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Review Paper

Stimuli-Responsive Supramolecular Hydrogels in Precision Medicine: Recent Advances, Challenges, and Translational Perspectives

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Abstract

Stimuli-responsive supramolecular hydrogels have emerged as a promising class of dynamic biomaterials with significant potential in advanced biomedical applications. These hydrogels are formed through reversible non-covalent interactions, enabling adaptive structural and functional responses to specific internal and external stimuli. Such responsiveness allows precise control over drug release, making them highly suitable for targeted drug delivery, cancer therapy, and tissue engineering. Recent advances in molecular design, hybrid nanocomposites, and multifunctional systems have further enhanced their performance and applicability in precision medicine. However, several challenges persist, including limitations in structural stability, concerns regarding biocompatibility, difficulties in large-scale manufacturing, and complex regulatory requirements. Addressing these issues is critical for successful clinical translation. Despite these challenges, the ability of these hydrogels to respond intelligently to biological cues and provide personalized therapeutic outcomes underscores their importance in next-generation healthcare. Their integration into precision medicine frameworks holds considerable promise for improving treatment efficacy, reducing side effects, and enabling more patient-specific therapeutic strategies.

Keywords: Precision medicine, stimuli-responsive hydrogels, supramolecular chemistry, targeted drug delivery.

Introduction

Hydrogels are three-dimensional, hydrophilic polymeric networks capable of retaining large amounts of water while maintaining structural integrity, rendering them highly suitable for biomedical applications. Their unique physicochemical properties, including tunable mechanical strength, high biocompatibility, and permeability, have led to extensive exploration in drug delivery, tissue engineering, and regenerative medicine[1,2]. In recent years, the emergence of supramolecular hydrogels—formed through non-covalent interactions rather than permanent covalent crosslinks—has opened new avenues for designing dynamic and adaptive biomaterials. These systems exhibit reversible assembly, self-healing behavior, and responsiveness to environmental cues, making them particularly attractive for next-generation therapeutic platforms[3].

Supramolecular hydrogels are stabilized by a variety of weak interactions, including hydrogen bonding, host–guest inclusion complexes, π–π stacking, electrostatic interactions, and van der Waals forces. Unlike conventional chemically cross linked hydrogels, these interactions enable reversible sol–gel transitions and dynamic reconfiguration of the network structure under specific conditions. For instance, host–guest chemistry involving cyclodextrins and aromatic moieties allows precise molecular recognition, while π–π stacking interactions facilitate ordered self-assembly of aromatic gelators[4,5]. Hydrogen bonding further contributes to structural stability and responsiveness, enabling the formation of hierarchical architectures with controllable properties. Such versatility in molecular design provides a robust platform for engineering materials that can respond intelligently to external and internal stimuli.

Stimuli-responsive hydrogels, also referred to as "smart hydrogels," are capable of undergoing physicochemical changes in response to specific triggers such as pH, temperature, light, enzymes, or redox conditions. These responses may include swelling–deswelling transitions, degradation, or controlled release of encapsulated agents. The incorporation of supramolecular interactions into these systems enhances their sensitivity and reversibility, allowing precise modulation of material behavior in complex biological environments[6]. This adaptability is particularly crucial in biomedical contexts, where micro environmental variations—such as the acidic pH of tumor tissues or the presence of specific enzymes—can be exploited for targeted therapeutic action.

The paradigm of precision medicine emphasizes the customization of healthcare strategies based on individual patient characteristics, including genetic, environmental, and lifestyle factors. In this context, stimuli-responsive supramolecular hydrogels offer significant potential as

intelligent delivery systems capable of site-specific and temporally controlled therapeutic release. By integrating responsiveness to disease-specific biomarkers, these materials can minimize systemic side effects and enhance therapeutic efficacy. Furthermore, their injectability and minimally invasive deployment align well with the clinical demands of personalized treatment approaches[7,8].

