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Emerging trends in biomaterials for cancer immunotherapy and genome editing: A comprehensive review

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Abstract:

Cancer poses a significant global health challenge, necessitating innovative approaches beyond conventional therapies. Cancer immunotherapy and precision genome editing emerge as promising fields to reshape treatment paradigms. Immunomodulatory biomaterials, like nanoparticles and hydrogels, play a crucial role in cancer immunotherapy, enabling precise delivery of immune-stimulating agents for controlled responses. Biomaterial-based cancer vaccines enhance antigen presentation, fostering robust immune reactions. Adoptive cell therapies, notably CAR-T cell therapy, rely on biomaterials for engineering and *in vivo* support within the tumour microenvironment. In genome editing, biomaterials, especially with CRISPR-Cas9, are vital for efficient and targeted component delivery. Nanoparticles, liposomes, and viral vectors serve as carriers, safeguarding components and boosting gene editing efficiency. Challenges persist, requiring focused research on safety, biocompatibility, and long-term biomaterial evaluation. Strategies to enhance delivery precision and mitigate off-target effects are crucial. Standardization, regulatory compliance, and personalized medicine integration are pivotal for clinical translation. Exploring combination therapies involving biomaterials, immunotherapies, and gene editing is essential. In conclusion, the synergy of biomaterials with cancer immunotherapy and genome editing holds promise for transformative cancer care, demanding rigorous scientific inquiry to address challenges and improve global patient outcomes.

Keywords:

Cancer immunotherapy, Precision genome editing, Biomaterials, CRISPR-Cas9, Combination therapies.

1. Introduction:

Cancer remains one of the most formidable challenges in modern medicine, affecting millions of lives worldwide each year [1]. Conventional therapies, such as chemotherapy and radiation, have made significant strides in treating certain types of cancer [2]. However, their limitations, such as off-target effects and drug resistance, have underscored the need for novel therapeutic approaches [3]. In recent years, cancer immunotherapy [4] and precision genome editing [5] have emerged as promising fields that hold the potential to revolutionize cancer treatment.

Harnessing the immune system to target and eradicate cancer cells has proven to be a game-changing strategy in oncology [6]. Immune checkpoint inhibitors [7], adoptive T cell therapies [8], and cancer vaccines [9] have demonstrated remarkable successes, leading to durable responses and improved survival rates in certain patients. Despite these achievements, challenges persist, including immune evasion by tumours [10] and the need for personalized approaches to enhance patient outcomes [11]. Meanwhile, the advent of precision genome editing, particularly the CRISPR-Cas9 technology [12], has revolutionized the field of molecular biology. CRISPR-Cas9 allows scientists to precisely modify specific genes, opening up vast possibilities for both basic research and therapeutic applications [13]. In cancer, the potential to target and correct genetic mutations implicated in tumour development offers unprecedented opportunities for precision medicine [14]. However, successful cancer immunotherapy and genome editing demand efficient and controlled delivery systems to ensure therapeutic agents reach their targets with minimal side effects [15]. This is where cutting-edge biomaterials play a pivotal role [16]. Biomaterials have emerged as essential tools to optimize cancer immunotherapy and genome editing by providing tailored platforms for drug delivery, enhancing immune response, and improving gene editing efficiency [17].

In this review article, we explore the latest advancements in harnessing the power of biomaterials for cancer immunotherapy and precision genome editing [18]. We delve into various types of biomaterials, including nanoparticles [19], hydrogels [20], and viral vectors [21], and their applications in enhancing therapeutic efficacy and minimizing off-target effects. Additionally, we discuss the challenges and future directions in the development of biomaterial-based strategies to overcome obstacles faced in cancer treatment.

2. Biomaterials for cancer immunotherapy:

2.1. Immune modulatory biomaterials:

Immune modulatory biomaterials are ingeniously designed to manipulate the immune response, creating a favourable microenvironment conducive to the activation of anti-tumour immune cells [17]. Their pivotal role in elevating the efficacy of cancer immunotherapy is evident through their ability to deliver immune checkpoint inhibitors and immune-stimulating cytokines with precision. These biomaterials are meticulously engineered to release therapeutic agents in a sustained and controlled manner, ensuring a durable and precisely targeted immune response against the tumour [22, 23]. Nanoparticles, operating at the nanoscale, stand as formidable carriers for immune modulatory agents within cancer immunotherapy [24]. Laden with immune checkpoint inhibitors such as anti-PD-1 or anti-CTLA-4 antibodies, effectively obstruct inhibitory signals, unleashing the potent activity of tumour-specific T cells [25, 26]. The controlled and gradual release of these antibodies from nanoparticles guarantees sustained immune activation, ultimately leading to profound tumour regression. On the other hand, hydrogels, intricate three-dimensional networks of crosslinked polymers, serve as exceptional vehicles for encapsulating and releasing immune-stimulating cytokines like interleukins (IL-2, IL-12) or interferons [27,28]. These hydrogels create a localized depot of these vital cytokines precisely at the tumour site, thus fostering the recruitment and activation of immune cells, thereby significantly amplifying the anti-tumour immune response. Furthermore, the versatility of hydrogels allows for the engineering of physical support and protection for immune cells, enhancing their survival and functionality within the challenging tumour microenvironment [27]. These advancements in biomaterials hold great promise in revolutionizing the landscape of cancer immunotherapy, offering new avenues to combat cancer with increased precision and effectiveness.

