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## Optogenetics' promise: pacing and cardioversion by light?

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## Electronic device therapy: the current gold standard in cardiac arrhythmia management

Electronic device therapy (i.e., implantable pacemakers and cardioverter–defibrillators [ICDs]) is currently the gold standard in the management of cardiac arrhythmias. According to the most recent survey by the World Society of Arrhythmias, over 1 million pacemakers and 300,000 ICDs were implanted in 61 countries worldwide in 2009 [1]. All countries surveyed showed significant increases in implantation rates since 2005, and the global market for cardiac rhythm management devices is expected to reach US\$15.2 billion by 2017.

Cardiac pacemakers and ICDs are relatively safe and reliable, as evidenced by significant decreases in device malfunction rates since the early 1980s. However, limited battery life requires device replacements (with potential surgical complications) every 4–7 years [2]. Another major drawback of ICDs, in particular, is the pain associated with the high-energy shocks required to terminate tachyarrhythmias. The discomfort is caused by the shocks' nonspecific effects; for example, unintended contractions of noncardiac tissue (chest muscles, diaphragm and vocal cords). As a result, ICD recipients tend to have higher incidences of anxiety and depression than the general population [3]. An approach to pacing and cardioversion that is more cardiac tissue-specific and requires lower energy will reduce, or completely eliminate, the need for reimplantations (due to battery life) and reduce the pain and anxiety in ICD recipients. The nascent field of optogenetics may provide such opportunities for restoring normal heart rhythm painlessly, and subsequently increase quality of life for device recipients.

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## Optogenetics' promise: the use of light for precise control of cellular function

Optogenetics is a new field of research using light to stimulate mammalian cells and tissues after genetic modification with microbial opsins (light-gated ion channels and pumps) [4]. It offers means for optical interrogation and control of biological function superior to traditional electrical and chemical stimulation; advantages include:

- Targeted cellular control via promoter- and/or site-specified opsin expression;
- High spatiotemporal resolution;
- Versatility (i.e., excitatory and inhibitory effects can be encoded within the same cell for bidirectional control of membrane excitability);
- The ability to stimulate with longer (low-light) pulses.

Since 2005, optogenetic approaches have been widely used in neuroscience to dissect neural circuitry and gain insight into brain function in health and disease [5]. As an optical interrogation tool for basic science, optogenetics is very likely to have a profound impact on cardiac research (cardiac electrophysiology, arrhythmias, cell signaling and drug discovery) [6]. More recently, the use of optogenetics in experimental therapeutic control of brain activity, beyond basic research, shows promise and relevance to cardiac applications.

## Lessons from optical control of abnormal electrical activity in the brain

Epileptic seizures and Parkinson's disease bear similarities to cardiac arrhythmias in that they are associated with aberrant electrical activity in regions of the brain. Current treatment options include deep-brain stimulation, a US FDA-approved electronic device therapy for the treatment of Parkinson's since 1997, which aims to alleviate symptoms by stimulating or electrically resetting specific regions with abnormal excitation. Recently, an optogenetics version of deep-brain stimulation has been explored as a means of optical stimulation of neural regions with more direct, cell-specific and effective perturbation, evoking the desired response (i.e., reduction or complete elimination of symptoms), while limiting undesired side effects seen in 'blind', nonselective electrical stimulation [7]. Studies have also shown promise for closed-loop control of epileptic seizures by targeted on-demand optogenetic intervention in rodents [8]. Such cell-specific treatment strategies can spare cortical function and limit side effects not attainable by currently available electronic, pharmacological and surgical options. Parallels in antiarrhythmic therapy can be envisioned for the heart – eliminating noncardiac effects in an optical version of an ICD and/or lowering energies by specific targeting of opsin expression to certain cardiac cell types for optimal pacemaking.

## Cardiac optogenetics for pacing & cardioversion: translational challenges

The expansion of optogenetics to the cardiac field by our group and others is in very early stages [6,9–14]. It has, however, been demonstrated that the same opsins used in neuroscience can facilitate the optical stimulation of cardiac cells and tissues without negative electrophysiological effects and without the addition of exogenous cofactors at relatively low-light levels. If optogenetics can offer superior solutions to cardiac pacing and

defibrillation, it is important to understand the potential hurdles to its translation as a clinical cardiac antiarrhythmia therapy.

As optogenetics requires the genetic modification of tissue prior to optical stimulation, the safety and long-term efficiency of the delivery vehicle(s) must be addressed. Light sensitivity can be inscribed in cardiac cells or regions by either direct viral gene delivery or by cell delivery (opsin-carrying donor cells that couple to native myocytes). For both of these approaches, there is evidence for feasibility and potential success when applied to the heart based on ongoing clinical trials with other genes of interest [15–17].

