

Surface functionalized calcium phosphate bioceramics for immunomodulatory biomaterials

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Calcium phosphate (CaP) bioceramics, including apatite (Ap)-based materials, are naturally biocompatible, but they frequently require surface functionalization to achieve optimal integration with biological systems, especially with immune cells. Surface functionalization strategies tailor CaP bioceramic nanoparticles to enhance cell adhesion, proliferation, differentiation, and overall biocompatibility. This is because functionalized surfaces interact more dynamically with immune cells, *i.e.*, macrophages, dendritic cells, and lymphocytes, through surface receptors and signaling pathways. The dynamic interaction may activate immune cells, release cytokine, differentiate cells, and regulate inflammation. Therefore, to resolve the limitations of natural CaP bioceramics, surface functionalization is crucial. Modified bioceramics nanoparticles' surface properties ensure more effective integration with biological tissues. In addition, biomolecule immobilization on CaP bioceramic surfaces provides a versatile approach in establishing a foundation for the development of immunomodulatory biomaterials. This review provides an overview of recent biomedical research on CaP bioceramics, especially Ap-based materials, focusing on advancements in surface functionalization strategies designed to improve interactions with immune cells. It also examines the role of immobilized biomolecules in modulating immune responses, highlighting their potential for clinical applications.

Keywords: Surface functionalization, Calcium-phosphate bioceramics, Immunomodulatory biomaterials, Adaptation, Sustainability

INTRODUCTION

Bioceramics, a class of inorganic and crystalline materials, are recognized for their biocompatibility and have become central to tissue engineering research^{1,2}. Among them, calcium phosphate (CaP) bioceramics, including hydroxyapatite (HAp) or apatite (Ap), for example, are commonly used in bone regeneration due to its strong affinity to hard tissues. Over the years, HAp have been explored for their potential in hard tissue repair, with a primary focus on osteoconductivity and osteoblastic activity³⁻⁶. However, while significant progress has been made in understanding their structural properties, research has often overlooked their potential bioactivity⁷, thus neglecting their capacity to induce biological effects like cell signaling. Although Ap is generally considered biologically less reactive (metastable), recent efforts aim to enhance their bioactivity by incorporating antibacterial properties⁸⁻¹¹. Despite promising developments, these approaches have encountered challenges in achieving effective clinical

outcomes^{12,13}

Research on Ap bioceramics applications fails to adequately address a crucial factor: the immune response, which is the body's primary reaction to biomaterials in both sterile and non-sterile environments. Immune-related failures can significantly hinder their clinical efficacy, resulting in additional health risks and financial costs for patients^{7,13}. Although ceramics biomaterials, including Ap, are generally viewed as biocompatible, they may still trigger immune reactions, such as inflammation and hypersensitivity, in surrounding tissues, which can disrupt cellular communication and compromise bio-integration. Inflammation alone is estimated to cause nearly 50% of biomaterial failures and is frequently associated with pain^{14,15}. Meanwhile, local immune system may damage the materials and the surrounding tissue by affecting their chemical components or reacting to their physicochemical properties^{7,16}.

Recent advancements reveal that biomaterials, including CaP bioceramics, especially Ap bioceramics, can be surface engineered to actively engage with the

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biological microenvironment, particularly immune cells, offering new opportunities for immunomodulation¹⁷. However, although the role of bioceramics in immune response regulation is crucial for therapeutic success, it remains underexplored. This shift toward active immune modulation represents a significant transformation in biomaterial science, positioning surface functionalization as a key strategy for improving cellular and immune interactions¹⁸.

Nowadays, surface functionalization is essential for controlling cellular interactions, enabling targeted delivery to immune cells through the attachment of specific targeting moieties. Incorporating bioactive molecules, such as peptides, proteins, or ligands, onto bioceramic surfaces allows for the precise modulation of cellular behavior and immune responses^{13,16-18}. Despite growing recognition of its potential, research on using surface-functionalized CaP bioceramics for immune

response modulation is still limited. Expanding this research could contribute to developing more effective, immune-integrative biomaterials, ultimately improving therapeutic outcomes. In view of the challenges, this review aims to bridge the gap by examining the latest surface functionalization techniques for CaP bioceramics, emphasizing their role in immunomodulation and their potential as immunomodulatory biomaterials in biomedical therapies. Although in general bioceramics have potential to be surface engineered to enhance their immune responsiveness and cell signaling capacity, but the scope in this study is limited to calcium and phosphate-based bioceramics, including Ap bioceramics.

CALCIUM-PHOSPHATE BIOCERAMICS IN BIOMEDICAL FIELD

To provide an updated overview of the recent use of

Table 1 Studies on bioceramics used for biomedical applications

Bioceramics	Biomedical Application	Surface modification approach	Activity	Ref.
Calcium carbonate	Bone tissue engineering	Coating	Antibacterial	19)
Hydroxyapatite	Bone tissue engineering	Coating	Antifungal	20)
β -tricalcium phosphate	Bone tissue engineering	Plasma treatment Coating	Cell attachment and proliferation	21)
Hydroxyapatite	NA	NA	Antibacterial Antibiofilm	22)
β -tricalcium phosphate Hydroxyapatite	Bone tissue engineering	NA	Antibacterial	23)
Hydroxyapatite	Bone tissue engineering	NA	Antibacterial Antioxidant	24)
Hydroxyapatite	NA	Coating	Cytokine release modulation	25)
Hydroxyapatite	Drug delivery Cell carriers	NA	Cell attachment Drug loading Antibacterial	26)
Carbonate apatite	Bone tissue engineering	Coating	Cell viability	5)
Hydroxyapatite	Bone tissue engineering	Coating	Antibacterial Antibiofilm	27)
Hydroxyapatite	Drug delivery	NA	Drug loading	28)
Hydroxyapatite	Drug delivery Bone tissue engineering	Adsorption	Drug loading Sustained release	29)
Hydroxyapatite	Imaging Drug delivery	Conjugation	Drug loading	30)
Hydroxyapatite	NA	Conjugation	NA	31)
Calcium phosphates	Bone tissue engineering Drug delivery	Coating	Drug loading	32)
Hydroxyapatite	Bone tissue engineering	Coating	Cytocompatibility and proliferation	33)

NA: not applicable/specified

CaP bioceramics in various biomedical fields over the past five years, particularly HAp and carbonate apatite (CHA), advanced search techniques were applied on PubMed. The search utilized the following keywords: (bioceramics [Title/Abstract]) OR (hydroxyapatite [Title/Abstract]) OR (carbonate apatite [Title/Abstract]) AND (biomedical [Title/Abstract]). This yielded a total of 735 articles. Review articles and those focused exclusively on the physicochemical properties of Ap bioceramics, without addressing their biomedical applications, were excluded. As of June 2025, approximately 325 articles were identified that specifically explored the use of bioceramics in biomedical applications, highlighting their continued relevance as a biomaterial for developing biocompatible materials across a range of uses. Some relevant studies of bioceramics modification approaches used in biomedical fields are listed in Table 1.

