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Composite biomaterials in immunomodulation: A new era in targeted therapy

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ABSTRACT

Therapeutic immunomodulation has progressed from broad-spectrum options to precision options that re-engineer immune responses in a spatially and temporally accurate manner. As researchers pursue improved immunomodulatory therapies, understanding how biomaterials impact immune cells is vital. Biomaterials are not simply passive supports for tissues to use, but can provide cues that can durably modulate immune responses and facilitate tissue healing. Researchers are developing biomaterials to shape immune cell behavior, which expands the opportunities for treating diseases (e.g. cancer) and enhancing tissue regeneration. In this review, we review the design principles of composite biomaterials for immunomodulation, focusing on how multicomponent constructions afford synergistic control over immune cell activation, trafficking, and memory. We discuss representative systems and mechanisms emphasizing mutual influences across cancer therapy, autoimmunity, and infectious diseases. In addition to performance functionality, we provide discussion of translational impediments like biocompatibility, regulatory concerns, and long-term safety that influence clinical potential.

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1. Introduction

Over the past 50 years, the idea of tuning the immune system, either through immunotherapy or biomaterials, has transformed medicine. What started out as an exploration for a way to "fight" metastatic cancer has become a prominent approach to treating diverse number of diseases associated with immune dysregulation [1]. The immune system is essential for combating threats to the body and repair of tissues, however when it is out of balance it creates great problems that range from the cancer not being immune to detection, to chronic inflammation with aging or diabetes [2-5]. Conventional immune therapies, including glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs), and immunosuppressants, are often non-specific and potent with considerable side effects [6]. Today, we are entering a new era of therapeutic immunomodulation, where immunotherapies consider spatial and temporal specificity, bypassing the traditional non-targeted immune therapies that could modulate an immune response. In this new landscape, clinical success depends on providing the right signals to the right cells at the right time, enabling the desired response with the lowest possible off-target effects [7, 8]. Advanced drugs delivery systems

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(DDSs), such as nanoparticles, liposomes, and engineered biomaterials (of polymers, lipids, self-assembled proteins, and inorganic compounds), can now be designed to access immune cells and modulate the production of cytokines, and the properties of which can even mimic the extracellular matrix (ECM) for the benefit of tissue regeneration. They can also enable controlled and sustained drug-release, provide tissue-like properties, and confidence of cell-specific targeting [9-12]. Composite biomaterials, in particular, are enabling personalized immunotherapy by providing multidimensional properties to modulate immune responses further with specificity and limited toxicity risk [11]. Subsequently, platforms that are providing composite biomaterials are developing new frontiers for vaccines [13], cancer therapies, and for treatments of chronic inflammation related to autoimmune and infectious diseases [7]. The introduction of immunomodulatory biomaterials represents an opportunity to rethink therapeutic paradigms, influence outcomes, and limit harmful adverse effects across various therapeutic uses [3, 10, 14]. This paper considers the use of composite biomaterials to induce immunomodulation as an approach towards a new era of targeted therapy. It also explores some of the important mechanisms of immunity regulation, interaction with immune cells, and examples of applications in cancer, autoimmune, and infectious diseases, and discusses some of the issues and emerging trends.

2. Mechanisms of immunomodulation

The immune system is an extremely adaptive system that continuously evaluates the body's internal and external environment, looking for signs of infection, injury, or abnormal proliferation of cells [15-17]. It does so through innate and adaptive response pathways that carefully work together to restore homeostasis, remove unsafe agents and create immunological memory [18]. However, in circumstances that disturb this balance, as is seen with chronic inflammation and as we age or through disease, tissue repair can be impaired and ultimately lead to persistent wounds, fibrosis or autoimmune conditions [15, 19]. Innate immunity serves as the body's first line of defense, providing rapid but nonspecific protection through macrophages, neutrophils, cytokines, complement proteins, monocytes, and acute-phase proteins (Fig. 1). When pathogens manage to resist or evade these mechanisms, the adaptive immune system is activated, offering highly specific responses mediated by T and B lymphocytes. Together, these complementary arms of immunity ensure both immediate host defense and the long-term capacity to recognize and eliminate recurring threats [20]. Biomaterials give us the tools we need to modulate the immune response [3, 5]. Following implantation, biomaterials will interact with the host and ultimately the host immune system, the process may initiate a foreign body response (FBR) which leads to recruitment of immune cells and release of cytokines; if not regulated correctly, this process can deteriorate the performance of the medical device or tissue scaffold [21, 22]. Immunomodulatory materials have been developed, with a particular focus on biodegradable polymers, to control immune cell function and reduce inflammation [21, 23]. A focused area of research is how biomaterials influence dendritic cells (DCs) that initiate adaptive immunity. Material composition, topography, and surface properties can all influence DC maturation and antigen presentation, and influence the ensuing immune response. In vitro studies of DC activation have often been utilized as predictive models of in vivo immunogenicity and therapeutic efficacy [18]. In addition to controlling cellular interactions, macroscale biomaterial scaffolds can provide spatial and temporal control over immune cell trafficking and function, assist with the controlled release of immunomodulatory agents (e.g., cytokines, chemokines, or antigens) and may increase the precision of therapeutic approaches while reducing systemic side effects [11, 24, 25].

