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Self-assembling nanocomposites for smart drug delivery: towards personalized and stimuli-responsive therapeutics

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Self-assembling nanocomposites (SANCs) represent a valuable and innovative drug delivery system that facilitates site-specific and stimulus-controlled drug administration. These composites have the capability to self-assemble into stimulus-responsive nanostructures, enabling the effective delivery of a wide range of therapeutic agents, from small molecules to biologics, to specific target sites. This advancement addresses crucial challenges in treating diseases like cancer and chronic inflammatory conditions. In this review, we briefly outline the advantages of SANCs in enhancing bioavailability, reducing systemic toxicity, and maintaining stability under physiological conditions. However, several significant obstacles remain, including challenges related to scalability, stability, storage, biocompatibility, and regulatory approvals that have not been met to obtain clinical applications. Furthermore, we explore the stimuli-responsive and biohybrid materials, as well as the integration of SANCs with artificial intelligence and nanotechnology to create intelligent drug delivery systems. Encouraging contributions for papers that emphasize the role of SANCs in personalized medicine, this review underscores the potential of these nanosystems in developing tailored, patient-specific treatment approaches. By establishing robust policy frameworks and fostering strategic partnerships, SANCs have the potential to usher in a new era of tailored solutions for delivering medications effectively, thereby advancing the field of modern medicine.

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1. Introduction

Conventional delivery systems, such as intravenous and oral formulations, are associated with several significant limitations, including low targeting precision, systemic toxicity, and suboptimal bioavailability.[1] These limitations account for off-target effects and limited therapeutic efficacy, particularly in oncology, where drugs often struggle to effectively penetrate the tumor microenvironment.[2] Nanotechnology has facilitated the creation of nanostructured carriers with functional properties like controlled size, shape, and surface chemistry, thereby enhancing the solubility, stability, and cell-specific uptake of the therapeutics.[3] However, despite extensive research efforts, translation to clinical settings remains limited, highlighting the need for newer, more versatile platforms.[4]

Self-assembling nanocomposites (SANCs) have emerged in nanomedicine as innovative colloidal tools that enable the precise engineering of complex drug-delivery profiles through self-assembly triggered by environmental cues.[5] This approach provides both temporal and spatial control over drug release,

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bolstering therapeutic efficacy while minimizing side effects. SANCs can be tailored to respond to environmental conditions, such as the acidic pH of tumor tissue or enzymatic activity at inflamed sites, for targeted delivery.[6] These nanocomposites are positioned to tackle current challenges in drug delivery, including controlled multidrug release and real-time adaptability to physiological changes. Despite rapid development, the SANC literature remains fragmented, with studies varying in design, functional mechanism, and therapeutic application. Prior reviews have predominantly focused on isolated aspects, offering limited insights into how the potential of SANCs may vary across diverse therapeutic contexts.[7]

SANCs have great potential benefits compared with traditional drug delivery systems, especially in overcoming limitations such as low drug solubility, instability, and lack of specificity. Using the concepts of molecular self-assembly, these nanostructures develop versatile platform delivery systems that improve pharmacokinetics and therapeutic efficiency. Recently conducted research has shown how SANCs have clinical potential to deal with such limitations. As an illustrative example, the *in vitro* aqueous solubility of a self-assembled nanoparticle system based on camptothecin-based dual-responsive nanomaterial was enhanced by 25-fold, along with high tumor-selective toxicity and low systemic toxicity *in vivo*.[8] In like manner, gelatin-oleic acid nanostructures increased the solubility of drugs such as valsartan and telmisartan, offering a controlled release with particle sizes measuring approximately 200–250 nm.[9] Further, paclitaxel- and doxorubicin-loaded casein-based nanomicelles provided superior tumor inhibition activity and high bioavailability in preclinical breast cancer models.[10] These results emphasize the potential of SANCs to address the traditional problems of drug delivery and, hence, a possible platform for future precision medicine applications.

Reza Emadi

Reza Emadi holds a Master's degree in Biochemistry and specializes in pharmaceutical science. His research primarily focuses on controlled drug delivery and drug discovery, employing pharmacodynamics experiments to investigate drug interactions and effectiveness. Additionally, Reza has explored the antiviral activity of natural extracts, contributing valuable insights to the development of potential therapeutic agents. His dedication to advancing pharmaceutical research continues to inspire new approaches to drug discovery and treatment options.

Zahra Amiri

Zahra Amiri holds a Master of Science in Medical Nanotechnology. Her research focuses on the application of nanotechnology in regenerative medicine and tissue engineering, with particular emphasis on stem-cell-based therapies and the design of biocompatible nanomaterials. She is committed to developing innovative nanoscale platforms to enhance biomedical performance and improve therapeutic outcomes. The completed and signed form has been attached, along with my photo. Please let me know if any additional information is needed.

Fatemeh Mortazavi Moghadam

Fatemeh Mortazavi Moghadam is a researcher from Iran with a PhD in nanobiotechnology. Her work has been carried out in advanced life science and engineering research centers, both in her home country and abroad. She is particularly interested in nanobiosensors and the intersection of nanotechnology with neuroscience and medicine. Through her research, she aims to help develop innovative technologies that can improve human health and quality of life.

Setareh Raoufi

Setareh Raoufi holds a Master's degree in Tissue Engineering and is currently pursuing a Master's in Industrial Nanobiotechnology. Her research interests include nanodrug design, tissue engineering, and advanced drug delivery systems. She focuses on integrating nanoscale materials into regenerative medicine to develop targeted, efficient therapeutic platforms. Her work emphasizes biomimetic scaffold design, intelligent drug carriers, and interdisciplinary strategies to improve the treatment of complex diseases, particularly neurological disorders. Setareh aims to contribute to the development of next-generation pharmaceutical and biomedical technologies while advancing innovative approaches in nanomedicine and tissue regeneration.

The application of SANCs has expanded to cover different therapeutic applications outside the conventional drug delivery area, such as cancer therapy, gene therapy, and infectious diseases. Peptide-engineered self-assembled nanofibers have shown potential in cancer therapy by their biodegradation and bioresponsiveness to, *e.g.*, pH or enzyme triggers. The combination of the nanostructures with monotherapies and a combination of chemo-immunotherapies, allowing successful tumor penetration and drug retention, is facilitated mainly by enhancing tumor penetration and drug retention.[11] Similarly, a hybrid peptide nanoplatform based on Luffa cylindrica exerted multitarget inhibition of cancer signalling pathways (Wnt/beta-catenin and p53), effectively inhibited tumor growth *in vivo*, and was highly biologically safe.[12]

Mahtab Zargar Moradi

Mahtab Zargar Moradi is pursuing a master's degree in Molecular Genetics, with research conducted on nanodrugs and their applications in cancer therapy. Innovative molecular approaches for targeted treatment and improved therapeutic outcomes are being investigated. More than five years of professional experience as a genetics technician in medical and pathobiology laboratories have been accumulated, with extensive expertise gained in molecular diagnostics and laboratory techniques. The completed and signed form has been attached, along with my photo. Please let me know if any additional information is needed.

Sepideh Asadi

Dr Sepideh Asadi is a nanobiotechnology and computational oncology researcher with a PhD in Nanobiotechnology from the University of Tehran. Her doctoral research focused on the molecular modeling and synthesis of thymoquinone-loaded cellulose-based electrospun nanofibers for breast cancer therapy. She specializes in early cancer diagnostics, precision nanomedicine, and AI-driven drug discovery, integrating computational modeling and biomaterials engineering to advance translational cancer research. Dr Asadi has authored several Q1/Q2 publications, serves as a peer reviewer for international journals, and has been awarded competitive national research grants as both principal investigator and co-investigator. She actively collaborates with research teams in the UK, South Korea, the USA, Italy, Austria, and Hong Kong, contributing to the development of clinically relevant and data-driven nanomedical solutions.

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Dr William Cho is a seasoned cancer researcher who has contributed over 700 peer-reviewed SCI papers to reputable journals, including The Lancet Oncology, Annals of Oncology, Molecular Cancer, Advanced Science, Nature Communications, PNAS, Science Advances, Journal of Thoracic Oncology, *among others. Additionally, he has authored over three dozen books, including "MicroRNAs in Cancer Translational Research" and "An Omics Perspective on Cancer Research", to name a few. Currently, his H-index stands at 103. As one of the top 2% most influential scientists globally since 2017, Dr Cho has recently been included in the 2023 and 2024 Global Highly Cited Researchers list by Clarivate.*

Jin Hee Park

Jin Hee Park is currently pursuing the integrated Master's and PhD program in the Department of Biological Engineering at Inha University, South Korea. She conducts her research in the Nano Bioengineering Analysis Laboratory under the supervision of Professor Yun Suk Huh. Her academic and research interests span a broad range within biomedical engineering, encompassing both the engineering of advanced nanocarriers and the investigation of underlying disease mechanisms. Specifically, she focuses on developing multifunctional nano systems to enhance tumor-targeting efficiency and therapeutic efficacy while also exploring the molecular and immunological pathways that drive disease progression. Her work aims to bridge engineering and medicine, advancing next-generation nanomedicine platforms for improved cancer treatment.

SANCs have been used in gene therapy, whereby they have facilitated the successful delivery of siRNA and DNA. In one case, it was shown that oncogenes (Eg5 and Survivin) were effectively silenced *in vivo* with a neutral surface chemistry to avoid lysosomal degradation as a mechanism to reduce tumor volume using a vitamin E siRNA nanocomplex.[13] In another study, 2-fold gene transfection efficiency was obtained with unmodified calcium–phosphate-based self-assembling complexes compared to Lipofectamine 2000, with stable expression of up to 10 days and minimal toxic effects *in vivo*.[14]

Enzyme-directed assembly of nanoparticles to enable a responsive release of antimicrobial agents has been studied as a potential application in the treatment of infectious disease. Such systems will be triggered by signals of infection (*e.g.*, enzyme levels) to release antimicrobial cargos at sites of infection, reducing off-target and resistance selection.[15] These results show the wide applicability of SANCs and how they can be used to promote precision and personalized medicine.

The present review is limited to SANCs to deliver drugs, as peer-reviewed articles located in PubMed, ScienceDirect, and Web of Science within the timeframe of January 2015 to November 2025 using keywords, including, but not limited to:

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Anahita Voosough is an undergraduate student in biotechnology at the University of Tehran, Iran. Her academic interests center on fundamental sciences, nanobiotechnology, Drug Delivery, and Cancer Treatment, and she has contributed to research papers in these fields.

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Dr Marzieh Ramezani Farani is an accomplished nanobiomaterials chemist with academic and industrial experience in Iran and South Korea. Her research focuses on the design of multifunctional nanomaterials for targeted drug delivery, cancer therapy, and regenerative medicine. She has authored over 50 peer-reviewed publications as the first or corresponding author, making significant contributions to nanomedicine and tissue engineering. She received prestigious fellowships from the National Research Foundation of Korea and worked as a senior researcher at Inha University. Dr Farani also reviews high-impact journals. Her interdisciplinary work integrates nanotechnology, materials science, and biomedical engineering to address critical healthcare challenges.

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Dr Seung-Kyu Hwang is a leading materials scientist at Inha University, working at the intersection of energy materials, sensors, radionuclide-removal absorbents, cancer-killing biomaterials, and microplasma technologies. With an h-index of 33 and more than 3400 citations, he has made significant contributions to advanced functional materials, including 2D nanomaterials, MXenes, and catalytic systems for environmental and biomedical applications. His research integrates fundamental materials chemistry with practical solutions for sustainable energy, pollution control, and therapeutic technologies. Hwang actively leads multidisciplinary collaborations and mentors young researchers, driving impactful innovations across environmental, biomedical, and energy-related fields.

Yun Suk Huh

Prof. Yun Suk Huh received his PhD in Chemical and Biomolecular Engineering from KAIST, Daejeon, Republic of Korea, in 2007. He is currently a Full Professor in the Department of Biological Engineering at Inha University, Incheon. His research focuses on the development of optical and electrochemical sensors for the ultrasensitive detection of biomolecules and diseases, as well as the design of bifunctional materials for drug delivery and therapy. Prof. Huh has published over 500 SCI-indexed articles and, in September 2025, was recognized among the top 2% of scientists worldwide for his outstanding contributions to science.

self-assembling nanocomposites, stimuli-responsive nanocarrier (pH/redox/enzyme/light), and targeted drug delivery. This review will include peer-reviewed articles that design, synthesize, characterize, or therapeutically evaluate SANCs in experiments or clinical settings. Studies involving the design, synthesis, or use of SANCs as drug carriers, along with experimental or clinical data published in peer-reviewed journals, were considered eligible. Two reviewers assessed titles and abstracts for inclusion, proceeded to full-text evaluation, and resolved disagreements with an arbiter. Data from this review were systematically extracted concerning study design, nanocomposite type, drug category, clinical applications, and therapeutic outcomes. Both qualitative and quantitative methods, including meta-analytic techniques, were employed to provide consolidated efficacy estimates, offering reliable insights into advancements in SANCs. We compiled the latest research on how SANCs could revolutionize targeted drug delivery to address unresolved issues, improve patient safety, and optimize therapeutic efficacy across various clinical applications.

In this review, we use the umbrella term self-assembling nanocomposites (SANCs) to describe multicomponent nanoarchitectures involving self-assembly; when we first refer to single-phase nano-objects, we call them self-assembling nanoparticles, and thereafter we harmonize the two to self-assembling nanocomposites. We go on to apply the core concepts of self-assembly, review recent achievements in stimuli-responsive SANC designs (pH/redox/enzyme/light), compare approaches to synthesis and characterization, examine drug-release behaviors in preclinical models, and discuss the future of personalized nanomedicine.

2. Research trends on SANCs

The increasing focus in recent years has been on the controlled application of SANCs in drug delivery, where they hold the promise of spatiotemporal control over delivery and, thereby, the promise of greatly increasing the therapeutic precision and avoiding the systemic toxicity of drugs. Their ability to spontaneously assemble into stable drug-carrying materials makes these nanostructures highly attractive since they are associated with high drug loading capacity, biodegradability, and responsiveness to the tumor microenvironment. A 2025 perspective was further summarized, extending the modern SANCs strategy to drug–drug conjugates, peptides, DNA scaffolds, and polymeric carriers, to provide greater selective tissue delivery, enable real-time imaging, and controlled devolution, with scalability and regulatory issues being a major challenge of translation.[16] Recent research in 2016 focused on highlighting the superior drug encapsulating ability of peptide-based nanostructures, whereby loading efficiencies as high as 80 percent

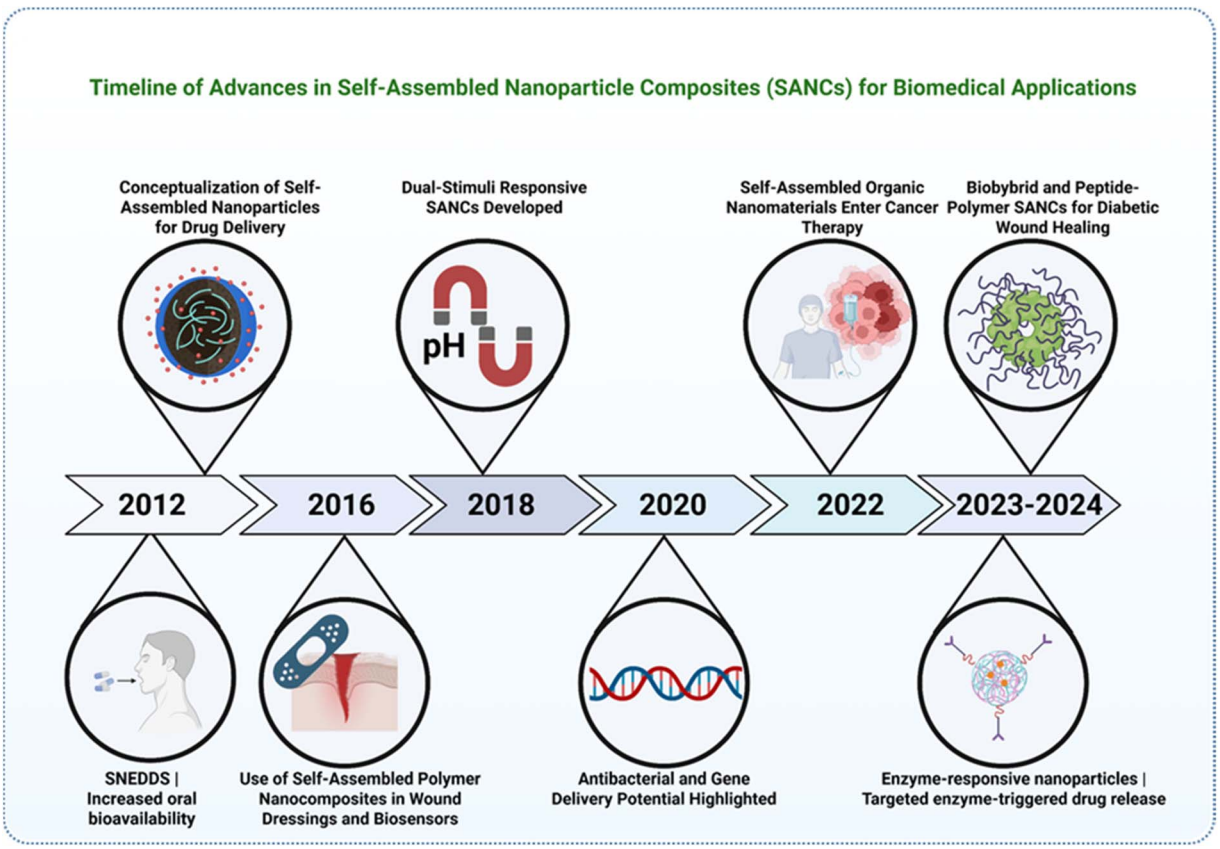

Fig. 1 Timeline illustrating the chronological development of self-assembled nanocomposite (SANC) systems for biomedical applications (2012–2024). The figure summarizes key technological milestones—from the conceptualization of polymeric SANCs for oral bioavailability improvement to the development of dual-stimuli-responsive, biohybrid, and peptide–polymer nanocomposites for targeted and enzyme-triggered drug delivery.

were observed, and both hydrophilic and hydrophobic delivery were conducted selectively due to environment-triggered release.[17] In 2024, progress in the field of pH-responsive self-assembling nanoparticles (SANPs, a subclass of SANCs) was reported; carriers that disassembled in the acidic environment of tumors had improved antitumor performance, and healthy cell damage was spared.[18] Another study published in 2024 described the chemical self-assembly of nanorings, which exhibited strong cytotoxic activity against cancer cells with at least a 9000-fold difference in EGFR expression (and the additional asset of causing immunogenic cell death).[19] In 2016, DNA-based self-assembled nanostructures achieved efficient doxorubicin delivery at pH 5.0 and overcame resistance in human lung adenocarcinoma cells, specifically A549 and its doxorubicin-resistant subline A549/ADR.[20] In studies published in journals with high impact like Nano Today, Bioconjugate Chemistry, and the International Journal of Nanomedicine, drug encapsulations of between 20 to 85 percent and optimal particle sizes of 90–220 nm have consistently been reported, and above 90 percent of the drugs were released in 24–48 hours. In a combined form, these findings allow us to state that SANCs cannot be considered purely hypothetical projects or even hypotheses: they are technologically feasible and demand more immediate implementation in practice, at least as a potential cure for complex diseases such as cancer. The main developments in SANC-based drug delivery over the past decade are summarized in Fig. 1.

