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Smart hydrogel bioinks integrated with two-dimensional nanomaterials for cardiovascular bioprinting and atherosclerosis modeling

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Abstract

Cardiovascular diseases remain the leading cause of mortality worldwide, and atherosclerosis underlies most ischemic cardiovascular events. However, conventional *in vitro* and i*n vivo* models fail to fully reproduce the complex cellular interactions, extracellular matrix remodeling, oxidative stress, and hemodynamic microenvironment of human vascular lesions. This review summarizes recent advances in stimuli-responsive hydrogel bioinks for three-dimensional bioprinting of atherosclerosis models. We discuss how disease-responsive biomaterials can dynamically regulate the cellular microenvironment and improve the physiological relevance of engineered vascular tissues. Particular emphasis is placed on the integration of two-dimensional nanomaterials. Graphene-based materials provide electrical conductivity, mechanical reinforcement, and sensing capabilities; black phosphorus offers biodegradability, photothermal responsiveness, and reactive oxygen species-sensitive behavior; and emerging Xene materials such as germanene present additional opportunities for multifunctional bioink design. We compare their respective advantages and limitations for cardiovascular bioprinting. Finally, we discuss key translational challenges, including material standardization, long-term biosafety, biological validation, manufacturing scalability, and regulatory approval. We propose that multifunctional, disease-responsive bioinks combined with advanced biofabrication technologies will accelerate the development of physiologically relevant cardiovascular disease models and precision medicine platforms.

Keywords: Cardiovascular bioprinting; Atherosclerosis modeling; Stimuli-responsive hydrogel bioinks; 2D nanomaterials; Organ-on-a-chip

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1. Introduction

Atherosclerosis is the principal pathological process underlying most cardiovascular

diseases (CVDs), including coronary artery disease, myocardial infarction, ischemic stroke, and peripheral arterial disease.[1-3] Although traditionally viewed as a lipid-storage disorder, atherosclerosis is now recognized as a multifactorial chronic inflammatory disease involving endothelial dysfunction, oxidative stress, immune-cell recruitment, vascular smooth muscle cell (VSMC) phenotypic modulation, extracellular matrix (ECM) remodeling, and biomechanical disturbances associated with altered blood flow.[4-7] These interconnected biological and mechanical processes create a highly heterogeneous vascular microenvironment that continuously evolves during disease initiation, progression, and plaque destabilization. Consequently, reproducing the complexity of the atherosclerotic niche remains one of the major challenges in cardiovascular research.[8,9]

Current experimental models only partially recapitulate the pathophysiological features of human atherosclerosis. Conventional two-dimensional (2D) cell cultures lack the three-dimensional (3D) architecture, multicellular interactions, ECM organization, and mechanical stimuli that regulate vascular homeostasis and disease progression. Animal models have substantially advanced our understanding of atherosclerotic mechanisms; however, species-specific differences in lipid metabolism, immune responses, and vascular biology often limit their translational relevance. More recently, microphysiological systems and organ-on-a-chip (OOC) technologies have emerged as promising platforms for modeling vascular diseases under controlled conditions. Nevertheless, many existing *in vitro* systems remain limited in their ability to simultaneously reproduce the structural complexity, cellular heterogeneity, and dynamic pathological microenvironment characteristic of human atherosclerotic lesions. These limitations underscore the need for advanced biofabrication strategies capable of reconstructing physiologically relevant and disease-specific vascular models.[10-12]

Recent advances in tissue engineering and biofabrication have positioned 3D bioprinting as a powerful approach for generating biomimetic vascular tissues and disease models. By enabling the spatially controlled deposition of living cells, biomaterials, and bioactive factors, 3D bioprinting offers unprecedented opportunities to recreate multicellular architectures and microenvironmental organization that more closely resemble native tissues.[13] Furthermore, the integration of bioprinting with OOC platforms, organoid technologies, and perfusion systems has expanded the capacity of engineered models to incorporate vascular flow, mechanical stimulation, and tissue-specific structural features.[13-16] Despite these advances, the success of bioprinted cardiovascular constructs remains fundamentally dependent on the design and functionality of the bioinks used to fabricate them.

Hydrogel-based bioinks have become the predominant class of materials used in cardiovascular bioprinting owing to their high water content, biocompatibility, tunable physicochemical properties, and structural resemblance to native ECM.[13] Natural biomaterials such as gelatin, collagen, fibrin, alginate, hyaluronic acid, and decellularized ECM have been widely investigated because they provide favorable environments for cell viability, proliferation, migration, and differentiation.[17,18] However, most conventional hydrogel bioinks behave as passive structural matrices and possess limited capacity to mimic the dynamic nature of pathological vascular microenvironments.[17] This limitation is particularly important in atherosclerosis, where disease progression is driven by continuously changing biochemical and biomechanical signals, including oxidative stress, inflammatory cytokines, lipid accumulation, matrix remodeling, and cyclic mechanical stimulation.[12] Consequently, there is growing interest in developing smart bioinks capable of actively responding to disease-relevant stimuli and dynamically regulating cellular behavior.

Stimuli-responsive hydrogels have emerged as a promising class of smart biomaterials capable of altering their physicochemical properties in response to environmental cues such as temperature, pH, reactive oxygen species (ROS), enzymes, light, electrical stimulation, and magnetic fields.[19-21] Unlike conventional static matrices, these adaptive materials enable spatiotemporal regulation of matrix mechanics, degradation, molecular delivery, and cell–matrix interactions. Such dynamic responsiveness offers unique opportunities to reconstruct pathological microenvironments more faithfully and to model disease progression in a controllable manner.[22-24] Among the various pathological hallmarks of atherosclerosis, oxidative stress has attracted particular attention because excessive ROS production contributes to endothelial dysfunction, lipoprotein oxidation, chronic inflammation, macrophage activation, VSMC phenotypic switching, and plaque instability.[25-26] Therefore, ROS-responsive bioinks represent an especially attractive strategy for developing disease-adaptive vascular models that more closely mimic *in vivo* pathological conditions.

In parallel with the evolution of smart hydrogels, 2D nanomaterials have emerged as powerful functional components for next-generation bioinks.[27] Owing to their unique structural, electrical, mechanical, optical, and surface properties, these materials can significantly

enhance biofabrication performance while introducing disease-relevant biological functionalities. Rather than serving solely as passive reinforcing agents, 2D nanomaterials increasingly function as active regulators of cellular behavior and microenvironmental cues.[28] Graphene-family nanomaterials have been extensively explored for improving mechanical stability, electrical conductivity, printability, and biosensing capabilities in cardiovascular tissue engineering.[29-31] Black phosphorus (BP), in contrast, offers distinctive advantages including intrinsic biodegradability, photothermal responsiveness, and ROS-sensitive degradation behavior.[32-33] Importantly, accumulating evidence suggests that BP-containing biomaterials can modulate oxidative stress, regulate inflammatory responses, and promote angiogenesis, characteristics that closely align with critical pathological processes involved in atherosclerosis.[27,32] Beyond graphene and BP, other emerging Xene-family materials such as germanene are beginning to attract attention owing to their unique electronic structures, surface reactivity, and multifunctional responsiveness.[27,34,35,36] Collectively, these advances substantially expand the design space of smart bioinks for cardiovascular biofabrication and provide new opportunities for engineering disease-responsive vascular microenvironments.[27,35]

Despite significant progress in cardiovascular bioprinting, hydrogel engineering, OOC technologies, and nanomaterial-based biomaterials, important knowledge gaps remain. Existing reviews have largely examined these research areas independently, focusing on bioprinting platforms, hydrogel bioinks, microphysiological systems, or specific classes of nanomaterials.[11-13] Comparatively little attention has been devoted to understanding how bioink design can be tailored to the unique pathophysiological requirements of atherosclerosis. In particular, the integration of stimuli-responsive hydrogels and functional 2D nanomaterials has not been systematically evaluated as a unified strategy for addressing key disease-specific challenges, including oxidative stress, chronic inflammation, vascular remodeling, and dynamic microenvironmental regulation.[26,37] Moreover, the emerging convergence of disease-responsive biomaterials, advanced biofabrication technologies, and vascular disease modeling has yet to be critically assessed from the perspective of constructing physiologically relevant and pathologically adaptive atherosclerosis platforms.[11,12]

In this review, we propose an atherosclerosis-oriented framework for the design of smart bioinks integrating stimuli-responsive hydrogels and functional 2D nanomaterials. We first discuss the pathophysiological requirements for reconstructing atherosclerotic microenvironments and the corresponding design criteria for advanced bioinks. We then summarize recent advances in stimuli-responsive hydrogel systems and evaluate the functional contributions of graphene-family nanomaterials, BP, and emerging germanene-based platforms. Subsequently, we examine their applications in vascular bioprinting and atherosclerosis-on-a-chip systems and discuss how these technologies may facilitate more physiologically relevant disease reconstruction. Finally, we highlight current challenges, translational barriers, and future opportunities toward the development of dynamic, disease-responsive, and patient-specific cardiovascular models for disease investigation, drug screening, and precision medicine.

2. Pathophysiological requirements for atherosclerosis modeling

The development of physiologically relevant atherosclerosis models requires more than simply reproducing individual cellular phenotypes or isolated biochemical pathways. Atherosclerotic plaques evolve through dynamic interactions among vascular cells, immune cells, ECM components, circulating lipoproteins, and biomechanical forces. Consequently, successful disease reconstruction depends on the ability to recapitulate multiple pathological features simultaneously within a controllable microenvironment.[2,7,8] Traditional *in vitro* models typically reproduce only one or several aspects of disease progression, such as endothelial inflammation or macrophage lipid uptake, whereas native plaques represent highly heterogeneous and continuously evolving ecosystems.[6] Therefore, understanding the key pathophysiological requirements of atherosclerosis is essential for guiding the rational design of next-generation bioinks and bioprinted vascular disease models.[11,12]

2.1. Endothelial dysfunction as the primary disease trigger

The vascular endothelium serves as a dynamic interface between circulating blood and the arterial wall. Under physiological conditions, endothelial cells maintain vascular homeostasis by regulating vascular permeability, thrombosis, inflammation, and vascular tone through the production of nitric oxide (NO), prostacyclin, and other vasoprotective mediators.[9]

Atherosclerosis is initiated when endothelial homeostasis becomes disrupted by cardiovascular risk factors, including hyperlipidemia, hypertension, diabetes mellitus, smoking, and disturbed blood flow. Dysfunctional endothelial cells exhibit reduced NO bioavailability, increased oxidative stress, elevated permeability to circulating lipoproteins,

and enhanced expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin.[7,9] These alterations promote leukocyte recruitment and lipoprotein retention within the arterial intima, thereby establishing a pro-inflammatory microenvironment that drives plaque initiation and progression.[7]

Most conventional endothelial culture systems fail to reproduce the 3D vascular architecture, physiological shear stress, and cell–matrix interactions that regulate endothelial behavior *in vivo*. Consequently, endothelial responses observed in static monolayer cultures frequently differ from those occurring in native arteries under physiological or pathological flow conditions.[11,12]

For bioprinted atherosclerosis models, the reconstruction of a functional endothelial barrier therefore represents a fundamental design requirement. Bioinks should support endothelial adhesion, junction formation, mechanosensing, and long-term barrier integrity while permitting dynamic responses to inflammatory and hemodynamic stimuli. Furthermore, endothelialized vascular constructs should enable real-time assessment of endothelial permeability, inflammatory activation, leukocyte adhesion, and barrier dysfunction as key indicators of disease initiation and progression.[11,12]

2.2. Vascular smooth muscle cell plasticity and arterial remodeling

Vascular smooth muscle cells are the predominant cellular component of the arterial media and are responsible for maintaining vascular contractility and structural integrity. In healthy vessels, VSMCs exhibit a contractile phenotype characterized by expression of α-smooth muscle actin (α-SMA), smooth muscle myosin heavy chain (SM-MHC), and calponin.[38,39]

During atherosclerosis progression, VSMCs undergo extensive phenotypic switching toward synthetic, inflammatory, osteogenic, and macrophage-like states. This phenotypic plasticity contributes to ECM production, plaque growth, vascular calcification, and fibrous cap formation.[40,41] Traditional 2D culture systems often fail to maintain physiological VSMC phenotypes because cell behavior is strongly influenced by matrix stiffness, dimensionality, and cell–cell interactions. Consequently, VSMCs cultured on rigid substrates frequently exhibit artificial activation profiles that do not accurately reflect disease progression.[42] Next-generation bioprinted vascular models should therefore provide tunable mechanical microenvironments capable of regulating VSMC phenotype in a controlled manner. Bioinks should enable spatial localization of VSMCs within arterial wall-like structures while supporting phenotypic transitions that occur during plaque development. Such capabilities are essential for reproducing arterial remodeling and fibrous cap formation.[38,42]

2.3. Immune cell recruitment and macrophage polarization

Atherosclerosis is increasingly recognized as a chronic inflammatory vascular disease driven by both innate and adaptive immune responses.[43,44] Among immune cell populations, macrophages play a central role in plaque initiation, progression, and destabilization.[44,45] Following endothelial activation, circulating monocytes infiltrate the arterial wall and differentiate into macrophages.[43,45] These macrophages internalize oxidized low-density lipoprotein (oxLDL), forming lipid-laden foam cells that constitute one of the earliest hallmarks of plaque formation.[44] As disease progresses, macrophages secrete inflammatory cytokines, matrix-degrading enzymes, and ROS that contribute to tissue remodeling and plaque instability.[44,46]

Importantly, macrophages exhibit rzemarkable phenotypic heterogeneity.[45,47] Pro-inflammatory macrophages promote lesion progression through secretion of tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6, whereas reparative macrophages participate in inflammation resolution and tissue repair.[45,47] The balance between these phenotypes significantly influences plaque stability and therapeutic outcomes.[45,47] Most existing vascular models either omit immune cells entirely or incorporate them only transiently. As a result, critical inflammatory processes remain poorly represented. Future bioprinted atherosclerosis models must therefore support immune-cell recruitment, macrophage infiltration, foam-cell formation, and dynamic polarization.[15,48] This requirement creates a strong demand for bioinks capable of regulating immune-cell behavior through biochemical and biophysical cues.[15,48]

2.4. Oxidative stress as a disease-defining microenvironment

Oxidative stress has emerged as one of the most important regulators of atherosclerosis progression. Excessive production of ROS contributes to endothelial dysfunction, low-density lipoprotein (LDL) oxidation, inflammatory activation, VSMC migration, and ECM degradation.[25,49] Unlike many pathological signals, oxidative stress exhibits significant spatial and temporal heterogeneity within plaques. Regions enriched with activated macrophages, inflammatory cell clusters, and necrotic-core-associated microenvironments frequently show enhanced oxidative and inflammatory signatures, whereas neighboring plaque regions may remain biologically distinct.[45,50-52] Such

heterogeneity is difficult to reproduce using conventional *in vitro* models.

