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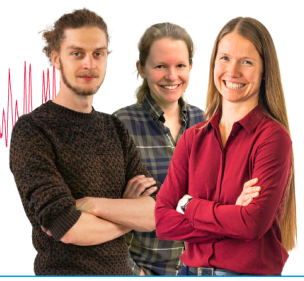

Shining light in a heartbeat: Controlling cardiac bioelectricity with membrane-targeted photoswitches

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ABSTRACT

The heart's rhythmic contractions are driven by bioelectric signals that coordinate the excitation and propagation of action potentials throughout the cardiac tissue. Maintaining precise control of this rhythm is essential for proper heart function and preventing life-threatening conditions. Traditionally, this regulation has relied on pharmacological interventions, tissue ablation, or electric shock delivery. However, these methods often come with off-target effects, tissue damage, and high energy demands. Optostimulation presents a promising alternative, offering highly precise and minimally invasive control with significantly fewer side effects. In this Perspective, we explore current light-based technologies designed to modulate cardiac bioelectricity, with a particular focus on an innovative approach based on sarcolemma-targeted photoswitches. Finally, we discuss the main translational opportunities and critically examine the key challenges that must be addressed to transition this technology from basic research to clinical application.

I. INTRODUCTION

The heart's rhythmic contractions are orchestrated by finely tuned bioelectric signals that coordinate the excitation and propagation of action potentials across the intricate network of cardiac tissue. These signals originate in the sinoatrial node, the heart's natural pacemaker, and travel along specialized conduction pathways to ensure a precise and synchronized contraction of both the atrial and ventricular chambers.

Any disruption to this delicate electrical system can interfere with the synchronized contraction of the heart, leading to arrhythmias.[1] Without timely intervention, these conditions can escalate to heart failure, stroke, or sudden cardiac death, underscoring the critical importance of maintaining precise control over the heart's electrical activity.

Historically, therapeutic strategies for managing arrhythmias have relied on pharmacological interventions, tissue ablation, or the application of electrical stimulation. Pharmacological treatments, while effective in some cases, often lack selectivity, leading to systemic side effects and variability in patient responses.[2] Ablation therapy, which involves the targeted destruction of arrhythmogenic cardiac tissue, can be curative but is invasive and irreversible, often resulting in scarring that can impair long-term cardiac function.[3] Electrical stimulation techniques, such as defibrillation, cardioversion, and tachypacing, deliver controlled energy to reset or modify the heart's rhythm. Defibrillation and cardioversion use high-intensity energy to restore rhythm, but can cause pain, tissue damage, and psychological distress.[4] Tachypacing delivers low-energy pulses to suppress abnormal rhythms, offering a less invasive, controlled, and potentially less painful alternative, but still requires careful patient monitoring.[5]

These challenges highlight the pressing need for innovative and minimally invasive solutions to precisely regulate cardiac rhythm while minimizing adverse effects. Optostimulation presents a promising alternative, utilizing the unique properties of light to control cellular activity with exceptional spatial and temporal precision. As the field evolves, this approach has the potential to revolutionize how arrhythmias are treated, offering safer and more effective solutions for patients with cardiac rhythm disorders.

In this Perspective, we aim to provide a concise overview of the primary light-based approaches to modulate cardiac activity. Among

the various optostimulation strategies, we will focus specifically on membrane-targeted photochromic molecules. By leveraging their ability to alter cell excitability and conduction dynamics, these photoswitches hold significant potential for controlling cardiac cell bioelectricity.

A. State of the art in light-based approaches to cardiac physiology

The leading technique for controlling the electrical activity of excitable cells using light is optogenetics.[6–8] This is achieved by expressing light-sensitive proteins, known as opsins, which act as ion channels or ion pumps activated by specific wavelengths.

Since 2010, this approach has been successfully applied in cardiac research, offering unprecedented opportunities to investigate and regulate heart function.[9–12] By modulating excitability, conduction, and repolarization with light, it has provided insights into arrhythmia mechanisms and potential therapies. Studies in cardiomyocyte cultures,[13] *ex vivo* heart preparations,[14] and *in vivo* animal models[15,16] have shown that optogenetic stimulation can pace cardiomyocytes, terminate arrhythmias, and even produce defibrillation-like effects with significantly lower energy than traditional electrical methods (Fig. 1).[17–21] Despite these promising outcomes, optogenetics face ethical limitations and safety concerns that hinder its clinical applicability. A major challenge is delivering the constructs to myocardial cells, as this typically relies on viral vectors, which can be targeted and neutralized by the host's immune system, reducing efficacy and raising safety issues.[22]

