

Non-genetic biointerfaces for programmable photoelectroceuticals

Guangqing Yang^{1,§}, Yuze Zheng^{1,§}, Pengju Li², and Bozhi Tian^{1,2,3}✉

¹ Department of Chemistry, The University of Chicago, Chicago, IL 60637, USA

² The James Franck Institute, The University of Chicago, Chicago, IL 60637, USA

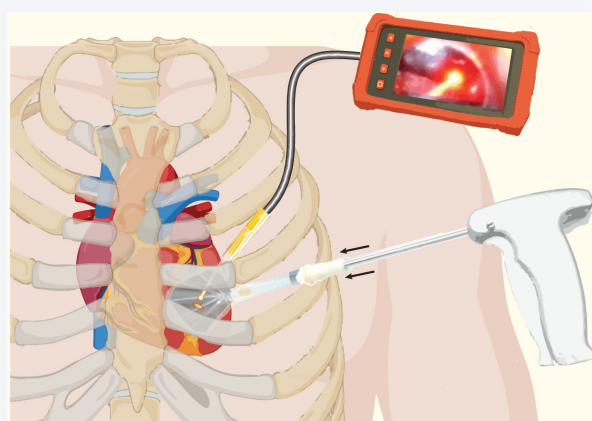
³ The Institute for Biophysical Dynamics, The University of Chicago, Chicago, IL 60637, USA

[§] Guangqing Yang and Yuze Zheng contributed equally to this work.



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ABSTRACT: Light-responsive biointerfaces have emerged as a powerful strategy for modulating cellular and tissue electrophysiology without genetic modification. Over the past decade, advances in nanomaterials, optoelectronic device architectures, and biointerface engineering have enabled the development of non-genetic photostimulation systems capable of converting optical energy into electrical, electrochemical, or ionic stimuli for controlling excitable biological systems. Recent studies have demonstrated diverse material platforms—including semiconductor nanowires, quantum dots, organic optoelectronics, and biomolecular assemblies—that enable efficient phototransduction at the nano-bio interface. At the device level, innovations in soft optoelectronic interfaces, photovoltaic implants, and flexible bioelectronic scaffolds have expanded photostimulation from single-cell modulation to organ-scale control. Concurrently, emerging strategies for spatial and spatiotemporal programming of optical stimulation are enabling increasingly precise and multiplexed control of biological circuits. These developments are now accelerating the translation of photostimulation technologies toward clinical applications, including retinal prostheses, cardiac pacing, and minimally invasive bioelectronic therapies. In this Perspective, we discuss recent progress in materials and device aspects of non-genetic photostimulation, advances in spatially programmable optical biointerfaces, and emerging translational pathways toward photoelectroceuticals. We further highlight future opportunities in engineered tissues, biomolecular optoelectronics, and programmable biointerfaces that may enable next-generation therapeutic systems integrating nanotechnology, bioelectronics, and regenerative medicine.



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KEYWORDS: photostimulation, photoelectroceuticals, optoelectronic biointerfaces, nanomaterials, bioelectronics, neuromodulation

1 Introduction

The ability to modulate electrophysiology with external physical stimuli lies at the core of modern bioelectronic medicine [1–3]. Conventional electrical stimulation platforms, from cardiac pacemakers to deep brain stimulators, have delivered major therapeutic benefits, but they remain constrained by invasive wiring, electrode-tissue mechanical mismatch, and limited spatial selectivity [4–6]. Light-driven biointerfaces have therefore emerged as an attractive alternative because they can offer wireless, remotely

addressable, and potentially multiplexed control over excitable tissues [7, 8]. Within this broader landscape, non-genetic photostimulation is particularly compelling because it preserves the advantages of optical control while avoiding the genetic manipulation required for optogenetics [9–11]. Although optogenetic therapy has achieved partial restoration of visual function in a clinical setting [12], wider adoption of gene-based strategies remains limited by vector delivery, regulatory complexity, and tissue-level deployment challenges. These barriers are especially pronounced in cardiac applications, where the requirements for viral vector delivery to large tissue volumes remain major obstacles [13].

Non-genetic photostimulation instead relies on photoresponsive materials and devices that convert incident light into electrical, electrochemical, or ionic signals capable of modulating biological

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✉ Address correspondence to btian@uchicago.edu

activity [14]. Early foundational studies demonstrated that semiconductor nanostructures—including silicon nanowires—could transduce optical energy into bioelectrical stimuli at the nano-bio interface, establishing a mechanistic basis for optically driven cell and tissue modulation [11, 14, 15]. These studies, together with broader conceptual frameworks for inorganic semiconductor biointerfaces, defined the foundation for later generations of non-genetic photostimulation systems.

Over the past decade, non-genetic photostimulation has evolved from proof-of-concept demonstrations into an increasingly mature field through convergent advances in materials science, device engineering, and biointerface design. Diverse nanomaterial platforms, including semiconductor nanowires, quantum dots, organic semiconductors, and hybrid nanocomposites, have been developed to optimize light absorption, charge generation, and interfacial electrochemical coupling [16–19]. In parallel, soft and flexible optoelectronic devices have improved mechanical compatibility with biological tissues, extending photostimulation from single-cell modulation to tissue- and organ-scale modulation [20, 21]. As a result, the central question in the field is no longer only whether light can stimulate excitable systems, but how photostimulation platforms can be made efficient, tissue-compatible, and physiologically relevant.

Beyond improving phototransduction efficiency, an equally important advance has been the ability to program where and when stimulation occurs [20, 22]. Advances in optical addressing and device architecture are enabling photostimulation platforms that deliver increasingly localized, dynamic, and multiplexed bioelectronic signals [20, 23]. A notable example is monolithic silicon photostimulation, which provides high spatiotemporal control of cardiac electrophysiology across multiple biological scales [20]. This shift from simple light-triggered activation to programmable bioelectronic control is especially important for translation, because future photoelectrochemical therapies will likely depend not only on stimulus generation, but also on the ability to reproduce physiologically meaningful stimulation patterns [20, 24].

In this Perspective, we argue that non-genetic photostimulation is entering a new stage defined by the convergence of materials innovation, device-level biointegration, and optical programmability. We therefore focus on three interconnected themes: materials and device strategies for optical bioelectronic transduction, emerging approaches for spatial and spatiotemporal programming, and ongoing efforts to translate these systems toward clinically relevant photoelectrochemicals. We conclude by discussing future directions in programmable biointerfaces, engineered tissues, and biomolecular optoelectronic systems, with particular attention to the challenges that still limit chronic stability, optical delivery, and therapeutic integration.

2 Materials and device aspects for non-genetic photostimulation

Non-genetic photostimulation is fundamentally enabled by materials that convert incident photons into bioelectrically relevant signals at the interface between synthetic structures and living tissues. The effectiveness of these systems therefore depends not only on intrinsic materials properties—including light absorption cross-section, carrier lifetime, and electrochemical stability—but also on device architecture and interfacial charge transport, which together govern stimulation efficiency, spatial selectivity, and

biocompatibility [11, 25]. We therefore organize this section around two complementary themes: the materials platforms that have been developed for optical bioelectronic transduction, and the device architectures that translate materials function into tissue-scale photostimulation. Importantly, advances in materials alone are insufficient for biological applications; effective photostimulation also depends on device architectures that efficiently deliver and localize these photo-generated signals within living tissues.

