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For Immediate Release

Human iPSC-derived Cardiomyocytes and Pyridyl-Phenyl Mexiletine Analogs

In the United States, almost one million individuals are hospitalized every year for cardiac arrhythmias, making arrhythmias one of the top causes of healthcare expenditures with a direct cost of almost $50 billion annually. Almost 300,000 individuals die of sudden arrhythmic death syndrome every year.

Ventricular cardiac arrhythmia arises in acquired or congenital heart disease. Arrhythmias are very common in older adults but unfortunately, drugs to treat arrhythmias have liabilities. In addition, numerous investigational drugs have been withdrawn from the market because they induce QT prolongation and a potentially fatal ventricular tachycardia, a condition called Torsade de Pointes. For normal heart cell function, sodium channels rapidly inactivate with depolarization. In depolarization of cardiomyocytes, sodium channels open briefly and allow influx of sodium. Correct regulation of ion currents in cardiomyocytes is key for proper heart function.

Cardiac action potential is initiated by the opening of the cardiac sodium channel conducting the large peak sodium current responsible for the action potential upstroke. In healthy individuals, the sodium channels inactivate with depolarization. However, Long QT syndrome type 3 (LQT3) patients have mutations in the sodium channel that impair channel inactivation and accelerate recovery from the inactivated state. Increased sodium channel current opposes repolarization and prolongs the action potential, thus prolonging the QT interval on the surface electrocardiogram.

Mexiletine is a drug that inhibits the sodium current and shortens the QT interval in LQT3 patients and decreases their risk of developing ventricular tachycardia and ventricular

fibrillation. Blockade of voltage-gated sodium channels that inhibits generation and propagation of action potentials can be antiarrhythmic and prevent pathological firing in cardiac tissue. However, mexiletine has liabilities. The FDA Approved Label states that severe liver injury and blood dyscrasias (i.e., leukopenia or agranulocytosis) and other adverse reactions including reversible gastrointestinal and nervous system problems have been reported after mexiletine treatment. Accordingly, in our studies, new mexiletine analogs were designed to improve pharmaceutical properties, increase the potency and improve the therapeutic to toxicity ratio.

We tested the hypothesis that a useful drug (i.e., mexiletine) with liabilities (i.e., potassium channel inhibition and adverse reactions) could be re-engineered by dynamic medicinal chemistry and evaluated in normal and human patient induced pluripotent stem cell-derived cardiomyocytes could afford new drug candidates with greater efficacy and less toxicity. Medicinal chemists and stem cell biologists at the Human BioMolecular Research Institute (HBRI), in San Diego, CA, and Stanford University, in Stanford, CA, and cardiovascular pharmacologists at Columbia University, in New York City, NY, respectively, reported on reengineered mexiletine compounds that showed improved potency and decreased toxicity.

The report showed that application of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) to evaluate proarrhythmic effects of pyridyl mexiletine analogs helped define chemical determinants responsible for anti-arrhthymia. In parallel, patient-derived hiPSC-CMs carrying a LQT3 sodium channel mutation were used to quantify the extent of action potential shortening of pyridyl mexiletine analogues. Human LQT3 CMs were used to determine pyridyl mexiletine analog beneficial effects, quantified as the potency for shortening the action potential duration, fold-shortening of the action potential duration and a concentration that caused shortening of the action potential. These results were compared to the concentration of a test compound required for cessation of cell beating, potency for shortening the action potential duration, and fold-shortening of the action potential duration in normal cardiomyocytes. The results led to identification of potent and selective sodium channel inhibitors with decreased proarrhythmic effects and improved physicochemical properties. Compounds were shown to be effective antiarrhythmic compounds in hiPSC-CM models of LQT3-associated arrhythmia.

This paper was featured in *Bioorganic and Medicinal Chemistry Letters.* Writing on June, 2021:

"The finding that "drug discovery in a dish" using a "disease in a dish" technology was successful is important because it showed that human drug development can be done efficiently using these approaches" explains co-author Dr. Jorge Gomez-Galeno. *"By selectively blocking a sodium channel in human cardiomyocytes, and decreasing off-target effects, new and safer drugs can be developed."* Given its potency, these new compounds may be of utility as antiarrhythmic drug candidates.

"*The new compounds may lead to treatment applications in a whole host of cardiovascular conditions that may prove efficacious in clinical trials*"… explains co-author Dr. John Cashman. "*As antiarrhythmic drug candidate drug development progresses, we expect the new analogs to be less toxic than current therapeutics for arrhythmia in* congenital heart disease*, and patients will benefit from improved safety, less side effects and possibly with significant cost-savings."*

Summary

Chemists and biologists at HBRI, Stanford University, and Columbia University are among the first group to do dynamic medicinal chemistry of small molecules and a high throughput assay using disease in a dish technology to obtain pharmacologically active compounds of use in cardiovascular disease. New pyridyl mexiletine analog compounds selectively block sodium channels. To our knowledge, this is one of the first reports to use human iPSC-derived cardiomyocytes from normal and diseased individuals to re-engineer a drug with deficiencies to an entirely new chemotype. Revealing links between drug development and selective human cardiomyocyte sodium channel inhibition might be fundamentally important.

Publication

"Human iPSC-derived Cardiomyocytes and Pyridyl-Phenyl Mexiletine Analogs." Mark Johnson, Jorge Gomez-Galeno, Daniel Ryan, Karl Okolotowicz, Wesley L. McKeithan, Kevin J. Sampson, Robert S. Kass, Mark Mercola and John R. Cashman. *Bioorganic and Medicinal Chemistry Letters.*

Media contacts: To arrange on-site, phone, or Skype interviews with the researchers involved in this study, please contact John Cashman at HBRI (858) 458-9305 or JCashman@hbri.org

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