REVIEW ARTICLE

Smart Carriers, Smarter Cures: Stimuli-responsive Nanomaterials for Precision Messenger RNA Delivery

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Abstract

Against the backdrop of modern medical progress, messenger RNA (mRNA) holds a bright future, yet its therapeutic potential highly relies on effective delivery. This review, "Smart Carriers for Smarter Cures," explores the innovative use of stimuli-responsive nanomaterials as protective and precise carriers for mRNA. We first understand the innate challenges of mRNA transport, including its susceptibility to enzymatic degradation and its difficulty in crossing cell membranes independently. The core of our discussion focuses on how these smart carriers support biological and external triggers for highly targeted drug release. Further, we study how they respond to a variety of cues, such as shifts in pH and redox potential within the body, as well as external stimuli like light. This focused approach reduces unintended effects and increases therapeutic capability. We also try and understand the variety of carrier types, such as lipid nanoparticles and polymeric systems. We deeply discuss the mechanisms that they use for cargo delivery too. In a nutshell, this review highlights the main impact of these technologies across various applications, like the important development of advanced mRNA vaccines and customized cancer treatments. By identifying the important delivery hurdles, these intelligent nanocarriers are recreating a new era in nanomedicine and gene therapy where our future is full of more effective and safer treatments.

Key words: Lipid nanoparticles, mRNA delivery, smart nanocarriers, stimuli-responsive nanoparticles, targeted drug delivery, technology

INTRODUCTION

Messenger RNA (mRNA) has brought in a new and flexible approach to current-day medicine. It is a temporary biological blueprint that gives cells the instructions to create specific proteins, which then prevent, manage, or reverse various diseases.[1] The incredible speed and adaptability of mRNA-based vaccines for COVID-19 were clear proof of their potential to create effective medical solutions within a given limited time.[2] Unlike the older treatments, which just supply a pre-made protein or drug, mRNA therapeutics let the body's own cells do the work.[3] This allows the researchers to quickly alter the mRNA sequence and develop personalized treatments for all sorts of conditions, including genetic disorders, viral infections, and different kinds of cancer.[4] Major advancements in delivery technology, especially growing lipid nanoparticles (LNPs), have made mRNA formulations more stable, efficient, and safer.[5] While there are still some hurdles to overcome, such as long-term storage, managing immune responses, and large-scale manufacturing, the growing clinical evidence shows the mRNA's powerful and transformative role and how it is quickly on the way of becoming a key player in shaping the future of precision medicine.[6]

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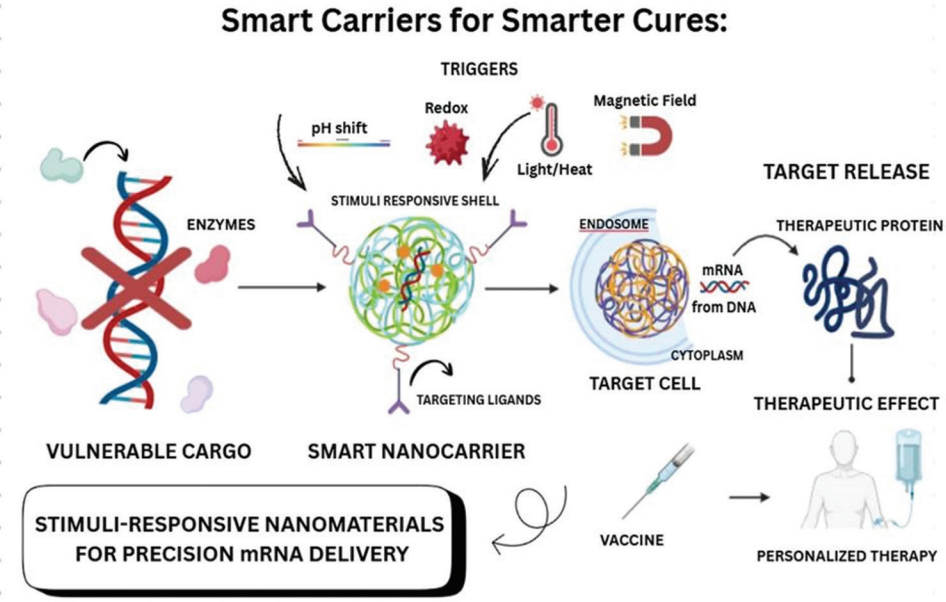