2.1 Nanomaterials for optical bioelectronic transduction

Nanomaterials are central to non-genetic photostimulation because their optical and electronic properties can be engineered to improve light absorption, carrier separation, and electrochemical coupling to biological media (Fig. 1) [11, 25, 26]. Among the earliest and most influential examples were semiconductor nanostructures, particularly silicon nanowires, which generate localized photocurrents under illumination and thereby enable optical modulation of neuronal and cardiac cells through photoelectrochemical interactions with the surrounding electrolyte [14, 15]. Their high surface-area-to-volume ratio promotes efficient carrier separation and interfacial charge transfer, making nanowires effective transducers at the nano-bio interface [27].

Beyond individual nanowires, nanowire networks have emerged as architected optoelectronic systems suitable for prosthetic applications [28]. A notable recent example is a retinal nanoprostheses based on tellurium nanowire networks (Figs. 1(a) and 1(b)) that supports broadband photovoltaic conversion from the visible to the near-infrared region [29, 30]. Owing to their narrow bandgap and defect-engineered lattice asymmetry, tellurium nanowires can generate strong photocurrents under zero external bias and stimulate retinal circuits without an auxiliary power source. In animal models of blindness, these networks restored light-evoked responses in the optic nerve and visual cortex and improved visual behavior in both mice and nonhuman primates, underscoring the translational potential of nanowire-based retinal prostheses.

Porous semiconductor architectures [20, 31, 32] extend this concept by combining strong light harvesting with efficient electrolyte coupling. Porosity-engineered silicon membranes can form heterojunction structures (Figs. 1(c) and 1(d)) that enhance photocarrier generation and interfacial charge injection through the combination of large internal surface area and built-in junction behavior [20, 32]. These nanoporous silicon systems have enabled efficient capacitive photostimulation of neural and cardiac tissues, including wireless optical pacing from cultured cardiomyocytes to large-animal models [20, 32]. The porous geometry also supports thin, flexible device formats that are advantageous for biointegration. Related work on bioresorbable thin-film silicon diodes further shows that transient optoelectronic stimulation and inhibition of neural activity can be achieved with resorbable semiconductor platforms [33].

Colloidal quantum dots provide a complementary route to photostimulation because their absorption profile can be tuned across the visible and near-infrared spectrum. Quantum-dot biointerfaces have been used to drive cardiac pacing through photoelectrochemical mechanisms in which optical excitation generates transient electric fields at the electrode-electrolyte interface [18]. Integration with soft hydrogel matrices can further improve ionic transport and mechanical compatibility, illustrating how nanoscale light absorbers and ion-conducting materials may

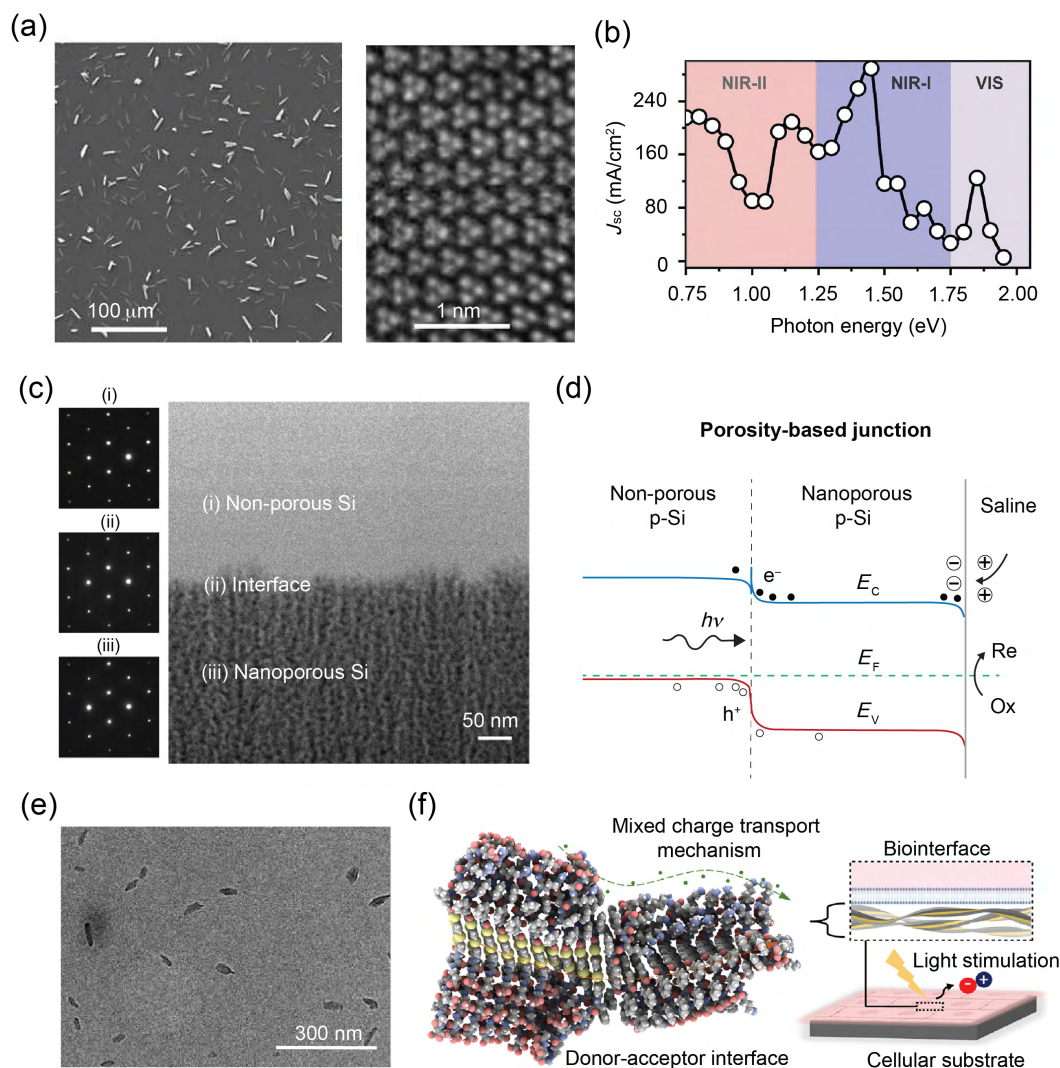


Figure 1 Nanomaterial innovations for non-genetic photostimulation. Tellurium-based optoelectronic materials: (a) Scanning electron microscope (SEM) (left) and high-angle annular dark-field scanning transmission electron microscope (HAADF-STEM) (right) images of Te nanowire networks (TeNWNs); (b) photocurrent response of Te under zero bias across wavelengths spanning the visible to the NIR-II range. Reproduced with permission from Ref. [29], © Wang, S. et al. some rights reserved; exclusive licensee American Association for the Advancement of Science 2025. The simulated model for photocurrent calculations consists of Au electrodes and a 12-nm-long Te channel with a Sn substitution. J_{sc} denotes the short-circuit current density. Porosity-based heterojunction materials: (c) STEM image showing the interface between non-porous and nanoporous silicon regions; (d) The band structure of the porosity-based heterojunction. Panels (c) and (d) are reproduced with permission from Ref. [32], © Prominski, A. et al. under exclusive licence to Springer Nature Limited 2022. Peptide-based optoelectronic materials: (e) Transmission electron microscopy (TEM) images of the coassembled DGREFEF-4T/KFKF-PDI system; (f) optimized geometry of the coassembly between DGREFEF-4T (ten molecules, left) and KFKF-PDI (ten molecules, right), illustrating mixed charge transport under light stimulation, along with a schematic of the cellular photostimulation platform enabled by photocurrent-generating peptide assemblies. Reproduced with permission from Ref. [48], © Yao, Z.-F. et al. Published by PNAS 2025.

be co-designed to optimize interfacial stimulation performance [34]. More broadly, the non-genetic wireless biomodulation repertoire also includes related wireless modalities such as photothermal modulation with cell-targeted gold nanoparticles [19, 35] and magnetothermal actuation using magnetic nanoparticle heating under alternating fields [36, 37].

