

# See the light: can optogenetics restore healthy heartbeats? And, if it can, is it really worth the effort?

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Cardiac optogenetics is an exciting new methodology in which light-sensitive ion channels are expressed in heart tissue to enable optical control of bioelectricity. This technology has the potential to open new avenues for safely and effectively treating rhythm disorders in the heart with gentle beams of light. Recently, we developed a comprehensive framework for modeling cardiac optogenetics. Simulations conducted in this platform will provide insights to guide *in vitro* investigation and steer the development of therapeutic applications – these are the first steps toward clinical translation. In this editorial, we review literature relevant to light-sensitive protein delivery and intracardiac illumination to provide a holistic feasibility assessment for optogenetics-based arrhythmia termination therapy. We then draw on examples from computational work to show that the optical control paradigm has undeniable advantages that cannot be attained with conventional electrotherapy. Hence, we argue that cardiac optogenetics is more than a flashy substitute for current approaches.

In the past 3 years, cardiac optogenetics has emerged as an exciting alternative to conventional electrical stimulation of heart tissue [1]. Experiments in cardiomyocytes, cell monolayers and transgenic animals have shown that cardiac expression of light-sensitive proteins (opsins) enables the induction of spatiotemporally precise bioelectric responses with light [2–4], but the feasibility of translating these strategies to clinical applications remains untested. To help overcome barriers to understanding cardiac optical control and to narrow the scope of *in vitro* investigations, we recently developed a comprehensive, biophysically detailed framework for simulating optogenetics in multiscale models of the heart [5]. Preliminary experiments in this virtual platform suggest that light-based treatments could yield novel, low-energy optogenetics-based approaches to managing cardiac arrhythmias; however, two important questions remain unanswered. First, can the heart be genetically modified to express opsins in a

safe and reliable way that leads to reasonably long-term expression? Second, can illumination (with appropriate wavelength and intensity) be delivered to a critical mass of heart tissue to elicit the desired therapeutic response? In our view, the response to both questions is ‘yes’ but there are several important challenges.

While light-sensitive protein insertion into the intact adult heart has not been reported yet, opsin delivery to cardiac tissue has been demonstrated *in vitro* (including adult cardiomyocytes) using both gene therapy (via viral infection of cardiomyocytes) [2,6] and cell therapy (coupling opsin-rich donor cells to normal myocytes) [3]. Clinical trials have demonstrated the feasibility of intracoronary injections for safe, reliable and long-term gene transduction [7] or stem cell engraftment in the heart [8]. Similar strategies could be applied to inscribe light sensitivity in the human heart by either gene or cell delivery of opsins. Experiments in transgenic mice [4]

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suggest that human hearts modified in this manner will be light-responsive. Since targeting different cardiac cell types can yield very different light responsiveness [5,6], and since donor cell distributions [9] and patterns of transgene expression [10] evolve over time and can be spatially heterogeneous, opsin delivery vehicles and intracoronary injection techniques need to be calibrated to ensure suitable optical control. As evidenced by insights gleaned from our initial studies [5,6], experimental challenges such as the above-described issue can be examined non-invasively using realistic simulations based on our framework.

Compared with the opsin delivery problem, to which informed solutions could be derived from ongoing cardiac gene and cell therapy experiments, developing effective, site-specific illumination strategies presents an even bigger challenge. Shining focused beams of light on photosensitized cardiac tissue is not intrinsically difficult [5]; existing clinical tools could be adapted to enable direct illumination of a small region of cells surrounding the tip of a catheter containing a bundle of optical fibers (an 'optrode'). However, this approach is severely constrained by the fact that visible light is subject to significant attenuation in the intracardiac environment due to energy absorption and photon scattering by opaque blood and tissue [11]; penetration depth (i.e., the spatial decay constant for brightness) is wavelength-dependent, ranging from <0.5 mm for near-ultraviolet to approximately 1.5 mm for near-infrared. This is particularly problematic for channelrhodopsin-2 (ChR2), currently the most commonly used opsin, which requires application of blue light that penetrates poorly (decay constant of 0.57 mm) [12].

Thus, we surmise that optogenetic control of the heart will be feasible in the near future for simple configurations with minimal modifications to existing tools (e.g., optical pacing from a single site with an optrode pressed against the ChR2-expressing epicardium or endocardium); our assertion is supported by experiments in transgenic animals [4] and simulations conducted using our virtual optogenetics framework [5]. This focal stimulation paradigm could be used to design highly effective light-based pacemakers, but it would not be effective for therapies that rely critically on simultaneous excitation of large volumes of cardiac tissue, such as cardioversion and defibrillation.