One approach to bypass gene transfer involves the use of emerging phototransducers made from inorganic and organic materials. Recent studies have employed these materials as photoactive interfaces for optical stimulation of cardiomyocytes.[23–31] For instance, cardiac action potential generation has been demonstrated using planar graphene-based biointerfaces, likely utilizing the photogeneration of charge carriers, as well as polymer–silicon nanowires leveraging their photoelectrochemical properties.[24,32] Similar results have been obtained by locally increasing temperature through the illumination of absorbers (e.g., gold nanoparticles, nanorod electrodes, and metasurface planar organic interfaces) in contact with cardiomyocytes (Fig. 2).[33,34]

It is worth noting that in a recent work, tunable spatiotemporal photostimulation was achieved using a non-genetic platform based on semiconductor materials.[35] The study utilized photoelectrochemical devices made from leadless, silicon-based monolithic structures, which were capable of delivering highly precise, spatially resolved, and time-controlled photostimulation. Through spatiotemporal profiling of photoelectrochemical currents, the researchers assessed the magnitude, precision, accuracy, and resolution of the photostimulation delivered to various cardiac systems. The system demonstrated its optoelectronic capabilities through optical overdrive pacing of cultured cardiomyocytes, *ex vivo* and *in vivo* rat hearts under ischemic conditions, and *in vivo* in mouse hearts via transthoracic stimulation. Most notably, the approach was extended to a large animal model, achieving optical override pacing and multisite photostimulation *in vivo* in a pig heart.

One of the most significant advantages of this approach lies in its ability to precisely target different regions of the heart with minimal invasiveness. The system also incorporated a custom endoscopic delivery device, which allowed for closed-thoracic operations and

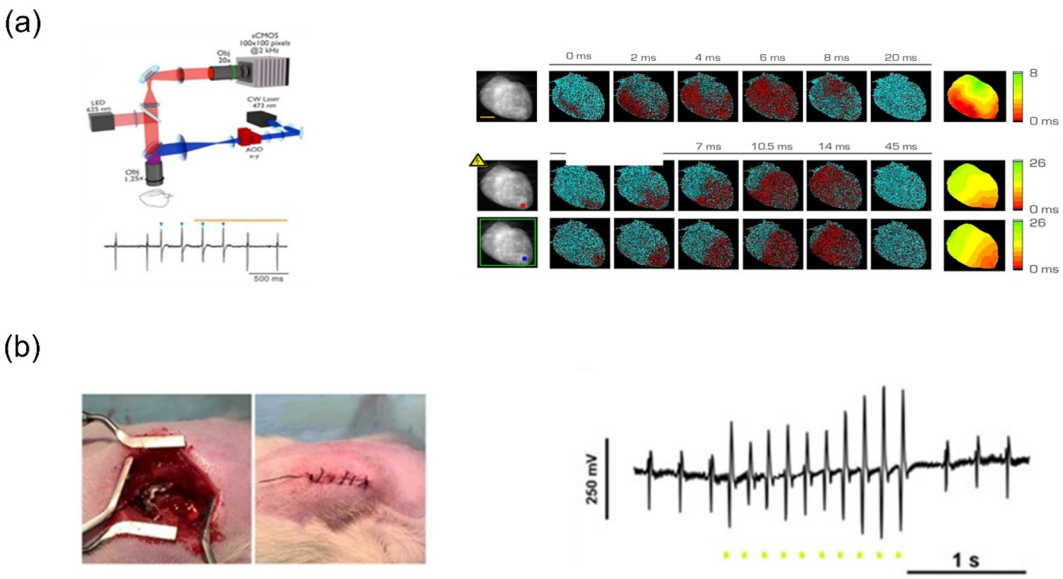

FIG. 1. Optogenetic control of cardiac electrophysiology. (a) Schematic of a wide-field fluorescence microscope for simultaneous voltage-sensitive dye imaging and ChR2 activation. The system includes a 625 nm LED for excitation, a 473 nm CW laser for optogenetic stimulation, and a scanning head with acousto-optical deflectors (AOD x-y). Imaging is performed at high temporal resolution (2 kHz) using a sCMOS sensor. Representative optical mapping images depict electrical activation patterns in ChR2-expressing hearts. Reproduced with permission from Crocini *et al.*, Sci. Rep. **6**, 35628 (2016). Copyright 2016 Crocini *et al.*, licensed under a Creative Commons Attribution (CC BY) license. (b) Picture of an LED device implanted at the ventricular apex of a rat heart, before and after surgical closure. The right panel shows an ECG trace demonstrating optical ventricular pacing via a 567 nm LED under closed-chest conditions. Reproduced with permission from Nyns *et al.*, Cardiovasc. Res. **118**, 2293–2303 (2022). Copyright 2022 Nyns *et al.*, licensed under a Creative Commons Attribution (CC BY) license.

