Researchers create first human heart cells that can be paced with light

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In a compact lab space at Stanford University, Oscar Abilez, MD, trains a microscope on a small collection of cells in a petri dish. A video recorder projects what the microscope sees on a nearby monitor. The cells in the dish pulse rhythmically, about once a second. The cells are cardiomyocytes, which drive the force-producing and pacemaker functions of the human heart. They are programmed to pulse. They will beat this way until they die.

Abilez holds up a finger as if to say, "Wait," and reaches for a small lever hidden behind the microscope. With the same finger, he flips the lever up. A pale, blue light floods the petri dish. Abilez flicks the light off and then on; first fast and then slow. Each time his finger goes up, the heart cells contract in concert with the light.

In a paper to be published Sept. 21 in the Biophysical Journal, lead author Abilez, a postdoctoral scholar and PhD candidate in bioengineering, and a multidisciplinary team from Stanford describe how they have for the first time engineered human heart cells that can be paced with light using a technology called optogenetics.

In the near term, say the researchers, the advance will provide new insight into heart function. In the long term, however, the development could lead to an era of novel, light-based pacemakers and genetically matched tissue patches that replace muscle damaged by a heart attack.

To create the light-responsive heart cells, the researchers first inserted

DNA encoding a light-sensitive protein called channelrhodopsin-2, or ChR2, into human embryonic stem cells. ChR2 controls the flow of electrically charged ions into the cell. For heart cells, the primary ion is sodium, which initiates an electrochemical cascade that causes the cell to contract. They then transformed the optogenetically engineered stem cells into cardiomyocytes unlike any others — those that respond to light.

Like the new heart cells, optogenetics is a product of Stanford. Bioengineer and psychiatrist Karl Deisseroth, MD, PhD, a co-author of the new study, has played a key role in the technology's development. It is an increasingly common research technique that allows researchers to fashion all manner of mammalian tissues that are responsive to light.

While Deisseroth has focused his research primarily on neurons in order to study neurological illnesses ranging from depression to schizophrenia, Abilez is the first to create optogenetic human heart cells.

The all-important protein for the experiment is ChR2, which is sensitive to a very specific wavelength of blue light and regulates tiny channels in the cell surface. When ChR2 is illuminated by the right wavelength of blue light, the channels open to allow an influx of electrically charged sodium into the cell, producing a contraction.

After creating the cells in a laboratory dish, Abilez next turned to Ellen Kuhl, PhD, the study's senior author and an associate professor of mechanical engineering, whose specialty is sophisticated computer modeling of the human body.

Using her algorithms, they tested their new cells in a computer simulation of the human heart, injecting the light-sensitive cells in various locations in the heart and shining a virtual blue light on them to observe how the injections affected contraction as it moved across the

heart.

"In a real heart, the pacemaking cells are on the top of the heart and the contraction radiates down and around the heart," Kuhl explained. "With these models we can demonstrate not only that pacing cells with light will work, but also where to best inject cells to produce the optimal contraction pattern."

The long-term goal is a new class of pacemakers. Today, surgically implanted electrical pacemakers and defibrillators are commonplace, regulating the pulses of millions of faulty hearts around the globe.

"But neither is without problems," said Abilez. "Pacemakers fail mechanically. The electrodes can cause tissue damage."

"Defibrillators, on the other hand," Kuhl said, "can produce tissue damage due to the large electrical impulses that are sometimes needed to restore the heart's normal rhythm."

The researchers foresee a day when bioengineers will use induced pluripotent stem cells fashioned from the recipient's own body, or similar cell types that can give rise to genetically matched replacement heart cells paced with light, circumventing the drawbacks of electrical pacemakers.

"We might, for instance, create a pacemaker that isn't in physical contact with the heart," said co-author Christopher Zarins, MD, professor emeritus of surgery and director of the lab where Abilez performed the experiments. "Instead of surgically implanting a device that has electrodes poking into the heart, we would inject these engineered light-sensitive cells into the faulty heart and pace them remotely with light, possibly even from outside of the heart."

The leads for such a light-based pacemaker might be placed outside the heart, but inside the pericardium — the protective sack surrounding the heart. Or, someday, the researchers say, there might be a pacemaker placed inside the heart chambers, as with traditional pacemakers, whose light can travel through the intervening blood to pace light-sensitive heart cells implanted inside.

"And, because the new heart cells are created from the host's own stem cells, they would be a perfect genetic match," Abilez added. "In principle, tissue rejection wouldn't be an issue."

"Much work and many technical hurdles remain before this research might lead to real-world application," said Zarins. "But, it may one day lead to more reliable, less invasive devices."

In the near term, however, the advance is promising on other fronts, said Abilez.

"Optogenetics will make it easier to study the heart. Not only can researchers turn cells on with light, but off as well," Abilez said.

Scientists might use these tools to induce disease-like abnormalities and arrhythmias in sample tissues in order to better understand how to fix them. There are likewise advantages inherent in pacing with light versus electricity.

"Heart researchers are often seeking to measure electric response in the heart," said Abilez, "but it takes quite a lot of electricity to stimulate the heart and the resulting electrical signal is relatively weak. This makes it hard to distinguish stimulus from response. It's like trying to hear a whisper in a crowded room." Pacing with light would eliminate that challenge.

Optogenetics could lead to advances beyond the heart, as well, the authors concluded in their study. It might lead to new insights for various neuronal, musculoskeletal, pancreatic and cardiac disorders, including depression, schizophrenia, cerebral palsy, paralysis, diabetes, pain syndromes and cardiac arrhythmias.

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