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Therapy for muscular dystrophy-caused heart failure also improves muscle function in mice

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Injections of cardiac progenitor cells help reverse the fatal heart disease caused by Duchenne muscular dystrophy and also lead to improved limb strength and movement ability, a new study shows.

The study, published today in *Stem Cell Reports*, showed that when researchers injected cardiosphere-derived cells (CDCs) into the hearts of laboratory mice with muscular dystrophy, heart function improved along with a marked increase in exercise capacity.

"We unexpectedly found that treating the heart made the whole body better," said Eduardo Marbán, MD, PhD, director of the Smidt Heart Institute and the investigator who developed the cardiosphere-derived cell technology used in the study. "These basic findings, which have already been translated to clinical trials, rationalize why treating the heart may also benefit skeletal muscle function in boys and young men with Duchenne."

Duchenne muscular dystrophy, which affects 1 in 3,600 boys, is a neuromuscular disease caused by a shortage of a protein called dystrophin, leading to progressive muscle weakness. Most Duchenne patients lose their ability to walk by their early teens. Average life expectancy is about 25. The cause of death often is heart failure because the dystrophin deficiency not only affects the muscles which control movement, but also the heart, crippling its ability to pump blood

effectively.

The new findings represent the preclinical basis for the Phase I/II HOPE-Duchenne clinical trial that was presented at the November 2017 American Heart Association Scientific Sessions. That study, the first to test cell therapy in Duchenne muscular dystrophy patients and sponsored by Capricor, Inc., showed improved arm strength after 13 patients received cell infusions (as compared to 12 patients randomly assigned to receive usual care only). Another, larger clinical trial, again sponsored by Capricor, is scheduled to begin later this year - with a key difference. The patients in the Phase II trial will receive multiple cell infusions via an intravenous drip during the course of a year, rather than a single dose injected directly into the heart during a Cath Lab procedure.

Investigators note two surprising results of the newest study, beyond the unexpected effects on skeletal muscle: first, the benefits of the cell therapy lasted long after the cells were naturally pumped out of the heart; and second, levels of the missing protein dystrophin were increased, although the effect was temporary and dystrophin levels remained lower than normal.

"We found that within a few weeks, the injected cells were undetectable," Marbán said, "but the benefits persisted for at least three months, which led us to discover that exosomes secreted by CDCs are responsible."

Exosomes are microscopic vesicles, shed by cells, which contain a diversity of biologically-active contents that are taken up by, and influence the behavior of, nearby and distant cells. Exosomes are increasingly being recognized for their therapeutic potential because they serve as messengers for cells to communicate with each other.

"We found that after receiving CDCs, the lab mice had elevated levels of

dystrophin, which likely enabled easier movement and improved survival," said Ronald G. Victor, MD, associate director of the Smidt Heart Institute and a primary investigator on the study. "Even just adding a small amount of dystrophin would make a tremendous difference for these young patients."

The cells used in the mouse study were manufactured in Marbán's laboratory at Cedars-Sinai. The cells used in the Phase I/II study were derived from donor hearts by Capricor Therapeutics. Marbán developed the process to grow CDCs when he was on the faculty of Johns Hopkins University; the process was further developed at Cedars-Sinai. Capricor has licenses the process from Johns Hopkins and Cedars-Sinai for clinical and commercial development. Capricor has licensed additional intellectual property from Cedars-Sinai and the University of Rome. Cedars-Sinai and Marbán have financial interests in Capricor. Victor has been a consultant to the company but was not paid by the company for his work on this study.

Provided by Cedars-Sinai Medical Center

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