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Engineering Active Materials for Biomedical Applications

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We welcome you to this Special Issue of *Advanced Materials* entitled "Engineering active materials for biomedical applications". This special issue focuses on the design and application of biomedical materials that are engineered to be active, in either or both a biological and mechanical context. Current and future biomedical materials at a variety of size scales are highlighted, including their design and screening, with a spectrum of articles describing research ranging from fundamental to translation-application focused.

Historically, biomaterials were designed to be inert in the human body, eliciting no response from the cells and tissues they contacted. Decades of clinical experience and research revealed, though, that implanted biomaterials always generated some response, and the body responses could lead to loss of function or significant inflammatory responses. This appreciation shifted attention in the field to tuning and controlling the body response via the design of specific mechanisms of engagement of biomaterials with the cells and tissues in the body, in order to generate favorable outcomes and maintain the functionality of the implanted materials. This approach has generated many successes, but the initial biomaterials designed from this perspective tended to be passive, with pre-designed features and functions, and little ability to dynamically interface or respond to the body, from either a biological or physical perspective. In contrast, many researchers are currently designing active biomaterials that directly interface in specific manners with the body, and actively direct biological processes over time. In this special issue, we highlight four areas in which this concept is currently being explored – mechanically active biomaterials, materials that actively direct the host immune response (immunomaterials), materials designed to promote tissue repair and regeneration, and dynamic materials. Each of these sub-topics is briefly reviewed in the following sections.

Mechanically Active Materials

Biomedical applications for mechanically active materials include "sense and respond" functions, muscle assist, controlled drug delivery, long-term monitoring of physiological parameters, and enhanced in vitro testbeds for cell culture. Nie et al. (adma.202205609) provide a review on using such materials for bio-interfaced sensors for continuous monitoring. Examples include sensors for measuring pressure at the skin interface, on the cardiac surface and for internal body processes. They describe future applications for materials that are highly sensitive, stable, and have a wide dynamic range, systems for noise reduction and for decoupling types of mechanical loads. Modifications of these mechanically active materials could have applications in soft robotics and human–machine interfaces. Pirozzi et al. (adma.202210713) review another class of mechanically active materials — artificial muscles — with a specific use case of cardiac assistance. Design requirements for this application are comprehensively outlined in addition to the key advantages of this approach over currently available mechanical circulatory support devices, specifically the ability to provide pulsatile support without contacting blood. They review pneumatic, magnetic, dielectric elastomers and electrohydraulic actuators for this application and contrast the benefits and challenges of each approach for the treatment of heart failure. Roy et al. (adma.202300017) describe a bilayer hydrogel folding system that can generate folding patterns, similar to the mucosal tissue in the epithelium of the upper respiratory airways. The hydrogel is composed of a double network of alginate and polyacrylamide. Cells can be encapsulated into the patterned hydrogels and programable, on-demand folding is enabled by incorporating magnetic microparticles to provide a dynamic culture system to study the influence of folding patterns on cellular function. Finally, mechanically active materials can be implanted in the body and deliver therapeutics on demand. Mendez et al. (adma.202303301) describe a hybrid hydrogel actuator that can elicit tunable mechanoresponsive release of drug from a hydrogel layer through pneumatic actuation. Dosing can be controlled by magnitude, frequency, and duration of actuation. The device can adhere to tissue with a flexible adhesive and in the future can be integrated with mechanical assist technologies for a mechanotherapeutic effect.

Immunomaterials

The past two decades has witnessed a roaring development of new material systems for orchestrating immune cells and the immune system toward favoring the treatment of diseases including cancer, autoimmune disorders, inflammatory diseases, and tissue injury. These immunomaterials can provide physicochemical and mechanical cues to control the activation status and phenotypes of immune cells, release immunomodulatory agents in a spatiotemporally controllable manner, and actively attract and modulate immune cells in situ.

In this special issue, Park et al. (adma.202311505) report the ability of tumor cells to utilize the mineralization of collagen in the extracellular matrix to evade the attack of natural killer cells. Using a combination of synthetic bone matrix models with controlled mineral content, nanoscale optical imaging, and selective manipulation of tumor cell glycan patterns, they demonstrated that collagen mineralization upregulates mucin-type O-glycosylation and sialylation by tumor cells, which increases their glycocalyx thickness while enhancing resistance to attack by natural killer cells. Han et al. (adma.202209778) provide a