Engineering solutions for effective mRNA transport

mRNA-based therapeutics are one of the most favorable evolution in modern medicine, but the success of it truly depends on overcoming some major issues related to delivery.[1] Unlike smaller drug molecules or even DNA, mRNA is a relatively large and delicate molecule which is chemically unstable.[7] It has to survive a series of biological defenses to work properly inside a cell. One of the big problems is its vulnerability of being broken down by enzymes called ribonucleases (RNases), which are found all over in our blood and tissues.[8] Without a solid protective carrier, most mRNA that is administered would be quickly destroyed by these RNases before it gets to where it needs to go.[9] Another major obstacle is that mRNA cannot get into a cell on its own in the absence of a supporting substance.[10] Due to its large size and a negatively charged backbone, mRNA just cannot cross the hydrophobic cell membrane independently.[11] To solve this problem, experts create special delivery systems like LNPs.[12] These tiny carriers wrap up the mRNA, shield it from enzymatic breakdown, and help it get into the cytoplasm where the proteins are made. Even with these solutions, creating accurate and safe delivery is still a challenge that remains to exist.[13] For a treatment to be effective, the mRNA needs to be sent only to the intended tissues, avoiding off-target areas and minimizing any unwanted immune reactions.[5] It is also tricky to find the right balance between how quickly a cell takes up the carrier and how long the protein expression lasts to maintain therapeutic levels.[14] To handle these issues, next-generation delivery platforms are constantly improved. This includes things like nanoparticles based on a polymer, specially designed extracellular vesicles, and an advanced lipid system that are mixed.[15] The main goal is to create new strategies that are safe, effective, and fully compatible with the body, allowing mRNA-based therapeutics to reach their full potential in clinical settings.[16]

Rise of smart nanomaterials

Over these years, nanomaterials have been constantly developing from a conceptual idea into one of the most powerful key in modern medicine.[2] Nanoparticles at the beginning were only used to increase drug solubility and circulation, but many advancements gave hope to smart nanomaterials, which act as a design system that sense, respond, and adjust to their biological surroundings in short period of time.[17] Unlike other usual carriers, smart nanomaterials are designed to engage directly with their environment.[18] They are able to identify and change the structure of disease-specific biomarkers, they also release therapeutic agents in a specific tuned way when provoked by a specific stimulus.[19] This intelligent responsiveness has transformed nanotechnology from a passive delivery approach into a dynamic, active, and precision-based therapeutic platform.[12] This rapid rise is powered by combining material science, biotechnology, and nanofabrication.[17] With developing ideas in advanced polymer processing, porous coordination networks, liposomal carriers, and composite nanosystems materials which are capable of responding to multiple causes such as pH, temperature, enzymatic activity, redox balance, and even light or magnetic fields are constantly being produced.[20] Such multi-factor responsiveness makes the treatment effects spatially focused and time-defined which reduces the systemic toxicities. Other than drug delivery, the ability of smart nanomaterials is wide such as, its applications in biosensing, imaging, and regenerative medicine.[21] They are creating a better path toward highly personalized treatments that adjust to patient-specific conditions, marking a fundamental shift in how diseases are diagnosed and managed.[22] At the end, the rise of smart nanomaterials shows more than just a development in technology, as it shows a change towards intelligent, interactive, and adaptive medicine in which the new era materials are creating the basics for a future where

treatments are able to think and respond just like living systems.[23]

The specific timelines and key events causing the bloom of smart nanomaterials is mentioned in the below picture with the suitable years in which they occurred.

Understanding stimuli-responsive nanomaterials

Stimuli-responsive nanomaterials act as smart nanocarriers that can sense their surroundings. Rather thana traditional drug capsule, which simply releases its contents, these are designed to change their behavior in response to a specific signal from their environment.[24] This signal can either come from within our body, like changes in factors like pH, temperature, or the existence of a type of enzyme. For example, a polymer capsule might stay stable as it travels through the bloodstream but dissolve rapidly in the slightly acidic environment of a tumor, which is a perfect signal for these nanomaterials to activate.[25] They can also be triggered by external cues, such as light, magnetic fields, or ultrasound, applied from outside the body.[26] Light-sensitive nanocarriers respond to an external laser source, which makes the treatment more precise and minimizes the damage to healthy tissue.[27] This unique capability allows us to accurately regulate when and where a therapeutic component should be released.[28] By only activating at the desired site, like a tumor or an inflamed area, they can improve treatment effectiveness and dramatically reduce unwanted side effects on healthy cells.[29]

mRNA delivery

Using these clever nanomaterials for mRNA delivery is revolutionary because mRNA is a very delicate cargo.[10] It is easily broken down by enzymes in the body and has a negative charge, which makes it hard for it to get inside cells on its own.[30] Standard delivery systems struggle to protect the mRNA throughout its journey and release it effectively at the right place.[13] Stimuli-responsive nanocarriers solve this problem by acting as protective shields. They encapsulate and protect the mRNA from degradation while it circulates in the bloodstream.[31] Specific stimulus, like the acidic environment of a tumor, causes a controlled change in the nanomaterial structure once the carrier reaches the intended target.[32] This change creates proper and efficient release of the mRNA directly into the cell's cytoplasm to make proteins.[33] This on-demand release not only ensures the mRNA survives its journey but also significantly boosts its therapeutic power by making sure it gets exactly where it needs to be to do its job.[34]

