SRI VENKATESWARA INTERNSHIP PROGRAM FOR RESEARCH IN ACADEMICS (SRI-VIPRA)

SRI-VIPRA

Project Report of 2023: SVP-2325

"Recent Developments in Supramolecular Nanostructure-based Drug Delivery Systems"

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SRIVIPRA PROJECT 2023

Title : Recent Developments in Supramolecular Nanostructure-based Drug Delivery System

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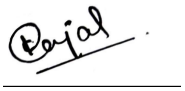
1		Kajal	1521116	B.Sc. (Hons.) Chemistry, Semester 5	
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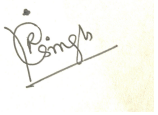
3		Ria Singh	1521062	B.Sc. (Hons.) Chemistry, Semester 5	
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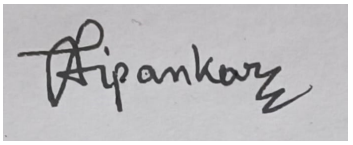
6		Dipankar Bagchi	1521023	B.Sc. (Hons.) Chemistry, Semester 5	
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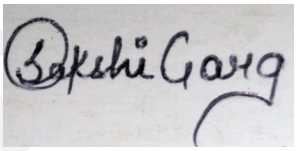
8.		Sakshi Garg	1521074	B.Sc. (Hons.) Chemistry, Semester 5	

Signature of Mentor

Certificate of Originality

This is to certify that the aforementioned students from Sri Venkateswara College have participated in the summer project SVP-2325 titled "**Recent Developments in Supramolecular Nanostructure-based Drug Delivery System**". The participants have carried out the research project work under my guidance and supervision from 15 June, 2023 to 15th September 2023. The work carried out is original and carried out in an online/offline/hybrid mode.

Signature of Mentor

Acknowledgements

We would like to express our heartfelt gratitude to the Sri Venkateswara College; our principal Prof. C Sheela Reddy and our project mentor and coordinator Dr. Shefali Shukla for giving us this golden opportunity to work on this wonderful research project on – **"Recent developments in supramolecular nanostructure- based drug delivery system."** Ma'am has been our guiding light throughout the completion of the project. Working on this project has enriched all of us with a great deal of information about the importance of nano-drug delivery systems in the medical field and is surely going to help us in the future.

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- **Objectives**

The main objective of this project is to give students practise at developing their research skills, scientific aptitude, and knowledge about supramolecular organic nanostructures in the diagnosis and treatment of various diseases with the concept of a drug delivery system.

- **Introduction**

Supramolecular complexes are formed by non-covalent interactions between two chemical moieties, which can be described as a host and a guest. Most commonly, the interacting species are held together by hydrogen bonds. The definition excludes compounds formed by electrostatic interactions, which are called ion pairs. Supramolecular chemistry may be divided into Host-Guest Recognition and Self-Assembly.

One of the most important aspects of a drug delivery system is to deliver the drug to the targeted site. In order to drop the drug to a specific site of disease lesion, a convenient, suitable drug or efficient drug delivery system is required. Supramolecular metal-based nanoparticles (SMNPs) have been coated with silica, lipid layers, nucleic acids, and others via electrostatic force driven self-assembly, hydrophobic-hydrophobic interactions, or coordination with metals in order to improve their drug delivery efficiency. Research in SMNPs drug delivery has garnered much attention in the past few decades for fabrication and development of drug-loaded nanocarriers for applications in different diseases

Ideal prerequisites of a drug delivery system are to deliver the drugs at a rate supporting the body needs and their transport directly to the target organ where it could achieve an efficient to exert its effects. As conventional drug delivery systems don't meet these demands, the need for SMNPs drug delivery systems arises as they can achieve sustained or controlled release profiles. This decreases the concentration of the active dose ultimately reducing the side-effects of the drugs . Specific targeting can also be achieved by employing carriers attached with special protein molecules or by functionalization.

Overall , recent advancements in this area offer options that are both accurate and effective for medication delivery, creating new opportunities for treating a variety of diseases with the least amount of side effects.

- **Synthesis And Characterization**

Supramolecular drug delivery systems are constructed by non-covalent interactions. These interactions can be reversible and can cause the system to respond to external stimuli. This allows for the design of smart nano-drug carriers. Researchers have developed various types of supramolecular nanostructures.

