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FOCUS ISSUE FOREWORD

Foreword to the focus issue: frontline research on biomaterials-based bioengineering for future therapy

Yuji Teramura[a,b,c] and Horacio Cabral[d]

[a]Cellular and Molecular Biotechnology Research Institute (CMB), National Institute of Advanced Industrial Science and Technology (AIST), AIST Tsukuba Central 5, Tsukuba, Ibaraki, Japan;
[b]Department of Immunology, Genetics and Pathology (IGP), Uppsala University, Uppsala, Sweden;
[c]Master's/Doctoral Program in Life Science Innovation (T-LSI), University of Tsukuba, Ibaraki, Japan;
[d]Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, Tokyo, Japan

Since 2017, Karolinska Institutet, KTH Royal Institute of Technology and Stockholm University in Sweden, and The University of Tokyo in Japan have fostered their research exchange and collaboration through interdisciplinary workshops within a strategic partnership framework. One of the key topics emerging from these workshops is biomaterials-based bioengineering, where leading researchers from Tokyo and Stockholm engage in discussions on pioneering therapeutic strategies. This focus issue presents the latest advancements structured around four major topics that are shaping the future of biomaterials-based bioengineering: biocompatible materials, nano/micro particles, hydrogels, and sensing materials and devices.

The papers on biocompatible materials explore innovative polymer-based approaches for medical applications. Prof. Ishihara from Osaka University reviewed the recent studies on bioinspired polymer materials for medical devices [1]. In particular, he focuses on zwitterionic polymers with intramolecularly balanced charges, like poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC), and their potential application in medical devices for cardiovascular, cerebrovascular, orthopedic, and ophthalmology fields. Furthermore, Suzuki, et al., from the National Institute of Advanced Industrial Science and Technology (AIST) report innovative coatings based on polymeric materials, which can serve as alternatives to PEG [2]. They synthesized poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC)-conjugated lipids and evaluated the surface characteristics of the coatings *in vitro*, demonstrating the high stability and inertness to anti-PEG antibody. The modified PMPC-liposome position as a promising next-generation alternative to conventional PEGylated liposomes for drug delivery.

The papers on the nano/micro particles explore cutting-edge advancements in new biomaterials for nanoparticle synthesis, artificial oxygen carriers, mRNA-loaded nanocarriers for systemic delivery, and quantum dots (QDs) for bioimaging. Zhang, et al., from KTH Royal Institute of Technology, Stockholm, report the synthesis of lignin microcarriers through a facile approach to utilizing waste canola straw lignin for drug delivery systems [3]. They separated lignin from a canola (rapeseed) straw and used the lignin with high degrees of acetylation for preparing microparticles with uniform sizes and smooth spherical surfaces. The particles showed high drug encapsulation efficiency and release performance, suggesting high potential as bio-based materials for drug delivery systems. Moreover, Zhang, et al., from The University of Tokyo review the recent progress in micro-sized oxygen carriers for supplementing sufficient oxygen to cells [4]. In this review paper, they describe the design, fabrication techniques, and applied biomaterials of micro-sized artificial oxygen carriers by comparing red blood cells. Also, they discuss existing and potential applications of different types of micro-sized artificial oxygen carriers. In addition, Yang, et al., from The University of Tokyo report mRNA-loaded nanocarriers as safe and effective carriers for mRNA for systemic delivery that overcome the limitations of current polymeric carriers [5]. They fabricate mRNA-loaded nanocarriers using biocompatible block copolymers of poly (ethylene glycol) (PEG)-poly(glycerol) having functional amino acid moieties. The formed polymeric micelles show excellent stability in biological environments, increasing cellular uptake and endosomal escape. These nanocarriers increased protein expression both *in vitro* and *in vivo*, suggesting high potential for therapeutic application. Finally, Zhao, et al., from The University of Tokyo, reported the modified quantum dots (QDs) for Positron Emission Tomography (PET)/fluorescence dual-modal imaging for deep penetration and high

CONTACT Yuji Teramura y.teramura@aist.go.jp Cellular and Molecular Biotechnology Research Institute (CMB), National Institute of Advanced Industrial Science and Technology (AIST), AIST Tsukuba Central 5, 1-1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan

resolution, which is promising for tumor diagnostics [6]. They used PEGylated heavy metal-free InP-based QDs due to less cytotoxicity and studied the characteristics in *vitro* and *in vivo*. They showed that the QDs accumulated in tumors, working as a dual-modal probe for precise tumor diagnosis by simultaneously emitting fluorescence and γ-rays.

The papers on hydrogels present innovative approaches to biomaterials for medical applications, emphasizing muco-adhesive and extracellular matrix (ECM)-mimicking hydrogels. Matthiesen, et al., from KTH Royal Institute of Technology, report 3D bioprinted structures of hyaluronan-based hydrogels that combine cell-adhesion peptides. They found that human fetal primary astrocytes have a higher degree of interaction with the hydrogel [7]. The results indicate that ECM-mimicking hydrogels can be available for the development of tissue and disease models of the central nervous system. Madhavikutty, et al., from The University of Tokyo report muco-adhesive hydrogel composed of cationic guar gum and boric acid, in which the hydrogel formation is pH-responsive, and can occur at physiological conditions [8]. They showed the hydrogel has pH-responsive self-healing ability and adhesive strengths that are comparable to clinical fibrin glue. These findings indicate their hydrogel has potential as a pH-responsive mucosal protectant biomaterial.

The papers on sensing materials highlight innovative strategies for bacterial detection and cancer diagnostics. Richter-Dahlfors, et al., from Karolinska Institutet and KTH Royal Institute of Technology reviewed recent research on bacterial and biofilm detection and diagnostics using optotracers [9]. They describe optotracers' chemistry and sensing capabilities for bacterial sensing and diagnostic methods. Moreover, Fujisaki, *et al.*, from Tokyo Medical and Dental University report the specific detection of sialic acid as a cancer biomarker using a poly (3,4-ethylenedioxythiophene): poly(styrenesulfonate)-based conducting polymer combined by label-free reagent-free potentiometry [10]. The sensing performance of this material is comparable to that of conventional sensors, like graphene-based electrical sensors. Thus, their method is promising for sialic acid-based cancer diagnostics.

We would like to extend our sincere gratitude to all the authors and reviewers who contributed to this Focus Issue. We strongly believe that the contributed three review papers and seven original papers will provide a compelling snapshot of the state-of-the-art of biomaterials-based research for bioengineering. Although the number of contributions is limited, this collection covers a broad range of cutting-edge advancements, providing valuable insights that we hope will inspire new ideas and innovations. We trust that our readers will find these studies thought-provoking and instrumental in shaping the future of biomaterials-driven biomedical applications.

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ORCID

Horacio Cabral http://orcid.org/0000-0002-4030-2631

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