Despite these promising attributes, several challenges hinder the widespread clinical translation of stimuli-responsive supramolecular hydrogels. Issues related to mechanical stability, reproducibility of synthesis, scalability of production, and long-term biocompatibility remain critical concerns. Additionally, the complexity of biological systems often limits the predictability of hydrogel behavior in vivo, necessitating more comprehensive studies to bridge the gap between laboratory research and clinical application. Regulatory hurdles and the lack of standardized evaluation protocols further complicate the translation process[9].

In light of these considerations, the present paper aims to provide a comprehensive overview of stimuli-responsive supramolecular hydrogels in the context of precision medicine. Specifically, it seeks to i. elucidate the fundamental principles governing supramolecular hydrogel formation and responsiveness, ii. examine recent advances in their biomedical applications, iii. critically analyze existing challenges and limitations, and iv. discuss future perspectives for their successful clinical translation. Through this integrated approach, the paper endeavors to highlight the transformative potential of these materials in advancing personalized therapeutic strategies.

Fundamentals of supramolecular hydrogels

Definition and Classification: Supramolecular hydrogels are a class of soft materials formed through the self-assembly of molecular building blocks via non-covalent interactions, resulting in a three-dimensional network capable of entrapping large volumes of water. Unlike conventional hydrogels that rely on permanent covalent crosslinks, supramolecular hydrogels are stabilized by reversible interactions, which impart dynamic and stimuli-responsive characteristics[10]. Based on their crosslinking mechanisms, hydrogels are broadly classified into physical and chemical hydrogels. Physical hydrogels are formed through weak interactions such as hydrogen bonding, ionic interactions, and hydrophobic forces, allowing reversible gelation. In contrast, chemical hydrogels involve covalent crosslinking, leading to permanent and mechanically robust networks but limited adaptability[11].

A significant subclass of supramolecular hydrogels is based on low molecular weight gelators, which are small molecules capable of self-assembling into fibrous networks through directional non-covalent interactions. These gelators often contain functional groups that promote intermolecular interactions, such as aromatic rings for π–π stacking or amide groups for hydrogen bonding. Their ability to form ordered nanostructures with minimal molecular weight offers advantages such as ease of synthesis, structural tunability, and enhanced responsiveness to environmental stimuli[12].

Supramolecular Interactions: The formation and stability of supramolecular hydrogels are governed by a range of non-covalent interactions that collectively drive self-assembly and network formation. Hydrogen bonding is one of the most fundamental interactions, providing directional and reversible linkage between molecular units. Host–guest interactions, particularly those involving macrocyclic molecules such as cyclodextrins, enable selective molecular recognition and inclusion complex formation, thereby enhancing structural specificity and responsiveness[13].

Additionally, π–π stacking interactions between aromatic moieties contribute significantly to the formation of fibrous nanostructures, promoting gelation through ordered aggregation. Electrostatic interactions between oppositely charged species further stabilize the network, especially in polyelectrolyte-based systems. Van der Waals forces and hydrophobic interactions also play supportive roles in maintaining the integrity of the assembled structure. The synergistic effect of these interactions allows the formation of hierarchical architectures with tunable mechanical and functional properties[14].

Structural Features: A defining characteristic of supramolecular hydrogels is their ability to undergo spontaneous self-assembly into well-organized nanostructures. This process is driven by the balance between attractive and repulsive forces at the molecular level, leading to the formation of fibrillar or tubular architectures that entangle to create a continuous three-dimensional network. The resulting structure is highly porous, facilitating the diffusion of water, nutrients, and therapeutic agents[15].

Network formation in these hydrogels is dynamic and reversible, allowing structural reorganization in response to environmental changes. This adaptability enables properties such as self-healing, where the hydrogel can recover its integrity after mechanical disruption. Furthermore, the nanoscale organization of the network plays a crucial role in determining macroscopic properties such as stiffness, swelling behavior, and degradation kinetics, which are critical for biomedical applications[16].

Properties Relevant to Biomedical Use: Supramolecular hydrogels exhibit several properties that make them highly suitable for biomedical applications. Biocompatibility is a key requirement, and these materials are often designed using bioinspired or biologically benign components to minimize cytotoxicity and immune responses. Their high water content and soft tissue-like consistency further enhance compatibility with biological systems[17].

