Smart Nanobiotechnological Platforms for Gene and Drug Delivery: From Biopolymers to Pharmaceutical Applications

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Smart nanobiotechnological platforms have become a solace of revolution in conquering the challenges linked to the traditional drug and gene delivery system. The platforms allow targeted, stimuli-responsive, and precise delivery of therapeutic agents by incorporating the benefits of nanotechnology, biotechnology, and pharmaceutical sciences. The biocompatibility, biodegradability and versatility of biopolymers have been vital in designing smart nanocarriers since the biopolymers can be used to efficiently encapsulate drugs and genetic materials and release them on demand. The given review will be a complete overview of the application of smart nanobiotechnological platforms in gene and drug delivery with a particular emphasis on the key principles of the design, nanocarrier biopolymers, and stimuli responsiveness. They are particularly stressed in relation to their use in gene therapy, cancer therapy, neurology, and infectious diseases. The review further talks of pharmacokinetic and pharmacodynamic factors, safety and toxicity issues, and regulatory issues that arise with nanobiomaterials. The latest developments, such as the AI-assisted nanocarrier design and individualized nanomedicine are also discussed. In general, this review highlights the promise of smart nanobiotechnological platforms, which can transform the concept of delivering therapeutic interventions and speed up the process of translating nanomedicine into clinical care.

Keywords: Biopolymer-based nanocarriers; Gene delivery; Nanomedicine; Pharmaceutical applications; Smart nanobiotechnology; Stimuli-responsive systems; Targeted drug delivery.

Evolution of Nanobiotechnology in Drug and Gene Delivery

The ever-growing development of pharmaceutical sciences has resulted in the investigation of new methods to enhance the therapeutic effectiveness and security of drugs and genetic materials. Nanobiotechnology as an interdisciplinary field, which brings together

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nanotechnology, biotechnology, and medicine has attracted a lot of attention due to its capacity to develop delivery systems at the nanoscale. The initial nanocarrier systems were developed mainly to increase the solubility and stability of drugs, but the swift developments in materials science and molecular biology have changed the systems into multifunctional systems and able to interact with biological systems precisely.[1] The design of nanocarriers was also more revolutionized by the introduction of the biopolymers and bio-inspired materials making them biocompatible and biodegradable. Within the framework of gene delivery, nanobiotechnological solutions have also offered non-viral-based alternatives that can prevent the degradation of nucleic acids as well as enable them to be readily taken up by the cells. Together, these advances have established nanobiotechnology as a platform technology within the current drug and gene delivery studies.

Limitations of Conventional Drug and Gene Delivery Systems

The traditional drug delivery methods such as oral, parenteral and topical formulations usually do not produce optimum therapeutic effects because of the inherent physicochemical and biological limitations. A significant proportion of therapeutic agents have low aqueous solubility, low permeability, and rapid systemic clearance as well as nonspecific biodistribution, which hinder their clinical efficacy.[2] Moreover, traditional formulations are unable to sustain therapeutic drug concentrations in the target site throughout prolonged durations, and thus in most circumstances, require regular dosing and enhancing the chances of adverse outcomes. As an even bigger problem, gene delivery is prone to biodegradation of the nucleic acid, cellular uptake, endosomal escape, and immunogenicity. Viral vectors, despite their efficiency, are associated with serious concerns on safety such as insertional mutagenesis and immunogenicity.[3] These shortcomings demonstrate the necessity of intricate delivery approaches that have the ability to offer security, aiming, and directed launch of therapeutic cargoes.

Rationale for Smart Nanobiotechnological Platforms

To address the deficiencies of traditional delivery systems, smart nanobiotechnological platforms have been engineered in a bid to imbue nanocarriers with responsiveness, flexibility and multifunctionality. Such platforms use biopolymer-based materials which can be programmed to detect a particular physiological or pathological signal, e.g. acidic tumor microenvironment, enzyme expression, redox gradients or outside-in stimuli such as light and magnetic fields. The smart nanocarriers can be used to deliver therapeutic agents in a site-specific manner with controlled release using these stimuli.[4] Also, surface modification using targeting ligands, antibodies or peptides can be used to increase selective uptake by diseased cells at minimal levels of off-target exposure. Smart nanobiotechnological platforms, in particular, their capacity to aid intracellular delivery, enhance release kinetics, and enhance co-delivery of drugs and genes, are especially important in the treatment of complex and chronic diseases.

Scope and Objectives of the Review

The purpose of the review is to present a systematic review of the state of smart nanobiotechnological platforms relating to drug and gene delivery, where the main emphasis is placed on biopolymer-based nanocarriers and their pharmaceutical application. It describes relevant design factors, typology of nanocarrier, and principles of stimuli-responsive behavior. The review also discusses how they are used in various fields of treatment, such as cancer, neurological, infectious diseases, and gene therapy.[5] Besides, there are critical problems concerning pharmacokinetics and pharmacodynamics, safety, toxicity and regulatory issues. This review aims to serve as a reference to all researchers and clinical practitioners in the recent past, as well as to point out the future directions of successful clinical translation of smart nanobiotechnological delivery systems.

