future medicine part of fsg

The light-hearted approach: 'optogenics', an emerging field with potential applications in interventional cardiology

An innovative study undertaken by Emilia Entcheva and colleagues at Stony Brook University in New York (NY, USA) has utilized the emerging field of 'optogenics' to explore the potential applications of this technology which could, in the future, lead to light-controlled pacemakers. Their new technique for remotely stimulating heart muscle cells with low energy light using a nonviral technique and a patient's own cells could potentially remedy many of the issues presently faced by current pacing mechanisms.

'Optogenics' involves the introduction of light-sensitive protein into 'excitable' cells, which can then generate electrical signals in a controlled fashion, in response to light. Highlighted by *Science* as a 'breakthrough of the decade' in 2010, a plethora of laboratories began using optogenic systems to study biological processes following the production of a single-component system suitable for use in mammals in 2005.

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The potentially developable light-based pacemaker would have many benefits; allowing remote access, the use of biocompatible optic fibers, as opposed to the currently used metal leads, alleviating issues with interference from magnetic fields and using a tenth of the energy of a conventional pacemaker. Theoretically, a pacemaker could then last 50 years instead of the current 5-year lifespan. An optogenic system would also allow for increased accuracy. "Eventually, optical stimulation may overcome some of these problems and offer a new way of controlling heart function," commented Entcheva.

Optical stimulation also has potential in heart research and drug testing. "Optical stimulation is a great tool to selectively probe and control different parts of the electrical circuitry of the heart, to better understand where the vulnerable sites are or what gives rise to lethal arrhythmias," explained Entcheva.

In this study, researchers used a tandem cell unit strategy to couple cells carrying channelrhodopsin-2, exogenous light-sensitive ion channels, to cardiomyocytes from canines and neonatal rats. This produced optically excitable heart tissue, which was used to trigger light-controlled muscle contractions. The resultant light-triggered electrical waves were quantitatively indistinguishable from electrically-triggered waves.

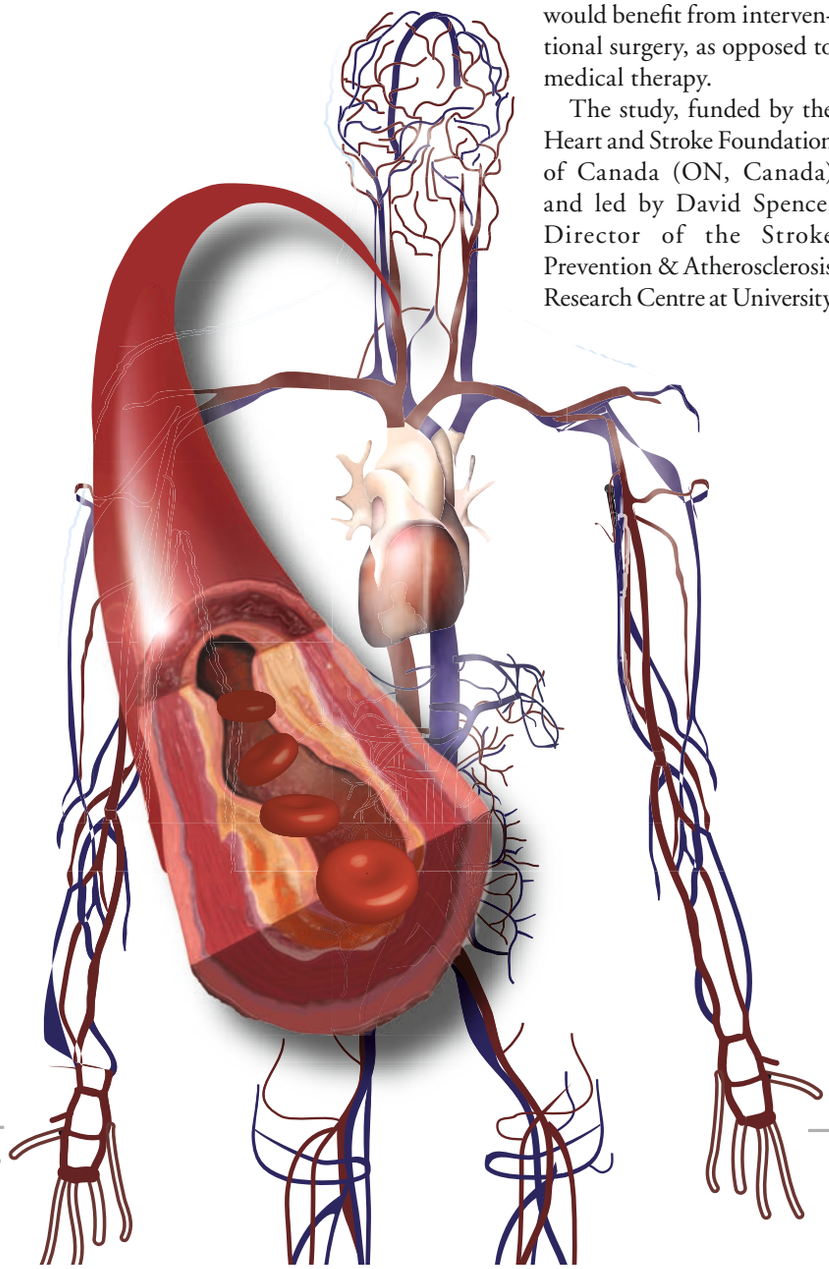
Another benefit of this technique is that it can utilise a person's own cells, reducing the possibility of rejection by the immune system. Entcheva added, "our method of nonviral cell delivery may overcome some hurdles toward potential clinical use by harvesting cells from the patient, making them light-responsive and using them as donor cells in the same patient."