Design considerations

When it comes to making a successful stimuli-responsive nanomaterial, getting the design right is everything. There are a few key things we have to get a handle on.[35] First up, our material choice really matters. Whether we go with polymers, lipids, or inorganic nanoparticles, each type has its own set of pros and cons.[36] Then there is the size of the nanocarrier, which is very important. A sweet spot is often between 10 and 400 nm.[37] This size range is small enough to slip into tissues with leaky blood vessels (a phenomenon called the Enhanced Permeability and Retention, or EPR, effect) but big enough to avoid being quickly removed by our body's immune system.[38] Surface chemistry is another big deal. We can alter the surface to make sure the nanomaterial is friendly to the body and stays in circulation longer, and can even be actively guided to specific cells.[39] Finally, picking the right trigger stimulus is crucial. A system for a tumor needs to be pH-sensitive, while one for an inflamed area should be built to react with certain enzymes.[40] Getting all these details perfectly optimized ensures the nanocarrier stays stable, delivers its contents effectively, and only releases it at the intended spot.[41]

STIMULUS TYPES AND MECHANISMS

pH-responsive systems

Among these various triggers for smart nanocarriers, changes in pH are the most used and flexible. This is mainly because pH levels can change greatly in different parts of the body, which creates natural on-off switches for drug release.[42] For example, the pH in our healthy blood and tissues is around 7.4, but in the microenvironment of tumors and areas of inflammation, it is different and more acidic, reducing to a pH of around 6.5.[43] This natural difference in pH provides a perfect cue for a nanocarrier to start releasing its content only where it is needed most.[44] Another critical pH change occurs within cells themselves. When a nanocarrier is taken up by a cell, it first enters a compartment called an endosome.[45] The pH inside the endosome gradually gets more acidic, dropping from about 6.0 to 5.0 in the later stages, before eventually fusing with a lysosome, which has an even lower pH than it does.[46] These acidic conditions provide another powerful signal for the nanocarrier to break down, allowing the mRNA to escape the endosome and move into the cell's cytoplasm, where it can do its work.[47] This strategy helps solve a major delivery problem which is getting the mRNA out of the endosome before it is destroyed.[48] By designing nanocarriers and making it sensitive to these pH changes, we can create a condition where the mRNA content is both protected but also released at the right time and place within the cell. This leads to more effective and focused treatment.[49]

Redox-responsive carriers

The body's natural redox potential, which is the balance of reducing and oxidizing agents, is another powerful internal trigger.[50] There is a huge difference between the environment

inside a cell and the one outside of it.[51] The inside of a cell is packed with a molecule called glutathione (GSH), making it a highly reducing environment. On the other hand, the blood and the space outside of cells have a much lower concentration of GSH; therefore, they are more oxidizing than inside a cell. This difference is the perfect switch for a smart nanocarrier to act.[52] Nanomaterials can also be crafted with special chemical bonds, like disulfide bonds, which are stable in the oxidizing environment of the blood but only break apart in the reducing environment inside a cell.[53] This means that the nanocarrier can stay intact during its journey but only release its contents if it enters the target cell successfully. This reduces any early or time-deviated content release.[54] This kind of tactic is wonderful to enable the drug to get exactly where it needs to be, right inside the cell, for a more accurate and effective treatment.[55]

Enzyme-responsive systems

Some nanocarriers are designed in a way that they only react to specific enzymes, which act like a core component to unlock the main contents present in them. Different diseases or biological states, like a tumor or inflammation, usually have unique enzymes that are amplified in those areas.[56] Building a nanocarrier with a bond that breaks only by specific enzymes can create a highly focused delivery system.[57] When the nanocarrier enters our body, it immediately deals with its intended tissue, and the unique enzymes present there break down the carrier and release the therapeutic content exactly where it's needed.[58] This approach is fantastic for ensuring that the drug is released only at the intended site, which helps to significantly minimize potential side effects on healthy cells and tissues. This highly specific method allows for a very localized and effective treatment.[59] The figure attached elucidates the mechanism of enzyme-responsive nanocarriers' action as essentially miniature, smart delivery systems for medication. They are coated in a protective shell which is then held together by special chemical links called peptides. These peptides are made reactive to specific enzymes that are found in high concentrations at disease sites, such as tumors or areas of inflammation. When a nanocarrier arrives at one of these sites, the upregulated enzymes clip the peptide links and make the protective shell fall apart. This uncovers the core of the nanocarrier, which is then absorbed by the diseased cells. The drug once released from the nanocarrier is delivered exactly where it's needed as soon as the nanocarrier enters the cell. This allows for highly focused drug delivery, which increases the medication capability while reducing side effects and damage to healthy tissues.