Tunability is another significant advantage, as the mechanical, chemical, and responsive properties of these hydrogels can be precisely controlled by modifying the molecular structure or interaction strength. This allows customization for specific applications such as drug delivery, tissue scaffolding, or biosensing. Additionally, the reversible nature of non-covalent interactions imparts stimuli-responsiveness and self-healing capabilities, enabling repeated use and prolonged functionality. Reversibility also facilitates controlled degradation and release profiles, which are essential for targeted therapeutic interventions in precision medicine[18].

Stimuli-responsive behaviour

Internal Stimuli: Stimuli-responsive supramolecular hydrogels exhibit dynamic physicochemical changes in response to endogenous biological triggers, enabling precise control over their structure and function. Among internal stimuli, pH is one of the most extensively studied factors, particularly due to its variation across physiological and pathological environments. pH-responsive hydrogels are typically designed using ionizable functional groups such as carboxylic acids or amines, which undergo protonation or deprotonation under different pH conditions. This results in changes in electrostatic interactions and osmotic pressure, leading to swelling, deswelling, or network disruption. Such systems are highly relevant in cancer therapy, where the acidic tumor microenvironment can trigger targeted drug release[19].

Enzyme-responsive hydrogels exploit the over expression of specific enzymes in diseased tissues to achieve site-specific activation. These systems incorporate enzyme-cleavable linkages or peptide sequences that undergo degradation in the presence of target enzymes, such as matrix metalloproteinases or proteases. The enzymatic cleavage leads to structural disassembly or increased permeability of the hydrogel network, facilitating controlled release of encapsulated therapeutics[20].

Redox-responsive hydrogels are designed to respond to variations in the oxidative environment, particularly differences in intracellular and extracellular redox potentials. These systems often utilize disulfide bonds or other redox-sensitive linkages that can be cleaved under reducing conditions, such as elevated intracellular glutathione levels, resulting in network degradation and drug release[21].

External Stimuli: In addition to internal triggers, supramolecular hydrogels can be engineered to respond to externally applied stimuli, allowing precise spatial and temporal control over their behavior. Temperature-responsive hydrogels are among the most widely studied systems, often based on polymers exhibiting a lower critical solution temperature. These materials undergo reversible sol–gel transitions in response to temperature changes, enabling injectable formulations that solidify at physiological conditions[22]. Light-responsive hydrogels provide non-invasive control through photoresponsive moieties such as azobenzene, which undergo reversible isomerization upon light irradiation, thereby altering network interactions and properties[23]. Magnetic field-responsive hydrogels incorporate magnetic nanoparticles that respond to external magnetic fields, generating localized effects such as heating or mechanical deformation, which in turn modulate hydrogel structure and function[24].

Mechanisms of Responsiveness: The responsiveness of supramolecular hydrogels is governed by physicochemical mechanisms that translate stimuli into macroscopic changes. One of the primary mechanisms is the sol–gel transition, wherein the hydrogel reversibly transitions between liquid-like and solid-like states through the formation or disruption of non-covalent interactions[25]. Another key mechanism involves conformational changes at the molecular level that alter interaction strength and network organisation, thereby influencing properties such as porosity, mechanical strength, and diffusion behaviour[26]. Figure-1 illustrates these mechanisms and the interplay between internal and external stimuli in regulating hydrogel behavior.

Applications in precision medicine

Targeted Drug Delivery: Stimuli-responsive supramolecular hydrogels have emerged as highly efficient platforms for targeted drug delivery due to their ability to release therapeutic agents in a controlled and site-specific manner. These systems can encapsulate a wide range of drugs, including small molecules, proteins, and nucleic acids, within their three-dimensional network. Controlled release is achieved through the modulation of non-covalent interactions in response to specific stimuli, enabling sustained and localized drug delivery profiles. This minimizes systemic toxicity and enhances therapeutic efficacy, which is a fundamental requirement in precision medicine[27].