3. Core materials of SANCs

SANCs are prepared with preselected core materials and functional groups that facilitate self-association, stability, and the delivery of drugs to disease sites. Each class of core material, lipid, inorganic particle, and natural polysaccharides, offers certain structural and functional advantages, and more importantly, selected functional groups provide for specific interaction and stimuli-responsive behaviors for efficient drug delivery.[21]

The materials that have been studied in the development of SANCs are quite numerous, and they have unique benefits depending on their physicochemical characteristics and compatibility. Synthetic and natural polymers are widely used because of the availability of their hydrophilic–hydrophobic balance to easily form micelles and encapsulate drugs.[22] Biocompatible lipids are also biomimetic of membranes and facilitate the spontaneous formation of vesicles, and have also been widely investigated as an oral route of administration or intravenous injection.[23] Toems include inorganic materials (silica and gold nanoparticles), making them structurally rigid/tunable surface properties with improved mechanical strength and deliberate release characteristics.[24] In the meantime, natural polysaccharides such as chitosan, starch, and dextran have good biocompatibility, mucoadhesiveness, and chemical flexibility characteristics to be used as constructing pH effects or enzyme-sensitive SANCs.[25] Modified chitosan nanoparticles, specifically paclitaxel-conjugated low-molecular-weight chitosan (LMWC-PTX) NPs, showed efficient delivery and therapeutic benefit in murine breast cancer models, with *in vitro* activity in 4T1 cells and *in vivo* efficacy after intravenous dosing in BALB/c mice bearing subcutaneous 4T1 tumors.[26] This material selection has a direct effect not only on the self-assembly mechanism, but also on drug loading, release kinetics, and *in vivo* distribution, so rational selection based on therapeutic targets and route of administration remains essential.

3.1 Polymers

Polymers form the backbone of a lot of SANCs, due to their versatility, ease of modification, and biocompatibility. Thus, they offer a solid yet tunable skeleton for specific therapeutic purposes. Generally speaking, polyethylene glycol is used to increase systemic stability and reduce immune clearance by forming a hydrophilic "stealth" layer, prolonging circulation, and thereby enhancing bioavailability. Meanwhile, hydrophobic polymers such as polycaprolactone (PCL) and poly(-lactic-*co*-glycolic acid) (PLGA) form the structural core, suitable for sustained drug release in chemotherapy and anti-inflammatory purposes. The degradation rate and hence the release profile can be precisely controlled by proper adjustment of the polymer composition, thus enabling applications with prolonged therapeutic exposure.[27,28]

3.2 Lipids

Lipids have been identified as fundamental components of SANCs because of their versatility in forming biocompatible structures similar to biological membranes. Particular examples of systems based on lipids are liposomes and lipid-polymer hybrid systems that provide highly effective ways of encapsulation of hydrophobic drugs and nucleic acids, offering stability and controlled release. Liposomes can encapsulate both hydrophobic and hydrophilic drugs simultaneously and thus find applications in various drug-delivery approaches, whereas in lipid-polymer hybrids, a polymer core combines with a lipid shell, enhancing encapsulation efficiency, circulation time, and target specificity.[29,30]

3.3 Inorganic materials

Inorganic nanoparticles provide mechanical robustness, versatile surface modification options, and stimuli-responsiveness, which make them especially valuable for controlled release applications. Mesoporous silica nanoparticles (MSNs) and gold nanoparticles (AuNPs) are basic examples: MSNs offer high surface area and pore volume, which enhance drug loading capacities, while AuNPs provide unique photothermal properties for combined therapeutic and diagnostic applications. This provides functionalized particles with the ability to respond to external stimuli, for example, a change in pH or light, triggering on-site drug release.[31,32]

3.4 Natural polysaccharides

This trend has been supported by chitosan, alginate, and hyaluronan, representing naturally derived polysaccharides. The reasons are that naturally derived polysaccharide materials have

inherently biocompatible and biodegradable properties, as well as being functionalizable. Hence, several ionic-gelation-supported self-assembly methods exploit these materials and yield highly stable nanostructures, most of which are useful for effective bioresponsive drug delivery. Due to the natural source, the polysaccharide systems naturally reduce immune response problems and/or related side effects. In addition, such flexible nanostructures are good alternatives for the delivery of proteins or nucleotides.[33]

3.5 Surface functionalization strategies of SANCs

To translate the self-assembly potential of these core materials into functional drug carriers, precise surface engineering is crucial. Surface functionalization is a key strategy to tune the physicochemical and biological properties of self-assembled nanocomposites (SANCs). The introduction of functional groups, polymeric coatings, and reactive ligands at the nanoscale interface governs colloidal stability, circulation time, and specific targeting capacity. Among these, PEGylation, esterification, and amidation reactions remain the most employed techniques due to their reproducibility, mild reaction conditions, and compatibility with biological systems.

3.5.1. PEGylation reactions. PEGylation refers to the covalent conjugation of polyethylene glycol (PEG) chains onto nanoparticle surfaces to reduce immune recognition and prolong systemic circulation. Common approaches involve amide bond formation using *N*-hydroxysuccinimide (NHS)-activated PEG or succinimidyl carbonate–PEG derivatives reacting with surface-exposed amine groups. These reactions are typically performed under mild aqueous conditions (pH 7.0–8.0, 25–37 °C) with reaction efficiencies exceeding 85–95%, yielding stable PEG layers confirmed by FTIR absorption at 1105 cm^{-1} (C–O–C) and 1730 cm^{-1} (C=O stretching).[34] PEGylation can also proceed *via* Steglich esterification, where PEG–OH reacts with carboxylated substrates under DCC/DMAP catalysis at ambient temperature, producing stable ester linkages without degradation of sensitive biomolecules.[35]

Recent advances in stimuli-responsive PEGylation have enabled dynamic control of PEG detachment in tumor environments. For example, PEG–poly(L-glutamic acid)–cisplatin nanocomposites incorporating pH- and enzyme-cleavable amide bonds exhibit a 4–5× longer circulation half-life than unmodified systems, followed by site-specific PEG cleavage at tumor sites to enhance internalization.[36] PEGylated graphene oxide or Fe_3O_4 nanocomposites synthesized by amide coupling reactions further show improved colloidal stability (zeta-potential shift from −32 to −12 mV) and enhanced drug loading capacity of up to 80%, confirming effective surface modification.[37]

3.5.2. Esterification and amidation mechanisms. Ester and amide bond formation represent versatile pathways for introducing ligands, drugs, or hydrophilic polymers onto SANC surfaces. Carbodiimide coupling using EDC/NHS chemistry remains the most widely adopted, yielding covalent linkages under mild conditions (pH 6–7, 25–30 °C). The esterification efficiency generally ranges between 70–90% for activated carboxyl surfaces, confirmed *via* FTIR signals at 1735 cm^{-1} and 1250 cm^{-1}.[38] Additionally, thiol–maleimide and azide–alkyne (click reactions) have gained traction for site-selective functionalization, providing near-quantitative yields (>95%) with minimal by-products.[39]

In emerging cleavable PEGylation systems, PEG linkers are designed to hydrolyze or enzymatically degrade in acidic or reductive environments, resolving the classical "PEG dilemma" of poor cellular uptake *versus* long circulation. Such systems exhibit up to 4.6× increased blood half-life while allowing responsive detachment in tumor microenvironments.[40]

3.6 Comparative analysis of synthesis and characterization methods of SANCs

Selecting core materials that consistently achieve controlled self-assembly and therapeutic performance requires an understanding of how various synthesis and characterization techniques shape the structural and physicochemical properties of SANCs. To provide a clearer understanding of the fabrication diversity across different types of SANCs, Table 1 summarizes representative synthesis routes, solvent systems, reaction conditions, particle size control strategies, and surface modification chemistries. This comparative overview highlights the methodological differences between polymeric, lipid-based, inorganic, and natural polysaccharide-derived SANCs, which influence particle uniformity, stability, and self-assembly efficiency.[41]

Table 1 Comparative summary of synthesis and characterization parameters for different classes of SANCs[a]

Type of SANC	Typical solvent/medium	Reaction conditions	Particle size control strategy	Surface modification chemistry	Ref.
Polymeric SANCs	DMSO, DMF, aqueous buffer	25–50 °C; pH 7–8	Block copolymer ratio, CMC adjustment	PEGylation, EDC/NHS amidation	42
Lipid-based SANCs	Ethanol, chloroform, PBS	30–60 °C; solvent evaporation/self-hydration	Sonication, extrusion, lipid ratio	Thiol–maleimide, phospholipid–PEG conjugation	40
Inorganic SANCs	Water, ethanol	50–100 °C; sol–gel or hydrothermal	Precursor ratio, surfactant templating	Silanization, ligand exchange	34
Natural polysaccharide SANCs	Water, acetic acid	25–45 °C; mild stirring	Ionic gelation, pH tuning	Chitosan–PEG grafting, Schiff-base linkage	37

[a] Abbreviations: SANC, self-assembling nanocomposite; DNA, deoxyribonucleic acid; LNPs, lipid nanoparticles; pH, potential of hydrogen.

3.7 Characterization techniques and their chemical significance

Accurate characterization of SANCs is crucial for connecting the intrinsic chemical properties of core materials with their self-assembly behavior, biological interactions and therapeutic performance. Characterization of SANCs is pivotal for correlating their structural organization with chemical composition and functional performance. Since these nanostructures rely on complex non-covalent and covalent interactions during assembly, multiple analytical methods are required to provide a holistic understanding of their morphology, surface chemistry, and interfacial behavior.

Dynamic light scattering (DLS) is one of the most essential techniques for assessing the hydrodynamic diameter and polydispersity index (PDI) of nanocomposites in suspension. It provides quantitative insights into colloidal stability and aggregation kinetics, which are directly linked to the quality of self-assembly. Typically, polymeric and lipid-based SANCs exhibit average diameters in the range of 20–300 nm with PDI values below 0.2, indicating uniform dispersion and strong steric or electrostatic stabilization. Such parameters are crucial because minor deviations in size distribution can dramatically influence biological uptake and interaction with biomolecules.[43]

Complementary to particle size analysis, Fourier-transform infrared spectroscopy (FTIR) provides detailed information about chemical bonding and molecular interactions during self-assembly. In particular, the emergence of characteristic stretching vibrations around 1730–1740 cm^{-1} for C=O groups and 1100–1150 cm^{-1} for C–O–C bonds confirms esterification or PEGylation reactions. Similarly, the appearance of amide I and II bands at 1640 and 1550 cm^{-1} indicates covalent cross-linking between polymeric matrices or between organic and inorganic phases. The strength and position of these bands provide direct chemical evidence of the bonding mechanisms driving the self-assembly process.[44]

X-ray photoelectron spectroscopy (XPS) further complements FTIR by identifying the oxidation state and chemical environment of surface atoms. For example, shifts in the N 1s peak from 399.0 eV to 401.0 eV typically correspond to amide bond formation following PEG conjugation, while the O 1s and C 1s spectra can distinguish between carboxyl, carbonyl, and hydroxyl functionalities. The method's high surface sensitivity (probing depth <10 nm) allows it to resolve subtle changes in surface chemistry that directly impact the thermodynamic stability and reactivity of the SANCs.[45]

Transmission electron microscopy (TEM) and its high-resolution variant (HRTEM) are indispensable for visualizing the internal morphology and crystalline arrangement of SANCs. These techniques reveal whether the nanocomposites adopt core–shell, layered, or network-like architectures. For example, high-resolution TEM images of $CuO/ZrO_2/TiO_2$/RGO nanocomposites show uniform dispersion of nanoparticles on graphene oxide sheets with distinct lattice fringes of 0.31 nm, confirming high crystallinity and well-defined interfaces between components. Such nanoscale ordering is essential for efficient electron transfer and chemical interaction across the composite interface.[46]

In addition to TEM, atomic force microscopy (AFM) provides complementary topographical and mechanical information at the nanometer scale. AFM phase imaging distinguishes between soft organic and rigid inorganic domains, while roughness and adhesion maps reveal how surface functionalization affects the physical behavior of the nanostructures. The ability of AFM-based nanoindentation to quantify mechanical stiffness and elasticity enables the correlation of interfacial chemistry with macroscopic mechanical performance.[47]

Spectroscopic methods such as UV-visible and Raman spectroscopy further expand the chemical interpretation of SANC behavior. UV-vis spectroscopy detects π–π stacking, conjugation length, and optical transitions that reflect molecular ordering within polymeric or hybrid systems, whereas Raman spectra provide vibrational fingerprints associated with specific bonds and crystalline phases. For instance, variations in Raman bands at 1340 cm^{-1} (D band) and 1580 cm^{-1} (G band) can indicate defects or functionalization on graphene-based SANCs, while enhanced UV absorption peaks correspond to stronger electronic coupling within conjugated domains.[48]

Recent advances have moved toward combining multiple techniques to achieve correlative imaging, where data from XPS, AFM, and FTIR are integrated to produce spatially resolved chemical maps of the nanocomposite surface. This multimodal approach provides a three-dimensional understanding of composition and structure, enabling the simultaneous evaluation of chemical states, roughness, and functional group distribution.[49]

Altogether, the integration of DLS, FTIR, XPS, TEM, AFM, and complementary spectroscopic techniques provides a comprehensive understanding of the chemical and structural nature of SANCs. These methods collectively bridge the molecular–scale interactions and the macroscopic performance of the materials, ensuring a rational foundation for their design in biomedical, catalytic, and electronic applications.[50]

4. Mechanisms of self-assembly in SANCs

4.1 Distinguishing molecular conjugation from supramolecular self-assembly in SANC design

Molecular conjugation represents a covalent pre-assembly strategy in which active molecules such as drugs, peptides, lipids, or polymers are chemically linked to form prodrugs or conjugates with defined stoichiometry and composition. In contrast, self-assembly is a non-covalent supramolecular process through which these molecular building blocks spontaneously organize into nanostructures such as micelles, vesicles, nanogels, or nanofibers. This conceptual distinction highlights that molecular conjugation enables and fine-tunes self-assembly, while self-assembly determines the emergent morphology, internal architecture, and responsiveness to external stimuli.[51]

To avoid conceptual overlap, self-assembled nanocomposites can generally be categorized into three functional groups. The first includes physically assembled systems, based purely on non-

covalent encapsulation within polymeric, lipidic, or peptidic matrices. The second comprises covalent conjugate-based systems, in which pre-formed prodrugs or polymer–drug conjugates undergo spontaneous supramolecular assembly. The third group involves host–guest supramolecular complexes, such as cyclodextrin inclusion or hydrogen-bonded frameworks [52].