Fundamentals of Smart Nanobiotechnological Platforms

Smart nanobiotechnological platforms constitute superior delivery systems that are designed to communicate intelligently with biologic surroundings. These systems combine nano-engineering and biological performance to address the drawbacks of traditional administration of therapeutic delivery. Their architecture allows them to gain close control over drug and gene delivery, release as well as targeting, enhancing

the therapeutic effects and reducing systemic toxicity.[6] Smart nanocarrier technology is based on the integration of biopolymers, stimuli-responsive devices, and targeting.

Concept of "Smart" Nanocarriers

Smart nanocarrier is characterized by the fact that it reacts or responds to certain physiological or pathological stimuli and changes its behavior. This is because this stimulus responsiveness ensures that the nanocarriers will be stable in the systemic circulation and only activate on reaching the target site. Some of the common internal stimuli are pH, enzymatic activity, redox potential, and reactive oxygen species, which are typical of diseased microenvironments like tumors, and inflamed tissues. Drug release and spatial localization can also be controlled using external stimuli like changes in temperatures, light exposure, ultrasound and magnetic fields.[7-10] Other than stimuli responsiveness, smart nanocarriers make use of the passive and active targeting strategies. Passive targeting capitalizes on the physiological distortions, including the preferential accumulation of nanocarriers, which are in the disease location using physiological characteristics of the disease tissue, including the enhanced permeability and retention effect. Active targeting entails the surface alteration using ligands that specifically bind the overexpressed cellular receptors, which increases cellular ingestion and delivery inside the cell. A combination of these properties gives smart nanocarriers adaptive behavior to enhance precision of therapeutic efficacy and safety.[11]

Design Principles of Nanobiotechnological Systems

Physicochemical design parameters and biological design parameters are highly determinant in the performance of the nanobiotechnological systems. Particle size is an important factor in the circulation time, tissue penetration, and cellular internalization and nanoscale dimensions are associated with better biodistribution and lesser clearance by the kidney. Surface charge has implications on the interaction with biological membranes, serum proteins and immune components hence affecting stability and clearance processes. Particle shape is also a factor that has been appreciated because non-spherical nanocarriers can have different flow characteristics and cellular uptake patterns.[12-13] To preserve structural integrity and avoid premature release of drugs in physiological conditions, stability is required. Biocompatibility and bio-degradability are also of great significance as they guarantee low toxicity and harmless excretion of the body once the therapy is done. The use of biopolymer-based nanocarriers will be of special benefit because, despite breaking down into non-toxic metabolites, they preserve functional performance.[14] These design principles are vital to the optimization of efficiency of delivery, compliance of regulations and effective clinical translation of smart nanobiotechnological platforms.

Role of Biopolymers in Smart Nanocarrier Design

Smart nanocarrier systems are built around biopolymers because they possess properties of inherent biocompatibility, bio degradability, and chemical versatility. Their molecular level of control enables them to be precisely regulated in terms of drug loading, drug release, and biological interactions. Natural and synthetic biopolymers have been widely studied in smart nanobiotechnological platforms to maximize the therapeutic activity and reduce toxicity. Moreover, nanocarriers, composed of bioplastics, can be surface engineered to allow enhanced targeting, greater circulation, and decreased immune targeting, which makes them extremely appropriate in improved drug and gene delivery applications.[15-20]

Natural Biopolymers

Natural biopolymers, including chitosan, alginate, gelatin, dextran, and hyaluronic acid have recently received significant interest in the design of smart nanocarriers because of their biological source and positive safety records. The use of chitosan in gene and drug delivery is common because of its cationic property that contributes to the electrostatic interaction with negatively charged cell membranes and nucleic acids, thereby leading to an increase in cell intake. The advantages of Alginate and gelatin are their weak gelation and pH-dependent behaviour, which enables the targeted and stimulus-dependent release of drugs. Dextran is a water soluble and chemically modifiable polymer and thus useful in targeted and sustained delivery system.[21-23] Hyaluronic acid plays a significant part in active targeting especially since it binds specifically to CD44 and other receptors

that may be over expressed in tumor cells and in inflammatory cells. Natural biopolymers allow the creation of smart nanocarriers, which are much closer to the biological systems and, therefore, can enhance biocompatibility and therapeutic efficacy.