Rather than relying on a single photoactive material, hybrid inorganic nanoassemblies combine complementary nanomaterials to simultaneously optimize light harvesting, charge separation, and interfacial charge injection. For example, a photovoltaic nanoassembly composed of ZnO nanowires sensitized with AgBiS₂ nanocrystals can generate capacitive photocurrents sufficient to stimulate retinal neurons under near-infrared illumination [38]. By interdigitating nanocrystals within nanowire arrays, this design

increases light absorption and charge injection while preserving submicrometer device thickness. Such heterostructured assemblies illustrate how complementary materials can be integrated to improve optical energy conversion, spectral response, and stimulation efficiency [39].

In contrast to inorganic nanomaterials, organic semiconductors emphasize mechanical softness and tissue compatibility while maintaining efficient optoelectronic transduction. A fully organic retinal prosthesis based on a conjugated polymer semiconductor was among the earliest demonstrations that organic materials could restore light sensitivity in a blind animal model [40]. Organic photovoltaic and photocapacitive interfaces typically generate capacitive currents with limited Faradaic contribution, which can support improved long-term stability and biocompatibility during

neural stimulation [41, 42]. These systems commonly employ donor-acceptor heterojunctions to facilitate exciton dissociation and charge transport under relatively low illumination intensities [43–45]. Additional organic architectures, including transparent transistor interfaces for simultaneous stimulation and recording [46] and pigment-based photocapacitors for direct neurostimulation [47], further illustrate the breadth of this materials class.

An emerging frontier in the field is the use of biomolecular optoelectronic materials. Recent work has shown that pi-conjugated peptide assemblies (Figs. 1(e) and 1(f)) can generate photocurrents through donor-acceptor interactions embedded within self-assembled nanostructures [48]. Because these systems derive function from sequence-programmed molecular organization, they suggest a route toward light-responsive biointerfaces built from inherently biocompatible building blocks. Biomolecular platforms are still at an early stage, but they are conceptually important because they point toward photostimulation materials that merge electronic function with biological programmability.

Taken together, these studies show that the materials landscape for non-genetic photostimulation is expanding from individual nanostructures to architected, hybrid, organic, and biomolecular systems. Each class offers a different balance among optical absorption, charge transport, softness, stability, and translational compatibility. Continued progress will therefore depend not only on discovering new photoactive materials, but also on matching each materials platform to the biological scale, stimulation modality, and clinical context for which it is best suited [7, 25, 49, 50].

2.2 Device architectures for tissue-scale photostimulation

Whereas nanomaterials define the fundamental mechanisms of phototransduction, device architecture determines how optical stimulation is delivered, localized, and maintained in biological systems. Early studies often relied on dispersed nanoparticles or nanowires in direct contact with cells, which were valuable for

demonstrating proof-of-concept optical modulation but offered limited control over stimulation geometry, reproducibility, and long-term stability.

To overcome these limitations, researchers have developed a broad range of optoelectronic biointerfaces that incorporate photoactive materials into structured devices. Photovoltaic retinal implants represent one of the most mature examples of this transition from materials demonstration to functional therapeutic architecture. By converting projected light patterns into electrical stimulation of retinal neurons, these systems have enabled partial restoration of vision in patients with degenerative retinal disease [29, 51, 52]. Their success establishes an important translational principle: optical energy can be used not only to trigger local phototransduction, but also to support implantable, wirelessly addressed bioelectronic therapy.

Recent progress has further improved device architectures through the use of soft and mechanically compliant materials [53]. Flexible optoelectronic interfaces based on ultrathin semiconductor membranes or organic films can conform to complex tissue geometries while maintaining stable electrical coupling [54–56]. This property is particularly important in mechanically dynamic organs such as the heart, where rigid devices are susceptible to motion-induced mismatch and loss of performance. Consistent with this need, stretchable optoelectronic stimulators built from rubbery semiconductor films and transparent nanomesh electrodes (Figs. 2(a)–2(d)) have been used to modulate cardiac tissue without imposing rigid mechanical constraints [22, 42, 57, 58].

A further device-level strategy is to embed optoelectronic elements directly within biological scaffolds or engineered tissues. Bioprinted scaffolds that contain microscale solar cells illustrate this concept by distributing photovoltaic function throughout a hydrogel matrix rather than confining stimulation to an external device surface [42]. When populated with cardiomyocytes, these constructs can modulate beating behavior under pulsed

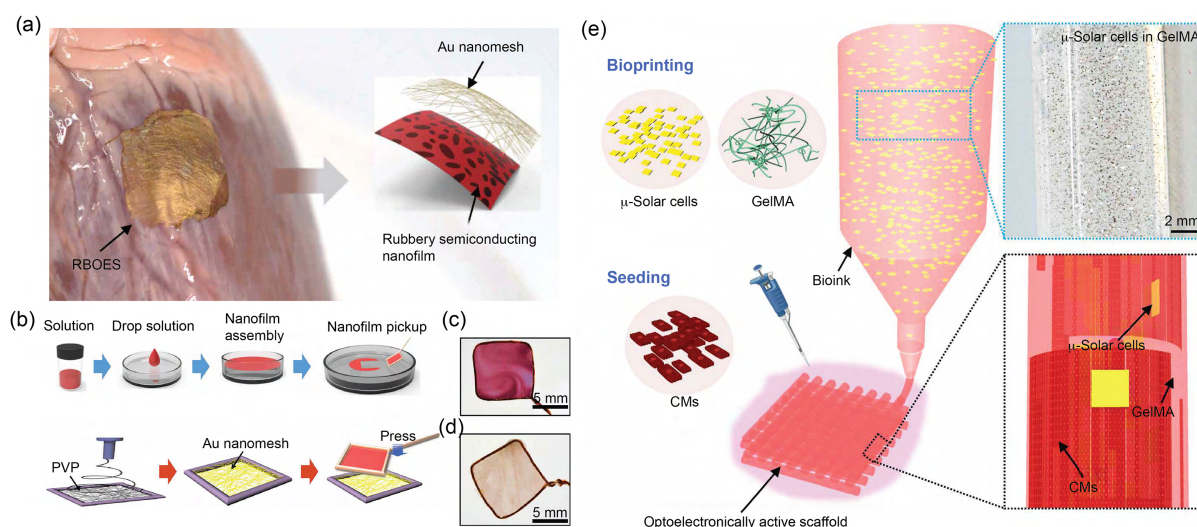


Figure 2 Scalable fabrication of optoelectronically active nanomaterial composites for photostimulation. (a)–(d) Ultrathin, stretchy, and self-adhesive rubbery bio-optoelectronic stimulator (RBOES): (a) Optical image of the RBOES applied to the surface of a porcine heart, showing how the RBOES conforms to the heart's texture. The inset on the right highlights the structure of the RBOES, consisting of a rubbery semiconducting nanofilm and a transparent, stretchable Au nanomesh conductor; (b) Schematic of the fabrication process for the rubbery semiconducting nanofilm and the fabrication flow of the RBOES by laminating the rubbery semiconducting nanofilm onto the Au nanomesh to form a bilayer stack. (c) The as-fabricated nanofilm mounted on a metallic frame. (d) RBOES assembled on a metallic frame. Reproduced with permission from Ref. [22], © Rao, Z. et al., some rights reserved; exclusive licensee American Association for the Advancement of Science 2024. (e) Optoelectronically active bioink composition and printing. Schematic of bioprinting combining μ -solar cells and gelatin methacryloyl (GelMA), followed by seeding with cardiomyocytes (CMs). Reproduced with permission from Ref. [42], © Ershad, F. et al. some rights reserved; exclusive licensee American Association for the Advancement of Science 2025.