Table 1 highlights that CaP bioceramics are predominantly used in bone regeneration and repair. The literature review further revealed that various modifications are primarily aimed at enhancing the physicochemical properties or antimicrobial activities of the implanted biomaterials; this is valid whether CaP bioceramics serve as the main component of the implant or as a part of the modification strategy employed. Drug delivery seems to be an emerging area of research, as evidenced by several studies reporting on the modified CaP bioceramics' ability to encapsulate and release drugs or biomolecules in a controlled manner^{26,28-30,32}.

Most surface modification approaches for bioceramics rely on coating, likely due to its effectiveness in enhancing implant adhesion, mechanical strength, electrical conductivity, wettability, and antibacterial properties³⁴. Many studies have utilized bioceramics, such as HAp, as coating agents on substrates to augment the biocompatibility and bioactivity of implants. This indicates that a deep understanding and widespread application of bioceramic coatings or functionalization are still emerging. One study demonstrated the use of HAp to coat iron oxide nanoparticles and reported slightly promoted pro-inflammatory cytokine production due to activation of calcium-dependent signaling pathways, that could reduce their cytocompatibility. This event reported to could be alleviated by dexamethasone distribution, showing the immune activation nature of Caps and the importance of their potential use to develop surface-modified biomaterial intended to activate immune responses²⁵. Additionally, nanoparticle bioconjugation has proven useful for imaging and stabilizing biomolecule delivery^{30,31}. Functionalizing nanoparticles thus offers significant advantages for applications in drug delivery and as implant coatings to modulate cellular interactions effectively.

Remarkably, the literature search only shows a single article that reported on the effects of CaP on immune cells, specifically the cytokine release from macrophages²⁵. This demonstrates a significant theoretical and evidential gap between the fabrication of CaP bioceramics and their application in clinical practice. The immune system encompasses a complex,

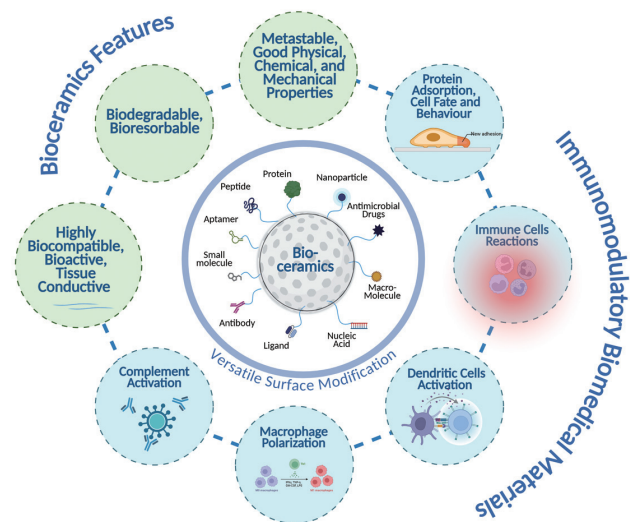


Fig. 1 Calcium phosphate bioceramics, particularly Ap-based bioceramics, has superior features which provide high versatility for tunable shapes and surface functionalization to result immunomodulatory biomedical materials. Apatite based bioceramics also have similarity to minerals of the human body.

diverse, and extensive array of components, including genes, molecules, peptides, proteins, vesicles, and cells; additionally, it comprises organs that work in concert to maintain homeostasis, respond to threats, repair damaged tissue, and, most importantly, determine the fate of implanted materials. The complex interactions between the immune system and biomaterials vary depending on the intended use, necessitating specific and controlled immuno-information to be incorporated into the fabrication design to enhance bioactivities customized to specific needs³⁵⁻⁴⁰.

Studies also show that bioceramics use in biomedical research is increasingly focusing on necessary characteristics such as biodegradability, multifunctionality, bioactivity, and anti-rejection properties as the next frontier biomedical materials⁴¹⁻⁴³. A previous study emphasized that biocompatibility, infection control, and cellular interactions controls represent the 21st-century challenges of biomaterial engineering⁴⁴. Based on the study, it can be emphasized the need for innovative strategies and diverse approaches to address challenges such as antimicrobial resistance (AMR), autoimmune or inflammatory syndrome induced by adjuvants (ASIA), implant-associated autoimmune reactions (ARIA), and other compromised conditions, while also achieving greater control over the clinical efficacy of bioceramics materials for various applications. Figure 1 provides overview on the features of CaP bioceramics, particularly Ap bioceramics, and their potential as immunomodulatory biomaterials.

CURRENT CHALLENGES IN CALCIUM PHOSPHATE BIOCERAMICS-IMMUNE CELLS INTERACTION

Bioceramics are a well-known class of biocompatible materials. Especially Ap bioceramics are closely resemble natural bone tissue, making them popular in bone tissue engineering. Some studies have reported a range of immune responses to bioceramics crucial for bone or tooth implant, such alumina and zirconia⁷. From those studies, it is well known that any implanted foreign material triggers an immune response, leading to what is known as the foreign body response (FBR). The nature of the immune response depends on the characteristics of the implanted foreign material and the specific immune reactions towards the triggers⁴⁵. In the context of bioceramics, immunological challenges vary and include issues such as uncontrolled inflammation, frustrated phagocytosis, FBR, improper biodegradation, low bioactivity, cytotoxicity, and chronic immune reactions⁷.

Calcium phosphate-based materials synthesized from natural raw materials, present several limitations in immunomodulatory applications, despite their inherent biocompatibility and bone regenerative properties¹. One of the key challenges is their limited ability to actively modulate immune responses, as they lack specific bioactive properties that can directly regulate immune system effectively. These limitations reduce bioceramics' effectiveness in precisely modulating immune responses. Unmodified bioceramics, including Cap-based such as Ap bioceramics, alumina, silica, and zirconia, often lack efficient interactions with immune cells, such as macrophages and dendritic cells, which are essential for both immune activation and suppression^{46,47}. This lack of specific interaction can lead to chronic inflammatory responses or FBR, which hinder tissue integration and long-term implant success⁴⁵. Moreover, Cap-based materials synthesized from natural raw materials typically fail to balance the transition between pro-inflammatory and anti-inflammatory phases of immune responses, which is essential for tissue regeneration⁴⁸. Many types of bioceramics were reported to induce prolonged immune response upon implantation. A study summarizes that alumina, zirconia ceramic, HAp, β -TCP, and bioglass implantation have resulted in immune responses. Most of the responses are both acute and chronic with visible tissue destruction and sometimes accompanied with allergies⁷. These inflammatory responses might also be caused by native pro-inflammatory effects triggered by excessive calcium ion release because of Cap degradation, leading to cytokine production and potential immunotoxicity due to mitochondrial damage⁴⁹.