Synthetic and Semi-Synthetic Biopolymers

Synthetic and semi-synthetic biopolymers offer the ability to exercise more control over molecular weight, composition and rate of degradation and consequently are extremely versatile in smart nanocarrier engineering. One of the best-researched biodegradable polymers is poly(lactic-co-glycolic acid) (PLGA), which is related to its established safety profile and tuneable drug release properties. PEG is widely applied to enhance the hydrophilicity and circulation time through minimizing the adsorption of proteins and immune recognition. Polycaprolactone (PCL) is available with slow rates of degradation and hence can be used in the long-term and sustained delivery.[24] Multicolor systems composed of these materials allow creating multifunctional nanocarriers with greater stability, stimuli responsiveness and targeting. Synthetic and semi-synthetic biopolymers are flexible and, therefore, nanocarriers can be tailored according to the desired therapeutic and clinical needs.

Functionalization and Surface Engineering

The key strategies to improve the application of biopolymer-based smart nanocarriers are functionalization and surface engineering. Ligand conjugation- Ligand conjugation is a method used to target inside the nanocarrier surface with targeting components like antibodies, peptides, folic acid or aptamers, which allow the nanocarriers to specifically bind to disease-specific receptors and enhance cellular uptake. PEGylation is a commonly used surface modification method where the nanocarriers are given stealth properties through the development of a hydrophilic corona that inhibits opsonization and increases systemic circulation. Surface engineering can also be used to enhance stimuli-responsive behavior and intracellular trafficking in addition to enhancing pharmacokinetics.[25-26] Such changes greatly increase the efficacy of targeting, therapeutic accuracy and general clinical potential of smart nanobiotechnological delivery systems.

Types of Smart Nanobiotechnological Delivery Systems

The variety of nanocarriers developed to date by smart nanobiotechnology delivery systems include enhanced therapeutic specificity using controlled release, targeting, and stimuli responsiveness. These systems vary in composition, construction and functional behavior and can be customized to the physicochemical characteristics of drugs or genetic components and the demands of particular disease conditions. The choice of a proper type of nanocarrier is extremely important in defining efficiency of the delivery, safety, and clinical uses.[27-28]

Polymeric Nanoparticles and Nanomicelles

Among the most studied approaches to smart nanocarriers are polymeric nanoparticles and nanomicelles, which have been suggested because of their ability to carry a wide range of therapeutic agent, structural flexibility, and stability. Polymeric nanoparticles are usually made out of biodegradable polymers and these enable diffusion and sustained release of drugs or degradation of the polymer. Nanomicelles are composed of amphiphilic polymers that can self-assemble into nanomicelles; nanomicelles have a hydrophobic core and a hydrophilic shell that allow them to be especially efficient in solubilizing poorly-water-soluble drugs. The two systems are capable of being engineered to react to certain stimuli like pH, temperature, or redox conditions allowing site-selective drug delivery.[29-31] Also, active targeting and increased cellular uptake is possible with surface functionalization, thus polymeric nanoparticles and nanomicelles can be used in drug and gene delivery studies.

Lipid-Based Nanocarriers

Nanocarriers made of lipids are one of the most flexible types of delivery systems, being highly similar to the biological membranes and thus, promoting better biocompatibility and cellular communication. Liposomes describe spherical vesicles which are made of phospholipid bilayers, which may entrap hydrophilic as well as hydrophobic therapeutic molecules. They have the potential to be surface-modified and stimuli-responsive, which has further increased their application in target drug and gene delivery. Solid

lipid nanoparticle provide a better physical stability and release control where drugs are included in a solid lipid matrix, whereas nanostructured lipid carriers use both solid and liquid lipids to increase the drug loading and avoids the expulsion of the drug in conditions of storage.[32] Such lipid-based systems may undergo further functionalization with targeting ligands or stimuli-sensitive components to allow an improvement of the pharmacokinetics, reduced toxicity and enhanced therapeutic efficacy.

Dendrimers and Hybrid Nanocarriers

Dendrimers are monodisperse, highly branched and macromolecules with a specific architecture and a high number of functional groups on the surface. This distinctive framework enables accurate regulation of drugs loading, surface modification and ligand attachment to targets. Dendrimers can be used especially in gene delivery because they can form stable complexes with the nucleic acids and be absorbed by cells. Hybrid nanocarriers are a combination of the advantages of more than one material like polymers and lipids, or organic and inorganic components to produce multifunctional delivery systems. Such systems facilitate the synergetic effects such as the ability to generate greater stability, stimuli responsive systems and dual drug or drug-gene delivery.[33-35] Dendrimers and hybrid nanocarriers are versatile and can be useful in the future in advanced therapeutic applications.

Inorganic and Bio-Inspired Nanoplatforms

The inorganic and bio-inspired nanoplatforms are receiving more and more interest due to their exceptional physicochemical characteristics and multifunctional aspects. Inorganic nanocarriers (e.g. gold nanoparticles, silica nanoparticles, magnetic nanoparticles) have the benefit of being highly structurally stable, having tunable surface characteristics, and being responsive to external stimuli, e.g. light or magnetic fields. Bio-inspired nanoplatforms such as virus-like nanoparticles and biomimetic nanoparticles use nature biological structures to increase the targeting capacity and immune compatibility. Such systems have currently been of special interest as theranostic systems, integrating diagnostic imaging with therapeutic delivery.[36-38] Despite the apprehensions on long-term toxicity and biodegradation, the current developments in material engineering have been pumping the issues out and increasing the clinical prospects of inorganic and bio-inspired nanobiotechnological platforms.