Temperature and light-induced systems

In many cases, an external signal is the best way to induce a carrier. That is where the temperature and light-triggered systems come in, giving us direct and precise control over drug delivery.[60] These methods are particularly useful because they do not rely on the body's internal environment and can be applied with great accuracy.[61] Certain polymers and materials will dramatically change their structure when they reach a specific temperature.[62] By applying a mild heat to a specific area, let's say, for instance, using focused ultrasound or radio waves, we can cause the nanocarrier to release its contents right on cue. This is a very promising approach for localized treatments, like those targeting a tumor, where the heat can be pinpointed to a very small area.[63] In the same way, some nanocarriers are made with photo reactive components that change when treated with a specific wavelength of light, like near-infrared light, which is used to travel deep into tissue.[64] This surface-level technique gives an incredible amount of control by allowing us to accurately dictate when and where the drug is released.[65]

TYPES OF NANOCARRIERS USED

LNPs

When we carry brittle therapeutic molecules like mRNA, the first thing that usually strikes our mind is LNPs.[12] They have become the gold standard, especially after their huge success in delivering mRNA vaccines during the COVID-19 pandemic.[66] LNPs are incredibly effective because they are made out of fats and fat-like molecules, which means that they can easily fuse with a cell's outer membrane to drop off their payload.[67] They can also be designed to respond to the acidic environment of endosomes within cells, helping them break apart and release the mRNA exactly where it needs to be, preventing it from being degraded.[68] LNPs are generally safe for the body, and scientists have been working hard to improve their stability, manufacturing processes, and how they perform inside the body.[69]

We can understand from this figure that LNPs are specifically crafted small delivery vehicles for medicine, which are designed to wrap up and protect fragile genetic material, like mRNA, ensuring it gets exactly where it needs to go in the body without being destroyed. They have a core that contains fats, or lipids. This helps in creating different structures to wrap the mRNA safely. Some could be small, hollow bubbles called liposomes, while others are solid spheres. Important components like cholesterol make the carriers more stable and help them merge with a cell's outer wall. This design allows these nanoparticles to be sly, avoiding early spotting and breakdown by of the body. When they arrive at the intended cells, they are efficiently absorbed. Then they escape the cell's internal recycling centers (endosomes) to release the mRNA, which then allows the cell to read the genetic instructions and make the needed protein. By changing the lipid recipe and particle size to our needs, we can regulate where the nanoparticles go in the body and how they release their components. This makes them a backbone of modern nucleic acid delivery, which transforms how we can develop new treatments and vaccines.

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Table 1: Understanding redox-sensitive carriers

System type	How it works	What it's best for	Key advantages	Main challenges
Disulfide-linked carriers	These carriers are held together by bonds that break only when they encounter high levels of a molecule called GSH, which is abundant in tumor cells.	Delivering chemotherapy drugs, siRNA, or mRNA.	Protects the drug until it's precisely where it needs to be, ensuring a targeted release.	Can be sensitive to random oxidative stress, which might cause early drug release.
Thioether-based polymers	Their structure changes and breaks down when exposed to reactive oxygen species (ROS), another common signal in diseased tissues.	Transporting protein and small-molecule drugs.	Responds directly to a specific disease signal, offering controlled and predictable degradation.	May be overly sensitive, triggering drug release too soon under mild conditions.
Selenium/ tellurium systems	These systems use bonds that break apart extremely quickly in the presence of ROS.	Targeted therapies, particularly for tumors.	Their high sensitivity to redox triggers allow for a faster and more powerful response than other systems.	The safety and potential toxicity of these materials are still a concern.
Redox-sensitive micelles	These tiny, spherical structures collapse completely when they encounter high GSH levels inside a cell.	Delivering potent drugs like doxorubicin.	Keeps the drug safely contained in the blood but can burst inside a tumor for maximum impact.	Can be unstable in environments that are even slightly reducing.
Dual-responsive carriers (redox+pH)	These require two signals, high GSH and acidic environment to trigger drug release.	Highly selective cancer treatment.	This dual system creates an accurate and selective drug release, which improves its capability.	Their complex design can make them difficult to produce on a large scale.

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Table 2: Overview of recent temperature- and light-triggered nanocarrier systems for controlled drug delivery

Stimulus type	Nanocarrier platform	Mode of triggered release	Therapeutic use	Key insights
Temperature-sensitive systems	Micelles derived from poly (N-isopropylacrylamide)	The polymer undergoes a structural shift close to body temperature, loosening the matrix and enabling controlled drug discharge	Anticancer formulations	Mild hyperthermia produced a finely tunable release pattern, which improved drug localization at tumor sites
Light and heat dual-responsive hybrid	Liposomal carriers integrated with gold nanorods	Light absorption by the rods generates heat, softening or disrupting the lipid bilayer to liberate the payload	Chemotherapeutic transport	Dual-stimulus activation allowed precise spatial and temporal release while reducing exposure to surrounding healthy tissues
Photo-switchable polymers	Nanoparticles containing azobenzene-modified polymers	Light causes azobenzene units to switch configuration, altering polymer packing and pushing the drug outward	Model drug-release studies	The system supported reversible, cyclical release when alternating light wavelengths were applied
NIR-activated carriers	Upconversion nanoparticles coupled with surface photosensitizers	Near-infrared light triggers localized heat or reactive species formation through upconversion, initiating release	Photothermal or photodynamic cancer therapy	The use of NIR light enabled deeper penetration and activation specifically at diseased tissue with limited unintended effects
Light-driven PDT systems	Photo-responsive polymeric micelles	Visible light stimulates ROS generation, weakening the micellar core and promoting drug liberation in tumor environments	Photodynamic therapy	Marked enhancement in cytotoxic activity was observed under light exposure, while the carriers remained stable without illumination
General stimuli-adaptive nanoparticles	Multifunctional polymer-based nanoparticles	These materials alter permeability or diffusion characteristics when exposed to heat or light	Various cancer models	Demonstrated broad adaptability of stimulus-responsive materials for precise and adjustable drug-delivery strategies