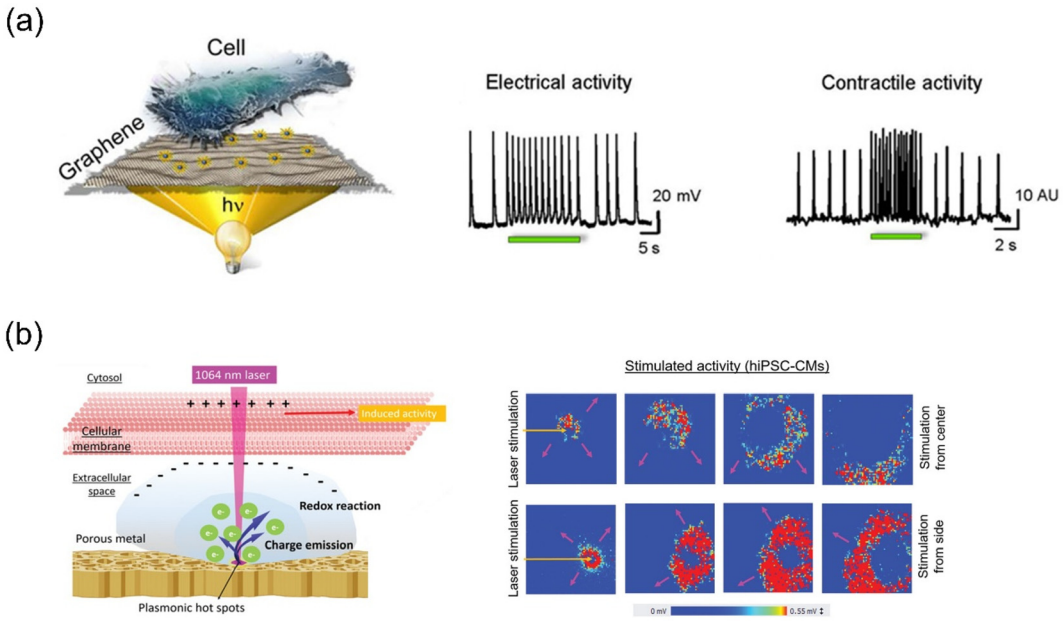

FIG. 2. Organic interfaces for cardiac stimulation. (a) Schematic representation of a graphene-based optoelectronic interface for optical stimulation of cardiomyocytes. The system leverages reduced graphene oxide (rGO) coatings to facilitate light-induced modulation of action potentials and contractile activity in human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). Representative traces illustrate the electrophysiological response to optical stimulation on rGO-coated coverslips. Reproduced with permission from Savchenko *et al.*, Sci. Adv. **4**(5), eaat0351 (2018). Copyright 2018 Savchenko *et al.*, licensed under a Creative Commons Attribution (CC BY) license. (b) Optical stimulation of cardiomyocytes using plasmonic metamaterials. The schematic highlights the mechanism of optical charge emission triggered by near-infrared (NIR) laser irradiation of metamaterials. Instantaneous maps depict the spatial propagation of stimulated electrical activity in hiPSC-CMs. Reproduced with permission from Bruno *et al.*, Adv. Sci. **8**(21), 2100627 (2021). Copyright 2021 Bruno *et al.*, licensed under a Creative Commons Attribution (CC BY) license.

endoscopic optical stimulation, further enhancing its potential for clinical applications. This adaptability is particularly crucial for cardiac resynchronization therapy (CRT), where traditional pacemaker leads often introduce complications. The leadless, lightweight, and multisite photostimulation platform demonstrated by this study offers a promising alternative to current CRT systems, suggesting that optoelectronic stimulation could overcome many of the limitations of traditional pacemaker systems.

Nevertheless, while inorganic phototransducers have demonstrated remarkable capabilities in achieving precise and minimally invasive cardiac stimulation, especially in large animal models, their integration with soft biological tissues remains challenging. To address this limitation, organic semiconductors have emerged as a promising alternative or complementary strategy. Particularly, organic materials offer the unique advantage of forming nearly seamless abiotic/biotic interfaces, owing to their mechanical softness and mixed ionic–electronic conductivity.[36,37] This compatibility facilitates stable, long-term coupling with excitable cells and provides the foundation for the modulation of cardiac bioelectricity via optically active biomodulation interfaces [Figs. 3(a) and 3(b)].

Although the mechanisms underlying light-induced cellular activation in organic systems may involve photothermal or photochemical pathways, whose chronic effects require further safety validation,[38] their potential to bridge the functional and mechanical gap between electronic devices and living tissues represents a critical step toward clinically viable, gene-free bioelectronic therapies.