Stimuli-Responsive Nanobiotechnological Platforms

The stimuli-responsive nanobiotechnological platforms are one of the several significant developments in smart drug/gene delivery because such applications can achieve controlled and local release of therapeutic agents in response to specific stimuli. These platforms are designed to have a specific ability to maintain stability in ideal biological environments as structural or chemical changes take place in response to exposure to disease-specific stimuli. These responsiveness increases the therapeutic accuracy, reduce systemic toxicity and increases the efficacy of treatment. Depending on the type of the trigger, stimuli-responsive systems may be divided into pH-, enzyme-, redox/ROS-, externally triggered platforms.[39-41]

pH-Responsive Systems

Differences in pH between normal tissues and pathological conditions like tumors, inflamed tissues and intracellular sites like endosomes and lysosomes are taken advantage of by pH-responsive nanocarriers. The polymers or linkers used to design these systems are normally protonated or swollen or broken under acidic conditions resulting in the release of the drug. PH-responsive nanocarriers exploit the acidic tumor microenvironment in cancer therapy by means of targeted drug delivery. In the case of gene delivery, pH-sensitive materials help in endosomal escape, which increases the efficacy of transfection. These systems are one of the most studied smart nanobiotchnological systems due to their simplicity and reliability, and the triggering of pH.[42]

Enzyme-Responsive Systems

Nanocarriers that are sensitive to enzyme activity are developed to release their therapeutic cargo in the presence of certain enzymes that are superexpressed in diseased tissues. The systems make use of enzyme-cleavable links or coatings which degrade with enzyme activity, creating site-specific delivery of drugs. Commonly targeted enzymes include matrix metalloproteinases, proteases and phospholipases which are highly expressed in cancer, inflammation and infectious diseases. Enzyme-responsive platforms are highly

specific because enzyme patterns of expression are disease specific. This is a specific sensitivity, which minimizes the off-target effects and the therapeutic index of drugs and genetic materials.[43-45]

Redox-Responsive and ROS-Sensitive Systems

Redox-responsive and reactive oxygen species (ROS)-sensitive nanocarriers take advantage of the disturbed redox state and the increased oxidative stress which is a frequent phenomenon in pathological processes including cancer and neurodegenerative diseases. Such systems may include disulfide bonds or redox-cleavable bonds which are stabilized in the extracellular medium but cleaved in the intracellular medium when glutathione is elevated. The nanocarriers which are sensitive to ROS are degraded or altered conformation in response to oxidative environments, releasing drugs. These systems are of specific use in delivering intracellularly, since they provide release of the payload in the cytosol with limited leakage prematurely in circulation.[46]

Thermo, Light, and Magnetic Responsive Platforms

Nanobiotechnological platforms that are external are able to provide a tight spatial and temporal control of therapeutic delivery. Thermo-responsive systems involve the use of temperature-reactive polymers which pass through phase transitions at defined temperatures to allow targeted drug delivery to heated areas. Nanocarriers that respond to light contain photoactive molecules that deactivate the drug when exposed to a particular wavelength enabling non-invasive and localized delivery. Magnetic responsive systems make use of magnetic nanoparticles that can be directed to specific tissue by external magnetic fields and

Table 1. Stimuli-Responsive Nanobiotechnological Platforms

Stimulus Type	Trigger Condition	Mechanism	Application Area
pH-responsive	Acidic tumor/endosome	Polymer swelling or cleavage	Cancer therapy
Enzyme-responsive	Disease-specific enzymes	Enzymatic degradation	Cancer, inflammation
Redox/ROS-responsive	High intracellular GSH/ROS	Disulfide bond cleavage	Intracellular delivery
Thermo-responsive	Elevated temperature	Phase transition	Hyperthermia therapy
Light/magnetic-responsive	External stimulus	On-demand release	Localized treatment

Table 2. Gene Types and Corresponding Nanobiotechnological Delivery Strategies

Genetic Material	Delivery Challenge	Nanotechnological Solution
Plasmid DNA	Large size, degradation	Polymeric nanoparticles
mRNA	Instability	Lipid/polymer nanocarriers
siRNA / miRNA	Poor cellular uptake	Stimuli-responsive carriers
Antisense oligonucleotides	Rapid clearance	Surface-modified nanocarriers
CRISPR/Cas systems	Complex delivery	Hybrid and smart nanocarriers