illumination without external electrodes or wired leads (Fig. 2(e)). Flexible electro-optical arrays extend this logic by enabling simultaneous multisite mapping and optical modulation within the same platform [59]. Together, such approaches suggest a shift from conventional device-tissue contact toward hybrid living systems in which optoelectronic functionality is integrated into the tissue construct itself.

Overall, progress in this area highlights the need to co-design materials and device architectures rather than treating them as separate layers of innovation. Nanomaterials determine light absorption and charge generation, whereas device engineering governs how those signals are delivered across tissue-scale geometries with appropriate mechanical compliance, stability, and spatial organization [21]. This convergence sets the foundation for the next major challenge in the field: achieving spatial and temporal control of optical bioelectronic stimulation that can match, and in some contexts surpass, the functional precision of conventional high-density electrode technologies [60].

3 Spatiotemporal programming

A defining advantage of photostimulation over conventional electrical stimulation is the ability to control biological activity with high spatial and temporal precision [24, 61]. Because light can be patterned, focused, and dynamically modulated, optoelectronic biointerfaces offer unusual opportunities to program electrophysiological responses across multiple biological scales [61, 62]. As the field matures, the key challenge is no longer simply to generate photocurrent, but to confine, shape, and temporally program stimulation delivery in ways that are biologically meaningful (Fig. 3) [20]. Recent work has therefore focused on the materials and device-level determinants of spatial resolution and temporal programmability in optical bioelectronic systems [20, 24].

3.1 Spatial precision in photostimulation interfaces

The spatial resolution of photostimulation is determined by more than the optical spot size alone. In practice, the effective stimulation

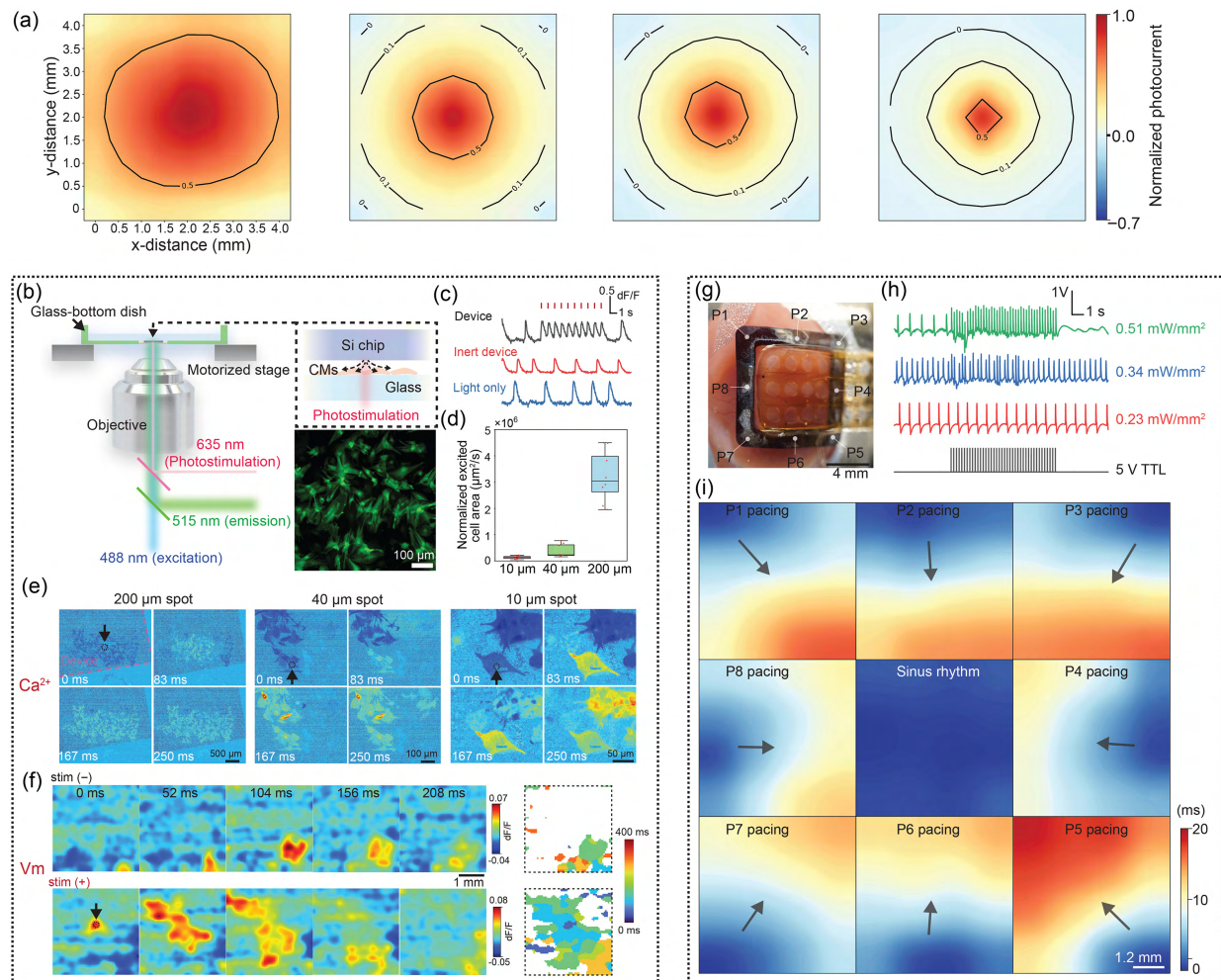


Figure 3 High spatiotemporal control of cardiac systems. (a) Spatial profiles of the device's photoelectrochemical responses. Resolution is determined by mapping the normalized photocurrent relative to the illumination center. (b) Experimental setup for photostimulation of *in vitro*-cultured CMs with fluorescent imaging. The inset shows a representative fluorescent image of CMs stained with Cal-520 AM from $N = 6$ different culture groups. (c) dF/F plot illustrating optical pacing of neonatal rat CMs at 1 Hz (4 mW, 1-ms pulse, 80-μm spot). The inert device used is pristine p-type silicon. (d) Plot of the excited cell area after photostimulation at various spot sizes within one frame (83 ms). The boxes represent the interquartile range (IQR) divided by the median, and the whiskers extend 1.5 times the IQR. (e) Spatiotemporal dF/F fluorescent images showing calcium influx and propagation following stimulation with different spot sizes. (f) Imaging of membrane voltage (V_m) before and after light stimulation. (g) *Ex vivo* rat heart setup for multisite stimulation and recording. (h) Pacing of the *ex vivo* rat heart at varying optical intensities, illustrating full capture, partial capture, and non-capture. (i) Isochrone map showing electrical signal activation delay following photostimulation of eight different locations on an open-window-structured monolithic Si device. Reproduced with permission from Ref. [20], © Li, P. et al., under exclusive licence to Springer Nature Limited 2024.

footprint reflects a combination of optical confinement, carrier diffusion within the photoactive material, electrochemical charge spreading at the interface, and ionic transport in the surrounding electrolyte [20, 24, 26]. Clarifying how these processes interact is essential for designing biointerfaces that can deliver genuinely localized stimulation rather than diffuse activation.

