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[Commentary] Will this novel stimulus be the catalyst for transforming biomedical shape memory polymers?

Sayan Basak[1]

1 Biocon (India)

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Abstract

Shape memory polymers (SMPs) circumscribe materials exhibiting responsive behavior to diverse external stimuli, ranging from heat and light to electric and magnetic fields. Originating in mid-20th-century studies, the realm of SMPs has expanded swiftly, tapping into the domains of biomedical applications, revolutionizing biomaterials, and finding applications from medical devices to regenerative medicine. Evolving beyond biocompatibility, the emphasis shifted to cytocompatible SMPs for cell mechanobiology, paving the way for direct cell-responsive SMPs. Recent breakthroughs in enzymatically triggered SMPs, particularly those influenced by cellular enzymatic activity, signify a transformative leap. This opens avenues for precision drug delivery and biosensors, merging SMPs with biomedical applications. This commentary celebrates the discovery of polymers responding to cells, unfolding the promising future of SMPs in personalized medicine, and seamlessly integrating advanced materials with cellular therapies for groundbreaking medical solutions.

Sayan Basak*

Biocon India, Biocon Park, Plot Nos. 2, 3, 4 and 5, Bommasandra- Jigani Link Road

Bangalore, Karnataka, India 560099

ORCID iD: 0000-0002-8322-4485

*Corrispondence: sayancupst@gmail.com

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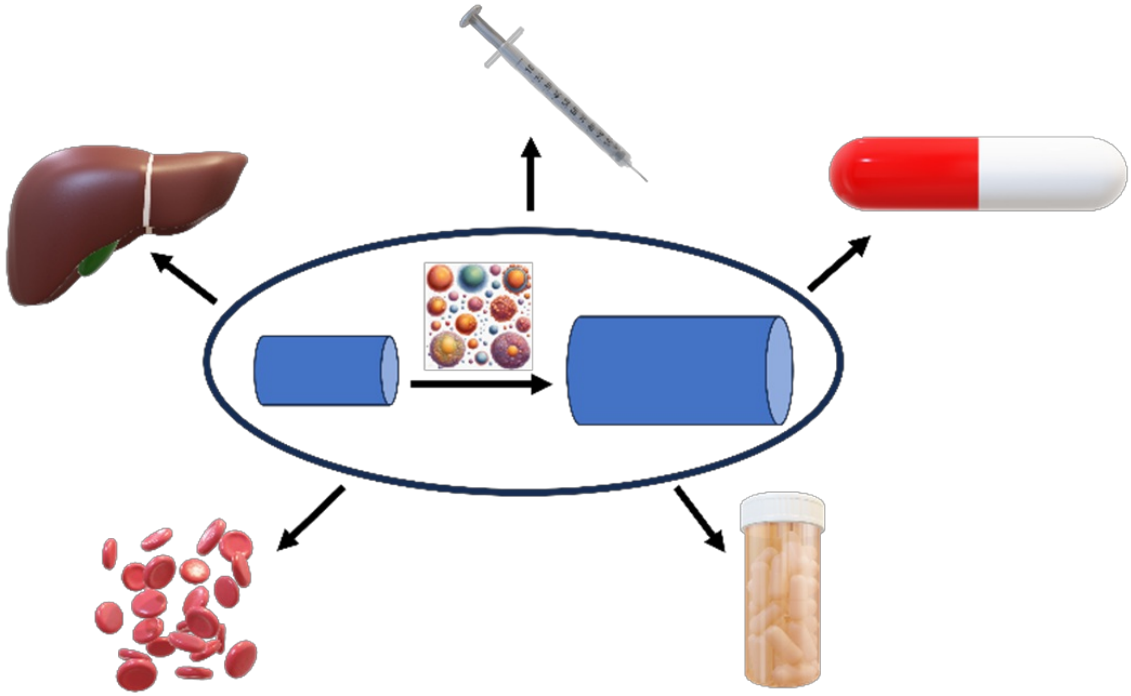
Graphical Abstract



Shape memory polymers (SMPs) represent a captivating class of materials that exhibit unique responsiveness to external stimuli, undergoing shape morphing and demonstrating the remarkable ability to return to their initial configuration after programmed deformation. The external triggers that induce these shape changes encompass a spectrum of stimuli, including heat, light, electric and magnetic fields, or moisture.[1] At their core, SMPs are characterized by a dual-network structure. The first network, constituting the permanent network, can be elastically deformed, allowing for the material to be shaped as desired. The second network, however, serves a distinctive role—it acts as a reversible, solid network responsible for fixing the deformed shape. [1][2].