Table 3. Pharmacokinetic Advantages of Smart Nanocarriers

PK Parameter	Conventional Systems	Smart Nanocarriers
Absorption	Limited	Enhanced
Distribution	Non-specific	Targeted
Metabolism	Rapid degradation	Protected payload
Elimination	Fast clearance	Prolonged circulation
Bioavailability	Low	Significantly improved

Table 4. Key Challenges and Future Directions

Challenge	Current Limitation	Future Direction
Scale-up	Complex manufacturing	Scalable formulations
Safety	Long-term toxicity concerns	Biodegradable materials
Clinical translation	Poor predictability	Better models & AI tools
Regulation	Lack of standardization	Harmonized guidelines

also triggered by magnetic hyperthermia.[47] These systems find special application in cancer treatment and localized treatment therapies since they allow on-demand release of drugs with little systemic exposure (Table 1).

Gene Delivery Applications

One of the most promising but difficult uses of smart nanobiotechnological platforms is gene delivery. Constitutional delivery of nucleic acids involves protection against enzymatic degradation, precise cellular intake, endosomal escape, and regulated discharge into the cells. The use of smart nanocarriers, especially biopolymers, has become an effective alternative to the use of traditional gene delivery vectors, which is non-viral. Their versatile nature, which allows the management of their physicochemical properties into tunable and stimuli-responsive characteristics, allows an increased capacity to transfect in addition to avoiding safety issues related to viral systems.[48-49] Recent developments have greatly expanded their utilization in gene therapy, vaccination and also precise medicine.

Delivery of Plasmid DNA and mRNA

The delivery of plasmid DNA and messenger RNA involves the use of nanocarriers that are able to protect large and weak nucleic acid molecules during systemic circulation and their transport to target cells. Cationic biopolymer nanocarriers comprising of chitosan and synthetic polymer complexes are nanocarriers that can form stable polyplexes with nucleic acids due to electrostatic interactions. Such systems ensure the protection of genetic material against the effects of nucleases and enhance the uptake of cells. mRNA delivery has acquired a significant relevance because of its transient expression and reduced genomic integration. Smart nanocarriers increase the stability of mRNA, endodosomal escape, and efficient cytoplasmic delivery, and are useful in gene therapy and vaccine design.[50-51] Stimuli-responsive design also enhances efficiency of expression because it allows release of intracellularly based on pH or redox conditions.

siRNA, miRNA, and Antisense Oligonucleotides

MicroRNA, antisense oligonucleotides and small interfering RNA provide an effective means of post-transcriptional regulation of genes. They have however limitations to their clinical usability because of quick degradation, low cellular uptake, and off-target effects. These challenges are overcome using smart nanobiotechnological platforms that entrap or complex these molecules into protective nanocarriers that increase their stability and specificity to the target. Nanoparticles made of biopolymers and lipid polymer hybrids make it easier to deliver them to the cytoplasm where gene silencing takes place. The Stimuli-responsive systems also improve therapeutic effects because they release these molecules selectively in diseased cells. This type of approach has demonstrated high potential in the treatment of cancer, inflammatory and genetic diseases.[52-54]

CRISPR/Cas-Based Gene Editing Delivery

CRISPR/Cas gene-editing system has transformed the process of genome engineering but it presents a serious problem of delivery because of the size and complexity of the components. CRISPR/Cas in its form of plasmid DNA, mRNA or ribonucleoprotein complex can be delivered using smart nanobiotechnological platforms. Stimuli-responsive and targeting nanocarriers enhance cellular uptake and deliver gene-editing components with great specificity to the intracellular location. Compared to viral vectors, non-viral nanocarriers minimize immunogenicity and off-target effects with an increased level of safety and control. These delivery methods are

essential towards transferring CRISPR-based therapies to the clinical practice of genetic diseases and cancer.[55-57]

Barriers to Gene Delivery and Nanotechnological Solutions

In spite of these developments, various biological obstacles continue to impede gene delivery such as instability of serum, biodistribution that is not specific, cellular uptake, endosomal entrapment, and nuclear transport. Special nanobiotechnological platforms, including surface modification, stimulable release, and conjugation of target ligand, are designed to overcome these barriers to allow control over endosomal escape, intracellular release, and circulation time, as well as solubility and immune clearance, respectively.[58] The critical barriers can be overcome by smart nanocarriers to improve the delivery of genes and therapeutic potential (Table 2).