The parameters governing self-assembly include the hydrophilic–hydrophobic balance, packing parameter, substitution degree or grafting density, medium conditions (pH and ionic strength), and molecular weight distribution. Collectively, these parameters define access to morphologies typically within the 50–200 nm range, which is optimal for tumor accumulation and systemic delivery.[53] At the conjugation stage, stimuli-responsive linkers such as pH-labile hydrazone or acetal bonds, redox-cleavable disulfides for GSH-rich cytosol, or enzyme-sensitive peptides can be covalently incorporated to achieve programmed disassembly and on-demand drug release. These chemical modifications are installed before self-assembly but act dynamically during or after assembly, allowing precise control of drug release in tumor-relevant microenvironments.[52]

4.2 Mechanistic basis, architectures, and characterization of self-assembled SANCs

Consequently, it is not surprising that the supramolecular self-assembly of SANCs plays such a decisive role in the synergy of all kinds of non-covalent interactions, thus enabling these nanostructured substrates to form stable and fully biocompatible colloid phases. The main driving forces contributing to this goal include hydrophobic interactions, electrostatic forces, hydrogen bonding, van der Waals forces, π– π stacking, and host–guest interactions, among others. In this section, we introduce the details of some basic self-assembly formats in SANCs, micelles, vesicles, nanofibers, and hydrogels, and outline major contributions to their optimization by illustrating different modes of action in various drug delivery tasks.[54]

Hydrophobic interactions are among the major driving forces in the core–shell structure in amphiphilic molecules, where hydrophobic segments aggregate to minimize their contact with water. Hydrophobic interactions are an important driving force in the encapsulation of hydrophobic drugs within the core of micelles and vesicles. For instance, poly(ethylene glycol)-*b*-poly(caprolactone) micelles have hydrophobic caprolactone segments that self-associate to form a stable core, allowing high encapsulation efficiency of hydrophobic drugs like paclitaxel (PTX).[55] Amphiphilic molecules organize themselves in water by concealing their hydrophobic unit inside a core of the formed aggregates: micelles, and vesicles. This rearrangement is thermodynamically beneficial, as it increases the system's entropy by forcing water molecules out of the hydrophobic surface to form a stable core–shell structure, which helps achieve the encapsulation of non-polar drugs.[56]

Electrostatic interactions between oppositely charged molecules support the formation of polyelectrolyte complexes and other charged assemblies. These forces are widely exploited in layer-by-layer nanostructures, where alternating layers of charged polymers provide a stable multi-layer system with tunable drug release profiles. For example, chitosan-alginate systems form polyelectrolyte complexes that stabilize the structure and allow for controlled drug release, which would be beneficial in combination therapies.[57] Such interactions direct the initial docking and orientation of molecular building blocks. Electrostatic attraction in SANCs may result in the emergence of rapid coacervation or ionic crosslinking, which depends on pH and the concentration of ions. This enables quick assembly of nanostructures with modulable surface charge, essentially an increase in endosomal escape and cellular uptake in gene or protein carriers.[58]

Hydrogen bonding also facilitates the preparation of stable, biocompatible nanostructures *via* hydrogels and peptide assemblies. H-bonds are characteristic of peptides that form β-sheets self-assembling into nanofibers and gels. Indeed, many peptides with regularly alternating hydrophobic and hydrophilic residues, such as FEFEFKFK, form hydrogen-bond-stabilized-β-sheet networks and have previously been used to encapsulate drugs within their hydrophobic pockets.[59] These bonds can undergo reversible co-disassembly under the precise conditions and are very sensitive to pH, which is why they can be used in the stimulus-responsive systems of controlled release.[60]

van der Waals interactions, which are weaker, contribute even further to cohesion and stability in self-assemblies by extra non-covalent binding. Such interactions often play a significant role in maintaining hydrophobic core structures and layer systems at positions where stronger interactions cannot dominate.[61] This effect is helpful for stabilizating vesicles that consist of lipids for long-term drug delivery.[62] Those non-covalent interactions are weak, but they are the key to molecular packing using the assembled nanostructure, and close packing in the assembled nanostructure. They aid in reducing emptiness or gaps in tightly packed peptide or polymer assemblies, where there are no powerful charge interactions.[63]

π–π stacking interactions of aromatic rings support the stability and assembly of nanostructures incorporating aromatic compounds, including some hydrophobic drugs and peptide assemblies. These provide the capability of loading a drug without chemical modification to the drug molecule itself, something of high value for developing environment-responsive drug delivery systems. Carbon nanotubes and graphene-based nanomaterials also use π–π stacking for the encapsulation and stabilization of drugs, and improve their controlled release upon changing pH.[64] Hierarchical self-organization has been proposed in systems with phenylalanine-rich peptides, graphene derivatives, or anthracycline drugs, and is supported by aromatic pi–stacking interactions. These interactions on the plane lead to the creation of stacked structures, and in the case of the delivery platforms that can work photoresponsive or dual-functional, potentially to the optical or mechanical tuning of the nanocomposite.[65]

In particular, host–guest interaction with cyclodextrin can provide reversible and responsive self-assembly. Cyclodextrins can assemble into inclusion complexes with complementary hydrophobic drugs, providing a sound structure that, depending on changed environmental conditions such as pH or ionic

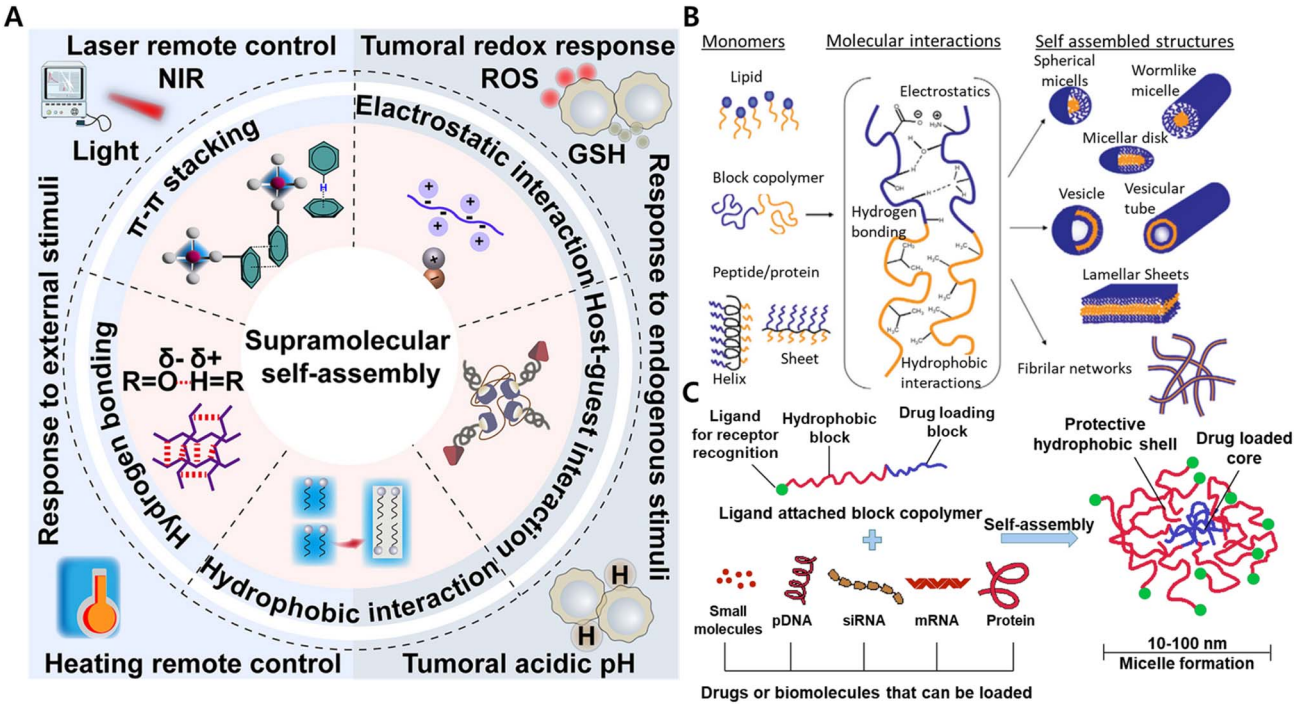

Fig. 2 (A) Schematic representation of supramolecular self-assembly driven by external stimuli-light, heat-and endogenous stimuli-pH, reactive oxygen species (ROS). Adapted with permission from ref. 85. Copyright 2023 Liu, Y. *et al.* Published by Elsevier Inc. on behalf of Cell Press. (B) The major molecular interactions that drive supramolecular self-assembly include hydrogen bonding, electrostatic, and hydrophobic interactions. Adapted with permission from ref. 86. Copyright 2015 Woodhead Publishing (Elsevier). (C) The resulting self-assembled structure formed may be in the form of micelles or vesicles and may encapsulate drugs or biomolecules for controlled therapeutic delivery. Reproduced with permission from ref. 87. Copyright 2021 Elsevier Ltd. All rights reserved.

changes, may allow the release by breaking the structures. Assemblies based on β-cyclodextrins encapsulate hydrophobic drugs and their release can be facilitated through pH change, which could be very instrumental in targeted cancer therapy since the pH is low.[66]

The working concept of supramolecular self-assembly and the responsiveness against various internal/external stimuli are shown in Fig. 2. Such ordered assemblies, including micelles and vesicles, can be obtained by aiding intermolecular interactions, including hydrogen bonding, π–π stacking, electrostatic, and hydrophobic forces. The possibility of such structures having immense therapeutic potential is of particular interest, especially in nanomedicine, whereby they may provide a case and carriage of drugs or biomolecules (like DNA, RNA, and proteins) in a controlled and targeted manner. This figure focuses on the adaptability and effectiveness of supramolecular systems in advanced applications for drug delivery.

4.3 Quantitative chemical insights into non-covalent interactions in SANC self-assembly

Linking molecular design decisions to the thermodynamic stability, responsiveness, and structural outcomes of SANCs requires a more thorough quantitative understanding of the non-covalent interactions that underlie self-assembly. The self-assembly of smart amphiphilic nanocomposites (SANCs) is governed by a balance of multiple non-covalent forces such as hydrophobic collapse, π–π stacking, hydrogen bonding, and electrostatic interactions, that collectively define the thermodynamic stability and architecture of nanostructures. Quantitative understanding of these interactions provides deeper insight into molecular design and enables predictive control over SANC performance.

Table 2 lists the common interaction energies found in the literature along with their main functional implications in order to put the energetic values of these non-covalent forces into context and make clear their unique functions in driving SANC assembly. This synthesis offers a framework for understanding the roles that various molecular interactions play in SANC systems' core formation, structural ordering, and stimuli-responsive behavior.

Hydrophobic interactions represent the primary driving force, minimizing the unfavorable contact between hydrophobic domains and polar solvents. The Gibbs free energy (ΔG) associated with hydrophobic aggregation has been reported to range from −20 to −45 kJ mol^{-1}, depending on polymer composition and environmental polarity.[73] Molecular dynamics simulations confirm that enhanced hydrophobic shielding increases self-assembly efficiency and reduces entropy penalties in water.[74]

In parallel, π–π stacking interactions provide directional aromatic stabilization that contributes approximately 20–60 kcal mol^{-1} per interacting pair.[75] Density Functional Theory (DFT) and experimental spectroscopy studies reveal that these interactions strongly influence nanoscale order and charge delocalization within π-conjugated domains. Moreover, the introduction of π-conjugated moieties can increase van der

Table 2 Summary of non-covalent interaction energies and their functional significance in the Self-Assembling Nanocomposites (SANCs)

Interaction type	Typical energy range (kJ mol^{-1})	Functional implication for SANCs	Ref.
Hydrophobic interactions	−20 to −45 kJ mol^{-1}	Primary driver for core formation; governs spontaneous assembly and hydrophobic domain packing	67–69
π–π stacking interactions	20 to 60 kJ mol^{-1}	Provides directional aromatic stabilization; promotes nanoscale ordering and favors lamellar/stacked morphologies	70
Hydrogen bonding	8 to 25 kJ mol^{-1}	Cooperative stabilization of supramolecular networks; modulates assembly kinetics and structural transitions	71 and 72
Electrostatic interactions	Up to −30 kJ mol^{-1}	Regulates surface charge and morphology; drives ordered assembly of oppositely charged components and contributes to tunable size/shape outcomes	70

Waals dispersion forces and favor lamellar over micellar morphologies in water.[76]

Hydrogen bonding, though individually weak (8–25 kJ mol^{-1}), acts cooperatively to stabilize higher-order supramolecular networks and control assembly kinetics. Experimental studies show that hydrogen-bonded peptide or polymer assemblies display distinct kinetic-to-thermodynamic transitions in aqueous media, with transformation rates dependent on H-bond strength and concentration.[77] This cooperative hydrogen bonding effect is particularly significant in β-sheet-like assemblies and cyclic peptide nanotubes.

Electrostatic interactions modulate the stability and morphology of SANCs by tuning surface charge densities. Studies have shown that attractive electrostatic assembly between oppositely charged macromolecules can yield highly ordered nanostructures with size- and shape–tunable properties. Thermodynamic analysis reveals enthalpy gains of up to −30 kJ mol^{-1} per electrostatic pairing, highlighting their key role in morphology regulation.[78] Advanced molecular simulations further demonstrate that the self-assembly free energy landscape of SANCs exhibits multiple metastable minima corresponding to micellar, vesicular, and fibrillar states. These states are separated by ΔG barriers ranging from 10 to 25 kJ mol^{-1}, depending on solvent polarity and ionic strength. This finding explains the experimentally observed reversibility and stimuli-responsiveness of SANC assemblies under physiological conditions.[69]

Collectively, these thermodynamic and molecular-level insights reveal that SANC self-assembly arises from a finely tuned synergy among hydrophobic collapse, π–π stacking, hydrogen bonding, and electrostatic coupling. The balance of enthalpic stabilization and entropic gain drives the spontaneous formation of robust, stimuli-adaptive nanostructures capable of dynamic reorganization in complex biological environments.

5. Common self-assembly structures

Micelles represent spherical structures of amphiphilic molecules with a hydrophobic core and a hydrophilic shell, highly suitable for the encapsulation of hydrophobic drugs. Polymer micelles, like those self-assembled from PEG-*b*-PCL, exhibit improved stability and a controlled release property, especially useful for hydrophobic chemotherapeutics. Micelles improve the solubility and blood circulation time of drugs, enabling their passive targeting accumulation in tumors.[79] Vesicles and liposomes have a bilayer structure similar to cell membranes, which enables them to encapsulate both hydrophobic and hydrophilic drugs within their lipid bilayers. These structures are versatile in drug delivery; for example, liposomes loaded with doxorubicin (DOX) (*e.g.*, Doxil) have shown prolonged circulation and targeted tumor accumulation, enhancing therapeutic efficacy while reducing systemic side effects.[80] Nanofibers and nanotubes provide elongated structures with high surface areas, often used in tissue engineering and sustained release drug delivery systems. Self-assembling peptides, such as those that form β-sheet nanofibers, allow encapsulation and sustained release, providing a scaffold that can be functionalized with bioactive molecules for targeted therapeutic effects.[81] Hydrogels are three-dimensional networks of physically or chemically crosslinked polymers capable of holding considerable amounts of water. Hydrogels based on physical junctions depend on forces of self-assembly, such as hydrogen bonding and hydrophobic interactions, for reversible gelation, an attribute that provides suitability for *in situ* drug delivery applications. Nanostructured architectures self-assembled hydrogels with controllable release profiles and stimuli-responsive ability of the hydrogel, provide improved localized delivery due to changes in environmental parameters such as pH or temperature,.[82]

The polyelectrolyte complexes (PECs) are multi-layered structures created through electrostatic interactions between oppositely charged polymers. Layer-by-layer PECs allow for the sequential loading and controlled release of drugs, especially useful in combination therapies for cancer treatment.[83] The underlying concept of nanocapsules is that of an encapsulated, hollow space surrounded by a solid shell; usually, this is created using some solvent-exchange methodology or through gradient-driven self-assembly. In these regards, peptide-based nanocapsules self-

organize in response to the presence of concentration gradients to afford high drug loading and controlled release within targeted tissues, among other attributes. These nanocapsules are highly versatile and therefore can be tuned to responsive capability *via* many triggers aimed at improving targeted delivery.[84]

6. Mechanisms controlling drug release in SANCs

The idea in SANCs rests on the precise modulation of drug release, driven by multiple stimuli-responsive mechanisms, each based on specific environmental cues in diseased tissues: pH, temperature, enzyme concentration, and/or redox potential. While all of these signals are particularly useful for targeting specific disease conditions, the advantages of using SANCs in drug delivery can be realized only when responding to them. SANCs may be developed in several controlled release mechanisms such as degradation, diffusion, and stimuli-responsiveness (*e.g.*, pH, redox, and enzyme-induced release). Notably, a conjunction of these components has been synergistic in enhancing treatment efficacy. As an example, an acidic pH/high glutathione content dual-responsive system exhibited a release of 80 percent in 24 hours in a tumor-like environment, whereas without redox stimulus, the same system only produced 25 percent drug release in neutral pH.[88] On the same note, a multimodal nanoparticle containing a photothermal agent and enzyme-cleavable linkers was found to have 2.3 times more tumor inhibition rate when compared to single-trigger systems. These findings emphasize that the combination of several release triggers not only improves site-specific drug levels but also reduces the occurrence of side effects involving the whole body. Some combinations can also be used in future systems to achieve accuracy in the mode of drug release; this can be timed and sequenced to match the complex diseases, such as cancer.[89] Some key mechanisms controlling SANC drug release are illustrated below.[90]

6.1 pH-sensitive release

pH-sensitive SANCs are designed to take advantage of the differences in acidity between healthy and diseased tissues. Tumors, as well as some infection sites, are characterized by a slightly acidic extracellular environment, with a pH range of 6.5–7.0, compared to normal tissue, which has a pH of 7.4, while intracellular compartments, such as lysosomes and endosomes, are even more acidic, with a pH range of 4.5–5.5.[91]

The pH-responsive systems most often rely on materials containing pH-sensitive linkers or coatings. For example, acid-degradable poly(L-histidine) or poly(β-amino esters) enable the rapid release of encapsulated drugs in tumor microenvironments or acidic intracellular compartments.[92]

Results from a recent study show that, for poly(L-histidine)-based nanoparticles encapsulating DOX, release can be accelerated in the tumor environment (acidic). In so doing, it has achieved superior drug accumulation in tumor tissues compared with its non-pH-responsive formulations. Thus, these pH-responsive nanoparticles enhanced therapeutic efficacy, achieving about a 60% increase in the tumor inhibition rate.[93]

pH-sensitive SANCs are designed to exploit the acidic microenvironment of tumors and endosomes to trigger controlled drug release. For example, PEG/PCL-based nanoparticles demonstrated a drug release of over 70% at pH 5.0 in the presence of 10 mM GSH, compared to less than 30% at physiological pH, significantly enhancing site-specific drug availability.[94] Similarly, magnetic mesoporous Fe_3O_4@SiO_2 SANCs grafted with biopolymers released 96% of the drug at pH 5.6, offering precise control in acidic environments.[95]

Due to this feature, pH-sensitive SANCs are widely used in oncology to precisely deliver chemotherapeutics with lower systemic toxicity in the acidic tumor microenvironment.[96]

6.2 Temperature-triggered release

Temperature-sensitive SANCs take advantage of the slight temperature difference between normal tissues and inflamed or tumor tissues. In addition, external heating methods, like focused ultrasound or laser irradiation, may be employed to selectively raise temperatures at certain sites, thus inducing drug release in a controlled fashion.[97] Thereby, temperature-sensitive polymers exhibit phase transitions above or below a specific temperature. Poly (*N*-isopropylacrylamide) has a lower critical solution temperature at approximately 32 °C, below which this polymer changes from hydrophilic to hydrophobic and thus disrupts the nanostructure and thereby releases the entrapped drug.[98] Thermosensitive liposomes loaded with DOX showed significant release upon mild hyperthermia (41–42 °C) induced by focused ultrasound. This targeted approach enhanced drug accumulation in tumor tissues, leading to tumor regression 70% higher compared to non-thermosensitive formulations.[99] Temperature-sensitive systems are widely used in combination with thermal therapies, such as hyperthermia or photothermal therapy, to improve drug delivery and maximize therapeutic efficacy.[100]

Thermosensitive nanocomposites are also designed to deliver medications when exposed to mild hyperthermia, which is a phenomenon that is prevalent in tumor tissue. The presence of PNIPAAm or other comparable polymers in such systems exhibits extreme release increments beyond LCST (~40 °C). As one example, a study has shown that at 42 °C, drug-loaded polymeric micelles were able to release their payload more than 2x as fast as when incubated at 37 °C, and this provides a means of spatio-temporal control.[101] This method is beneficial in increasing therapeutic effect and reducing systemic adverse effects.