The inability to model dynamic redox microenvironments represents a major limitation of current atherosclerosis platforms. Consequently, ROS-responsive biomaterials have attracted increasing attention because they offer opportunities to engineer disease-relevant feedback mechanisms directly into bioinks.[26] For cardiovascular bioprinting, ideal bioinks should not only tolerate oxidative environments but also dynamically respond to ROS accumulation through matrix remodeling, cargo release, signal amplification, or biosensing functions.[26,53] These requirements provide a strong rationale for incorporating disease-responsive nanomaterials such as BP into hydrogel systems.[54,55]

2.5. Extracellular matrix remodeling and plaque stability

The ECM provides structural support and biochemical cues that regulate vascular-cell behavior. During atherosclerosis progression, extensive remodeling occurs within the ECM, including collagen accumulation, elastin fragmentation, proteoglycan deposition, and matrix degradation mediated by matrix metalloproteinases (MMPs).[5,56]

The composition and organization of the ECM strongly influence plaque stability. Stable plaques generally contain thick collagen-rich fibrous caps, whereas vulnerable plaques are characterized by increased proteolytic activity, inflammatory infiltration, and thinning of the fibrous cap.[38,57] Plaque rupture, which underlies most acute cardiovascular events, is closely associated with ECM destabilization and excessive matrix degradation driven by inflammatory cells and MMP activity.[58,59]

Most hydrogel-based models provide static extracellular matrices that cannot reproduce progressive matrix remodeling. Therefore, future bioinks should support controlled degradation, matrix deposition, and mechanical evolution over time. Dynamic ECM remodeling capabilities will be essential for modeling plaque progression and vulnerability.[5,56]

2.6. Hemodynamic regulation and mechanobiological signaling

One of the defining characteristics of atherosclerosis is its non-random localization within the vasculature. Plaques preferentially develop at arterial bifurcations, branch points, and curved regions exposed to disturbed blood flow and oscillatory shear stress.[9,60-62] Hemodynamic forces regulate endothelial function through mechanotransduction pathways involving Krüppel-like factor 2, nuclear factor kappa B, yes-associated protein/transcriptional coactivator with PDZ-binding motif, platelet endothelial cell adhesion molecule-1, and integrin signaling.[60,63] Laminar shear stress generally promotes anti-inflammatory and atheroprotective phenotypes, whereas disturbed flow induces endothelial activation, oxidative stress, and inflammatory signaling.[9,60,63] Conventional static cultures fail to reproduce these critical biomechanical influences. Consequently, integrating perfusion systems and microfluidic technologies with bioprinted constructs has become increasingly important for CVD modeling.[64,65] Future bioprinted atherosclerosis platforms should therefore incorporate controllable flow conditions, physiologically relevant shear stress profiles, and patient-specific vascular geometries. Such systems would allow investigation of the complex interplay between mechanical forces and biochemical disease cues.[64,65]

2.7. Design criteria for next-generation bioprinted atherosclerosis models

To summarize the relationship between atherosclerotic pathology and bioink engineering requirements, Figure 1 presents a disease-oriented framework linking key pathological features with the functional criteria required for next-generation smart bioink design. Collectively, current understanding of atherosclerosis pathogenesis reveals several essential requirements for physiologically relevant disease reconstruction.[9,44,66] An ideal bioprinted model should integrate: (i) a functional endothelial barrier; (ii) spatially organized VSMCs with phenotype plasticity; (iii) dynamic immune-cell recruitment and macrophage polarization; (iv) heterogeneous oxidative stress microenvironments; (v) tunable ECM remodeling; and (vi) physiologically relevant hemodynamic stimulation.[9,46,56,66,67] Meeting these requirements exceeds the capabilities of conventional biomaterials and highlights the need for multifunctional bioinks capable of actively interacting with disease-associated signals.[48,68] Stimuli-responsive hydrogels offer dynamic control over matrix properties and cellular behavior,[69,70] whereas 2D nanomaterials introduce conductivity, photothermal responsiveness, biosensing capability, and redox regulation.[71,72] The convergence of these technologies provides a promising foundation for constructing next-generation CVD models with unprecedented physiological relevance.[48,68,73] The major pathological features of atherosclerosis and their corresponding bioink design requirements are summarized in Table 1. The following section therefore focuses on stimuli-responsive hydrogel bioinks and examines how smart biomaterials can be rationally designed to satisfy the biological and engineering requirements outlined above.

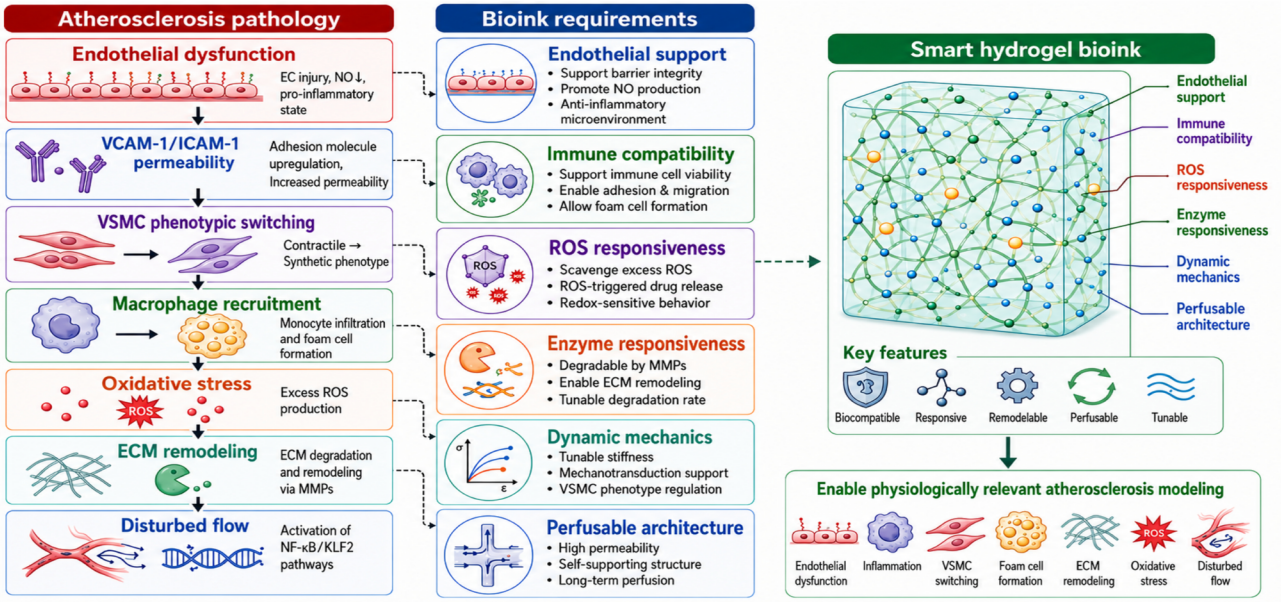

Figure 1. Pathophysiological requirements and bioink design criteria for atherosclerosis modeling. The progression of atherosclerosis involves endothelial dysfunction, oxidative stress, macrophage recruitment, foam-cell formation, VSMC phenotypic switching, ECM remodeling, and disturbed flow. These pathological features define the functional requirements of next-generation bioinks, including dynamic matrix remodeling, ROS responsiveness, tunable mechanics, immune-cell compatibility, and perfusion stability. Created in BioRender. Chu, R. (2026). https://BioRender.com/ygc93cd, with assistance from ChatGPT (OpenAI, GPT-5.5 Thinking) for preliminary figure drafting, visual refinement, and layout optimization.
Abbreviations: EC: Endothelial cell; ECM: Extracellular matrix; ICAM-1: Intercellular adhesion molecule 1; KLF2: Krüppel-like factor 2; MMPs: Matrix metalloproteinases; NF-κB: Nuclear factor kappa B; NO: Nitric oxide; ROS: Reactive oxygen species; VCAM-1: Vascular cell adhesion molecule 1; VSMC: Vascular smooth muscle cell.

Table 1. Disease-specific pathological features of atherosclerosis and corresponding bioink design requirements

Pathological feature	Representative readouts	Bioink design requirement	Representative implementation
Endothelial dysfunction[3,9,65]	TEER, permeability, eNOS, NO	Barrier-supportive matrix	Endothelialized lumen
Oxidative stress[25,26,68,74]	ROS, oxidative biomarkers	ROS-responsive matrix	Thioketal/BP systems
Inflammation[75,76]	VCAM-1, ICAM-1, cytokines	Immune-compatible bioink	Cytokine-responsive systems
ECM remodeling[56,59,77,78]	MMP activity, collagen organization	Enzyme-responsive degradation	MMP-cleavable hydrogels
Disturbed flow[7,60,79]	KLF2, NF-κB	Perfusable vascular architecture	Microfluidics/OOC
VSMC phenotypic switching[40,80]	α-SMA, SM-MHC	Dynamic mechanical adaptability	Mechanoadaptive bioinks

Abbreviations: α-SMA: Alpha-smooth muscle actin; BP: Black phosphorus; ECM: Extracellular matrix; eNOS: Endothelial nitric oxide synthase; ICAM-1: Intercellular adhesion molecule 1; KLF2: Krüppel-like factor 2; MMP: Matrix metalloproteinase; NF-κB: Nuclear factor kappa B; NO: Nitric oxide; OOC: Organ-on-a-chip; ROS: Reactive oxygen species; SM-MHC: Smooth muscle myosin heavy chain; TEER: Transendothelial electrical resistance; VCAM-1: Vascular cell adhesion molecule 1; VSMC: Vascular smooth muscle cell.

3. Stimuli-responsive hydrogel bioinks for atherosclerosis modeling and cardiovascular applications

3.1. From passive scaffolds to disease-responsive bioinks

Hydrogels have become the predominant biomaterial platform for cardiovascular bioprinting owing to their high water content, tissue-like mechanical properties, and ability to support cellular viability and function. Conventional hydrogel bioinks primarily serve as passive structural matrices that provide physical support for encapsulated cells during and after the printing process. While these materials have enabled substantial advances in vascular tissue engineering, they are often unable to reproduce the dynamic and evolving microenvironments characteristic of cardiovascular tissues and vascular diseases.[81,82] In native vessels, cells continuously respond to biochemical signals, mechanical forces, oxidative stress, inflammatory mediators, and metabolic alterations, while the ECM undergoes constant degradation and remodeling. Consequently, static biomaterials are insufficient to fully capture the adaptive nature of vascular pathophysiology.[83]

This limitation is particularly relevant for atherosclerosis, a multifactorial disease involving chronic inflammation, oxidative stress, endothelial dysfunction, ECM remodeling, and progressive plaque development. Successful disease modeling therefore requires bioinks that can actively interact with and respond to pathological cues rather than merely providing structural support. Stimuli-responsive hydrogels offer a promising solution by dynamically altering their physicochemical properties in response to environmental triggers such as ROS, enzymes, light, electrical signals, mechanical stress, temperature, or pH. Through such responsiveness, bioinks can regulate matrix stiffness, degradation behavior, cellular interactions, and therapeutic delivery in a spatiotemporally controlled manner.[26,70,84]

Rather than functioning solely as passive scaffolds, smart bioinks actively participate in disease-relevant microenvironmental regulation. This transition from structural support to dynamic pathological modulation represents a key step toward next-generation vascular disease models and forms an important foundation for emerging four-dimensional bioprinting strategies.[21,82]

3.2. Atherosclerosis-specific design requirements for smart bioinks

Unlike many tissue-engineering applications that primarily focus on tissue regeneration, atherosclerosis modeling requires bioinks capable of reproducing complex pathological microenvironments. Therefore, the design of smart bioinks should be guided not only by printability and biocompatibility but also by disease-specific biological requirements.[85]

Oxidative stress is a hallmark of atherosclerosis and contributes to endothelial dysfunction, LDL oxidation, VSMC phenotypic switching, macrophage activation, and plaque progression. Bioinks capable of sensing and responding to ROS are therefore highly desirable for reproducing disease-associated oxidative microenvironments.

Chronic vascular inflammation drives all stages of atherosclerotic development. The recruitment of immune cells and sustained production of pro-inflammatory cytokines create complex biochemical gradients within plaques. Smart bioinks should therefore support the establishment of inflammatory microenvironments and enable dynamic regulation of immune-related signaling pathways.

Atherosclerotic lesions undergo continuous ECM remodeling mediated by MMPs, elastases, and other proteolytic enzymes. These processes contribute to fibrous cap formation, plaque destabilization, and vascular structural changes. Bioinks capable of cell-mediated degradation and remodeling are essential for reproducing disease progression.[86]

Blood vessels are continuously exposed to pulsatile pressure, cyclic strain, and shear stress. Moreover, vascular stiffening and altered biomechanics are characteristic features of atherosclerosis. Therefore, bioinks should possess adaptive mechanical properties that enable dynamic responses to physiological and pathological mechanical stimuli.[81]

Collectively, these requirements highlight the need for disease-responsive bioinks capable of recapitulating the multifactorial nature of atherosclerosis rather than simply supporting vascular cell growth.[68]

3.3. Reactive oxygen species-responsive bioinks

Among the various stimuli investigated for cardiovascular applications, ROS have attracted particular attention because oxidative stress is a central pathological feature of atherosclerosis, myocardial infarction, ischemia–reperfusion injury, and vascular aging.[87-89] Excessive ROS production contributes to endothelial dysfunction, LDL oxidation, inflammatory activation, VSMC phenotypic modulation, and plaque instability, making oxidative stress one of the most representative hallmarks of atherosclerotic disease progression.[90-92]

Compared with conventional hydrogels, ROS-responsive systems offer several advantages for atherosclerosis modeling. First, they enable disease-specific matrix remodeling that directly reflects local oxidative conditions. Second, they facilitate controlled release of therapeutic molecules in response to disease progression. Third, they create feedback-regulated microenvironments capable of dynamically adapting to pathological severity.[78,90] In cardiovascular tissue engineering, ROS-responsive and ROS-scavenging hydrogels have demonstrated beneficial effects in modulating oxidative microenvironments, reducing inflammatory responses, and supporting tissue repair following myocardial infarction and ischemia–reperfusion injury.[78,93] These findings highlight the potential of ROS-responsive biomaterials for constructing disease-relevant vascular models.