Building upon this versatility, another promising strategy based on organic materials involves the use of photochromic compounds. These small molecules can interact with biological structures either through covalent binding to ion channels[39–41] or non-covalent integration into the plasma membrane [Fig. 3(c)].[42] This approach is gaining increasing attention due to its high stimulation efficiency, versatility, and potential to extend stimulation wavelengths into the near-infrared region, thereby improving tissue penetration and reducing energy requirement.[43,44] In the Sec. I B, we will discuss our contribution to the field and the implications in the control of cardiac bioelectricity.

B. Membrane-targeted photoswitches: An emerging frontier in cardiac photomodulation

Photoisomerizable compounds, or "photoswitches," have been employed as artificial photoreceptors.[45] These light-responsive small molecules can switch between *trans*- and *cis*-configuration upon illumination with specific wavelengths of light. Light absorption triggers trans-cis and cis-trans isomerizations with high quantum yield, occurring within microseconds, without producing long-lived excited states, reactive intermediates, or competing reactions.[42,46,47]

Recently, our group synthetized a family of amphiphilic membrane-targeted azobenzenes for non-genetic optical stimulation of living cells.[48–58] Among these, we will describe two compounds that stand out for their efficacy: Ziapin2 and MTP2.

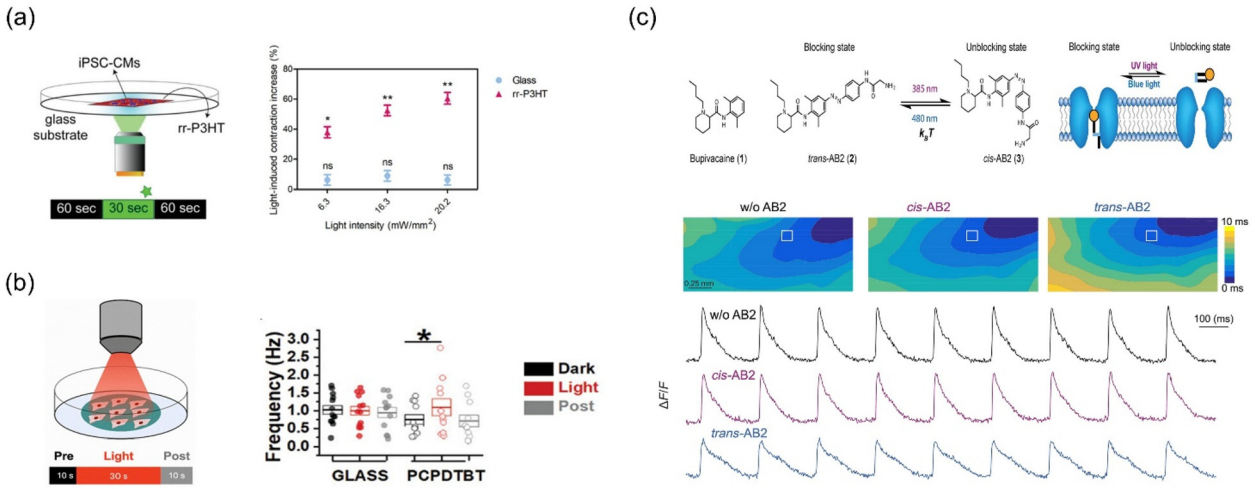

FIG. 3. Optical modulation of cardiac electrophysiology using organic materials. (a) hiPSC-CMs cultured on a rr-P3HT thin film respond to green light (550 nm) stimulation with a modulation of contraction rate. The relative variation in contraction rate is quantified under different photoexcitation densities (6.3–20.2 mW/mm^2) compared to dark conditions. Reproduced with permission from Lodola *et al.*, Adv. Healthc. Mater. **8**(13), 1900198 (2019). Copyright 2019, Wiley-VCH. (b) hiPSC-CMs seeded on the far-red responsive polymer PCPDTBT exhibit changes in spontaneous beating frequency during illumination, demonstrating the potential of conjugated polymers as photoactive interfaces for cardiomyocytes. Reproduced with permission from Ronchi *et al.*, Adv. Sci. **11**(3), e2304303 (2024). Copyright 2024 Ronchi *et al.*, licensed under a Creative Commons Attribution (CC BY) license. (c) The photochromic ligand azobupivacaine 2 (AB2) undergoes reversible cis-trans isomerization under UV (385 nm) and blue (480 nm) light, modulating sodium channel activity. When UV light (385 nm) is applied, AB2 binds less effectively to Nav1.5, allowing relatively normal sodium current flow and conduction. Conversely, when blue light (480 nm) is applied, AB2 switches to the trans-form, which strongly blocks Nav1.5, reducing sodium current and slowing conduction velocity. Reproduced with permission from Fehrentz *et al.*, Br. J. Pharmacol. **182**(5), 1125–1142 (2025). Copyright 2025 Fehrentz *et al.*, licensed under a Creative Commons Attribution (CC BY) license.