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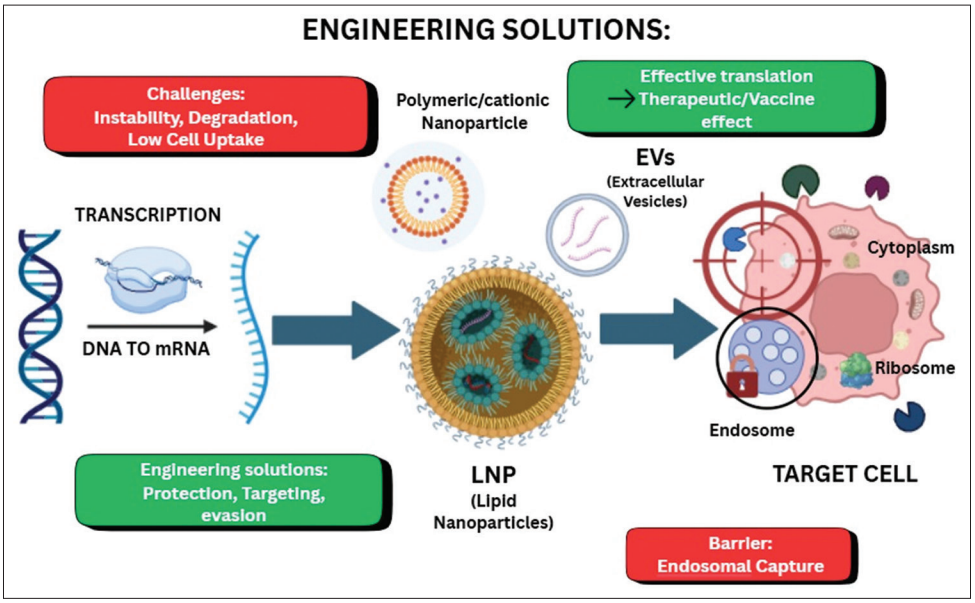
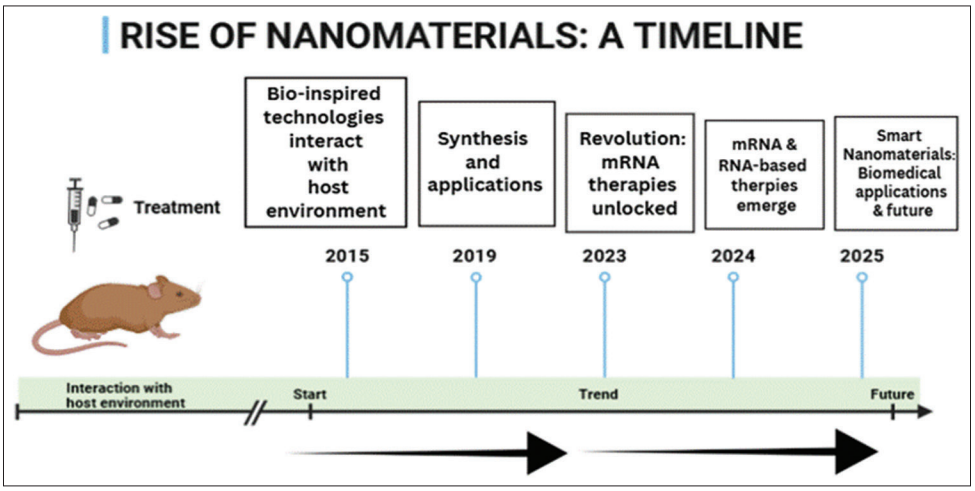
Table 3: A guide to polymeric carriers

Kind	Process flow	Upsides
Polymeric Micelles	Act as tiny, water-friendly bubbles that hide drugs that do not dissolve well.	They allow hard-to-dissolve drugs, like many chemotherapy agents, to be used effectively.
Polymeric Nanoparticles	They are solid, customizable nanospheres that carry drugs inside or on their surface.	They are highly flexible and can be designed to focus on specific cells, which makes them great for customized medicine.
Polymeric Hydrogels	They are like soft, water-containing sponges that release a drug gradually.	They are gentle on the body and perfect for long-term, local drug delivery, like in wound care.
Dendrimers	They are perfectly structured, tree-like polymers with many arms for holding drugs.	Their precise shape allows for very controlled and high-capacity drug loading, ideal for gene therapy