6.3 Enzyme-responsive release

Enzyme-responsive SANCs are designed to degrade in the presence of specific enzymes overexpressed in certain pathological conditions, such as cancer or inflammation. This approach allows SANCs to selectively release their payload in the presence of high levels of an enzyme, thus enabling targeted release within the diseased tissues.[97] Linkers consisting of enzyme-sensitive linkers, such as peptides or polysaccharides, can be degraded by enzymes. For instance, matrix metalloproteinases in tumors can be common enzymes that target the degradation of peptide-based nanocomposites, while hyaluronic acid is degraded at inflammation sites by the action of

hyaluronidase.[102] One such study has shown that matrix metalloproteinase-sensitive nanoparticles encapsulating PTX and DOX have increased tumor penetration and drug release. In BALB/c mice with subcutaneous C26 colon carcinoma, MMP-2-cleavable PEGylated liposomes demonstrated superior DOX release and antitumor efficacy using a single i. (v). dose equal to 10 mg kg^{-1} DOX; survival was monitored for up to 70 days and tumor volume was tracked for 33 days, outperforming non-enzyme-responsive controls (98).[103]

The enzyme-responsive SANCs find strong applications in cancer therapy, where the tumor-specific enzymes enable degradation and drug release in a very localized fashion. They are also researched in inflammation and wound healing applications due to localized enzyme production in affected tissues.[104] SANCs that contain enzyme-cleavable linkers can also be used to release the drug in the overexpressing tissue, *e.g.*, MMPs or azo-reductases. Indicatively, polymeric ES-Azo nanoparticles demonstrated an increase of 5.5 times in their localization and drug release in the inflamed colonic tissue in contrast to the control particles which was evidence of the enzyme-activated responsiveness. This enzyme specificity cuts down use of off-target toxicity and enhances therapeutic selectivity.[105]

6.4 Redox-responsive release

In contrast, the strategy of redox-responsive SANCs has taken advantage of the high concentration of glutathione inside cells, especially in tumor cells, where its concentration can be as high as 100–1000 times greater than in extracellular fluids. Drugs linked through redox-sensitive moieties are therefore selectively released under reductive intracellular conditions.[106] The most used linkers in redox-responsive systems are disulfide linkers. Such linkers are stable in the normal oxidative extracellular environment but cleave under reductive conditions. Disulfide bonds are thus often introduced into the core–shell structure of redox-responsive micelles and vesicles to ensure stability during circulation with triggered release upon cellular uptake in high glutathione (GSH) environments.[107] DOX-loaded redox-sensitive micelles prepared from (PEG–SS–PCL; poly(ethylene glycol)-disulfide–poly(ε-caprolactone)) polymers showed selective release in high GSH conditions characteristic of cancer cells. Such micelles exhibited *in vitro* cell inhibition of up to 80% in chemoresistant cancer lines compared to standard formulations.[108] In dextran-based nanogels, methotrexate release was five-fold greater under 10 mM GSH and pH 5.0 conditions that resemble the intracellular tumor environment.[109] Other systems that survive the problem of drug resistance are the redox response systems; in one study with doxorubicin-loaded nanocomposites, the IC_{50} of resistant cancer cells dropped to 8.55 mL g^{-1} with a drug response to >100 mL g^{-1}.[110]

6.5 Multi-responsive SANCs

Some SANCs respond to multiple stimuli, such as pH, temperature, and redox conditions, enabling highly sophisticated, stepwise drug release. Multi-responsive systems hold particular promise in cancer therapy, where the tumor microenvironment displays a complex topography of pH, enzymatic activity, and redox potential.[111] pH integrates into multi-responsive SANCs in combination with temperature-sensitive lipids and redox-sensitive linkers to create a hierarchical design. Such approaches can allow the drugs to be released sequentially as the SANCs encounter a variety of stimuli during both their systemic circulation and subsequent cellular uptake.[112] Multi-stimuli-responsive nanogels containing disulfide and pH-sensitive linkers have demonstrated effective encapsulation and targeted release of hydrophobic drugs like PTX. These nanogels exhibited a controlled release profile in response to both acidic pH and high GSH, achieving more than 85% tumor inhibition in murine cancer models.[113] The multi-responsive SANCs show high adaptability in a complex disease environment, realizing the controlled multi-stage release profile that improves the therapeutic index and allows highly customized drug delivery strategies.[111] Although stimuli-responsiveness offers significant advantages for controlled drug release, it is not the only determinant of an efficient delivery system. Practical formulation design must also balance responsiveness with colloidal and chemical stability to prevent premature release or aggregation during circulation. For instance, excessive incorporation of pH- or redox-sensitive linkages can increase hydrolytic degradation, while thermo-responsive polymers may reduce long-term storage stability. Therefore, rational design of SANCs should integrate multiple criteria—including particle size control, surface charge optimization, and biocompatibility—to ensure both responsiveness and stability throughout the drug delivery process.[114]

Fig. 3 illustrates in detail the concept and mechanism behind stimuli-responsive drug delivery systems, highlighting how each environmental trigger varies in response to pH, temperature, and light control of the drug release profile. Advanced delivery systems, such as co-assembled nanoparticles, may be applied in targeted therapies by coupling controlled release, localization, and real-time therapeutic feedback of the cargo, as indicated by the figure. It gives evidence for the versatility and precision of modern approaches to drug delivery.

6.6 Design advantages of SANCs for drug delivery

Unlike carrier-laden systems, SANCs represent a new class of programmable material where the active ingredients and linkers themselves control particle formation, payload encapsulation, and on-demand disassembly. This allows for much higher payload densities while reducing the amount of inert excipient content.[118] With minimal carrier-related toxicity, many SANCs can reach drug loading levels well beyond those of liposomal formulations or classical polymeric particles due to their construction from drug–drug or drug–polymer conjugates. The sensible incorporation of cleavable linkers (pH-labile, redox-sensitive, enzyme-cleavable, or hybrid chalcogen bonds) allows for spatially restricted activation within heterogeneous tumor microenvironments and minimizes premature systemic leakage.[118–120]

SANCs address several major disadvantages while incorporating the key practical advantages of multiple platforms due to their composition and architecture. Hierarchical co-assembly

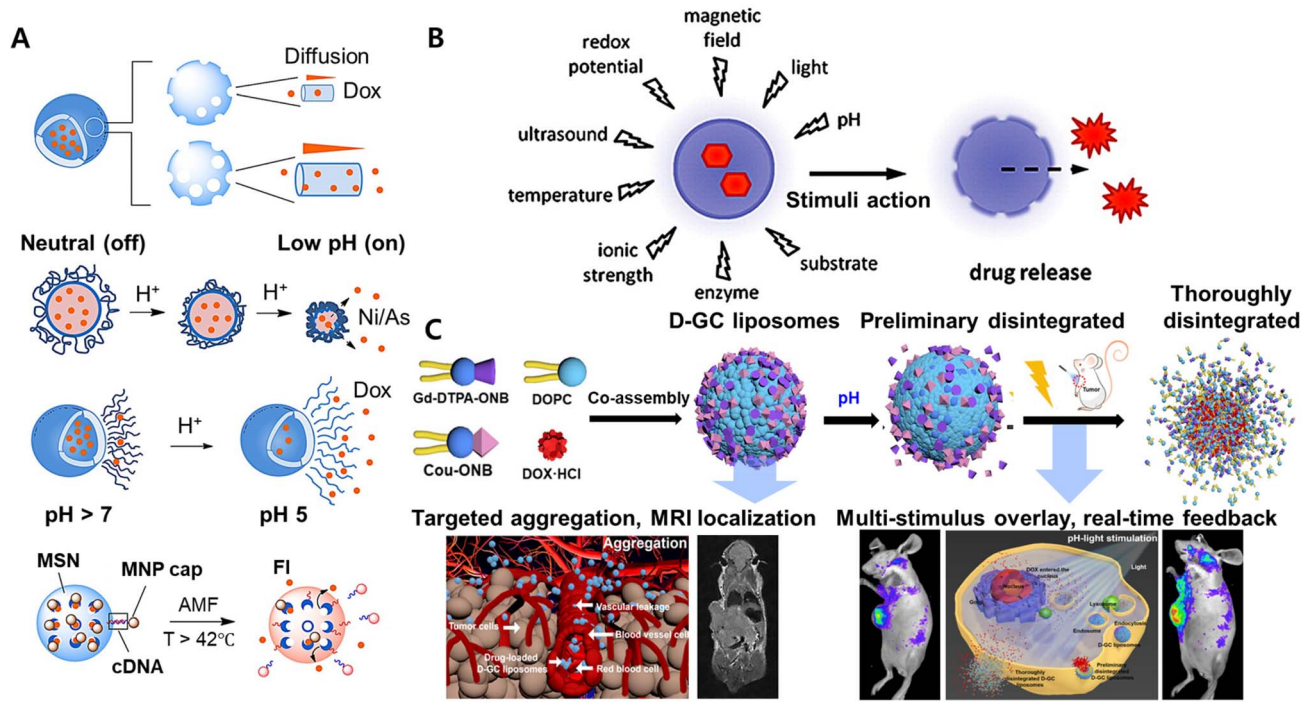

Fig. 3 Stimuli-responsive drug delivery systems. (A) pH-responding drug release through structural changes and diffusion in acidic environments. Adapted with permission from ref. 115. Copyright 2015 American Chemical Society. (B) Various stimuli, including pH, temperature, redox potential, magnetic field, and light, can trigger drug release. Adapted with permission from ref. 116. Copyright 2012 Elsevier B.V. All rights reserved. (C) Co-assembled liposomes for pH-sensitive drug delivery showing MRI localization, targeted aggregation, and multi-stimuli disintegration with real-time therapeutic feedback. Reproduced with permission from ref. 117. Copyright 2021 Elsevier Ltd. All rights reserved.

allows co-delivery of small molecules, nucleic acids, and biologics with preserved bioactivity; stimulus-responsive supramolecular architectures allow for sequential or multistep release, difficult to achieve in single-phase formulations; and carrier-free or carrier-sparing prodrug nanoassemblies increase drug content and reduce excipient burden.[118,119] Importantly, in contrast to many conventional systems, the linker and bonding chemistries can be selected to enhance *in vivo* stability-longer circulation-while enabling quick, environment-triggered activation at the target site. This balance increases tumor accumulation and decreases off-target exposure.[119] Although these advantages are compelling for drug delivery, practical translation requires regulatory characterization, long-term stability, and strong control over self-assembly manufacturing reproducibility. Thus, pairing the design advantages above with scalable and standardized production strategies will be critical for clinical uptake.[118,121]

7. Comprehensive comparative analysis of SANCs in drug delivery

With their accurate, regulated, and active release of a therapeutic agent, SANCs have the potential to completely transform drug delivery. Such nanostructures exploit different stimuli-responsive mechanisms, like pH, redox potential, or enzymatic activity, toward the optimization of drug delivery at active sites to improve both efficacy and safety profiles. Their versatility involves the use of different materials, including polymers, lipids, and inorganic particles, in diverse therapeutic applications.[122] This review discusses the recent advances in the field of SANCs regarding drug loading efficiency, kinetics of release, and bioavailability, to open more effective and personalized treatment options in modern medicine.

7.1 Drug loading efficiency and release kinetics

DNA nanoconstructs, such as AS1411 aptamer-tethered DNA nanotrains (AS1411NTrs), have a super-high drug loading capability with self-controlled release. The obtained AS1411NTrs possess the ability to load almost 20 : 1 DOX to carrier structure, revealing an excellent sustained release pattern under the treatment of DNase I, which may digest the DNA with great control.[123] Moreover, the thermodynamic study of mithramycin-loaded DNA nanotrains with different metal ions like Mg^{2+} and Zn^{2+} showed that the binding affinity and release rate could be modulated with higher stability and higher cytotoxicity against HepG2 cells than their non-nanostructured counterparts.[124] Chitosan/polycaprolactam (PCL-CS) nano complexes, modified chitosan-polycaprolactam loaded with quercetin, had a 21.5% drug load and showed controlled release in a pH-buffered environment, making this more efficient for cancer treatment. Its conjugation with folic acid enhanced its targeting ability toward the cancer cells since the viability in FR-expressing cells decreased compared to controls.[125]

Table 3 Comparison of SANC types based on loading capacity, release profiles, bioavailability, and key applications[a]

SANC type	Loading capacity	Release profile	Bioavailability	Therapeutic targeting	Key applications	Ref.
DNA nanostructures	High (~20 molecules)	Enzyme-responsive, sustained	Selective	High specificity	Cancer targeting	123 and 124
Polymer-based micelles	Moderate	Controlled, steady release	Moderate	Systemic delivery	Chemotherapy, systemic delivery	131
Lipid-based LNPs	High	Responsive to pH and enzyme activity	Enhanced	Broad applications	Gene therapy, hydrophobic drugs	132
Chitosan–polycaprolactam complex	21.5%	pH-dependent, controlled	Enhanced for cancer	Folate-targeted	Cancer therapy	125
Self-nanoemulsifying systems	High	Rapid and sustained	2.2-Fold increase	Non-specific	Oral delivery of poorly soluble drugs	129
Redox-sensitive dipeptide vesicles	Variable	Redox-triggered release	Selective for cancer cells	High tumor selectivity	Cancer-specific intracellular delivery	133
Temperature/ultrasound amphiphiles	Variable	Triggered by ultrasound	Variable	Selective targeting	Targeted liver cancer therapy	134

[a] Abbreviations: SANC, self-assembling nanocomposite; DNA, deoxyribonucleic acid; LNPs, lipid nanoparticles; pH, potential of hydrogen.

The designed nanocages based on apoferritin for pH and ROS responsiveness can exhibit a dual mechanism of controlled release. Under low pH and laser irradiation, the release rate increased from 26.1% to 92%, which enables the precise delivery of drugs in an acidic tumor environment. Such a dual-trigger release system achieved up to 83% cell inhibition in models of breast cancer.[126] PEG-disulfide PTX nanoparticles have been developed, showing a redox-responsive delivery mechanism with a high drug content of 15.7% and entrapment efficiency of 93.3%. Under normal conditions, the system was quite stable; however, it collapsed under reductive conditions that mimic the conditions inside the tumor cells, which could facilitate targeted release. By this mechanism, superior anti-tumor efficacy in breast cancer xenografts was achieved than that achieved by traditional PTX formulation.[127] AuNP-based vesicles showed controlled pH-responsive disassembly, enhancing drug release in acidic intracellular compartments. These vesicles could effectively release drugs and allow surface-enhanced Raman scattering-based bioimaging, hence showing dual functionality for cancer targeting and traceable drug delivery.[128]

7.2 Bioavailability and pharmacokinetic profiles

Self-nanoemulsifying drug delivery system (SNEDDS) shows high enhancement in the bioavailability of hydrophobic drugs and achieves a 2.2-fold increase in oral bioavailability for a given formulation compared to a non-emulsified version. This technique employs droplets at a nano-size that aids in increasing their solubility and, thereby, absorption; this renders it an appropriate candidate technique for oral administration of several poorly water-soluble drugs.[129] Gelatin-oleic acid nanoparticles improved the aqueous solubility of the poorly water-soluble drugs valsartan and telmisartan. These nanoparticles showed a pH-dependent controlled-release profile, with sizes in the range of 200–250 nm, which is optimal for enhanced bioavailability upon oral and systemic applications.[9] In comparison to free drugs, this system achieved a 6.4-fold increase in the blood half-time of betulinic acid and improved therapeutic effects with improved bioavailability. These nanoparticles co-delivered betulinic acid and hydroxy camptothecin with enhanced bioavailability and prolonged circulation time; the drug loading efficiencies were 23% and 21.15%, respectively.[130] Table 3 summarizes representative SANC classes, highlighting loading capacity, typical release behavior, comparative bioavailability outcomes and primary therapeutic applications to facilitate direct comparison across platforms.

8. Potential therapeutic areas for SANCs

SANCs have emerged as a promising tool in modern drug delivery systems by offering precise and controlled release of therapeutic agents. Their ability to efficiently deliver a wide range of drugs, including small molecules, nucleic acids, and proteins, makes them suitable for various therapeutic applications. SANC increases the bioavailability of a drug, reduces systemic toxicity, and, in turn, enhances targeting capability. Thus, they are especially useful in the treatment of cancerous disorders, infections, and gene therapy.[135] In this section, we will explore the diverse therapeutic potentials of SANCs, focusing on the development of personalized treatments that offer higher efficiency in modern medicine through the use of SANCs.