Source: Jia Z, Valiunas V, Lu Z et al. *Stimulating cardiac muscle by light: cardiac optogenetics by cell delivery.* Circ. Arrhythm. Electrophysiol. *DOI: 10.1161/CIRCEP.111.964247 (2011) (Epub ahead of print).*

3D ultrasound proves an effective technique to identify asymptomatic carotid stenosis patients with high-stroke risk who would benefit from intervention

The recent conclusion of a 3-year study performed at the University of Western Ontario (ON, Canada), has demonstrated that the use of 3D ultrasound to pinpoint ulcers in the carotid arteries allows the more accurate identification of high-risk patients suffering with asymptomatic carotid stenosis, who would benefit from interventional surgery, as opposed to medical therapy.

The study, funded by the Heart and Stroke Foundation of Canada (ON, Canada) and led by David Spence, Director of the Stroke Prevention & Atherosclerosis Research Centre at University Hospital, London Health Sciences Centre (ON, Canada), found that the presence of three or more ulcers within the carotid arteries indicated that the patient had a high risk of stroke and would benefit from intervention. The ultrasound technique is comparable to the transcranial Doppler, which detects incidences of microemboli breaking off from plaques and entering the bloodstream and has been used to assess stroke risk. "Now we've developed two ways to identify the few who could benefit from surgery or stenting," commented Spence.



The team assessed patients with asymptomatic carotid stenosis and carotid stenosis of greater than 60% using both the Doppler and 3D ultrasound methods to detect ulcers and microemboli and followed them for 3 years. Of the assessed patients, 4% had three or more ulcers, 6% had microemboli and 10% had both. All patients harboring microemboli or ulcers carried an increased stroke risk. Using 3D ultrasound for detection doubled the proportion of patients who would benefit from endarterectomy or stenting.

> "...thanks to this effort, we are that much closer to providing ways to improve system care for stroke patients."

Manuel Arango, Director from the Heart and Stroke Foundation of Canada commented on the study, "thanks to this effort, we are that much closer to providing ways to improve system care for stroke patients."

Source: Madani A, Beletsky V, Tamayo A, Munoz C, Spence JD. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound vs TCD microemboli. Neurology *77(8), 744–750 (2011).*

Selective use of drug-eluting stents has huge financial benefit yet little clinical effect: evidence from the EVENT registry

A team of scientists from the Saint Luke's Mid America Heart Institute (MO, USA) using data from the US-based Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry have recently demonstrated that the decline in the use of drug-eluting stents (DES) since 2004–2006 has not resulted in a change in risk of death or heart attack for patients, and has only slightly increased the need for target lesion revascularization.

It is estimated that the selective use of DES is saving the US healthcare system an average of US$401 per patient – this is approximately $400 million a year.

