mission of TERM is to develop tissue-engineered products that improve patient quality of life. Despite the large number of research articles published on TERM each year, the question remains: why have these efforts not led to more widespread adoption of tissue engineering therapies in the clinic? This was the subject of the Fellows of Tissue Engineering and Regenerative Medicine Panel on “Global Challenges in TERM Research and Its Translation.”

One of the primary global challenges in TERM research and its translation is the high cost of scaling up production, which has led to substantial expenditure of limited investments, resulting in numerous corporate closures. In addition, the globalization of health care presents further challenges, as most countries cannot afford the high cost of tissue-engineered products and therapies. Moreover, the complexity of creating denser organ-like constructs continues to slow progress, requiring innovative approaches for tissue vascularization and innervation. These challenges have limited TERM’s impact on day-to-day clinical therapies. By way of example (here and below), to address these challenges, Professor Buddy Ratner (University of Washington) has pioneered an innovative approach that leverages the human body as a natural bioreactor to bypass expensive biomufacturing processes and complicated surgical procedures. By utilizing the inherent capabilities of the body, such as temperature regulation, oxygen supply, sterility, and precision growth medium with biological molecules, Ratner’s team has developed a precision porous biomaterial, trademarked as STAR™. This biomaterial is implanted without the need for external cells or proteins, leading to positive outcomes in over 2400 humans.

The translation of TERM products to clinical settings is also considered highly challenging in South America, such as in Colombia as highlighted by Professor Martha Fontanilla (National University of Colombia). These challenges include financial and regulatory issues, the need to scale up the production process, the importance of close collaboration between researchers and clinicians, as well as positive personal and institutional motivation. At the precommercial and commercial stages, factors such as product patenting, patent licensing, preclinical and clinical studies, company operation strategies, and business operations can create barriers to commercial translation. Overcoming these challenges requires a strategic approach, including diversifying product portfolios, conducting marketing surveys, implementing clear marketing policies, training sales teams effectively, and finding effective ways to convey the clinical benefits of TERM products to health care providers. Addressing these factors will be key to making TERM therapies more accessible and improving patient outcomes.

Professor Antonella Motta (University of Trento, Italy) considered another central challenge in the clinical translation of tissue-engineered products, which is the lack of biological function, and highlighted the importance of

considering difficulties in replicating complex biological processes through engineered tissues or products. To address this challenge, innovations in biomaterials design, such as incorporating vascularization and immunomodulation, must be integrated with advanced biofabrication techniques that allow for precise control over tissue structure, ultimately defining a clear roadmap to clinical applications. Integration of these strategies with interdisciplinary collaboration and cost-effective scale-up processes will be crucial to the successful clinical translation of TERM technologies.

Pediatric Tissue Engineering—Clinical Translation and Recent Advances

Pediatric tissue engineering is a rapidly evolving field within TERM, focused on creating or regenerating tissues and organs for children, and noting that they have unique physiological needs compared with adults due to issues such as size, the need to accommodate growth, and a demand for long-term viability. Developing TERM approaches for pediatric patients requires a specialized focus on their distinct growth and developmental requirements as well as the wide range of conditions they may experience. Solutions must be carefully tailored to meet these needs while also being practical for clinical implementation. The field is progressing by adapting novel approaches to the design, manufacture, and repair of tissue-engineered products to meet these specific challenges.

In pediatric tissue engineering, several advanced technologies are making significant progress, either in clinical use or advanced preclinical development. For example, bioengineered organs such as the bladder and trachea have shown promising results in preclinical trials. Gene and cell therapies, particularly those using CRISPR and stem cells, are progressing toward treating genetic disorders and various pediatric conditions. In addition, 3D printing and customized scaffolds are in preclinical stages, aimed at creating patient-specific solutions, while smart bioactive materials are being developed to enhance tissue integration and functionality. These emerging technologies are pushing the boundaries of pediatric tissue engineering, addressing the unique needs of growing children and improving clinical outcomes.

Supercritical Fluid Technology for Scaffold Fabrication and Sterilization

With the rapid growth of innovations in TERM, the application of greener processes and effective sterilization methods for complex biomaterials has become increasingly important. These considerations are best addressed early in the research process. Supercritical fluid technology plays a crucial role in advancing tissue engineering by enabling the creation of high-quality, functional, and biocompatible scaffolds while also providing gentle and efficient sterilization processes. This technology can help solve key challenges in environmentally responsible bioprocessing, as well as the decellularization and sterilization of complex or bioactive biomaterials.

The utility of supercritical carbon dioxide (scCO₂) allows for precise control over scaffold properties, such as pore size, structure, and surface texture, ensuring optimal cell

growth and tissue formation. In addition, $scCO_2$ enables the fabrication of highly porous structures with biomimetic complex architectures. It also provides a gentle and effective sterilization method, avoiding the high temperatures and harsh chemicals used in traditional sterilization techniques, thus preserving the integrity of sensitive biomaterials. Another significant advantage of $scCO_2$ is its versatility in processing a wide range of materials used in tissue engineering, including polymers and natural biomaterials. However, challenges remain, particularly in the regulatory approval of $scCO_2$ -based processes. These include the need for validating and standardizing processing protocols, ensuring biocompatibility and efficacy, determining the appropriate regulatory classification, conducting long-term outcome studies, and managing the costs and resources for compliance. Addressing these challenges requires a thorough understanding of regulatory requirements, careful planning, and rigorous testing to meet all necessary safety and efficacy standards for utilization in tissue engineering.