1. Ziapin2: Opto-mechanical modulation

Ziapin2 is an azobenzene derivative in which one phenyl ring is connected to two alkyl chains, each terminating in a pyridine group, while the other phenyl ring is attached to an azepane group [Fig. 4(a), **top**].

Molecular dynamics simulations have demonstrated that in its trans-configuration, Ziapin2 promotes dimer formation within the cell membrane. Upon exposure to visible light (470 nm), the molecule undergoes photoisomerization, disrupting these dimers [Fig. 4(a), **bottom**]. This dimerization induces local membrane shrinkage, resulting in an increase in membrane capacitance (Cm) in the absence of light. Light-induced isomerization reverses this process, nearly restoring the original membrane thickness. This change in Cm modulates the membrane potential, leading to an initial hyperpolarization followed by a transient depolarization.[49] This phenomenon has been observed in various cellular models and has been shown to trigger action potential firing in cardiac excitable cells through stretch-activated channels (SACs) activation by modulating the whole excitation–contraction process [Fig. 4(b)].[53,57] Of particular interest, when added to an engineered cardiac microphysiological system with anisotropic orientation that reproduces myocardial cellular organization and mechanical properties, Ziapin2 enabled the control of cardiac conduction upon light stimulation [Fig. 4(c)].[54,59]

Altogether, these promising results suggest the possibility to achieve a non-genetic, contactless, and heatless control of cardiac electrical activity, thus displaying a high potential for anti-arrhythmic applications.

In this regard, Ziapin2 supra-threshold stimulation (i.e., photostimulation capable of depolarizing the membrane potential beyond the threshold needed to activate voltage-gated Na^+ channels, which leads to the initiation of an action potential) can be ideally effective for both bradyarrhythmias and tachyarrhythmias. In the former condition, it can work as an optical pacemaker helping to overcome the slow conduction and potentially restore normal pacing and rhythm. In the latter case, often caused by reentrant circuits or hyper-excitability, Ziapin2 can play a role in terminating or disrupting the abnormal electrical patterns by depolarizing key cells at specific points in the circuit, resetting the electrical wavefront and terminating the arrhythmia.

2. MTP2: Opto-electrical modulation

Despite its efficacy, Ziapin2 has two major drawbacks: (i) poor solubility in water, and (ii) the lack of a true off/on switching behavior. These limitations hinder its broader application, particularly in biological systems where solubility and precise control over its switching states are essential. With the purpose of achieving a better balance between water solubility, the affinity of the molecule for the membrane environment, and its dark-state activity, we synthesized MTP2, an azobenzene molecule with a "push–pull" character.[50]

MTP2 shares a similar structure with Ziapin2 but substitutes the azepane group with a nitro group (NO_2), a strong electron-withdrawing group [Fig. 5(a)]. This modification transforms the molecule into a "donor–acceptor" system, consisting of a π-conjugated framework with an electron donor (D) and an electron acceptor (A) group. In these D–π–A molecules, visible light excitation (470 nm) induces intramolecular charge transfer (ICT), resulting in a significant change in the molecular dipole moment.[60,61] This leads to charge redistribution and an inward current across the membrane, causing membrane potential depolarization [Fig. 5(b)].

