Preface

Gabriela Voskerician¹ · Maria Siemionow²

Received: 27 April 2017 / Accepted: 2 May 2017 / Published online: 19 May 2017
© Springer Science+Business Media New York 2017

The human potential for autologous 3-D anatomic and physiologic restoration is limited. To address this need, innovative reconstructive techniques are being developed. While addressing the problem from professionally distinct perspectives, tissue engineered regenerative medicine and vascularized composite allotransplantation converge towards the same goal of restoring tissue and organ functionality.

Under the title of “Tissue Regeneration or Regeneration of Engineered Tissues?”, this special Issue aims to facilitate the thought process and collaboration between related fields of study to converge on joint scientific and clinical goals. Can we reach the goal faster independently or by working together? Can we learn from each other? And most importantly, how can we jointly accelerate the advancement of science for the benefit of patients in urgent need of a solution?

To this end, we have curated a series of invited scientific papers focused on advances in the fields of tissue engineering for regenerative medicine and vascularized composite allotransplantation. By bringing these two communities together, we hope to encourage our readers to explore the featured advances in both fields, while challenging concepts, outcomes, and methodologies. Please consider this Special Issue to be a brainstorming “sand-box” for your own interdisciplinary research and innovation.

Our intention was to open the issue to active regenerative application efforts, in both tissue engineering and vascularized composites allotransplantation rather than to focus on a single tissue problem. For simplicity, we introduce the two groups of papers separately below, together with the history that brought us here.

1 The tissue engineered regenerative medicine contributions

The “Healing of Justinian by Saint Cosmas and Saint Damian” (Fra Angelico, circa 1438–1440) depicts the transplantation of a graft limb onto a wounded soldier. The work of art signals that the roots of tissue engineering are deeply embedded into the practice of medicine for hundreds of years.

Fast forwarding several centuries, for restoring tissue structure and function, late 20th century research and clinical application continued to use the term “tissue engineering” category relatively loosely, even indiscriminately applying it to the use of prosthetic devices as well as the surgical manipulation of tissues. In 2005, the scope of tissue

✉ Gabriela Voskerician
gxv4@case.edu

¹ Department of Biomedical Engineering and Medicine, Case Western Reserve University, Cleveland, OH 44106, USA

² Department of Orthopaedics, University of Illinois, Chicago, IL, USA

engineering was formalized through the emergence of the Tissue Engineering and Regenerative Medicine International Society, the “glue” that has established one of the most exciting and highly multidisciplinary fields of study today.

Drawing from the multi-faceted interest of researchers driving tissue engineering breakthroughs, the “Regeneration of Engineered Tissues” portion of this Special Issue focuses its attention on three fundamental fields of innovation: composite scaffolds, validation methodologies, and predictive modeling.

Craniofacial bone defects, such as alveolar clefts, affect the esthetic appearance of a patient and are responsible for associated functional limitations. Professor Nuntanarant and his colleagues describe the investigation of a biomaterial-stem cell composite intended to help maxillofacial surgeons address this problem [1]. With encouraging outcomes, this solution is currently under clinical investigation.

How could the efficacy of tissue glues be improved to solve the complex problem of meniscal repair? Professor Buma and his group propose a method of collagenase surface modification complemented by the addition of the TGF- β 3 [2]. This project emerged from a multicenter academia-industry collaboration.

At the intersection of biomaterial science, electrical engineering, and medicine, Professor Sezer and his collaborators advance solutions in nerve regeneration through a logical and out of the box approach: manipulating signal conductivity to address the problem of mature neuronal tissue regeneration [3]. Have we unearthed the “holy-grail” of restoring neuronal function?

To advance neuronal tissue regeneration, appropriate investigative methods must be available. Ms. Pollins and her colleagues propose a fresh look at a well-established technique, mass spectrometry, to assess the success of peripheral nerve regeneration [4]. In the process of their investigation, a novel pool of proteins was isolated, providing an active research bed for innovation in the space of protein network mechanisms.

The problem of developing a viable solution for the replacement of damaged ultra-small diameter vascular grafts remains. This problem is further escalated by the goal of innovating to develop an off-the-shelf construct. Dr. de Mel and her colleagues describe the challenges and strides their research made in achieving this goal [5]. The group further describes the design flexibility of such constructs capable of being customized to multiple regenerative medicine organ applications.