In addition, bioceramics surfaces limit their ability to support cell adhesion, proliferation, and differentiation, reducing their capacity to modulate the immune environment for enhanced tissue repair⁵⁰. Furthermore, surface unmodified surfaces might lack the reactive functional groups needed to immobilize immunomodulatory molecules, which are essential for

enhancing bioactivity and interactions with immune cells. Unintended immune reactions can also arise, especially with various nanoscale bioceramics that are readily phagocytosed by immune cells, potentially triggering reactive oxygen species (ROS) production and heightened inflammatory responses⁵¹. To address these limitations, surface functionalization strategies that incorporate bioactive molecules or ligands are essential. Such modifications enhance bioceramics' immunomodulatory properties, improve their interactions with immune cells, and reduce unwanted immune reactions, thereby boosting their effectiveness in various clinical applications. In this context, Ap bioceramics are considered potential candidates to modulate immune environments due to their features and versatility, as described in Fig. 1. While bioceramics, particularly Cap-based materials, exhibit inherent biocompatibility, their limited capacity for active immunomodulation can restrict their therapeutic potential. The functionalization strategies illustrated here are intended to complement these intrinsic properties, and can be tailored to elicit specific immune responses depending on the clinical context. Further rationale for biomolecule selection and surface engineering approaches is discussed in a subsequent section.

SURFACE FUNCTIONALIZATION STRATEGY FOR IMMUNOMODULATORY BIOMATERIALS

The surface of biomaterials is the component that interacts most extensively with the microenvironment. The interaction between these biomaterials and the surrounding tissues, cells, proteins, and molecules play a significant role in shaping the response and determining the success of their intended purpose⁵²⁻⁵⁴. The performance of these materials can be optimized by modifying the interface between them and the human body, which is essential for effective biomaterial design⁵⁵. Therefore, surface functionalization serves as a fundamental strategy in the design of biomaterials.

Calcium phosphate surface functionalization involves altering the surfaces to introduce new functionalities distinct from the unmodified material^{54,56}. The improved functional surfaces can be engineered to bind or conjugate with ligands that directly interact with surrounding cells, controlling cellular activities, intercellular communications, and immune responses. This interaction determines whether the material is recognized as a danger or growth signal^{18,45,57-59}. Surface functionalization approaches play critical roles in promoting biointegration and enhancing nano-biointerfacial functions between biomaterials and immune cells. These modifications can lead to improved cell adhesion, biocompatibility, controlled degradation, and delivery rates, as well as permeability and stability^{54,55,60,61}. Surface-functionalized nanomaterials also have been reported to address several problems related to physicochemical properties, such as rapid aggregation, oxidation, and instability, particularly when nanoparticles are dispersed in colloidal applications^{62,63}.

Surface functionalization strategies enhance the versatility of biomaterials for applications, including drug delivery⁶⁴, tissue engineering⁶⁵, diagnostics⁶¹, immunomodulation^{66,67} and cellular grafting⁶⁸. When immobilized on these materials, particular biomolecules can mimic artificial extracellular matrices (ECM)⁵⁵, thereby improving cellular adhesion, proliferation, and viability—key factors in tissue engineering^{69,70}. Specific adhesion peptides can be anchored to biomaterials to direct mesenchymal stem cells (MSCs) to specific locations, fostering a microenvironment resembling the body's complex conditions⁷¹. This approach also enables the engineering of specific ligands for surface attachment, enabling targeted intracellular delivery for therapeutic effects, immunomodulation, or tissue repair⁷²⁻⁷⁷. Moreover, functionalization with antimicrobial peptides and metal ions aims to create antibacterial implants that prevent microbial overgrowth and biofilm formation on implants⁷⁸⁻⁸⁰. Thus, surface functionalization offers significant potential to leverage a diverse array of materials and biomolecules to address a wide range of health issues.

Recent studies have explored the possibilities of combining diverse surface functionalization methods to create multifunctional biomaterials^{81,82}. Such multifunctional surfaces can be designed to simultaneously present various biological signals from different biomolecules, whether bioinert or bioactive, in a controllable manner⁸¹. This approach allows for the concurrent conjugation of various biomolecules, such as growth factors⁸³, ECM proteins⁸³⁻⁸⁵, peptides^{86,87}, antigens^{88,89}, exosomes⁹⁰, and other biomolecules^{85,91}. Multifunctional biomaterials are considered the ideal substrates to replicate interactions between the ECM, cells, and administered biomaterials as living interfaces^{82,92}. A thorough understanding of the intricate strategies of surface functionalization is essential for developing optimal multifunctional bioceramics suitable for a variety of applications. This review focuses on the current knowledge of surface chemistry of CaP and interface modification through biomolecule immobilization to generate immunomodulatory biomaterials.

CURRENT APPROACHES IN SURFACE FUNCTIONALIZATION FOR CALCIUM PHOSPHATE

Numerous studies have investigated various approaches to modify and functionalize the surfaces of nanoparticles and scaffolds to achieve specific desired properties. However, there is currently no universal or gold standard protocol suited to all purposes. Surface functionalization is tailored to the specific material, conditions, and objectives⁵⁴. This section examines the status of surface functionalization techniques for CaP materials and covers the feasibility of each technique to be used in CaP-based ceramics.

Previous sections cover the use of CaP and their relatively lack of immune-instructive functionality that present limitations in applications requiring

immunomodulation. Therefore, surface functionalization strategies explored as a means to compensate for these deficiencies by enhancing cellular interactions, modulating immune responses, and integrating bioactive cues. This section focuses on surface functionalization techniques specifically adapted or designed for CaP ceramics to advance their surface potential as immunomodulatory biomaterials by enabling biomolecule immobilization on its surface. While some techniques may be drawn from polymer surface modification methods, these strategies are critically evaluated in the context of the unique chemical and structural characteristics of CaP bioceramics.

In general, surface functionalization techniques can be broadly categorized into covalent and non-covalent approaches. Activation of covalent binding on substrates has been known to result in stable, strong, and permanent connections, which are essential for the durable immobilization of functional groups and biomolecules⁹³. In contrast, non-covalent binding, although characterized by weaker bond strength, effectively interacts with the microenvironment while preserving the properties of the materials⁹⁴. Each method and its associated reagents are selected based on specific goals of the applications⁹⁴, and the interactions may vary significantly between different materials.

Protein adsorption

Adsorption, the attachment of proteins/peptides to substrates in non-covalent manner, is influenced by chemical and physical factors, resulting in either single or multiple layers on the substrate surfaces⁹⁵. Protein adsorption is a unique native characteristic of HAp and Ap once distributed into biological niches, and crucial factor in biocompatibility and biological integration⁹⁶. The interaction between proteins and biomaterials can alter the biomaterials' biological properties, physicochemical characteristics, and toxicity. Protein adsorption on CaP nanoparticles also forms a protein corona that impacts how these nanoparticles interact with surrounding cells and niches⁹⁷.

Adsorption enables easy protein immobilization and surface functionalization through physical immobilization, yet it is unstable and reversible compared to chemical bioconjugation, which forms covalent bonds⁹⁶⁻⁹⁸. Despite its lack of stability, physical adsorption was reported to enable denser and faster protein immobilization and cover a larger surface area than covalent bonding⁹⁹. Non-covalent functionalization offers a straightforward, mild, and feasible alternative, avoiding the labor-intensive procedures and harsh conditions often associated with covalent bioconjugation, which can compromise both protein functionality and surface integrity¹⁰⁰. These factors indicate that physical adsorption could be an effective, feasible, and simpler method to immobilize proteins on substrates. Utilization of natural physicochemical characteristics of bioceramics, particularly Ap bioceramics, to interact with proteins could be a promising approach to modify their biological characteristics.