A key application lies in tumor microenvironment targeting, where hydrogels are engineered to respond to characteristic features such as acidic pH, elevated enzyme levels, and redox gradients. For instance, pH-responsive supramolecular hydrogels can selectively release anticancer drugs in acidic tumor tissues while remaining stable under physiological conditions. Similarly, enzyme-responsive systems exploit tumor-associated enzymes to trigger drug release. These strategies enable highly selective targeting, thereby improving treatment outcomes and reducing adverse effects[28].

Cancer Therapy: In cancer therapy, supramolecular hydrogels function as smart drug carriers that can adapt to the dynamic tumor environment. Their injectability allows minimally invasive administration, followed by in situ gel formation at the tumor site. This localized delivery enhances drug retention and reduces systemic exposure. Furthermore, their ability to incorporate multiple functional components enables the design of multifunctional therapeutic systems[29].

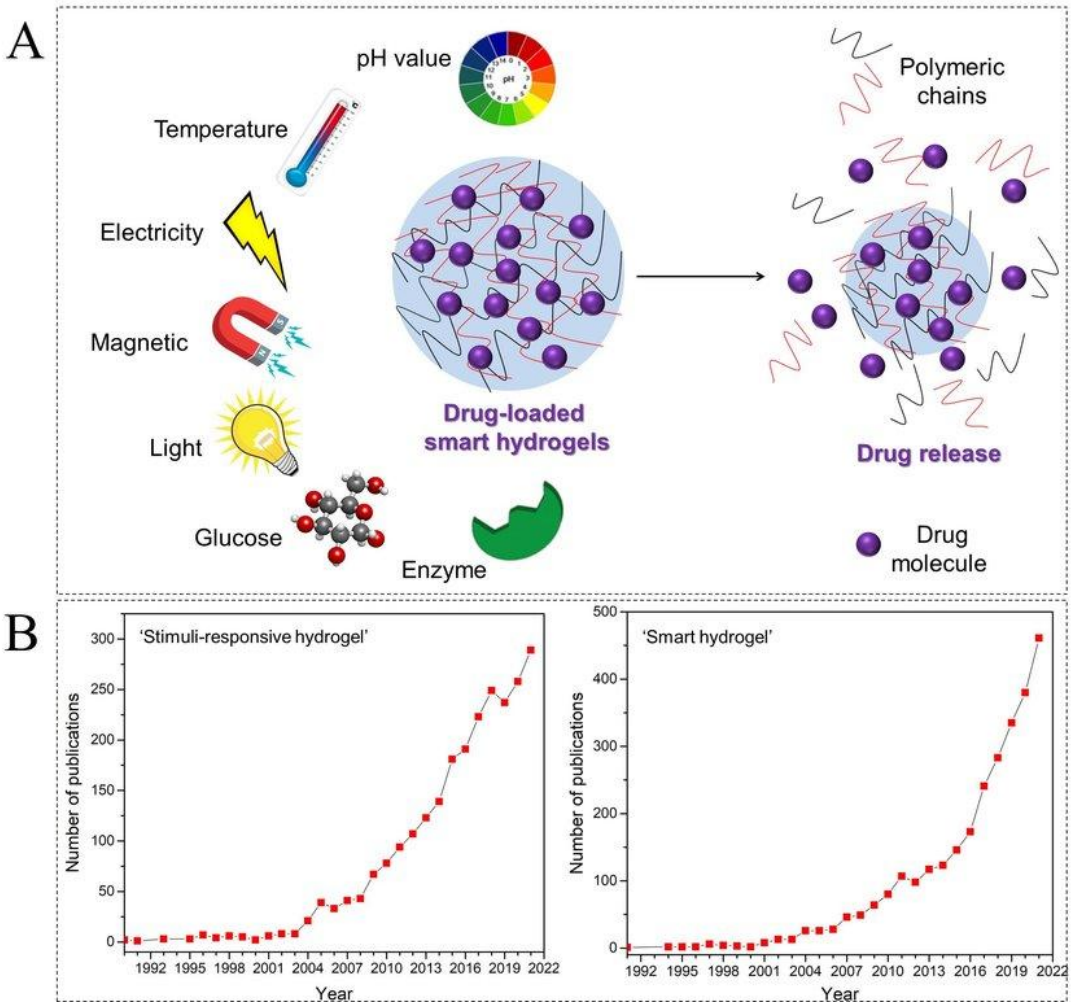


Figure-1: Mechanism of stimuli-responsive supramolecular hydrogels.

