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Introduction to stimuli responsive materials for biomedical applications

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Stimuli-responsive materials exhibit large and abrupt changes in architecture or other properties in response to environmental stimuli, including temperature, light, pH, and/or biological cues. The development of stimuli-responsive materials provides ample opportunity for smart biomaterials for applications in drug delivery, biologically-responsive scaffolds, sensors, diagnostics, and soft robotics. In recent decades, researchers have explored stimuli-responsive materials to a greater extent because of their non-invasive nature, equipped with temporal control over activation of molecules and/or processes. The development and use of stimuli-responsive materials is highly multidisciplinary and involves research efforts from materials science, chemistry, biomedical engineering, polymer science, biology, and physics.

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Mary Beth B. Monroe

Dr Mary Beth B. Monroe is currently an Assistant Professor in Biomedical and Chemical Engineering at Syracuse University. She received her PhD in Biomedical Engineering from Texas A &M University in 2013. Her dissertation research on tissue engineered vascular grafts was recognized by the NSF Graduate Research Fellowship. Dr Monroe conducted postdoctoral research on protein engineering for wound healing at the Texas A &M Health Science Center in Houston, Texas, which was supported by the NIH National Research Service Postdoctoral Award. Prior to starting her current position, Dr Monroe was a research scientist in the Biomedical Device Lab at Texas A &M, where she worked on shape memory polymer-based medical devices. Her current research on using smart materials to improve wound healing was recognized by the Society for Biomaterials 2024 Young Investigator Award. Her work is supported by a talented team of undergraduate and graduate student researchers and by funding from the NIH and DoD.

N. D. Pradeep Singh

Professor N. D. Pradeep Singh earned his BSc and MSc in Chemistry from the University of Madras before completing his PhD in organic photochemistry in 2001 under Prof. Geetha Gopalakrishnan 's supervision. He holds the position of Professor of Chemistry at the Indian Institute of Technology, Kharagpur, having served as a Postdoctoral Fellow at the University of Leeds and the University of Cincinnati. Throughout his tenure at IIT Kharagpur, he has received numerous accolades, including the Dr S. S. Deshpande Award and the Bronze Medal from the Chemical Research Society of India. Professor Singh 's dedication to teaching has been recognized with the Top Teaching Feedback Award multiple times. Pradeep 's lab is engaged in studying the interface of chemistry, biology, and materials sciences with light as an essential tool, covering areas such as the development of new photoremovable protecting groups and their applications, photoredox catalysis for organic transformations, and organic reactive intermediates.

Of the potential applications for stimuli-responsive materials in biomedical applications, drug delivery is perhaps the most studied. The review of Damiri *et al.* (**https://doi.org/10.1039/D3TB01712E**) covers the use of polysaccharide nanogels in this space. Using an array of natural polysaccharides, researchers have developed gels that swell/de-swell in response to changes in pH, temperature, enzymes, glucose, light, magnetic fields, ultrasound, redox, and electrical fields for controlled drug release in cancer therapy, diabetes, hyperthermia, and gene delivery. In another review, Karmakar *et al.* (**https://doi.org/10.1039/D3TB03004K**) specifically discuss near infrared (NIR) light-responsive carriers for photothermal control over chemotherapy release in cancer treatments. These carriers can be based on carbon-based nanomaterials, metal-based nanoparticles, polymeric hydrogels, nanomicelles, or supramolecular vesicles, and NIR light provides a tool for targeted and controlled release of encapsulated chemotherapeutics. Within this scope, Rybak *et al.* (**https://doi.org/10.1039/D3TB02693K**) present a new system based on an injectable hydrogel that includes polydopamine particles that respond to NIR light. Upon application of light, an anti-inflammatory drug is released to provide antibacterial activity *via* a combined chemical and photothermal approach. In another approach, Choi *et al.* (**https://doi.org/10.1039/D3TB02834H**) developed acid-degradable nanoparticles as vaccine antigen carriers that release their payload after being internalized by antigen presenting cells. Using a prime and booster injection series in mice, the researchers efficiently delivered green fluorescent protein (GFP) as a model antigen to induce anti-GFP antibody production.