Protein immobilization *via* adsorption relies on physical interactions such as hydrophobic, electrostatic, van der Waals, ionic, and hydrogen bonding. These interactions are influenced by the properties of the substrate, protein, and surrounding biofluids. Protein–surface interactions are typically multifactorial and complex, affected by physicochemical characteristics, contact time, temperature, and pH^{96–98}. This section covers the principles of protein adsorption on Caps.

1. CaP bioceramics native affinity for protein adsorption and potential modification for immunological purposes
Calcium phosphate based bioceramics have a distinct ability to adsorb proteins. Once implanted, proteins from microenvironment rapidly adsorbed onto the surface¹⁰¹. Protein adsorption is mainly caused by electrostatic force between charged groups or ions on a substrates and functional group of proteins (amine, carboxyl, carbonyl, and aromatic). The Ca²⁺ and PO₄³⁻ sites on CaP surfaces are widely known as the protein binding sites for adsorption¹⁰². Protein adsorption onto CaP surfaces is strongly influenced by electrostatic interactions, particularly the calcium-to-phosphate (Ca/P) ion ratio and the orientation of the protein¹⁰³. Study on Ca/P ratio is important as each Cap has different distribution of Ca/P orientation, which affects adsorption behavior¹⁰¹. It also reported that in general, higher surface area and topography of bioceramics results in higher efficiency of adsorption^{101,102}. A computational study reported that proteins are more likely to adsorb on HAp surfaces than to free ions. Pre-formed water layers on HAp could also affect protein adsorption, and protein often needs water-bridged hydrogen bond to initiate binding to the substrates. It is also reported that the Ca and P ions compete with water molecules to act as mediators of

protein binding to OH⁻ in HAp surfaces through the formation of CaOH and POH groups. This competition could affect the adsorption energy of proteins to surfaces¹⁰⁴.

Different types of proteins can interact in various ways with Caps. Acidic residues typically engage with surfaces through water molecules, while basic residues are more likely to interact *via* phosphate (PO₄) and hydroxyl (OH⁻) of HAp or water molecules. Neutral residues interact through their carboxyl (CO⁻) and amino (NH₂) groups. Basic proteins have been shown to exhibit higher interaction energy and binding affinity toward CaP ceramics¹⁰⁴. Acidic proteins tend to prefer binding to positively charged calcium ions, while basic proteins favor binding to negatively charged phosphates¹⁰⁵. Proteins possess specific adsorption sites that interact with bioceramics, primarily carboxyl and amino groups. Carboxyl groups are known to create electrostatic attractions with calcium, whereas amino groups interact with phosphates through hydrogen bonds between nitrogen-containing groups and phosphates on the surface of HAp¹⁰³.

Table 2 summarizes the factors influencing protein adsorption onto bioceramics, particularly CaP materials. Factors that affect protein adsorption are also factors that affect the FBR upon material implantation in biological niches. Calcium phosphate bioceramics facilitate rapid and robust protein adsorption from body fluids within seconds of implantation, triggering cellular attachment within minutes¹⁹. Modifying the surface characteristics of CaP bioceramics can regulate protein conformation and adsorption, thereby controlling their biological activity. Optimization strategies can also be employed to prevent protein desorption and minimize weak multilayer formation¹⁰². This suggests that non-

Table 2 Factors influencing protein adsorption on CaP bioceramics

Sites	Factors	Effects to protein adsorption	Ref.
	Hydrophobicity	Hydrophobicity promotes adsorption	101,102)
	Pores	High porosity increase surface area Influence protein behaviour and spatial distribution	101,102)
Calcium phosphate bioceramics	Topography	Higher roughness increase surface area Affects spatial distribution	102)
	Ca/P ratio	Ca and P acts as adsorption sites of proteins	103,105)
	Surface charge	Influence charge density, distribution and electrostatic force	101)
	Crystallinity	Lower crystallinity promotes adsorption	102)
	Size	Bigger protein has larger amount of binding sites Vroman effects	101)
Proteins	Binding affinity	Influenced by each protein natural characteristics	106)
	Unfolding rate	Higher rate promotes adsorption	101)
	Surface charge	Protein nearing isoelectric point promotes adsorption	101)
Interface	pH	Affects electrostatic interaction	106)

covalent functionalization of CaP materials may offer a more feasible and straightforward approach to achieving immunomodulatory effects, owing to their inherent high protein affinity.

Bioconjugation

Bioconjugation involves creating irreversible and strong covalent bonds between biomolecules and substrates or amongst biomolecules themselves to create novel multifunctional entities¹⁰⁷. This process can involve proteins¹⁰⁷, peptides¹⁰⁸, and nucleic acids^{109,110}. Research showed that covalently bonded proteins exhibit greater stability and overall functionality after 25 days of storage than those immobilized by adsorption¹¹¹. Several techniques have been streamlined to reinforce chemoselectivity, allowing reactions with specific functional groups, and site-selectivity—targeting particular amino acid residues¹⁰⁷. Selecting the appropriate strategy is crucial, as inadequate modifications might affect the enzymatic active sides of proteins, alter their structure, and thus change their bioactivity¹¹².

1. Bioconjugation of biomolecules on CaPs bioceramics

Bioconjugation on CaP bioceramics involves targeting specific functional groups to establish permanent and stable covalent bonds between CaP surface and biomolecules. To achieve this, it is essential to ensure that these functional groups are present on both the target biomolecules and the CaP surface, which often requires modification to introduce the necessary groups. Calcium phosphates cannot be covalently functionalized directly due to its ionic crystalline structure, which lacks reactive functional groups such as amines or carboxyls. However, surface modification strategies can introduce these functional groups, thereby enabling indirect covalent conjugation for practical biomedical applications¹¹³. Calcium phosphates materials like HAp and β -type CHA are rich in OH^- , $(\text{PO}_4)_3^{2-}$, and CO_3^{2-} groups¹¹⁴. Hydroxyapatites, with surface-exposed OH^- groups, have been particularly studied for reactions with silanes to attach amines, facilitating further

functionalization^{115,116}. This highlights the significance of introducing and activating specific functional groups on the CaP for chemical modifications.

Bioconjugation encompasses a wide range of chemistries, including amide formation, thiol–maleimide coupling, click chemistry, and aldehyde-based linkages, where each chosen based on the specific functional groups. Bioconjugation of CaP surface commonly involves forming covalent amide bonds between amine and carboxyl groups on interacting surfaces, making it one of the most frequently used functionalization strategies¹¹⁷. Amino silanes are one of the predominantly used to functionalize biomaterials with primary, secondary, and tertiary NH_2 for further bioconjugation^{118,119}. As shown in Table 3, (3-Aminopropyl) triethoxysilane (APTES) has been widely applied for functionalizing bioceramics with biomolecules, including miRNA^{109,110}, peptides¹²⁰ or proteins^{121,122}.