2.2. Cancer vaccines:

Biomaterial-based cancer vaccines have emerged as a compelling approach to augment the body immune response against cancer cells [28]. These innovative vaccines are designed to bolster antigen presentation and stimulate robust immune reactions targeting tumour-specific antigens. One avenue of this strategy involves utilizing biomaterials like liposomes, nanoparticles, and virus-like particles as carriers for tumour-specific antigens [29]. These biomaterial carriers serve a dual purpose by safeguarding the antigens from degradation and enhancing their uptake by antigen-presenting cells (APCs) [30]. This, in turn, facilitates the efficient presentation of these antigens to T cells, igniting a potent and highly specific T cell response directed against cancer cells [31]. Additionally, biomaterial-based cancer vaccines can incorporate adjuvants, substances known to enhance immune responses to antigens. Adjuvants like Toll-like receptor (TLR) agonists and cytokines are commonly integrated into

these vaccines [32]. These adjuvants play a critical role in further amplifying the activation of APCs and T cells. By creating a pro-inflammatory microenvironment, they assist in the recruitment and activation of immune cells, ultimately reinforcing the immune assault on cancer [33]. This multifaceted approach harnessing biomaterials and adjuvants holds substantial promise in reshaping the landscape of cancer immunotherapy, offering innovative strategies to combat cancer more effectively and precisely.

2.3. Adoptive cell therapies:

Adoptive cell therapies (ACT), a groundbreaking approach in cancer treatment, involve the isolation and manipulation of a patient's own immune cells, primarily T cells, to target and eliminate cancer cells. Notably, chimeric antigen receptor (CAR) T cell therapy has demonstrated remarkable success in specific cancer types [34-37]. Biomaterials play a pivotal role in the ex vivo engineering of CAR-T cells, functioning as delivery vehicles for CAR constructs and other genetic material into T cells [35, 36]. This enables the T cells to express specific receptors (CARs) designed to recognize and engage cancer antigens effectively. Nanoparticles and viral vectors are frequently employed biomaterials, ensuring efficient gene delivery into T cells during this process. Moreover, the challenges encountered by CAR-T cells upon reinfusion into the patient's body within the complex tumour microenvironment are substantial [35-37]. To address this, biomaterials, including hydrogels and scaffolds, can be custom-designed to provide physical support and essential nutrients to CAR-T cells. This support is crucial for their survival and persistence amidst the harsh conditions of the tumour microenvironment. Additionally, these biomaterial-based scaffolds can function as reservoirs for cytokines and other immune-modulating agents, further enhancing the anti-tumour activity of CAR-T cells [34-37]. This multifaceted approach that combines the power of biomaterials with CAR-T cell therapy holds immense promise in advancing the field of cancer immunotherapy, offering novel strategies to combat cancer more effectively by equipping engineered immune cells with the tools they need to navigate and conquer the complex tumour landscape.