8.1 Applications of SANCs in cancer therapy

SANCs significantly enhance drug targeting at tumor sites while ensuring non-toxic, biocompatible excipients that improve stability and respond effectively to environmental stimuli for on-demand drug delivery. Through the attachment of active ligands or using enhanced permeability and retention, SANCs present tumor-specific accumulation and limited, if any, distribution among nontarget tissues to diminish unfavorable

side effects. These nanocomposites often include a stimuli-responsive component, either pH-sensitive or redox-responsive linkers, as a trigger for on-demand drug release inside the tumor microenvironment and thus grant even higher specificity and potency to the treatment.[136] Among these, Chien *et al.* reported photo-controlled targeting and drug delivery with upconversion nanoparticles. In this regard, SANCs that use upconversion nanoparticles as near-infrared (NIR) light active materials can afford highly controlled activation and drug delivery. In the case of a study by Chien *et al.*, upconversion nanoparticles were functionalized with folic acid for tumor targeting and thiolated doxorubicin for achieving controlled release upon NIR exposure. This system demonstrated increased tumor targeting *in vivo*, with drug release being selectively obtained inside the tumor, while the adverse effects were minimal and the bioimaging was effective along with chemotherapy.[137] Other promising vehicles could be the CXCR4-Targeting Biparatopic Protein Nanoparticles. Biparatopic protein nanoparticles have been engineered with particularly high specificity and efficiency regarding tumor targeting in cancers that express high levels of the chemokine receptor CXCR4. Using the CXCR4-binding peptides EPI-X4 and T22, Cano-Garrido *et al.* thus developed self-assembling protein nanoparticles characterized by precise targeting of the CXCR4+ colorectal cancer cells. Moreover, this dual-ligand approach significantly enhanced nanoparticles' biodistribution and greatly improved therapeutic efficacy with intensive tumor destruction in animal models while sparing healthy tissues from exposure to toxic activity.[138]

Concerning pH-responsive nanostructured lipid carriers for chemotherapy, Gao *et al.* developed a nanostructured lipid carrier incorporating docetaxel and modified it with folate and TMSPs. The resulting system allowed for dual-targeting *via* folate receptor-mediated endocytosis and enzymatic cleavage by overexpressed MMP-2/9 proteases. Indeed, the targeted system demonstrated significantly higher cytotoxicity against tumors overexpressing folate receptors with minimal systemic toxicity, thus representing a clear advance compared to conventional delivery of docetaxel.[139] In the case of drug-resistant triple-negative breast cancer, Ding *et al.* prepared "stealth" nanogels self-assembled from epigallocatechin gallate and small interfering RNA. These nanogels were functionalized with hyaluronic acid and cell-penetrating peptides, allowing for selective targeting of tumor cells and evasion of drug resistance mechanisms. Such nanogels showed a 15-fold increase in cytotoxicity against resistant breast cancer cells compared to free epigallocatechin gallate, resulting in a significant reduction in tumor growth *in vivo* with no toxic effects on normal tissues.[140] Li *et al.* developed a tumor vascular-targeted delivery system for the co-delivery of an anti-angiogenic agent, combretastatin A4, and DOX by using MSNs. Fast release of combretastatin at the tumor vasculature triggered vascular disruption, while subsequent release of DOX was done inside the tumor cells. This caused a synergistic action at low drug doses to produce significant tumor regression and reduced systemic toxicity with efficient destruction of the tumor cells.[141] Hou *et al.* reported self-assembling prodrug nano aggregates based on methotrexate conjugated to camptothecin and DOX *via* reduction-sensitive disulfide and pH-sensitive hydrazone linkers. These nano aggregates are self-assembled in the tumor microenvironment, selectively releasing the drug in response to the acidic and redox conditions of tumor cells. This system achieved synergistic antitumor effects in xenograft models with minimal systemic exposure, superior to single-agent therapies.[142]

SANCs can carry a broad array of genetic cargos, such as pDNA, siRNA, and mRNA, which self-assemble into protective nano complexes *via* electrostatic interactions, hydrogen bonding, and hydrophobic forces. In every way, this supports that, while traveling, genetic material would not degrade prematurely before arrival in target cells.[143] Generally, DNA nanocomplexes are formed through electrostatic binding between the negatively charged nucleic acids and positively charged gene carriers. This approach was demonstrated in a study by Ho *et al.*, who showed that DNA nanocomplexes synthesized through a controlled microfluidic setup produced uniform size and stability, thus optimizing cellular uptake and transfection efficiency.[144] In this respect, the study points to controlled synthesis as a means of overcoming limitations with bulk-mixed nano complexes and achieving higher efficacy in gene delivery with SANCs.

8.2 Gene therapy

Tarvirdipour *et al.* developed a self-assembling amphiphilic peptide platform carrying a nuclear localization signal to create multi-compartment micelles capable of carrying oligonucleotides directly to the nucleus. Such nuclear localization signal-functionalized micelles showed high levels of transfection efficiency and nuclear targeting in cancer cells, reaching as high as 86% knockdown of anti-apoptotic BCL2 genes in breast cancer cells. The above precision delivery forms a great example of SANCs' capabilities, which help to improve target specificity and increase the efficiency of gene therapies through attacking intracellular compartments.[145] Wang *et al.* have elaborated triangular self-assembling nanoparticles loaded with mTOR siRNA, realizing stable siRNA delivery with high transfection efficiency. The triangular structure promoted cellular uptake *via* both macropinocytosis and clathrin-mediated endocytosis, thus ensuring highly effective silencing of the mTOR expression in cancer cells. The above example outlined that SANCs have structural flexibility in hosting different genetic cargos and promoting efficient cellular internalization with ensured gene silencing.[146] Also, SANCs enable the encapsulation and targeted release of antibiotics and antiviral agents to optimize their pharmacokinetic profile, reduce undesirable side effects, and allow for pathogen-specific targeting. To achieve this, several kinds of nanocomposites have been attempted, among which are graphene-based nanomaterials, polymeric nanoparticles, and nanocomposites based on metals.[147] Graphene nanoribbons combined with cationic porphyrins comprise a self-assembled dual-wavelength phototherapeutic nanocomposite, which creates ROS upon illumination and selectively kills resistant bacteria. In the work from Yu *et al.*, this system exerted

high efficacy against multidrug-resistant strains such as *E. coli* and *S. aureus*, with reduced minimum inhibitory concentrations, *in vitro*, by half under photodynamic activation. *In vivo* studies in infected mouse wounds demonstrated a complete eradication of the bacteria, which was considerably superior to conventional antibiotics.[148] Curcumin-loaded polymeric nanoparticles exhibit broad-spectrum antimicrobial activity by harnessing the natural antibacterial properties of curcumin. Zhen *et al.* found that polymeric nanoparticles-curcumin had a minimum inhibitory concentration of 8–32 μg mL^{-1} against all Gram-positive and Gram-negative bacterial strains, including multidrug-resistant species like methicillin-resistant *Staphylococcus aureus* (MRSA). This could be explained by the idea that nanoparticles can diffuse through the bacterial cell walls to cause damage to the bacterial membrane. Importantly, it did not develop resistance with repeated exposures; hence, polymeric nanoparticles-curcumin can be regarded as a promising approach to combat multidrug-resistant infections with minimum development of resistance.[149]

SANCs based on AuNPs conjugated with antibiotics have also been explored to enhance both the efficacy and target specificity of antibiotics. Fan *et al.* synthesized ampicillin-conjugated AuNPs on PEGylated rosette nanotubes, obtaining enhanced efficacy against MRSA and *Staphylococcus aureus*. The system reduced the minimum inhibitory concentration of ampicillin by 18%, effectively concentrating the antibiotic at the injection site, and showed no cytotoxicity toward mammalian cells. Such site-specific delivery methods are important in reducing systemic exposure and thus minimizing potential side effects associated with high-dose antibiotic treatments.[150] Although the number of studies on antiviral SANCs lags behind those on antibiotic SANCs, some peptide- and lipid-based SANCs have shown promising results in delivering antiviral drugs. For example, self-assembled nanocomposites with lipid-based vesicles enhance intracellular uptake of nucleoside analogs by protecting them from viral degradation and extending the therapeutic window for antiviral activity. Initial studies have identified that such SANCs can enhance cellular delivery up to a level that can maintain effective antiviral concentrations without inducing cytotoxicity.

Fig. 4 illustrates the design and applications of nanoparticle-based drug delivery systems for cancer therapy. It shows how nanoparticles can be engineered for precise drug delivery by passive and active targeting mechanisms, taking advantage of leaky tumor vasculature and receptor-mediated endocytosis. It also shows their application in gene silencing: cellular uptake, endosomal escape, and siRNA-induced knockdown. This figure

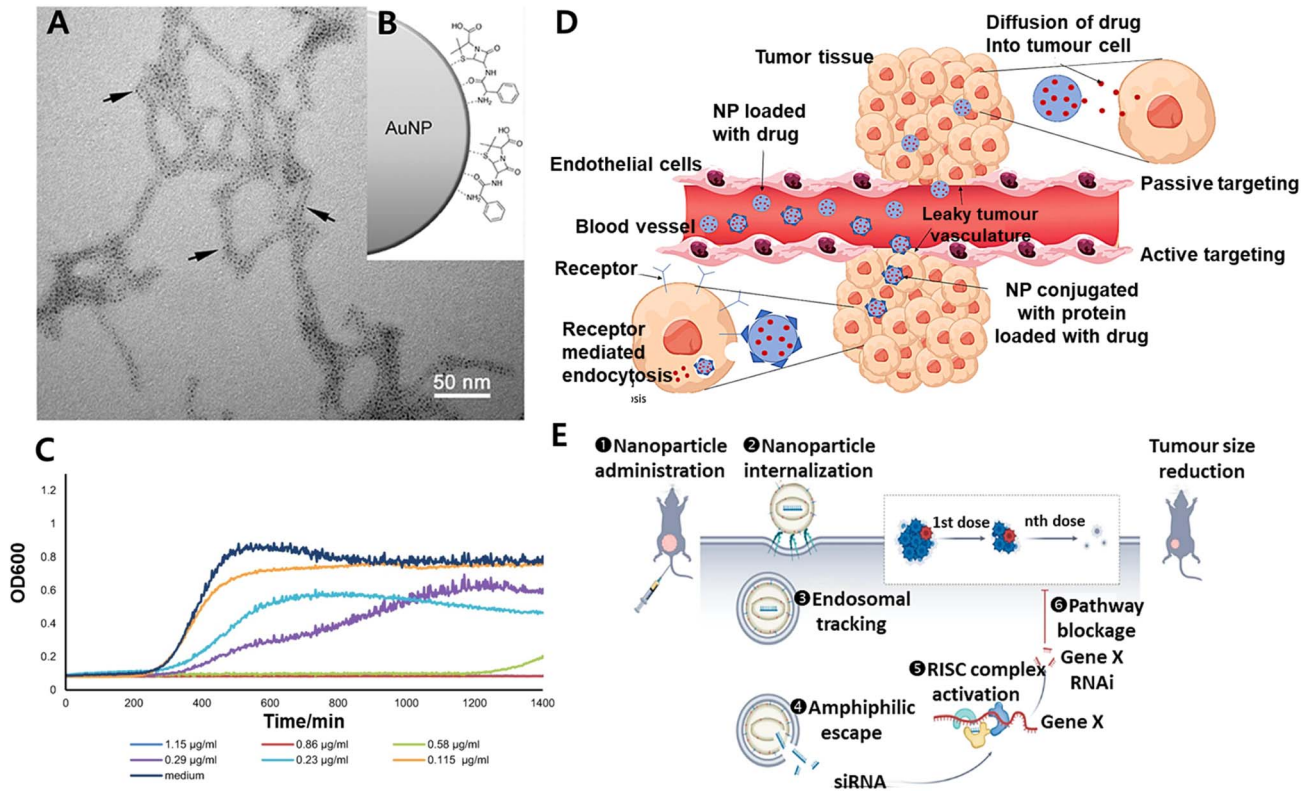

Fig. 4 Nanoparticle-based approaches in cancer treatment. (A) TEM image from nanoparticle assemblies. (B) Schematic of functionalized surface ligands on an AuNP. (C) Measured optical density as a function of time to estimate the behavior of nanoparticle interaction/agglomeration at various concentrations. Adapted with permission from ref. 150. Copyright 2019 Fan, Y. Published by Dove Medical Press Limited. (D) Passive and active targeting of tumors *via* leaky vasculature and receptor-mediated endocytosis, respectively. Adapted with permission from ref. 151. Copyright 2023 Holder, J. *et al.* Published by Frontiers Media S.A. (E) Schematic of gene silencing using nanoparticles through cell uptake, endosomal release into the cytoplasm, and subsequent gene knockout promoted by siRNA. Adapted with permission from ref. 152 Copyright 2021 Tieu, T. *et al.* Published by Wiley-VCH GmbH.

emphasizes the versatility and multifunctionality of nanoparticles toward the advancement of targeted cancer therapies.

SANCs have also been explored for the modulation of immune responses in autoimmune and inflammatory diseases because of their local delivery of anti-inflammatory agents. Such systems, upon the incorporation of self-assembled structures responsive to pH and redox changes, are capable of releasing drugs selectively in inflamed tissues. For example, in one recent study, polymeric nanocomposites were shown to load methotrexate, an immunosuppressant, whereby a formulation based on PEG-chitosan-iron oxide reduced inflammation markers with reduced systemic toxicity.[153] Ehtesham *et al.* reported that neural stem cells (NSCs) delivering tumor necrosis factor-related apoptosis-inducing ligand induced significant apoptosis, reducing tumor size by over 50% and effectively inhibiting tumor growth in glioblastoma models.[154] SANCs are emerging as a means of controlled delivery for insulin and other antidiabetic medications. Glucose-responsive SANCs are designed to release insulin in response to high levels of blood glucose, thus providing precise glycemic control. In addition, protein nanocages that self-assemble into pH-sensitive structures can protect insulin from degradation, enhancing stability and bioavailability for more effective diabetes management.[155] Neurological diseases face several challenges in drug delivery, with the most significant being the blood–brain barrier. SANCs could overcome this challege by self-assembling into nanostructures that may be able to cross the BBB. For instance, biocompatible and stable peptide-based SANCs, have been used to transport neuroprotective agents to specific sites in the brain and may offer potential treatments for conditions such as Alzheimer's and Parkinson's disease.[156]

8.3 Inflammatory and autoimmune diseases

Kim *et al.* reported that genetically modified NSCs expressing cytosine deaminase led to a 74% reduction in glioblastoma tumor volume with direct intratumoral injection, demonstrating the potential for targeted therapies.[157] Phototherapy has drawn much interest due to its localized targetability and low invasiveness. A variety of self-assembling nanomaterials, including gold and graphene-based composites, have been used to deliver photosensitizers capable of producing cytotoxic ROS through light activation. These nanocomposites enhance the effectiveness of phototherapeutic effects while reducing the destruction of healthy tissues, thus serving as a promising tool in cancer treatment and antibacterial applications.[158] Bago *et al.* demonstrated that tumor-homing NSCs reduced glioblastoma size by 250-fold in three weeks and extended survival from 22 to 49 days, showcasing the effectiveness of cytotoxic NSCs in tumor therapy.[159] Targeted thrombolytic delivery systems are highly needed in the treatment of cardiovascular diseases to reduce clot formation and prevent ischemic events. Recent studies have engineered SANCs with thrombolytic agents to self-assemble into structures responsive to blood flow and clot microenvironments, enhancing clot penetration and stability. Applications could revolutionize treatments by reducing the risk of systemic bleeding commonly associated with thrombolytic drugs.[160] SANCs represent promising colloid platforms for immunotherapy due to their potential to deliver vaccines and immunostimulatory agents directly to immune cells, enhancing the specificity of the immune response. DNA nanostructures and peptide-based nanoassemblies are under exploration for their capacity to deliver antigenic material effectively in a stable and protective environment that enhances vaccine efficacy. Recent DNA nanomaterials demonstrated improved targeting of immune cells and induced sustained immunogenic responses in tumor models.[161] The therapeutic design of SANCs varies across different biomedical applications, depending on factors such as drug type, target tissue, and delivery route. To clearly illustrate how these requirements influence material design, Table 4 summarizes recent examples of SANC-based systems, outlining their delivery needs, design rationale, and therapeutic outcomes across various diseases.

Fig. 5 illustrates the design and application of multifunctional nanoparticles in targeted cancer therapy. It indicates that such nanoparticles (NPs) can combine photothermal therapy (PTT), photodynamic therapy (PDT), and chemotherapy; pH-sensitive drug release, heat generation under NIR laser irradiation, and suppression of tumor growth.

