Dean&Francis
ISSN 2959-6157

Exploration of Synthesis Pathways for Multifunctional Nanobiomaterials Based on Biomedical Demands

Yiming Xiang

Nanjing Foreign Language School Yuhua International Academy, Nanjing, Jiangsu, China, 210000, xymnflsyuhua2023@hotmail.com

Abstract:

Recent progress in multifunctional nanobiomaterials has paved novel avenues for precision medicine. These materials enable the integration of targeted delivery, imaging, and therapeutic functionalities within a single system. They include chemical ways like coordination self-assembly and polymerization, biomimetic methods such as cell membrane coating and biotemplate synthesis, and nucleic acid scaffold methods like DNA origami. We evaluate the performance of these methods in physiological environments. For example, carbon nanotubes with branched PEG have a longer blood half-life of about 22.1 hours, while those without PEG last only 5.4 hours. Also, nanocarriers coated with red blood cell membranes exhibit robust immune evasion capabilities in animal models. We discuss how cross-linking, multilayer coating, and dynamic shielding can improve biocompatibility, and how to design materials that respond to outside signals. At the end, we look at problems like reproducibility, scale-up, and clinical translation, and suggest future directions. This review aims to provide a comprehensive overview for the rational design of clinically applicable nanobiomaterials.

Keywords: multifunctional nanobiomaterials; biomimetic coating; DNA origami; biocompatibility; targeted delivery; clinical translation

1. Introduction

Diseases such as cancer, cardiovascular disorders, and neurodegenerative diseases continue to impose a substantial global health burden. We need better and safer treatments. Conventional therapeutic approaches frequently induce adverse effects due to their limited specificity. They also have poor tissue penetration and cannot easily track therapy in real time. Because of this, multifunctional nanobiomaterials have become an important research topic. Their small size, changeable surface, and modular design allow them to carry drugs, help imaging, and react to their surroundings at the same time. Over the past

ISSN 2959-6157

decade, researchers have developed diverse strategies for fabricating nanomaterials capable of functioning in complex physiological microenvironments. Some react to pH changes in tumors, some to overexpressed enzymes, and others to outside forces like magnets or light.

An ideal nanomaterial should: Evade immune system-mediated clearance; Stay stable inside the body; Target diseased tissues; Combine therapy and imaging. But no single method can do all these things perfectly. So in real use, researchers often combine different methods to balance their advantages and disadvantages. This paper will discuss three main types of synthesis methods:

(1) Chemical methods: These include coordination-driven self-assembly and polymer-based building. They have good control and can be scaled up for production.

(2) Biomimetic methods: These use ideas from nature, such as coating materials with cell membranes or using biological templates. They help materials avoid immune attack and improve safety.

(3) Modular nucleic acid scaffolds: Especially DNA origami, which can place molecules very precisely at the nanoscale.

2. Synthesis Approaches for Multifunctional Nanobiomaterials

2.1 Chemical Synthesis Methods

Chemical synthesis serves as the primary strategy for fabricating nanomaterials, owing to its advantages of flexible design, precise regulation, and facile scalability. Common methods include coordination self-assembly, block copolymer assembly, and template deposition.

First, coordination-driven self-assembly gives a clear way to design materials. By selecting metal ions and ligands responsive to pH or redox stimuli, researchers can construct stimuli-responsive nanocarriers that achieve targeted drug release. These systems can hold a lot of drugs, and their behavior can be easily adjusted through chemical changes. Second, polymer nanoparticles are also common. Polymers such as PLGA-PEG or PCL can self-assemble in aqueous solutions to form micelles or vesicles. Methods such as emulsion, nanoprecipitation, and microfluidic-assisted synthesis help produce uniform particles. Some systems combine polymers and inorganic parts. For example, gold nanoparticles can attach to polymers or shells using thiol chemistry, adding optical or heat-based therapy functions.

However, chemical synthesis approaches exhibit inherent limitations. Some residual reagents or catalysts may introduce potential cytotoxicity. It is also hard to keep results consistent when scaling up from small to large production. Maintaining the stability of nanoparticles in biological fluids remains another critical challenge that requires further addressing.

2.2 Biomimetic Strategies

The main idea of biomimetic methods is to copy natural systems to help materials survive in the body and reach their targets. A representative example is cell membrane coating, which involves wrapping synthetic nanoparticle cores (e.g., PLGA) with natural cell membranes derived from red blood cells, platelets, white blood cells, or cancer cells. The coated carrier keeps the surface proteins and sugars of the original cell, so the immune system sees it as "self" and does not clear it quickly.