The use of APTES on CaP surfaces may require prior silica coating to enhance surface reactivity and binding stability. One study reported the use of tetraethyl orthosilicate (TEOS) to deposit a uniform, hydroxyl-rich silica layer on CaP, which was subsequently functionalized with APTES for biomolecule conjugation in targeted cell delivery applications¹²⁵. Beyond functionalization, surface amines also contribute to colloidal stability by imparting surface charge, promoting nanoparticle dispersion for biomedical applications^{123,126–129}. While aminosilane agents introduce reactive amine groups, protein carboxyl groups often require activation for covalent coupling. This is commonly achieved using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), which forms a transient O-acylisourea intermediate that reacts with surface amines to generate stable amide bonds^{117,118}. These combined strategies demonstrate that covalent surface modification using amino silanes and EDC/NHS chemistry is highly promising and among the most widely studied approaches for achieving stable biomolecule immobilization on CaP surfaces, which is crucial for applications such as drug delivery and targeted therapy.

Table 3 Previous research on aminosilanes for surface functionalizing biomaterials

Reagents	Materials	Purpose	Ref.
APTES	Hydroxyapatite	Bioconjugation for bone tissue engineering	109,110)
APTES	Carbonated hydroxyapatite	Bioconjugation	115)
APTES	Silicon dioxide and silicon nitride	Bioconjugation for optical biosensors	121)
AEAPDMS	Nanocrystalline cellulose	NA	119)
AHAPS	Silica	Colloidal stability enhancement	123)
APTMS	Silica	NA	124)
APTES	Calcium phosphates	Bioconjugation for bone tissue engineering	120)

APTES: (3-Aminopropyl) triethoxysilane, AEAPDMS: 3-(2-aminoethylamino) propyl-dimethoxymethylsilane, AHAPS: N-(6-aminoethyl)-3-aminopropyltrimethoxy silane, AEAPTMS: [3-(2-aminoethylamino)-propyl] trimethoxysilane, APTMS: 3-aminopropyltrimethoxysilane, NA: not applicable/specified

However, challenges remain, particularly in optimizing reaction conditions, and the chemical steps complexity and harsh conditions involved can limit scalability and practical biomedical use.

Covalent bioconjugation techniques on CaP surfaces remain relatively underexplored compared to other biomaterials, particularly polymers or metals. As summarized in Table 4, most reported studies have focused on HAp, the predominant CaP bioceramics used in covalent functionalization. For example, Limlawan *et al.*¹¹⁰ demonstrated the conjugation of microRNAs to APTES-functionalized HAp nanoparticles for delivery to osteoblasts, highlighting the potential of CaP as a gene delivery platform. Importantly, bioconjugation of CaP has also been explored for immunological applications, such as in vaccine delivery systems. Damm *et al.*¹³⁵ reported that CaP nanoparticles conjugated with HIV antigens enhanced B cell activation and IgG1 antibody responses, suggesting a role for functionalized CaP in adaptive immune modulation. Despite recent progress, the immunomodulatory potential of covalently functionalized CaP surfaces remains poorly understood. Most studies focus on delivery or structural applications, with limited insight into how surface chemistry affects immune cell behavior or cytokine responses.

Translational and clinical considerations of covalent and non-covalent surface functionalization in immunomodulatory CaP bioceramics

The successful translation of immunomodulatory CaP

bioceramics into clinical applications depends heavily on the safety, effectiveness and practicality of their surface functionalization strategies¹³⁶. From a clinical and translational standpoint, both covalent and non-covalent surface functionalization strategies offer distinct opportunities and challenges for the development of immunomodulatory CaP biomaterials.

Covalent functionalization techniques offer superior stability and long-term biomolecule retention. This features essential for consistent therapeutic performance in vaccine delivery or implantable immune-modulating devices¹¹¹. However, these methods often involve complex chemistries and synthesis protocols also harsh reaction conditions¹¹³.

The clinical translation of surface functionalized CaP as an immunomodulatory biomaterial requires careful evaluation of several critical parameters. Ensuring that the surface chemistry does not provoke adverse immune reactions or disrupt immune tolerance is essential^{18,45}. Biological safety and biocompatibility must be addressed, as some chemicals needed may introduce toxicity residues and unintended inflammatory responses^{137,138}. Reproducibility and stability are also equally crucial, as functionalized CaP materials must maintain consistent ligand density, molecular orientation, and bioactivity to ensure predictable immunomodulatory effects^{139,140}. Additionally, the functional performance of these materials in immune contexts must be validated, as variations in linker length or surface chemistry may affect cytokine production, antigen presentation, or

Table 4 Previous research on CaP bioceramics surface modification and bioconjugation

Bioceramics	Biomolecules	Surface modification	Bioconjugation chemistry	Biomedical application	Ref.
Hydroxyapatite	miRNA 302a-3p	Silanization with APTES	NA	Bone tissue engineering	107,130)
Hydroxyapatite	α Actin	MHA, MPA and MSA	EDC/sulfo-NHS	Bioimaging and biosensing	131)
Calcium phosphates	c-(DfKRG)	Silanization with APTES	PEG-NHS	Bone tissue engineering	120)
Hydroxyapatite	Fibronectin Collagen	Silanization with APTES	WSC	NA	132)
Hydroxyapatite	EGFP Lipase	DCC DIC EDC	NA	NA	133)
Calcium phosphosilicate	Avidin Holotransferrin Anti-CD71	NA	EDC PEG-maleimide	Drug delivery system	134)
Calcium phosphates	HIV envelope protein	CuAAC	Oxime ligation CuAAC	Antigen delivery system	135)

MHA: 16-mercaptohexadecanoic acid, MPA: 3-mercaptopropionic acid, MSA: mercaptosuccinic acid, c-(DfKRG): integrin-adhesive cyclic-pentapeptides, WSC: water soluble carbodiimide, NA: not applicable/specified, DCC: N,N'-dicyclohexyl carbodiimide, DIC: N,N'-diisopropylcarbodiimide, EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, CuAAC: copper-catalyzed azide-alkyne cycloaddition, HIV: human immunodeficiency virus

immune cell uptake^{141,142}). From a regulatory perspective, some chemicals used in covalent functionalization might not yet be universally approved or characterized for clinical use, necessitating detailed biocompatibility, degradation, and toxicology assessments. Scalability also presents a challenge, as surface modification protocols must be streamlined to allow for consistent and cost-effective production^{143,144}.

In contrast, non-covalent approaches, which rely on physical interactions like electrostatic or hydrophobic forces, are typically more amenable to simple, cost-effective, and clinically adaptable processes. These approaches use mild, aqueous conditions that better preserve the bioactivity of sensitive proteins or peptides, thus making them attractive for short-term immunotherapies. Nonetheless, their weaker binding strength poses a risk of biomolecule desorption and less predictable physiological performance, especially under physiological flow or enzymatic conditions^{100,145}.

As such, while non-covalent methods may be more immediately translatable in terms of manufacturing and regulatory ease, covalent strategies offer better long-term performance but require further optimization to meet clinical and regulatory standards. Future translational efforts should aim to balance the functional robustness of covalent methods with the simplicity and biocompatibility of non-covalent techniques, potentially through hybrid systems that harness the benefits of both. Clinically, this trade-off between stability versus simplicity must be carefully considered based on the intended application. Both approaches hold promise but require further *in vitro* and *in vivo* studies to fully elucidate their stability, safety, and translational potential in clinical immunomodulatory applications.