AQ3 **Figure 1:** Engineered nanocarriers for improved delivery of messenger RNA



AQ3 **Figure 2:** Timeline of smart nanomaterials

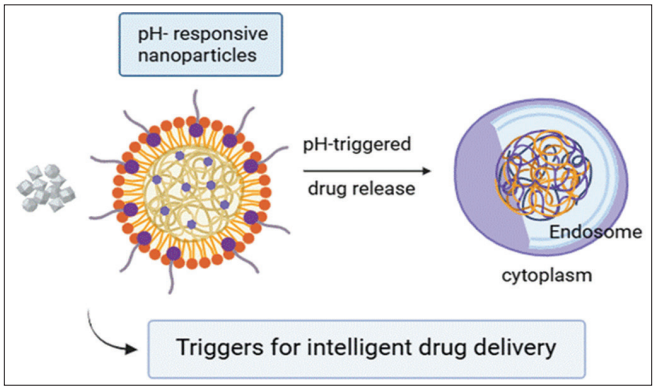
Polymeric nanocarriers

While LNPs are the star of the show right now, polymeric nanocarriers offer an interesting alternative.[70] These are made from different types of polymers, which are long chains of molecules. One of the biggest advantages of using polymers is that they are highly customizable.[71] We can easily change their chemical structure, size, and shape to create a carrier with specific functions as we need.[70] We can even make them with multiple capabilities, like adding an ability to respond to more than one type of stimulus (like both pH and temperature) or to carry more than one type of

drug we need. This created space for much more flexible and diverse drug delivery system.[72]

Inorganic and hybrid systems

Beyond lipids and polymers, a lot of incredible work is being done with inorganic and hybrid nanocarriers.[73] Inorganic carriers are built from materials such as silica, gold, or carbon, and they offer incredible stability and strength.[74] For instance, gold nanoparticles are easy to synthesize, and their surface can be modified to attach drugs or targeting molecules.[75] Meanwhile, hybrid systems are where things get innovative. These are basically a mix of organic and inorganic materials, combining the best features of both worlds.[76] For example, we can create an inorganic core (for stability) surrounded by a responsive organic polymer shell (for controlled release). This creates a carrier that is both durable and highly reactive to its environment.[73] These are still in the early stages of study, but they hold great probability of success for creating new-gen carriers with amplified capability and performance.[77]