Combination therapies represent a significant advancement in this field, where hydrogels are used to co-deliver multiple therapeutic agents, such as chemotherapeutic drugs, immunomodulators, and photosensitizers. These systems can be engineered to release different agents in a sequential or simultaneous manner in response to specific stimuli. For example, a hydrogel may release a chemotherapeutic drug under acidic conditions while activating a photosensitizer upon light exposure. Such synergistic approaches improve therapeutic efficacy and help overcome drug resistance, a major challenge in cancer treatment[30].

Tissue Engineering and Regenerative Medicine: Supramolecular hydrogels play a crucial role in tissue engineering due to their structural similarity to the extracellular matrix and their ability to support cell growth and differentiation. Their tunable mechanical properties and porous architecture make them ideal candidates for scaffold design. By adjusting the strength and type of supramolecular interactions, the stiffness, degradation rate, and bioactivity of the scaffold can be precisely controlled to match the requirements of specific tissues[31].

Cell encapsulation is another important application, where living cells are embedded within the hydrogel matrix for therapeutic purposes. The mild gelation conditions and biocompatibility of supramolecular hydrogels ensure high cell viability and functionality. Additionally, stimuli-responsive behavior allows dynamic regulation of the cellular microenvironment, such as controlled release of growth factors or changes in matrix stiffness. These features are essential for promoting tissue regeneration and achieving successful clinical outcomes[32].

Biosensing and Diagnostics: The integration of supramolecular hydrogels into biosensing platforms has enabled the development of highly sensitive and selective diagnostic systems. These hydrogels can respond to specific biological or chemical signals, leading to measurable changes in properties such as swelling, optical characteristics, or electrical conductivity. Such responsive detection systems are particularly useful for real-time monitoring of biomarkers associated with diseases[33].

In precision medicine, these hydrogels can be tailored to detect specific analytes, such as enzymes, metabolites, or nucleic acids, with high specificity. The incorporation of functional recognition elements within the supramolecular network enhances sensitivity and enables rapid signal transduction. Moreover, the reversible nature of these systems allows repeated use and continuous monitoring, making them suitable for point-of-care diagnostics and wearable biosensing devices[34].

Table-1: Applications of stimuli-responsive supramolecular hydrogels in precision medicine.

Application	Hydrogel Type	Stimulus
Targeted drug delivery	pH-responsive supramolecular hydrogel	pH (tumor acidity)
Controlled release systems	Redox-sensitive hydrogel	Redox (glutathione levels)
Cancer therapy	Injectable supramolecular hydrogel	Temperature, pH
Combination therapy	Multi-responsive hydrogel	Light, pH
Tissue engineering	Self-assembling hydrogel scaffold	Enzymes, mechanical stress
Cell encapsulation	Biocompatible supramolecular hydrogel	Temperature, pH
Biosensing	Functionalized hydrogel sensor	Enzymes, metabolites
Diagnostics	Smart responsive hydrogel	Optical/light stimuli

Recent advances

Novel Gelators and Smart Materials: Recent years have witnessed significant progress in the design of novel gelators and smart supramolecular materials with enhanced functionality and responsiveness. Advances in molecular engineering have enabled the development of low molecular weight gelators with precise control over self-assembly pathways and hierarchical organization. These gelators are increasingly designed using bioinspired motifs such as peptides, nucleobases, and saccharides, which enhance biocompatibility and facilitate specific molecular recognition. Furthermore, the incorporation of dynamic covalent chemistry alongside non-covalent interactions has led to hybrid systems with improved stability and adaptability. Such innovations have expanded the scope of supramolecular hydrogels in biomedical applications, particularly in precision medicine, where responsiveness and selectivity are critical[35].