If cancer cell membranes are used, the carrier can even target tumor tissues because of the "homologous targeting" effect [1]. Experimental results demonstrate that this coating strategy prolongs the blood circulation time of nanocarriers and reduces their phagocytosis by the immune system. Another method is biotemplate synthesis, which uses biological structures such as viruses, proteins, or bacteria as templates to grow nanomaterials [2]. This can give the material special shapes or biological functions. These biomimetic approaches typically employ mild reaction conditions, mimicking natural biological processes, thereby avoiding the use of toxic chemicals and enhancing biocompatibility [3].

But biomimetic coatings also have three big problems: First, it is hard to make them in large quantities because producing uniform membranes is not easy. Second, the coated layer may undergo detachment or degradation during in vivo circulation. Third, differences between batches of membranes can cause quality changes.

2.3 Modular Nucleic Acid Platform

Nucleic acid-based scaffolds, particularly DNA origami, have gained significant attention due to their ability to achieve ultrahigh-precision molecular positioning. The method uses many short DNA strands to fold a long DNA chain into a planned 2D or 3D shape. Because of this, researchers can put drugs, imaging agents, and targeting molecules exactly where they want. This helps in com-

bined therapy and multi-function detection.

But DNA structures are fragile. Naked DNA origami nanostructures are susceptible to degradation in the bloodstream due to enzymatic hydrolysis and changes in ionic strength:

(1) Internal reinforcement: Cross-link DNA strands to make the structure tougher and more resistant to breakdown.

(2) External protection: Wrap DNA with PEG polymers or positive polymers to create a protective layer.

(3) Surface coating: Add a silica or inorganic shell around the DNA, which protects it from enzymes [4].

In lab tests, well-protected DNA origami can stay stable for 24–48 hours and carry drugs or imaging agents. However, maintaining such stability under physiological conditions in vivo remains a major challenge. Making them stable while keeping all their designed functions is the main goal of current studies.

3. Biocompatibility Optimization and In Vivo Stability

3.1 Avoiding In Vivo Clearance

Upon entering the bloodstream, nanocarriers are prone to clearance by the body's immune system. Their survival depends on size, surface charge, hydrophobicity, and surface coating.

Nanoparticles with a size range of 10–100 nm demonstrate optimal performance. Smaller ones (<10 nm) are cleared by the kidneys, and larger ones (>200 nm) are captured by the liver and spleen [5]. Once nanoparticles are in the body, they quickly collect a layer of proteins called the protein corona, which changes how they move and where they go [1]. A widely adopted strategy to evade clearance is PEGylation, which involves conjugating PEG chains to the nanoparticle surface. For example, carbon nanotubes with branched PEG stay in the blood for about 22.1 hours, while those without PEG last only 5.4 hours [6]. But PEG is not perfect. Following repeated injections, the body may generate anti-PEG antibodies, which accelerate the clearance of PEG-coated nanoparticles [7] [8]. Size also matters. Research shows that nanoparticles smaller than 15 nm are quickly filtered by kidneys, while those larger than 100 nm are more likely eaten by immune cells. So, 20–100 nm is usually the best size range [9].

3.2 Immune Response and Safety

Safety means not only staying in the body but also avoiding strong immune reactions. These reactions, like inflammation or complement activation, can reduce the effect of treatment and cause side effects.

The chemical composition of nanomaterials plays a crucial role in determining their biocompatibility. Some materials like metal oxides, silica, or strong-charged polymers can cause stress or damage to cells if used in high amounts [10]. So, before clinical use, scientists test them carefully by checking inflammation markers, tissue changes, and long-term behavior in the body.

To make materials safer, new design ideas are used. For example: Zwitterionic coatings mimic the neutral charge property of cell membranes, rendering nanomaterials more "immune-invisible"; Self-markers like CD47 peptides can tell immune cells "don't eat me"; Dynamic shields hide targeting parts in the blood but expose them when they reach a tumor (for example, in response to pH changes or enzyme overexpression).

3.3 Structural Stability in the Body

For smart nanocarriers, it is important that they stay whole until they reach the target. If they break early, drugs leak out too soon.

Ways to keep them stable include:

(1) Covalent cross-linking: Add chemical bonds to make the shell stronger.