Drug Delivery Applications

Smart nanobiotechnological systems have played a major role in drug delivery by allowing the targeted delivery of drugs, controlled release and increase in pharmacokinetic profiles of therapeutic agents. The combination of biopolymer-based nanocarriers, stimuli-responsive and targeting strategies, solubility of these nanocarriers is poor, nonspecific distribution and toxicity to the body are avoided. Their versatility has enhanced their use in various disease fields such as cancer, neurological diseases, infectious diseases and other alternative routes of administration.[59]

Targeted Drug Delivery in Cancer Therapy

The recent aspect of smart nanobiotechnological drug delivery has been cancer treatment, as it demands selectivity targeting and limited toxicity. Nanocarriers used in cancer therapy take advantage of passive targeting where the enhanced permeability and retention effect is harnessed, and active targeting where ligands are used to recognize receptors. Stimulus response systems can also be used to improve specificity to cause drugs to release in response to acidic tumor microenvironment, enzymatic activity, or redox conditions. These measures enhance the accumulation of drugs in the intracellular compartment, multidrug resistance, and minimized the harm to normal tissues. Nanocarriers made of biopolymers have shown great prospects in the delivery of the following agents: chemotherapeutic, combination and theranostic agents thus enhancing patient outcomes and treatment efficacy.[60-61]

Nanobiotechnological Platforms for Neurological Disorders

The bloodbrain barrier is quite restrictive and thus delivery of drugs to the central nervous system is quite challenging. The development of smart nanobiotechnological platforms provides promising solutions in which the transportation of drugs through this barrier is enabled by the surface modification, receptor mediated transcytosis and stimuli responsive release. Nanocarriers made of biopolymers enhance the stability and bioavailability of neurotherapeutics and reduce the systemic exposure. The platforms have demonstrated potential in treatment of neurodegenerative conditions, brain tumors and neuroinflammatory diseases. The use of controlled and directed delivery increases the efficacy of the therapy and decreases the adverse effects of the traditional delivery of the CNS drugs.[62-63]

Delivery Systems for Infectious and Inflammatory Diseases

During the treatment of infectious and inflammatory diseases, successful delivery of drugs into the target tissue or immune cells is necessary whereby the drug concentrations in the site of infection or inflammation are sustainably high. Localized and sustained delivery of antimicrobial and anti-inflammatory drugs can be achieved through smart nanobiotechnological platforms, where the therapy is more effective and dosing infrequent. Stimuli-responsive systems can be triggered by inflammatory markers, e.g., a pH change and enzyme activity, to guarantee selective release of drugs. Intracellular targeting of pathogens and immune modulation is also better when using nanocarrier based delivery, thus they are useful in treating chronic infections and inflammatory disorders.[64]

Oral, Transdermal, and Pulmonary Delivery Approaches

Along with parenteral delivery, the smart nanobiotechnological platforms have increased the possibilities of alternative drug delivery routes. Nanocarriers in oral delivery help both to prevent degradation of drugs in the gastrointestinal tract and promote absorption across intestinal barriers. To enhance penetrativity of nanocarriers at the dermal system, transdermal delivery systems are

created to deliver drugs in a controlled manner, which lowers systemic side effects. The nanoscale carriers of pulmonary delivery allow deep lung deposition and speedy action of therapy. These are route-specific nanobiotechnological methods that enhance the patient adherence and increase the clinical utility of smart drug delivery systems.[65]

Pharmacokinetic and Pharmacodynamic Considerations

The pharmacodynamics and pharmacokinetics of smart nanobiotechnological platforms are key to determining the success of the therapeutic outcome of these platforms. Nanocarrier-based delivery systems are able to increase the efficacy and safety of therapeutic agents significantly by modulating the presence of drug-binding physiological processes, such as absorption, distribution, metabolism and elimination. Smart nanocarriers are engineered to do not only deliver drugs and genes in the most efficient manner but also to enhance their engagement with biological systems, bringing about foreseeable and controlled therapeutic reactions. Smart nanocarriers are absorbed differently depending on the size of the particles, the characteristics of the surface and the administration route.[66-67] Nanoscale sizes augment cellular internalization and transport across biological impediments, such as epithelial membranes and bloodbrain barrier. Site-specific absorption is further enhanced by using surface modification with biopolymers and targeting ligands and decreases nonspecific uptake. Smart nanocarriers provide preferential deposition of therapeutic agents in target tissue by passive and active targeting in vivo, which facilitates decreased systemic exposure and off-target effects with regard to distribution.[68]

Nanbiotechnological delivery systems also have significant changes in metabolism and elimination. Drug encapsulation using nanocarriers prevents premature actions of enzymes degrading drugs, thus increase circulation time and increase therapeutic availability. Based on the biodegradable nanocarriers, the process occurs in a controlled manner so that it breaks down to non-toxic metabolites which can be removed safely through the body. PEGylation decreases opsonization and clearance by the reticuloendothelial system, which further increases the systemic circulation and therapeutic efficacy. Smart nanobiotechnological platforms are characterized with controlled and sustained release behavior. Nanocarriers have the potential to deliver therapeutic agents into the body in a controlled release and a controlled degradation thereby allowing the delivery of therapeutic agent over prolonged time by integrating stimuli-responsive materials and matrices that are degraded.[69-71] This controlled release ensures the levels of drugs do not exceed the therapeutic range, lower the dose frequency, and minimize toxicity that happens at peak. These release schemes are especially useful with long-term chronic illnesses. Another significant benefit of the smart nanobiotechnological systems lies in an increase in bioavailability. Lipophobic drugs and those that are not very stable are well encapsulated in nanocarriers that enhance solubility, deter degradation and increase tissue penetration. The smart nanobiotechnological platforms can enhance the pharmacodynamics and overall therapeutic performance through optimization of the pharmacokinetic profiles and efficient delivery of the targetsites (Table 3).