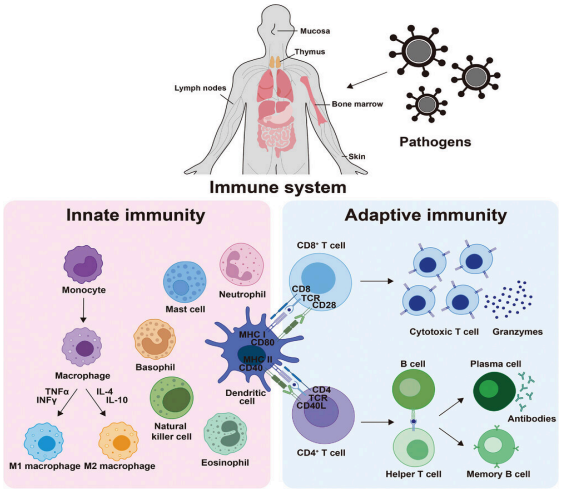

Fig. 1. The immune system comprises innate cells (dendritic cells, macrophages, natural killer (NK) cells, neutrophils, and mast cells) and adaptive cells (B and T lymphocytes). Interactions between dendritic cells and T cells, memory B cells against pathogens, antibody-producing plasma cells, and activate cytotoxic T cells [20].

In the example of cancer immunotherapy, scaffolds have been utilized in in situ vaccination strategies in which granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor antigens, and danger signals are delivered in a localized manner to recruit immature DCs, activate DCs, and support effective antigen presentation [2, 15]. In addition, composite biomaterials, comprising organic and inorganic elements, may recapitulate the extracellular matrix to drive immune-mediated tissue regeneration. These advances represent a movement toward therapies where materials are active contributors in healing rather than passive elements that may support healing [2, 3, 13].

3. Applications of composite biomaterials in targeted therapy

3.1. Cancer

Immunotherapy has transformed cancer treatment by recruiting the immune system to eradicate malignant cells [26]. Types of immunotherapies, including checkpoint inhibitors and CAR-T cells have emerging use, but there are challenges with the precision in delivery, off-target events, and durability of effect, or the specificity of activity especially in solid tumours. As composite biomaterials include smart designs for controlled release, targeted delivery, and response with a variety of therapeutic agents, it is clear that there are new opportunities for smart biomaterials to address these issues [27]. Composite biomaterials address several aspects of the DC vaccine, adoptive T-cell therapies, and cytokine-based therapies (e.g. IL-2, IL-12), as these smart approaches enhance activation of the immune response to recognize the tumour [26]. In smart vaccines, nanomaterials improve vaccines through the delivery of directed antigens and adjuvants, such that the adjuvants can accrete in lymph nodes, with the hopes of driving robust cytotoxic response, and humoral responses. Metal-based nanomaterials have also modulated immune response in a unique manner when disengaged. They have caused tumor cell death via pathways leading to pyroptosis, ferroptosis, and immunogenic cell

death (ICD) [28]. Metal based-nanomaterials have also enhanced immune presentation and enhanced T-cell infiltration. The transition of metals like manganese, zinc, magnesium, and calcium influence aspects of immunity, related to their functions, such as in the maturation of dendric cells and the formation of immune/ T-cell memory via the cGAS-STING activity [26, 29, 30]. In the newly emerged field of study known as metalloimmunology, the ability of nutritional metal ions (e.g. Ca^{2+}, Fe^{3+}, Zn^{2+}) as strong adjuvants in terms of nano-vaccines, is examined. When coupled with immune checkpoint blockade, metal-based nanomaterials are capable of induction of ICD and promote abscopal effects underlining greater targeting of metastatic cancer cells on a systemic level with established long-lasting immune memory against cancer recurrence [31, 32].