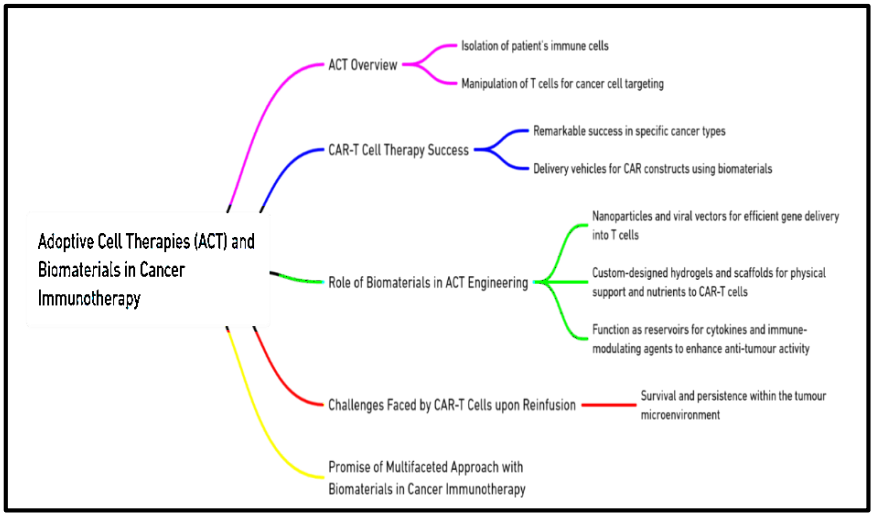

Figure. 1: Biomaterials for cancer immunotherapy

2.4. Biomaterials for genome editing:

Biomaterials have emerged as essential tools in the field of genome editing, particularly with the advent of CRISPR-Cas9 technology. Genome editing aims to precisely modify the DNA sequence of living organisms, offering unprecedented potential for treating genetic diseases, understanding gene function, and advancing biotechnology. Biomaterials play crucial roles in facilitating efficient and targeted delivery of CRISPR-Cas9 components, protecting these components from degradation, and enhancing gene editing efficiency [12, 13]. The various types of biomaterials used in genome editing are:

2.5. Delivery of CRISPR-Cas9 components:

Efficiently delivering the CRISPR-Cas9 system to target cells or tissues is a central challenge in genome editing, and biomaterials play a pivotal role in overcoming this obstacle [38]. These versatile carriers encapsulate and protect essential CRISPR-Cas9 components, including the Cas9 protein or mRNA and guide RNA (gRNA) molecules, ensuring their successful delivery to the desired cellular destinations [39]. Three commonly used biomaterials in this context are nanoparticles, liposomes, and viral vectors [40].

Nanoparticles made from biocompatible materials, such as lipids or polymers, have shown remarkable efficacy as carriers for CRISPR-Cas9 components. They protect the cargo from degradation and allow for efficient uptake by target cells. Due to the large molecular weight of the Cas9 protein (approximately 4.5 kb in genetic size) and its low stability against serum enzymes and proteins, the entry of the Cas9/sgRNA or RNP complex into cells is challenging [41,42]. However, nanoparticle delivery systems, such as lipid-based nanoparticles and cationic polymer nanoparticles, have been developed to address these challenges. These

delivery systems can be modified to target specific cell types, reducing off-target effects and improving gene editing precision. For instance, a DNA nanoclew [NC]-based delivery system has been shown to efficiently load the Cas12a/crRNA RNP [42, 43]. Additionally, systemic nanoparticle delivery of CRISPR-Cas9 ribonucleoproteins has demonstrated effective tissue-specific genome editing. The development of nanoparticle-based technology for CRISPR-Cas9 delivery holds promising prospects for clinical gene editing, as evidenced by the completion of the first CRISPR/Cas9 clinical trial in 2016 [44]. Furthermore, various studies have highlighted the potential of nanoparticle delivery systems for the efficient and targeted delivery of CRISPR-Cas9 components. Lipid nanoparticles, polymeric nanoparticles, solid-lipid nanoparticles, nanostructured lipid carriers, and niosomes have all shown great potential in the delivery of CRISPR compounds to target cells. Additionally, polyamidoamine-aptamer modified CRISPR/Cas9 and sorafenib-loaded hollow mesoporous silica nanoparticles have exhibited targeted delivery of CRISPR/Cas9 for precise gene editing [45].

Liposomes, characterized by a lipid bilayer structure, play a pivotal role in genome editing, encapsulating various agents like nucleic acids and proteins. Their targeted delivery, responsiveness to environmental cues, and versatility in CRISPR/Cas9 applications make them indispensable. Key aspects in CRISPR delivery include:

2.5.1. PEGylation:

Enhancing efficiency, PEG-modified liposomes optimize CRISPR delivery by improving pharmacokinetics and minimizing immune responses.

2.5.2. Endosomal escape:

Facilitating the release of CRISPR-Cas9 cargo into the cellular cytoplasm, liposomes ensure effective genome editing.

2.5.3. Stimuli-responsive design:

Tailored to environmental cues, liposomes provide spatial and temporal control over CRISPR cargo release.

2.5.4. Targeting strategies:

Surface modifications enable precise delivery to specific cells or tissues, enhancing CRISPR/Cas9 precision.

2.5.5. Light-sensitive delivery:

Innovative light-sensitive liposomes, like those loaded with a photosensitizer, offer precise spatial and temporal control in CRISPR/Cas9 gene editing.

Despite challenges like low transfection efficiency, the adaptability of liposome formulations allows customization for specific CRISPR requirements. Noteworthy liposome types include:

2.5.6. EG-bearing liposomes:

Tailored with PEG, these liposomes, like the ones carrying CRISPR components, enhance genome editing efficiency by improving pharmacokinetics and minimizing immune responses.

2.5.7. Charged liposomes:

Positively or negatively charged liposomes, exemplified by those carrying CRISPR payloads, target specific cells, contributing to precise genetic modifications.

2.5.8. Stimuli-responsive liposomes:

Engineered to respond to environmental cues, liposomes, such as those used in CRISPR delivery, ensure spatial and temporal control over cargo release, enhancing gene editing precision.