Recent studies have shown that materials properties strongly influence spatial precision in optoelectronic devices. For example, work on organic photostimulation interfaces has demonstrated that carrier diffusion length within the photoactive layer is a key determinant of stimulation resolution, revealing a trade-off between photocurrent magnitude and lateral confinement [26, 63]. Longer carrier lifetimes can increase photocurrent output, but they may also broaden the stimulation footprint through lateral transport. Such findings emphasize that spatial precision is not simply an optical problem; it is a coupled transport problem that must be addressed through materials design as well as illumination strategy.

Nanostructured materials offer additional routes to spatial localization because their geometry can confine light absorption and charge generation to very small dimensions. In nanowire-based systems, for instance, individual structures can serve as distributed nanoscale photodiodes that enable highly localized modulation of neuronal activity [14, 23]. Semiconductor nanowire arrays have therefore been used to stimulate individual neurons within complex neural tissues [23]. Similarly, nanowire-nanocrystal photovoltaic assemblies can generate spatially confined photocurrents that activate retinal ganglion cells under near-infrared illumination [38]. They also provide a useful contrast with high-density electrical interfaces such as silicon neural probes [64, 65] and conformable electrocorticography arrays [66], which remain important benchmarks for functional resolution.

Device architecture provides another major route to spatial precision. Micropatterned photoelectrode arrays and structured photovoltaic interfaces can translate projected optical patterns into localized stimulation across defined regions of tissue. Retinal prostheses provide a particularly clear example: pixelated photovoltaic arrays convert incident images into corresponding stimulation patterns, and the achievable spatial resolution is closely related to the implant pixel geometry [67]. In rodent models, photovoltaic implants with 70 μm pixels restored prosthetic visual acuity near the natural spatial resolution of the rat retina [68]. At the same time, pixel size should not be treated as identical to biological resolution, because neural integration and current spread can broaden the functional response. Even so, these systems demonstrate how optical addressing enables parallel, spatially multiplexed stimulation over large tissue areas [69].

These examples illustrate how nano- and microscale structures can enhance local charge generation, thereby improving the precision of photostimulation. Representative spatial resolutions achieved by these systems span multiple biological scales. Individual nanowire photodiodes can localize stimulation to dimensions comparable to single neuronal somata (approximately 10–20 μm), enabling activation of individual neurons within complex neural tissues [23]. In retinal prostheses, photovoltaic arrays employing 70 μm pixels have restored prosthetic visual acuity approaching the natural spatial resolution of the rat retina [68], while the functional stimulation footprint remains somewhat larger because of current spread and neural integration. More generally, these characteristic dimensions compare favorably with relevant biological structures, ranging from individual neurons (10–20 μm) and cardiomyocytes

(approximately 100 μm in length) to retinal microcircuits (50–100 μm), illustrating how nano- and micro-structured optoelectronic interfaces can bridge localized phototransduction with biologically meaningful spatial precision.

3.2 Temporal control of bioelectronic stimulation

Temporal programmability is equally important because many physiological processes depend not simply on activation, but on precisely timed patterns of electrical activity. By controlling light intensity, pulse width, and stimulation frequency, optical biointerfaces can be tuned to mimic or perturb the native electrophysiological rhythms of excitable tissues [61, 62]. This capability is especially important in organs such as the brain and heart, where function depends on coordinated spatiotemporal patterns rather than isolated activation events [70].

Recent studies have begun to demonstrate programmable photostimulation systems capable of multisite, time-varying stimulation. A leading example is the monolithic silicon photostimulation platform, in which photoelectrochemical heterojunction structures support localized photocurrent generation at user-selected illumination sites without individually wired electrodes (Fig. 3) [20]. This architecture enables random-access stimulation (Figs. 3(b)–3(f)), multisite pacing (Figs. 3(g)–3(i)), and dynamically reconfigurable activation patterns across cardiac tissue. The significance of such systems lies not only in their performance, but also in the design principle they establish: light can serve simultaneously as the energy source and the addressing mechanism for high-density bioelectronic control [20].

This represents a substantial departure from traditional electrode-based stimulation, where each active site typically requires a dedicated electrical connection. Optical multiplexing can therefore increase the number of controllable stimulation sites without proportionally increasing wiring complexity or device bulk [20, 61]. In this respect, optogenetics remains an important benchmark because it has demonstrated subcellular spatial resolution and millisecond temporal precision [71]. For non-genetic photostimulation, the challenge is to approach comparable programmability through materials and device engineering alone.

Beyond cardiac applications, temporal programmability is equally important in neural photostimulation systems, where millisecond-scale stimulus timing is required to engage physiologically relevant neural codes. Nanostructured retinal implants, for example, can evoke temporally precise neuronal responses under short optical pulses [38]. Photovoltaic nanoassemblies have been shown to trigger retinal ganglion cell activity with millisecond-scale latency following near-infrared stimulation, indicating that optoelectronic interfaces can operate within physiologically relevant neural timescales. These results are important because they show that non-genetic photostimulation is capable not only of activating neurons, but of doing so with timing compatible with neural coding.

Returning to cardiac systems, programmable optical stimulation has also proven valuable as an experimental tool for probing electrophysiological dynamics beyond simple pacing. In cardiac systems, optical platforms can be used to stimulate different regions of the myocardium in controlled sequences, allowing researchers to investigate conduction patterns, pacing hierarchies, and the emergence of arrhythmogenic behavior [20, 70, 72]. In this sense, spatiotemporal photostimulation is valuable not only as a therapeutic modality, but also as a method for studying how excitable tissues process and propagate bioelectrical signals.

Overall, advances in spatiotemporal programming are redefining photostimulation from a simple trigger mechanism into a programmable bioelectronic platform. By combining nanoscale materials design with optical addressing and device-level control, researchers are beginning to build systems capable of coordinating biological activity across complex tissues with increasing precision. These capabilities will be central to future photoelectroceutical therapies [24], particularly where therapeutic success depends on delivering stimulation patterns that reproduce, modulate, or restore native electrophysiological dynamics.

4 Toward translational and clinical photoelectroceuticals

Early studies in non-genetic photostimulation established that photoresponsive materials could modulate excitable cells and tissues under controlled experimental conditions [14, 15]. More recent work has shifted this field toward translational questions, including implant format, tissue integration, stimulation efficiency, and surgical deployability. In this context, photoelectroceuticals can be viewed as therapeutic systems that use non-genetic, light-responsive biointerfaces to regulate physiological function without genetic modification [51]. Progress in materials engineering, mechanically compliant device design, and minimally invasive implantation strategies is beginning to support photostimulation platforms that operate under increasingly clinically relevant conditions, including wireless activation, chronic biointegration, and in selected cases tissue-scale modulation [25, 73].