Importantly, ROS-responsive bioinks are particularly attractive for atherosclerosis research because the triggering stimulus originates directly from disease progression itself. Such systems may enable localized simulation of inflamed plaque regions while preserving relatively healthy vascular compartments within the same construct. Although direct ROS-responsive bioink platforms specifically designed for atherosclerosis remain relatively limited, this area is emerging as a promising direction for next-generation vascular disease modeling.[68,94]

3.4. Enzyme-responsive bioinks for dynamic matrix remodeling

Extracellular matrix remodeling is a defining characteristic of CVD progression. Dysregulated interactions between vascular cells and the ECM contribute to alterations in vascular structure, mechanical properties, and inflammatory signaling, thereby driving disease development and progression. MMPs, elastases, and other proteolytic enzymes play critical roles in ECM degradation and reorganization during vascular remodeling, atherosclerotic plaque progression, plaque destabilization, aneurysm formation, and post-myocardial infarction repair processes.[95,96]

To reproduce these dynamic pathological processes, enzyme-responsive hydrogels incorporate protease-cleavable peptide sequences that can be selectively degraded by disease-associated enzymes. Such systems enable localized matrix degradation, controlled release of bioactive factors, and adaptive structural evolution in response to cellular activity.[97,98]

Compared with conventional hydrolytically degradable hydrogels, enzyme-responsive materials provide greater biological specificity because degradation occurs predominantly in regions exhibiting active remodeling and elevated protease expression. This feature allows cell-mediated matrix adaptation and closely mimics native tissue dynamics. Consequently, enzyme-responsive hydrogels have emerged as promising platforms for modeling fibrous cap remodeling, plaque destabilization, angiogenesis, vascular regeneration, and post-infarction tissue repair.[97,99]

3.5. Electrically responsive bioinks

Electrical signaling plays an essential role in cardiovascular physiology. Although electrical responsiveness has been extensively investigated in cardiac tissue engineering, increasing evidence suggests that electrical cues can also influence endothelial behavior, vascular maturation, NO signaling, and mechanotransduction pathways relevant to vascular function.[100]

Traditional hydrogel bioinks generally exhibit poor electrical conductivity, limiting electrophysiological communication and bioelectronic integration. Electrically responsive hydrogels address this limitation through incorporation of conductive components such as graphene-based materials, conductive polymers, carbon nanomaterials, metallic nanostructures, and other conductive additives.[28,101,102] These materials improve electrical signal transmission and facilitate interactions between engineered tissues and external bioelectronic systems. In addition to supporting cellular communication, conductive bioinks may enable integration with biosensors, soft bioelectronics, and real-time monitoring platforms. Recent advances in conductive hydrogel electrodes and bioelectronic interfaces further highlight their potential for dynamic disease monitoring and functional assessment.[103]

However, compared with cardiac applications, direct evidence supporting electrically responsive bioinks for atherosclerotic vascular disease modeling remains relatively limited. Nevertheless, emerging studies indicate that electrical stimulation may influence vascular formation, endothelial function, and mechanobiological responses, suggesting a potentially valuable but still underexplored direction for vascular bioengineering.[104,105]

3.6. Photoresponsive bioinks for spatiotemporal control

Photoresponsive hydrogels provide unique advantages because light can be precisely controlled in terms of wavelength, intensity, duration, and spatial localization. As a result, photoresponsive systems enable highly controllable modulation of biomaterial properties and biological functions after construct fabrication.[106,107] Current photoresponsive bioinks are commonly based on photocrosslinkable polymers, photoswitchable molecules,

photothermal agents, and light-triggered delivery systems. Through external optical stimulation, these materials can regulate matrix stiffness, degradation behavior, cellular interactions, and bioactive factor release with high spatial and temporal precision.[106,107]

For vascular tissue engineering and disease modeling, photoresponsive bioinks may facilitate controlled vascular network formation, regulation of angiogenic signaling, and dynamic remodeling of engineered microenvironments.[108] Furthermore, incorporation of photothermal nanomaterials can enable remote regulation of cellular behavior and tissue remodeling through near-infrared (NIR) irradiation. Although most current studies remain focused on regenerative applications, photoresponsive systems offer substantial potential for constructing programmable vascular disease models with externally controlled functionality. Emerging 2D nanomaterials may further expand opportunities for photoresponsive biofabrication and dynamic vascular microenvironment regulation.[36,109,110]

3.7. Toward multifactorial atherosclerosis-mimetic bioinks

While individual responsive mechanisms provide important advantages, atherosclerosis is fundamentally a multifactorial disease involving oxidative stress, chronic inflammation, ECM remodeling, endothelial dysfunction, biomechanical abnormalities, and disturbed hemodynamics.[44,111,112] Consequently, single-stimulus bioinks are unlikely to fully reproduce the complexity of disease progression.

Future bioink design will therefore require integration of multiple responsive functions within a single platform. Multifunctional systems capable of simultaneously sensing oxidative stress, responding to enzymatic remodeling, adapting to mechanical alterations, and regulating therapeutic delivery may provide more physiologically relevant disease models.[53,55,68,69] Such disease-responsive bioinks move beyond traditional biomaterials toward active microenvironmental regulators capable of sensing, interpreting, and responding to pathological signals. In this context, advanced nanomaterial-enabled hydrogels have attracted increasing interest because they offer opportunities to combine conductivity, biosensing, photothermal responsiveness, ROS regulation, and mechanical reinforcement within a unified platform.[108-111] More broadly, recent advances in smart nanomaterials have demonstrated a clear shift toward multifunctional platforms that integrate diagnostic, therapeutic, and regenerative capabilities, providing an important conceptual foundation for the development of next-generation disease-responsive bioinks .[113-116]

The development of multifunctional, disease-responsive bioinks is therefore expected to become a central direction in next-generation atherosclerosis modeling and vascular tissue engineering. The major classes of stimuli-responsive bioinks and their potential roles in cardiovascular tissue engineering and disease modeling are summarized in Figure 2.

3.8. Transition toward nanomaterial-enabled smart bioinks

The design principles discussed above demonstrate that effective atherosclerosis models require bioinks capable of responding to oxidative stress, inflammatory signaling, matrix remodeling, and dynamic vascular microenvironments. Achieving these functions within a single material system remains a significant challenge. A comparison of the major classes of stimuli-responsive bioinks and their cardiovascular relevance is provided in Table 2.

Two-dimensional nanomaterials have emerged as particularly promising candidates for addressing this challenge because they can simultaneously provide mechanical reinforcement, electrical conductivity, photothermal responsiveness, ROS regulation, and biosensing functionality. As summarized in Figure 3, hydrogel matrices provide the structural and biological foundation of bioinks, whereas 2D nanomaterials function primarily as physicochemical and bioactive enhancers that improve mechanical stability, conductivity, cellular regulation, and printability. Consequently, the following sections examine how graphene-family nanomaterials, BP, and emerging Xene-based materials can be incorporated into smart hydrogel bioinks to construct next-generation platforms for vascular disease modeling and cardiovascular bioprinting.

4. Graphene-based smart bioinks: Functions, evidence, and design boundaries

4.1. Graphene derivatives and formulation logic

Graphene-family nanomaterials are among the most mature and extensively investigated 2D materials in bioprinting and tissue engineering. Since the discovery of graphene, numerous derivatives—including graphene oxide (GO), reduced GO (rGO), graphene nanoplatelets, and graphene quantum dots—have been developed to improve processability, dispersibility, conductivity, and biocompatibility.[29]

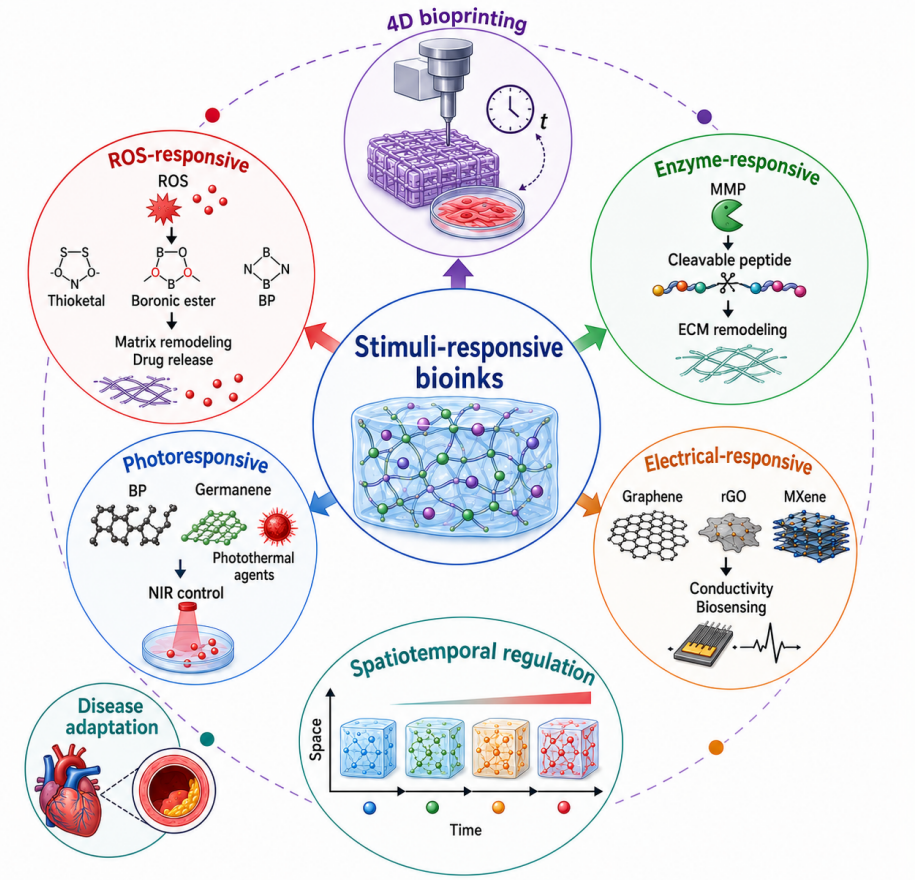

Figure 2. Stimuli-responsive hydrogel bioinks for cardiovascular applications. Smart hydrogel bioinks respond to disease-associated stimuli including ROS, enzymes, electrical signals, light, and mechanical stress. These responses regulate hydrogel degradation, stiffness, drug release, cell behavior, and tissue maturation, enabling dy namic reconstruction of cardiovascular microenvironments. Created in BioRender. Chu, R. (2026). https://BioRender.com/5813oka, with assistance from ChatGPT (OpenAI, GPT-5.5 Thinking) for preliminary figure drafting, visual refinement, and layout optimization. Abbreviations: 4D: Four-dimensional; BP: Black phosphorus; ECM: Extracellular matrix; MMP: Matrix metalloproteinase; MXene: Two-dimensional transition-metal carbide, nitride, or carbonitride; NIR: Near-infrared; rGO: Reduced graphene oxide; ROS: Reactive oxygen species.

Table 2. Stimulus–response mechanisms and cardiovascular relevance of smart hydrogel bioinks

Bioink type	Trigger	Representative materials	Cardiovascular application	Atherosclerosis relevance
ROS-responsive[25,26,68,74]	ROS	Thioketal polymers, BP	Controlled degradation, drug release	High
Enzyme-responsive[98,117]	MMPs, elastases	Protease-cleavable hydrogels	ECM remodeling	High
Electrically responsive[101,118-121]	Electrical stimulation	Graphene, rGO, conductive polymers	Signal transmission, sensing	Moderate
Photoresponsive[101,107]	NIR/light	BP, germanene, photothermal agents	Remote regulation	Moderate
Multifunctional[53,68,114,122]	Multiple stimuli	Hybrid nanomaterial systems	Disease-adaptive regulation	High

Abbreviations: BP: Black phosphorus; ECM: Extracellular matrix; MMPs: Matrix metalloproteinases; NIR: Near-infrared; rGO: Reduced graphene oxide; ROS: Reactive oxygen species.

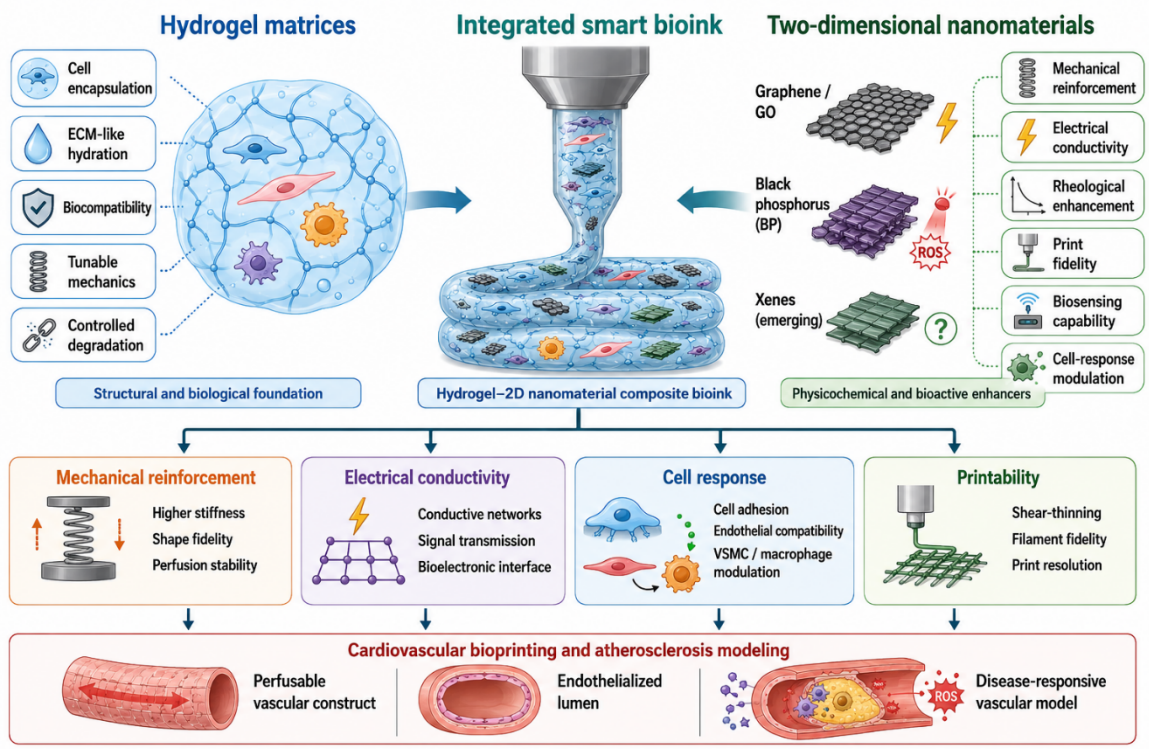

Figure 3. Complementary roles of hydrogel matrices and 2D nanomaterials in smart bioink systems. Hydrogel matrices provide the foundational ECM-like framework for cell encapsulation, hydration, biocompatibility, tunable mechanics, and controlled degradation. 2D nanomaterials serve as physicochemical and bioactive enhancers that improve mechanical reinforcement, electrical conductivity, rheological behavior, print fidelity, biosensing capability, and cell-response modulation. Their integration enables multifunctional smart bioinks with enhanced structural stability, bioelectronic functionality, cellular regulation, and printability for cardiovascular bioprinting and atherosclerosis modeling. Created in BioRender. Chu, R. (2026). https://BioRender.com/ia11euo, with assistance from ChatGPT (OpenAI, GPT-5.5 Thinking) for preliminary figure drafting, visual refinement, and layout optimization. All figure concepts, scientific labels, annotations, and final visual content were reviewed, revised, and approved by the authors.
Abbreviations: ECM: Extracellular matrix; GO: Graphene oxide.

For cardiovascular bioink design, graphene is attractive not because of a single material property but because it can simultaneously influence multiple aspects of biofabrication. Depending on the derivative selected, graphene-based additives may improve rheological behavior, mechanical reinforcement, electrical conductivity, surface bioactivity, and biosensing capability.[28,123] Consequently, different graphene derivatives are typically chosen according to the intended function of the bioink rather than conductivity alone.