2.5.9. Light-sensitive liposomes:

Innovations like light-sensitive liposomes loaded with CRISPR components provide high control in gene editing, allowing for flexibility and precision.

2.5.10. AD liposomes and cationic lipids:

Liposomes derived from AD liposomes, as well as those using cationic lipids like DOTAP and DLin-MC3-DMA, showcase enhanced delivery efficiency in nucleic acid and CRISPR/Cas9-mediated gene editing. These liposomes optimize genome-editing efficiency by modulating endocytic pathways. [46, 47].

Viral vectors, such as adeno-associated viruses (AAVs) and lentiviruses, have a well-established history in gene therapy and are now integral to genome editing. These vectors deliver the CRISPR-Cas9 system to target cells with remarkable efficiency and offer the advantage of providing long-term expression of Cas9 and gRNA, making them particularly suitable for genetic diseases requiring sustained correction [42]. The use of viral vectors in gene therapy has seen significant progress, with nearly 70% of clinical trials utilizing viral vectors, highlighting their continued importance in the field. Despite their successes, challenges still limit their full potential, and ongoing research aims to address these limitations.

Viral vectors have been employed for the treatment of various diseases, including metabolic, cardiovascular, muscular, hematologic, ophthalmologic, and infectious diseases, as well as different types of cancer [43, 44]. For example, AAV-based gene therapy has been used to treat spinal muscular atrophy, a rare genetic disease that causes muscle weakness and wasting. In this case, the AAV vector was used to deliver a functional copy of the SMN1 gene to motor neurons, resulting in improved motor function and survival in patients. Another example is the use of lentiviral vectors in the treatment of HIV/AIDS. Lentiviral vectors have been used to deliver functional copies of the CCR5 gene, which encodes a co-receptor for HIV, to CD4+ T cells. This approach has been shown to protect against HIV infection in animal models and is currently being tested in clinical trials [48]. The development of nanoparticle systems to deliver the CRISPR-Cas9 system to target cells has overcome obstacles such as the large molecular weight of the Cas9 protein and its low stability against serum enzymes and proteins. Additionally, the use of viral carrier systems has been shown to provide high efficiency in genome editing. While viral vectors have demonstrated significant promise, ongoing research and development are focused on addressing challenges and further improving their applicability. The field of gene therapy continues to see innovative modifications and support from the pharmaceutical and biotech industries, indicating a continued commitment to advancing viral vector-based therapy. Therefore, viral vectors, particularly AAVs and lentiviruses, remain crucial tools in the landscape of gene therapy and genome editing, with ongoing efforts to enhance their efficacy and safety for clinical applications [46-48].

2.6. Gene editing in stem cells:

Stem cells hold immense potential for regenerative medicine and cell-based therapies Stem cells possess the unique ability to self-renew and differentiate into various cell types, making them promising candidates for regenerative medicine and cell-based therapies [49]. Precisely modifying their genes via CRISPR-Cas9 unlocks their full therapeutic potential, and biomaterials play a crucial role in achieving this effectively. Let's dive deeper into recent developmental examples across different delivery strategies:

2.7. Transfection reagents:

Lipid Nanoparticles (LNPs): Recent advances involve LNPs modified with cell-specific targeting ligands. For instance, researchers conjugated folate ligands to LNPs for targeted delivery to pluripotent stem cells expressing folate receptors. This led to efficient gene editing with minimal off-target effects [48].

2.8 Polymer-peptide hybrids:

Novel synthetic polymers with peptide conjugation offer enhanced cellular uptake and endosomal escape. A recent study employed chitosan-based polymers conjugated with cationic peptides for CRISPR-Cas9 delivery to mesenchymal stem cells, achieving high editing efficiency with improved biocompatibility [48, 49].

3. Electroporation platforms:

3.1. Microfluidic chips:

Researchers are now integrating microfluidic chips with temperature control to enhance cell viability during electroporation. A recent study used a temperature-controlled microfluidic chip for CRISPR-Cas9 delivery to neural stem cells, demonstrating improved cell survival and editing efficiency compared to conventional methods [50].

3.2. Conductive hydrogels:

Development of hydrogels with specific electrical properties allows for localized, tissue-specific CRISPR-Cas9 delivery. Scientists developed a conductive hydrogel scaffold for *in vivo* delivery to cardiac stem cells residing within heart tissue. This approach facilitated targeted gene editing with minimal impact on surrounding tissues [49, 50].

4. Viral vectors:

4.1. Engineered AAV vectors:

Adeno-associated viral (AAV) vectors are gaining popularity due to their safety and low immunogenicity. Recent efforts focus on enhancing their targeting capabilities. Researchers engineered AAV vectors with stem cell-specific promoters, achieving efficient and selective gene editing in human embryonic stem cells without harming neighbouring cell types [51].

