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EDITORIAL

# In Honor of Robert Langer's 70th Birthday - Vol 2

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I am delighted to serve as an editor and to introduce you to this special issue, "S.I.: TC: In Honor of Robert Langer's 70th Birthday - Vol 2" of *Regenerative Engineering and Translational Medicine*. This special issue is published to honor the outstanding contributions of MIT Institute Professor Robert Samuel Langer, a doyen in the field of drug delivery, biomaterial science, and translational research. This special issue has contributions by select research groups from India and USA, who had either connections with the Langer group in the past or who are indeed inspired by his research. In particular, this special issue has five reviews or perspective articles and four original research articles, which were rigorously reviewed by the referees, who by tradition remain anonymous.

Dr. Robert Samuel Langer, Jr., known to many as simply, "Bob," has had a profound impact on many disciplines including chemical engineering, biomedical engineering, medicine, and the biotechnology industry. He has written over 1500 articles, which have been cited over 413,000 times; his h-index of 320 is the highest of any engineer in history and the third highest of any individual in any field. His patents have been licensed or sublicensed to over 400 companies; he is a cofounder of several companies including Moderna. Dr. Langer served as Chairman of the FDA's Science Board (its highest advisory board) from 1999 to 2002. His over 220 awards include both the US National Medal of Science and the US National Medal of Technology and Innovation (he is one of three living individuals to have received both these honors), the Charles Stark Draper Prize (often called the Engineering Nobel Prize), Queen Elizabeth Prize for Engineering, Albany Medical Center Prize, Breakthrough Prize in Life Sciences, Kyoto Prize, Wolf Prize for Chemistry, Millennium Technology Prize, Priestley Medal (highest award of the American Chemical Society), Gairdner Prize, Hoover Medal, Dreyfus Prize in Chemical Sciences, BBVA Frontiers of Knowledge Award in Biomedicine, Balzan Prize, and the Dr. Paul Janssen Award. He holds 41 honorary doctorates, including Harvard, Yale, Columbia, and Northwestern, and has been elected to the National Academy of Medicine, the National Academy of Engineering, the National Academy of Sciences, and the National Academy of Inventors.

Now, I shall introduce some of the key highlights of the papers published in this special issue. 3D and 4D (bio)printing are expected to revolutionize the field of regenerative medicine, and this area has been covered in this special issue. For example, Rajput et al. presented a research article entitled "Embedding Silk Fibroin-Alginate Hydrogel in a 3D-Printed Porous Poly(Lactic Acid) Bone Tissue Scaffold Augments Stem Cell Function." They used silk fibroin-alginate blend hydrogel loaded with human mesenchymal stem cells in the inter-strut areas of a 3D-printed PLA scaffold. The good proliferation and osteogenic differentiation of the hMSCs within the hydrogels were modulated, when constrained in the 3D printed structure, compared to the gels when they were not encapsulated in the 3D scaffold. Such a hybrid approach essentially demonstrates the key advantages of the mechanical integrity of the 3D-printed PLA scaffold on stem cell differentiation. In a review article entitled "4D printing in biomedical engineering: a state-of-the-art review of technologies, biomaterials and application," Ghosh et al. reported the recent advancements in the area of 4D printing. Both the fundamental aspects of 4D printing and the current challenges in clinical translation are sufficiently described in the review article. Some of the challenges include unreliable actuation or regulating the different states of deformation, and these challenges need to be addressed in future development so that 4D bioprinting can be clinically translated. In the context of emerging and diverse applications of silk-based biomaterials, Dey et al., in their review article entitled "Photocrosslinkable Silk-Based Biomaterials for Regenerative Medicine and Healthcare Applications," described different types of photo-crosslinkable silk-based biomaterials

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for bone and skeletal muscles, cartilage, skin and cornea, heart, and blood vessel regeneration applications. The biofabrication strategy of these 3D printable (e.g., digital light processing, DLP) silk biomaterials involves the mono/double crosslinking mechanisms based on photooxidation, Ruthenium (III)/persulfate, and Riboflavin. The authors also presented the key summary of several published studies in this important area of research, with an emphasis on emerging applications in the field of bioelectronics.