Transition metal-type nanozymes evolve as an additional opportunity, which could replicate enzymatic activity with high functionality structural stability in response to environmental contexts. Smart type nanosystems, have been employed to regulate metals ion release along with stability and reduce toxicity [33, 34]. Transition metal oxide (TMO) types such titanium, manganese, iron, and zinc oxides have provided multifunctional possibilities in multiple stages of the tumor immunity cycle, as sorts of support for antigen presentation, immune cell priming and activation, /tissue trafficking, tumor cell recognition, and even memory. These properties, along with their biocompatibility, electrical and magnetic properties and large surface area afforded a unique range of possibilities amongst multifunctional platforms. TMOs also synergize with therapies like photodynamic therapy (PDT), photothermal therapy (PTT), and sonodynamic therapy (SDT) and magnetic hyperthermia therapy (MHT).

This synergy enhances the production of reactive oxygen species (ROS), promotes ICD, and stimulates the maturation of dendritic cells, ultimately boosting tumor immunogenicity and triggering a robust anti-tumor immune response [35, 36]. Fig. 2 shows a Schematic illustration of commonly used medical devices in clinical practice.

Biomaterials are employed in the fabrication of artificial joints, dental implants, cardiovascular stents, pacemakers, catheters, and internal fixation devices. These devices support disease diagnosis and treatment or serve as substitutes for impaired organ functions. Despite their widespread application, device-associated infections remain a significant clinical challenge [37]. Moreover, Table 1 shows different types of bio-composites and their effect on the immunological system.

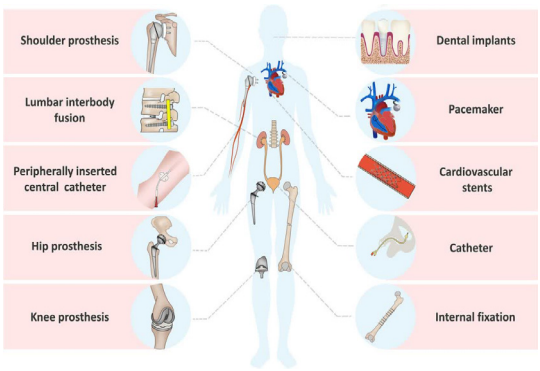

Fig. 2. Schematic illustration of commonly used medical devices in clinical practice [37].