David J Cohen, senior author of the study noted the following: "the bottom-line was that using drug-eluting stents in a relatively unselected way was only resulting in marginal improvement compared with more selective use." The 1-year study analyzed data from the EVENT registry, which comprised of 10,144 patients affected by the decline in DES use. They found only a 1% rise in the need for repeat angioplasty procedures and no significant change in risk of death or heart attack.

> "Other studies are currently underway, which aim to allow the easy identification of patients who would benefit from the use of DES..."

The use of DES has declined since 2007 due to reports from the previous year, in 2006, that their use resulted in a higher risk of clotting, heart attack and death. The use of DES subsequently decreased from 92% in the period ranging from 2004–2006 to 68% in 2007. The EVENT registry study not only highlights the negligible effect of DES in many patients, but also that previous fears were unfounded.

Other studies are currently underway, which aim to allow the easy identification of patients who would benefit from the use of DES and Cohen hopes that policy makers will appreciate that increased selectivity when using DES will have little effect on clinical outcome, whilst having a large effect on US healthcare costs. Cohen believes that, "there are ways that we can enhance this treatment pattern through healthcare policies, professional guidelines or appropriate use criteria."

Source: Venkitachalam L, Lei Y, Stolker JM et al. *Clinical and economic outcomes of liberal versus selective drug-eluting stent use: insights from temporal analysis of the multicenter EVENT Registry.* Circulation *DOI: 10.1161/CIRCULATIONAHA.110.978593 (2011) (Epub ahead of print).*

A nanoscale VEGF mimic indicates a potential strategy for blood vessel growth and ischemic tissue repair

A team of researchers from Northwestern University (IL, USA) have recently developed a novel nanostructure that has the potential to help restore blood flow after myocardial infarction and repair ischemic tissue. The synthetic structure mimics VEGF, a catalyst for the stream of events that can lead to angiogenesis.

The nanostructures self-assemble to take the form of fibers, carrying a high density of VEGF-mimetic peptides on their surface. This structure allows the nanofiber to act as a potent and stable therapeutic, unlike natural VEGF, which has a short half-life and requires repeat dosing. The structure is designed to induce phosphorylation of VEGF receptors, promoting angiogenic behavior in endothelial cells.

The effectiveness of the nanostructure was demonstrated in an animal model of peripheral arterial disease, where blood flow to the limbs had been constricted to between 5 and 10% of normal. Treatment with the nanofiber restored blood flow to between 75 and 80% of normal levels, whilst treatment with the peptides alone had no effect. Immunohistological evidence supported the theory that the therapeutic enhanced microcirculatory angiogenesis in the limb.

> "Our nanostructure shows the promise of a general approach to mimicking proteins for broader use in medicine and biotechnology."

Douglas Losordo, from Northwestern's Feinberg Cardiovascular Research Institute (IL, USA), commented that, "one of the major challenges in the field of ischemic tissue repair is sustained delivery of therapeutic agents to target tissue." The ability of the nanostructure to remain in the tissue for an extended period of time, combined with its ease of use and its relative lack of expense when compared with

using natural VEGF, gives it the potential to be an ideal cell-free therapeutic for the treatment of ischemic cardiovascular disease. The team intend their next step to involve investigating the use of the nanostructure in an animal model of heart attack.

"An important goal in regenerative medicine is the ability to grow blood vessels on demand," comments Samuel Stupp, leader of the study. "Our nanostructure shows the promise of a general approach to mimicking proteins for broader use in medicine and biotechnology."

Source: Webber MJ, Tongers J, Newcomb CJ et al. *Supramolecular nanostructures that mimic VEGF as a strategy for ischemic tissue repair. Proceedings of:* The National Academy of Sciences *DOI: 10.1073/pnas.1016546108 (2011) (Epub ahead of print).*

ABSORB EXTEND trial of Abbot's bioresorbable stent begins in Japan

The first patient has been treated using the Abbot ABSORB™ bioresorbable vascular scaffold (BVS) as the global ABSORB EXTEND clinical trial begins in Japan. The two-stage ABSORB trial aims to evaluate the BVS for the treatment of coronary artery disease.