These nanostructures are assembled using reversible non-covalent interactions. The host molecules used to synthesize these systems include: Calixarenes, Cucurbiturils, Cyclodextrins, Pillararenes. There are many types of supramolecular nanostructures that can be used for drug delivery systems, such as liposomes, micelles, dendrimers, nanotubes, nanocrystals, quantum dots, etc. These nanostructures can form self-assembled systems that

can encapsulate, transport and release drugs in a controlled and targeted manner. Some of the recently discovered types of supramolecular nanostructures-based drug delivery systems are:

- **Carrier-free nanodrugs:** These are self-assembled nanoscale drug delivery systems that do not require any additional carriers or excipients. They are formed by the covalent or non-covalent interactions between drugs or drug conjugates. They can improve the solubility, stability, bioavailability and efficacy of drugs.

- **Peptide-based self-assembled delivery systems:** These are self-assembled nanostructures that are composed of peptides or peptide derivatives. They can form various shapes and sizes, such as nanofibers, nanotubes, nanospheres, etc. They can be used to deliver drugs, genes, proteins and other biomolecules.

- **Metal-polyphenol self-assembly:** This is a self-assembly process that involves the coordination between metal ions and polyphenols. Polyphenols are natural compounds that have antioxidant and anti-inflammatory properties. They can form stable and biocompatible nanostructures with metal ions, such as iron, copper, zinc, etc. These nanostructures can be used to deliver drugs, imaging agents and theragnostic agents.

- **Natural small-molecule self-assembled nanodrug delivery systems**: These are self-assembled nanostructures that are derived from natural small molecules, such as curcumin, resveratrol, quercetin, etc. These molecules have various biological activities and can form stable and biodegradable nanostructures with different morphologies and functions. They can be used to deliver drugs for the treatment of various diseases.

Method of Synthesis

Carrier-free nanodrugs/Self-Assembled Systems

Most self-delivery nanoscale drug-delivery systems are formed by conjugating a hydrophobic drug with a hydrophilic one. This creates an amphiphilic structure. Supramolecular recognition between engineered DNA strands and nucleoside analogues can also be used to create multifunctional nanoscale delivery systems.

Most commonly reported nanoscale drug delivery systems with self-delivery capabilities are created by directly linking a hydrophobic drug molecule to a hydrophilic one, resulting in the formation of an amphiphilic structure. This approach has gained widespread acceptance and garnered significant praise in the field of drug delivery, as it offers promising prospects. Several preliminary research studies have substantiated the viability of self-delivering drug systems.

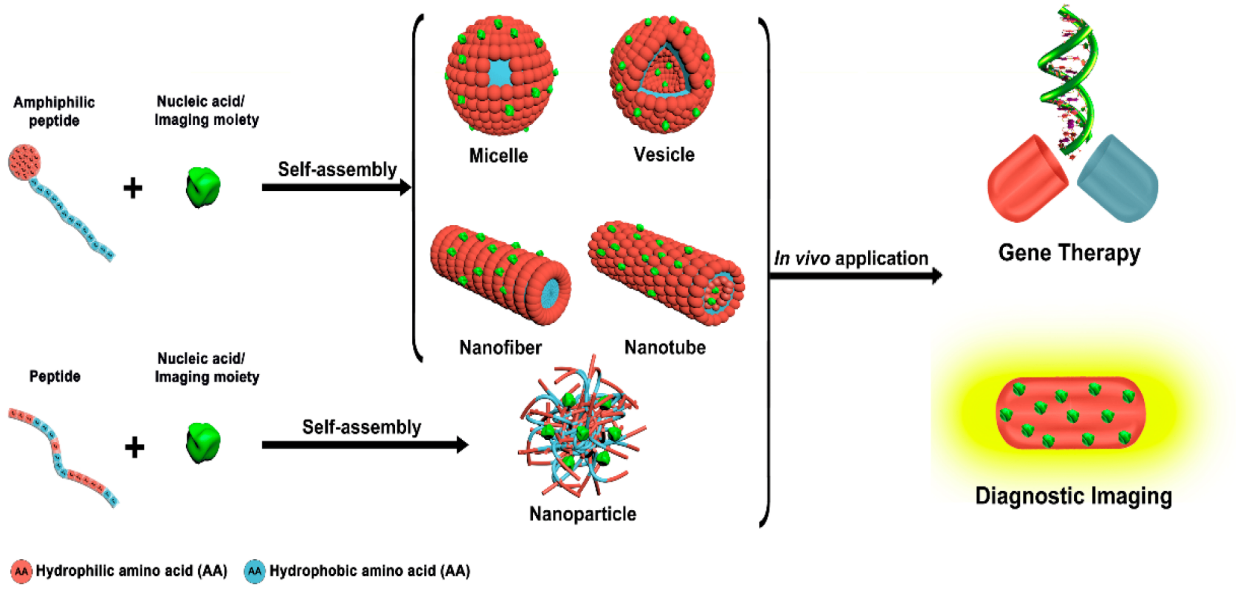
The formation of supramolecular amphiphiles, which have the ability to self-assemble into nanoparticles or nanogels, can be mediated by specific supramolecular interactions like host-guest interactions and multivalent hydrogen bonding. By effectively utilising the

