**Stimuli-sensitive and responsive polymer biomaterials**

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Precision and personalized medical treatments require biomaterials that are able to specifically interface and interact with their biological surroundings1-2. This requires stimuli-sensitive and responsive materials that can sense and actuate specific biological signals and are able trigger a therapeutic action appropriate to local pathological or physiological environments. Polymer biomaterials that possess these capabilities cannot remain static but need to be able to respond dynamically.

The 2017 International Conference on Materials for Advanced Technologies (ICMAT2017), which was held in Singapore from June 18-23, 2017, featured a symposium on “*Stimuli-sensitive and responsive polymer biomaterials*” that was specially dedicated to address these challenges and to showcase the latest advances in the development of stimuli-sensitive and responsive polymer biomaterials. This Special Issue includes nine papers, which were presented at this ICMAT symposium. These papers cover a wide range of subjects including hydrogels, bioadhesives, polymer interfaces, composite biomaterials, biosensors and antimicrobial polymers. Together, these contributions not only provide an excellent overview of the current state-of-the-art in the field, but also point out exciting challenges and opportunities for further, future work.

The contribution by Laura J. Macdougall *et al.* advances responsive biomaterials by overcoming one of the major challenges of hydrogels, specifically their inherent swelling characteristics3. Through the judicious choice of responsive poly(ethylene glycol) (PEG)-based precursors, either by incorporating a thermoresponsive unit or by tuning their architecture, the authors are able to modulate the swelling and mechanical response of the resulting hydrogel biomaterials to obtain load-bearing soft tissue mimics that retain their mechanical performance for at least 15 days. Most importantly, these materials exhibit high cytocompatibility and achieve compressive strains up to 98%, which makes them ideal matrices for tissue engineering applications. Given the high likelihood of hydrogel and biomaterial as tissue engineering scaffolds and medical implants, new methods are required to address selective growth of microorganisms, either by chemical or energy directed means.

The growing threat of multidrug resistant bacteria against small molecule antibiotics requires more novel mechanisms than antibiotic release. Polymeric antimicrobial materials are postulated to be less susceptible to the development of resistance than antibiotic drug depots due to their unique electrostatic antimicrobial mode of actions. To explore the coulombic interactions between cationic polymers and bacterial membranes, Cho et al systematically varied guanidinium salt functionalized aliphatic polycarbonates with a range of charge densities through efficient post-synthesis modification via copper-catalyzed azide–alkyne cycloaddition (CuAAC) click chemistry4. The concept of passive diluting group is introduced for the first time, whereby the cationic charge density of the polymer is tuned without changing bulk hydrophilicity. This yields new polymeric antimicrobial materials that are optimized for high antimicrobial activity with the least cytotoxicity. Future applications include antimicrobial peptide mimics and controlled drug delivery, such as gene delivery.

Charge density poses a vexing problem for gene delivery, as high cationic polymer to nucleotide ratios create advantages of long term colloidal stability with good transfection and vector shuttling of oligonucleotides within mammalian cells. Unfortunately, too high of a polyplex dose induces membrane cytotoxicity. Novel cytocompatible gene delivery vectors are incorporating advanced combinatorial polymerization techniques to alleviate the limited polyplex doses allowed. Despite significant advances in this field, the most challenging aspect remains the design of safe and efficient biocompatible delivery vectors in a cost-effective manner. Ahern and Sigen et al employ a combinatorial polymerization approach that facilitates tailoring of low charge density polymers and provides a versatile platform for constructing novel gene delivery vectors5. These new brush-like cationic polymers with ultra-low charge density provide further insight into overcoming the widely established problem of excess charge density opens new directions for efficient, tailorable gene delivery vectors.

To further enhance cytocompatibility and cell growth, hydrogels and biomaterials need to respond to mammalian cell stimuli, especially cell-mediated degradation and matrix deposition in addition to exogenous cues directing cell phenotype (i.e. regulation of cell adhesion). To explore these numerous structure-activity relationships, model substrates are required towards the study of cell-biomaterial interactions with assessment of associated remodelling. Polymer brushes such as poly(oligoethylene glycol methacrylate) (POEGMA) have allowed the design of robust cell based assays, owing to their ease of patterning and excellent protein and cell resistance. However, they remain difficult to biofunctionalise and bioactivate, especially *in situ*, for the design of more advanced assays aiming to study cell-mediated remodelling. Colak et al proposes radical thiol-ene coupling6. Thiol-ene chemistry with photo-responsive interfaces allowing the control of cell-matrix interactions via the POEGMA brushes. Cell selectivity is retained through the combination of bio-inertness and the presentation of integrin specific peptides. Direct photo-patterning for biofunctionalisation and the formation of cell arrays is readily demonstrated with the POEGMA model system.