Table 1
Types of bio-composites and their effect on the immunological system

Bio-composites	Target location (Applications)	Impact on immunology	Ref.
Hydroxyapatite (HA), Polylactide (PLA)	Application in bone, tooth and cartilage regenerative medicine	The result of PLA degradation is an inflammatory response that changes immune cell metabolism (immunometabolism)	[38]
SYNTEKIST Hydroxyapatite-based bio-composite	Anterior bone trauma (FBT), anterior bone trauma immune system	Serum levels of immunoglobulin IgE, interleukins (IL) 1 and IL10, and (Ig)M, IgG, IgA, interferon gamma (IFN γ), transforming growth factor (TGF) β, circulating immune complexes (CIC), and agglutination antibodies against allogeneic connective tissue antigens were examined.	[39]
Pure titanium (Ti), titanium alloy (TiAlV), polyether ether ekrettone (PEEK), 316L stainless steel (SS)	Craniofacial and orthopedic implants	Neutrophils produced higher levels of neutrophil extracellular traps, myeloperoxidase, and neutrophil elastase in response to PEEK and SS compared to neutrophils receiving Ti or TiAlV.	[40]
Bio-multifunctional composite sponges	Full-thickness skin repair	Through electrostatic interaction, chitosan and alginate are bound to fucoidan - Ca2 crosslinking - preparation of lyophilization processes - better hemostatic and antibacterial performance of Alginate/ Chitosan/ Fucoidan (ACF) sponge containing 10% fucoidan (ACF 1) - improved wound closure	[41]
Poly (vinyl alcohol) (PVA)	Controlled drug delivery for gene therapy	Polymeric material for designing new biocompatible nanostructured devices with excellent physical properties - soluble in water - creation of wall-to-wall chemical hydrogels - possibility of injection - also microgels were seen in the PVA raw material without reducing biocompatibility	[42]
Metal-phenolic network (MPN) complexes based on tannic acid (TA) / Zn^{2+}	In bacterial infection, as biodegradable scaffolds	Moderate control of initial severe acute inflammation - Complete inhibition of chronic inflammation caused by biodegradation - Long-lasting antibacterial function and its duration - Stable scaffold stability due to constant Zn^{2+}release rate - Prevention of Zn^{2+} cytotoxicity	[21]
Dual immunotherapy nanoparticles (DINP), polymer synthesized by mPEG-PLGA* and PLGA-PEG-Mal* (7:3 weight ratio)	B16-OVA tumor cells_ bilateral B16-F10 melanoma tumors	Using nanoparticles (NPs) enables precise spatiotemporal delivery of aPD1 and aOX40, improving T-cell activation, enhancing immunological memory, and increasing therapeutic efficacy	[43]
Bio-nanocomposites such as Silver, gold, iron oxide, and zinc oxide nanoparticles	The target organ is usually solid tumor tissue, and the cancer types in most models are breast, skin, pancreas, and lung	An important role in enhancing anti-cancer immunology, inducing apoptosis, and specifically targeting tumors with minimal side effects and maximum therapeutic efficacy	[44]
A theranostic nanocage system (Fe3O4@OA-AD-SP NCs) synthesis by Anti-cancer drug (AD) and biosurfactant Saponin (SP).	anti-cancer agents camptothecin (CPT) and luotonin A (LuA)	Serum protein binding efficacy - specific targeting - better chemotherapy efficacy - high lipophilic AD loading efficiency (>80%)	[45]
Calcium hydroxyapatite microspheres (CHAM) bio-composite	Prevention of progressive left ventricular (LV) remodeling after myocardial infarction (MI)	Effect on macrophage and fibroblast differentiation - CHAM increased proliferation, fibroblast SMA expression, and migration - reduced undesirable left ventricular dilation	[46]
Polylactic acid (PLA) composite woven from cotton fabric	wound treatment	High release concentration - limited bacterial infections - water-resistant dressing - reduced fabric porosity leads to increased drug loading capacity	[47]

*Note. Nanoparticles mPEG-PLGA (AK029; LA:GA=50:50 (w:w); MW: ~3000:36,000 Da), PLGA-PEG-Mal (Maleimide)

3.2. Autoimmune diseases

Autoimmune diseases (AD) emerge from abnormal immune responses in which the body's immune system produces a disease state due to the host mirroring its own tissue (for example, pain and inflammation). One of the basic principles of immune self-regulation is the involvement of immune cells and the ECM. This bidirectional dialogue directs immune cell activation, proliferation, differentiation, and function to maintain tissue homeostasis. When there is damage or disease, immune cells will infiltrate tissues' ECM (and along with immune cell activity) will produce the components of ECM: glycoproteins, proteoglycans, glycosaminoglycans, etc., for repair and regeneration [48].

Biomaterials have been employed for some time in medical implants, tissue engineering, and drug delivery, and they are designed to interface with biological systems [49]. However, wherever they are implanted, they typically incite a foreign body response (FBR), an inflammatory response initiated by immune recognition of the material. The FBR can considerably impact biomaterial integration/ performance; therefore, to effectively integrate all polymeric systems into practice, we must better understand and direct the inflammatory factors in FBR for the development of biomaterials with immune tolerance and optimal functionality [20].

Recent advances have revealed that biomaterials-assisted local therapies such as radiotherapy, chemotherapy, and phototherapy, can stimulate immune responses by inducing ICD. When combined with immune checkpoint blockade (ICB) therapies, these approaches may elicit systemic immune effects, including the abscopal effect, which targets metastatic lesions and fosters immune memory. While this strategy is more established in oncology, its principles are increasingly being explored for autoimmune modulation [32].

Upon implantation, biomaterials are rapidly coated by host proteins, initiating immune recognition. The chemical composition, geometry, and spatial configuration of the scaffold influence protein adsorption, cell differentiation, and immune cell behavior. Surface properties such as hydrophobicity, topography, porosity, and functional group presentation, play fundamental roles in shaping the immune response [50].