structural properties of these supramolecular amphiphiles, composed of one hydrophobic drug and one hydrophilic therapeutic component, it becomes feasible to develop a self-delivering nano drug delivery system. In cases involving hydrophilic chemotherapy drugs and peptide therapeutics, the hydrophilic portion collaborates with the hydrophobic therapeutics to create nanoscale delivery systems. To achieve well-ordered nano-assembly and ensure therapeutic efficacy, the interactions between these two types of drugs should be clearly defined and specific.

Peptide-based self-assembled delivery systems

Supramolecular Nanodrug delivery systems (SNDDs) based on self-assembling peptides, composed of naturally occurring amino acids, not only offer the benefits of traditional nanomedicine but also exhibit unique characteristics such as exceptional biocompatibility, biodegradability, adaptable responsiveness, specific biological functions, and ease of synthesis.

These versatile peptide-based SNDDs can be created through physical methods, enzymatic reactions, chemical processes, and biosurface induction, with their adaptability being a primary advantage. Through the incorporation of various functional peptides and numerous covalent modifications, these systems gain precise control and multifunctionality. Capitalizing on these advantages, researchers have harnessed self-assembling peptide-based SNDDs to achieve precise drug delivery to the target site.



Metal-polyphenol self-assembly

Metal-polyphenol self-assembly represents a pivotal supramolecular phenomenon characterized by the spontaneous formation of stable nanostructures or complexes through the interaction between metal ions and polyphenolic compounds. This assembly process hinges

on coordination bonds that arise from the interaction between metal ions (e.g., iron, copper, or silver) and the polyphenolic moieties intrinsic to compounds such as tannic acid or catechins. The outcome of this self-assembly, including the size, morphology, and physicochemical properties of the resultant structures, can be influenced by both the choice of metal ion and the specific polyphenolic compound employed.

The applicability of metal-polyphenol self-assemblies extends to various domains, with notable implications in drug delivery systems. This stems from their inherent biocompatibility and capacity to entrap therapeutic agents within their architectures. These assemblies serve as protective matrices, shielding drugs from premature degradation, ameliorating solubility concerns, and enabling controlled and targeted drug release. Beyond pharmaceutical applications, metal-polyphenol self-assembly has found utility in the design of nanocarriers, functional coatings, and advanced materials, thus underscoring their significance in diverse scientific and technological realms.

Similar to many layer-by-layer self-assembly technologies, Metal-Polyphenol Nanocomposites (MPNs) exhibit a flexible structural nature that allows them to manifest in diverse forms. Their functionality is remarkably adaptable, contingent upon the specific polyphenolic compounds and metal ions integrated into their composition. For instance, employing the layer-by-layer assembly method, MPN films, exemplified by Fe3+-Tannic acid films, have been successfully synthesized. This technique enables precise control over the thickness and morphology of MPN films in both two-dimensional (2D) and three-dimensional (3D) configurations.

Polyphenols, as fundamental constituents, serve as building blocks within MPNs, showcasing an inherent capability to assemble into a wide array of superstructures, a feature amenable to manipulation by surface functionalization. It is essential to note that the ratio of catechol (C) to galloyl (G) moieties within the polyphenolic structure governs their binding affinity towards metal oxides, metal ions, or even polymeric surfaces.