Learning from Successful Failures in Tissue Engineering and Regenerative Medicine

Scientific advancement has traditionally depended on positive results and successful outcomes from the research community. The field of TERM has indeed made significant progress over the past two decades, thanks to valuable contributions and successful reports. However, negative experimental outcomes, such as a lack of correlation between *in vitro* cellular responses and *in vivo* treatment efficacy, are often viewed as failures and are frequently left unreported. This omission represents a substantial loss to the field, as these failures can offer crucial insights for advancing the field.

Learning from failures in TERM requires a comprehensive approach. Key strategies include thoroughly investigating the root causes of problems, refining experimental models and biomaterial designs, and adopting multidisciplinary and systems biology approaches. It is also worthwhile to publish and share negative results, as doing so enables collective learning, helping the scientific community understand what did not work and to help prevent the repetition of the same mistakes. Furthermore, a focus on translational research and close collaboration with clinicians ensures that experimental advancements are aligned with clinical needs. These steps can help overcome challenges, optimize technologies, and accelerate progress in the field.

Translational Strategies in TERM

Transitioning research from the benchtop to the bedside was discussed in the plenary session, “Translational Strategies in TERM: Panel Discussion on Regulatory Affairs, Manufacturing, and Scale Up.” Translational strategies in TERM are essential for bridging the gap between laboratory research and clinical application. These strategies help navigate regulatory affairs, optimize manufacturing processes, and address challenges related to scaling up production, ensuring that tissue-engineered products are safe, effective, and commercially viable. Compliance with regulatory standards is crucial for clinical translation and can be achieved through rigorous preclinical and clinical trials, navigating regulatory pathways, developing standardized processes and protocols, and identifying and mitigating risks such as

immunogenicity and toxicity to obtain regulatory approval. On the manufacturing side, scaling up tissue-engineered products from the lab to clinical and commercial manufacturing poses significant technical and logistical challenges. Process optimization is required to produce consistent, high-quality tissue-engineered constructs or scaffolds. In addition, these manufacturing processes must comply with Good Manufacturing Practice standards and be cost-effective in scaling production while maintaining product integrity and functionality. For complex biological systems such as cells and tissues, ensuring that they retain their functionality at larger production scales is critical. Achieving reproducibility and meeting regulatory requirements at higher production volumes are essential to maintaining product safety and efficacy.

Current challenges in translating cell-based therapies to patients include manufacturing scalability, regulatory complexity, high development costs, and logistical issues, such as cell preservation and distribution. Ensuring the safety, quality, and long-term efficacy of cell-based treatments is critical to eliminating concerns related to immune rejection and tumorigenicity. In addition, patient variability, ethical considerations, and high therapy costs create barriers to clinical adoption and reimbursement. Overcoming these challenges requires collaboration between academia, industry, and regulatory agencies as well as the development of advanced manufacturing processes such as cell culture systems, bioreactors, and new funding models to accelerate progress.

Regulatory pathways and guidelines for tissue-engineered products vary across regions, including the United States, Asia, and Europe, due to different regulatory frameworks, approval processes, and classification criteria. It is critical to consider ethical variations for cell-based therapies and clinical trial requirements in different regions to ensure compliance with the national bioethics guidelines. Researchers and companies must adapt their translational strategies based on the regulatory landscape of each region to ensure compliance and successful product approval,^{1,2} and this changing area merits regular review.

For a successful translational path, researchers should integrate long-term regulatory, manufacturing, and market considerations early in the research and development. Understanding and aligning with regulatory pathways, anticipating changes, and designing scalable and reproducible processes are critical for a smooth transition from research to market. Collaboration with regulatory agencies, industry partners, and clinicians can help streamline this process, ultimately leading to faster and more efficient product development.

Inclusive Research Strategies in TERM

In the evolving field of TERM, inclusive research strategies are paramount to ensure that advancements in therapies benefit diverse populations and address the broad spectrum of patient needs. This was highlighted in the plenary session with panel discussion, “Inclusive Research Strategies in TERM.” Designing better health care for all involves striking a balance between developing targeted therapies for specific groups and ensuring accessibility to broader populations. Although it might be pragmatic to initially design therapies for a few and then scale them, there is an ethical obligation to consider diverse patient variables

from the outset to avoid disparities in health care outcomes. A key point of this discussion was that by not studying relevant patient-specific variables such as sex, our ability to recognize significant effects of perturbations and interventions may be confounded. Incorporating diverse data sets and cell and tissue sources will enable researchers to create more comprehensive and effective therapies that improve outcomes for all patients. It was recognized that a primary challenge with this approach is that it requires a substantial investment given the cost and time associated with the expanded experimental design. This approach may slow progress due to increased costs and resource demands, but it ensures that treatments are effective across different demographics. In addition to these technical considerations in conducting TERM research, it is also crucial to foster an inclusive environment that embraces diverse perspectives and encourages innovative solutions in the field. As part of our ongoing efforts to build global communities, networking lunches offered members valuable opportunities to connect and exchange strategies that support the career growth and development of everyone in our community. Overall, embracing inclusive research strategies is essential to achieving the goal of equitable health care, advancing the field responsibly, and fostering trust within the broader community.

