Jaan Biotherapeutics
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Healing the heart by manipulating microRNAs

Jaan Biotherapeutics is developing first-in-class therapies that repair damaged heart muscle and treat cardiovascular diseases by reactivating an endogenous regeneration process that has been shut down in the adult human heart during evolution, but is active in human fetal hearts.

Cardiovascular diseases remain major contributors to high mortality rates in developed countries. Ischemic heart disease is the single largest cause of death worldwide, and heart failure has also become a global public health problem. One significant hurdle is that adult mammals do not naturally regenerate heart tissue to recover function after injury. Because many experimental therapies such as exogenous stem cell replacement have demonstrated questionable clinical efficacy for the treatment of myocardial infarction, there is an urgent need to identify effective solutions for regenerating endogenous cardiac muscle.

To address this problem, Jaan Biotherapeutics (JBT) is developing first-in-class regenerative therapies that modulate the activity of microRNAs (miRs) to repair damaged heart muscle and treat cardiovascular diseases. miRs are noncoding RNAs that function in RNA silencing and post-transcriptional regulation of gene expression. The company's proprietary technology manipulates miRs to activate an endogenous cardiac muscle regeneration process that has been shut down in the adult human heart during evolution, but is active in human fetal tissue.

Currently, JBT has two lead therapies that initially target acute myocardial infarction, including ischemic heart disease, cardiomyopathy associated with Duchenne muscular dystrophy and familial hypertrophic cardiomyopathy. "Our current focus is ischemic heart disease, but the therapy can be applied to many cardiac diseases where cardiac muscle regeneration is required, by essentially reprogramming human adult diseased heart tissue to behave like fetal regenerating heart tissue," said JBT's CEO and founder Bhawanjit Brar.

Reviving regeneration

JBT's oligonucleotide combination therapy for ischemic heart disease and Duchenne muscular dystrophy, known as JN-101, works by inhibiting miR-100, miR-99, let-7a and let-7c. As reported in 2014 in *Cell Stem Cell*, downregulation of these four miRs is sufficient to promote endogenous heart regeneration after injury in adult zebrafish. Although this process fails to occur naturally in adult mammals, in vivo manipulation of this evolutionarily conserved molecular machinery in mice results in cardiomyocyte dedifferentiation, proliferation and ultimately heart regeneration, leading to improved cardiac function after injury.

> "We look forward to establishing future partnerships to fully realize the vast potential of our novel approach

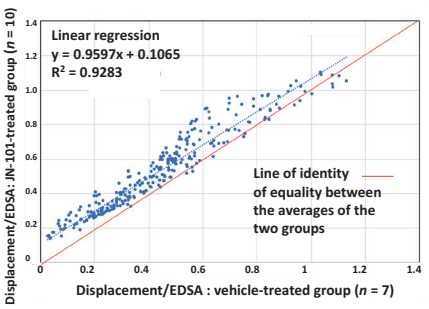

Fig. 1 | Significant increase in LV wall motion (nodal displacement) and EDSA in the weeks following ischemic reperfusion injury in mice treated with JN-101 compared with vehicle. Reconstructed from short axial magnetic resonance cross-sectional images. Displacement normalized to left ventricular (LV) end diastolic surface area (EDSA; as an index of LV size) on the horizontal axis for the vehicle-treated group against the very same index for the JN-101-treated group. Note the upward shift of the plot for the great majority of nodes in the JN-101 group significantly enhancing basal myocardial contraction.

A single optimal dose of JN-101 given to mice after a 60-minute left coronary artery occlusion significantly decreases end diastolic and systolic volumes weeks after injury and leads to increased wall motion, as determined by 3D cardiac magnetic resonance imaging (**Fig. 1**, and see supplemental movie on the Jaan Biotherapeutics online profile at biopharmadealmakers.nature.com), with increasing global hemodynamic function "These findings in double-blinded studies are a validation of the results published in the *Cell Stem Cell* report and indicate that JN-101 promotes the generation of endogenous, functional, electrically coupled cardiomyocytes in the ischemic heart," said Aitor Aguirre, lead author of the original study from the Salk Institute and current assistant professor of biomedical engineering at Michigan State University.

Unlike stem cell strategies, JBT's technology removes the potential for rejection of exogenous cells and offers a straightforward, simple approach to therapy by producing cardiac progenitors without the need to collect, culture and transplant stem cells. When administered with reperfusion therapy, JN-101 could further enhance heart muscle regeneration after myocardial infarction. JN-101 is ready for investigational new drug (IND)-enabling studies for ischemic heart disease, with further safety studies required prior to clinical translation.

Expanding opportunities

In addition to ischemic heart disease, JN-101 holds promise for the treatment of Duchenne muscular dystrophy—an X-linked recessive form of muscular dystrophy that affects approximately 1 in 3,600 boys. This orphan disease results in muscle degeneration and premature death, primarily owing to heart failure, when the patients are between 20 and 40 years of age. When used in combination with gene-correction methods, JBT's therapeutics could induce the proliferation and regeneration of a genetically normal cardiac myocyte pool, thereby reducing the adverse pathophysiologic consequences associated with this disease. JBT has filed a patent for combination therapy for muscular dystrophy.

JBT's second lead drug candidate is JN-210, a viral vector that delivers an activator of miR-133 for the treatment of hypertrophic cardiomyopathy. This orphan disease is the single largest cause of sudden cardiac death in young athletes and individuals younger than 30 years of age. When administered at the time of diagnosis, JN-210 could potentially treat certain patients affected by this disease.

To support development of these innovative drug candidates, JBT has been awarded National Institutes of Health Small Business grants and is currently seeking additional funding. The company is also engaged in strategic partnership discussions for cross-licensing technology and for potential mergers and acquisitions. "We look forward to establishing future partnerships to fully realize the vast potential of our novel approach to repairing damaged heart muscle and treating cardiovascular diseases," said JBT's CFO Joseph Hansen.

For the data presented, contact Kirk L. Peterson, professor of medicine and director at Seaweed Canyon Physiology Laboratory, Division of Cardiology, University of California, San Diego, USA.

contact
Joseph Hansen, CFO
Jaan Biotherapeutics
San Diego, CA, USA
Tel: +1-858-373-8473
Email: info@jaanbio.com