Natural small-molecule self-assembled nanodrug delivery systems

Natural small-molecule self-assembled nanodrug delivery systems represent a cutting-edge development in drug delivery science. This approach harnesses the intrinsic self-assembly properties of natural small molecules to fabricate nanoscale drug carriers with remarkable precision. These natural small molecules, often sourced from biological materials, possess unique physicochemical properties that enable the formation of stable, controlled, and biocompatible nanostructures for drug encapsulation and targeted delivery. The synthesis of these nanodrug delivery systems typically involves the careful selection and modification of natural molecules such as lipids, peptides, or polysaccharides.

These molecules are chosen for their biocompatibility and biodegradability, ensuring minimal adverse effects upon administration. Through judicious design and chemical modification,

these small molecules are tailored to self-assemble into nanoscale carriers, which can encapsulate a wide range of therapeutic agents, including hydrophobic and hydrophilic drugs.

During the synthesis process, these natural small molecules are often engineered to exhibit site-specific drug release behaviour, enabling precise targeting of therapeutic payloads to the intended tissue or cell types. Furthermore, the stability of these self-assembled nanodrug delivery systems ensures protection against premature drug degradation, prolonging drug circulation time in the body. This approach, with its emphasis on utilizing natural small molecules and their inherent self-assembly capabilities, holds great promise in enhancing drug efficacy, and minimizing unwanted side effects in the realm of medical therapeutics.

Characterization Techniques

Characterization techniques hold paramount importance in makingthe structural and functional attributes of supramolecular nanostructure-based drug delivery systems. These intricate systems, engineered to enhance drug solubility, stability, and targeted delivery, necessitate rigorous analysis to unravel their inherent complexities. The following sophisticated characterization methodologies are usually used:

Transmission Electron Microscopy (TEM): TEM is a pivotal technique facilitating the high-resolution visualization of nanostructures within SNDDS. It offers insights into the precise dimensions, morphology, and structural integrity of supramolecular assemblies, thereby validating their existence.

Scanning Electron Microscopy (SEM): SEM complements the assessment of nanostructure surface properties and topography, thereby affording a comprehensive understanding of their structural features.

Atomic Force Microscopy (AFM): AFM, by employing a sharp tip to scan the sample's surface, delivers nanoscale surface imaging capabilities, permitting characterization of height, roughness, and mechanical properties of the nanostructures.

Dynamic Light Scattering (DLS): DLS assumes a critical role in ascertaining the hydrodynamic size and size distribution of nanoparticles within SNDDS, thereby facilitating an appraisal of colloidal stability and aggregation tendencies.

Zeta Potential Analysis: Determining the electrostatic charge at nanoparticle surfaces, zeta potential analysis provides valuable insights into the colloidal stability and the propensity for aggregation or flocculation of nanostructures within SNDDS.

X-ray Diffraction (XRD): XRD serves as an indispensable tool for the evaluation of the crystallinity and crystallographic features of supramolecular nanostructures, enabling the confirmation of specific crystalline phases and their orientation.

Nuclear Magnetic Resonance (NMR) Spectroscopy: Employed for elucidating the molecular structure and dynamic behavior of supramolecular complexes, NMR spectroscopy confirms the formation of host-guest complexes and monitors drug release dynamics.

Fourier-Transform Infrared (FTIR) Spectroscopy: FTIR spectroscopy is instrumental in elucidating the chemical composition and functional moieties within supramolecular nanostructures, shedding light on the intricate intermolecular interactions.

UV-Visible Spectroscopy: This technique facilitates the assessment of absorbance and optical properties within SNDDS, enabling the quantification of drug loading and monitoring of drug release kinetics.

Thermogravimetric Analysis (TGA): TGA, by measuring weight changes with respect to temperature, offers invaluable insights into the thermal stability and decomposition behavior of supramolecular nanostructures.

Differential Scanning Calorimetry (DSC): DSC elucidates heat flow associated with phase transitions and chemical reactions within SNDDS, thereby providing information on their thermal behavior and stability.

Fluorescence Spectroscopy: Fluorescence spectroscopy is a versatile tool for investigating interactions between supramolecular nanostructures and fluorescently tagged drugs. It aids in real-time monitoring of drug release and tracking of drug delivery dynamics, both in vitro and in vivo.

In vitro Drug Release Studies: These investigations involve the meticulous monitoring of drug release profiles from supramolecular nanostructures under controlled conditions, encompassing variations in pH, temperature, and the presence of specific enzymes.