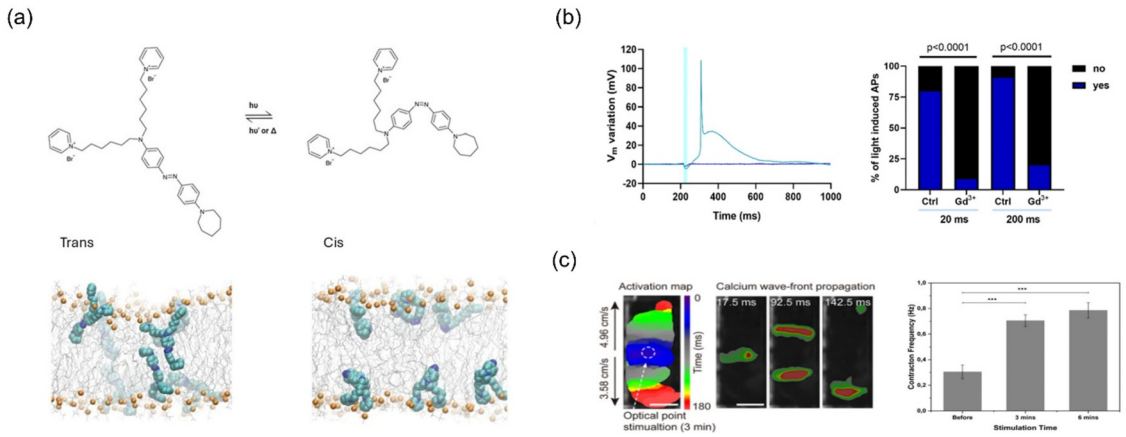

FIG. 4. Optical modulation of cardiac dynamics by Ziapin2. (a) Ziapin2 structure and molecular dynamics simulation of its internalization process in the cell membrane. Briefly, in the trans-conformation, Ziapin2 molecules anchor to the opposite leaflets of the membrane, forming dimers. This causes a local thinning of the membrane, resulting in an increase in membrane capacitance (left). Upon millisecond pulses of visible light ($\lambda = 470$ nm), Ziapin2 undergoes isomerization into its cis-form. In this configuration, the hydrophobic tails of opposing molecules are too far apart to dimerize, causing a rapid drop in capacitance due to membrane relaxation (right). Reproduced with permission from DiFrancesco *et al.*, Nat. Nanotechnol. **15**, 296–306 (2020). Copyright 2020, Nature Publishing Group. (b) Gadolinium (Gd^{3+}) blockade demonstrates the critical involvement of stretch-activated channels in light-induced action potential (AP) generation in Ziapin2-loaded adult murine ventricular myocytes (AMVMs). Representative AP traces are shown before (Ctrl) and after (Gd^{3+}, 50 μM) treatment under 20 ms-long light pulses and quantification of light-induced APs. Traces have been reported as relative Vm variation to better appreciate the light-induced effect; photoexcitation is represented by the cyan shaded area. Reproduced with permission from Florindi *et al.*, J. Transl. Med. **22**, 1068 (2024). Copyright 2024 Florindi *et al.*, licensed under a Creative Commons Attribution (CC BY) license. (c) Optical mapping of Ziapin2-driven cardiac activation in MTF-engineered heart tissue. Left panel shows a representative Ca^{2+} wave triggered by Ziapin2 photostimulation, while histogram on the right depicts the contraction frequency at baseline (spontaneous activity, time = 0) and during 1 Hz pulsed stimulation (3 and 6 min). Reproduced from Vurro *et al.*, APL Bioeng. **7**(2), 026108 (2023), with the permission of AIP.

The functional impact of MTP2 was evaluated in cardiac cells, specifically human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). Photostimulation of MTP2-loaded hiPSC-CMs with visible light pulses led to a rapid depolarization that occurred immediately upon light exposure [Fig. 5(c)]. This Vm modulation gradually returned to physiological resting levels, followed by a mild rebound hyperpolarization phase after light cessation. Interestingly, the effect was strongly dependent on light intensity and generally of small magnitude, insufficient to reach the threshold for Nav1.5 channel activation and, consequently, unable to generate action potentials.