Hybrid Systems (Nanocomposites): The integration of nanomaterials into supramolecular hydrogels has led to the emergence of hybrid nanocomposite systems with superior mechanical, electrical, and functional properties. These systems often incorporate nanoparticles such as graphene oxide, gold nanoparticles, silica, or magnetic nanostructures to enhance performance. The synergy between supramolecular networks and embedded nanomaterials enables improved mechanical strength, stimuli sensitivity, and multifunctionality. For instance, conductive nanocomposite hydrogels have been developed for applications in bioelectronics and tissue engineering, while magnetic nanocomposites enable remote actuation and controlled drug release. Such hybrid systems represent a major advancement in the field, bridging the gap between soft materials and functional nanotechnology[36].

Injectable and Self-Healing Hydrogels: Injectable supramolecular hydrogels have gained considerable attention due to their minimally invasive delivery and in situ gelation capabilities. These systems are typically designed to undergo sol–gel transitions under physiological conditions, allowing easy administration followed by rapid gel formation at the target site. This property is particularly advantageous in localized drug delivery and tissue regeneration. In parallel, the development of self-healing hydrogels has introduced a new dimension of durability and reusability. The reversible nature of supramolecular interactions enables these materials to recover their structure and function after mechanical damage. Recent studies have focused on enhancing the mechanical robustness and healing efficiency of these systems, making them more suitable for dynamic biological environments[37].

Clinical and Preclinical Studies: The translation of stimuli-responsive supramolecular hydrogels from laboratory research to clinical application has accelerated in recent years, with numerous preclinical studies demonstrating promising results. These studies have explored applications in cancer therapy, wound healing, and regenerative medicine, highlighting improved therapeutic outcomes and reduced side effects. Advances in vivo evaluation techniques have provided deeper insights into the behavior, degradation, and biocompatibility of these materials within biological systems. Additionally, early-stage clinical investigations are beginning to validate the safety and efficacy of certain hydrogel-based systems, particularly in drug delivery and tissue repair applications. Despite these advancements, challenges related to large-scale production, regulatory approval, and long-term stability remain key areas of ongoing research[38].

Challenges and limitations

Stability Issues: Despite significant advancements, the practical application of stimuli-responsive supramolecular hydrogels is often limited by their inherent stability issues. Since these systems are primarily stabilized by weak non-covalent interactions, they are susceptible to environmental fluctuations such as temperature, pH, ionic strength, and mechanical stress. This can lead to premature degradation, loss of structural integrity, or uncontrolled drug release. In physiological conditions, particularly in vivo, maintaining the balance between sufficient stability and desired responsiveness remains a critical challenge. Efforts to enhance stability through hybrid crosslinking strategies or incorporation of reinforcing components have shown promise; however, achieving long-term

functional stability without compromising responsiveness is still an area requiring further investigation[39].

Toxicity and Biocompatibility Concerns: Biocompatibility is a fundamental requirement for any material intended for biomedical applications, yet concerns regarding the toxicity of certain supramolecular components persist. While many supramolecular hydrogels are designed using bioinspired or biodegradable building blocks, the inclusion of synthetic gelators, nanoparticles, or responsive moieties may introduce cytotoxic effects or trigger undesirable immune responses. Additionally, degradation products formed under physiological conditions must be carefully evaluated for their safety and clearance pathways. Long-term in vivo studies are still limited, and comprehensive toxicological assessments are necessary to ensure clinical safety. Addressing these concerns requires a multidisciplinary approach involving material design, biological evaluation, and regulatory compliance[40].

Scale-Up and Manufacturing: The transition from laboratory-scale synthesis to large-scale manufacturing presents significant challenges for supramolecular hydrogel systems. Many of these materials rely on precise self-assembly processes that are highly sensitive to concentration, temperature, and environmental conditions. Reproducing these conditions consistently on an industrial scale is difficult, leading to variability in material properties and performance. Furthermore, the cost of specialized building blocks and the complexity of synthesis may limit commercial viability. Developing scalable, cost-effective, and reproducible fabrication methods is essential for the successful translation of these materials into clinical and industrial applications[41].

