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Stanford research team builds tiny broken heart to study lethal ailment

A Stanford University research team has built a tiny broken heart to test new drugs, so sick children need not endure experimentation.

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SAN JOSE, Calif. — A Stanford University research team has built a tiny broken heart, with a beat as erratic as a crippled metronome.

This "disease in a dish" is being used to test new drugs, so sick children need not endure experimentation. And it lets scientists study illness at the cellular level, accelerating the pace of discovery.

Using skin cells from children who have a severe genetic heart defect, the scientists have generated heart cells that carry the identical error and so struggle to keep accurate time.

"What is wrong in these patients, we see in these cells," said Ricardo Dolmetsch, a neurobiologist at Stanford University School of Medicine and senior author of the study, published online Wednesday in the journal Nature.

The technique offers a more efficient and humane strategy for studying the lethal ailment, Timothy syndrome; someday, the approach may be used for other genetic diseases. Dolmetsch's lab is using a similar approach to grow human brain cells in their lab, to study autism. Other labs are building cell lines from patients with muscular dystrophy, Type 1 diabetes, Parkinson's disease, Huntington's disease and immune deficiencies.

"You can't go into the heart of a sick little boy or girl and take the cells out to study what's going on," said Dolmetsch. "And mice are not a good model, because their hearts are very different," thumping at a rate of 500 times a minute, he said.

The Stanford team has tried about 20 drugs on the new tissue in an effort to regulate rhythm. One particular agent seems to have promise.

The "hearts," mere round specks to the naked eye, float in petri dishes.

"They don't look like real hearts," Dolmetsch said. Without a microscope, "they're really tiny. But you can see something moving."

They are the result of the discovery, several years ago, that ordinary skin cells can be reprogrammed into embryoniclike cells, called iPS cells. These embryoniclike cells can be coaxed, through a cocktail of chemicals, to become specialized.

The Stanford team, led by Dolmetsch and assistant Masayuki Yazawa, created three types of heart cells: atrial, ventricular and nodal cells.

When introduced to each other, the three cells types spontaneously self-organized, clumping

together to form something resembling a one-chambered heart. Then they started beating — in unison.

"We are not building a complete heart," said Dolmetsch. "But these developing cardiac cells migrate around and form the same kinds of connections, and conduct impulses, like normal heart cells do," he said.

However, while hearts derived from healthy cells beat an average of 60 times a minute, these sick hearts beat only 30 times a minute, with poor pacing. The researcher explained: Instead of "Lub-dub, lub-dub," their rhythm is "lub ... dub ... lub ... dub."

The faulty hearts beat very slowly, or miss beats, or suddenly start racing. This ultimately," said Dolmetsch, "leads to life-threatening arrhythmias."

At Stanford, the organs live in incubators kept at body temperature and are fed a broth rich in glucose, calcium, magnesium and other components of human blood. Following "an ancient developmental clock," the lab's hearts form at the same rate as in an embryo, 80 to 100 days.

Timothy syndrome interested Dolmetsch because it is caused by a single gene mutation and creates an abnormality in the heart's electrical system that causes irregular heartbeats.

Patients with the syndrome also tend to have structural heart defects, and often autism. The average life span of a child with Timothy syndrome is 2.5 years.

Why Timothy syndrome patients have cardiac arrhythmia has not been known; it has been very hard to study heart cells, Dolmetsch said.

Now, using special dyes, the Stanford team can visually inspect the Timothy syndrome heart cells. This has helped identify the specific source of the problem: the heart's ventricular cells, not atrial or nodal cells.

The research team administered different drugs, and watched how these cells responded.

With one drug — roscovitine, currently in clinical trials for an unrelated ailment — a regular heartbeat was restored. Still, much more testing is required before it can be considered a treatment.

But it is a promising compound, and Stanford's Office of Technology Licensing has applied for U.S. patents. Dolmetsch is starting a company that intends to license those patents once they're granted.

A similar approach could help patients suffering from the dozen or so other gene mutations known to cause disruptions in heart patterns.

Dolmetsch's team also has taken skin cells from children with early-onset schizophrenia, Velo-Cardio-Facial syndrome and autism caused by a mutation on chromosome 16. "Our hope is to advance our basic understanding to the point where we can do a better job of delivering treatment," he said.