9. Potential for overcoming drug resistance through targeted delivery

The major advantage of SANCs in the treatment of infectious diseases is that they can bypass most mechanisms of drug resistance. Targeted delivery and specific intracellular mechanisms by SANCs enhance the efficacy of drugs and reduce the selection pressure for resistance, also disrupting biofilms, which normally protect pathogens from antibiotics.[172] Accordingly, Kang *et al.* reported an approach whereby polymeric derivatization was applied to CRISPR-Cas9 self-assembling nanoparticles targeting the mecA gene in MRSA bacteria. This gene editing brought back antibiotic susceptibility into such resistant strains by selectively knocking out resistance genes without selecting for other bacteria and dampening bacterial growth. Indeed, a parallel study has shown that gene-targeting SANCs can directly address resistance at much higher levels of the genetic level and represent an interesting approach to resistance mitigation.[173]

The nanoparticles of Dzuvor *et al.* are loaded with endolysin and engineered by a self-assembling protein platform that enhances endolysin stability and activity against Gram-positive bacteria, including MRSA. In general, the mechanism of action of the endolysins involves degrading the peptidoglycan layer in bacterial cell walls; this provides a mechanism of action quite different from traditional antibiotics and, as such, is less likely to be vulnerable to conventional resistance pathways. These SANCs have demonstrated potent bactericidal activity at low doses, with a reduced likelihood of inducing resistance in preclinical models.[174]

Biofilm-associated infections are notoriously difficult to treat with conventional antibiotic therapies, as biofilms shield the bacterial community from drug infiltration and immune

Table 4 Comparative overview of SANC-based nanocomposites for various biomedical applications: design rationale, delivery requirements, and representative studies[a]

Application/disease	Delivery requirements	Design rationale of SANCs	Representative system/ Composition	Key outcome/Performance	Ref.
Cancer therapy	Controlled release, tumor targeting (EPR effect), biocompatibility	PEGylated polymer–lipid hybrid SANCs for prolonged circulation and selective accumulation in tumors	PEG–PLGA/DOX-loaded self-assembling nanogels	Enhanced tumor inhibition (≈90%) and reduced systemic toxicity	162
Gene delivery	High transfection efficiency, minimal cytotoxicity	Cationic peptide or polymer SANCs to protect nucleic acids and facilitate cell uptake	Poly(L-lysine)–hyaluronic acid nanogels	Improved siRNA stability and 80% gene silencing efficiency	163
Antibacterial therapy	Localized ROS generation, infection control, biocompatibility	Metal cluster–carbon quantum dot heterostructures with photothermal conversion	Au–C quantum dot SANCs	Photothermal antibacterial efficiency >99% (MRSA)	164
Wound healing (infected)	Antibacterial, anti-inflammatory, angiogenic stimulation	ZIF-8@Rutin nanocomposites modulate macrophage polarization	ZIF-8-Rutin SANCs	98% antibacterial activity; accelerated wound closure *in vivo*	165
Diabetic wound healing	Control of glucose, enhanced angiogenesis	GOx-based multifunctional SANCs enabling multimodal therapy (PDT + PTT)	GOx–CuO nanocomposites	Reduced bacterial infection; 3× faster healing rate	166
Normal wound healing	Hemostasis, tissue regeneration, antibacterial activity	Self-assembled peptide hydrogels (*e.g.*, $(RADA)_4$ motif) with rapid hemostatic response	BSAP hydrogel (5% concentration)	Complete wound closure within 3 days; no cytotoxicity	166 and 167
Tissue engineering	Structural support, biocompatibility	3D peptide/carbon-based self-assemblies (CNT, graphene) for scaffold formation	3D nanostructured peptide–graphene composites	Enhanced cell proliferation and mechanical stability	163
Antifungal wound healing	Biofilm inhibition, antioxidant activity	AgNPs + pomegranate peel extract in HA-based hydrogels	PPE–HA–AgNPs nanocomposite	Reduced *Candida albicans* infection; upregulated VEGF and TGF-β1	168
Anti-inflammatory therapy	Targeted immune modulation, cytokine regulation	Polymer–metal hybrid SANCs with Cu^{2+} release and peptide modification	CuCFR/PLCL fibrous membrane	Reduced TNF-α; increased angiogenesis and collagen deposition	169
Multifunctional systems	Stimuli-responsive, self-healing, adaptive response	PVA/ZIF-8@TA nanocomposite hydrogels with garlic extract	pH-responsive, self-healing hydrogel	Tensile strength 109–353 kPa; 100% bacterial inhibition	170

[a] Abbreviations: SANCs, self-assembling nanocomposites; EPR, enhanced permeability and retention (effect); PEG, poly(ethylene glycol); PEGylated, PEG conjugation; PLGA, poly(lactic-*co*-glycolic acid); DOX, doxorubicin; siRNA, small interfering RNA; ROS, reactive oxygen species; MRSA, methicillin-resistant *Staphylococcus aureus*; ZIF-8, zeolitic imidazolate framework-8; GOx, glucose oxidase; PDT, photodynamic therapy; PTT, photothermal therapy; CuO, copper(II) oxide; RADA, arginine–alanine–aspartate–alanine (self-assembling peptide motif); 3D, three-dimensional; CNT, carbon nanotube(s); HA, hyaluronic acid; AgNPs, silver nanoparticles; PPE, pomegranate peel extract; VEGF, vascular endothelial growth factor; TGF-β1, transforming growth factor beta 1; Cu^{2+}, copper(II) ion; PLCL, poly(L-lactide-*co*-ε-caprolactone); TNF-α, tumor necrosis factor-alpha; PVA, poly(vinyl alcohol); TA, tannic acid; BSAP, self-assembling peptide hydrogel (as named).

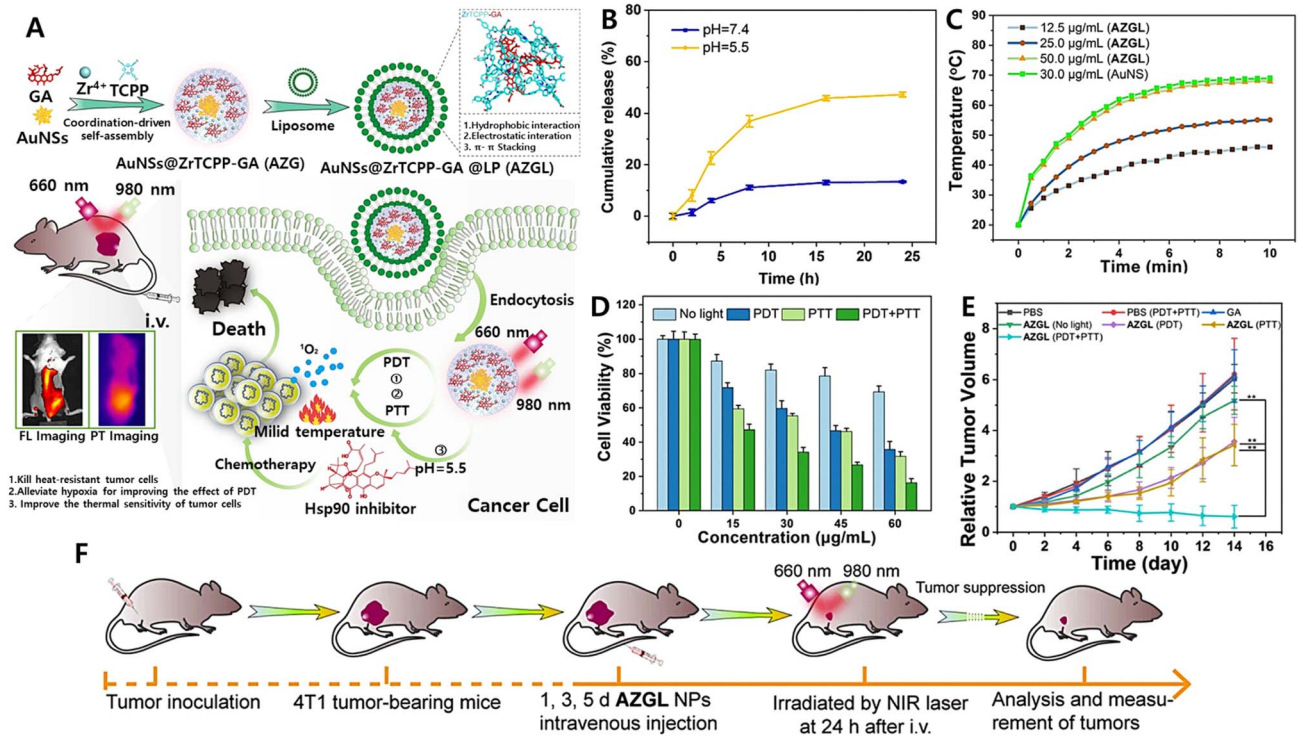

Fig. 5 Multimodal nanotherapeutics for cancer: (A) Schematic representation of the design of AuNS@ZIF/TCPP-GA NPs for combined PTT-PDT-chemotherapy with targeted delivery. (B) pH-sensitive drug release profile at acidic pH. (C) Elevation in temperature upon NIR laser irradiation for PTT. (D) Cell viability under different treatment combinations showing the enhanced effect of PDT and PTT. (E) Tumor growth suppression over time with various treatments. (F) Workflow of *in vivo* experiments, from tumor inoculation to therapy and analysis. Adapted with permission from ref. 171. Copyright 2022 Li, R.-T. *et al.* Published by BioMed Central Ltd.

elimination. One study demonstrated that SANCs prepared by combining berberine with cinnamic acid showed biofilm inhibition and bactericidal activity against MRSA biofilms. Such a nanocomposite achieved successful penetration into the biofilms due to increased binding to cell membranes and disruption, thus presenting a novel strategy to eradicate biofilm-related pathogens.[175] He *et al.* developed MSNs that self-assemble with antibiotics, affording pH-responsive release in the acidic infection sites. This kind of nanocomposite could selectively release its antibiotic payload at the site of infection, reducing off-target effects and systemic exposure. MSNs precisely increase the concentration of the drug at the targeted site, enhancing the efficacy of the antibiotic against the pathogens and reducing the risk for the development of resistance to this antibiotic in the resistant bacterial strains.[176]

SANCs are being applied in the frame of infectious diseases for a new frontier in antiresistance drug delivery, outstanding stability of the antimicrobial agents, innovative mechanisms of targeted delivery, and new activities such as CRISPR-mediated gene editing and/or endolysin-mediated bacterial lysis. Comparative studies have revealed a few key advantages: graphene-based and polymeric nanocomposites improve bioavailability and penetrate membrane barriers in resistant strains; berberine-based nanocomposites and endolysin nanoparticles break up biofilms effectively. CRISPR-loaded nanocomposites edit resistance genes directly, while endolysin-based SANCs degrade bacterial cell walls enzymatically. Though scalability, safety, and long-term efficacy are some of the future studies to be focused on, such advances point toward a new era in precision-targeted antimicrobial therapies, especially against multidrug resistance.

10. Advantages of SANCs over traditional drug delivery systems

SANCs show much higher advantages compared to conventional drug delivery systems through their improvement in stability, bioavailability, and active targeting of therapeutic agents. The advanced nanocomposites ensure precision at the site of drug delivery for improved therapeutic outcomes with minimal off-target effects and systemic toxicity. The highly performing SANCs are achieved *via* multi-targeting approaches, receptor-mediated endocytosis, and stimulus-responsive mechanisms, which optimize the drug delivery performance at active disease sites. They are the game-changing platform for modern medicine by reducing toxicity, enhancing stability, and improving bioavailability, hence offering treatments in a personalized and efficient manner for a wide array of diseases.[135]

SANCs combine several design units, *i.e.*, core–shell structures, porous scaffolding structures, and supramolecular bonding to reach ultrahigh drug loading (up to 90%) compared

to polymeric nanoparticles (20–30).[177] PEGylation, stealth coatings, and crosslinked shells support prolonged circulation, while targeting ligands (antibodies, peptides) and responsive bonds (*e.g.*, pH- or redox-sensitive) facilitate controlled drug delivery at disease sites.[178]

Such multiple-component targeting, with both passive (EPR) and active targeting, achieves a tumor volume reduction ratio of about 35 percent over, say, surgery or radiotherapy, at significantly less systemic toxicity, in preclinical tumor models.[179] In addition to that, the modularity of SANCs enables co-delivery of chemotherapeutics with genes or immunomodulators, and further increases the efficacy of specific therapeutics. The synthesis of complexes in constant size and with surface chemistry, sensitivity to biological conditions (pH and ionic strength, proteins in serum), and the developing regulatory circuits of complex nanosystems can be cited as the main obstacles.[16] Nevertheless, With recent advancements in microfluidic manufacturing, programmed self-assembly, and standardized characterization, these challenges are being progressively overcome, leading to personalized nanomedicines that are ready for clinical application.

10.1 pH-responsive targeting in tumor microenvironments

The acidic microenvironment of most tumors provides a unique trigger for SANCs to release their drug payloads precisely within the tumor tissue. Gong *et al.* showed that RGD-functionalized peptide nanoparticles selectively targeted integrin receptors, such as $\alpha v\beta 3$, overexpressed on the surface of cancer cells. These nanoparticles encapsulated DOX and remained stable at physiological pH but released the drug under acidic conditions, such as in the tumor microenvironment, at pH ~6.8. This pH-sensitive release mechanism caused the intratumor accumulation to be 4–5 times higher when compared with non-targeted delivery, thereby optimally giving the therapeutic effect with less damage to normal tissues.[180] The pH sensitivity enhances the kinetics of drug release through an acid-labile bond in the nanocomposite structure, cleaving off under a lower pH environment to ensure quick and locality-based drug release. This approach not only ensures maximum drug concentration at targets, but also guarantees an important advantage for rapid proliferation and acidic tumors, for which conventional delivery would normally have its shortcomings.[181]

10.2 Stimuli-responsive block copolymers for site-specific drug release

Among other advantages, block copolymers that self-assemble into SANCs are responsive to internal and external stimuli such as pH, redox potential, and temperature. According to Ge and Liu, block copolymers designed with responsive elements can undergo structural changes within the unique biochemical environment of tumors. This dynamic adaptation allows not only selective drug release but also enhanced imaging sensitivity, enabling real-time monitoring of drug delivery and treatment response.[182] Such polymers could allow controlled release in both extracellular and intracellular environments through multimodal targeting. For example, a tumor environment of high redox potential may easily result in the release of its drug payload into the cytoplasm by a redox-sensitive block copolymer, with maximum intracellular delivery. This is even more advantageous in complicated tissues, especially in metastatic cancers where multi-step targeting would improve the outcomes.[183,184]

10.3 Receptor-mediated endocytosis (RME) for cancer cell targeting

The mechanisms behind RME of SANCs depend on decoration with proper ligands that bind with high affinity to overexpressed receptors on the surface of cancer cells. Song *et al.* prepared self-assembled AuNPs that were functionalized with targeting peptides and able to recognize tumor cells thanks to an effective binding selectively to surface receptors such as folate or HER2. Eventually, the final NPs, loaded with an antitumoral drug, showed a pH-triggering release in the acidic endosomal compartment, providing remarkable specificity to controlled intracellular drug delivery.[185] RME therefore increases targeting specificity by reducing Drug uptake in cells that do not express the receptor. However, several challenges persist regarding striking a balance between the stability of SANCs while in circulation and their rapid degradation following endocytosis. Recently, a number of works have concentrated on the optimization of ligand density on the surface of nanoparticles for the fine-tuning of binding affinity. This approach has achieved 90% selectivity for receptor-overexpressing cells, together with the limitation of premature degradation in circulation, which is so important for increasing both the targeting accuracy and systemic stability.

10.4 Multi-targeting for enhanced precision in tumor sites

These multiple-targeting SANCs, conjugated with dual ligands binding to at least two distinct receptors, usually on tumor cells, express higher selectivity indices than single targeting. Indeed, the hyaluronic acid-based nanoconjugate of Song *et al.* used two targeting molecules, which included folate and one other ligand of the CD44 receptor, targeted towards the cells overexpressing the two targeting receptors. Enhanced tumor site retention of an antitumor agent improved three-fold compared with the same ligand delivered using traditional targeting methods with reduced accumulations in off-targeting tissues.[186] Additionally, multi-targeting increases the specificity and reduces off-targets, since cellular uptake needs two binding events, consequently minimizing the uptake by normal cells that may express only one of the receptors. Second, in more recent developments, "intelligent" dual-targeted SANC adapts to the dynamic environment of the tumor, increasing specificity and providing prolonged drug presence within the tumor.

Fig. 6 illustrates some of the new concepts in targeted drug delivery and gene therapy. It introduces the concept of responsive nanoparticles able to adapt to different biological environments for enhanced delivery efficiency. These systems enable specific targeting at the levels of organs and tumors, among others, and illustrate also the therapeutic potential of DNA nanostructures in drug delivery diagnostics, and gene

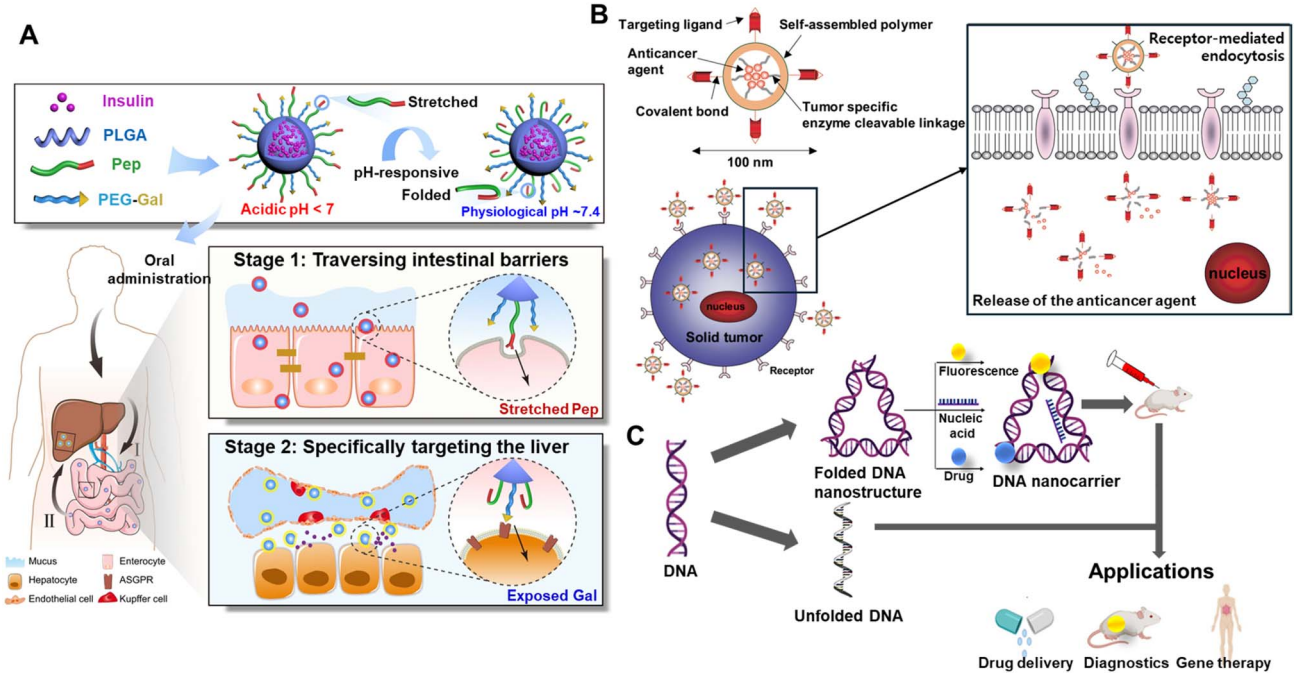

Fig. 6 Advanced active targeting approaches for drug delivery and gene therapy: (A) oral administration of pH-responsive nanoparticles, where the pH change from acidic to physiological pH allows intestinal barrier crossing and liver targeting. Adapted with permission from ref. 187. Copyright 2022 Yang, T. *et al.* Published by Springer Nature. Licensed under CC BY 4.0. (B) Tumor targeting delivery using polymer nanoparticles bearing targeting ligands that enable RME and intracellular drug release. Adapted with permission from ref. 188. Copyright 2005 Elsevier Ltd. All rights reserved. (C) DNA nanostructures for drug delivery, diagnostics, and gene therapy with an emphasis on folding and targeted active therapeutic applications. Adapted with permission from ref. 189. Copyright 2020 Elsevier B.V. All rights reserved.

therapy applications. This figure emphasizes the versatility and effectiveness of modern delivery platforms in medical applications.