Towards using drug delivery to drive healing, Roy *et al.* (**https://doi.org/10.1039/D3TB02871B**) developed an enzyme-responsive hydrogel that releases a matrix metalloprotease-13 (MMP-13) blocker in the presence of inflammatory enzymes. This hydrogel reduced cartilage damage in a rat model. Beyond drug delivery, stimuli-responsive materials are often used as scaffolds for healing. To that end, Bonetti *et al.* (**https://doi.org/10.1039/D3TB02414H**) describe an injectable methylcellulose hydrogel that gels upon exposure to body-temperature heating for use in bone regeneration. In a similar approach, Roberts *et al.* (**https://doi.org/10.1039/D4TB00050A**) developed porous poly(ε-caprolactone) (PCL)-based thermoreponsive shape memory polymers with tunable thermal properties. By designing scaffolds with higher transition temperatures (37–55 °C), the PCL scaffolds can be softened and compressed to enable fitting into bone defects. Upon cooling to body temperature, the scaffolds stiffen to provide scaffolding for the bone. Formulations with lower transition temperatures (∼37 °C) could be used as stents that are crimped before delivery and subsequently expand in place in response to heating to body temperature.

Stimuli-responsive materials also show great potential for use in sensors and diagnostics. Mo *et al.* (**https://doi.org/10.1039/D4TB00365A**) review the self-assembly of peptides in living cells for a range of applications in imaging (fluorescence, photoacoustics, positron emission tomography, and magnetic resonance) and theragnostics for chemo-, immune-, and combination therapies. Sreejaya *et al.* (**https://doi.org/10.1039/D3TB02697C**) provide an overview of the use of viscosity-dependent fluorescent probes for more accurate diabetes detection. Zhang *et al.* (**https://doi.org/10.1039/D4TB01055H**) discuss the development of liquid crystal polymer (LCP) actuators with a focus on the regulation of mesogen alignment and geometry of LCP actuators for complex actuations. They cover newly designed reprogrammable LCP materials that are capable of undergoing multiple actuations. Barmin *et al.* (**https://doi.org/10.1039/D3TB02950F**) present a new approach to encapsulate metal phthalocyanines with photoacoustic abilities into acoustically-responsive microbubbles, along with hydrophobic drugs. These materials display high contrast during photoacoustic and ultrasonic imaging.

This themed collection also presents studies on fundamental chemistry to enhance future development of stimuli-responsive materials. Zhou *et al.* (**https://doi.org/10.1039/D3TB02610H**) review the development and use of stimuli-responsive peptide hydrogels for biomedical applications. They describe systems that are thermo-, pH-, ionic-, photo-, and enzyme-responsive for use in tissue engineering, drug delivery, wound healing, antibacterial agents, 3D cell culture,

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and biosensor applications. Yao *et al.* (**https://doi.org/10.1039/D3TB01803B**) provide a perspective on efforts to dendronize chitosan to impart thermo-responsiveness. They describe the process for preparation of dendronized chitosan and the ability to tune thermo-responsive behavior to enable future fabrication of dedronized chitosan-based functional materials. A novel approach to fabricate thermo-magnetic responsive soft robots is described by Siebenmorgen *et al.* (**https://doi.org/10.1039/D3TB02839A**). They trapped ferromagnetic particles in poly-*N*-isopropylacrylamide hydrogels to make robots that can shape, move, pick-and-place, and release using independent thermal and magnetic triggers. Within the field of shape memory polymers, Ramezani *et al.* (**https://doi.org/10.1039/D3TB02472E**) presents a new solvent-free method for rapid and facile synthesis of segmented polyurethanes with shape memory properties. The synthesis technique produced polymers with higher molecular weight and crystallinity to enhance mechanical and shape memory properties. Oguntade *et al.* (**https://doi.org/10.1039/D4TB00112E**) used thermally-responsive shape memory polymers to generate silk fibroin surface wrinkles. They demonstrated control over wrinkled surface morphology using fabrication and processing variables. Cell attachment to the surfaces indicates potential future use in fundamental studies on cell mechanobiology and/or applied work in wound healing.

These examples of multidisciplinary research highlight the emerging importance and utility of stimuli-responsive materials in biomedical applications. The exciting studies in this themed collection demonstrate the continual progress in this area. We hope that you enjoy reading through the collection.