In addition to a transgenic animal approach [11,12] to cardiac optogenetics, direct viral delivery and functionality of opsins in cardiomyocytes has been demonstrated *in vitro* [13,18], including in adult cardiomyocytes [14]. Transduced heart cells maintain normal electrophysiology and respond to light pulses at low-light levels (0.1–5 mW/mm<sup>2</sup>). Recent clinical uses of gene therapy are focusing on adeno-associated viruses (AAVs) owing to certain advantages over other viral vectors, such as adenoviral and lentiviral, including lower mutagenicity, differential tissue tropism from 12 currently characterized serotypes, transduction of nondividing cells and long-term expression profiles [19]. Cardiac studies have reported long-term transgene expression, although the success of expression is intimately linked to viral dosing in order to achieve maximal transgene expression with minimal immune responses. Pre-existing immunity to specific AAV serotypes, however, can compromise transgene delivery; for instance, 72% of the worldwide population has neutralizing antibodies for AAV serotype 2 [20]. The development of ‘designer’ AAV proteins with both enhanced tissue specificity and expression profiles may increase the feasibility of this approach in the larger population [20]. Cardiac clinical trials are ongoing, testing the efficacy of delivering SERCA2a, a Ca<sup>2+</sup> ATPase, to the heart to reduce heart failure-related hospitalizations using AAV serotype 1 as a delivery vehicle (CUPID trial) [15]. In addition to efficacy, this study demonstrated safety – no reported adverse effects due to the administration of AAV1–SERCA2a. Therefore, AAV-mediated delivery of other transgenes, including opsins, to the heart may be a viable translational strategy.

Feasibility for a potentially safer, nonviral cell-delivery approach to optogenetics was demonstrated in our recent *in vitro* study using a cell line stably expressing the excitatory opsin, ChR2, and relying on low-resistance cell coupling between the ChR2-expressing donor cells and host cardiomyocytes [10], requiring low energies (<0.5 mW/mm<sup>2</sup>). An *in vivo* strategy would involve autologous sources of somatic cells, such as fibroblasts or stem cells, optimized as opsin delivery vehicles, to mitigate immune responses. Although there is currently no FDA-approved somatic gene therapy, there are several ongoing clinical trials for cell delivery to the heart (e.g., SCIPIO [16] and CADUCEUS [17]). In all cases, for optogenetic applications, long-term studies must be undertaken to monitor the persistence of transgene (i.e., opsin) expression within the myocardium.

Other outstanding challenges to the translation of cardiac optogenetics *in vivo* concern light delivery and optimization of the employed opsins. The ‘optogenetics toolbox’ includes a rapidly growing compendium of mutant opsins for either excitation or inhibition of electrical activity that exhibit application-optimized kinetics and red-shifted spectral responses [21].

Red-shifted opsins are of particular interest in cardiac applications as the dense nature of the cardiac syncytium does not allow for deep penetration of shorter wavelengths of light and clinical optogenetic applications may be hampered by the selective sensitivity of ChR2 to blue light or other short-wavelength excitation spectra. Consequently, these alternative opsins [21], involving not only red-shifted light sensitivity, but also enhanced photocurrents, may allow for the engagement of deeper myocardial structures.

Solutions to limited light penetration in the heart and the need for localized targeting will likely be sought through endoscopic routes using fiber optics. Computational optogenetics studies can provide proof-of-principle guidance and optimization to these challenges [9,14]. For example, energy for optical pacing can be reduced by cell-specific opsin expression and localized light delivery to the conduction system structures (e.g., Purkinje and His bundle) [9,14]. Cardioversion, however, unlike pacing, requires spatially distributed targeting in most cases and thus suitable light delivery. Nevertheless, the availability of both excitatory and inhibitory opsins and the ability to employ long pulses may provide new opportunities for control at lower energies. Furthermore, the miniaturization of optoelectronics, specifically light-emitting diodes, may offer fully integrated and possibly multisite actuation within the cardiac tissue itself, without the need to thread fiber optic illumination leads through the vasculature [22].

## Future perspective

In summary, we believe that optogenetics can be used to restore healthy heartbeats in patient populations requiring implantable devices. If energy benefits of optical control over conventional electronic devices are confirmed, it will present an attractive option in cardiac rhythm management as a strategy addressing battery life and pain reduction. *In vivo* testing of safety, efficacy and overall functionality in cardiac tissues are necessary, but if the hurdles discussed here can be surmounted, light-based antiarrhythmic therapies have the potential to offer significant improvements over traditional electronic device therapy.

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