10.5 Reduced toxicity and side effects

By precisely targeting disease sites and controlling drug release, SANCs reduce off-target effects, enhance drug stability, and offer a safer therapeutic profile.[190] Several of those enzyme- and redox-sensitive SANCs have been engineered to selectively release their therapeutic payload within the diseased tissues, reducing overall drug exposure to otherwise normal organs. For instance, Zhou *et al.* developed a cabazitaxel dimer-constructed redox response self-assembling nanoplatform by using a bioactivatable spacer. Such cabazitaxel dimers formed nanoparticles in an aqueous solution, which was relatively stable during circulation but could disintegrate within the reductive tumor environment, allowing intracellular drug release only at the action site. This targeted release drastically reduced systemic toxicity, allowing higher doses to be administered safely, and reduced immunotoxicity with enhanced tolerability was achieved in animal models.[191]

The redox-responsive mechanism avoids the premature release of drugs in nontarget tissues, an especially crucial factor in highly potent and toxic drugs such as chemotherapeutics. This would minimize side effects and afford improved patient comfort and safety throughout the entire treatment course.[192] Peptide-based SANCs make use of naturally occurring amino acids in the construction of drug delivery vehicles that are well-tolerated by the immune system. Yang *et al.* illustrated that peptide-based nanostructures could self-assemble into stable drug carriers that avoid recognition and clearance by immune cells, thus prolonging systemic circulation and reducing inflammatory responses. These peptide nanocomposites are highly modifiable; precise modification can be carried out to further minimize their immunogenicity. The hemolysis rate of peptide SANCs was remarkably lower than 5%, representing improved biocompatibility during preclinical testing as compared to synthetic polymers; thus, it would be ideal for repeated dosing applications.[193] The innate compatibility of peptide-based SANCs reduces immune activation, hence assuring safer, sustained drug delivery profiles. This aspect is particularly important in the case of chronic diseases, where frequent dosing is necessary to avoid cumulative toxicity.[194]

Most conventional drug delivery systems require the use of excipients to stabilize and solubilize the therapeutic agent, which may introduce toxic by-products. Self-assembling prodrug nanocomposites represent a way to avoid additional excipients in the formulation of stable delivery systems. Ren *et al.* prepared cabazitaxel prodrugs able to self-assemble into nanoparticles with high drug loading efficiency, thus avoiding the use of stabilizing agents. The presented nanocomposite prodrug retained the pharmacological action of cabazitaxel with minimal excipient-related side effects, revealed in preclinical trials with this system achieving prolonged blood circulation

and minimal systemic toxicity.[195] This self-assembly of prodrug-based formulations further minimizes the incorporation of possibly harmful additives, enhances safety, and increases patient tolerance, especially in drug therapies that must be done in high dosages. Therefore, the simplicity of such a composition would entail less complexity in its therapeutic profile and enhance the prospect of better compliance among the patients with a minimized adversarial response.[196]

Acidic-environment-responsive structures of tumor targeting SANCs limit the release of drugs in normal conditions at neutral pH, hence reducing systemic toxicity. Using pH-sensitive amphiphiles, Chen *et al.* constructed a supramolecular drug delivery system that could selectively release the anthracycline chemotherapeutic agent DOX in acidic tumor microenvironments and reduce the accumulation of the drug in nontarget organs. *In vivo*, it was shown that the cardiac tissue, one of the most common sites of toxicity, presented lower levels of DOX after the administration of pH-responsive formulations compared to non-targeted ones.[197]

Due to the selectivity of the release inside the tumors, pH-responsive SANCs avoid serious side effects related to wide drug distribution and, therefore, it is much safer for patients who receive aggressive treatments, such as chemotherapy.[198] Examples include on-demand drug release systems, of which electrically controlled SANCs are a part. These systems allow one to achieve localized, temporally controlled drug release so one can minimize systemic exposure. Weaver *et al.* produced graphene oxide nanocomposite materials that, through electrical stimulation, were able to release anti-inflammatory drugs, having the capability to precisely control dosage and release time with this system. The nanocomposite exhibited zero passive diffusion in tests without electrical stimulation; thus, it preserved the drugs inside the target site without releasing them until their release was triggered. This approach of controlled release effectively circumvented systemic side effects – no toxic by-products were produced during electrical activation *in vitro*.[199] Therefore, the ability of on-demand release systems to deliver locally without systemic dispersion is an important step toward the minimization of off-target toxicity, especially in those therapies that require high precision with periodic dosing, such as in inflammatory diseases.[200]

10.6 Advantages of SANCs in stabilizing drugs and enhancing their bioavailability

The SNEDDS are among the most powerful SANC formulations for the enhancement of hydrophobic drug solubility. For example, one study concerned with SNEDDS of diacerein indicated that the formulation achieved a solubility of approximately 309 μg mL^{-1}, almost twice that of conventional SNEDDS (162 μg mL^{-1}), due to the simultaneous formation of nanoemulsions and nanosuspensions. This dual mechanism facilitated the fast dissolution and prolonged absorption of diacerein; thus, 210% relative bioavailability over the aqueous drug suspension was achieved.[201] The better solubilization effect thus enhances the drug to attain more therapeutic plasma levels, therefore improving its bioavailability and therapeutic outcome. The sub-200 nm droplet size from SNEDDS minimizes the energy required for the solubilization and stabilizes the drug in a lipid matrix that protects it from premature degradation in the gastrointestinal tract.[202]

Chitosan-coated nanocomposites are specifically more useful in stabilizing peptide and protein drugs, which normally get degraded by enzymes easily. Very recently, in one such study, it has been proved that insulin-loaded chitosan-coated zein nanocomposites enhanced the stability and bioavailability of insulin upon oral administration. Thus, nanocomposites evidenced a 12-fold increase in transepithelial permeability compared to raw insulin and a relative bioavailability of 15.19% *in vivo*, showing considerable improvement in comparison with standard formulations.[203] Mucoadhesive properties of chitosan allow drugs to adhere to mucosal surfaces, slowing down the release rate and increasing stability. This coating acts as a physical barrier against enzymatic degradation, important for maintaining the integrity of peptides and optimizing absorption in the small intestine.[204]

Other advantages include enhanced bioavailability *via* amorphous nanoplexes. The nanoplexes of amorphous drugs and polyelectrolytes are a novel approach to enhance the rate of dissolution of poorly soluble drugs. In one recent work, Cheow and Hadinoto reported that ciprofloxacin nanoplexes exhibited a two-fold increase in dissolution rate and solubility concerning raw drug crystals, due to the intrinsically higher dissolution characteristics of the amorphous form. These nanoplexes, which are prepared by the self-assembly of ciprofloxacin and dextran sulfate, demonstrated stable retention in dry-powder form and were stable for one month under standard conditions.[205] Amorphization within the nanoplex structure prevents recrystallization, hence sustaining a high-energy state that enhances dissolution. This is manifested in a significant increase in bioavailability, which is required in drugs that need a fast onset or when high drug loading is required to attain therapeutic needs.

In another aspect, porous silicon-based SANCs leverage their high surface area and biodegradability for high drug loading capacity and enhanced pharmacokinetics. Beavers *et al.* demonstrated that self-assembled polymer/porous silicon nanocomposites complexed with peptide nucleic acids showed increased intracellular bioavailability and stability of anti-microRNA agents targeting miR-122, which is critical for liver cancer therapies. The porous structure allowed for endosomal escape and sustained release, leading to a significant increase in the peptide nucleic acid concentration in target cells.[206] With PSi, high drug loading efficiency together with a controlled release profile is achievable, thus providing long exposures to therapeutic agents in several chronic conditions that would call for protracted drug delivery. This reduces the frequency of dosing and thereby enhances compliance.[207]

The interfacial cohesion in the bioadhesive techniques makes it possible for SANCs to maintain hydrophobic drugs in a very stable nano-sized form appropriate for prolonged circulation and enhanced accumulation in tumors. Shen *et al.* have developed interfacial bioadhesive molecules that are applied to stabilize anticancer drug nanocomposites against Ostwald

ripening; these have resulted in uniform and stable particles with very high accumulation in tumors and very low systemic toxicity. Resultant bioadhesive nanoparticles showed considerably improved stability and a five-fold higher concentration of the drug in tumors compared to traditional formulations.[208] The approach of bioadhesion consequently extends particle stability by preventing aggregation, which preserves the desired particle size and distribution profile for targeted delivery. Enhanced stability will be important in maintaining consistent drug exposure within high metabolic activity or mechanically stressed therapeutic areas.[209]

SANCs represent a multifaceted solution to improve the stability and bioavailability of drugs. Techniques like SNEDDS for solubilization, chitosan coating for protection against degradation, and porous silicon for sustained release have contributed to achieving therapeutic goals that are not readily achievable with conventional drug delivery systems. Each method is based on the self-assembling nature of nanocomposites to create stable, bioavailable formulations that minimize degradation and maximize the therapeutic efficacy of drugs. These advances represent a critical step toward the optimization of drug delivery for hydrophobic, unstable, or rapidly metabolized drugs and point the way toward more effective treatments across a wide range of clinical applications.

11. Innovative approaches in SANCs for enhanced drug delivery

Prodrug nano assemblies enhance stability and increase the loading capacity of nanoformulations by self-assembly mechanisms of small molecule drugs, taking advantage of the unique properties of small molecule prodrugs. Most conventional SANCs require additional stabilizers or carriers, which may dilute the content of drugs and probably introduce toxic components. In contrast, for prodrug nanoassemblies, drugs serve as major structural components; this greatly raises the drug loading capacity, mostly over 80% by weight, and minimizes the use of excipients.[210,211]

In the study conducted by Li *et al.*, drug molecules self-assembled themselves into nanoparticles through hydrophobic and π–π stacking interactions, whereby one can achieve spontaneous generation in the absence of any extra carrier materials.[212] As a result, a suitable nanostructure is realized where stability against degradation in the flow can be achieved for reaching target tissues with very high concentrations of drugs. On one hand, this assembly mechanism may act in the controlled release of drugs, which in itself is achieved by a changed linker chemistry in prodrug molecules; hence, it can have an accurate delivery on precisely the very optimal site needed, with minimal effects resulting in increased bioavailability of drugs and positive outcomes on target.

Layer-by-layer assembly enables the precise control of drug release by arranging therapeutic agents into sequential, degradable nanolayers. This technique permits the independent, controlled release of both macromolecules and small molecules through the design of each layer with specific degradation properties in response to environmental triggers such as pH, enzymatic presence, or redox conditions. The system used hydrolytically degradable polymers to encapsulate in the study by Kim *et al.* both heparin, a large, negatively charged biomolecule, and PTX, a hydrophobic small molecule.[213] Each layer was engineered to engineer the degradation profile of small molecule and macromolecule release for a possibly synergistic therapeutic effect: for example, the early release of PTX is used to attack proliferating tumor cells, and late-stage heparin release blocks angiogenesis with tumor growth. The versatility of this system allows the layer-by-layer assembly to deliver several therapeutics in combination therapy with the added advantage of maintaining separate, distinct release profiles. This level of control is of real benefit in complex disease models where synchronized or sequential delivery can dramatically enhance therapeutic efficacy.[214]

Protein-based nanocomposites represent an ideal platform for biopharmaceutical delivery owing to their intrinsic biocompatibility, biodegradability, and capacity for molecular recognition that enhances cellular uptake while minimizing immune responses. Maham *et al.* illustrated that protein-based carriers, such as ferritin and apoferritin cages, form stable structures that can encapsulate small drugs and large biomolecules like peptides and enzymes.[215] The predictable tertiary and quaternary conformation due to the special structural properties of proteins makes possible the preparation of precisely shaped nanocomposites that would increase cellular uptake through RME. The protein carriers, like ferritin, have pH-responsive drug release due to the conformational changes at acidic pH values either in the tumor sites or at inflamed tissues. Besides, the biodegradability of protein carriers ensures that they degrade into nontoxic amino acids that are easily metabolized, reducing toxicity and immunogenicity even further. These attributes make protein-based SANCs especially suited for the delivery of sensitive biological drugs that require preservation in circulation and controlled release.[216]

DNA-based nanostructures, for example, tetrahedral DNA nanostructures (TDNs) have improved the stability and intracellular delivery of nucleic acids through their programmable, biocompatible scaffold. Structural stability imparts on nucleic acid stability from enzymatic degradation, the major problem in gene delivery. Zhang *et al.* employed TDNs for siRNA and antisense oligonucleotide delivery, taking advantage of the ability of DNA to form stable, precisely shaped nanostructures that shield genetic material during circulation.[217]

TDNs improve cellular uptake by mimicking naturally occurring cellular entry pathways. They can be engineered with aptamers or ligands that target specific cell surface receptors, enhancing selective uptake by target cells and making sure the nucleic acids are delivered efficiently to their intended site. This selective targeting, in addition to intrinsic stability, acts to enhance the efficacy of gene therapies while reducing off-target effects and offering a path to personalized medicine approaches where specific genetic targets are involved.[218] This gives a special dual loading capability to peptide-based SANCs through the encapsulation of hydrophilic and hydrophobic drugs, thus making them efficient platforms for combination

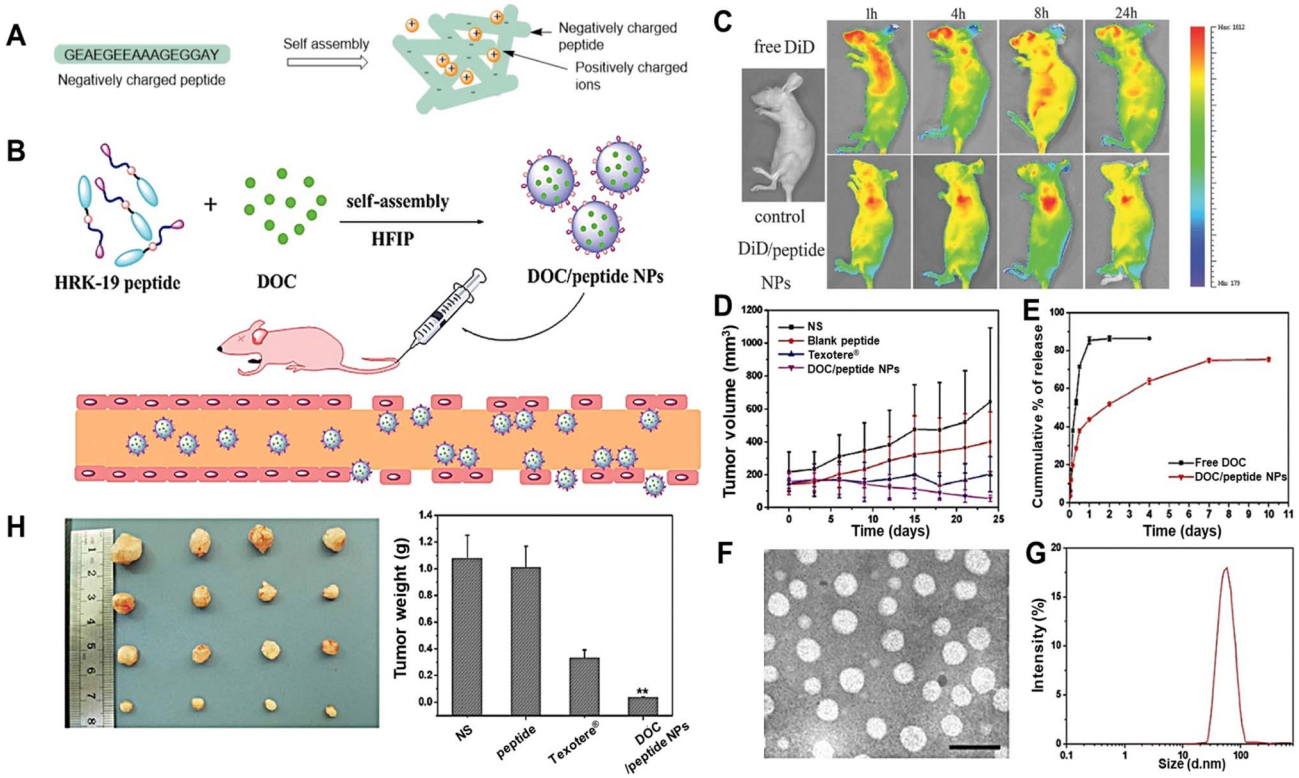

Fig. 7 Design and application of peptide-based nanoparticles for targeted drug delivery: (A) self-assembly of negatively charged peptides with positive ions. Adapted with permission from ref. 221. Copyright 2017 Elsevier B.V. All rights reserved. (B) Formation of DOX-loaded nanoparticles and injection into animal models, (C) biodistribution monitored *via* fluorescence imaging, (D) tumor volume reduction as a function of time, (E) controlled drug release profile, (F) TEM visualization of uniform nanoparticles, (G) size distribution analysis *via* DLS, and (H) significant tumor weight reduction in nanoparticle-treated groups. Adapted with permission from ref. 222. Copyright © 2017 The Author(s). Published by Wiley-VCH Verlag GmbH & Co. KGaA. Licensed under CC BY 4.0.

therapies. Such dual loading may be facilitated by the nature of some peptides, being amphiphilic and therefore capable of self-assembling into core–shell nanostructures possessing distinct hydrophilic and hydrophobic domains. This is illustrated by Wang *et al.*, who have designed peptide nanostructures forming a hydrophobic core that is capable of encapsulating drugs such as PTX while the hydrophilic shell may carry water-soluble drugs or peptides simultaneously.[219]

Its peptide nature provides a modular structure, self-assembling into morphologies, micelles, vesicles, or nanofibers, each one designed to optimize the particular conditions of loading efficiency and release profile. The design of the amphiphilic peptide also supports the assembly of stimuli-responsive structures that can release both hydrophobic and hydrophilic agents in response to specific triggers, such as pH or enzyme presence. Because it is so structurally and functionally diverse, this makes peptide-based SANCs the ideal candidate to meet various therapeutic needs, including chemotherapy to immune modulation, by hosting multiple drugs with diverse properties in one single, stable system.[220]

Thus, each type of SANC has its advantages against a particular class of drugs, reflecting the broad versatility of SANCs across different therapeutic agents. In the case of SANCs, self-assembly mechanisms can be exploited to improvement the stability, bioavailability, and release profiles of both small molecules and complex macromolecules. Advanced designs support applications ranging from cancer therapy to gene delivery while offering a flexible platform to adapt to the evolving needs of personalized and combination therapies in modern medicine. Fig. 7 gives an overview of the development and application of peptide-based nanoparticles through a design and application approach, demonstrating the self-assembly of peptides into nanoparticles, with further encapsulation of an antitumor drug inside those nanoparticles, used in a study on animals to find its biodistribution and efficacy. It gives a controlled profile for drug release, the uniformity of the nanoparticle structure, and tumor weight and size reduction. This figure gives a comprehensive overview of the potential of peptide-based nanoparticles as an advanced platform to improve drug delivery and therapeutic outcomes in cancer treatment.