Graphene oxide is the most commonly used derivative for hydrogel bioinks because its oxygen-containing functional groups improve aqueous dispersibility and facilitate interactions with polymer networks through hydrogen bonding, electrostatic interactions, and physical entanglement. These characteristics make GO particularly suitable for enhancing printability and structural stability.[123] In contrast, rGO partially restores the conductive sp^2 carbon network and is therefore preferred for applications requiring electrical signal transmission and electrophysiological coupling. rGO–gelatin methacryloyl (GelMA) hydrogels have been widely investigated as conductive cardiac scaffolds that improve electrical and mechanical properties.[124] This distinction is important for bioink design because vascular applications may prioritize dispersion, printability, and cytocompatibility, whereas cardiac applications often require higher conductivity and electromechanical coupling.[119]

From a formulation perspective, graphene derivatives can be viewed as functional nanofillers that provide distinct advantages depending on the target application. For vascular bioinks, GO is primarily utilized to improve printability, support endothelial-cell compatibility, and enhance scaffold stability. For cardiac bioinks, rGO is commonly incorporated to enhance conductivity and tissue maturation. For biosensing-enabled platforms, graphene derivatives may serve as conductive interfaces

that facilitate real-time monitoring of cellular and biochemical activities. Therefore, rational selection of graphene derivatives should be guided by the specific requirements of the target cardiovascular application rather than by a generalized assumption that all graphene materials provide identical functions.

4.2. Rheology, mechanics, and printability

One of the most established contributions of graphene to bioink development is the enhancement of rheological properties and mechanical performance. Conventional hydrogels often suffer from insufficient mechanical strength, poor shape fidelity, and structural instability during long-term culture or perfusion. These limitations are particularly problematic for cardiovascular applications, where constructs must withstand extrusion, handling, fluid flow, and cyclic mechanical loading.[81,125] Graphene nanosheets possess exceptionally large surface areas and high aspect ratios, allowing extensive interactions with polymer chains through hydrogen bonding, electrostatic attraction, van der Waals forces, and π–π interactions. As a result, graphene incorporation can increase viscosity, improve shear-thinning behavior, enhance post-shear recovery, and reinforce hydrogel networks.[126,127]

Numerous studies have demonstrated improved printability and mechanical performance following graphene incorporation. GO-containing GelMA, collagen, alginate, and gelatin-based bioinks have shown enhanced shape fidelity, filament stability, compressive strength, and viscoelastic behavior.[123-126,128] In extrusion-based bioprinting, graphene additives frequently improve filament formation and reduce structural collapse after deposition, facilitating fabrication of multilayered vascular constructs and perfusable architectures.

Despite these advantages, graphene concentration must be carefully optimized. Excessive loading may induce aggregation, heterogeneous mechanical properties, nozzle clogging, and reduced cellular compatibility.[127,128] Furthermore, improvements in bulk mechanical properties do not necessarily translate into improved biological performance, emphasizing the need for simultaneous evaluation of rheological and cellular outcomes. Current evidence suggests that graphene is one of the most effective nanofillers available for improving bioink printability and structural stability. Consequently, its greatest immediate value in vascular bioprinting lies in mechanical reinforcement and fabrication support rather than disease-specific biological regulation.

4.3. Conductive cardiac bioinks

Electrical conductivity represents another defining characteristic of graphene-based bioinks. Native myocardium relies on synchronized electrical signal propagation to coordinate contraction, whereas most conventional hydrogels are electrically insulating and therefore poorly suited for supporting electrophysiological communication between cardiomyocytes.[119,129] By incorporating conductive graphene derivatives, hydrogel matrices can form interconnected conductive networks that facilitate electrical signal transmission and improve intercellular communication.

Graphene-containing hydrogels have been reported to enhance the expression of cardiac maturation markers such as connexin-43, cardiac troponin T, and α-actinin while improving calcium handling and synchronized beating behavior in engineered cardiac tissues.[124,130,131] In particular, rGO–GelMA hydrogels have demonstrated improved sarcomere organization and electrophysiological coupling, supporting functional maturation of bioprinted cardiac constructs.[124]

This conductive function is highly relevant for cardiovascular bioprinting because the maturation of engineered cardiac tissues remains a major bottleneck in the development of clinically relevant tissue models. Recent studies have highlighted that conductive graphene-based biomaterials can improve electrophysiological integration, promote anisotropic tissue organization, and generate more physiologically representative cardiac tissue models for disease modeling and drug screening applications.[129,132] These findings have established graphene as one of the most extensively studied conductive additives for cardiac tissue engineering and bioprinting.

However, most available evidence originates from myocardial applications rather than vascular disease models. Conductivity alone cannot overcome other challenges associated with tissue maturation, including vascularization, nutrient transport, mechanical matching, and long-term tissue remodeling.[119,133] Although conductive graphene bioinks provide valuable proof-of-concept for electroactive biofabrication, their direct relevance to atherosclerosis modeling remains limited. Their primary contribution lies in demonstrating how nanomaterial-enabled conductivity can be integrated into multifunctional cardiovascular bioinks.[129]

4.4. Vascular endothelialization and angiogenesis

Beyond cardiac applications, graphene-based materials can influence endothelial behavior through modulation of surface chemistry, nanotopography, mechanical properties, and electrical characteristics. Endothelial cells are highly responsive to these environmental cues, making graphene an attractive component for vascular bioinks.[134]

Previous studies have reported enhanced endothelial adhesion, proliferation, migration, and spreading on graphene-containing substrates and hydrogels.[135] A collagen/GO bioink developed for 3D-bioprinted vascular graft fabrication demonstrated improved mechanical performance and favorable endothelial-cell compatibility.[128] In addition, graphene-based systems have been associated with vascular endothelial growth factor-related angiogenic activity and phosphoinositide 3-kinase/protein kinase B-mediated signaling pathways that regulate endothelial survival, migration, and vascular formation.[136] Such effects may facilitate microvascular network formation and improve oxygen and nutrient transport within thick bioprinted tissues.[137]

Most current studies evaluate endothelial viability and proliferation rather than disease-relevant endothelial dysfunction. However, endothelial dysfunction is a central event in atherosclerosis and involves alterations in barrier integrity, inflammatory activation, leukocyte recruitment, and NO signaling. Therefore, favorable endothelial growth does not necessarily indicate successful disease modeling. Future atherosclerosis-oriented bioinks should assess endothelial barrier function, VCAM-1 and ICAM-1 expression, monocyte adhesion, permeability changes, and responses to disturbed flow rather than relying solely on conventional cell viability measurements.[138]

4.5. Biosensing-enabled disease monitoring

Among the various applications of graphene in cardiovascular biofabrication, biosensing may represent its most distinctive and underexploited capability. Graphene exhibits high electrical conductivity, large surface area, excellent surface functionalization potential, and remarkable sensitivity to interfacial chemical changes, making it highly suitable for bioelectronic sensing.[121,127,139] Graphene-based sensing platforms have been explored for monitoring cellular activity, metabolic changes, inflammatory signaling, oxidative stress, and endothelial barrier function.[140-142]

In CVD models, continuous assessment of endothelial dysfunction, cytokine secretion, thrombosis-related responses, and inflammatory activation is increasingly recognized as essential for understanding disease progression.[79] Despite considerable interest, fully integrated sensing bioinks remain relatively uncommon. Most current graphene-containing hydrogels focus primarily on mechanical reinforcement, printability, or conductivity rather than embedded sensing functionality.[127,139,143] Consequently, real-time monitoring remains largely separated from the biofabrication process itself. For atherosclerosis modeling, biosensing may represent the most unique contribution of graphene. Sensor-integrated vascular constructs could transform disease modeling from endpoint-based analysis toward continuous and non-destructive monitoring of pathological progression.

4.6. Design boundaries and future directions

Despite its versatility, graphene should not be regarded as a universal solution for atherosclerosis bioink design. Graphene performs exceptionally well as a mechanical stabilizer, conductive component, endothelial-supportive additive, and biosensing interface.[123,128,144,145,146] These properties directly address several challenges associated with vascular bioprinting, including printability, structural integrity, bioelectronic integration, and real-time monitoring.[81] However, graphene exhibits important limitations when viewed from the perspective of disease-responsive bioink design.

Unlike ROS-responsive materials, graphene does not intrinsically respond to oxidative stress, inflammatory signaling, or disease-associated biochemical changes.[147-149] Furthermore, many graphene derivatives exhibit limited biodegradability and may persist within biological environments for extended periods.[148,150] Consequently, graphene alone cannot adequately reproduce the dynamic oxidative and inflammatory microenvironments characteristic of atherosclerotic plaques.[90]

From an application standpoint, graphene is most suitable for four major scenarios: (i) mechanically stable perfusable vascular constructs, (ii) conductive cardiovascular tissues, (iii) biosensor-integrated vascular disease models, and (iv) multifunctional hybrid bioinks. Among these, hybrid systems are likely to be particularly important.[54,55] Combining graphene with ROS-responsive hydrogels, degradable matrices, or complementary nanomaterials may overcome the limitations of single-component designs while integrating structural stability, conductivity, biosensing capability, and disease responsiveness within a single platform.[149,151]

Therefore, graphene should be viewed primarily as a structural, conductive, and sensing component in atherosclerosis bioinks, whereas disease-specific responsiveness will likely need to be provided by complementary biomaterials. This distinction is critical for rational material selection and provides a useful framework for evaluating other emerging nanomaterials discussed in subsequent sections.

5. Black phosphorus-based disease-responsive bioinks: Opportunities and translational challenges

5.1. Black phosphorus as a disease-responsive nanomaterial

Among currently available 2D nanomaterials, BP possesses a material profile that is particularly relevant to CVD microenvironments. Unlike graphene-family materials, which are primarily valued for mechanical reinforcement, electrical conductivity, and biosensing capabilities,[30,31] BP exhibits intrinsic biodegradability, oxidative sensitivity, photothermal responsiveness, and redox-regulatory activity.[152,153]

This distinction is especially important for atherosclerosis. The disease is characterized by chronic inflammation, oxidative stress, endothelial dysfunction, macrophage activation, ECM remodeling, and progressive plaque destabilization. These pathological features generate disease-specific biochemical signals that may be directly recognized or modulated by BP-containing biomaterials.[32,55] Recent studies have demonstrated that BP nanosheets possess ROS-scavenging capability, regulate inflammatory signaling pathways, and influence macrophage polarization in CVD models.[55,154]

Consequently, BP should not be regarded merely as a reinforcing nanofiller. Instead, it represents a potentially active disease-responsive component capable of interacting with pathological microenvironments.[55,154] This property distinguishes BP from most currently used nanomaterials and makes it particularly attractive for the development of atherosclerosis-oriented smart bioinks.[85,132]

5.2. Physicochemical properties and bioink formulation considerations

Black phosphorus consists of phosphorus atoms arranged in a puckered layered structure, giving rise to unique optical, electronic, and physicochemical properties.[155,156] When exfoliated into nanosheets or quantum dots, BP exhibits high surface area, NIR responsiveness, and thickness-dependent electronic behavior.[157,158] These characteristics provide a physicochemical foundation for constructing photoresponsive and multifunctional hydrogel bioinks.[122,159]

A major advantage of BP is its biodegradability. Under physiological conditions, BP gradually oxidizes and degrades into phosphate-containing products that may participate in normal biological processes and tissue remodeling.[158,160,161] This characteristic potentially reduces long-term accumulation concerns associated with nondegradable nanomaterials.[160,161]

From a bioink formulation perspective, BP nanosheets can interact with polymer networks through hydrogen bonding, electrostatic interactions, physical adsorption, and coordination effects, enabling incorporation into commonly used hydrogel systems such as GelMA, hyaluronic acid, alginate, chitosan, and composite polymer matrices.[115,122,159] However, the same oxidative sensitivity that makes BP biologically responsive also creates important formulation challenges. BP readily undergoes degradation during preparation, storage, and processing. Variations in nanosheet size, oxidation state, surface chemistry, and storage conditions may significantly influence biological performance and reproducibility.[159,162] Therefore, BP-based bioinks require careful optimization of exfoliation methods, stabilization strategies, polymer encapsulation, and storage protocols. Importantly, these characteristics simultaneously create opportunities for disease responsiveness and challenges for bioink standardization.

5.3. Reactive oxygen species responsiveness and atherosclerosis-relevant microenvironment regulation

Reactive oxygen species are among the most important pathological drivers of atherosclerosis. Excessive ROS production contributes to endothelial dysfunction, LDL oxidation, macrophage activation, foam-cell formation, VSMC phenotypic switching, inflammatory amplification, and plaque destabilization.[25]

Because BP is intrinsically sensitive to oxidative environments, its degradation behavior is closely linked to disease-associated redox conditions. In contrast to conventional nanomaterials that remain relatively inert under oxidative stress, BP undergoes oxidation and gradual degradation in the presence of ROS, generating phosphate-containing degradation products.[163] This property creates a unique opportunity to couple material behavior directly to pathological microenvironments.

Recent studies have demonstrated that BP-containing hydrogels can regulate oxidative stress, attenuate inflammatory responses, and promote tissue repair in CVD models. For example, ROS-responsive Gel-pBP@Mg hydrogels enabled ROS-triggered degradation, sustained BP release, reduced oxidative stress, suppressed inflammatory signaling, and promoted angiogenesis following myocardial infarction.[55] Similar BP-based systems have been reported to regulate macrophage polarization and improve tissue regeneration through redox-dependent mechanisms.[154,164]

Although most available evidence originates from myocardial repair studies,[165] the underlying mechanisms

are highly relevant to atherosclerosis because oxidative stress and inflammation represent common pathological pathways. Consequently, BP-integrated bioinks may enable the construction of vascular models in which oxidative stress gradients dynamically regulate matrix behavior, cellular responses, and therapeutic release. Among currently available 2D nanomaterials, BP is arguably the material whose intrinsic responsiveness most closely aligns with the pathological microenvironment of atherosclerosis. This disease-matched responsiveness represents its greatest advantage for smart bioink development.

5.4. Photothermal regulation and external control

Black phosphorus nanosheets exhibit strong NIR absorption and efficient photothermal conversion, enabling localized heat generation under external optical stimulation. This property has attracted considerable interest in drug delivery, tissue repair, and regenerative medicine applications.[166] BP-based nanospheres/nanosheets have been reported as biodegradable photothermal agents for *in vivo* cancer photothermal therapy and cancer theranostics, while recent reviews further summarize their antibacterial and tissue-regenerative applications.[158]

Within hydrogel systems, photothermal responsiveness provides an opportunity for remote control of matrix degradation, molecular release, and cellular activity. Compared with chemically triggered systems, light-mediated regulation offers superior temporal and spatial precision. BP-containing hydrogels have demonstrated NIR-triggered release of bioactive molecules and externally controlled modulation of material behavior.[74,167] However, the relevance of photothermal regulation to atherosclerosis modeling remains less clear than its relevance to ROS-responsive regulation. Excessive photothermal stimulation may impair endothelial viability, compromise vascular barrier integrity, and induce inflammatory responses. Recent studies have shown that BP nanosheets may influence endothelial permeability, transendothelial electrical resistance (TEER) values, and junctional protein expression under certain conditions.[168]

Therefore, endothelial safety must be rigorously evaluated when developing photoresponsive BP bioinks. Future studies should assess endothelial viability, barrier integrity, vascular endothelial cadherin (VE-cadherin) expression, zonula occludens-1 (ZO-1) organization, inflammatory activation, and macrophage responses under photothermal conditions rather than relying solely on standard cytocompatibility assays.[167] At present, photothermal responsiveness should be regarded as a potentially useful auxiliary function rather than the primary rationale for BP incorporation into atherosclerosis-oriented bioinks.

