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For Immediate Release

Reengineering mexiletine by chemical synthesis to decrease toxicity and improve pharmacological properties with patient-derived iPSC cardiomyocytes.

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. In the United States, 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 In addition, numerous investigational drugs have been withdrawn from the market because they induce QT prolongation and a potentially fatal ventricular tachycardia, a condition called Torsade de Pointes.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.

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. For mexiletine, 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. In our published studies, new mexiletine analogs were designed to improve pharmaceutical properties, increase the potency and improve the therapeutic to toxicity ratio.

In a commentary, I summarize several published papers that showed that application of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) to evaluate proarrhythmic effects of 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 mexiletine analogues. Human LQT3 CMs were used to determine 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 published in *Archives of Clinical Toxicology.* Writing on May, 2022:

"Modification of selected mexiletine analogs showed that improvement to pharmacologic and pharmaceutical properties can be achieved. In conclusion, studies highlighted the utility of using hiPSC-cardiomyocytes to guide medicinal chemistry and obtain new chemotypes for "cardiovascular drug discovery in a dish" explains author Dr. John Cashman. These new compounds may be of utility as antiarrhythmic drug candidates.

Summary

Chemists and biologists at HBRI did dynamic medicinal chemistry of small molecules using disease in a dish technology to obtain pharmacologically active compounds of use in cardiovascular disease. New 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 chemically re-engineer a drug with deficiencies to an entirely new chemotype. Links between drug development and selective human cardiomyocyte sodium channel inhibition might be fundamentally important.

Publications

"Reengineering Mexiletine by chemical synthesis to decrease toxicity and improve pharmacological properties with patient-derived iPSC cardiomyocytes." John R. Cashman. *Archives of Clinical Toxicology*.

"Antiarrhythmic Hit to Lead Refinement in a Dish Using Patient-Derived iPSC Cardiomyocytes." John R. Cashman, Daniel Ryan, Wesley L. McKeithan, Karl Okolotowicz, Jorge Gomez-Galeno, Mark Johnson, Kevin J. Sampson, Robert S. Kass, Arash Pezhouman, Hrayr S. Karagueuzian, and Mark Mercola. *Journal of Medicinal Chemistry*.

"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.*

"Human-induced pluripotent stem cell-derived cardiomyocytes: Cardiovascular properties and metabolism and pharmacokinetics of deuterated mexiletine analogs." Jorge Gomez-Galeno, Karl Okolotowicz, Mark Johnson, Wesley L. McKeithan, Mark Mercola and John R. Cashman. *Pharmacology Research Perspectives*.

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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