12. Challenges and limitations of SANCs

SANCs represent a significant advancement in targeted drug delivery, offering unparalleled precision, stability, and bioavailability. However, scaling up production while maintaining structural integrity remains a substantial barrier. Self-assembly is highly dependent on finely tuned

physicochemical conditions, such as pH, ionic strength, and temperature; even minor deviations can lead to inconsistencies in particle size, morphology, and drug loading. The challenge is exacerbated at a large-scale: traditional batch techniques inevitably result in batch-to-batch variations, while continuous and reproducible processes necessitate significant infrastructure investments and technical expertise. Additionally, each SANC formulation requires specific production parameters, making it difficult to establish a universal production pipeline. Consistent self-assembly is also problematic due to the sensitivity of non-covalent forces, such as hydrophobic and electrostatic interactions, to minor environmental changes, potentially leading to aggregations or alterations in the structural integrity in large-scale procedures.[223,224]

Apart from manufacturing, critical limitations include stability during storage and transportation. Many SANCs degrade or aggregate in response to fluctuations in temperature or humidity, leading to premature drug release or disruption of their nanostructure. While lyophilization offers a potential solution, the integrity may not always be fully restored upon rehydration, and the use of additional stabilizers can alter the drug release pattern. Toxicity and biocompatibility concerns also significantly impact the utilization of SANCs. For instance, inorganic NPs may pose potential long-term inflammatory effects, while certain polymers can trigger immune reactions or cytotoxicity at higher concentrations. Although biodegradable materials like PLGA mitigate some toxicity risks by breaking down into harmless by-products, monitoring degradation rates and residue accumulation is crucial. In addition to technical and biological challenges, navigating stringent regulatory and clinical obstacles is a formidable task. Current approval frameworks often fall short in accommodating the multifaceted composition and stimulus-responsive nature of SANCs, leading to extended validation timelines. Furthermore, translating promising preclinical data into human trials has unveiled new challenges related to biodistribution and immune responses, necessitating thorough and costly testing. Overcoming these challenges could pave the way for significant technological advancements in large-scale production, closer collaboration with regulatory bodies to find more effective solutions, and the development of robust stability measures. Addressing these challenges would position therapies based on SANCs to revolutionize precision medicine, offering safer and more effective treatments for a range of pathologies.[225–228]

Though having encouraging properties, the currently existing self-assembling nanocomposites (SANCs) have a number of significant limitations that restrict their universal use in clinical practice. An example is that of the formulation stability which is a great problem. It has been observed that some of the SANCs degrade structurally in 12–48 hours at physiological settings, depending on the utilized matrix.[229] On top of this, the leakage of drugs as a result of unstable assemblies has been as high as 30 percent of the drugs encapsulated.[230]

Regarding biocompatibility, even though SANCs have had promising results *in vitro*, problems are noted *in vivo*. PEG/poly-gamma-glutamic acid nanoparticle-based study showed good cellular uptake with immunotoxicity being observed in 15–20% of the animal models questioning systemic safety.[231] Toxicity is another issue particularly that of high drug loading and rapid release. As can be illustrated, *e.g.*, with cabazitaxel-loaded SANCs that contained >86% of the drug, the systemic toxicity was significantly decreased compared to the case with the free drug, but the drug still demonstrated a mild systemic cytotoxicity in the hepatic tissues in 10% of preclinical models.[232] These data emphasize the necessity of a compromise between release and safety profiles. Regulatory Regarding regulatory, problems arise with the lack of standardised manufacturing processes and batch-to-batch replication. Mean regulatory delivery cycle of nanomedicines particularly nanomedicines with self-assembled platforms still takes more than 7 years *versus* ~4.5 years of conventional drugs. Besides, there are only a few self-assembling systems that have received FDA clearance and in many cases, this is often done when they are constructed using previously authorized components.[233]

In this regard, a number of solutions are under development, that is, staging the use of PEGylated coatings to stabilize the colloidal phase, drug conjugation with covalent linkages to eliminate the burst release effect, integration of degradable connector molecules to improve biocompatibility, and development of predictive models of quantitative assembly to support the reproducibility and scalability of the assemblies.[229,233]

13. Future directions

Of the three key trends, the growth of SANCs is likely to be influenced by precision-targeted therapy, integration with artificial intelligence (AI), and the exploration of multifunctional nanoplatforms. Ligand-functionalized SANCs which can recognize overexpressed receptors (*e.g.*, folate, transferrin) are being developed in targeted medicine to provide cell-specific targeting to reduce off-target toxicity. Recent work has shown over 85 percent inhibition of tumors in xenograft models with a receptor-targeted nanocomposite.[229]

AI is quickly finding its way as a method of optimizing the design of nanostructures, forecasting self-assembly effects, and personalizing drug delivery dosage. AI-based modeling has demonstrated over 90% accuracy in predicting nanoparticle shape, drug retention kinetics, and pharmacokinetics in some systems.[234] It is also contributing to screening candidates for safe SANCs by profiling immune interactions and toxicity using deep learning.[235]

Recent AI/ML studies report concrete, quantitative gains that move beyond conceptual framing in nanocarrier design. In microfluidic LNP manufacturing, supervised learning combined with Bayesian optimization has been used to identify and tune critical process parameters (*e.g.*, FRR, TFR, buffer pH, lipid ratios) for size/PDI control across small datasets; for example, a study on mRNA–LNPs developed 24 formulations and used XGBoost/Bayesian and ensemble models to predict and optimize CQAs, reporting close agreement between model predictions and experiments across the formulation set.[236,237] In a distinct process domain, particle size prediction in electrospraying was trained on a 445-record dataset: XGBoost and

Table 5 Properties and applications of stimuli-responsive nanocomposites[a]

Nanocomposite type	Stimuli sensitivity	Loaded drug/Gene	Biocompatibility	Release profile	Applications	Driving forces	Benefits	Drawbacks	Ref.
pH-sensitive polymeric micelle	Acidic tumor environments	Doxorubicin	High	Controlled, rapid in acidic pH	Cancer therapy	Hydrophobic interactions, H-bonds	Selective delivery, reduced side effects	Sensitive to storage conditions	251
Redox-responsive vesicles	High intracellular GSH	siRNA, paclitaxel	Moderate to high	Triggered by reductive conditions	Gene therapy, cancer targeting	Disulfide bonds	High specificity, minimal off-target effects	Complex synthesis	252
Temperature-sensitive hydrogel	Mild hyperthermia (40–42 °C)	Insulin	Excellent	Temperature-triggered burst release	Diabetes management	Hydrogen bonding, van der Waals forces	Prolonged circulation, on-demand release	Limited control in systemic environments	253
Light-responsive liposome	UV or near-infrared (NIR)	Photosensitizers, doxorubicin	High	Light-triggered release	Photothermal/ photodynamic cancer therapy	π-π stacking interactions	Non-invasive control, dual therapeutic roles	Requires external activation	254
Enzyme-responsive nanoparticles	Protease (*e.g.*, MMP-2/9)	Hyaluronic acid, doxorubicin	High	Enzyme-catalyzed gradual release	Cancer and inflammation therapy	Electrostatic interactions	Selective release in diseased tissues	Limited scalability	255
pH/redox dual-responsive micelle	Low pH and high GSH	Cisplatin, siRNA	Moderate to high	Sequential, multi-stage release	Combination cancer therapies	Hydrophobic and electrostatic forces	Enhanced targeting, multidrug delivery	High production cost	256
Natural polysaccharide-based SANC	pH and enzyme sensitivity	Proteins, nucleic acids	Excellent	Sustained release in specific sites	Anti-inflammatory, drug delivery	Ionic gelation	Biodegradable, minimal immunogenicity	Prone to enzymatic degradation	257
Magnetic nanocomposites	Magnetic fields	Antibiotics, chemotherapeutics	Moderate	Magnetically directed release	Targeted cancer therapy	Magnetic dipole interactions	High precision, minimal systemic exposure	Requires external magnetic devices	258
Electro-responsive hydrogels	Electric fields	Hydrophilic drugs, peptides	High	Pulsatile, on-demand release	Neurological disease treatment	Ionic interactions, hydrogen bonding	Precise control, reusable systems	Infrastructure for stimulation required	259
pH-responsive lipid nanoparticles	Acidic conditions	mRNA	High	Controlled release in acidic pH	Vaccine delivery	Hydrophobic forces	Enhanced stability, easy delivery	Limited application for non-acidic tissues	260
Host-guest cyclodextrin complexes	pH, temperature	Anti-inflammatory drugs	High	pH-dependent reversible binding	Autoimmune disease therapy	Host-guest interactions	Reversible release, tunable response	Limited drug loading capacity	261
Carbon-based nanocomposites	Redox, light	Antibiotics, photosensitizers	Moderate	Light or redox-triggered release	Infection treatment, phototherapy	π-π stacking, hydrophobic forces	Broad functionality, dual therapeutic uses	Long-term toxicity concerns	262

[a] Abbreviations: SANC, self-assembling nanocomposite; pH, potential of hydrogen; DOX, doxorubicin; GSH, glutathione; siRNA, small interfering RNA; UV, ultraviolet; NIR, near-infrared; MMP-2/9, matrix metalloproteinase-2/9; π–π, pi–pi stacking interaction; PDT, photodynamic therapy; PTT, photothermal therapy; HA, hyaluronic acid; NPs, nanoparticles; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; mRNA, messenger RNA; H-bonds, hydrogen bonds; PLGA, poly(lactic-*co*-glycolic acid); CNT, carbon nanotube; BSAP, self-assembling peptide hydrogel; GSH, glutathione; TNF-α, tumor necrosis factor alpha.

Random Forest achieved 5-fold cross-validation RMSE values of 3.91 μm and 6.19 μm, respectively, and an in-house experimental validation RMSE of 1.30 μm for XGBoost, enabling rapid screening of operating conditions prior to bench runs.[238] For self-assembly outcomes, a graph neural network trained on STM-derived experimental datasets outperformed classical ML methods in predicting on-surface assembly patterns of functional PAHs on metals, demonstrating that learned molecular-graph features can forecast emergent morphologies from chemical structure.[239] At the mesoscale, an ML-plus-simulation pipeline mapped chemical descriptors to self-assembled structures and to the critical packing parameter, quantitatively analyzing which molecular features (*e.g.*, amphiphilicity) steer morphology selection under given conditions.[240] Design-theoretic advances further show that ML-guided multi-objective optimization can discover interaction potentials that jointly maximize thermodynamic yield and kinetic accessibility of target polymorphs, operationalizing inverse design for self-assembled materials under competing pathways.[241]

The integration of AI and machine learning (ML) into the design of SANCs has moved beyond theoretical predictions toward practical data-driven optimization. Recent advances demonstrate that ML algorithms can predict physicochemical properties, optimize self-assembly parameters, and accelerate material discovery with minimal experimental effort.

For instance, quantitative structure–activity relationship (QSAR) models and neural networks have been successfully employed to predict particle size and surface charge of polymeric nanocomposites based on descriptors such as hydrophobicity, molecular weight, and polymer ratio. In one study, a random forest model achieved an R^2 value of 0.93 for predicting nanoparticle diameter and polydispersity using less than 200 training samples, dramatically reducing experimental workload.[242] Similarly, deep neural networks trained on molecular dynamics (MD) simulation data have been used to estimate self-assembly energies (ΔE_sa) with mean absolute errors below 0.15 kcal mol^{-1}, enabling rapid screening of amphiphilic block copolymers.[243]

AI-driven optimization has also been applied to formulation design. For example, gradient boosting regression models have identified optimal solvent compositions and stirring speeds for lipid-based SANC synthesis, predicting particle sizes within ±10 nm error margins compared to experimental results.[244] Furthermore, generative adversarial networks (GANs) have been utilized to design novel inorganic–organic nanostructures with desired stability profiles by learning structural features from large-scale databases.[245]

Beyond prediction, AI has been integrated with molecular simulation pipelines for energy landscape exploration. Reinforcement learning frameworks have demonstrated the ability to autonomously explore self-assembly pathways, minimizing the total free energy (ΔG_total) by adaptively tuning temperature, solvent polarity, and molecular orientation.[246] These approaches provide a quantitative and automated route for optimizing the self-assembly process of complex SANC systems, bridging computational chemistry and materials informatics.

Together, these studies show that machine-learning-guided design is transforming the development of SANCs—from manual trial-and-error to data-driven prediction and optimization. Incorporating these AI methodologies can significantly accelerate discovery, improve reproducibility, and reveal hidden correlations between chemical structure and assembly behavior, making AI an indispensable tool in next-generation nanocomposite engineering.

Before credible translational impact can be achieved, a number of related obstacles must be addressed in quantitative AI/ML advancements for SANC design: first, only a few high-quality, interoperable datasets exist for nanoscale systems. Bulk-focused repositories cannot capture the proper size and surface dependence of nanomaterials, making curated standardized data and metadata highly important for model transferability.[247] Second, unless strict reporting standards and validation protocols are implemented, methodological flaws in machine learning workflows-including data leakage, inconsistent split/metric reporting, and limited reproducibility of training environments-lead to overly optimistic claims.[248] Many high-performance models are also computationally costly and inaccessible; interpretable or physics-informed machine learning and hybrid experiment-simulation loops can reduce the amount of required data and increase mechanistic trust.[247,249]

Finally, there is multifunctional SANCs, which incorporates imaging, therapy, and responsive release, which produce highly complex diseases such as cancer and neurodegeneration. As one example, SANCs incorporating MRI contrast, pH-responsive release, and photothermal therapy have shown distinct, and synergistic, efficacy in animal models [4]. These advances portend a new future where SANCs are not just a method of delivery, but as disease-specific and smart theranostic vehicles.[250] Table 5 consolidates key stimuli-responsive SANC platforms discussed in this section, outlining how their triggering mechanisms, release behaviors, and application domains enable next-generation therapeutic and theranostic functions. The table offers a framework for identifying which nanocomposites are best suited for different drug-delivery strategies anticipated in SANC development.

14. Conclusion

SANCs represent a novel class of drug carriers with the unique ability to enable precise, controlled, and active release of therapeutics. By addressing challenges such as improved drug stability, reduced systemic toxicity, and enhanced bioavailability, these nanocomposites contribute to overcoming limitations in current systems. With the capacity to respond to a variety of biological stimuli, SANCs hold enormous potential for treating complex diseases like cancer, infectious diseases, and chronic inflammation. However, alongside these promising advantages, challenges persist in production scalability, storage stability, and obtaining regulatory approval. Overcoming these challenges will undoubtedly drive advancements in materials science, nanotechnology, and possibly leverage the power of AI to propel SANC-based therapies forward. The integration of

functionally intelligent, adaptive SANCs with personalized medicine could potentially revolutionize modern therapeutic medicine by enhancing treatment safety, efficacy, specificity, and personalization across various therapeutic domains.

Finally, this review has shown various uses, mechanisms, and design methods of SANCs in drug delivery. The explanation of various stimuli-responsive behaviors, elaborate mechanisms of interactions, and the advantages of SANCs compared to traditional systems are some of the major inputs. This work is innovatively put together with sophisticated combination of molecular design concepts with newly emerging control of stimulation triggered launches and material formulation specifications. Future studies are expected to focus on establishing AI bound SANC platforms capable of predictive performance modeling, creating SANCs that are multi-responsive in the case of complex diseases, preparing production on a large-scale with regulatory compliance and sustainability. Besides, searching clinical translation routes and testing long-term safety will play a pivotal role in the broader use of SANCs in precision medicine.

Author contributions

R. E.: conceptualization and study design. Z. A.: literature search and drafting the manuscript. F. M. M.: data collection, analysis, and visualization. S. R.: reviewing and critical evaluation of sources. M. Z. M.: writing, reviewing, and editing. S. A.: manuscript revision and quality control. W. C. C.: critical feedback and final approval of the manuscript. J. H. P.: literature search, data collection, and visualization. A. V.: literature search, data collection, and analysis. M. R. F.: supervision and overall guidance. S.-K. H.: literature search, data collection, analysis, supervision. Y. S. H.: corresponding authors, supervision, responsible for communication with the journal.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Abbreviation

AuNPs	Gold nanoparticles
DOX	Doxorubicin
GSH	Glutathione
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSN	Mesoporous silica nanoparticle
NIR	Near-infrared
NP	Nanoparticle
NSC	Neural stem cell
PCL	Polycaprolactone
PCL-CS	Chitosan/polycaprolactam
PDT	Photodynamic therapy
PEC	Polyelectrolyte complex
PEG	Polyethylene glycol
PLGA	Poly(lactic-co-glycolic acid)
PTT	Photothermal therapy
PTX	Paclitaxel
RME	Receptor-mediated endocytosis
ROS	Reactive oxygen species
SANCs	Self-assembling nanocomposites
SANPs	Self-assembling nanoparticles
siRNA	Small interfering RNA
SNEDDS	Self-nanoemulsifying drug delivery system
TDN	Tetrahedral DNA nanostructure

Data availability

Data will be made available in a repository on acceptance.

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