4.1 Retinal prostheses as the leading clinical example

Among the candidate therapeutic targets for non-genetic photostimulation, retinal prostheses currently represent the clearest and most clinically advanced example of photoelectroceutical translation. Degenerative retinal disorders such as age-related macular degeneration and retinitis pigmentosa cause progressive photoreceptor loss while leaving substantial portions of the downstream retinal circuitry—including bipolar cells, ganglion cells, and optic nerve pathways—at least partially preserved [74, 75]. This anatomical organization makes the retina unusually well suited for prosthetic photostimulation, because artificial photoreceptors or photovoltaic implants can bypass degenerated native photoreceptors and directly engage surviving neural circuits [74, 76].

A leading example is the photovoltaic retina implant microarray (PRIMA), which uses a subretinal array of silicon photodiodes to convert patterned near-infrared illumination into localized electrical stimulation. External image-capture hardware projects near-infrared patterns onto the implant, enabling wireless retinal activation without transscleral leads. Preclinical studies established that photovoltaic stimulation could restore visually evoked responses and high prosthetic acuity in animal models [77], and early human studies provided initial evidence of feasibility [78]. More recently, a multicenter clinical study showed that subretinal photovoltaic implantation can restore measurable visual acuity in patients with geographic atrophy secondary to age-related macular degeneration (Fig. 4(a)) [51]. Complementary electrophysiological work further suggests that photovoltaic retinal stimulation can engage visual pathways with temporal and spatial features approaching physiological visual processing [79].

In addition to clinical validation, ongoing work has focused on

improving the resolution, stability, and long-term adaptability of retinal prostheses. For example, recent studies have shown that next-generation photovoltaic implants can be surgically removed and replaced with upgraded devices within the same subretinal location while preserving retinal responsiveness [52]. This concept of upgradeable retinal implants highlights an important translational consideration: implantable photoelectroceutical systems may need to evolve alongside advances in materials and device engineering, requiring designs that allow revision or replacement without compromising retinal function. High-density photovoltaic epiretinal devices with more than 10,000 pixels have demonstrated single-pixel illumination precision and network-mediated responses from retinal ganglion cells *in vitro* [80, 81]. In a large-animal model, a foldable photovoltaic epiretinal implant restored light-evoked responses in blind Göttingen minipigs following implantation [82].

Beyond planar photodiode-based implants, nanostructured photoreceptor substitutes have broadened the design space for retinal photoelectroceuticals by more closely matching the scale and geometry of native photoreceptors. Earlier foundational work on titanium oxide nanowire arrays demonstrated restoration of light responses in blind mice, with behavioral experiments confirming restored light perception, improved visual acuity, and moving-object detection [83]; electrophysiological recordings further confirmed signal transmission from retinal ganglion cells to the visual cortex. More recent studies have extended this approach, demonstrating nanowire arrays in the subretinal space as artificial photoreceptors capable of converting light into photocurrent signals that activate retinal ganglion cells (Fig. 4(b)) [84].

Complementary translational progress has been demonstrated using tellurium nanowire networks as broadband photovoltaic retinal prostheses [29]. As described in Section 2, these narrow-bandgap networks generate photocurrents across the visible to near-infrared range without external power. From a translational perspective, what distinguishes this platform is its validated function across multiple biological scales: implantation in blind mice restored light-evoked responses in the visual cortex and improved visual learning behavior, and the system subsequently demonstrated feasibility in nonhuman primates [29, 30]. This multispecies progression represents a meaningful step in the translational path toward human application. Moreover, the broadband spectral sensitivity of tellurium nanowires suggests that future prosthetic devices built on this platform may extend visual perception into near-infrared wavelengths inaccessible to native photoreceptors, potentially offering a functional advantage over silicon photodiode implants.

These studies illustrate the rapid evolution of retinal photostimulation technologies from early device prototypes to clinically validated therapies and advanced translational platforms. Silicon photovoltaic implants have demonstrated the feasibility of restoring vision in human patients, while nanostructured photoreceptor systems—including semiconductor nanowires and nanowire networks—are expanding the design space for future retinal prostheses. Continued progress in nanomaterial engineering, device miniaturization, and surgical integration may ultimately enable retinal implants with higher spatial resolution, broader spectral sensitivity, and improved long-term biocompatibility. As a result, retinal prostheses provide a compelling example of how non-genetic photostimulation can transition from nanoscale materials innovation to clinically meaningful photoelectroceutical therapies.