Three research articles in this special issue are written by some of the leading clinician-scientists in the area of regenerative engineering. In one such article by Amanso et al. entitled "Local Delivery of FTY720 induces neutrophil activation through chemokine signaling in an oranasal fistuala model," the authors presented original research results, to demonstrate the treatment of oral mucosal defects using a tissue-engineered scaffold. Based on the preclinical study using a mouse model, the local delivery of FTY720 nanofiber scaffolds is reported to potentially shift early gene transcription associated with immune cell recruitment and modulation towards pro-regenerative immune signaling, based on the identification of the inflammatory immune response pathways and the gene ontology enrichment analysis. In an original research paper by Parik and Edelman entitled "Tissue-Engineered Endothelial Cells Induce Sustained Vascular Healing Through Early Induction of Vascular Repair," the time course and mechanism of perivascular injury have been addressed. The authors developed genetically modified tissue-engineered endothelial cells, which have the potential to express the "suicide gene," to exert their inhibitory effect on long-term neointimal hyperplasia. The outcome of this in vivo study suggests a putative mechanism involved in the vascular injury mediated by the use of tissue-engineered endothelial cell. In another original research article entitled "Autologous Culture Expanded Iliac Crest Chondrocytes in Chitosan Hyaluronic Acid Dialdehyde Gel Regenerate Caprine Growth Plate," Madhuri et al. reported the cartilage regeneration using an immature goat model. Based on the quantitative histological analysis, their study clearly demonstrated the feasibility of encapsulating autologous chondrocytes in the chitosan-hyaluronic acid dialdehyde hydrogel for growth plate regeneration. Such outcomes have the potential clinical translation, for the treatment requiring growth plate cartilage regeneration in pediatric surgery.

Despite the significant advances in regenerative medicine, the development of immunomodulatory biomaterials has not been significantly explored. In an important review article entitled "Harnessing Biomaterials for Immunomodulatory-Driven Tissue Engineering," Zhong et al. presented the need for such materials to create a pre-reparative microenvironment for tissue repair. The research results of the recent studies related to the immunomodulation of innate and adaptive immune cells are described in reference to biophysical cues, drug delivery, chemical modification, and sequestration. It is expected that these immuno-modulatory biomaterials, which can exhibit vascularization bone repair wound healing and auto-immune regulation can bring a paradigm shift in the field of regenerative medicine.

In another review article entitled "Emulsion Gel: a Dual Drug Delivery Platform for Osteoarthritis Treatment," Das et al. reviewed the translational potential of emulsion gels, which consist of oil droplets. Such gels can be intelligently synthesized by dispersing oil droplets inside hydrogels, and those hydrogels can be used as a platform for dual drug delivery. For example, hydrophobic drugs can be loaded into the oil part, while hydrophilic drugs can be incorporated into the hydrogels. Importantly, the potential of intelligence stimuli-responsive emulsion gel for the regeneration of chondrocytes in endogenous stimuli-mediated microenvironment has been emphasized and such an approach is expected to facilitate tissue growth and recovery in the treatment of osteoarthritis.

The bone regeneration around an orthopedic or dental implant significantly depends on the design features. In an original research article entitled "Contact guidance mediated by hybrid thread topography enhances osseointegration of as-machined Ti6Al4V dental implant," Mishra et al. presented the results of a preclinical study demonstrating the impact of dental implant design on osteogenesis in the rabbit model. In particular, the implants with hybrid threads are reported to induce 20% higher bone-to-implant contact length post 12-week implantation, compared to the commercial Straumann implant. Importantly, the authors emphasized the contact guidance mechanism with more osteoblastic attachment to the designed threads, in modulating the neobone formation and a better host bone engagement, around the hybrid threaded implant. The up-regulation of VEGF genes indicated better angiogenesis during the osseointegration.

In bringing out this issue, I would like to place on record my thanks to all the authors for their valuable contributions and to all the referees of the manuscripts, for sparing their valuable time in reviewing the manuscripts to the standards of archival publications. I am grateful for the assistance provided by Dr.Lakshmi S. Nair (Managing Editor, RETM), Anita Lekhwani, Yasotha Sujeen, Jeff Davis, and Michelle Randazzo at various stages in commissioning this special issue. I am sure that Professor Bob Langer will continue to inspire many generations of researchers around the world in the decades to come. Finally, I trust that the readers will enjoy this special issue.