IMMUNE MODULATION THROUGH BIOMOLECULE FUNCTIONALIZATION OF CALCIUM PHOSPHATE BIOCERAMICS

Immunomodulatory strategies for biomaterials generally aim to either suppress FBR or activate immune responses by designing non-immunogenic or immunogenic surfaces. Modifying surface chemistry and immobilizing immunomodulatory molecules are the key approach to fine-tuning immune interactions. The following section discusses types of biomolecules that can be functionalized to achieve these effects.

Potential biomolecules to modulate biomaterial-immune system interplay

Immune cells are the first responders to administered biomaterials, and improper interactions can lead to therapy failure¹⁴⁶. Challenges such as implant rejection, infection, improper wound healing, chronic inflammation, and poor integration persist in both the short-term and long-term applications of implanted materials. Additionally, immune activity can alter the chemical properties of both biomaterials and surrounding tissue, disrupting material–host interactions¹⁴⁷. While most research has focused on the physicochemical properties

of CaP materials, there is a significant knowledge gap regarding their immunological interactions.

Immunomodulatory biomaterials can be designed to either promote or suppress the immune cell responses in reaction to specific signals, enabling the creation of active, responsive, adaptive, or autonomous materials. The choice of biomolecules significantly impacts the effectiveness and efficiency of the material¹⁴⁸. The choice of functionalized molecules should align with the desired immunological outcome, whether promoting innate or adaptive responses, or inducing pro- or anti-inflammatory effects. For instance, cytokines like TNF- α or IL-12 can activate immune responses in vaccine delivery, whereas^{45,149,150}, anti-inflammatory signals are preferred in tissue regeneration to support healing and reduce rejection^{13,17}.

Biomolecule selection should also be tailored to the targeted immune cell type, as different cells, such as macrophages, dendritic cells, or T cells, require specific signals for activation or suppression⁴⁵. Combining multiple biomolecules can produce synergistic effects, enhancing immune modulation in complex applications like cancer immunotherapy, vaccines, or tissue regeneration¹⁶⁴. Ultimately, aligning biomolecule choice with immune targets, surface characteristics, and therapeutic goals is key to effective immunomodulation. Table 5 summarizes previously reported biomolecules functionalized on biomaterials for immune modulation.

1. Biomolecules for cellular adhesion and targeting

Cellular interactions with bioceramics can be purposefully engineered by modifying surface chemistry and conjugating specific proteins to direct immune cell behavior. These biomolecules not only enhance initial cell-material interactions but also guide immune cell recruitment, activation, and differentiation by interacting with specific surface receptors. Cell adhesion is a crucial initial step that influences subsequent behaviors such as migration, proliferation, and cell–material communication¹⁶⁵.

In the context of immunomodulation, the recruitment and activation of immune cells to the CaP interface is critical. The ECM proteins such as fibronectin and collagen can be immobilized to promote adhesion of immune cells, while short peptides like RGD enhance integrin-mediated binding that facilitates early-stage interactions critical for downstream cellular responses¹⁶⁶. For instance, integrin-coated surfaces were shown to modulate macrophage responses by reducing cytokine production¹⁶⁷. Similarly, chemokines, particularly C-X-C motif chemokine 12 (CXCL12), have been shown to enhance tissue regeneration once immobilized on scaffolds by stimulating MSCs, keratinocytes, and fibroblasts¹⁵¹.

Specific immune cell targeting can be achieved by immobilizing antibodies against cell surface markers, also known as cluster of differentiation (CD) molecules, that are unique to each immune cell subset. For example, anti-CD11c can be used to target DCs, anti-CD206 for M2 macrophages, and anti-CD80 for M1 macrophages. By

Table 5 Previous studies on biomolecules used for immunomodulatory biomaterials

Biomolecules	Purpose	Ref.
CXCL12	Increased cell migration for wound healing	151)
PEG	Immune escape	152)
PEG-NH ₂	Promoted passive uptake	153)
Antibodies	Promoted active uptake	154)
Toll-like receptors	Promoted innate response	155)
Fibronectin	Reduced immune response and inflammation	156)
Fucoidan	Immune escape	157)
Carboxyl groups Amine groups	Reduced dendritic cell maturation	158)
CD47	Reduced phagocytosis by M1	159)
Azide-modified CpG	Promoted specific Th1-biased responses	160)
TGF- β	Reduced inflammatory markers, promoted Treg and Ag-specific tolerance	161)
PI _{C19-A3}	Enhanced DC's uptake efficiency	162)
N- α -fucosyl- β -alaninyl amide	Enhanced DC-SIGN targeting and internalization	163)

CXCL12: C-X-C motif chemokine 12, PEG: polyethylene glycol, PEG-NH₂: polyethylene glycol-amine, M1: type I macrophages, CpG: cytosine-phosphate-guanosine, Th1: T-helper 1 cells, TGF- β : transforming growth factor β , DC: dendritic cells, DC-SIGN: DC-specific intercellular adhesion molecule-3 grabbing nonintegrin

directing biomolecule presentation toward these specific markers, modified CaP surfaces can modulate the behavior of innate immune cells, such as macrophages and DCs, thereby shaping downstream adaptive immune responses, including T cell activation or suppression. This approach enables greater control over immune cell recruitment, activation, and polarization in a context-dependent manner¹⁶⁸.

Once adhesion is established, directed immune activation becomes essential. This can be achieved by functionalizing biomaterials with immune-relevant ligands such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Toll-like receptor (TLR) ligands like CpG DNA or lipopolysaccharide (LPS) can stimulate DC activation and pro-inflammatory cytokine production, whereas ligands for inhibitory receptors (PD-L1) can promote immunosuppression. Molecules like heat shock proteins and high mobility group box 1 (HMGB1) also serve as inflammatory cues that can direct immune cell migration and activity⁴⁵. Continued exploration of ligand-receptor interactions and immune-targeted surface functionalization will be essential to fully harness the potential of CaP bioceramics in directing complex immune responses.

2. Biomolecules for inflammation control

Inflammation plays a vital role in responding to danger signals from injuries and pathogens to prevent diseases and pathologies. However, when inflammatory responses

are insufficient or excessive, they can lead to pathological conditions such as chronic infections, tissue damage, or implant failure. Immunomodulatory biomaterials are therefore designed to regulate these responses by either amplifying protective signals or suppressing harmful ones^{17,169,170}. In the context of CaP bioceramics, controlling inflammation is especially important, as CaP can activate pro-inflammatory pathways through elevated intracellular calcium levels, which may induce the expression of IL-6, MMP-1, COX-1, and COX-2^{171,172}. Proper regulation of these inflammatory responses is essential to prevent excessive immune activation and ensure therapeutic efficacy.

Surface modification strategies can facilitate immune evasion by coating nanoparticles with hydrophilic PEG, that would prolong circulation time and avoid early phagocytosis, thus limiting unwanted immune clearance¹⁷³. Conversely, CaP nanoparticles can be engineered for active uptake by immune cells by modulating phagocytic behavior, thus enabling intracellular drug delivery¹⁷⁴. Phosphatidylserine modification also found could targets macrophages and signals for inflammation resolution¹⁷⁵. Targeting ligands such as mannose can also direct biomaterials to specific immune subsets, inducing responses like IL-8 expression in macrophages¹⁷⁶. These strategies highlight the versatility of biomolecular functionalization for precise inflammatory control.