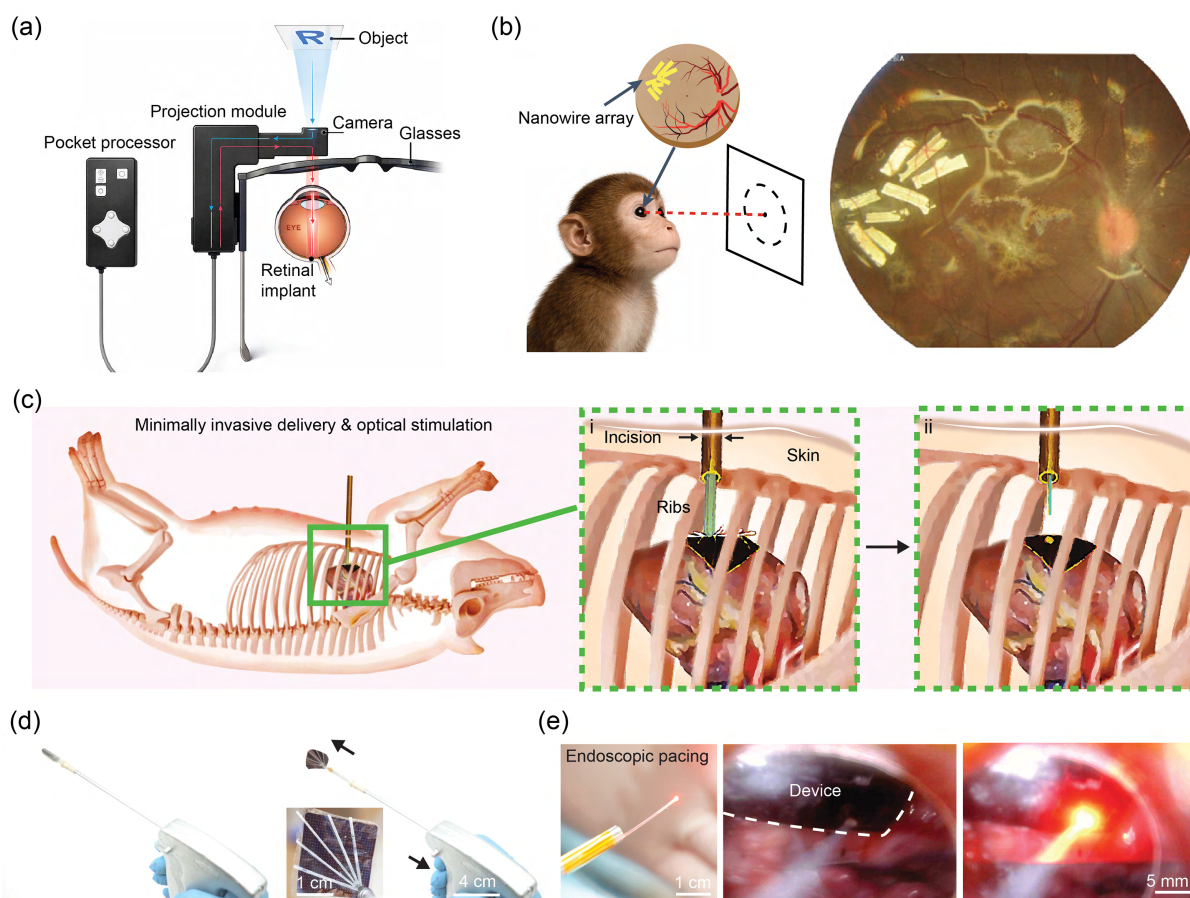


Figure 4 Translational applications. (a) PRIMA system for vision restoration. Schematic of the PRIMA system integrating a subretinal photovoltaic implant, a pocket processor, and projection glasses. A camera captures visual information (e.g., the letter R), which is processed and transmitted to the glasses. The glasses project near-infrared light (880 nm) onto the retinal implant to stimulate inner retinal neurons. Reproduced with permission from Ref. [51], © Massachusetts Medical Society. All rights reserved 2025. (b) Nanowire array retinal implants for visually guided behavior. Left: Schematic of the visually guided saccade (VGS) behavioral task performed by monkeys implanted with nanowire (NW) retinal arrays. Right: Fundus photograph showing the NW array implanted in the monkey retina. Reproduced with permission from Ref. [84], © Yang, R. et al. under exclusive licence to Springer Nature Limited 2023. (c)–(e) Minimally invasive cardiac photostimulation for heart modulation. (c) Schematic of the closed-thoracic procedure involving an intercostal incision, catheter-based delivery of a silicon photostimulation device, and subsequent optical-fiber-guided photostimulation. (d) Photographs of the flexible membrane device inside the custom catheter delivery system (top) and its deployment following trigger release (bottom). The inset shows a magnified view of the silicon membrane device mounted on the substrate. (e) Photographs of an optical-fiber-coupled endoscope and representative endoscopic views during minimally invasive photostimulation and pacing of the pig heart. Reproduced with permission from Ref. [20], © Li, P. et al., under exclusive licence to Springer Nature Limited 2024.

4.2 Expanding photostimulation toward cardiac and neural therapies

Although retinal prostheses remain the most clinically advanced photostimulation application, related strategies are increasingly being explored for cardiac pacing, peripheral nerve modulation, and selected neural interfaces. These targets are attractive because optical biointerfaces can in principle enable wireless activation, distributed stimulation, and reduced dependence on rigid wired leads [25]. At the same time, translation in these settings is less mature than in the retina and remains constrained by tissue motion, optical penetration depth, packaging requirements, and long-term implant stability.

Recent work has demonstrated that optoelectronic biointerfaces can achieve cardiac pacing and electrophysiological modulation using light-responsive semiconductor platforms. For example, monolithic silicon photostimulation systems have been shown to pace cardiac tissues across multiple biological models, including cultured cardiomyocytes, *ex vivo* rodent hearts, and large-animal

cardiac systems (Figs. 4(c)–4(e)) [20]. These devices rely on photoelectrochemical heterojunctions formed within nanoporous silicon structures, which generate localized capacitive currents upon illumination. Such currents can depolarize nearby cardiomyocytes and initiate cardiac excitation. Importantly, these monolithic systems achieve reliable pacing in representative large-animal models using optical power densities on the order of approximately $0.1\text{--}1\text{ mW}\cdot\text{mm}^{-2}$, while simultaneously enabling spatially programmable stimulation patterns [20]. Operating at such relatively low optical intensities reduces tissue heating, increases safety margins with respect to optical exposure limits, decreases energy requirements for implantable light-delivery systems, and facilitates chronic wireless photostimulation, all of which are important considerations for future clinical translation [70].

In parallel, advances in materials engineering are enabling photostimulation devices that are better suited for implantation within mechanically dynamic organs such as the heart. Ultrathin rubbery optoelectronic stimulators composed of stretchable semiconductor nanofilms and transparent conductive nanomesh

electrodes have recently been demonstrated for untethered cardiac stimulation [22], consistent with the broader development of soft bioelectronics for cardiovascular disease management [21, 55]. Because these devices are mechanically compliant and extremely thin, they can conform intimately to the beating myocardium without causing significant mechanical mismatch. Such soft biointerfaces maintain stable optoelectronic performance even under repeated mechanical deformation, addressing one of the key challenges for long-term implantable bioelectronic devices in moving tissues [54].

Another emerging direction involves integrating photostimulation systems into minimally invasive (Figs. 4(c)–4(e)) or bioresorbable electrotherapeutic devices, which could expand the clinical applicability of photoelectroceuticals. A particularly notable example is the development of millimeter-scale bioresorbable pacemaker systems in which optoelectronic elements act as wireless control interfaces for temporary cardiac pacing [85–87]. These devices represent a new class of transient cardiac implants designed to provide pacing support during short-term clinical scenarios, such as post-surgical recovery or temporary conduction abnormalities, building on the broader field of physically transient and bioresorbable silicon electronics [88, 89], which has since matured into a diverse repertoire of minimally invasive wireless implants [90].

Unlike conventional permanent pacemakers, these miniaturized devices are constructed from bioresorbable materials that gradually dissolve after completing their therapeutic function, eliminating the need for surgical extraction. Representative bioresorbable pacing systems are designed to remain functional for periods ranging from several days to a few weeks before gradually losing electrical performance as bioresorption progresses, depending on device design and encapsulation strategy [85–87]. These operational lifetimes align well with common clinical indications for temporary cardiac pacing, such as post-operative rhythm management or transient conduction abnormalities, where pacing support is typically required only during the acute recovery period. Their millimeter-scale dimensions enable delivery through catheter-based or injectable procedures standard in interventional cardiology, and distributed deployment across multiple cardiac sites opens the possibility of multisite pacing strategies including biventricular synchronization [91]. Optically addressed nodes can be selectively activated using patterned illumination, providing wireless programmability without inductive power transfer. Together, these properties—bioresorbability, catheter-deliverable scale, and wireless optical addressability—distinguish this platform from conventional wired pacemakers and point toward a new category of temporary cardiac intervention suited to post-operative and transitional pacing needs.

Beyond cardiac pacing, such minimally invasive photoelectroceutical systems could eventually be adapted for neuromodulation and peripheral nerve stimulation, where temporary stimulation devices are often required following surgical procedures or traumatic injury. Wireless bioresorbable electronic systems have already demonstrated sustained therapeutic nerve stimulation that accelerates axonal regeneration following peripheral nerve injury [92], and bioresorbable peripheral nerve stimulators have been applied for on-demand analgesic nerve block enabled by electronic control [93]. The ability to deploy biodegradable, wirelessly controlled stimulation modules may significantly reduce the risks associated with long-term implants

and simplify post-treatment management.

Recent demonstrations of multifunctional fiber-based optoelectronic probes capable of wireless modulation of gut and brain neural circuits without genetic modification [94] further illustrate the trajectory toward highly integrated, minimally invasive photostimulation systems. These developments collectively illustrate the trajectory of non-genetic photostimulation from proof-of-concept demonstrations to clinically actionable systems. The key enabling convergence—nanomaterials engineering, soft bioelectronics, and minimally invasive delivery—has produced platforms that are wireless, programmable, and increasingly tissue-compatible [25]. What remains is to extend this foundation toward adaptive, feedback-controlled, and biologically integrated systems, which is the focus of the following section. As these technologies continue to evolve, they may ultimately expand the scope of bioelectronic medicine by providing new strategies for treating neurological, cardiovascular, and sensory disorders using light-driven therapeutic interfaces.