To address these limitations, chimeric antigen receptor T-cell (CAR-T) therapy has emerged as a more precise option. By engineering T cells to specifically recognize and eliminate auto-reactive B cells, CAR-T therapy holds the potential to induce long-lasting remission in patients with refractory autoimmune diseases.

Another promising avenue involves regulatory T cells (Tregs), which play a crucial role in maintaining immune tolerance. Treg-based therapies are being actively explored not only for autoimmune disorders but also in the context of transplant rejection, with the goal of reducing dependence on lifelong immunosuppressive drugs [51].

As autoimmune disease therapeutics evolve, researchers are exploring new immunomodulatory approaches to inhibiting an overactive immune response. One approach is B-cell depletion therapies (BCDTs), which use monoclonal antibodies that target CD19 and CD20. Early results show promise at eliminating more aggressive B cells that drive inflammation. However, these BCDTs, while successful at suppressing hyperactive B cells, have not demonstrated efficacy in preventing chronic inflammatory disease where auto-reactive B cells are established within lymphoid tissues, (e.g. in systemic lupus erythematosus (SLE), or other autoimmune diseases where complete elimination of auto-reactive or memory B cells is a challenge) [6].

This limitation of BCDTs has led to research with CAR-T therapy. By engineering T cells to directly recognize and eliminate the auto-reactive B cells causing disease, CAR-T therapy has the ability to provide long-term remission in patients suffering from auto-reactive refractory autoimmune disease [52].

Relatedly, research is underway using regulatory T cells (Tregs) to maintain immune tolerance. Treg-based therapies are rapidly being explored for various autoimmune diseases as well as chronic transplant rejection, ultimately to reduce the dependence on lifetime immunosuppressive drugs [53].

Recent advances in understanding both antigen-specific and polyclonal Treg biology have paved the way for new therapeutic possibilities that could reshape how we manage immune-related conditions [54].

Among the various classes of biomaterials, polymers stand out for their outstanding versatility. Their mechanical, chemical, and degradation properties can be finely tuned, making them ideal candidates for a wide range of biomedical applications [55]. For example, one promising polymer is polydopamine (PDA), known for its antioxidant and photothermal properties. PDA’s ease of synthesis and capacity for functionalization make it a compelling option for treating autoimmune diseases. Moreover, polymeric hydrogels, which can be synthesized from either functional monomers or naturally derived polymers, have garnered significant attention in drug delivery and tissue engineering due to their adaptability and biocompatibility [56].

In addition to polymers, inorganic nanomaterials such as gold nanoparticles, semiconductor quantum dots, and iron oxide nanoparticles (IONPs) offer unique optical and magnetic properties. These materials can be conjugated with bioactive molecules to enable targeted delivery and are especially well-suited for stimuli-responsive drug carriers, an essential feature for precision immunotherapy [55, 57].

Nanoparticles (NPs) play a crucial role in autoimmune therapy through two primary strategies. First, they can act as immune adjuvants, modulating immune cell responses based on their physicochemical characteristics and internalization pathways. When engineered with targeting ligands, these NPs can selectively interact with specific immune cell subsets, thereby enhancing therapeutic precision.

Second, NPs can serve as delivery vehicles for immunomodulatory agents, designed to reach targeted immune cells directly. Factors such as particle size, surface charge, and shape significantly influence cellular uptake and biodistribution, while active targeting ligands are crucial for achieving cell-specific activation and minimizing off-target effects [58].

Beyond active targeting, the manipulation of biomaterial properties also enables passive targeting. For instance, particles smaller than 5 micrometers are readily phagocytosed and tend to accumulate in immune cells like dendritic cells (DCs), which subsequently migrate to lymph nodes. Moreover, the enhanced permeability and retention (EPR) effect can be harnessed to concentrate nanocarriers in inflamed tissues, a common feature of many autoimmune disorders [59].

3.3. Infectious diseases

Biomaterials are tremendously promising to manipulate immune actions along with fighting infections. Depending on the biomaterial design, they can facilitate the body's response to implants, invading pathogens, or damaged tissues [60]. A major benefit of integrating biomaterials with drugs is their capability to accurately target and deliver therapeutic agents within the body [61]. This drug delivery mechanism is exemplified in the following illustration (Fig. 3)[62]. Perhaps, one of the best ways to approach this design is through an engineered biomaterial surface. Engineers can use surface topographies and chemical functionalities to limit bacterial adhesion and facilitate optimal immune cell interactions [60].