(2) Multilayer coating: Build several layers to add strength and slow down leakage.

(3) Responsive stabilization: Use chemical bonds that stay closed in normal conditions but open at the target site (for example, in acidic or reducing environments).

For DNA nanostructures, silica coating has been proven effective because it protects them from enzymes [4]. However, a balance must be struck: excessive protection may impair the nanocarrier's ability to release drugs or bind to target sites.

3.4 Composite Coatings

To get more than one good property at once, researchers now use composite coatings—mixing different layers to combine strengths. Some examples are membrane-polymer hybrid coatings (a cell membrane layer modified with PEG or polysaccharides, which endows nanocarriers with both biological identity and structural robustness), hybrid

ISSN 2959-6157

membranes(mix membranes from different cell types, like red blood cells and platelets, so the material can both circulate longer and stick to damaged vessels), logic-gated coating systems (the outer layer protects nanocarriers in normal tissues; upon reaching the target, the outer layer degrades and exposes the inner targeting layer)

The main goal of these composite designs is to make a nanocarrier that can move safely in the body, stay long enough in the blood, find the target accurately, and release the drug at the right place and time, with fewer side effects.

4. Challenges and Progress in Functional Integration Platforms

4.1 Real Bottlenecks in Integrated Diagnosis and Treatment

Combining both diagnosis and treatment in one platform is one of the main goals in nanomedicine. For example, gold nanorods can absorb near-infrared light to kill tumors, carry chemotherapy drugs, and also help with imaging at the same time. Iron oxide particles can be used for MRI imaging and magnetic drug delivery together.

But mixing several functions in one system is not easy. The different functional components may exhibit mutual interference. For example, imaging signals like fluorescence may get weaker if too many drugs are attached, or drug loading might change after surface modification. Maintaining the activity of all integrated functions without mutual interference remains a major challenge.

4.2 Stimuli Responsiveness

To make nanocarriers more "smart," researchers design them to respond to certain triggers. Some triggers are endogenous (e.g., the acidic microenvironment, high reductive potential, or overexpressed enzymes in tumors), while others are exogenous (e.g., light, ultrasound, or magnetic fields), which enable external control of drug release.

The key challenge lies in ensuring these "switches" work only where needed. They must stay inactive while circulating, and only turn on when they reach the target. This balance is key for both safety and efficiency.

4.3 Targeting Design and Spatial Arrangement

Adding targeting molecules like antibodies, peptides, or aptamers helps nanoparticles go directly to diseased cells. But their placement on the surface is very important. The targeting moieties must be exposed to ensure efficient binding to target cells. Drug-carrying and imaging parts should not block each other. Using precise tools like DNA origami or polymer chemistry helps put these molecules in the right place.

Multivalent display of targeting molecules can enhance binding affinity. But if there are too many, the material may also stick to healthy tissues or trigger immune reactions. So careful control is needed.

4.4 From Laboratory to Clinic

Even with these challenges, some examples show that multifunctional nanoplatforms can work well in real biological tests. In preclinical animal models, these nanoplatforms have demonstrated the ability to deliver drugs to tumors, eliminate cancer cells, and improve therapeutic outcomes. For example, a gold nanorod platform that combined photothermal therapy, chemotherapy, and fluorescence imaging achieved over 90% tumor removal in a breast cancer model.

Also, the lipid nanoparticles (LNPs) used in mRNA vaccines are a successful real-world example. They consist of multiple lipid components—ionizable lipids for encapsulating and protecting mRNA, helper lipids for enhancing stability, and PEGylated lipids for conferring stealth properties. Together, they solved many major problems in nucleic acid drug delivery [11].

These cases show that combining multiple functions is possible. But in real use, signal fading, early drug leakage, and reduced targeting accuracy are still big issues that must be improved step by step.

5. Challenges and Future Directions in Clinical Translation

5.1 Reproducibility, Scalability, and Standardization

Many nanoplatforms can be made only in small amounts in the lab. When scaling up production from milligram to gram or kilogram scales, batch-to-batch variations often occur. This makes it hard to keep quality stable.

To solve this, we need standardized production processes, strict quality control (for size, charge, and drug loading), and clear systems to test stability. The development of modular and plug-and-play nanoplatforms can also facili-

tate more efficient and reproducible production.