Regulatory Barriers: Regulatory approval represents another major obstacle in the clinical translation of stimuli-responsive supramolecular hydrogels. The complexity and multifunctionality of these systems often do not fit easily within existing regulatory frameworks, which are typically designed for conventional pharmaceuticals or medical devices. Challenges include the classification of these materials, standardization of evaluation protocols, and demonstration of long-term safety and efficacy. Additionally, the lack of established guidelines for assessing stimuli-responsive behavior further complicates the approval process. Collaboration between researchers, industry stakeholders, and regulatory agencies is crucial to develop standardized methodologies and accelerate the translation of these innovative materials into clinical practice[42]. hydrogels[45].

Translational perspectives

Clinical Translation Pathways: The successful clinical translation of stimuli-responsive supramolecular hydrogels requires a systematic integration of material design, preclinical validation, and regulatory approval processes. A key aspect involves the development of robust preclinical models that accurately simulate human physiological conditions, enabling reliable assessment of safety, efficacy, and degradation behavior. Standardization of characterization techniques, including mechanical properties, responsiveness, and drug release kinetics, is essential to ensure reproducibility and comparability across studies. Furthermore, scalable and reproducible synthesis methods must be established to meet clinical-grade manufacturing requirements. Addressing these factors will facilitate the transition of supramolecular hydrogels from experimental systems to clinically viable therapeutic platforms[43].

Industry–Academia Collaboration: Collaboration between academic institutions and industry plays a critical role in accelerating the translation of supramolecular hydrogels into practical applications. Academic research provides fundamental insights into material design and mechanism, while industry contributes expertise in large-scale production, quality control, and commercialization. Such partnerships can bridge the gap between innovation and application by enabling the development of standardized protocols, pilot-scale manufacturing processes, and regulatory strategies. Additionally, interdisciplinary collaboration involving chemists, material scientists, clinicians, and regulatory experts is essential to address the multifaceted challenges associated with biomedical translation. Strengthening these collaborative frameworks will enhance the efficiency and success rate of bringing advanced hydrogel systems to market[44].

Future Research Directions: Future research in stimuli-responsive supramolecular hydrogels is expected to focus on enhancing precision, multifunctionality, and clinical applicability. The integration of advanced technologies such as artificial intelligence and machine learning can facilitate the rational design of hydrogels with optimized properties and predictable behavior. Additionally, the development of multi-responsive systems capable of simultaneously responding to multiple stimuli offers significant potential for complex therapeutic applications. Efforts are also directed toward improving long-term stability, biocompatibility, and biodegradability to meet clinical requirements. Moreover, the incorporation of bioactive components and personalized design strategies will further align these materials with the goals of precision medicine. Continued research in these areas is essential to unlock the full translational potential of supramolecular hydrogels[45].

Conclusion

Stimuli-responsive supramolecular hydrogels represent a rapidly evolving class of smart biomaterials with significant potential in precision medicine. This paper has highlighted the fundamental principles governing their design, including the role of non-covalent interactions, self-assembly mechanisms, and dynamic responsiveness to internal and external stimuli. The integration of such properties enables the development of highly adaptable systems capable of controlled drug delivery, targeted cancer

therapy, tissue engineering, and advanced diagnostic applications. Recent advances in molecular design, hybrid nanocomposites, and multifunctional systems further demonstrate the versatility and transformative potential of these materials.

Despite these promising developments, several challenges remain, including issues related to stability, biocompatibility, large-scale manufacturing, and regulatory approval. Addressing these limitations is essential for bridging the gap between laboratory research and clinical application. The advancement of interdisciplinary collaboration, along with the development of standardized evaluation protocols, will play a crucial role in overcoming these barriers.

In the context of precision medicine, stimuli-responsive supramolecular hydrogels offer a unique platform for personalized and targeted therapeutic interventions. Their ability to respond to specific biological cues and deliver therapeutics in a controlled manner aligns closely with the goals of individualized healthcare. Future research focusing on multi-responsive systems, improved biocompatibility, and integration with emerging technologies such as artificial intelligence is expected to further enhance their clinical relevance. Overall, these materials hold considerable promise for revolutionizing next-generation biomedical therapies and advancing the field of precision medicine.

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