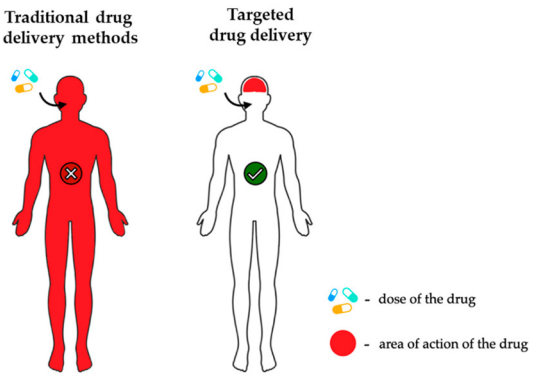

Fig. 3. Comparison between conventional and targeted drug delivery approaches [62].

In addition to considering surface design, biomaterials can be designed using biochemicals to direct immune cell actions. For example, the release of cytokines and chemokines from biomaterials may be controlled in such a way that specific immune cells can be recruited or activated to promote tissue generations with minimized inflammation [63].

In addition to cytokine manipulation, we can create a biomaterial that mimics an ECM to direct immune responses. ECM-based biomaterials can (1) provide a structural scaffold, (2) provide bioactive signal to promote healing and immune tolerance [64, 65]. While ECM-biological resemblance biomaterials can use the natural biological similarities to engage the immune system or regenerate tissue, there is growing interest in nanotechnology. Nanotechnology introduces tools that allow precision in the influence and modulation of the immune system where biomaterials are more limited in the manipulation of the immune system. The use of nanoparticles allows for targeted delivery to immune cells of drugs, antigens, genetic material or biologics to enhance therapeutic efficacy while reducing off-target effects [66, 67].

To expand the use of nanoparticles, metal-phenolic networks (MPNs) can be formulated to create multifunctional, bioactive and more chemically stable delivery system biomaterials. MPNs can remove reactive ROS while simultaneously, deliver antimicrobials and manipulate immune responses [68].

Similarly, glycomaterials can engage with carbohydrate-binding receptors to precisely modulate immune responses as the introduction of potential antigens are commonly reliant on natural glycan structures to promote cellular signaling and immune recognition [69].

These immune-modulating methods are especially relevant for enhancing the long-term viability of transplanted biomaterials by stopping fibrotic encapsulation and slowing chronic inflammation, thus improving integration and function [70]. Kim et al. [70] These multifunctional materials can furthermore significantly influence macrophage polarization, which is an important driver of immune outcomes. These biomaterials can promote macrophage polarization towards a pro-regenerative state, which can accelerate and enhance healing while minimizing chronic inflammation.

More recently, worldwide health issues associated with the COVID-19 pandemic have sown the maturation of responsive biomaterials, especially in the field of immunotherapy, as biomaterial-based vaccines, and antiviral and sterilant coatings potentially have contributed to controlling viral transmission and enhancing immune protections [71, 72].

Chronic wound care also represents a treatment space of great potential where immune-modulating biomaterials could improve patient outcomes by favorably favouring the local immune environment for tissue repair and preventing infection in infected and chronic wounds that respond poorly to convention treatments [73].

4. Challenges and innovations

Medical biomaterials development encompasses two major challenges: achieving therapeutic efficacy while ensuring biocompatibility and minimizing off-target effects, both acute and chronic. While some progress has been made in the development of stimulus-responsive biomaterials that can activate in targeted biological environments, it is still difficult to ensure that the activated biomaterials precisely target tissues, while remaining as systemically non-contacting as possible [74].

The post-implantation dilemma arises when biomaterials undergo the inevitable recognition by the host immune system as a foreign entity resulting in a cascade of responses that leads to Foreign Body Reaction (FBR). This chronic inflammatory and fibrotic tissue response has been observed to be detrimental to the integration of medical devices. Despite the development of various strategies to limit the physiologic immune response, attempts to overcome chronic FBR are limited by current knowledge of the immune mechanisms and a lack of predictive models reflecting those mechanisms [75].