Large-scale production must also meet GMP standards, which include safety, sterility, and no endotoxin contamination. These rules are important if nanomaterials are to be used in clinical medicine.

5.2 Barriers to Clinical Application

Even though many multifunctional nanomedicines look promising, only a few have reached late clinical trials. The main reasons are:

(1) Unknown long-term safety. Some inorganic nanoparticles exhibit long-term in vivo retention, and their degradation products may pose potential cytotoxic risks. This makes regulators and doctors cautious.

(2) Differences between patients. Differences in immune systems and protein corona formation among patients can alter the therapeutic efficacy of nanomaterials. Tumors also vary in structure, making results less predictable.

(3) High cost and complexity. The fabrication of multifunctional nanomedicines requires multiple materials, complex processes, and rigorous quality control, leading to increased costs.

Because of these problems, each new material must go through long and careful preclinical tests before human trials.

5.3 Future Development

To move forward, new ideas and tools are appearing in this field: AI-assisted design (Machine learning can predict the best nanoparticle size, charge, and coating for specific uses. This can save time, reduce trial-and-error, and find better designs for stability, targeting, and drug loading [12]); Green synthesis (instead of harsh chemical reagents, researchers utilize plant extracts, enzymes, or microorganisms for nanomaterial fabrication, which are safer, more sustainable, and environmentally friendly [13]); Adaptive intelligent systems (These next-generation carriers can sense changes in their surroundings and dynamically adjust their surface properties or behaviors). For example, they can stay hidden in normal tissues but activate when near a tumor

These directions show how the field is changing—from simple drug carriers to smart, safe, and eco-friendly systems that can adapt to real biological conditions.

6. Conclusion

Multifunctional nanobiomaterials stand at the intersection of chemistry, biology, materials science, and medicine. With methods such as chemical synthesis, biomimetic design, and precise DNA-based assembly, researchers are striving to create nanocarriers that can prolong circulation, evade immune attack, home to target tissues, and integrate both therapy and imaging.

Significant progress has been made. For example, PEGylation and membrane coating can make nanocarriers last much longer in blood, and many animal studies have shown strong results. But some problems still hinder these systems from reaching clinical use. These include inconsistent performance, production differences, safety issues, and strict approval standards. The future of this field will likely focus on the development of hybrid and adaptive nanosystems, which may be designed via AI assistance, fabricated through green and safe approaches, and validated using global standardized benchmarks.

By combining these advanced ideas, multifunctional nanomedicine can move from theory to real clinical tools that help patients.

References

[1] Kyriakides, T. R., et al. (2021). Biocompatibility of nanomaterials and their immunological responses. Frontiers in Nanotechnology.

[2] Altammar, K. A., et al. (2023). A review on nanoparticles: characteristics, synthesis, and biomimetic approaches. Frontiers in Microbiology.

[3] Low, S. S., et al. (2021). Sonoproduction of nanobiomaterials: a critical review. PMC.

[4] “In situ small-angle X-ray scattering reveals strong condensation of DNA origami during silicification.“ (2022). Journal/ source.

[5] Nagime, P. V., et al. (2024). A comprehensive review of nanomaterials synthesis. Elsevier.

[6] Prencipe, G., Tabakman, S. M., Welsher, K., Liu, Z., Goodwin, A. P., Zhang, L., & Dai, H. (2009). PEG branched polymer for functionalization of nanomaterials with ultralong blood circulation. arXiv.

[7] Haroon, H. B., et al. (2022). A brief history of long circulating nanoparticles. Journal of Colloid and Interface Science.

[8] Mitchell, M. J., et al. (2020). Engineering precision nanoparticles for drug delivery. Nature Reviews Materials.

ISSN 2959-6157

[9] Hoshyar, N., Gray, S., Han, H., & Bao, G. (2016). The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction. ACS Nano / PMC.

[10] Yusuf, A., et al. (2023). Nanoparticles as drug delivery systems: a review of the biological, physicochemical, and toxicity aspects. MDPI.

[11] Hou, X., Zaks, T., Langer, R., & Dong, Y. (2021). Lipid nanoparticles for mRNA delivery. Nature Reviews Materials.

[12] Yang, R. X., et al. (2022). Big Data in a Nano World: A Review on Computational, Data-Driven Research. ACS Nano.

[13] Noah, N., & Ndangili, P. (2021). Green synthesis of nanomaterials from sustainable materials for biosensors and drug delivery. arXiv.