In general, inflammation control could be reached by functionalizing surfaces with pro- or anti-

inflammatory agents and pro-resolving agents. Cytokine presentation on material surfaces can amplify or suppress local inflammation. For example, IL-4 or IL-10 functionalization can polarize macrophages toward an anti-inflammatory (M2) macrophage phenotype¹⁷⁷, whereas IFN- γ or TNF- α functionalization can promote pro-inflammatory (M1) responses¹⁷⁸. The local cytokine milieu modulates not only immune cell phenotype but also affects angiogenesis, matrix remodeling, and tissue integration in later stages¹⁷⁹.

In summary, the integration of inflammation-regulating biomolecules into CaP surfaces provides a versatile platform to fine-tune immune responses. By leveraging targeted delivery, controlled release, and receptor-specific interactions, these systems hold great promise for reducing adverse inflammatory reactions and enhancing the clinical success of immunomodulatory bioceramics.

3. Biomolecules for vaccines development

Biomaterial-based vaccines are often utilized to deliver antigens safely to immune cells. Surface functionalization of antigen with covalent bonding is usually preferred, as non-covalent bonding has resulted in uncontrolled deliveries¹⁸⁰. Nanoparticles are used to deliver proteins or antigens effectively and efficiently to DCs. Their physicochemical properties offer favorable pharmacokinetics for many purposes. Various studies reported enhanced delivery¹⁶², specific targeting, and internalization¹⁶³ of biomolecules towards cells, resulting in increased therapeutic potential. A study reported their findings on the high binding affinity of CHA for intracellular delivery¹⁸¹. Enhanced internalization would provide researchers with an option to select appropriate biomolecules for targeting specific cells.

Immunomodulatory vaccine adjuvant often requires complex multicomponent to regulate and control the desired characteristics. Multifunctional bioconjugation on CaP surface enables multiple signals to be emitted on the same platform. These signals could be designed to be in synergy through signalosomes. Multiple TLRs bioconjugation form structural and signaling synergies that are more likely to represent physiological conditions compared to individual receptors¹⁸². These synergies can result in a more robust increase in antibody production, cytokine expression, and signaling those results from the activation of signaling pathways in DCs¹⁸²⁻¹⁸⁶. A study conducted high throughput nanoimmunoassays to detect a novel synergistic vaccine adjuvant and reported that a combination of monophosphoryl-lipid A and TLR agonists or gardiquimod (an imidazoquinolinone compound with TLR7/8 agonist properties) could significantly increase immune responses, particularly cytokines and cellular responses¹⁸⁷. This shows that optimized, specific strategies could lead to the development of either immunogenic or tolerogenic vaccines.

Cytokine profiles could influence the direction of the specific desired immune response during vaccination. The dominance of CD4⁺Foxp3⁺ regulatory T cells (Tregs)-specific cytokines could create antigen-

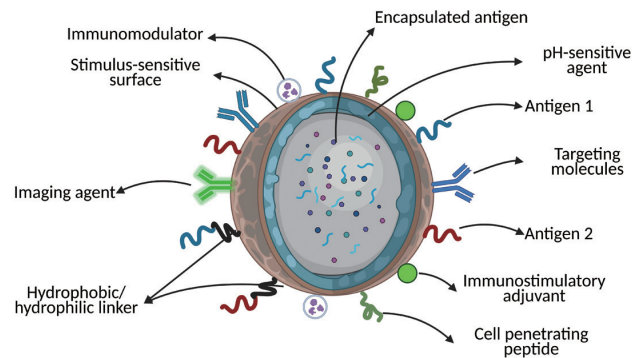


Fig. 2 Multifunctional bioconjugation for potential nano vaccines.

specific immune tolerance for tolerogenic vaccines¹⁸⁸. Meanwhile, the dominance of Th1 and Th17 cell-specific cytokines could direct the immune response to create an antigen-specific immune response to eliminate antigens for immunogenic vaccines¹⁸⁹. Authors of a study reported their findings on the fabrication of tolerogenic nanoparticles to induce activation of Tregs specific for an autoimmune disease, encephalomyelitis¹⁹⁰. Functionalizing immunomodulatory molecules could direct the immune response towards intended end-responses to create various diseases, such as cancer, autoimmunity, or infections.

Multifunctional bioconjugation enables the combination of various biological and chemical cues needed in nano vaccines. Biological cues are the signal molecules that activate DCs, such as PAMPs, DAMPs, and antibodies. Cell-penetrating, photosensitive, and pH-sensitive agents could be conjugated in the system to act as chemical cues¹⁹¹. Fabrication of vaccine delivery systems using multifunctional smart nanoparticles could utilize various biomolecules, such as antigens, targeting molecules, molecular adjuvants, immunomodulators, stabilizing agents, hydrophilic or hydrophobic linkers, imaging agents, stimulus-sensitive agents, and cell-penetrating agents, both on the surface or encapsulated within the nanoparticles¹⁹²⁻¹⁹⁴, as illustrated in Fig. 2. Double conjugation strategies could produce multiantigenic nanoparticles for immunotherapies and vaccines. A study reported that the conjugation of multiple peptides to lipid adjuvants significantly inhibits tumor growth¹⁹⁵. This would potentially create biomimetic nano vaccines to resemble viral structures, named virus-like nanoparticles, which is a revolutionary novel platform for vaccine manufacture due to its stability and robust immuno-activation properties¹⁹⁶.

Interaction of functionalized nano-bioceramics, protein corona, and immune cells

Nanoparticles, especially nano-bioceramics such as nano-apatite, could form protein coronas when introduced to biological fluids. Forming layered adsorbed proteins remains a challenge for bioceramic use, whether *in vitro* or *in vivo*. The protein corona affects the biodistribution,

interaction, and behavior of the nanoparticles in the cells. Protein coronas are composed of proteins that bind to a surface with varying strength, depending on the surface chemistry and the composition of the surrounding biological fluid^{197,198}. Protein coronas may influence the stability and behavior of functionalized nanoparticles by interacting with vacant binding sites or conjugated proteins, thereby affecting the performance and stability of CaP nanoparticles both *in vitro* and *in vivo*¹⁹⁹. Hydroxyapatite reported to forms large protein aggregates in culture media, leading to increased particle size, colloidal instability, enhanced uptake, and cytotoxicity in human macrophages²⁰⁰.

The interaction between bioceramics and proteins can modulate immune responses, with the protein corona composition influencing immunostimulatory or immunosuppressive outcomes, including potential immunotoxicity²⁰¹. The immune activation nature of the protein corona could be caused by the opsonin and complement proteins that promotes phagocytosis. Proteins such as bovine fibrinogen, Igy, transferrin, bovine serum albumin (BSA), and FBS usually reduce cytotoxicity, while IgG and complement components mainly promote immunotoxicity because of enhanced phagocytosis²⁰¹. Minimizing nonspecific protein adsorption requires saturating CaP surfaces with target biomolecules through high-affinity cross-linking strategies that enhance binding specificity^{56,202}. Residual reactive sites can be further developed using blocking agents, as shown by the use of BSA on CaP ceramics to inhibit undesired protein interactions²⁰³.