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comprehensive review of the design principles of bioresponsive immunotherapeutic materials that can release immunoactive agents in a controllable manner to recruit, house, and manipulate immune cells. These immunomaterials can respond to pH, temperature, redox species, ATP, enzymes, hypoxia, and platelets by releasing various types of immunoactive agents to regulate the properties and functions of dendritic cells, T cells, neutrophils, macrophages, and B cells. Further, Bo et al. (adma.202210452) discuss how immunomaterials have enabled one to skip the time-consuming and costly process of identifying tumor-specific antigens, by facilitating the generation of antigens from tumor cells in situ and making the best use of the in situ generated antigens to provoke potent effector T cell response. A step further to their accumulating understanding of immune responses associated with regenerative biomaterials, Han et al. (adma.202310476) now find that the signatures of inflammation and interleukin-17 signaling (sign of type-3 immune activation) increase with injury and treatment both locally and regionally in aged animals. Their results indicate that age-associated senescent-T cell communication promotes type-3 immunity in T cells, and local administration of IL17-neutralizing antibodies results in improved healing and muscle repair in older animals.

Materials for Tissue Repair and Regeneration

Wound healing and tissue regeneration are complex, multi-step, processes that involve signaling activities between cell populations and their surrounding environment that vary in space and time. Biomaterials are often utilized to provide a physical space in which these processes can be engineered while providing and organizing key signals to interacting cells to enhance therapeutic outcomes. The chemistry of these materials, along with their physical properties, can be crucial both to the biological outcome, and to the practicality of strategies to promote healing and regeneration.

In this special issue, a number of papers demonstrate the potency of appropriately designed biomaterials in orchestrating biological processes to promote desirable outcomes. From the perspective of materials chemistry, Latif et al. (adma.202208364) have screened 315 polymer surfaces for those that regulate fibroblast function, as these connective tissue cells are key players in the wound healing process. They identified chemistries that promoted regeneration-relevant cell processes, and subsequently fabricated the promising chemistries into microparticles that enable ready application to diabetic skin wounds. Pro-regenerative chemistries identified in the screen were demonstrated to enhance wound closure with a single application, indicating exciting potential for the treatment of chronic wounds. Mammalian cells utilize specific cell-surface receptors to bind and interact with the surfaces of materials, and many of the ligands for these receptors have been identified and can be incorporated into materials to provide highly specific regulation over cell engagement and function. Here, Rijns et al. (adma.202300873), exploit hydrogels fabricated from dynamic supramolecular fibers to decouple the impact of the ligand density from local gel mechanical properties on the ability of epithelial cells to orient appropriately. Epithelial cell orientation, or polarity, is key to formation of organoids and cysts, which are widely used as models of development and disease, and increasingly to serve as a test-bed for therapy testing. Their findings demonstrate an interplay between gel mechanics and ligand presentation in controlling appropriately polarized epithelial cysts. In addition to their utility in cell culture models of tissue, transplantation of cells into patients is an increasingly approach to therapy in many disease settings. While biomaterials are often utilized as vehicles for cell therapy, recent efforts have demonstrated that the cells themselves can be used as a delivery vehicle for materials into the body – these biomaterials may be used to control the behavior of the transplanted cells, and/or engage with host cells with which the transferred cells interface. Adebowale et al. (adma.202210059) provide a review of recently developed strategies to decorate the surfaces of various cell types with polymer coatings or particles at varying size scales (nm to micron). Studies to date have demonstrated that this strategy can enhance the function of the cell carrying the material, be utilized to deliver particles to specific anatomic sites and cell types in the body, and provide novel drug delivery strategies. Cardiovascular disease, particularly heart failure, impacts many patients, and the development of biomaterials that can enhance tissue repair and regeneration has been an active area of research for decades. However, delivery of the materials without inducing additional tissue damage can be a challenge, and Chen et al. (adma.202300603) provide an overview of recent approaches to develop materials that can be delivered to the heart via the bloodstream – minimizing the invasiveness of the delivery procedure and allowing rapid treatment. Important aspects in the design of these materials include enhancing their localization to the heart, and making them responsive to local environmental conditions.

Dynamic Materials

The integration of materials into the human body has shaped medicine in general. In the past decades, researchers have acknowledged the importance of this integration by mimicking biological materials in all aspects, e.g., from their mechanical properties to how they present bioactive signals to cells, and by designing interactive materials that react on biological stimuli. In nature, tissues are formed by complex, intricate molecular compositions held together by both covalent and directed non-covalent interactions. These molecular interactions give tissues their dynamic behavior. Building these dynamics into biomaterials, as well as introducing interactivity, are emerging approaches to make materials for biomedical applications such as regenerative medicine, tissue engineering, and cell therapy.