4.2. Hybrid viral vectors:

Combining different viral vectors leverages their unique strengths. A recent study used a hybrid vector combining AAV and lentiviral vectors, achieving sustained and efficient gene editing in hematopoietic stem cells with minimal insertional mutagenesis [52].

4.3. In-vivo genome editing:

In vivo genome editing holds immense promise for treating genetic disorders directly within the patient's body [40]. However, delivering CRISPR-Cas9 components to target tissues or organs in a specific and efficient manner remains a significant challenge. Innovative strategies are being developed to overcome these challenges and propel the field forward.

4.3.1. Targeted nanoparticles:

These miniature cargo ships can be engineered to carry CRISPR-Cas9 components and adorned with ligands that bind to receptors unique to specific tissues. This targeted delivery approach minimizes off-target effects and enhances overall efficiency. For example, researchers at MIT crafted nanoparticles coated with folate ligands, precisely targeting receptors abundant on cancer cells, enabling gene editing specifically within tumors and laying the groundwork for personalized cancer therapies [41, 42].

4.3.2. Controlled-release scaffolds:

These biomaterials function as custodians, encapsulating CRISPR-Cas9 components and releasing them gradually over time. This controlled, sustained delivery mechanism ensures localized gene editing within the target area, amplifying the therapeutic impact. For instance, a biodegradable hydrogel scaffold loaded with CRISPR-Cas9 was employed to treat Leber's hereditary optic neuropathy, a challenging mitochondrial disease affecting the retina. This localized editing within the eye demonstrated improved vision in animal models, offering promise for conditions previously deemed untreatable [20, 35, and 36].

4.3.3. Engineered viral vectors:

Repurposed viruses can be adeptly delivered into cells, with their capsids (outer shells) and promoters (genetic switches) meticulously engineered to target specific tissues. This targeted delivery strategy ensures that the editing machinery reaches its intended destination, minimizing risks and maximizing efficacy. For example, scientists modified an AAV vector with a muscle-specific promoter, not only delivering CRISPR-Cas9 but correcting a mutation causing Duchenne muscular dystrophy in muscle cells. The result: significant improvements in muscle function observed in animal models [48, 49].

4.3.4. Beyond delivery:

Researchers are advancing high-fidelity Cas9 enzymes and guide RNAs with heightened specificity, reducing the risk of unintended edits. Strategies involve sustained delivery systems or inducible editing approaches to enhance the persistence of gene editing. Careful

consideration of ethical implications, especially concerning germline editing and equitable access, is crucial for responsible development [20, 28,52].

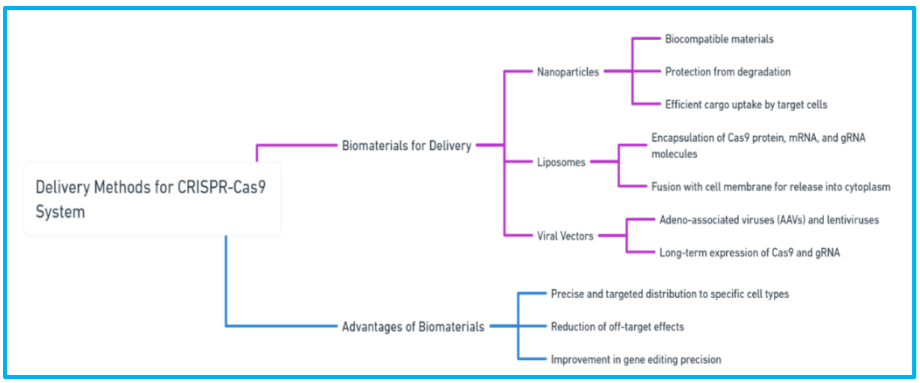

Figure. 2: In-vivo gene editing

5. Challenges and future directions in biomaterials for cancer immunotherapgy and genome editing:

The development of biomaterial-based therapies presents a myriad of complex challenges that necessitate rigorous scientific investigation and innovative solutions [53]. Foremost among these challenges is the imperative to ensure safety and biocompatibility. As these biomaterials interact intimately with the patient's immune system and biological processes, a comprehensive assessment of their biocompatibility is essential to mitigate the risk of adverse reactions or immune responses [17, 54]. This extends to the imperative of long-term evaluation of the effects of biomaterials, especially when employed in the context of chronic treatments, where potential impacts must be thoroughly understood [17, 53, and 54].

Efficient delivery and precise targeting represent pivotal facets of therapeutic success. Achieving optimal outcomes hinges on enhancing the delivery efficiency of biomaterials, particularly in the often-hostile tumour microenvironments [55]. Innovative strategies must be devised to bolster the targeting specificity and improve tissue penetration, addressing the unique challenges presented by biomaterial-based therapies. The potential immunogenicity of certain biomaterials, notably viral vectors, poses a substantial concern, potentially limiting their effectiveness upon repeated administration [56, 57]. Therefore, it is imperative to explore avenues for mitigating immunogenicity without compromising therapeutic efficacy [57]. This calls for the development of novel biomaterials engineered to exhibit reduced immunogenic potential or the implementation of immune-evasion strategies to enhance their clinical applicability [58].