The immunomodulation potential of functionalized nano-bioceramics could be tailored for various applications, particularly to either induce or attenuate immune signals. Most research in this field has focused on osteoimmunology, revealing that CaP, particularly

HAp, exhibit immunogenicity by triggering immune responses, as they are recognized as foreign bodies that activate pro-inflammatory mediators²⁰⁴. This shows that modification of HAp could modulate activation signaling for macrophages and other immune cells for many purposes.

Table 6 presents a selection of previous studies on the modification of nano-bioceramics, especially CaP and silica, for immunomodulation. The field of biomolecule immobilization on nano-bioceramics for immunomodulation is still relatively nascent, with few conclusive findings. Most studies have primarily focused on the physicochemical properties of nano-bioceramics, including size, shape, surface charge, and topography. Additionally, research involving immune cells is limited, as many studies apply surface functionalization principles mainly for osteogenesis and osteointegration. Notably, silica has emerged as the most used nanomaterial in research related to immune cells. This highlights a significant gap in future research to explore the biological signaling pathways between nano-bioceramics and the immune system. The development of immunomodulatory bioceramics has the potential to address various challenges and questions that arise in the clinical application of biomaterials.

This review focuses and limits on the surface functionalization of bioceramics to develop immunomodulatory biomaterials *via* biomolecule immobilization strategies. It does not delve into other functionalization techniques or mechanical aspects. Figure 3 shows recent methods in surface functionalization and its functions. However, there are numerous additional methods that could enhance the interaction between biomaterials and the immune system, including modifications to mechanical properties and nano topography as depicted in Fig. 4, which are

Table 6 Preceding studies on surface- modified nano/micro-bioceramics such as CaP bioceramics and silica for immunomodulation

Bioceramics	Surface modification	Immunomodulation	Ref.
Hydroxyapatite	Hyaluronic acid	Targeted delivery to CD44 cells Reduced cytotoxicity Anti-inflammation	205)
Hydroxyapatite	Surface nano-topography	Macrophage polarization into M2 Anti-inflammation	206)
Carbonate apatite	miR-497a-5p	Activation of TGF-β/Smad Inhibited pro-inflammatory cytokines	207)
Calcium phosphate	Surface submicron topography	Macrophage polarization into M2	208)
Silica	Amine	Reduced ROS formation <i>via</i> NOX2	209)
Silica	Polyethylene glycol	Promoted inflammatory cytokines NLRP3 activation Increased DC migration into scaffold	210)
Silica	Poly(2-vinylpyridine)	Deliver immunostimulatory R848 into immune cells in pH-sensitive way	211)

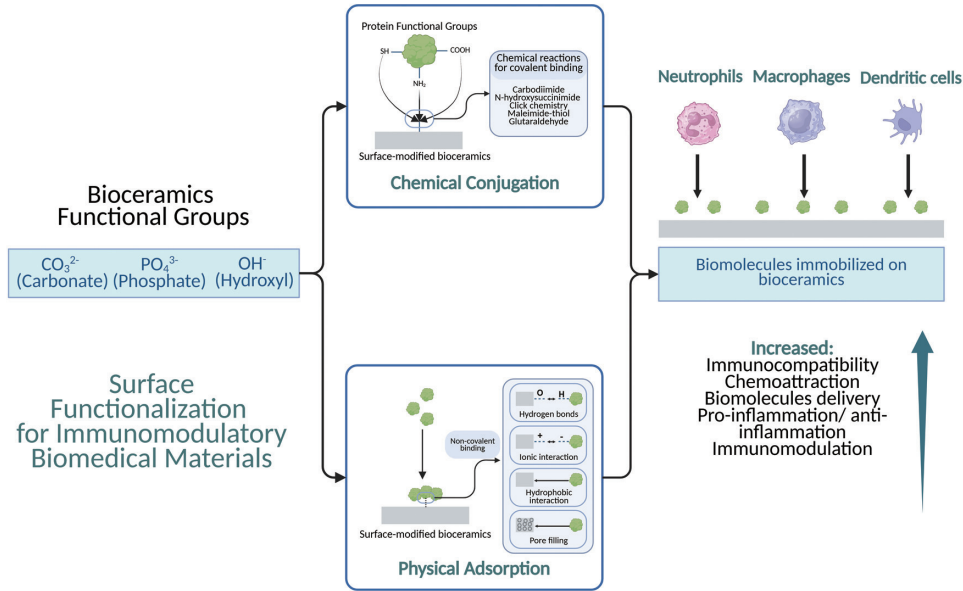


Fig. 3 Recent functionalization methods.

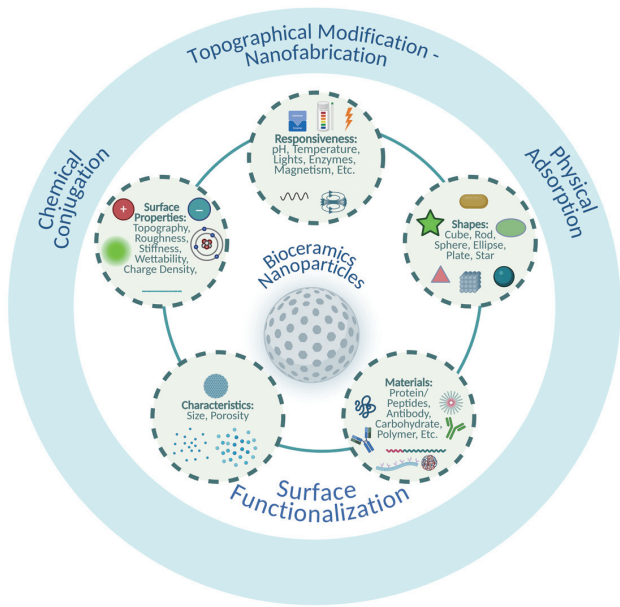


Fig. 4 Numerous additional methods to enhance the interaction between biomaterials and the immune system, including modifications to mechanical properties and nano topography.

not covered here. Future research should explore these techniques and evaluate their effects on the development of immunomodulatory biomaterials.

CONCLUSION

Surface functionalization of CaP bioceramics has proven to be an essential strategy in overcoming the inherent limitations of these materials, especially in

the context of immunomodulation. By incorporating biomolecules, CaP bioceramic nanoparticles can interact with immune cells, such as macrophages and dendritic cells, facilitating improved immune responses while mitigating adverse reactions. This approach holds immense promise in developing next-generation immunomodulatory biomaterials that can significantly enhance biocompatibility and immune system interactions. However, surface functionalization techniques are still infrequently applied to bioceramics highlighting critical research gaps that could be leveraged to tackle various clinical challenges in the future. This shows the research gaps that could be utilized to answer and solve various clinical problems in the future. Further research and exploration are needed to create the ideal nanoplatform capable of modulating immune responses and delivering immunomodulatory biomolecules, paving the way for potential clinical applications in immune-related therapies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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