Ma et al. (adma.202306358) describe the importance of the design of enzyme-activatable polymers for both diagnosis and therapy. They review how to design and synthesize different polymers and materials that can react to enzymes, and show the perspective of the field to introduce multiple activatable groups, as well as revolutionary ideas for novel design concepts for the future. Furthermore, Nelson et al. (adma.202211209) showed the use of dynamic covalent bonds to make adaptable hydrogels. They applied 1,2-dithiolanes as dynamic covalent photocrosslinkers. In this way hydrogels could be made for multiple photoinduced dynamic processes, such as the tuning of mechanical properties such as stress relaxation and stress stiffening, as well as the introduction of bioactivity through network functionalization. Rijns et al. (adma.202300873) applied supramolecular chemistry to make dynamic supramolecular hydrogels as synthetic extracellular matrices that could be applied to study cyst formation of epithelial cells. Using a modular approach, the ligand concentration steering cell adhesion and concomitant polarization of the cysts could be controlled. They found that the effective ligand concentration is the determining factor in steering epithelial polarity. Fernández-Galiana et al. (adma.202210807) reviewed the use of Raman-based techniques to design and develop biomedical materials. They showed the many aspects of Raman measurements, such as spatial mapping of biomolecular species in bioactive materials and the occurrence of solid-to-solid phase transitions. They also highlight studies that used Raman spectroscopy to characterize both natural and synthetic materials.

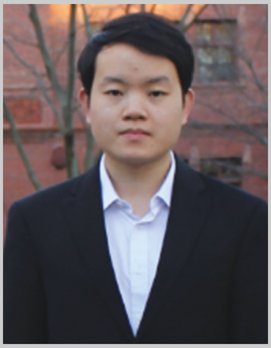
Conflict of Interest

The authors declare no conflict of interest.

David Mooney is the Pinkas Family Professor of Bioengineering in the Harvard School of Engineering and Applied Sciences, and a Founding and Core Faculty Member of the Wyss Institute. He earned his B.S. at the University of Wisconsin, Madison, and his Ph.D. in Chemical Engineering at the Massachusetts Institute of Technology, and was formerly on the faculty at the University of Michigan. His laboratory designs biomaterials to promote tissue regeneration and immunotherapy, and has made significant advances in tissue engineering, drug delivery, and mechanotransduction. The laboratory emphasizes the education of students and fellows, with many lab alumni holding faculty positions and the remainder largely in the biotechnology, pharmaceutical, and medical device industries. He is a member of the National Academy of Engineering, the National Academy of Medicine, and the National Academy of Inventors. His inventions have been licensed by a number of companies, leading to commercialized products, he has founded several companies, and is active on industrial scientific advisory boards.

Patricia Dankers is professor in Biomedical Materials & Chemistry at the Eindhoven University of Technology (TU/e). She studied chemistry in Nijmegen, The Netherlands. Her Ph.D. studies were performed at TU/e on supramolecular biomaterials (2006). She worked for SupraPolix, and the University Medical Center, Groningen. Her second Ph.D. thesis work was performed in medical sciences on kidney regenerative medicine, in Groningen (2013). She worked at Northwestern University, Chicago, USA (2010). She climbed every step on the academic ladder, starting in 2008, ending in 2017 as a full professor. She received Veni, Vidi & Vici (2008, 2017, 2023) and ERC starting & ERC PoC (2012, 2017) grants. She has been awarded the KNCV Gold Medal (2020) and the Ammodo Award for Fundamental Science (2021). She is a co-founder of the spin-off companies UPyTher (2020) and VivArt-X (2022), and the Helmond Biotech-materials Hub (HBH, 2023). Her research group aims to control and understand material-based curing and regeneration of the human body using a supramolecular chemistry approach.

Ellen Roche is an Associate Professor with tenure at the Institute for Medical Engineering and Science and the Department of Mechanical Engineering at the Massachusetts Institute of Technology. She directs the Therapeutic Technology Design and Development Lab. She completed her Ph.D. at Harvard University School of Engineering and Applied Sciences. Her research focuses on applying innovative technologies to the development of cardiac devices. Her research includes development of novel devices to repair or augment cardiac function using disruptive approaches such as soft robotics, combination of mechanical actuation with delivery of cell therapy, and use of light activated biodegradable adhesives. Prof. Roche was previously employed in the medical device industry as a research and development engineer and employs her understanding of the medical device industry and the regulatory pathways to medical device commercialization in her academic research. She is the recipient of multiple awards including the Fulbright International Science and Technology Award, the Wellcome Trust Seed Award in Science, a National Science Foundation CAREER Award, an NIH Trailblazer Award, a Charles H. Hood Award for Excellence in Child Health Research, the Faculty Founders Initiative Grand Prize, the Harold E. Edgerton Award for Outstanding Faculty Achievements and an Additional Ventures Single Ventricle Research Fund Award.



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