Recent innovations in optical devices and molecular biology may offer relevant solutions by enabling deeper-penetrating, spatially distributed optical stimulation appropriate for anti-arrhythmia therapy. For example, thin film deposition allows the manufacturing of interconnected arrays of inorganic light-emitting diodes in ultra-thin plastic sheets that are flexible, stretchable and biocompatible [13]; conceivably, similar sheets could be implanted in conjunction with ChR2-transduction and used to elicit simultaneous excitation from an entire region or cardiac surface, such as the endocardium. Alternatively, the illumination problem can be tackled by molecular optimization of the opsin itself. Lin *et al.* [14] recently reported the development of a ChR2 variant with dramatically increased peak photocurrent (2–5x larger than the commonly used ChR2-H134R

variant) and peak sensitivity to illumination by longer-wavelength red light, which has a penetration depth approximately 2x that of blue light. This development is highly relevant to cardiac optogenetics, since it effectively allows optical stimulation to 'reach' cells twice as deep in opaque tissue (hence the new opsin's name – 'ReaChR'). Importantly, as technologies such as these continue to emerge, our framework for modeling cardiac optogenetics has the flexibility to allow 'plug-and-play' incorporation of new opsins and illumination methodologies as soon as they are described. As such, detailed simulations can serve as a first-line screening tool for conceiving and evaluating potential light-based treatments as new components are added to the cardiac optogenetics toolbox.

Thus far, we have established that there are indeed feasible ways in which healthy heartbeats could be restored with light; however, feasibility is not the only barrier to clinical translation of optogenetics-based therapies for cardiac arrhythmia. Although conventional electrotherapy devices are hardly perfect, they are part of a status quo for anti-arrhythmia treatment that will be difficult to disrupt due to widespread usage and well-defined patient eligibility guidelines [15]. In addition to this incumbency issue, there is a high threshold for clinical acceptance of any gene therapy approach (a baseline requirement of cardiac optogenetics) unless it has clear-cut advantages that cannot be achieved otherwise. To be of clinical relevance, these methods must offer dramatic improvements compared with existing techniques. Here, we identify two benefits of optogenetics that do not exist for electrical stimulation and discuss how they might be leveraged to design novel light-based therapies.

The first potentially paradigm-shifting advantage stems from an issue cited above as a shortcoming – namely, the need for genetic tissue modification. This aspect of optogenetics is in effect a 'double-edged sword' because opsin delivery vectors can be customized to selectively target specific cardiac cell or tissue types, as has been demonstrated in neuroscience [16]. As such, it should be possible to cast light on an entire region of the heart but only elicit a response in a desired subpopulation of illuminated cells; this level of selectivity cannot be achieved in conventional electrotherapy, which is a limiting factor for some types of pacemaking. For example, site-specific direct His-bundle pacing was recently used to restore synchronous contraction and improve cardiac function in heart failure patients who were non-responsive to conventional resynchronization therapy [17]; however, dangerous beat-to-beat changes in activation sequence were frequently observed when the electrical stimulus excited the ventricular septum instead of purely the His bundle. This problem could be resolved by developing a gene therapy with high affinity for the cardiac conduction system, which would enable reliable His bundle capture from a single optrode. Moreover, preliminary simulations suggested that optogenetics-based direct His-bundle pacing would have relatively low energy requirements [5].

Another major advantage of cardiac optogenetics is that it broadens the range of possible actuation schemes for

manipulating bioelectric behavior in excitable tissue. Conventional stimuli are limited in duration and amplitude due to the risk of toxicity from Faradaic reactions at the electrode-tissue interface [18]. This concern does not apply to optogenetics because, instead of directly polarizing the cell membrane, light stimuli perturb the membrane potential by triggering self-terminating currents [1]. This enables the use of long-duration stimulating pulses, which could be useful for anti-arrhythmic treatments. As an initial proof-of-concept, we simulated ChR2 delivery (uniform distribution) to an image-based atrial model from a patient with persistent atrial fibrillation (AF) [19]; we found that application of a single long (100 ms), low-energy (1 mW/mm<sup>2</sup>) light pulse to the endocardium terminated AF [BOYLE PM *ET AL.*, UNPUBLISHED DATA]. Since it involves selective stimulation of only the endocardium, this type of AF treatment could offer a dramatic improvement compared with the existing standard of electric cardioversion shocks, which can eliminate arrhythmias but cause intense pain due to skeletal muscle excitation [20]. Needless to say, many more detailed experiments are needed before the feasibility of light-based cardioversion can be fully confirmed; nonetheless, we consider this an exciting preliminary result, since it shows that long-lasting optical stimuli, which are impossible by conventional means, could enable

disruptive technologies, such as light-based AF termination, in the not-so-distant future.

In conclusion, we are confident that the future is bright for the prospects of optogenetics-based treatments to restore healthy heartbeats. Moreover, we believe that light-based therapies will offer significant improvements compared with conventional methods. Finally, we posit that simulations will accelerate the development of successful optogenetics-based strategies by providing a realistic, non-invasive platform for assessing the vast gamut of possible opsin delivery and illumination combinations.

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