There is growing interest in appraising biomaterials as immunomodulatory agents, but a migration from immune-suppression to immune-modulation will be delayed and thwarted by a lack of uniform assessment platforms. Unlike pharmacological agents, which have standardized test or treatment pathways, biomaterials suffer from a lack of reliable in vitro assays and fragmentation in nomenclature. Consequently, assessing the immunomodulatory capacity of biomaterials across contexts often leads to poor and biologically ambiguous conclusions [76, 77].
Clinical translation of biomaterials for medical applications is also limited by long-term safety. Prolonged activation of the immune response could lead to alterations in homeostasis. Inevitably, variability across patient populations and the differences between laboratory animal models and physiology (including immaturity in an infant) makes predicting outcomes difficult. Adverse events such inflammation, fibrotic tissue and rejected devices emphasize the need for more insight in the microenvironment of tissues [5].

Developing biomaterials with predictable immune behavior is also challenging because of the breadth of material property diversity and immensity [78]. Macrostructure (i.e., geometry, diameter, surface shape) and surface chemistry (i.e., charge, hydrophobicity) considered independently affect how the immune system recognizes biomaterials to varying degrees, but isolating each of these parameters has proven notoriously complex. As materials bio-degrade, changing immunogenicity adds uncertainty to measuring immune response and further complicates development [79, 80].

For antimicrobial uses, surface modifications are generally intended to resist bacterial colonization, but there is no established micropattern that consistently prevents attachment across various microbial species. This is still a large hurdle for designers, especially for clinical use and wider varieties of pathogens [37].

Despite the greatest vigor of biomaterials like metal ion-releasing dressings, microneedle hydrogel vaccines, and electrostimulation composites, limitations still exist. These biomaterials show potential to control tissue oxidative stress, macrophage polarization, and after-injury tissue regeneration; however, the specific mechanisms of action and long-term toxicity of each material are primarily undefined [81].

Biomaterial-based immunomodulation has shown promise in complex surgical procedures such as vascularized composite allotransplantation (VCA), however, overcoming localized

immune regulation without the use of systematic immunosuppression is a technical challenge, and product durability remains in doubt [82].

Injectable macroscale biomaterials utilized for cancer immunotherapy provide a minimally invasive delivery pathway with some sustained local release profiles, but suffering may arise in therapeutic resource intensity versus the systemic toxicity risk. Anything beyond mere use of the biomaterial may further depend on reproducible control over the timing and extent of immune activation [83]. Ultimately, while biomaterials have potential to be used for immune modulation, they face key challenges i.e. limited mechanistic insight, unpredictable long-term effects, and risks in clinical translation. Overcoming these requires sustained interdisciplinary collaboration across materials science, immunology, and medicine.

5. Conclusion

Composite biomaterials are transforming our understanding of immunomodulation and regenerative medicine. By combining biopolymers, nanoparticles, plant-derived compounds, and essential trace elements such as selenium and magnesium, these materials enable precise modulation of immune responses and support cell and tissue repair. Utilizing innovative delivery systems like liposomes and nanoscale carriers for immunomodulatory agents, these composites also advance the trend toward personalized medicine.

The immunobiological function and efficacy of these materials largely depend on their physicochemical properties, particularly those influencing elemental delivery and immune cell recognition. Characteristics including surface charge, hydrophobicity, and scaffold architecture critically affect cytokine production, inflammatory initiation, and cellular responses. Whether serving as nanoscale carriers or macroscale scaffolds, biomaterials must carefully balance immune activation and suppression while minimizing systemic toxicity. Progressing research towards understanding biomaterial interactions within complex, pathological, and immunocompromised environments will provide valuable insights for managing the foreign body response. Future platforms that modulate chemical signals derived from the extracellular matrix and harness dendritic cells to activate or suppress immune responses hold promise for improved immune control and therapeutic efficacy. Ultimately, composite biomaterials offer a versatile and effective platform for targeted therapies, merging materials science and immunology to create safer and more effective individualized treatments, including precision immunotherapy.

Author contributions

Tanaz Ghasabpour: Investigation, Writing – Original Draft Preparation, Writing –Review & Editing; **Sepehr Puria:** Writing – Original Draft Preparation, Writing –Review & Editing; **Firoozeh Niazvand:** Conceptualization, Writing – original draft, Writing – review & editing; **Seyedeh Sana Ghazimirsaeid:** Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare no conflict of interest.

Data availability

No data is available.

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