Off-target effects, a notable challenge in gene editing therapies, where CRISPR-Cas9 may inadvertently edit unintended genomic sites, necessitate continual refinement of the specificity and accuracy of CRISPR-Cas9 systems. This ongoing pursuit aims to minimize off-target effects and bolster the safety profile of genome editing treatments [59]. Practical considerations regarding manufacturing scalability and standardization come to the forefront. Ensuring reproducibility, quality, and alignment with regulatory standards is imperative to meet the burgeoning demand for clinical trials and future commercialization [60]. Standardization of manufacturing processes and strict adherence to regulatory compliance are pivotal for the widespread adoption of biomaterial-based therapies [61].

Moreover, the vision of personalized medicine, integral to both cancer immunotherapy and genome editing, requires the seamless integration of biomaterials with patient-specific genomic and immunological data [62]. Realizing this ambition hinges on advancements in high-throughput sequencing and bioinformatics, which are poised to play instrumental roles in optimizing biomaterial-based therapies tailored to individual patient profiles [63]. Combination therapies that harness the synergy between diverse biomaterials, immunotherapies, and gene editing strategies hold immense promise for enhancing cancer treatment. Nevertheless, unravelling the intricacies of optimal combinations and understanding potential interactions between various biomaterials and therapies poses a multifaceted scientific challenge that demands meticulous exploration [64-66]. Lastly, as biomaterial-based therapies transition from the realm of research to clinical trials, successfully navigating the complex regulatory landscape and securing approvals from regulatory agencies emerges as a pivotal step [64]. This necessitates collaborative efforts encompassing academic researchers, industry partners, and regulatory authorities to ensure the safe and efficient translation of these pioneering therapies into clinical practice [64, 65].

6. Conclusion:

The fusion of biomaterials with groundbreaking techniques like cancer immunotherapy and genome editing represents a major leap forward in cancer treatment. Biomaterials act as crucial carriers for immune-modulating agents, amplifying the effectiveness of these therapies while minimizing unintended side effects. They're like architects, designed to encapsulate and deliver agents to the tumor microenvironment, enhancing the immune response of the body against cancer. These materials can also enhance sustained release, ensuring immune cells stay exposed to therapeutic agents, optimizing treatment outcomes, and minimizing systemic toxicity.

Overcoming challenges in biocompatibility and delivery efficiency is key, as is tailoring treatments for personalized medicine based on individual genetic profiles. The dedication of researchers in addressing these hurdles is pivotal, promising a future where biomaterials transform cancer care, providing safer, more effective, and personalized treatment avenues with a global impact.

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7. References:

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5):646-74.
2. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019; 69(5):363-85.
3. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell. 2015; 161(2):205-14.
4. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011; 480(7378):480-489.
5. Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science. 2012; 337(6096):816-21.
6. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015; 27(4):450-61.
7. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012; 366(26):2455-65.
8. Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med. 2011;365(8):725-33.
9. Sahin U, Derhovanessian E, Miller M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature. 2017; 547(7662):222-26.

10. Vinay DS, Ryan EP, Pawelec G, et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. Semin Cancer Biol. 2015; 35:S185-S198.
11. Burrell RA, McGranahan N, Bartek J, Swanton C. The causes and consequences of genetic heterogeneity in cancer evolution. Nature. 2013; 501(7467):338-45.
12. Doudna JA, Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. Science. 2014; 346(6213):1258096.
13. Hsu PD, Lander ES, Zhang F. Development and applications of CRISPR-Cas9 for genome engineering. Cell. 2014; 157(6):1262-78.
14. Garraway LA, Lander ES. Lessons from the cancer genome. Cell. 2013; 153(1):17-37.
15. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. Nat Rev Mater. 2016; 1:16014.
16. Hutmacher DW, Schantz JT, Lam CX, Tan KC, Lim TC. State of the art and future directions of scaffold-based bone engineering from a biomaterials perspective. J Tissue Eng Regen Med. 2007;1(4):245-60.
17. Stephan SB, Taber AM, Jileaeva I, et al. Biopolymer implants enhance the efficacy of adoptive T-cell therapy. Nat Biotechnol. 2015; 33(1):97-101.
18. Smith TT, Stephan SB, Moffett HF, et al. In situ programming of leukaemia-specific T cells using synthetic DNA nanocarriers. Nat Nanotechnol. 2017; 12(8):813-20.
19. Dreaden EC, Alkilany AM, Huang X, Murphy CJ, El-Sayed MA. The golden age: gold nanoparticles for biomedicine. Chem Soc Rev. 2012; 41(7):2740-2779.
20. Annabi N, Tamayol A, Uquillas JA, et al. 25th Anniversary Article: Rational Design and Applications of Hydrogels in Regenerative Medicine. Adv Mater. 2014; 26(1):85-123.
21. Wang H, La Russa M, Qi LS. CRISPR/Cas9 in Genome Editing and Beyond. Annu Rev Biochem. 2016; 85:227-264.
22. Tang D, Cao Y, Li J, Wang L, Li X, Wu J, et al. Biomaterial-based strategies for enhanced cancer immunotherapy. Biomaterials. 2022; 283:121548.
23. Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF, Langer R, Farokhzad OC. Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. Chem Soc Rev. 2012; 41(7):2971-3010.
24. Shi J, Wang L, Zhang S, Zhang J, Wang S, Li Y, et al. Biomaterial-based delivery of CRISPR-Cas9 system for cancer therapy. Bioact Mater. 2020;5(4):38
25. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, McDermott DF, Powderly JD, et al. Safety and activity of anti-PD-1 antibody (nivolumab) in patients with recurrent or metastatic non-small-cell lung cancer. J Clin Oncol. 2012; 30(17):2112-20.