In vivo Imaging: Utilizing techniques such as positron emission tomography (PET), magnetic resonance imaging (MRI), or fluorescence imaging, in vivo imaging enables the tracking of drug distribution and release from supramolecular nanostructures within living organisms.

The judicious integration of these advanced characterization methodologies empowers researchers to garner a comprehensive and in-depth comprehension of the physical, chemical, and biological attributes of supramolecular nanostructure-based drug delivery systems, thereby facilitating their refinement for therapeutic applications.

- **Applications of Supramolecular Nanostructure-based Drug Delivery Systems (SNDDS)**

DDS generated from Supramolecular Nanostructures are capable of being an effective alternative to small molecular chemotherapeutics due to the improved accumulation in tumour site and enhanced retention in blood. Nevertheless, most DDSs have low loading efficiency or even pose a high threat to normal organs caused by severe side effects. Ideally, supramolecular drug-drug delivery system (SDDDS) made up of pure drugs via supramolecular interaction finds application for treatment of one of the major causes of worldwide fatality, commonly termed as cancer. Cancer is the leading cause of death worldwide with one in six people facing death due to cancer. Cancer is defined by accumulation of genetic differentiations that gradually convert a normal living cell to its malignant form. A malignant cell depicts traits such as angiogenesis, insensitivity to growth suppressive signals and resistance to apoptotic cell death. Also, malignant cancer cells possess the ability to develop growth autonomy via modulation of their own growth receptors and forced activation of intracellular growth signalling pathways.

Supramolecular Nanostructures are one of the most widely used DDS in chemotherapy to prevent cancer angiogenesis or even cause cellular apoptosis in cancer cells. Chemicals also known as chemotherapeutic agents are tested both in-vivo and in-vitro for their ability to activate selective cell death mechanisms in cancer cells and simultaneously prevent cell-repair mechanism by blocking growth receptors and through other methods. These DDS are capable of acting as as main force between drugs and carriers, where non-covalent and specific affinity will governed the drug loading/release behaviour. The ability to adjust the chemical properties of supramolecular metal-based nanoparticles (SMNPs) allows for the inclusion of a wide range of therapeutic substances, such as both water-soluble and water-insoluble chemotherapy drugs, light-sensitive compounds, radiation-enhancing agents, and biological treatments. This enhances their effectiveness in delivering these therapies to tumor sites[18]. An additional functional benefit realizes in the ease of stimuli-responsive drug release. A large variety of therapeutics can be used as supramolecular building blocks, Most chemo-drugs owned incorporate planar aromatic structure, such as CPT, PTX and so on; a large number of protein therapeutics show specific binding affinity to certain ligands; and other drugs belongs to cytotoxic nucleoside analogues, such as floxuridine. All these structures offer strong affinities to govern a reliable supramolecular drug loading procedure.**[1]**

SNDDS facilitates Chemotherapy for non-small cell lung cancer (NSCLC)

Zhihao Zhang proposed a simple technique for creating SDDDS by combining two types of chemotherapeutic drugs for non-small cell lung cancer (NSCLC), gefitinib (GEF) and tripeptide tyroservatide (YSV), through a variety of intermolecular interactions, including hydrogen bonding and -stacking. GEF and YSV self-assemble into nanoparticles with regular morphology and uniform size which is evident through the characterization techniques such as transmission electron microscope (TEM) and dynamic light scattering (DLS). This self-assembly process enhances the distribution of both medications. When compared to a single GEF, YSV, or GEF/YSV medication combination, in vitro tests show that the SNDDS is significantly more effective at penetrating cancer cells and preventing the proliferation of cancer cells. In vivo tests reveal that the SNDDS can concentrate specifically in tumour tissue, improving treatment efficacy significantly without overt side effects. Thinking about the.advantages of the SNDDS, it is concluded that this strategy provides a promising

route for enhanced anticancer therapy in nanomedicine, with SNDDS acting as flexible carriers for a variety of drug**[3]**

Supramolecular science encompasses a wide-ranging and interdisciplinary area of study that focuses on the non-covalent interactions among molecular components and the creation of molecular structures. Researchers in this field are primarily interested in organised and precisely defined structures formed by these molecular assemblies. These assemblies are often colloidal in nature and are composed of the very building blocks from which they are constructed, making them particularly intriguing to scientists working in the realm of supramolecular chemistry[19]]