Bioresorbable vascular scaffold technology is expected to become a new therapy option for the treatment of coronary artery disease (CAD). Shigeru Saito, who treated the Japanese patient at Shonan Kamakura Hospital (Kanagawa, Japan), commented that "for Japanese patients, this technology will hold tremendous appeal, as it is designed to treat a clogged blood vessel like a drug-eluting stent and then dissolve, thereby restoring a more natural vessel function without leaving a permanent metallic implant behind in the body." Abbot's BVS is made from the biocompatible material polylactide, which is commonly used in other dissolving medical implants, such as sutures. It is hoped that treatment of vessels with BVS will restore their natural ability to flex, pulsate and dilate. The drug-eluting device aims to open clogged vessels, providing support until it dissolves after approximately 2 years. It elutes an antiproliferative drug that inhibits neointimal growth at the treated site.

The device has received CE Mark approval in the EU for the treatment of CAD and is under clinical investigation in several countries. In total the ABSORB EXTEND trial will include approximately 1000 patients suffering from complex CAD worldwide. The trial aims to assess the safety of the device with regards to major adverse cardiac events (MACE) and treated-site thrombosis rates, following patients at regular intervals for 3 years. It also aims to assess the performance of the BVS. The first stage of the clinical trial, which included 30 patients who were followed for up to 5 years, is reported to have been successful. It is stated that patients were successfully treated for CAD and experienced no thromboses, MACE or cardiac deaths during the subsequent period of follow-up. The second stage, which enrolled 101 patients, saw a 6.9% rate of MACE and no reports of thromboses during the 12-month follow-up period.

"...the global ABSORB EXTEND trial is a significant milestone and an important contribution to evaluating this technology in patients..."

Robert Hance, senior vice president at Abbott (IL, USA) believes that "the enrollment of the first Japanese patient in the global ABSORB EXTEND trial is a significant milestone and an important contribution to evaluating this technology in patients with heart disease in Japan."

Source: Abbot press release: first patient in Japan treated with Abbott's bioresorbable vascular scaffold as part of global clinical trial: www.abbott.com/press-release/2011-august16.htm

Trial documenting high restenosis risk published: 1-year follow-up results from the abandoned TRI-stent Adjudication study

The 1-year follow-up results from the TRIAS HR trial have recently been published following the premature conclusion of the trial in 2009.

The TRIAS HR trial aimed to compare the novel Genous™ stent, which was designed to capture circulating endothelial progenitor cells in order to promote healing with a group of four first-generation drug-eluting stents (DES). The study performed by Robert J de Winter of the Academic Medical Center (Amsterdam, The Netherlands) was halted early due to disappointing results, yet has continued to follow the patients enrolled in the trial at its point of ending.

The 1-year follow-up demonstrated that target lesion failure was elevated in the patients who had received the Genous stent with stent thrombosis and target lesion revascularization (TLR) increased almost threefold when compared with the conventional DES. Sorin J Brener from Weill Cornell Medical College (NY, USA) suspects the reason for the failure was that "they probably did not quite get the right kind of anti-$CD34^+$ antibodies that were sufficient to attract progenitor cells from the blood stream." He also added that, "we need a better way to imbed the antibodies so that they are sufficiently exposed to the blood stream to attract those cells." de Winter expects that as the 5-year follow-up continues, there will be increased levels of thrombosis and TLR in the patients treated with conventional DES.

David E Kandzari of the Piedmont Heart Institute (GE, USA) notes that, "the DES arm of the study consisted mostly of paclitaxel-eluting stents and zotarolimus-eluting stents. There were very few second-generation stents." This may have large implications for the trial. "Recognizing that TLR largely drove the difference in the composite end points between the [treatment groups] in the trial, we would only expect now that with the commonly used second-generation stents that the difference between [Genous] and DES would be even greater."

> "...theoretically, the mechanism for this stent technology is attractive ... but much remains unknown, and to date, as demonstrated by these data and previous studies, it remains clinically unproven."

Kandzari concludes that "theoretically, the mechanism for this stent technology is attractive – capturing endothelial progenitor cells to promote more rapid and hopefully complete healing with a stent – but much remains unknown, and to date, as demonstrated by these data and previous studies, it remains clinically unproven."

Source: Klomp M, Beijk MA, Varma C et al. *1-year outcome of TRIAS HR (TRI-stent adjudication study–high risk of restenosis): a multicenter, randomized trial comparing genous endothelial progenitor cell capturing stents with drug-eluting stents.* J. Am. Coll. Cardiol. Intv. *4, 896–904 (2011).*