5.5. Angiogenesis and vascular remodeling

Black phosphorus-containing biomaterials have demonstrated significant pro-angiogenic potential in multiple regenerative medicine studies. Controlled BP degradation, redox modulation, and interactions with endothelial cells have been associated with enhanced endothelial migration, neovascularization, and tissue repair.[55,169]

For tissue engineering applications, angiogenesis is generally viewed as a beneficial outcome because vascularization improves oxygen and nutrient transport within thick engineered tissues. BP-integrated hydrogels have therefore been widely investigated for promoting vascular regeneration in myocardial repair and other ischemic conditions.[55,169,170] However, angiogenesis has a dual role in atherosclerosis. While vascularization may support tissue regeneration, intraplaque neovascularization is strongly associated with plaque progression, hemorrhage, inflammation, and plaque vulnerability.[171,172] Consequently, increased angiogenesis should not automatically be interpreted as a favorable outcome in atherosclerosis-oriented bioink design.

This distinction highlights the importance of disease-specific evaluation criteria. Rather than simply measuring vascular growth, future BP-based atherosclerosis models should investigate how BP influences pathological neovascularization, endothelial dysfunction, inflammatory activation, and plaque remodeling.

5.6. Translational gap between therapeutic hydrogels and true bioinks

A major limitation of the current BP literature is that most reported systems have been developed as injectable therapeutic hydrogels rather than bioprintable bioinks. Existing studies provide substantial evidence supporting the biological activity of BP-containing hydrogels, including ROS scavenging, inflammatory regulation, macrophage modulation, angiogenesis promotion, and tissue repair.[55,154,164,173] However, these studies typically focus on therapeutic efficacy after injection and rarely evaluate the material properties required for bioprinting.

Consequently, critical biofabrication parameters remain insufficiently characterized, including viscosity, shear-thinning behavior, yield stress, filament formation, extrusion fidelity, crosslinking kinetics, post-printing cell viability, long-term construct stability, and perfusion compatibility.[174-176] This distinction is important because therapeutic performance should not be equated with biofabrication suitability. A hydrogel that performs well as an injectable matrix may fail to satisfy the rheological and biological requirements necessary for successful

bioprinting. Therefore, the current evidence base supports BP primarily as a promising therapeutic hydrogel component rather than as a fully validated cardiovascular bioink additive.

5.7. Design requirements for black phosphorus-based atherosclerosis bioinks

To realize the full potential of BP in cardiovascular bioprinting, future studies must simultaneously address disease relevance and biofabrication performance. From a biofabrication perspective, BP-based systems should be evaluated for extrusion rheology, shear-thinning behavior, viscosity recovery, filament fidelity, print resolution, post-printing viability, and long-term structural stability under perfusion. These parameters remain largely absent from the current literature.[177-179]

From a disease-modeling perspective, evaluation should extend beyond conventional cytocompatibility measurements. Future BP-containing bioinks should be validated under oxidative stress, inflammatory stimulation, oxLDL exposure, macrophage co-culture, disturbed-flow conditions, and long-term vascular perfusion.[65,180,181]

Particular attention should be paid to functional endpoints directly associated with disease progression, including ROS-responsive degradation behavior, endothelial barrier integrity and permeability, expression of junctional proteins such as VE-cadherin and ZO-1, endothelial activation markers including VCAM-1 and ICAM-1, macrophage polarization profiles, inflammatory signaling pathways, VSMC phenotypic switching, and construct stability under physiologically relevant flow conditions.[9,44,55,65,180] These parameters collectively provide a more rigorous framework for evaluating the biological relevance and translational potential of BP-enabled vascular disease models.

Ultimately, BP-containing hydrogels should not be considered atherosclerosis-specific bioinks solely on the basis of their antioxidant or photothermal properties. Rather, only materials that simultaneously satisfy stringent biofabrication requirements and faithfully reproduce disease-associated vascular microenvironments can be regarded as validated BP-containing bioinks for atherosclerosis modeling and cardiovascular bioprinting.

5.8. Summary and comparison with graphene

The distinct roles of graphene and BP in cardiovascular bioink design are summarized in Figure 4 and are further compared with other representative 2D nanomaterials in **Section.6.4**. Overall, graphene primarily contributes structural stability, conductivity, and biosensing functionality,[29,118,123,182] whereas BP contributes disease-responsive, redox-regulatory, and immunomodulatory capabilities.[55,115,154] Rather than functioning as competing nanomaterial platforms, graphene and BP provide complementary functionalities that may be integrated within multifunctional bioinks.

For atherosclerosis modeling, graphene may be most useful for constructing mechanically stable and sensor-integrated vascular platforms, whereas BP may be more suitable for reproducing or modulating redox-active plaque-like microenvironments, given the central role of oxidative stress and ROS-responsive biomaterials in cardiovascular pathology.[65,92,183] Therefore, graphene and BP should not be viewed as competing materials, but as complementary modules within multifunctional bioinks. Hybrid graphene–BP systems may integrate conductivity, mechanical reinforcement, biosensing capability, ROS responsiveness, biodegradability, and photothermal regulation; this concept is supported by recent GO/BP composite scaffold studies, although direct validation in atherosclerosis-on-a-chip bioinks remains an important future direction.[184] Such systems could be especially powerful for atherosclerosis-on-a-chip platforms requiring both real-time monitoring and disease-responsive remodeling.[65,185]

6. Emerging Xenes beyond graphene and black phosphorus

6.1. Why look beyond graphene and black phosphorus?

To clarify the distinct functional roles of different 2D nanomaterials, Figure 5 compares graphene, BP, and emerging Xenes in terms of disease responsiveness, multifunctionality, and translational maturity. Graphene and BP currently represent the two most extensively investigated 2D nanomaterials for cardiovascular bioink development.[29,119,154] As discussed in the preceding sections, graphene primarily contributes mechanical reinforcement, electrical conductivity, and biosensing capability, whereas BP provides biodegradability, ROS responsiveness, and disease-adaptive functionality. Together, these materials address many of the structural and biological challenges associated with cardiovascular bioprinting and atherosclerosis modeling.

Nevertheless, neither material fully satisfies all requirements of next-generation smart bioinks. Graphene exhibits limited disease-specific responsiveness, while BP faces challenges related to instability, reproducibility, and bioprinting validation. Consequently, increasing attention has been directed toward emerging members of the Xene family as potential candidates for future multifunctional bioink systems.

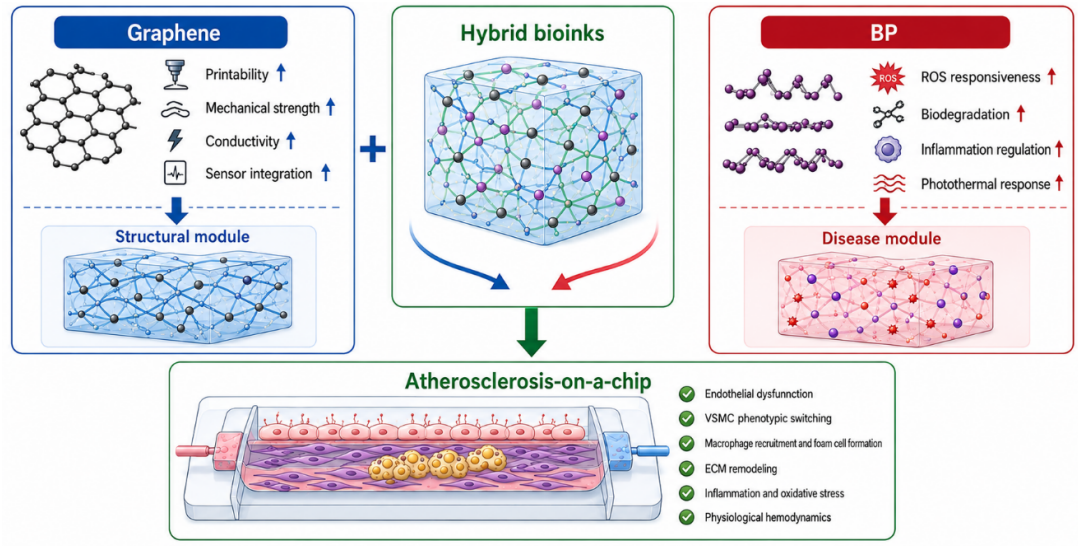

Figure 4. Complementary rather than competitive roles of graphene and BP in smart bioinks. Graphene- and BP-based nanomaterials contribute distinct but complementary functionalities to cardiovascular bioink design. Graphene primarily serves as a structural and bioelectronic component by enhancing mechanical reinforcement, printability, electrical conductivity, and biosensing capability, thereby supporting construct stability, electrophysiological integration, and real-time monitoring. In contrast, BP functions predominantly as a disease-responsive component owing to its biodegradability, ROS-sensitive behavior, photothermal responsiveness, and potential immunomodulatory effects. These properties enable dynamic regulation of oxidative stress, inflammation, and tissue remodeling within pathological vascular microenvironments. Rather than representing competing nanomaterial platforms, graphene and BP provide complementary modules that may be integrated within multifunctional smart bioinks to simultaneously improve biofabrication performance and disease-specific responsiveness for advanced cardiovascular tissue engineering and atherosclerosis modeling. Created in BioRender. Chu, R. (2026). https://BioRender.com/4iakeoo, with assistance from ChatGPT (OpenAI, GPT-5.5 Thinking) for preliminary figure drafting, visual refinement, and layout optimization.
Abbreviations: BP: Black phosphorus; ECM: Extracellular matrix; ROS: Reactive oxygen species; VSMC: Vascular smooth muscle cell.

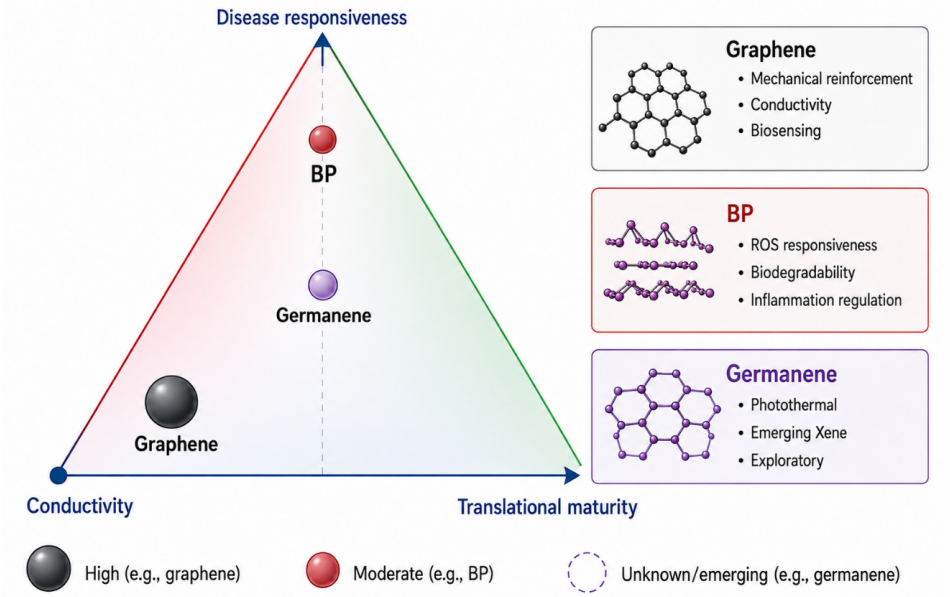

Figure 5. Functional positioning of graphene, BP, and emerging Xenes in cardiovascular bioink design. Graphene primarily contributes conductivity, mechanical reinforcement, and biosensing functionality. BP provides biodegradability, ROS responsiveness, photothermal activity, and angiogenic potential. Germanene represents an emerging Xene platform with photothermal and programmable functionalities but currently has limited cardiovascular evidence. Created in BioRender. Chu, R. (2026). https://BioRender.com/5lvir0n, with assistance from ChatGPT (OpenAI, GPT-5.5 Thinking) for preliminary figure drafting, visual refinement, and layout optimization.
Abbreviations: BP: Black phosphorus; ROS: Reactive oxygen species.

Among these emerging materials, germanene has attracted particular interest because of its photothermal properties, surface reactivity, and potential compatibility with hydrogel-based biomaterials.[186-188] However, compared with graphene and BP, its biomedical development remains at a much earlier stage.[189,190] Therefore, germanene should currently be regarded as a frontier material that may expand future bioink-design strategies rather than as an established component of cardiovascular bioprinting platforms.

6.2. Germanene and emerging Xenes: Exploratory opportunities

Germanene is a 2D germanium-based nanomaterial belonging to the broader Xene family. Although originally investigated for electronic and photonic applications, recent studies have suggested potential biomedical utility owing to its photothermal responsiveness, surface functionalization capability, and compatibility with hydrogel systems.[186-188] From a bioink-design perspective, the most relevant features of germanene are not its electronic structure alone but its potential contribution to externally regulated and multifunctional hydrogel systems. First, germanene exhibits efficient NIR photothermal conversion, enabling remote modulation of material behavior.[191] Second, its chemically active surface may facilitate conjugation with polymers, peptides, therapeutic molecules, or targeting ligands.[192-194] Third, emerging studies suggest that germanene may eventually support sensing or bioelectronic applications if stable and biocompatible interfaces can be established.[195]

Collectively, these properties suggest that germanene and related Xenes could contribute to future hydrogel systems requiring remote regulation, multifunctional surface modification, or integrated sensing functions. However, these possibilities remain largely conceptual and have not yet been validated in cardiovascular biofabrication.[81,196,197]

Importantly, the currently available germanene-containing hydrogel evidence should be interpreted cautiously. The strongest biomedical evidence remains derived mainly from antibacterial and wound-healing applications rather than vascular tissue engineering or atherosclerosis modeling. For example, germanene-modified chitosan hydrogels have demonstrated NIR-triggered photothermal antibacterial activity and accelerated healing in infected skin wound models.[36] Although such studies provide useful proof-of-concept evidence that germanene can be incorporated into hydrogel matrices, they do not establish germanene as a vascular bioink component. Critical parameters required for cardiovascular bioprinting—including bioink rheology, shear-thinning behavior, extrusion fidelity, endothelial-cell compatibility, immune-cell interactions, and long-term perfusion stability—remain insufficiently investigated.[81,86,198]

Therefore, the discussion of germanene in this review is intentionally positioned as exploratory rather than confirmatory. At present, there is no direct evidence demonstrating germanene-enabled vascular bioinks, cardiac bioinks, atherosclerosis-on-a-chip platforms, or bioprinted CVD models. This distinction is important to avoid overextending conclusions from non-cardiovascular hydrogel systems to vascular biofabrication.

6.3. Evidence gaps and bioink validation requirements

Several major barriers must be addressed before germanene or other emerging Xenes can be considered practical components of cardiovascular bioinks. Material stability remains one of the most significant challenges. Germanene is susceptible to oxidation and structural degradation under ambient and aqueous conditions,[191,199,200] potentially affecting reproducibility, biological activity, and long-term functionality. Stable formulations compatible with hydrogel precursor solutions have not yet been systematically established.