Although the origins of these studies date back to the mid-20th century, with the first report on shape memory appearing in a 1941 patent, describing it as 'elastic memory', The formal recognition of shape memory polymers as a distinct class of materials took place in the 1980s. [3] This emergence was likely influenced by various factors, including the growing interest in shape memory metals, an increasing variety of polymers with structure-property tunable one-way shape memory, and their recognized utility in high-value applications, particularly in the medical devices sector. The field of shape memory polymers experienced significant growth in the subsequent years, buoyed by advancements in polymer science and engineering. This expansion involved the incorporation of new chemistries and processing techniques, further broadening the scope and capabilities of shape memory polymers.

The milestone in biocompatible shape memory polymers (SMPs) was marked in 2002 with the groundbreaking work of Lendlein and Langer, who reported the development of the first material of this kind. This seminal contribution paved the way for a new era in biomaterials, setting the stage for a plethora of innovative applications. One of the initial envisioned applications was the creation of smart biodegradable sutures, showcasing the potential for SMPs to revolutionize the field of medical interventions and wound closure.[4] The subsequent years witnessed a rapid evolution in the field of

biocompatible SMPs, with researchers exploring and expanding their applications across various biomedical domains. The versatility of these materials became increasingly apparent as they found utility in diverse areas, ranging from drug delivery systems to the treatment of vascular diseases. Biocompatible SMPs have proven to be particularly promising in the realm of regenerative medicine, where they play a pivotal role in bone tissue engineering, offering a dynamic and responsive platform for innovative solutions.[5]

As the science of shape-memory materials has progressed, there has been a concerted effort to develop SMPs that not only exhibit biocompatibility but are also cytocompatible. The emphasis has shifted towards triggers that can be safely applied without harming cells, both in vitro (cell culture-compatible) and in vivo. Prior research has delved into the realm of shape memory polymers (SMPs), using platforms triggered by thermal, solvent, or photothermal events to study cell mechanobiology. For example, Henderson et al. investigated whether (*thermoresponsive*) shape memory activation could influence cell seeding outcomes (scaffolds (for scaffold-based tissue engineering and regenerative medicine), specifically examining the number of cells seeded in a scaffold and the distribution in terms of average infiltration distance of cells post-seeding.[6] You et al. developed (*water-responsive*) shape memory poly(butanetetrol fumarate) and describe an exciting prospect for various applications in the field of tissue engineering and regenerative medicine. Similarly, at the intersection of nanotechnology and cell manipulation, researchers have successfully fabricated *(light-responsive)* SMPs (crosslinked of poly(ε-caprolactone) in the presence of gold nanorods) and demonstrated the remote control of cell morphology through the ingenious use of near-infrared (NIR) light. [7]

Until now, studies involving shape memory polymers (SMPs) for cell mechanobiology primarily relied on indirect tethering of cell activity. Recognizing the limitations of this approach, there emerged a critical need to develop a strategy enabling the direct triggering of SMPs by cellular activity. This groundbreaking shift in methodology opens up novel avenues for biomaterials science research and introduces innovative biomedical strategies. One significant area of impact is in drug delivery. With SMPs directly responsive to cell activity, drug-delivery vehicles can be tailored to target specific cells or organs based on the dynamic behavior of the surrounding cells. This level of precision allows for more effective and targeted therapeutic interventions, minimizing off-target effects and enhancing the overall efficacy of drug delivery systems. Moreover, this direct triggering of SMPs by cell activity opens up possibilities for decision-making biosensors. These biosensors, integrated with SMPs, can provide real-time feedback on cellular activities, allowing for dynamic adjustments in patient treatment strategies. The ability to respond directly to the cellular milieu creates a feedback loop, offering a level of control and customization in biomedical interventions that was previously unattainable.

In an attempt to address this shortcoming, Henderson et al. recently showcased the development of enzymatically triggered SMPs that undergo isothermal shape changes in response to enzymatic activity. [8] The direct responsiveness to enzymatic cues, especially at physiological temperatures, holds immense promise for the development of advanced biomaterials, including drug delivery systems and tissue engineering constructs, where precise and dynamic control over material properties is crucial for interacting with biological systems.

While this prior study successfully demonstrated the enzyme responsiveness of the SMP, it should be noted that the triggering was achieved in response to artificially prescribed enzyme concentrations, and cells were not present in the

experimental setup. The study, however, serves as a crucial stepping stone, laying the groundwork for future research endeavors aiming to achieve cell-responsive SMPs, thus unlocking a myriad of possibilities for advancements in biomaterials science and biomedical applications.