Safety, Toxicity, and Regulatory Considerations

Clinical translation of smart nanobiotechnological platforms has not only relied on the therapeutic efficacy of the type of platform but also careful interpretation of their safety, toxicity, and regulatory compliance. Nanocarriers are bioreactive at the cellular and molecular level, which is causing questions of immunogenicity, chronic toxicity, and environmental costs. These problems should be solved by means of systematic assessment and regulation alignment, in order to implement nanobiotechnological delivery systems safely and effectively into the clinical practice.[72]

Biocompatibility and Immunogenicity

In order to be used in biomedical applications, nanobiotechnological platforms should meet a basic requirement of biocompatibility. The use of biopolymer in nanocarriers is most preferred because of low toxicity, biodegradability, and lower immunogenicity. Nevertheless, it is also possible that surface properties, particle size, and chemical composition can have a substantial effect on immune recognition and inflammatory responses. Nanocarriers can activate the immune cells or cause complement activation resulting in adverse reactions. PEGylation and biomimetic coating are widely used surface engineering

techniques in order to reduce immune response and enhance systemic tolerance. The wise choice of materials and optimization is thus important to make sure that they do not cause any trouble with biological systems and patient safety.[73-75]

Toxicological Evaluation of Nanobiomaterials

The assessment of nanobiomaterials in toxicology entails a detailed assessment that goes beyond the routine toxicity testing. The cellular uptake, biodistribution and profiles of toxicity depend on factors like particle size, shape, surface chemistry and degradation products. In vitro studies will give you first clue on cytotoxicity, oxidative stress, and genotoxic activity, and in vivo studies will be necessary in evaluating the systemic toxicity, organ build-up, and long term effects. The issue of chronic exposure and accumulation of non-biodegradable nanomaterials is also of concern. Regulatory testing protocols and predictive toxicology models are being put more focus to guarantee reproducibility as well as proper risk evaluation of smart nanobiotechnology platforms.[76-78]

Regulatory Landscape and Translational Challenges

The regulation of nanotechnological products has specific difficulties as their complex structure and multimodality make them hard to regulate. Regulatory bodies demand thorough characterization of nanocarriers, such as, physicochemical characteristics, consistency of manufacturing, safety, and effectiveness. The fact that there are no universally harmonized guidelines that are particular to nanomedicine makes the approval process difficult, however. The reproducibility, scale-up, and quality control of the manufacturing also contribute to the impediment of clinical translation. Moreover, concerns of the nanomaterial behavior in vivo, which are usually unclear, may often need long-term safety data and post-marketing surveillance data. These regulatory and translational barriers will only be overcome through working closely with researchers, industry, and the regulatory authorities, to have clear structures that will enable the safe commercialization of smart nanobiotechnological platforms.[79]

Recent Advances and Emerging Trends

The accelerated change in computational sciences, systems biology, and precision medicine has resulted in the recent progress of smart nanobiotechnological platforms. These novel tendencies are radically changing the design of nanocarriers, rendering empirical strategies rather data-oriented, patient-centered strategies. The combination of the concepts of artificial intelligence, personalized medicine, and theranostic functionalities is altering the future of the drug and gene delivery. The design of nanocarriers with the help of AI has become an anaerobic trend because machine learning and deep learning platforms allow optimizing the properties of nanobiomaterials quickly.[80-81] Computerized models can determine drug-carrier interactions, stability, toxicity, and targeting efficiency and can therefore minimize experimental procedures of trial and error. AI-based methods will enable selecting biopolymers, surface alterations and stimuli-responsible components rationally and depending on massive datasets. This fosters the speed of formulations, increases reproducibility, and augments translational capability of smart nanobiotechnological vehicles.

Another significant new trend is personalized and precision nanomedicine, which is aimed at customizing the delivery of therapeutic agents to the specific characteristics of the patient. The response to treatment is determined by variations in genetic composition, phenotype of the disease, and microenvironment influences. Smart nanocarriers can be tailored in regard to targeting ligands, drugs combinations and kinetics in release to suit patient specifications. This patient-centered measure enhances the effectiveness of therapy, reduces side effects, and conforms to the current trend of precision healthcare, especially in cancer and genetic diseases.[82]

Theranostic nanobiotechnological systems combine diagnostic capabilities of a nanosystem with therapeutic capabilities of a nanosystem. These multipurpose systems allow detecting a disease, monitoring it in real-time, and addressing it in a specific way. Visualization of biodistribution, response to treatment and disease progression The incorporation of imaging agents with therapeutic payloads enables the visualization of the biodistribution, treatment response and disease progression. The theranostic nanocarriers have been especially useful in the treatment of cancer and precision medicine since they enable the

new adaptive therapeutic approaches and enhance clinical decision-making.[83] It is anticipated that further developments in material engineering and imaging technologies will increase the clinical usefulness of theranostic nanobiotechnological platforms even more.