AQ3 **Figure 3:** pH-responsive nanoparticles for intelligent drug delivery

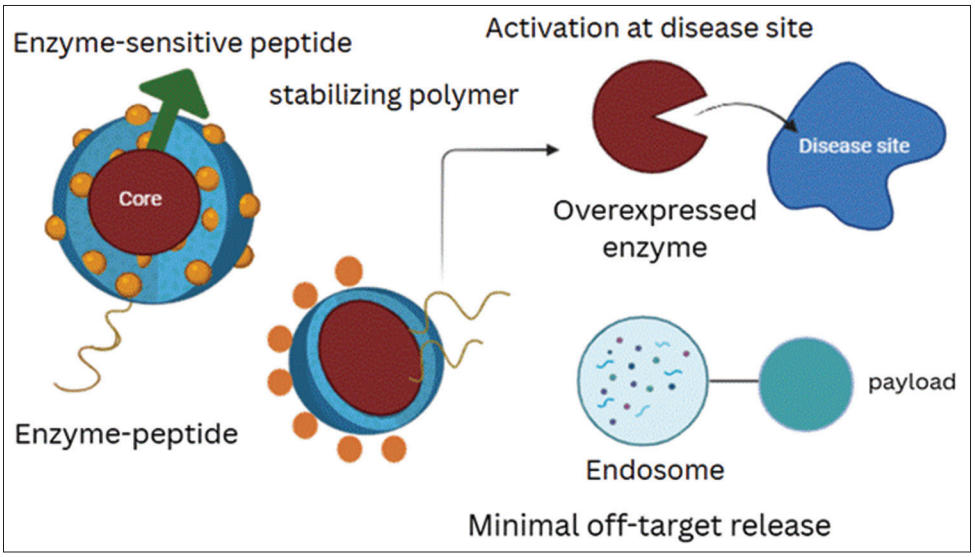
APPLICATIONS IN MEDICINE

mRNA cancer immunotherapy

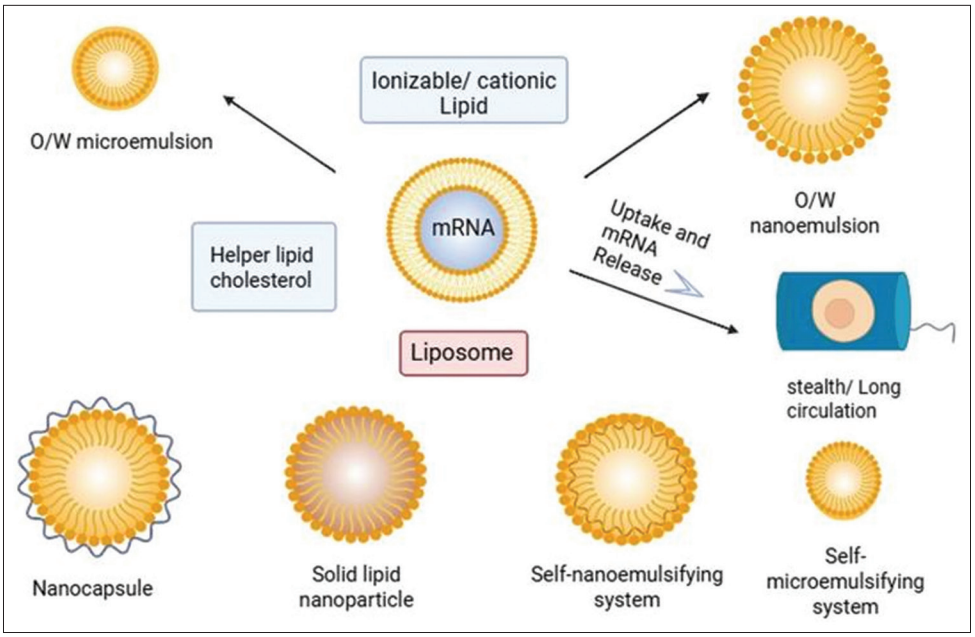
One of the most notable developments in advanced medical care over the years is the use of mRNA in cancer immunotherapy, in which it is used to create customized cancer treatments.[14] The main idea of it is to teach our own defensive system to identify and attack the cancer cells in our body.[78] In the first step, a sample of the patient's tumor is taken and studied to identify the unique proteins (or antigens) on the surface of the cancer cells. After that, a special mRNA sequence is formed to encode these specific antigens. This mRNA is then wrapped in a smart nanocarrier and administered to the patient.[79] The nanocarrier then delivers its mRNA contentsto instruct the patient's cells to produce cancer-selective antigens.[80] These immunogens then carry a most-wanted poster in the body, which trains the patient's immune cells to find and destroy only the cancer cells, leaving healthy cells untouched.[81]

mRNA vaccines against infectious diseases

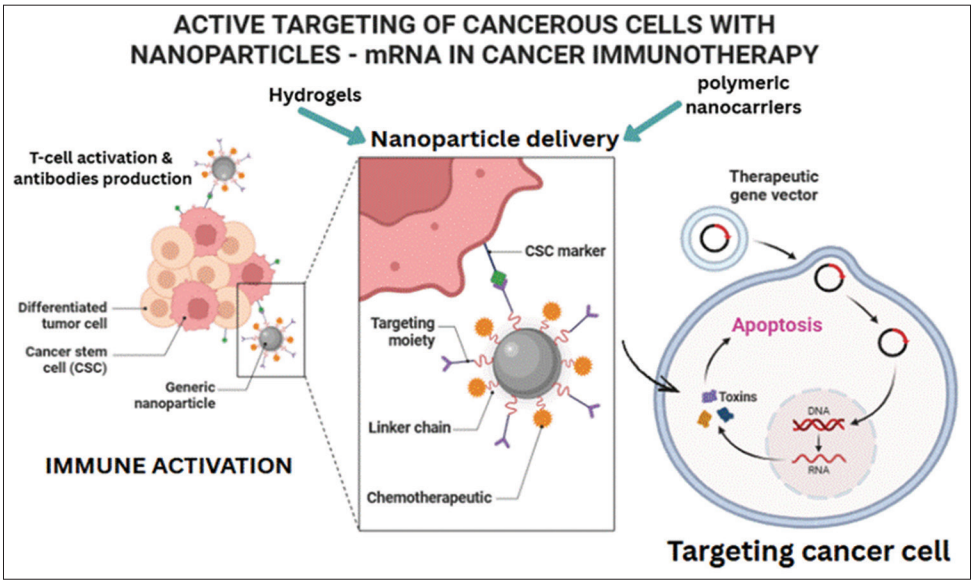
The world became well-known with mRNA during the COVID-19 pandemic, but its application against infectious diseases is far broader than that. This tech can also be rapidly modified to react to new and developing immunogens.[82] This offers a possibility for treatment for diseases that have historically been challenging to create vaccines for, such as HIV, influenza, and Zika, mRNA.[9] Using smart nanocarriers to accurately deliver the mRNA, experts make sure that the



AQ3 **Figure 4:** Mechanism of enzyme-responsive nanocarrier activation at disease sites



AQ3 **Figure 5:** Lipid-derived carriers for transporting messenger RNA



AQ3 **Figure 6:** Lipid-derived carriers for transporting messenger RNA for cancer treatment

defense response of the body is strong and durable. These developments provide a new way to face some of the most sustained global health threats.[83]

mRNA-based protein replacement

mRNA-based protein replacement therapy gives an impactful substitute to traditional treatment for patients suffering from diseases that are caused by the lack in a specific protein.[84] Conditions such as cystic fibrosis or certain rare genetic disorders are often managed by regular and expensive infusions of the missing protein.[85] With mRNA therapy, a nanocarrier can be made to deliver an mRNA molecule containing the blueprint for the correct protein with ease. Inside the patient's cells, the mRNA is translated, and the cells begin to create the functional protein.[86] This method could plausibly provide a more sustained and natural level of the necessary protein by giving a more effective and less burdensome long-term solution for patients with chronic protein deficiencies.[87]