26. Palucka K, Ueno H, Fay J, Banchereau J. Dendritic cell-based therapeutic vaccines. Annu Rev Immunol. 2010; 28:237-69.
27. Zhu J, Tang D, Cao Y, Li J, Wang L, Wu J, et al. Injectable hydrogels for combination immunotherapy of cancer. Mater Sci Eng C Mater Biol Appl. 2023; 133:112642.
28. Chen Z, Yue Z, Wang R, Yang K, Li S. Nanomaterials: A powerful tool for tumour immunotherapy. Front Immunol. 2022; 13: 979469.
29. Li Y, Li S, Jiang Z, Tan K, Meng Y, Zhang D, et al. Targeting lymph node delivery with nanovaccines for cancer immunotherapy: recent advances and future directions. J Nanobiotechnol. 2023; 21(1).
30. Bezbaruah R, Chavda VP, Nongrang L, Alom S, Deka K, Kalita T, et al. Nanoparticle-Based Delivery Systems for Vaccines. Vaccines. 2022; 10(11):1946.
31. Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. Nat Rev Cancer. 2012; 12(4):237-51.
32. Zhang R, Billingsley MM, Mitchell MJ. Biomaterials for vaccine-based cancer immunotherapy. J Control Release. 2018; 292:256-76.
33. Gonzalez H, Hagerling C, Werb Z. Roles of the immune system in cancer: from tumour initiation to metastatic progression. Genes Dev. 2018; 32(19–20):1267-84.
34. Olson DJ, Odunsi K. Adoptive Cell Therapy for Nonhematologic Solid Tumours. J Clin Oncol. 2023; 41(18):3397-407.
35. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. Nat Rev Cancer. 2008; 8(4):299-308.
36. Kirtane K, Elmariah H, and Chung CH, Abate-Daga D. Adoptive cellular therapy in solid tumour malignancies: review of the literature and challenges ahead. J Immunother Cancer. 2021; 9(7):e002723.
37. Juat DJ, Hachey SJ, Billimek J, Del Rosario MP, Nelson EL, Hughes CCW, et al. Adoptive T-Cell Therapy in Advanced Colorectal Cancer: A Systematic Review. Oncologist. 2022; 27(3):210-19.
38. Doudna JA, Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. Science. 2014; 346(6213).
39. Wang M, Zuris JA, Meng F, Rees H, Sun S, Deng P, et al. Efficient delivery of genome-editing proteins using bioreducible lipid nanoparticles. Proc Natl Acad Sci U S A. 2016; 113(11):2868–73.