Challenges and Future Perspectives

In spite of major progress, clinical implementation of smart nanobiotechnological platforms is still limited because of a number of scientific, technical and translational challenges. To tackle these problems is the key to closing the gap between the innovation on the laboratory scale, and its practical therapeutic applications. One limiting factor to commercialization of smart nanobiotechnology delivery systems is scale-up and manufacturing issues. The development of many nanocarriers involves multistep, complicated synthesis and formulation procedures which cannot be easily replicated at an industrial level. The large-scale production can have variability in the size of particles, surface characteristics, and drug loading that can influence the consistency of products, their stability, and their therapeutic efficacy. Besides, batch-to-batch reproducibility, long-term stability in storage, and good manufacturing practice requirements are also paramount issues.[84] Industrial translation requires simplification of formulation approaches and use of manufacturing technology, which can be scaled.

The lack of clinical translation also obstructs the achievement of effective smart nanobiotechnological implementation. Post-promising preclinical findings do not always translate into clinical success as there exist differences in the biological complexity between experimental systems and the human systems. Poor predictive models, lack of long-term safety data, and the lack of knowledge about nanocarrierhost interactions are the reasons of high attrition rates in clinical trials. Moreover, uncertainty in regulations and unification of evaluation standards stall approval procedures. To overcome these translational challenges, it is more important to strengthen the nature of interdisciplinary collaboration and formulate clinically relevant testing frameworks. The areas of future research in smart nanobiotechnology are aimed at creating safer, more predictable, and patient-centric systems of delivery. It is necessary to focus on biodegradable and biomimetic materials, better targeting and combine stimuli-responsive and multifunctional capabilities.[85] The accelerated rational nanocarrier design and optimization is likely to be fastened by advances in artificial intelligence, high-throughput screening and systems biology. Moreover, superior emphasis on individual nanomedicine, chronic toxicity evaluation, and real-time analysis of the treatment results will promote the subsequent generation of smart nanobiotechnological platforms into successful clinical practice (Table 4).

CONCLUSION

Smart nanobiotechnological systems have become potent and multi-faceted in overcoming the drawback of the traditional drug and gene delivery systems. It has been demonstrated in this review that biopolymers play a vital role in designing smart nanocarriers with biocompatibility, biodegradability, and functional adaptability, which are vital in targeted, stimuli-responsive, and controlled delivery of therapeutics. Developments in nanocarrier structure, surface engineering, and stimulus responsive processes have played a major role in enhancing pharmacokinetic and pharmacodynamic properties and increasing bioavailability and decreasing systemic toxicity of a large variety of therapeutics. Another theme that is made apparent in the review is the increasing role of smart nanobiotechnological platforms in gene therapy, cancer treatment, neurological disorders, infectious diseases and alternative routes of drug delivery. The latest advances in the field of nanocarriers include AI-aided nanocarrier design, personalized nanomedicine, and theranostic systems, which depict the current sophistication of such platforms and their ability to change the pharmaceutical sciences. Although there are currently various challenges associated with the mass production of products, safety testing, and medical translation, further interdisciplinary studies and regulatory standardization are likely to hasten the effective implementation of smart nanobiotechnological delivery systems in clinical environments. In general, smart nanobiotechnological platforms are a promising future of pharmaceutical sciences, that provide innovative solutions to precision therapy and better

patient outcomes. Further progress in material science, computer technologies, and translational studies will be inevitably needed to reach their full clinical potential and become the part and parcel of the next-generation therapeutic approach.

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This research does not involve any clinical trials.

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Not Applicable

Author Contribution

Shaik Aminabee: conceived the idea of the review, designed the overall structure, coordinated the manuscript development, and performed critical revision of the content. Ogirala Umamaheswar Rao: contributed to literature collection and analysis related to nanobiotechnological platforms and stimuli-responsive delivery systems. K. Ravi Shankar*:* contributed to sections on drug delivery applications, pharmacokinetic considerations, and translational aspects. Naga Venkata Chenchu Lakshmi Kollipara: contributed to biopolymer-based nanocarriers, formulation strategies, and surface engineering concepts. Saritha Karnati: assisted in drafting sections related to gene delivery systems, safety, toxicity, and regulatory considerations. A.V.S Ravi Sai Nadh: contributed to emerging trends, future perspectives, and assisted in manuscript editing and formatting. All authors read, reviewed, and approved the final manuscript.

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