Uniform dispersion within hydrogel precursor solutions is also essential for maintaining consistent mechanical and biological performance.[188,189,201] Aggregation of germanene nanosheets may result in heterogeneous material properties, nozzle clogging, uneven photothermal responses, and concentration-dependent cytotoxicity. Effective stabilization and surface-modification strategies will therefore be required before any cell-laden printing application can be realistically considered.

Because current germanene-based hydrogel systems have not been validated as vascular bioinks, cytocompatibility should not be presented as an established cardiovascular function. Instead, future studies should first evaluate basic vascular-cell compatibility using endothelial cells, VSMCs, macrophages, and cardiomyocytes, together with functional endpoints such as endothelial barrier integrity, inflammatory activation, oxidative-stress response, macrophage polarization, and long-term cellular functionality.[17,81] These assays should be interpreted as validation requirements rather than evidence of current applicability.

Perhaps the most important limitation is the complete lack of bioprinting validation. To date, no germanene-containing system has been systematically characterized as a cardiovascular bioink. Essential biofabrication parameters—including viscosity, shear-thinning behavior, viscosity recovery, filament fidelity, extrusion pressure, crosslinking compatibility, post-printing cell viability, and long-term perfusion stability—remain unknown.[81,86,202,203] Accordingly, germanene currently remains a hydrogel-compatible nanomaterial with exploratory potential rather than a validated bioink additive for cardiovascular bioprinting.[187,204]

Future research should therefore proceed in a stepwise manner: first establishing stable and dispersible germanene formulations, then confirming compatibility with cell-laden hydrogels, and finally evaluating vascular-relevant functions under oxidative stress, inflammatory stimulation, endothelial dysfunction, and dynamic perfusion conditions.[204,205] Only after these criteria are met can germanene-containing systems be reasonably assessed for atherosclerosis modeling or cardiovascular biofabrication.

6.4. Comparison with graphene and black phosphorus

Graphene, BP, and germanene occupy distinct positions in the development landscape of 2D nanomaterial-integrated bioinks. Among these materials, graphene represents the most mature platform. Extensive studies have demonstrated its ability to improve printability, mechanical strength, electrical conductivity, and cellular responses in biofabricated constructs, supporting applications in tissue engineering, regenerative medicine, and biosensing. Recent reviews have highlighted graphene-based nanomaterials as one of the most extensively investigated 2D material families for 3D bioprinting and bioink development.[29] Furthermore, conductive graphene- and GO-based bioinks have shown promise for enhancing cell adhesion, electrical signal propagation, and functional maturation in cardiac tissue engineering applications.[123,206]

Compared with graphene, BP is less mature from a translational perspective but possesses stronger disease-oriented relevance owing to its intrinsic biodegradability, ROS-responsive behavior, photothermal properties, and potential pro-angiogenic effects. Recent studies have emphasized BP as a multifunctional biomaterial capable of regulating oxidative stress, promoting tissue regeneration, and facilitating controlled therapeutic delivery.[115] BP-incorporated hydrogels have demonstrated beneficial effects in diabetic wound healing through combined antibacterial and antioxidant mechanisms,[207] while ROS-responsive BP-based hydrogel systems have shown promising therapeutic efficacy in myocardial infarction repair by enhancing angiogenesis and cardiac tissue regeneration.[55]

In contrast, germanene remains the least developed of these three categories of 2D materials for biomedical applications. Current evidence is largely limited to photothermal antibacterial hydrogel systems, particularly germanene-modified chitosan hydrogels designed for infected wound treatment.[36] Although germanene may offer unique surface reactivity and optoelectronic characteristics relative to graphene due to its buckled atomic structure and semiconductor-like behavior, it currently lacks direct evidence in vascular bioinks, CVD models, or atherosclerosis-on-a-chip platforms. Consequently, germanene should not be considered a direct competitor to graphene or BP at the present stage of development. Its more realistic role is that of a long-term frontier material that may broaden the functional diversity of smart bioinks only after physicochemical stability, aqueous dispersibility, cytocompatibility, bioprintability, and perfusion compatibility have been systematically addressed.[27] The functional positioning, evidence maturity, and translational readiness of the principal 2D nanomaterials discussed in this review are compared in Table 3.

7. Integrated atherosclerosis-on-a-chip and patient-specific bioprinted models

7.1. From biomaterials to integrated disease models

Atherosclerosis is a spatially heterogeneous and temporally progressive vascular disease involving coordinated interactions among endothelial cells, VSMCs, macrophages, lipoproteins, ECM components, and hemodynamic forces.[3] Conventional 2D cell cultures and animal models have provided important mechanistic insights, but they cannot fully reproduce the 3D architecture, human-specific cellular interactions, or dynamic microenvironment of human atherosclerotic plaques.[3]

Recent advances in 3D bioprinting and OOC technologies have enabled the development of engineered vascular disease systems that more closely recapitulate human pathophysiology.[14,79] These platforms allow spatially controlled positioning of vascular cells, immune cells, biomaterials, and disease-associated biochemical stimuli within perfusable architectures. Combined with microfluidic flow systems, they provide opportunities to reproduce endothelial mechanobiology, inflammatory

Table 3. Comparative physicochemical, biological, printability, and cardiovascular features of representative 2D nanomaterials for smart bioinks

2D nanomaterial	Key physicochemical properties	Biological functions	Printability enhancement	Cardiovascular/ atherosclerosis applications	Evidence and limitations
GO[123,128,143,208]	Hydrophilic oxygenated sheets; large surface area; strong polymer interactions	Supports adhesion and endothelial-cell compatibility; may modulate inflammatory responses	Improves viscosity, shear-thinning behavior, filament fidelity, and scaffold stability	Perfusable vascular constructs; endothelialized scaffolds; sensor-compatible matrices	Strong bioink evidence; dose, purity, and long-term persistence require control
rGO/graphene nanoplatelets[101,124,209]	Partly restored sp2 network; higher conductivity; lower dispersibility than GO	Enhances electroactive cell communication and bioelectronic interfaces	Reinforces hydrogels but aggregation can impair homogeneity and cell viability	Conductive cardiac bioinks; vascular biosensing; real-time monitoring	Mature in cardiac models; direct atherosclerosis evidence remains limited
Graphene quantum dots[210,211]	Nanoscale carbon dots; high surface functionality; optical activity	Potential antioxidant, imaging, and biosensing functions	Limited reinforcement compared with sheets; may improve dispersion in hydrogels	Bioimaging, sensing interfaces, and adjunctive bioink additives	Promising but less validated as structural bioink components
BP[32,54,55,154]	Puckered degradable nanosheets; ROS-sensitive oxidation; NIR photothermal response	ROS regulation, anti-inflammatory activity, macrophage modulation, angiogenesis support	May tune mechanics and degradation, but bioprinting rheology remains underreported	Redox-responsive vascular models; myocardial repair hydrogels; disease-adaptive matrices	High atherosclerosis relevance; stability and reproducibility remain major barriers
MXenes/ transition-metal dichalcogenides[212-214]	Conductive or semiconductive layered materials; tunable surface chemistry	Potential photothermal, antibacterial, and sensing functions	Can improve conductivity and mechanics depending on formulation	Bioelectronic scaffolds, photothermal platforms, and sensing-enabled models	Emerging; cardiovascular bioink evidence is still sparse

Abbreviations: 2D: Two-dimensional; BP: Black phosphorus; GO: Graphene oxide; MXene: Two-dimensional transition-metal carbide, nitride, or carbonitride; NIR: Near-infrared; rGO: Reduced graphene oxide; ROS: Reactive oxygen species.

activation, lipid accumulation, and vascular remodeling under physiologically relevant conditions.[79,215]

Importantly, the objective of next-generation atherosclerosis models is not simply to fabricate vessel-like structures but to reconstruct disease-relevant vascular microenvironments in a controllable and measurable manner.[65] This requires simultaneous integration of endothelial dysfunction, VSMC remodeling, macrophage infiltration, oxLDL exposure, oxidative stress, ECM remodeling, and disturbed flow within a unified experimental platform.[65]

7.2. A model architecture for next-generation atherosclerosis platforms

An ideal bioprinted atherosclerosis model should integrate structural, cellular, biochemical, mechanical, and sensing elements within a unified vascular platform. At the luminal interface, endothelial cells form a dynamic barrier that regulates vascular permeability, leukocyte recruitment, NO signaling, and overall vascular homeostasis. Because endothelial dysfunction is one of the earliest and most critical events in atherogenesis, faithful reconstruction of endothelial behavior is essential for disease modelin.[3,9]

Beneath the endothelium, a VSMC-rich medial layer provides structural support while enabling investigation of key pathological processes, including VSMC phenotypic switching, migration, proliferation, and ECM remodeling during plaque development.[39-41,77,216,217]

To recapitulate the complexity of atherosclerotic lesions, plaque-mimicking compartments may incorporate

macrophages, foam cells, ECM-like matrices, and lipid-rich microenvironments. These regions can be selectively exposed to oxLDL, pro-inflammatory cytokines, oxidative stress, or matrix-degrading enzymes to reproduce localized plaque progression and heterogeneity.[66,180,218-220]

The incorporation of smart bioinks can further enhance physiological relevance. ROS-responsive hydrogels may recreate oxidative microenvironments;[26] enzyme-responsive matrices may support dynamic ECM remodeling;[77] graphene-containing systems may facilitate integration with sensing components;[28,29,31] and BP-containing bioinks may provide redox-responsive regulation and disease-adaptive functionality.[74]

Accordingly, a next-generation atherosclerosis-on-a-chip platform should ideally integrate an endothelialized vascular lumen, a VSMC-containing medial layer, a macrophage-rich plaque niche, oxLDL and inflammatory stimulation, disturbed-flow microfluidic systems, ROS-responsive or enzyme-responsive matrices, and embedded biosensing modules for continuous monitoring.[11,76,79] Such a platform would move beyond conventional vascular tissue engineering by reconstructing the key cellular, biochemical, and biomechanical drivers of atherosclerotic progression within a controllable and physiologically relevant *in vitro* system. Based on the concepts discussed above, Figure 6 illustrates an integrated atherosclerosis-on-a-chip platform incorporating multicellular vascular architecture, pathological stimuli, responsive biomaterials, and real-time sensing modules.

To provide a clearer overview of the current modeling landscape, Table 4 compares major atherosclerosis models in terms of their key features, advantages, limitations, representative matrix or bioink compositions, and key supporting references. This comparison highlights that no single model fully recapitulates the cellular complexity, lipid accumulation, inflammatory activation, ECM remodeling, and hemodynamic regulation of human atherosclerosis.

Table 4. Comparative overview of atherosclerosis models and representative bioink or matrix compositions

Model type	Key features	Associated bioink/ matrix composition	Main advantages	Major limitations	Best-fit applications
Conventional 2D vascular cell culture[221,222]	Endothelial cells, VSMCs, macrophages, or foam cells cultured on flat substrates; commonly stimulated with oxLDL, TNF-α, IL-1β, or inflammatory cues	Tissue-culture plastic; collagen-, gelatin-, fibronectin-, or Matrigel-coated surfaces	Simple, low cost, high throughput, easy molecular analysis	Lacks 3D architecture, ECM organization, physiological stiffness, flow, and multicellular spatial interactions	Mechanistic screening of endothelial activation, macrophage lipid uptake, inflammatory signaling, and VSMC phenotypic switching
Static 3D hydrogel-based plaque models[223,224]	Vascular cells or immune cells embedded in 3D ECM-like matrices; may incorporate oxLDL, cytokines, ROS, or disease-related remodeling cues	Collagen, fibrin, GelMA, alginate, hyaluronic acid, Matrigel, or dECM-based hydrogels	Better mimics 3D cell–matrix interactions and local inflammatory niches than 2D culture	Limited control over perfusion, shear stress, spatial plaque geometry, and long-term disease progression	Modeling macrophage infiltration, foam-cell formation, ECM remodeling, and cell–matrix crosstalk
Spheroid/pseudo-plaque vascular models[225-228]	Self-assembled or hanging-drop plaque-like aggregates containing inflammatory, stromal, or vascular components	Scaffold-free spheroids; hanging-drop aggregates; Matrigel, collagen, fibrin, or ECM-mimetic matrices	Captures compact multicellular organization and plaque-like cell–cell interactions	Poor control over vascular geometry, luminal structure, perfusion, and mechanical stimulation	Studying multicellular inflammatory responses, pseudo-plaque formation, immune recruitment, and drug screening

(*Cont'd...*)

Table 4. (***Continued***)

Model type	Key features	Associated bioink/ matrix composition	Main advantages	Major limitations	Best-fit applications
Microfluidic vascular models[12,79,229-231]	Endothelialized channels exposed to laminar, disturbed, or geometry-dependent flow; may include monocyte adhesion and permeability assays	PDMS/glass chips coated with collagen, fibronectin, gelatin, or ECM proteins; hydrogel-patterned channels	Enables controlled shear stress, real-time imaging, dynamic perfusion, and flow-dependent endothelial analysis	Often simplified wall structure; limited incorporation of VSMC-rich media, plaque ECM, and advanced lesion architecture	Studying endothelial dysfunction, leukocyte adhesion, permeability, and shear-stress-regulated inflammatory activation
Atherosclerosis-on-a-chip platform[s65,76,232,233]	Integrated microfluidic systems combining endothelialized lumen, VSMCs, immune-cell recruitment, oxLDL exposure, and inflammatory stimulation	Collagen, fibrin, GelMA, hyaluronic acid, dECM, or composite hydrogel matrices integrated into microfluidic devices	Reproduces dynamic flow, inflammatory activation, lipid exposure, and multicellular crosstalk in a controllable platform	Technical complexity, limited standardization, variable material compatibility, and difficulty modeling advanced plaque rupture	Disease-mechanism studies, anti-inflammatory drug screening, plaque microenvironment modeling, and patient-specific testing
3D-bioprinted vascular constructs[234-238]	Spatially patterned endothelial cells, VSMCs, fibroblasts, macrophages, and ECM-like matrices within tubular or multilayered vascular structures	GelMA, collagen, fibrin, alginate, hyaluronic acid, dECM, and hybrid hydrogel bioinks	Enables controlled multicellular organization, vessel-like architecture, and customizable geometry	Requires optimized bioink rheology, post-printing viability, lumen perfusion, and long-term construct stability	Engineering vascular wall-like structures, testing bioink performance, and reconstructing early plaque-like microenvironments
Nanomaterial-enabled smart bioink models[239-242]	Hydrogel bioinks integrated with GO/ rGO, BP, MXenes, or other 2D nanomaterials to enhance mechanics, conductivity, sensing, ROS regulation, or responsiveness	GelMA/GO, collagen/ GO, alginate/GO, BP-containing hydrogels, conductive polymer–graphene composites, or multifunctional hybrid bioinks	Improves print fidelity, mechanical reinforcement, electrical conductivity, biosensing, and disease-responsive regulation	Potential cytotoxicity, aggregation, batch variability, incomplete biodegradation, and limited atherosclerosis-specific validation	Smart vascular bioinks, ROS-responsive disease models, biosensing-enabled constructs, and multifunctional cardiovascular platforms
Patient-specific/ iPSC-derived models[243,244]	Uses imaging-derived vascular geometry, CFD-guided shear maps, patient-derived cells, or iPSC-derived vascular organoids	Patient-specific cell-laden GelMA, collagen, fibrin, hyaluronic acid, dECM, blood vessel organoids, or composite smart bioinks	High translational relevance; can capture interpatient heterogeneity, individualized geometry, and patient-specific cellular responses	High cost, complex fabrication, limited throughput, and lack of standardized validation criteria	Precision cardiovascular modeling, individualized drug screening, and disease-risk stratification

Abbreviations: 2D: Two-dimensional; 3D: Three-dimensional; BP: Black phosphorus; CFD: Computational fluid dynamics; dECM: Decellularized extracellular matrix; ECM: Extracellular matrix; GelMA: Gelatin methacryloyl; GO: Graphene oxide; IL-1β: Interleukin 1 beta; iPSC: Induced pluripotent stem cell; MXenes: Two-dimensional transition-metal carbides, nitrides, or carbonitrides; oxLDL: Oxidized low-density lipoprotein; PDMS: Polydimethylsiloxane; rGO: Reduced graphene oxide; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor alpha; VSMC: Vascular smooth muscle cell.