Moreover, further applications of SNDDS have been discussed below in the table:

Table: Colloidal systems under development, in clinical trials or on the market

Formulation	Drug	Product	Application	Status
PEGylated liposome	Doxorubicin	Doxil	Ovarian and multiple myeloma	Phase I-II
			Acute Myeloid Leukaemia	Phase II
			Relapsed or Refractory Cutaneous T-cell Lymphoma	Phase I
			Breast cancer	Phase I
Liposomes		Thermodox	Primary liver	Phase III
			Breast cancer	Phase I-II
			Liver metastases	Phase I
Polymeric micelles (PEG-poly(aspartic acid) block copolymer		NK911	Solid tumours in mice	Phase I
			Advanced breast, advanced non-small lung and advanced pancreatic cancers	On the market
Albumin nanoparticles	Paclitaxel	Abraxane	Multiple Myeloma	Phase I-II
			Metastatic pancreatic cancer	Phase II
			Metastatic Melanoma	Phase II
			Coloured and small Bowel Adenocarcinoma)mas	Phase II
			Recurrent and Refractory Lymphoma	Phase I-II
Polymeric micelles (poly(ethylene glycol)-poly(D,L-lactide)copolymer)Cetyl alcohol/polysorbate nanoparticles		Genexol-PM	Non-small lung and breast cancer	On the market
			Advanced malignancies	Phase I
			Advanced breast cancer	Phase II
			Locally Advanced Head and Neck Cancer	Phase II

			Brain tumours: U-118, HCT-15 cells	Under development
PEGAuNPs	Human tumour necrosis factor alpha, TNF	Aurimune (CYT-6091)	Advanced Solid Tumours	Phase I
Liposomes	Uridine		Metastatic solid tumour	Phase I
Polymeric micelles	Cisplatin	NC-6004	Advanced and Metastatic Pancreatic Cancer	Phase I-II
			Solid cancer, Pancreatic and non-small lung cancers	Under development
Polymeric nanoparticles	Docetaxel	Docetaxel[1]PN	Advanced solid malignancies	Phase I
Liposomes	Amphotericin B	AmBisome	Fungal infections	On the market
			Acute Leukaemia	Phase II
			Visceral leishmaniasis in HIV coinfected Ethiopian patients	Phase III
			Advanced HIV infections	Phase I-II
nanocrystals	paclitaxel and camptothecin		Human lung cancer and murine breast cancer	Under development
	1 platinum anticancer drugs		Human cervical cancer and the human hepatocarcinoma HepG2 cells	
	paclitaxel		Development of Multifunctional Hybrid Nanocrystals for Cancer Therapy and Diagnosis	
nanoparticles	FUS1	FUS1-nanoparticles	Lung cancer	Phase IV
Liposomes	P53 gene	SGT-53	Solid tumours	Phase I
	Daunorubicin	Daunoxome	Kaposi's sarcoma	On the market
			Myeloid Leukaemia	Phase II

Apart from cancer, a recent therapeutic outcome towards treatment of gout has been developed using SNDDS :

Enzymes mediate Host Guest Interaction for Developing Multi Enzyme based SNDDS for Gout Treatment

A typical guest drug has highly hydrophobic structure, which acts as proton-donating agent to form multiple hydrogen bonds with proton-accepting structure of the host molecules Such supramolecular complexation realizes in molecular-level protection from drug degradation or deactivation. Host–guest interaction with high association constant provides many opportunities for hydrophobic drug loading. Enzymes are raising stars in disease treatment as they have clear mechanism and high therapeutic

effect. As a macromolecule with sophisticated structure, the delivery of enzymatic therapeutics is always of great difficulties. Moreover, two or more enzymes might be in need for cooperation in order to treat a symptom for most diseases [93,94]. Liu and coworkers utilized host–guest affinity to integrate uricase (UOx) and catalase (Cat) dynamically, resulting in a feasible and effective serum uric acid (sUA) control therapy with low systematic toxicity In their study, CD and adamantine (Ad) work as host–guest pair and were conjugated to UOx and Cat through a PEG linker, respectively and facile platform for multi-enzyme therapeutic systems. **[4]**

SMNPs with synergistic functional modalities: Co-delivery of chemotherapeutic agent