5 Future directions

Despite rapid progress in materials and device engineering for non-genetic photostimulation, significant opportunities remain for advancing these technologies toward fully programmable and clinically scalable bioelectronic systems. Emerging research directions are increasingly focused on integrating nanomaterial innovation, biological functionality, and system-level programmability to create next-generation photoelectroceutical platforms [25, 95]. These developments are expected to expand the scope of photostimulation from isolated device demonstrations to adaptive, multifunctional therapeutic systems.

5.1 Living and engineered optoelectronic tissues

Endogenous bioelectric signaling orchestrates embryogenesis, regeneration, and cancer progression [96]. Optoelectronic interfaces capable of programming these signals may therefore have broad implications beyond neuromodulation. One promising direction involves integrating photostimulation capabilities directly into engineered tissues and regenerative constructs. Traditional bioelectronic interfaces typically rely on external devices attached to tissues, which can introduce mechanical mismatch and limit long-term integration. Recent advances in tissue engineering suggest that embedding optoelectronic components within biomaterial scaffolds may provide a more seamless approach to interfacing with biological systems [97]. Macroporous nanoelectronic networks [98] and syringe-injectable mesh electronics [99] represent early visions of electronics seamlessly integrated within biological tissue.

For example, optoelectronically active cardiac scaffolds fabricated through bioprinting have demonstrated the ability to modulate cardiomyocyte activity under optical stimulation without requiring wired electrodes [42]. In these systems, micro-solar cells embedded within hydrogel matrices generate electrical stimuli upon illumination, enabling distributed and wireless modulation of cardiac tissue behavior. Such approaches suggest a future in which engineered tissues themselves possess intrinsic optoelectronic functionality, potentially allowing implanted constructs to dynamically interact with host physiology.

More broadly, integrating optoelectronic materials into living tissues could enable hybrid systems that combine biological sensing

and electronic actuation. Such platforms may eventually support closed-loop bioelectronic therapies, where optical stimulation is automatically adjusted in response to real-time physiological signals [95]. Achieving this vision will require advances in biocompatible materials, stable long-term interfaces, and scalable manufacturing strategies for biointegrated electronics.

5.2 Biomolecular optoelectronics

As discussed in Section 2, pi-conjugated peptide assemblies represent a nascent but conceptually significant class of optoelectronic material, capable of generating photocurrents through sequence-programmed donor-acceptor interactions [48]. The future directions for this platform are distinct from those of conventional inorganic or organic semiconductors and deserve separate consideration. Because their function emerges from molecular self-assembly rather than top-down fabrication, biomolecular systems open design strategies that are currently inaccessible to solid-state devices. For example, sequence variation can in principle tune not only the electronic structure of the assembled chromophore array, but also the chemical identity of the cell-contacting surface—potentially enabling simultaneous control of phototransduction and cell adhesion within a single molecular construct. Functional integration with biological recognition motifs (e.g., receptor-targeting peptide sequences or enzyme-responsive linkers) could allow stimulation specificity at the cellular or subcellular level, an ambition that inorganic nanostructures can only approximate through surface functionalization. Realizing this potential will require establishing reliable synthetic routes to sequence-defined, electronically active assemblies with reproducible photocurrent outputs, and demonstrating their stability and function in physiologically relevant ionic environments over therapeutically relevant timescales.

Future work in this area will likely focus on expanding the library of photoactive biomolecular systems and improving their electronic performance. For example, incorporating donor-acceptor chromophore systems with absorption in the far-red or near-infrared region may improve tissue penetration and reduce phototoxicity. Such advances could enable biomolecular photostimulation platforms capable of operating in complex physiological environments.

5.3 Programmable photoelectroceuticals

Beyond individual materials and devices, the long-term vision of photostimulation technologies lies in the development of programmable photoelectroceutical systems. In such systems, optical stimulation patterns would be dynamically tailored to regulate biological functions in real time. Achieving this goal will require advances in several key areas, including optical addressing technologies, multisite stimulation architectures, and closed-loop bioelectronic control systems.

The trajectory from these early demonstrations points toward several unresolved engineering challenges that will define the next generation of programmable systems. First, achieving true closed-loop operation—where stimulation parameters are continuously updated based on real-time electrophysiological feedback—will require co-integrating optical stimulators with implantable recording modalities capable of operating simultaneously and without cross-talk. Second, current optical addressing strategies depend on external projection hardware or implanted waveguides, both of which impose constraints on implant geometry and optical

penetration depth; extending programmable stimulation into deep tissues will require advances in near-infrared materials, fiber-optic coupling, or implantable micro-LED architectures. Third, the clinical scalability of multisite stimulation platforms will depend on standardizing wireless power delivery, perhaps through emerging wide-field strategies [100] that do not require precise optical alignment between external hardware and the implanted device. Addressing these challenges in concert—rather than optimizing each in isolation—will be necessary for programmable photoelectroceuticals to move from controlled laboratory demonstrations toward adaptive therapies.

In addition, integrating photostimulation with emerging technologies such as artificial intelligence-driven signal processing and real-time physiological monitoring may allow the creation of adaptive therapeutic systems. Such platforms could automatically adjust stimulation parameters based on feedback from implanted sensors, enabling personalized treatment strategies for conditions such as arrhythmias, neurological disorders, and sensory impairments.

5.4 Outlook

Looking ahead, the continued maturation of photoelectroceutical technologies will depend on resolving several persistent challenges that current platforms have not yet fully addressed. Optical penetration depth remains a fundamental constraint: most demonstrated systems operate under near-surface or surgically accessed illumination, and extending non-invasive photostimulation into deep cardiac, spinal, or visceral targets will require either far-red or near-infrared materials with improved two-photon or upconversion efficiencies, or implantable light-delivery elements that themselves must meet biocompatibility and longevity standards [38]. Long-term device stability presents an equally important barrier; the chronic performance of photoactive materials in ionic physiological environments—including potential surface passivation, photodegradation, or delamination—remains incompletely characterized for most platforms beyond silicon. Regulatory translation of non-genetic photostimulation devices will also require establishing biocompatibility standards and efficacy endpoints specific to optoelectronic interfaces, which differ substantially from the electrical stimulation context in which most existing implant regulations were developed.

At the same time, emerging capabilities in machine-learning-driven signal processing, implantable physiological sensors, and responsive drug delivery are creating opportunities for photoelectroceuticals to be embedded within broader closed-loop therapeutic architectures rather than functioning as standalone stimulators [95]. Advances in near-infrared photostimulation materials [38], flexible biointerfaces [22], and clinically validated implant systems [51] collectively suggest that the field is transitioning from feasibility demonstration to translational engineering. Ultimately, realizing the full potential of photoelectroceuticals will require integrating nanomaterials, programmable optoelectronics, regenerative biology, and clinical medicine into unified therapeutic systems capable of precise, adaptive, and personalized bioelectronic intervention.

Data availability

Not applicable.

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Declaration of competing interest

All the contributing authors report no conflict of interests in this work.

Author contribution statement

G. Q. Y.: Writing manuscript. Y. Z. Z.: Figure preparation. P. J. L.: Writing manuscript. B. Z. T.: Project administration, funding acquisition, writing manuscript. All the authors have approved the final manuscript.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

During the preparation of this manuscript, the authors used Generative Pre-trained Transformer Pro (GPT Pro) to assist with language editing. The authors reviewed and edited all generated content and take full responsibility for the content of the publication.

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