7.3. Functional readouts and validation criteria

A major challenge in atherosclerosis modeling is determining whether a printed construct genuinely reproduces disease-relevant phenotypes. Therefore, standardized functional readouts are required. Endothelial integrity should be evaluated using measurements of TEER, permeability, NO production, endothelial nitric

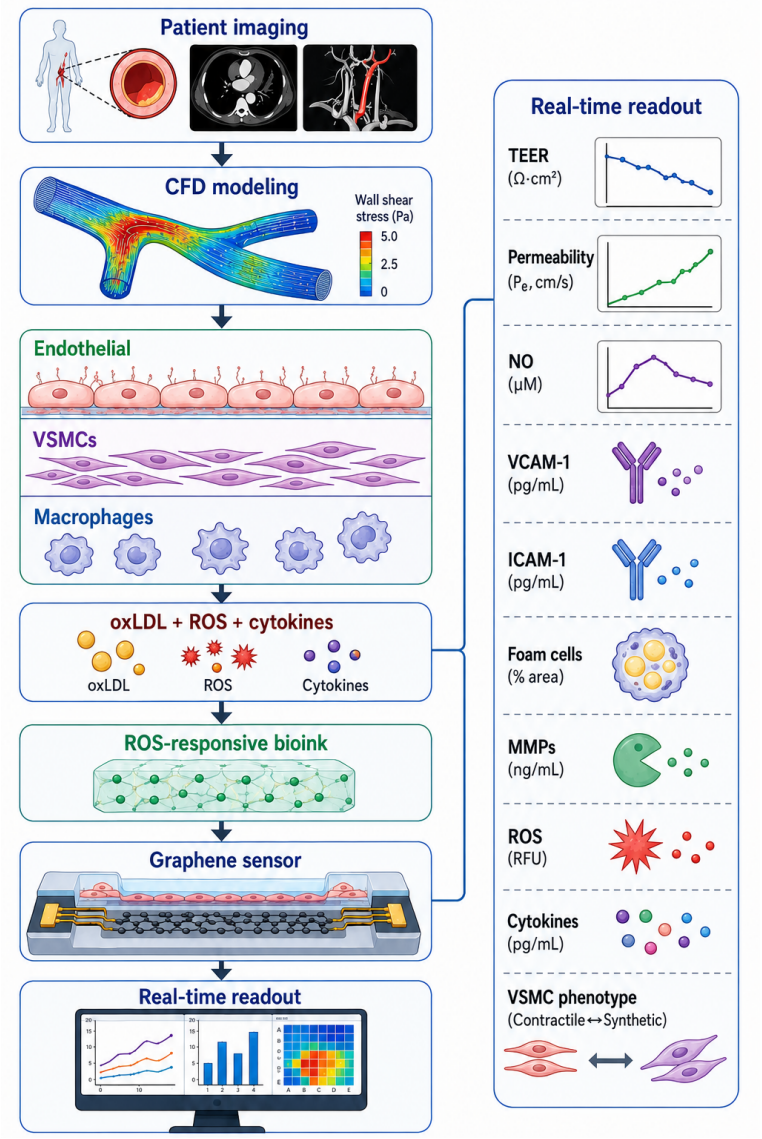

Figure 6. Integrated atherosclerosis-on-a-chip platform. Schematic illustration of a next-generation bioprinted atherosclerosis model integrating disease-relevant cellular, biochemical, mechanical, and sensing components within a perfusable vascular platform. The model consists of an endothelialized lumen, a VSMC-containing medial layer, and a macrophage-rich plaque niche exposed to pro-atherogenic stimuli such as oxLDL, ROS, inflammatory cytokines, and disturbed flow conditions. Smart hydrogel bioinks incorporating stimuli-responsive materials and functional 2D nanomaterials provide dynamic regulation of matrix properties and pathological microenvironments. Integrated biosensing modules enable continuous monitoring of endothelial barrier integrity, inflammatory activation, oxidative stress, extracellular matrix remodeling, and cellular phenotypic changes. By combining 3D bioprinting, OOC technology, microfluidic perfusion, and real-time sensing, the platform enables mechanistic investigation of atherosclerotic progression, therapeutic screening, and the development of patient-specific vascular disease models for precision cardiovascular medicine. This framework represents the conceptual convergence of disease-responsive bioinks, functional nanomaterials, OOC systems, and patient-specific vascular modeling, which together define a future direction for predictive atherosclerosis-on-a-chip platforms. Created in BioRender. Chu, R. (2026). https://BioRender.com/cgmdnyp, with assistance from ChatGPT (OpenAI, GPT-5.5 Thinking) for preliminary figure drafting, visual refinement, and layout optimization.

Abbreviations: CFD: Computational fluid dynamics; ICAM-1: Intercellular adhesion molecule 1; MMPs: Matrix metalloproteinases; NO: Nitric oxide; OOC: Organ-on-a-chip; oxLDL: Oxidized low-density lipoprotein; RFU: Relative fluorescence units; ROS: Reactive oxygen species; TEER: Transendothelial electrical resistance; VCAM-1: Vascular cell adhesion molecule 1; VSMC: Vascular smooth muscle cell.

oxide synthase (eNOS) expression, and endothelial barrier function. Inflammatory endothelial activation should be assessed through VCAM-1, ICAM-1, E-selectin, and leukocyte adhesion assays, which represent established hallmarks of endothelial dysfunction.[66,76,245,246] Macrophage behavior should be monitored through infiltration, lipid uptake, foam-cell formation, CD68 expression, M1/M2-associated markers, cytokine secretion, and ROS production.[247-252] Monocyte adhesion and transendothelial migration provide additional indicators of inflammatory progression and vascular immune activation.[253]

Plaque progression is strongly associated with matrix remodeling and oxidative stress. Relevant endpoints include MMP activity, collagen organization, ROS accumulation, antioxidant responses, and ECM degradation. VSMCs should be evaluated using markers associated with contractile and synthetic phenotypes, including α-SMA, SM-MHC, collagen production, migration, and proliferation.

Collectively, these readouts provide a standardized framework for determining whether bioprinted systems accurately reproduce key aspects of human atherosclerotic pathology.

7.4. Hemodynamic control and plaque localization

Atherosclerotic plaques develop preferentially at arterial bifurcations, curvatures, and branch points exposed to disturbed or oscillatory flow. Such hemodynamic conditions promote endothelial activation, lipid retention, oxidative stress, and leukocyte recruitment.[9,246] Therefore, physiologically relevant atherosclerosis models must incorporate flow. OOC and microfluidic platforms can generate precisely controlled shear-stress profiles that regulate endothelial behavior. Laminar flow typically promotes an atheroprotective phenotype, whereas disturbed flow induces inflammatory activation and barrier dysfunction.[245,254]

Patient-specific vascular geometries may further improve disease relevance. Medical imaging modalities such as computed tomography angiography, magnetic resonance angiography, intravascular ultrasound, and optical coherence tomography can provide individualized vascular architectures.[9,254]

When combined with computational fluid dynamics (CFD), these imaging-derived geometries can generate patient-specific shear-stress maps that identify plaque-prone regions and local hemodynamic abnormalities.[9,254] Such information can subsequently guide fabrication of bioprinted vascular constructs that reproduce clinically relevant disease localization and progression.

7.5. Real-time monitoring and closed-loop disease modeling

Most current vascular disease models rely heavily on endpoint analyses such as immunostaining, gene expression profiling, and biochemical assays. While informative, these approaches provide limited temporal information regarding disease evolution.[181,255] Integration of biosensing technologies into bioprinted vascular constructs offers opportunities for continuous and non-destructive monitoring of disease progression. Graphene-based materials are particularly attractive because of their electrical conductivity, surface sensitivity, and compatibility with electrochemical sensing systems.[28,29,121,256]

Real-time monitoring may enable dynamic assessment of endothelial barrier integrity, TEER, permeability, ROS generation, cytokine secretion, metabolic activity, monocyte recruitment, foam-cell formation, and matrix remodeling.[68] Importantly, future platforms may combine biosensing modules with responsive biomaterials. For example, graphene-based sensors could continuously monitor oxidative and inflammatory signals, while BP-integrated ROS-responsive matrices could dynamically regulate therapeutic release or material behavior in response to disease progression.[26,74,92] Such integration may ultimately enable closed-loop disease models capable of both monitoring and regulating pathological processes in real time.[65,255,257-259]

7.6. Patient-specific atherosclerosis models

Atherosclerosis exhibits substantial interpatient heterogeneity arising from differences in genetics, metabolism, vascular anatomy, immune responses, age, and environmental exposures. Consequently, personalized disease models are increasingly needed.[9]

Human induced pluripotent stem cells (hiPSCs) provide a promising source of patient-specific endothelial cells, VSMCs, and macrophage-like cells.[255,257,260] Incorporation of these cells into bioprinted vascular constructs may enable individualized modeling of endothelial dysfunction, inflammatory responses, lipid metabolism, and therapeutic sensitivity.

In parallel, patient-specific vascular geometries derived from medical imaging can reproduce anatomical features associated with disease susceptibility, including carotid bifurcations, coronary branch points, and restenosis-prone vascular segments.[261] A comprehensive personalized platform may therefore integrate hiPSC-derived vascular and immune cells, medical imaging-derived vascular geometries, CFD-generated shear-stress distributions, disease-responsive bioinks, and real-time biosensing systems.[255,257,260-262] Such systems could provide

unprecedented opportunities for investigating patient-specific disease mechanisms and therapeutic responses.

7.7. Current challenges and future directions

Despite significant progress, several challenges continue to limit translation of bioprinted atherosclerosis models. First, biological complexity remains difficult to reproduce. Advanced plaque features—including necrotic core formation, calcification, intraplaque hemorrhage, fibrous cap rupture, and long-term disease evolution—remain challenging to model *in vitro*.[263] Second, bioink standardization remains an important obstacle. Smart bioinks must simultaneously support printability, multiple vascular cell populations, long-term perfusion, and disease-specific responsiveness while maintaining reproducibility and safety.[81] Third, integration of biosensing and responsive biomaterials remains technically challenging. Although graphene-based sensing platforms and BP-containing responsive hydrogels show promise, fully integrated closed-loop disease systems remain largely experimental.[26,27,29,121] Finally, clinical validation remains limited. Standardized benchmarking criteria and clinically relevant endpoints are required before widespread adoption in drug discovery and precision medicine.[261,264]

Ultimately, the goal of cardiovascular biofabrication is not simply to fabricate vascular tissues but to construct predictive, patient-specific disease platforms capable of reproducing atherosclerotic progression, therapeutic responses, and clinical heterogeneity. The convergence of smart bioinks, microfluidics, stem cell engineering, biosensing technologies, medical imaging, and computational modeling is expected to drive the next generation of atherosclerosis-on-a-chip systems for mechanistic investigation, drug screening, and precision cardiovascular medicine.[257,260,264-266]

8. Challenges and translational perspectives

8.1. Distinguishing bioink from hydrogels: The need for bioprinting validation

A translational checklist for evaluating smart bioinks intended for atherosclerosis modeling is presented in Table 5 Stimuli-responsive hydrogels integrated with 2D nanomaterials have generated considerable interest for cardiovascular bioprinting and atherosclerosis modeling. However, a critical distinction must be made between a hydrogel and a bioink. Many reported systems are injectable hydrogels, wound dressings, or therapeutic matrices that have not been systematically validated for bioprinting applications.[125]

A material should not be considered a functional bioink solely because it exhibits favorable biological activity. Instead, successful bioinks must simultaneously satisfy biological and manufacturing requirements, including cytocompatibility, shear-thinning behavior, viscosity recovery, extrusion fidelity, crosslinking controllability, post-printing shape stability, long-term cell viability, and compatibility with perfusion culture.[125,198,267]

Table 5. Key translational barriers and validation criteria for nanomaterial-enabled smart bioinks

Challenge	Key question	Recommended evaluation	Current status
Bioink validation[15,18,81,125,128,143,176,178,264]	Can it be printed reliably?	Rheology, shear-thinning behavior, shape fidelity	Partially addressed
Material standardization[24,268-270]	Can results be reproduced?	Size, oxidation, zeta potential, purity	Poorly standardized
Disease relevance[198,267,271]	Does it mimic plaque biology?	VCAM-1, foam cells, ROS, MMPs	Limited validation
Safety[81,153,272-275]	Is the material biocompatible?	Inflammation, hemocompatibility	Incomplete
Long-term perfusion[177-179]	Can it tolerate flow?	Perfusion stability, endothelialization	Emerging
Sensor integration[121,276-280]	Can it support real-time monitoring?	TEER, ROS, cytokines	Early-stage
Manufacturing[24,281-283]	Can it be scaled up?	Batch consistency, sterilization	Major challenge
Regulatory feasibility[24,264,267,282-285]	Can it be translated?	GMP compatibility, degradation products	Largely unexplored

Abbreviations: GMP: Good manufacturing practice; MMPs: Matrix metalloproteinases; ROS: Reactive oxygen species; TEER: Transendothelial electrical resistance; VCAM-1: Vascular cell adhesion molecule.1

This distinction is particularly important for nanomaterial-containing systems. Graphene, BP, and germanene can significantly alter hydrogel rheology, network formation, optical behavior, conductivity, degradation kinetics, and cellular responses. Consequently, each nanomaterial-integrated formulation should be evaluated as a complete printing system rather than as a simple hydrogel composite.[29]

The translational gap between conceptual biomaterial platforms and validated bioprinting systems remains one of the most significant challenges facing the field. Materials that perform well as bulk hydrogels may exhibit poor printability, inadequate structural fidelity, or loss of biological function after printing. Therefore, future studies should prioritize comprehensive biofabrication validation rather than relying solely on hydrogel performance.