To further advance the realm and in an attempt to develop direct cell responsive SMPs, recently, the same research group attempted to demonstrate the enzymatic triggering of a shape memory polymer (SMP) in direct response to the presence of human cells capable of secreting enzymes. Building on prior enabling research, they conducted a comprehensive study, focusing on HepG2 cells—an established human liver cancer cell line known for its expression of hepatic triglyceride lipase activity. The study involved programmed polymers exhibiting cell-triggered shape recovery and cytocompatibility when cultured with HepG2 cells, establishing the feasibility of cytocompatible SMPs that respond directly to the presence of viable cells through a cellular trigger. Both random and aligned polycaprolactone (PCL) and Pellethane® (thermoplastic polyurethanes) dual-jet electrospun fibers underwent shape recovery triggered by heparin-treated cells, with random fibers displaying a greater change in shape than their aligned counterparts. The observed increase in lipase concentrations in heparin-treated cells contributed to the triggering effect.

The extracellular and intracellular lipase secreted by HepG2 cells, especially in the presence of heparin, played a crucial role in shaping the recovery mechanism. The described four-step sequence of enzymatic degradation, including enzyme adsorption, transition complex formation, PCL chain scission, and interaction with other polymer portions, was instrumental in regulating the programming and the responsive process. The fascinating part of the resreah was that despite the prolonged recovery time and incomplete PCL degradation within a month, the indirect cytocompatibility of HepG2 cells with SMPs remained evident (complementing previous findings on direct cytocompatibility).

The promising findings of this research spark intriguing possibilities for future applications, particularly in the realms of biosensing and targeted drug delivery. The potential extrapolation of these discoveries could pave the way for the development of advanced biosensors designed to detect pathological lipase secretion. Such biosensors, leveraging the unique responsiveness of shape memory polymers (SMPs) to enzymatic activity, could serve as valuable tools for monitoring the presence of specific cellular activities associated with conditions like hepatic cancer. Furthermore, the study hints at the prospect of employing SMPs as sophisticated drug delivery vehicles, especially in targeting liver tumors. The envisioned strategy involves the strategic degradation of the PCL fixing phase in close proximity to the tumor site. This controlled degradation mechanism, triggered by the intricate interplay of cellular enzymatic activity, holds the potential to release anticancer drugs precisely where needed. Such precision-targeted drug delivery mechanisms, facilitated by the dynamic properties of SMPs, could revolutionize therapeutic approaches, offering a more effective and localized treatment strategy for liver tumors. The bridging of SMPs with biosensing and drug delivery opens up avenues for innovative biomedical applications with significant implications for personalized medicine and enhanced treatment strategies.

Expanding on this breakthrough, researchers are harnessing the potential of cell-responsive shape memory polymers to revolutionize the treatment of Crohn's disease, a complex form of inflammatory bowel disease notorious for causing fistulas—tunneling wounds that connect different parts of the urinary, reproductive, and digestive systems. A recent

achievement by Dr. Monroe's group introduces a shape memory polymer designed with polyvinyl alcohol (PVA) and cornstarch (CS), incorporating a disulfide polyurethane crosslinker.[9] This innovative polymer exhibits controlled degradation facilitated by amylase, an enzyme naturally present in the digestive tract. Furthermore, the reduction of thiol species, such as glutathione and dithiothreitol, actively contributes to the regulated degradation of the material. This advancement represents a significant leap forward in the search for a dependable and stable solution for filling fistulas associated with Crohn's disease. The distinctive quality of this polymer lies in its seamless implantation, providing stability throughout the healing process, followed by a controlled and gradual degradation. Notably, this characteristic eliminates the necessity for secondary removal surgeries, presenting a more patient-friendly and effective approach to managing the challenging complications of Crohn's disease-related fistulas.[9]

The future holds a transformative breakthrough as we bring together the remarkable features of stimulus responsiveness, shape memory, and self-healing capabilities in smart polymeric materials. This advancement carries profound implications, especially in the realms of tissue engineering, medical devices, and cell therapy. A crucial question arises: Can these polymers, responsive to cellular cues, be the key to addressing the current challenges in precision medicine?

The intentional design of smart polymeric materials not only drives the evolution of injectable self-healing hydrogels but also propels advancements in the creation of controlled-release drug delivery systems, effectively tackling the spatial considerations crucial in medical treatments. A pivotal aspect of this progress is the integration of patients' stem cells into 3D-printed bioink—a standout fabrication technique that seamlessly blends smart polymeric materials with cell therapy, placing a strong emphasis on personalized medical interventions.[10][11] Envisaging the application of cell-responsive materials and phenomena in biomedical fields, there is a promising horizon for expanding the range of SMP triggering mechanisms to include biological cells. On a broader scale, the cost-effectiveness and highly adaptable nature of these material components establish them as a valuable biomaterial platform, opening up extensive possibilities in tissue engineering and regenerative medicine applications. This comprehensive approach not only addresses current challenges but also paves the way for innovative solutions in precision medicine, promising a future where advanced materials seamlessly integrate with cellular therapies for personalized medical breakthroughs.

Statements and Declarations

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Conflict of interest

Sayan Basak declares that he has no conflict of interest.

Human/animal rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

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