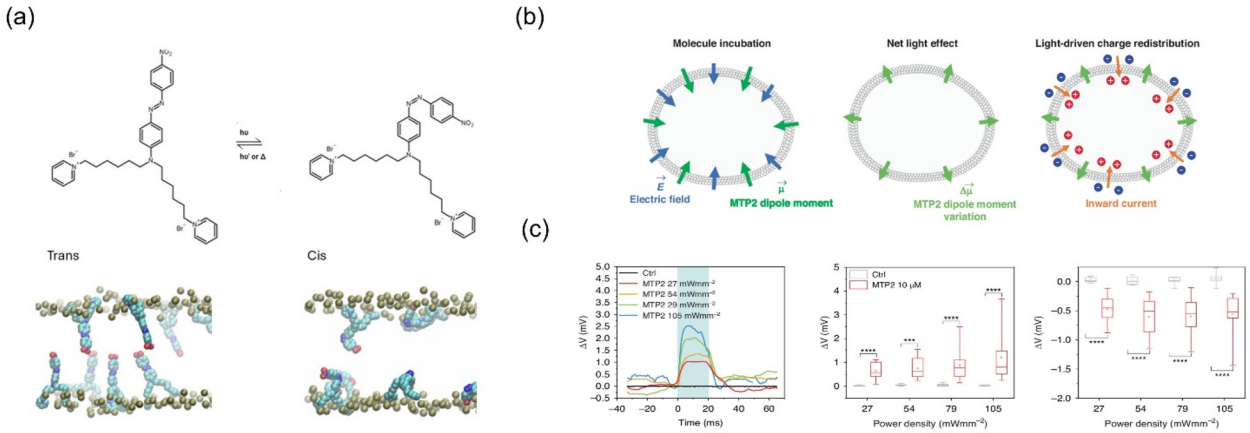

FIG. 5. Light-driven membrane potential modulation by MTP2. (a) MTP2 structure in trans-conformations and molecular dynamics simulation showing 8 molecules of MTP2 (trans and cis) embedded in the membrane (POPC lipid model); lipid phosphate atoms are shown as tan spheres; water molecules and acyl chains are not reported for clarity. (b) Sketch illustrating the MTP2 mechanism of light-driven membrane potential modulation in cells. The molecule is internalized within the membrane (left). When light is shined on the cells, an additional dipole moment appears (centre), which induces a redistribution of charges and an inward current across the membrane (right). (c) Representative whole-cell current clamp traces recorded from hiPSC-CMs after MTP2 incubation and quantification of ΔV_m *variation. The cyan shaded area indicates photoexcitation.* Reproduced with permission from Sesti *et al.*, Light Sci. Appl. **14**(1), 8 (2025). Copyright 2025, Springer Nature.

Nevertheless, modulating cardiac activity without inducing full depolarization is a promising strategy for managing arrhythmia and other cardiac dysfunctions, particularly under pathological conditions. Sub-threshold stimulation slightly alters the cardiac cell membrane potential without initiating firing. This modulation can still affect the propagation of electrical impulses and potentially prevent the initiation or maintenance of reentrant circuits that lead to arrhythmia.[62]

C. From bench to bedside: A roadmap toward clinical translation

The distinct mechanisms of membrane interaction and modulation enabled by Ziapin2 and MTP2 offer significant potential for precise, light-dependent control of cardiac cell biophysics. Ziapin2 can induce supra-threshold depolarizations and trigger action potentials, offering a promising approach for rhythm control. In contrast, the advantages of MTP2 lie in its improved water solubility, greater chemical tunability due to its donor–acceptor architecture, and its ability to modulate membrane potential in a sub-threshold manner. This gentle "nudging" of excitability, without eliciting spontaneous electrical activity, could be particularly valuable for stabilizing conduction or preventing the onset of reentrant circuits. In this light, while Ziapin2 may serve as a robust tool for active modulation, MTP2 offers a refined, noninvasive, and energy-efficient strategy for the precise control of cardiac excitability.

The path toward the clinical application of these compounds remains challenging. Major issues to be addressed include: (i) *in vivo* delivery, encompassing specific targeting and tissue penetration; (ii) the fate of the compounds post-injection; and (iii) deep-organ stimulation, particularly considering the limited penetration of light. Although these are formidable challenges, the roadmap to address them is well defined.

The strategy involves a clear progression from basic research to increasingly complex, clinically relevant models. Initially, it is essential to conduct whole-organ *ex vivo* studies, using preparations such as Langendorff-perfused hearts. This phase enables detailed characterization of compound distribution, threshold light requirements, and conduction modulation within intact cardiac structures. *Ex vivo* studies provide a crucial opportunity to evaluate the physiological relevance of the photoswitches in a controlled yet complex environment, offering critical insights into their behavior within cardiac tissues.

Following this, the next critical milestone involves *in vivo* proof-of-concept studies, typically conducted in small animal models such as mice or rats. In these studies, the photoswitches would be administered either systemically or locally, with the goal of elucidating key pharmacokinetic parameters, including biodistribution and acute functional effects on cardiac physiology. These studies also allow for the assessment of safety, feasibility of localized light-induced modulation, and initial indicators of therapeutic potential.

The final stage of this progression involves chronic studies in larger animal models, such as pigs or larger rodents. Here, the focus shifts toward assessing the long-term effects of repeated dosing and optical stimulation. Critical factors to evaluate include compound persistence within cardiac tissues, potential immune responses, and the effects of prolonged optical stimulation on cardiac function. Understanding these aspects is essential for defining the therapeutic window and for advancing the photoswitches toward clinical use as safe and sustainable rhythm control therapies.

To pursue these goals, several aspects may be considered. First, it may be beneficial to develop photoactuators that operate in the near-infrared (NIR) region. Indeed, both Ziapin2 and MTP2 are excited at 470 nm, a wavelength within the visible spectrum that suffers from limited tissue penetration. Engineering the photoswitches with extended conjugated systems or donor–acceptor architectures to red shift their absorption spectra might represent a promising alternative, potentially enabling noninvasive stimulation of deeper regions of the myocardium.

Another crucial aspect is the targeted delivery of photoactive molecules to the heart. For systemic applications, integrating photoswitches with targeting moieties (such as aptamers or peptide ligands selective for cardiac receptors) could reduce nonspecific uptake and ensure precise molecular delivery. This strategy would enhance the therapeutic potential of these molecules while limiting off-target interactions.