8.2. Nanomaterial standardization and reproducibility

A second major challenge is the lack of standardized characterization of 2D nanomaterials. The biological and physicochemical behavior of nanomaterials is highly dependent on parameters such as lateral size, thickness, oxidation state, surface charge, functionalization, aggregation state, purity, degradation behavior, and endotoxin contamination.[268,269,286]

This issue is particularly relevant for graphene-family materials, BP, and emerging Xenes. GO and rGO exhibit substantial differences in conductivity, surface chemistry, dispersion stability, and biological interactions.[27,268] BP nanosheets are highly sensitive to oxidation and environmental conditions, which may significantly influence degradation behavior and biological activity.[287,288] Germanene remains even less standardized because reproducible synthesis, stabilization, and formulation strategies are still under development.[269]

Without rigorous physicochemical characterization, results cannot be reliably compared across laboratories. Future studies should report material size distribution, layer number, zeta potential, oxidation degree, conductivity, surface chemistry, degradation kinetics, endotoxin levels, and batch-to-batch variability.[268,270] Standardization of these parameters will be essential for reproducibility, cross-study comparison, and eventual regulatory acceptance.

8.3. Disease relevance and model validation

A major concern in the current literature is that many vascular constructs are evaluated primarily on the basis of cell viability, proliferation, or morphology. While these measurements are important, they do not necessarily demonstrate successful disease modeling. A bioprinted vascular construct should not automatically be considered an atherosclerosis model. The defining feature of a disease model is its ability to reproduce disease-relevant biological processes rather than merely support vascular cell survival.[3,9] Current systems often reproduce selected early pathological events such as endothelial inflammation, monocyte adhesion, or oxLDL-induced foam-cell formation. However, advanced features of human atherosclerosis—including necrotic core formation, fibrous cap thinning, calcification, cholesterol crystal deposition, intraplaque hemorrhage, and plaque instability—remain difficult to recapitulate *in vitro*.[3,248]

Therefore, disease validation should extend beyond conventional cell-based assays. Future models should be evaluated using standardized pathological endpoints. For endothelial dysfunction, these include endothelial permeability, eNOS expression, nitric oxide production, VCAM-1, ICAM-1, E-selectin, and monocyte adhesion.[9] For VSMC remodeling, α-SMA, SM-MHC, calponin expression, migration, matrix production, and osteogenic differentiation should be assessed.[3] For macrophage-driven pathology, relevant endpoints include CD68 expression, macrophage polarization, oxLDL uptake, foam-cell formation, cytokine secretion, ROS production, and matrix-degrading enzyme activity.[45,248]

Advanced models should additionally incorporate spatial measurements of lipid distribution, ROS gradients, ECM organization, and multicellular interactions within layered vascular constructs.[257,266] Such validation frameworks are essential for determining whether a model faithfully reproduces atherosclerotic pathology rather than simply representing an inflamed hydrogel.

8.4. Safety, degradation, and immune compatibility

The incorporation of nanomaterials introduces unique safety considerations that extend beyond conventional hydrogel systems. 2D nanomaterials can interact directly with cell membranes, proteins, immune receptors, and intracellular organelles, potentially influencing oxidative stress, inflammatory signaling, mitochondrial function, and cellular homeostasis.[272,273]

This issue is particularly relevant for atherosclerosis modeling because inflammation and oxidative stress are central disease mechanisms. If a nanomaterial independently induces inflammatory activation, it may confound interpretation of experimental results and obscure disease-specific responses.[272]

Graphene-based materials have raised concerns regarding persistence, accumulation, and chronic inflammatory effects.[269,286] BP offers improved biodegradability, but uncontrolled oxidation may alter

local phosphate concentrations, redox balance, or pH.[272,273] Germanene remains largely unexplored in cardiovascular systems, and its long-term biodegradation, biodistribution, and immunological consequences remain unclear.

Consequently, future studies should evaluate nanomaterial safety under both baseline and disease-relevant conditions. Cytotoxicity alone is insufficient. Comprehensive assessment should include oxidative stress responses, inflammatory cytokine production, macrophage activation, endothelial barrier integrity, hemocompatibility, thrombogenicity, and long-term degradation behavior.[275]

8.5. Long-term perfusion and immune-cell compatibility

Physiologically relevant CVD models require long-term perfusion. Static culture systems cannot adequately reproduce shear stress, convective transport, endothelial mechanotransduction, immune-cell recruitment, or hemodynamic regulation.[79,289,290] However, perfusion introduces substantial engineering challenges. Printed vascular channels must remain patent, resist collapse, maintain endothelialization, and tolerate continuous flow while preserving matrix remodeling and cellular migration.[81,291,292]

For atherosclerosis models, additional complexity arises from the need to support circulating immune cells, macrophage recruitment, inflammatory signaling, lipid transport, and chronic oxidative stress over extended culture periods. Nanomaterial-containing bioinks must also maintain homogeneous distribution during perfusion while avoiding aggregation, leaching, or loss of functionality.[142,260]

Importantly, short-term static culture is insufficient for validating atherosclerosis-relevant bioinks. Long-term perfusion studies incorporating immune-cell interactions and hemodynamic stimulation will be essential for assessing physiological relevance and predictive value.[79,142,289]

8.6. Real-time monitoring and closed-loop disease platforms

Most current disease models rely on endpoint analyses, providing limited information regarding the temporal evolution of disease processes. Because atherosclerosis develops gradually through dynamic interactions among endothelial dysfunction, inflammation, oxidative stress, lipid accumulation, and matrix remodeling, longitudinal monitoring is highly desirable.[215,293-295] Recent advances in graphene-based sensors, electrochemical interfaces, optical reporters, and microfluidic biosensing technologies provide opportunities for continuous measurement of barrier integrity, cytokine secretion, ROS production, metabolic activity, and matrix degradation.[276-280]

Looking forward, the integration of biosensing technologies with responsive biomaterials may enable closed-loop disease platforms. For example, a graphene-based sensor could detect inflammatory activation or oxidative stress, while a BP-containing ROS-responsive hydrogel dynamically regulates therapeutic release in response to local disease progression.[296-298] Such systems would transform bioprinted disease models from passive observation platforms into adaptive experimental systems capable of sensing, interpreting, and responding to pathological signals in real time.[277,299]

8.7. Regulatory and manufacturing feasibility

Clinical and industrial translation requires more than biological performance. Manufacturing reproducibility, scalability, sterilization, storage stability, quality control, and regulatory classification represent equally important challenges.[267,281] Nanomaterial-integrated bioinks are particularly complex because variations in synthesis, processing, storage, and degradation may significantly alter material properties and biological responses.[282] Regulatory agencies will likely require comprehensive characterization of nanomaterial composition, degradation products, manufacturing workflows, and biological safety profiles before clinical use can be considered.

Sterilization presents another important challenge. Heat, radiation, filtration, or chemical sterilization may alter hydrogel chemistry, nanomaterial structure, conductivity, photothermal properties, or degradation behavior.[283] Consequently, sterilization protocols must be validated individually for each formulation. Although *in vitro* disease models face fewer regulatory barriers than implantable products, reproducibility remains essential for drug screening, interlaboratory comparison, industrial adoption, and future regulatory acceptance.[267,284]

8.8. Perspective: From material innovation to predictive disease platforms

The major developmental stages and validation requirements for translating nanomaterial-enabled smart bioinks into clinically relevant disease models are summarized in Figure 7. Despite substantial progress in nanomaterial-enabled bioinks, future advances should focus less on material novelty and more on disease-oriented functionality and translational relevance. Historically, bioink development has often been driven by improvements in printability, mechanical properties, conductivity, or photothermal behavior. While these characteristics remain important, the ultimate objective of

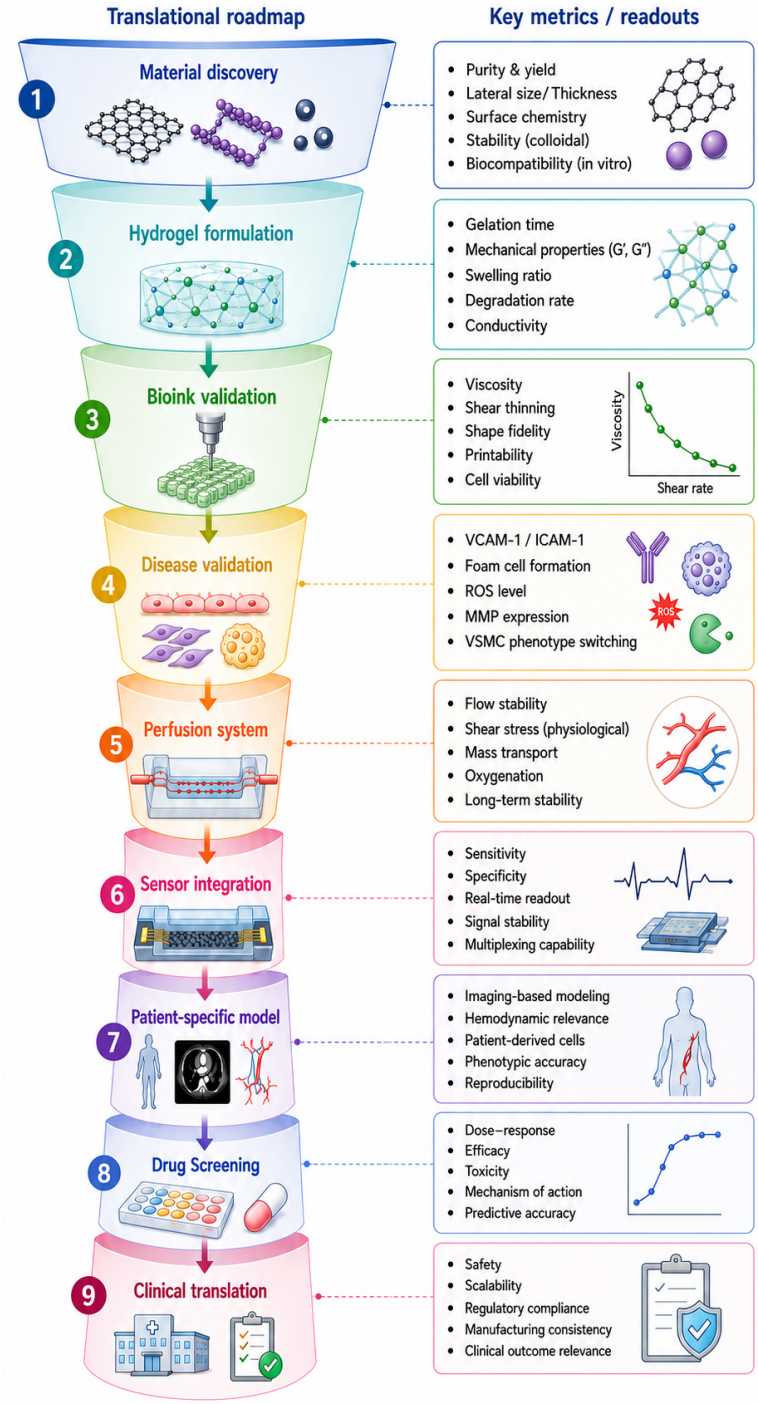

Figure 7. Translational roadmap for nanomaterial-enabled smart bioinks. Conceptual framework illustrating the progression from material development to clinically relevant cardiovascular disease modeling. The translational pathway includes nanomaterial discovery, hydrogel formulation, bioink validation, disease-specific model construction, long-term perfusion culture, biosensing integration, and patient-specific platform development. At each stage, critical validation criteria—including physicochemical characterization, rheological performance, printing fidelity, cellular functionality, disease relevance, immune compatibility, and long-term stability—must be systematically addressed. The roadmap highlights the transition from material-centered innovation toward disease-oriented and validation-driven biofabrication strategies, ultimately enabling predictive atherosclerosis-on-a-chip systems for drug screening, mechanistic investigation, and precision cardiovascular medicine. Created in BioRender. Chu, R. (2026). https://BioRender.com/h9k8aej, with assistance from ChatGPT (OpenAI, GPT-5.5 Thinking) for preliminary figure drafting, visual refinement, and layout optimization.

Abbreviations: ICAM-1: Intercellular adhesion molecule 1; MMP: Matrix metalloproteinase; ROS: Reactive oxygen species; VCAM-1: Vascular cell adhesion molecule 1; VSMC: Vascular smooth muscle cell.

cardiovascular biofabrication is to improve the accuracy and predictive value of disease models.[265,268]

Future bioinks should therefore be designed around specific pathological processes, including endothelial dysfunction, oxidative stress, inflammatory activation, lipid accumulation, vascular remodeling, and immune-cell interactions. Disease-responsive matrices capable of actively sensing and responding to pathological cues may provide more physiologically relevant platforms than passive structural materials alone.[267,281]

At the same time, increasing biological complexity will be required. Future atherosclerosis models should integrate endothelial cells, VSMCs, macrophages, ECM remodeling, lipoprotein transport, ROS gradients, hemodynamic stimulation, biosensing modules, and patient-specific vascular geometries within unified experimental systems.[300,301]

The convergence of smart bioinks, OOC technologies, stem cell engineering, biosensing systems, medical imaging, and computational modeling is expected to drive the next generation of CVD platforms. Graphene-based materials may contribute conductivity and biosensing capability, BP may provide disease-responsive redox regulation, and emerging Xenes may offer additional programmable functionalities.[302]

Nevertheless, enthusiasm surrounding advanced nanomaterials should be balanced by rigorous validation. The true value of nanomaterial-enabled bioinks will ultimately depend on whether they improve disease-modeling accuracy, predictive power, and translational utility beyond what can be achieved using conventional hydrogel systems. If these challenges can be successfully addressed, smart bioinks integrated with functional nanomaterials may become powerful tools for investigating atherosclerosis pathogenesis, accelerating therapeutic discovery, and enabling patient-specific CVD modeling.

9. Conclusion

Smart hydrogel bioinks integrated with 2D nanomaterials represent a promising strategy for constructing dynamic and physiologically relevant vascular disease models. Unlike conventional hydrogels that primarily provide structural support, smart bioinks can actively regulate cellular behavior, matrix remodeling, oxidative stress, and disease-associated signaling pathways. By combining responsive hydrogel chemistry with advanced biofabrication technologies, these materials offer new opportunities to reconstruct key features of atherosclerosis, including endothelial dysfunction, inflammation, ECM remodeling, and disturbed-flow-mediated vascular pathology.

Among currently available nanomaterials, graphene-family materials remain the most mature additives for cardiovascular bioinks, providing mechanical reinforcement, electrical conductivity, and biosensing functionality. In contrast, BP exhibits a more disease-matched profile owing to its biodegradability, ROS responsiveness, and redox-regulatory behavior, making it particularly attractive for atherosclerosis-oriented bioink design. Emerging Xenes such as germanene remain at an exploratory stage, with limited evidence supporting cardiovascular bioprinting applications. Consequently, graphene should be viewed primarily as a structural, conductive, and sensing component, whereas BP represents a promising disease-responsive module that still requires rigorous bioprinting and vascular-model validation.

Looking forward, future progress will depend less on the development of increasingly complex materials and more on the establishment of biologically relevant and rigorously validated disease platforms. Key priorities include standardized nanomaterial characterization, validation of bioprinting performance, integration of multicellular and perfusable vascular systems, incorporation of real-time sensing technologies, and benchmarking against human plaque biology. The convergence of smart bioinks, OOC systems, patient-derived vascular cells, biosensing technologies, and computational modeling may ultimately enable predictive and patient-specific platforms for mechanistic investigation, therapeutic screening, and precision cardiovascular medicine.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

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