Besides modifiying cell-matrix interactions, polymer brushes can be incorporated to induce thermosresponsive nanoparticles. Grafting of a polymer brush to superparamagnetic nanoparticles used in biomedical imaging and drug delivery leads to a radial distance dependence of the density and structure of the shell. This translates into size-dependent variation in properties of nanoparticles with thermoresponsive brush shells and to that the thermal transition is not the same in the outer and inner parts of the shell. Kurzhals et al. demonstrates this by grafting block copolymers with different lower critical solution temperatures and thereby radially tailoring the thermal hydration transition7. This opens the possibility to directly observe their influence on the colloidal interactions of core-shell nanoparticles. These insights could be used to design nanoparticles capable of changing their interactions in vivo by local magnetic heating.

Alternative methods of cell stimulation take advantage of the advancement in biocompatible, electrically conductive biomaterials. Chan et. al. embedded nanofiber scaffolds with a composite of electrically conductive polythiophene phenylene (PThP) and bioresorbable poly(lactide-co-glycolic acid) (PLGA)8. PThP’s inherent properties allow rapid grafting onto backbone side chains and the insertion of functional groups in selective locations. The nanofiber scaffold was functionalized with the cell adhesive arginylglycylaspartic acid (RGD) peptide through click-chemistry, which enhanced the scaffold’s ability to support improved cell proliferation. RGD represents one of many potential moieties that can be appended and potentially creating novel tissue engineering scaffolds with multiple modes of interaction.

One of the characteristics of tissue that is probably most difficult to emulate in synthetic materials is its ability to undergo self-healing. Polymer biomaterials that can readily repair themselves with little outside interference are highly attractive to a wide range of applications. Previously, self-healing has been mimicked with the reversible catechol−metal coordination bonds of the blue mussel byssus. However, catechol oxidation leads to covalent cross-linking over time resulting in loss of the self-healing and pH-responsive properties over time. Andersen et al. prevent the losses by functionalizing amine-polymers with an oxidation-resistant catechol analogue9. With metal ions, pH responsive coordination crosslinking affords an injectable liquid at low pH that stiffens to a self-healing hydrogel near physiological pH. Incorporation of a covalent crosslinking mechanism affords double-crosslinked hydrogel with tunable moduli that retains self-healing and pH-responsive properties.

Applications of self-healing materials with ‘dial-in’ stiffness will likely spur the next generation of mechanically graded self-healing materials. Self-healing properties and ‘dial-in’ stiffness are one of many attributes currently unmet in bioadhesive hydrogels towards soft tissue repair 10-11. For several decades, bioadhesive catechols have endeavored to bond soft tissues in an attempt to yield adhesion values found in one of the oceans biggest economical pests. Mussels secrete mussel adhesive proteins (MAPs) which enable them to bond substrates in wet environment, making this a good model system for designing bioinspired moisture-resistant adhesives. MAPs contain a catechol-based amino acid along with anionic and cationic residues, which are responsible for interfacial interaction. Narkar et al found that adding anionic species to catechol-based synthetic adhesive preserved the catechol in its reduced and adhesive state even at a mildly basic pHs of 7.5-8.512. This simple strategy overcomes mussel’s more complex methods with potential applications towards soft tissues or marine environments.

Like the hydrogels above, some bioadhesives are attempting to moderate environmental stimuli that have a degenerate affect. Nanda et al evaluate dendrimer bioadhesives in regards to potential for human platelet activation13. Adhesion of blood contacting tissues is a current unmet clinical need as nearly all methods of tissue fixation rely on sutures, barbs, or staples. Simple composites incorporating polysaccharides mixed and cured with the previously developed bioadhesive based carbene crosslinking dendrimers are found to prevent platelet adhesion, activation, or both depending on the additive ratio. Blood from healthy human volunteers is exploited to reach a better level of relevance. The research pushes the field of bioadhesives into mending soft tissues, required for anastomoses and blood vessel transplants.

As one can see, the investigation of biomaterials and ‘smart’ polymers is a consequence of forging new paths to solve today’s unmet engineering challenges. Akin to the materials themselves, the research progress is anything but static. Multimodal mechanisms will be the new norm and the challenge remains on how to incorporate multiple stimuli-responsive attributes towards theranostics, personalized medicine, minimally invasive surgeries, and preventative medicine.

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