Any active field of study, such as tissue engineering, leads to prolific publication and dissemination of findings. But, what is the potential for each innovation to cross the test of bench to clinic? Further, competition to developing

viable solutions relies on intelligent use of research resources, from awarded funding to personnel. Thus, the notion of composite predictive efficacy has been established. To advance the notion to a tangible solution, Professor Voskerician proposes the development of a decision logic artificial intelligence that predicts the efficacy of a construct at three critical medical device development stages: in vitro, in vivo, and clinical [6].

We hope that the brief introduction of several of the current advances within the active field of Tissue Engineering and Regenerative Medicine will stimulate creativity, interdisciplinary collaboration, and fuel active translational research projects to accelerate and stimulate the development of active bedside solutions.

2 The vascularized composite allotransplantation contributions

The new field of vascularized composite allotransplantation (VCA) was introduced in 1998 by the first successful hand transplantation from a human donor. This encouraged many pioneers of VCA research to extend clinical applications of these techniques to transplantation of the face, larynx, abdominal wall, trachea, uterus and penis. Currently there are over 120 recipients of a hand transplant, 36 of face transplants, at least 15 of uterus transplants, and a limited number of cases of trachea or penis transplants.

Despite the success, this new generation of reconstructive transplants opened a scientific and ethical debate on the risks and benefits of VCA procedures. For the patient who lost both hands, it is clear that the better reconstructive option is transplantation from a human donor when compared to prostheses that lack both the feeling of human flesh and the sensation of touch. However, to prevent rejection, VCAs require life-long immunosuppression—similar to solid organ transplants which limits their routine application in the clinical sphere.

In this issue we will focus on the clinical applications of VCA, including human hand and face transplants which represent already established procedures. In addition, we will share the experience of surgeons performing uterus, trachea and penis transplants, which, due to the limited number of cases, are still in the early development phase. These articles address the surgical indications and, patient selection process, the logistics, and the technical aspects and the outcomes of VCA transplants. We share with you the complexity of these procedures as well as the challenges encountered before, during, and after transplantation.

Severe facial disfigurements with tissue loss cannot be reconstructed with currently available procedures. Thus, face transplantation represents a promising reconstructive option that restores not only the missing function and facial

aesthetic, but also the social life of the disfigured patients. Professor Siemionow, the pioneer in the field of VCA and the surgical lead of the team performing the first face transplantation in the United States in 2008, reviews the face transplant outcomes from the VCA surgeon perspective [7].

Drs. Brandacher and Lee summarize the outcomes of their large and most versatile series of hand transplants performed in the United States [8]. This review includes patients with single and bilateral hand transplants as well as the case of bilateral arm transplantation. The outcomes vary from excellent functional results in some patients and lost of the hand allograft in non-compliant patient. Finally, these investigators share their unique experience with so called “Pittsburgh immunosuppression protocol” based on the tacrolimus monotherapy and bone marrow transplantation.

Professor Matts Brännström presents his experience with a unique application of VCA—the uterus transplantation [9]. The uterus transplant differs from other VCA procedures since its purpose is to serve as the temporal “incubator” for in vitro fertilization, replacing the uterus of women who have a history of miscarriage and cannot get pregnant. In contrast to other VCA, the uterus is explanted after successful delivery of child/children and thus requires only limited-time immunosuppression.

Another fascinating application of VCA is trachea transplantation presented by Professor Jan Vranckx and colleagues [10]. This case represents the closest example of *in vivo* tissue engineering, where the donor trachea seeded with recipient cells is implanted into the recipient forearm which again serves as an incubator for the created tracheal construct allowing for stem cell engraftment after seeding. Once this created construct resembles a normal trachea, it is removed from the forearm and transplanted into the defect site. Again, only short time immunosuppression is required.

Professor van der Merwe, shares his team experience including challenges encountered during the first successful penile transplantation [11]. Currently, there are only single reports on penis transplantation and, since the penis is considered a composite organ, it requires life-long immunosuppression.

Finally, Professor Scott Levin reports the first bilateral hand transplantation in a child who was already on immunosuppressive therapy as a recipient of a kidney transplant [12]. This heroic and successful VCA transplant, the first in a pediatric patient, teaches us about differences between adult and childhood populations in response to immunosuppression protocol as well as rejection rate and speed of functional recovery.