Ethics in TERM: Navigating Responsibilities and Innovations

As the TERM field continuously pushes the boundaries of science and medicine, researchers must carefully consider and continue to update the ethical ramifications and our responsibilities as researchers.^{3,4} The rapid advancements in TERM, from stem cell research to gene editing, present not only unprecedented opportunities to treat and cure diseases but also raise complex ethical questions. Key ethical questions and frameworks were discussed in the final plenary session of the congress, “Philosophy and Ethics in TERM Panel Discussion.” Some of the ethical considerations highlighted were the continued use of animal models, the source and use of biological materials, the implications of genetic modifications, the equitable distribution of cutting-edge therapies, and our responsibility for community engagement and education. The role of TERM researchers in reducing and replacing animal models is pivotal and time-sensitive, particularly given the European directive to replace animal research. The development of tissue-engineered models that accurately predict human responses requires rigorous validation to determine when these models are sufficiently reliable to replace animal testing and ensure patient safety. Another consideration is the responsibility of scientists in public communication and dissemination of scientific advances. Ethical communication requires transparency about the inherent uncertainties and developmental stages of new technologies. Scientists must adopt clear, honest, and accessible language to convey the nuances of their findings without overstating the implications. Combating the loss of trust in science necessitates addressing the impact of “celebrity science” and political agendas by reinforcing evidence-based information and encouraging an open dialog with the public to rebuild trust and dispel misinformation. In addition, the

emergence of generative artificial intelligence (AI) in publishing requires an updated ethical framework to address issues such as paper mills, deepfakes, and the unintentional misuse of computational tools by under-trained users, ensuring the integrity of scientific literature. Scientists, in their multifaceted roles as researchers, educators, public communicators, and activists, must navigate the balance between what is “good to do” and what is “necessary”. By embracing these roles, scientists can drive meaningful societal impact, foster trust in scientific endeavors, and contribute to the overarching goal of better health care for all.

Future Perspectives

While TERM faces perennial issues such as barriers to growth that reflect limitations in science and engineering, as well as financial challenges from the high cost of clinical translation leading to regulatory approval, the field is positive and powering ahead scientifically and innovatively. Researchers are increasingly moving away from silos to progress to a more holistic approach to the development of TERM that encompasses an appreciation of the strengths of diverse research tools to generate big data and more sophisticated models, while genuine commercial successes provide guiding principles to navigate the complex ethical and financial journey to deliver innovative TERM products that help the broader community.

In the future, several exciting and evolving research areas have the potential to drive advancements in the field of tissue engineering. For instance, advances in the development of smart biomaterials that respond and adapt to the body’s environment will create new opportunities for on-demand drug delivery systems and responsive polymeric scaffolds to improve tissue regeneration. Integrating these smart biomaterials with advanced 3D printing and bioprinting technologies will enable the creation of personalized implants tailored to individual anatomy, enhancing integration with natural tissue and leading to better outcomes. In addition, combining stem cells with gene-editing techniques, such as CRISPR, will boost regenerative capacity, making treatments for complex diseases more effective. With rapid progress in engineering immunomodulatory biomaterials and an increasing understanding of biomaterial-tissue interactions, it is expected that the issue of immune rejection will decrease, allowing for more reliable integration and longer-lasting engineered tissue constructs. Furthermore, future biomaterials may incorporate electronic sensors or stimulators to monitor and enhance healing, potentially revolutionizing postsurgical care and patient monitoring.

To ensure the long-term success of tissue engineering, the field must evolve in key areas to meet future challenges and make significant strides toward broader, more impactful applications. Clearer regulatory pathways and transparent ethical frameworks, along with public education, will help accelerate the translation of these technologies for patient use. Cross-disciplinary collaboration and the integration of bioelectronics and AI can also enable real-time monitoring, optimize biomaterial designs, and enhance tissue regeneration. In addition, scaling production through automation and cost-effective materials will make tissue

engineering more accessible, whereas eco-friendly biomaterials and sustainable lab practices can reduce its environmental impact. By focusing on these changes, tissue engineering can overcome current barriers and make a lasting impact on health care.

Authors' Contribution

N.A., E.C.-H. and A.S.W. wrote the article.

Disclosure Statement

A.S.W. is the founding scientist of Elastagen Pty. Ltd., now sold to Allergan, Inc., an AbbVie company. N.A. holds equity in GelMEDIX Inc. E.C.H. is a founding scientist of Rhythio Medical, holds equity in E.C.M, Biosurgery, and is a paid consultant for several companies.

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Supplementary Material

Supplementary Data S1

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