Advantages and limitations over traditional delivery systems

mRNA nanocarriers are more fruitful than traditional delivery systems in many ways such as viruses, which have been used

for many years to deliver genes in gene therapy.[6] One main benefit is their non-viral nature, which removes the risk of viral infection, unwanted immune responses, or insertional mutagenesis, which is the capability of the genetic material to combine into the host cell's DNA and cause a new problem.[88] mRNA nanocarriers are very easy to produce because they can be created quickly on a large scale. This was very important during the rapid development of COVID-19 vaccines.[89] They can also be designed to be highly focused, which makes them deliver their contents to specific cells or tissues by reducing unintended effects and increasing its capability.[90] Still, even with these advantages, mRNA nanocarrier systems face some challenges. The biggest limitation of all is the innate instability of the mRNA molecule itself due to which it is easily broken down by enzymes in the body.[91] Nanocarriers are designed to protect the mRNA, but maintaining stability during storage, transportation, and delivery remains a major focus of studies, which still remain. Another challenge is the risk that the nanocarrier itself could trigger an unwanted defense reaction which is called immunogenicity. This might reduce the effectiveness of the treatment and cause some side effects.[92] Improving nanocarrier design to overcome these demerits and unlock the full therapeutic capability of mRNA tech is important to make it function better.[93]

Ethical and translational considerations

mRNA nanocarriers moving from laboratory research to clinical application give us a new set of ethical and practical questions that must be addressed.[94] An important consideration is the cost and accessibility of these advanced treatments. Many questions arise, like, how can we make sure that these life-saving treatments are available to everyone who needs them and not just a privileged few? Another important area is patient consent and education.[95] It is important to make the patients fully understand the working, possible risks and benefits of it before proceeding.[94] Finally, there are regulatory hurdles to solve, as new rules and guidelines must be established for the safe and effective approval of these therapies.[96] Balancing scientific development with a commitment to equity and safety is needed for the successful incorporation of mRNA nanocarriers into mainstream medicine.[97]

Future perspectives and research gaps

The future of mRNA nanocarrier technology is very bright, but there are still a lot of changes to be made to make it better. The current focus of studies is on improving the stability of both the mRNA and the nanocarriers to increase the shelf life and more effective delivery.[98] Scientists are also working to develop even more intricate nanocarriers that can specifically target certain cell types, reducing unintended and side effects.[99] There is a lot of gaps in studies in understanding and in creating universal nanocarriers that could be used for a wide range of mRNA treatment, where there could be disadvantages like the long-term effects of repeated mRNA administrations. This makes production and distribution more efficient.[100] Overcoming these challenges is important to expand the use of mRNA tech to components other than vaccines and into new therapeutic areas such as gene editing and biological repair medicine.[101]

Latest developments

In recent years, stimuli-responsive nanomaterials have developed as one of the most powerful innovations in precision medicine, particularly for mRNA-based therapies. Recent studies have shown how these systems are revolutionizing mRNA cancer vaccine delivery, enabling higher stability and on-demand release inside tumor microenvironments. pH-sensitive LNPs are reliable for body circulation, but the issue is that they break apart rapidly in regions of acidic tumor, which creates localized mRNA expression. This method has improved both immune activation and antitumor responses together.[102] Other than oncology, compostable, and condition-responsive nanodelivery systems are being designed for immune-mediated and inflammatory conditions where exact drug localization can reduce multi-organ toxicity and recover defense balance.[103] Materials that degrade only in response to disease-specific stimuli provide a sustainable, biocompatible route for chronic treatments. At the material design level, new generations of dendrimer nanogels and polymeric systems exhibit remarkable control over mRNA encapsulation and release dynamics.[102] These designs improve the launching of foreign genetic material in eukaryotic cell for changing the genetic makeup efficiency by reacting to intracellular redox concentration differences or enzymatic changes. This causes improved cytosolic delivery. Many applications in neurodegenerative diseases have also increased support to this. Brain-targeted, stimuli-responsive nanoparticles are used to cross the blood-brain barrier and release therapeutic mRNA or proteins in response to neural oxidative stress.[25] Collectively, these advances show us a shift toward next-generation smart nanomaterials capable of personalized, site-specific, and temporally controlled mRNA delivery. This marks a major step forward in precision nanomedicine.[103]

CONCLUSION

In brief, the journey toward effective mRNA delivery depends on smart carriers that can protect their content and only release it at the right moment. In this review, we have seen how these lipid-based and polymeric systems are already solving major challenges with stability and focused delivery. The capability is enormous, creating innovative ways of producing new-gen vaccines and customized therapies. Importantly, moving this technology from the lab to patients will need a collaborative, interdisciplinary effort to manage the remaining challenges and make sure a new era of safe and effective nanomedicine.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

All authors contributed to the review. Sambasivam Gopinath: Conceptualization, supervision, writing-review and editing, data curation, and data analysis. Sabrin S: writing-review and editing. Pratheesha. Vijaya Kumar Rajathi: writing-review and editing. Ramaiyan Velmurugan: supervision and writing-review and editing. Adhithya Balasubramanian: Writing original draft and editing, data curation, literature search, and data analysis. All authors read and approved the final manuscript.

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