We hope that this outline of several of the most interesting clinical trials in the field of VCA transplants will be educational for both surgeons and researchers working in

biomaterials and tissue engineering, and will stimulate new and exciting collaborative projects.

On behalf of *Journal for Materials Science: Materials in Medicine*, the Issue Editors wish you happy hunting for the next best idea in the complex field of human tissue regeneration.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. Wongsupa N, Nuntanarant T, Kamolmattayakul S, Thuaksuban N. Biological characteristic effects of human dental pulp stem cells on poly-ε-caprolactone-biphasic calcium phosphate fabricated scaffolds using modified melt stretching and multilayer deposition. *J Mater Sci Mater Med*. 2017;28(2):25. doi:[10.1007/s10856-016-5833-z](https://doi.org/10.1007/s10856-016-5833-z).
2. Bochyńska AI, Hannink G, Verhoeven R, Grijpma DW, Buma P. The effect of tissue surface modification with collagenase and addition of TGF-β3 on the healing potential of meniscal tears repaired with tissue glues in vitro. *J Mater Sci Mater Med*. 2017;28(1):22. doi:[10.1007/s10856-016-5832-0](https://doi.org/10.1007/s10856-016-5832-0).
3. Sezer Aydemir, Ozturk K, Aru B, Yanikkaya Demirel G, Sezer S, Bozkurt MR. Zero valent zinc nanoparticles promote neuroglial cell proliferation: a biodegradable and conductive filler candidate for nerve regeneration. *J Mater Sci Mater Med*. 2017;28(1):19. doi:[10.1007/s10856-016-5831-1](https://doi.org/10.1007/s10856-016-5831-1).
4. Pollins AC, Kim JS, Boyer RB, Thayer WP. Mass spectrometry comparison of nerve allograft decellularization processes. *J Mater Sci Mater Med*. 2017;28(1):20. doi:[10.1007/s10856-016-5834-y](https://doi.org/10.1007/s10856-016-5834-y).
5. Chaves C, Gao C, Hunckler J, Elsayy M, Legagneux J, Renault G, Masquelet AC, de Mel A. Dual-acting biofunctionalised scaffolds for applications in regenerative medicine. *J Mater Sci Mater Med*. 2017;28(2):32. doi:[10.1007/s10856-017-5849-z](https://doi.org/10.1007/s10856-017-5849-z).
6. Voskerician G. Design considerations of an analytic intelligence for predicting the efficacy of tissue engineered composites. *J Mater Sci Mater Med*. 2017;28(2):26. doi:[10.1007/s10856-016-5842-y](https://doi.org/10.1007/s10856-016-5842-y).
7. Siemionow M. The decade of face transplant outcomes. *J Mater Sci Mater Med*. 2017;28(5):64. doi:[10.1007/s10856-017-5873-z](https://doi.org/10.1007/s10856-017-5873-z).
8. Shores JT, Malek V, Lee WP, Brandacher G. Outcomes after hand and upper extremity transplantation. *J Mater Sci Mater Med*. 2017;28(5):72. doi:[10.1007/s10856-017-5880-0](https://doi.org/10.1007/s10856-017-5880-0).
9. Brännström M. Uterus transplantation and beyond. *J Mater Sci Mater Med*. 2017;28(5):70. doi:[10.1007/s10856-017-5872-0](https://doi.org/10.1007/s10856-017-5872-0).
10. Den Hondt M, Vranckx JJ. Reconstruction of defects of the trachea. *J Mater Sci Mater Med*. 2017;28(2):24. doi:[10.1007/s10856-016-5835-x](https://doi.org/10.1007/s10856-016-5835-x).
11. Merwe AV, Zarrabi A, Zühlke A, Barsdorf N, Moosa R. Lessons learned from the world's first successful penis allotransplantation. *J Mater Sci Mater Med*. 2017;28(2):27. doi:[10.1007/s10856-016-5836-9](https://doi.org/10.1007/s10856-016-5836-9).
12. Momeni A, Chang B, Levin LS. Technology and vascularized composite allotransplantation (VCA)-lessons learned from the first bilateral pediatric hand transplant. *J Mater Sci Mater Med*. 2016;27(11):161. doi:[10.1007/s10856-016-5771-9](https://doi.org/10.1007/s10856-016-5771-9).