Duan and colleagues (Duan et al., 53) devised a novel approach using core-shell OxPt/DHA NCPs, which contained oxaliplatin in the core and dihydroartemisinin (DHA) in the outer layer. Their research demonstrated that OxPt/DHA had a synergistic effect in prompting immunogenic cell death and bolstering the effectiveness of tumor treatment in subcutaneous mouse tumor models. The released DHA led to the generation of reactive oxygen species (ROS) within tumor cells, resulting in the exposure of calreticulin (CRT) and the release of damage-associated molecular patterns (DAMPs). This, in turn, facilitated the recruitment of antigen-presenting cells (APCs). When combined with anti-PD-L1 therapy, OxPt/DHA successfully eliminated CT26 colon tumors and established long-lasting anti-tumor immunity that persisted for more than three months. [18[

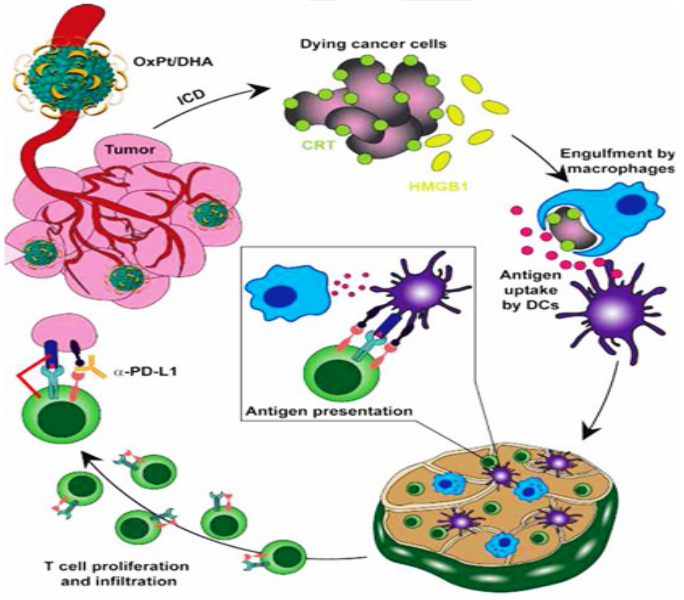


Figure: Diagram illustrating the boosted immunogenic cell death triggered by OxPt/DHA and its cooperative effect with an anti-PD-L1 antibody.

- **Conclusion and Future Scope**

In the field of biomedicine, due to the rapid advancement of nanotechnology, small-scale assemblies, particularly supramolecular nanostructures, have been skillfully designed and

employed as highly prospective carriers for delivering drugs. It offers creative solutions for biological tasks like drug and gene delivery due to controlled drug-delivery systems characterised by dynamic drug-release properties that are predictable, precise, and minimally impact off-target areas. With significant advancements in designing nano-carriers and sophisticated drug-loading techniques driven by supramolecular interactions, the nanoscale drug-delivery approach has now transitioned into a self-delivery era. Within the realm of supramolecular chemistry, large cyclic molecules like calixarenes, cyclodextrins, cucurbiturils, and pillar arenes stand out as excellent hosts, capable of binding guest molecules depending on their electron density and cavity size. However, when compared to conjugated drug-delivery systems, the bio-stability of supramolecular systems and early burst release and effective transition of SDDS from lab to clinical application is still a clinical concern. Therefore, there is a need for increased efforts to enhance the biocompatibility, stability within the body, and targeting efficiency of supramolecular nanoparticles. Additionally, a thorough assessment of their distribution in the body, potential long-term toxicity, and circulation characteristics is also essential. [2,16]

In this report we have summarised various supramolecular nanoparticle based drug delivery including BODIPY-functionalized quaternary ammonium derivative known as G9 which serves a dual purpose as a photosensitizer and as a guest molecule, forming a supramolecular amphiphile in combination with WP5 through host-guest interactions and can self-assemble into supramolecular vesicles which demonstrate a high capacity to encapsulate the chemotherapy drug DOX efficiently. [17] AuNP incorporation into polysaccharide-based matrix, metal based nanoparticles and polymeric nanoparticles[2]

Over the next few years, it is anticipated that there will be a growing interest in utilising noncovalent host-guest interactions to create engineered supramolecular nanostructures, with a specific focus on their potential in the field of biomedical applications, especially in drug delivery.[17]

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