40. Pan X, Veroniaina H, Su N, Sha K, Jiang F, Wu Z, et al. Applications and developments of gene therapy drug delivery systems for genetic diseases. Asian J Pharm Sci. 2021; 16(6):687–703.
41. Chen G, Abdeen AA, Wang Y, Shahi PK, Robertson S, Xie R, et al. A biodegradable nanocapsule delivers a Cas9 ribonucleoprotein complex for *in vivo* genome editing. Nat Nanotechnol. 2019; 14(10):974–80.
42. Sahel DK, Vora LK, Saraswat A, Sharma S, Monpara J, D'Souza AA, et al. CRISPR/Cas9 Genome Editing for Tissue-Specific *In Vivo* Targeting: Nanomaterials and Translational Perspective. Adv Sci. 2023; 10(19).
43. Liang C, Li F, Wang L, Zhang ZK, Wang C, He B, et al. Tumour cell-targeted delivery of CRISPR/Cas9 by aptamer-functionalized lipopolymer for therapeutic genome editing of VEGFA in osteosarcoma. Biomaterials. 2017; 147:68–85.
44. Duan L, Ouyang K, Xu X, Xu L, Wen C, Zhou X, et al. Nanoparticle Delivery of CRISPR/Cas9 for Genome Editing. Front Genet. 2021; 12.
45. Iqbal Z, Rehman K, Xia J, Shabbir M, Zaman M, Liang Y, et al. Biomaterial-assisted targeted and controlled delivery of CRISPR/Cas9 for precise gene editing. Biomater Sci. 2023; 11(11):3762–83.
46. Yin X, Harmancey R, McPherson DD, Kim H, and Huang SL. Liposome-Based Carriers for CRISPR Genome Editing. Int J Mol Sci. 2023; 24(16):12844.
47. Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: structure, composition, types, and clinical applications. Heliyon. 2022; 8(5):e09394.
48. Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. Nat Rev Drug Discov. 2019; 18(5):358–78.
49. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. Stem Cell Res Ther. 2019; 10(1).
50. He R, Weng Z, Liu Y, Li B, Wang W, Meng W, et al. Application of Induced Pluripotent Stem Cells in Malignant Solid Tumours. Stem Cell Rev Rep. 2023; 19(8):2557–75.
51. Valenti MT, Serena M, Carbonare LD, Zipeto D. CRISPR/Cas system: An emerging technology in stem cell research. World J Stem Cells. 2019; 11(11):937–56.
52. Xu CL, Ruan MZC, Mahajan VB, Tsang SH. Viral Delivery Systems for CRISPR. Viruses. 2019 Jan 4; 11(1):28.
53. Alshangiti DM, El-damhougy TK, Zaher A, Madani M, Mohamady Ghobashy M. Revolutionizing biomedicine: advancements, applications, and prospects of

nanocomposite macromolecular carbohydrate-based hydrogel biomaterials: a review. RSC Adv. 2023; 13(50):35251–91.

54. Sánchez-Bodón J, Diaz-Galbarriatu M, Pérez-Álvarez L, Moreno-Benítez I, Vilas-Vilela JL. Strategies to enhance biomedical device performance and safety: a comprehensive review. Coatings. 2023; 13(12):1981.
55. Yousefpour P, Ni K, Irvine DJ. Engineered biomaterials for targeted modulation of immune cells and tissues. Nat. Rev. Bioeng. 2023 Jan 30; 1(2):107–24.
56. Lewis JS, Roy K, Keselowsky BG. Materials that harness and modulate the immune system. MRS Bull. 2014; 39(1):25–34.
57. Han X, Alu A, Liu H, Shi Y, Wei X, Cai L, et al. Biomaterial-assisted biotherapy: A brief review of biomaterials used in drug delivery, vaccine development, gene therapy, and stem cell therapy. Bioact. Mater. 2022; 17:29–48.
58. Mariani E, Lisignoli G, Borzì RM, Pulsatelli L. Biomaterials: foreign bodies or tuners for the immune response? Int. J. Mol. Sci. 2019 Feb 1; 20(3):636.
59. Naeem M, Majeed S, Hoque MZ, Ahmad I. Latest developed strategies to minimize the off-target effects in CRISPR-Cas-mediated genome editing. Cells. 2020; 9(7):1608.
60. Guo C, Ma X, Gao F, Guo Y. Off-target effects in CRISPR/Cas9 gene editing. Front. Bioeng. Biotechnol. 2023; 11:1143157.
61. Zhang XH, Tee LY, Wang XG, Huang QS, Yang SH. Off-target effects in CRISPR/Cas9-mediated genome engineering. Mol. Ther. Nucleic Acids. 2015; 4:e264.
62. Ho D, Quake SR, McCabe ERB, Chng WJ, Chow EK, Ding X, et al. Enabling technologies for personalized and precision medicine. Trends Biotechnol. 2020 May; 38(5):497–518.
63. Abdeen A, Cosgrove B, Gersbach C, Saha K. Integrating biomaterials and genome editing approaches to advance biomedical science. Annu. Rev. Biomed. Eng. 2021; 23(1):493-516.
64. Dubey AK, Mostafavi E. Biomaterials-mediated CRISPR/Cas9 delivery: recent challenges and opportunities in gene therapy. Front. Chem. 2023; 11.
65. Hasanzadeh A, Ebadati A, Dastanpour L, Aref AR, Sahandi Zangabad P, Kalbasi A, et al. Applications of innovation technologies for personalized cancer medicine: stem cells and gene-editing tools. ACS Pharmacol. Transl. Sci. 2023 Nov 14; 6(12):1758–79.
66. Dai X, Blancafort P, Wang P, Sgro A, Thompson EW, Ostrikov K (Ken). Innovative precision gene-editing tools in personalized cancer medicine. Adv. Sci. 2020 Apr 23; 7(12).