In parallel, optimizing the residence time of these molecules within the membrane is equally essential. Studies in cardiac cultures have demonstrated efficacy for up to a week post-administration, yet systemic clearance, membrane retention, and biodegradation are likely to vary *in vivo*, thus further improvements in stability are needed. Functionalization strategies (e.g., incorporating longer alkyl chains, cholesterol-like motifs, or lipid anchors) could enhance membrane association and prolong activity. However, any modification must be rigorously tested to ensure these modifications do not alter the intended mechanism of action of the molecules. Fluorescent labeled analogs might be used to track distribution and retention over time, alongside time-course functional assays to evaluate functional effects after a single administration. Furthermore, stability might be monitored through analytical techniques like HPLC and mass spectrometry to track the compounds' chemical integrity in biological fluids and tissues.

The frequency of reapplication will depend on both the molecular half-life and the desired duration of modulation. Ideally, formulations could be developed to allow for slow release, such as depot injections, liposomal encapsulation, or cardiac patches, to extend the therapeutic window. Structural optimizations, like incorporating lipid anchors or PEGylated side chains, could further enhance membrane binding, prolong residence time, and maintain reversibility of function.

Moreover, an effective translational pathway, advancing light delivery strategies, is essential for achieving clinically viable applications. Even if NIR wavelengths offer advantages such as superior tissue penetration, reduced scattering, and lower energy absorption, making them ideal for deep tissue stimulation, the challenge lies in designing devices that ensure precise spatial control while minimizing off-target effects and potential phototoxicity.[63,64] Despite technological progress developed for optogenetic strategies, further innovation is required to achieve minimally invasive, efficient, and precise light-based devices. Minimally invasive approaches, such as catheter-based optical fibers, represent a promising solution. Additionally, emerging technologies, including wireless photonic implants and transcutaneous NIR systems with optimized focusing optics, could further enhance clinical feasibility by enabling non-surgical light modulation of cardiac function.[65–67]

Finally, biocompatibility remains a cornerstone of any clinical application. Current evidence indicates that both Ziapin2 and MTP2 exhibit a favorable biocompatibility profile, with no significant cytotoxicity or adverse effects observed following incubation or repeated

stimulation.[49,50,53,54,57,59] However, progressing toward *in vivo* and clinical applications requires to proactively focus on long-term safety and systemic delivery.

To this end, several improvements can be envisioned. As previously mentioned, strategies to enhance cardiac targeting (e.g., via conjugation with receptor-specific ligands) may increase membrane residency time while preventing uncontrolled accumulation. Alongside this, improving molecular stability could limit degradation and off-target effects. Although these molecules are currently activated by visible light (470 nm), the development of red-shifted analogs responsive to NIR wavelengths could improve tissue penetration and minimize the risk of phototoxicity.

Encapsulation in biocompatible delivery systems, such as liposomes or hydrogels, along with surface modification, may further reduce immune interactions while maintaining functional efficacy. These improvements, while not strictly necessary at this stage, would be highly beneficial for safe and efficient systemic administration in future clinical contexts.

Simultaneously, light-stimulation devices must be designed with inert or bioinspired materials that minimize immune responses and ensure long-term stability.[68,69] Encapsulation strategies are crucial to prevent degradation and maintain functionality over extended periods, reducing the need for frequent replacements or recalibration.[70] Innovations in durable light-emitting components, protective coatings, and stabilization techniques for photoactive molecules will play a fundamental role in making these approaches clinically viable.

II. CONCLUSIONS

This perspective highlights emerging photostimulation strategies based on non-covalent, membrane-targeted photoswitches as promising tools for cardiac control, with potential translational relevance in arrhythmia management.

Although still at the proof-of-concept stage, this approach holds considerable promise. With further optimization in terms of phototransducers efficiency and light delivery, membrane-targeted photochromic compounds could pave the way for an emerging class of light-based therapies. Their ability to modulate cardiac bioelectricity with high spatial and temporal precision positions them as promising candidates for noninvasive arrhythmia management, reducing reliance on traditional interventions and their associated side effects.

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AUTHOR DECLARATIONS

Conflict of Interest

G.L. and F.L. are inventors of "PHOTOCHROMIC COMPOUNDS" Patent No. EP 3802491 (02/07/2020).

Author Contributions

Chiara Florindi: Conceptualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Giulia Simoncini:** Writing – original draft (equal); Writing – review & editing (equal). **Guglielmo Lanzani:** Conceptualization (equal); Funding acquisition (equal); Writing – review & editing (equal). **Francesco Lodola:** Conceptualization (equal); Funding acquisition (equal); Supervision (equal); Writing – original draft (lead); Writing – review & editing (equal).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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