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Reengineering a drug guided by patient-derived hiPSC-cardiomyocytes

San Diego, California – September, 2020. Medicinal chemists at the Human BioMolecular Research Institute (HBRI), in San Diego, CA, and biologists at Sanford-Burnham-Prebys Medical Discovery Institute (SBPMDI), in San Diego, CA, and at Stanford University, Stanford, CA, Columbia University, New York, NY, and Northwestern University, Chicago, IL, respectively, have reported on improving an antiarrhythmic drug using patient-derived human induced pluripotent stem cell cardiomyocytes (hiPSC-CMs) in a high throughput manner *in vitro.* This may have importance for heart disease and other drug discovery efforts.

High throughput studies with hiPSC-CMs derived from patients possessing the cardiac rhythm disorder long QT syndrome type 3 (LQT3) harboring an F1473C missense mutation in SCN5A was used to chemically refine an antiarrhythmic drug, mexiletine. The effect of SCN5A sodium channel mutations is to prolong the QT interval of the electrocardiogram. Using iterative cycles of medicinal chemical synthesis and testing, we defined novel chemical modifications that increased potency and selectivity for late sodium current (I_{NaL}) and decreased propensity for prolonging the cardiac action potential and arrhythmic activity. Chemically refined analogues were effective at inhibiting late sodium current across a panel of 7 LQT3 sodium channel variants as well as suppressed arrhythmic activity across genetic (*SCN5A* F1473C and N406K) and pharmacologic hiPSC-CM models of LQT3 in different genetic backgrounds. The new analogues can be exploited as mechanistic probes of I_{NaL} selectivity and cardiac arrhythmia as well as for clinical development. Drug development may be of particular utility for young children suffering from ventricular tachycardia because in extreme cases, this can result in sudden cardiac death.

Writing in September, 2020, in the journal *Cell Stem Cell,* the authors describe the first high throughput, automated and robust analysis of the effect of chemical modifications on mexiletine analogs on AP kinetics and drug-induced proarrhythmia in hiPSC-CMs. Medicinal chemists

were able to do drug discovery and improve the pharmacological and pharmaceutical properties of mexiletine.

The approach was successful to use patient-derived hiPSC-CMs and improve the proarrhythmic effects of mexiletine and produce new drug candidates. A high throughput method for determining arrhythmias in vitro enabled development of compounds to treat patients with heart disease and to develop safer drugs that do not induce arrhythmias.

"*The work has led to compounds that were potent in vitro, and safer than mexiletine. Ultimately, this may result in a more efficacious cardiovascular medication and greater patient tolerance, and less side effects*"… explains lead co-author Dr. Wesley L. McKeithan. "*In the future, as less toxic drugs become available, patients will benefit from improved safety, possibly with significant cost-savings."*

The chemists and biologists at HBRI, SBPMDI, Stanford University, Columbia University (in the lab of Professor Rocky Kass), and Northwestern University (in the lab of Professor are the first group to apply high throughput methods to develop new proarrhythmic drug candidates. Armed with this expertise, the researchers will apply similar strategies to development of other drugs, where new drug candidates may show increased efficacy.

Wesley L. McKeithan, Dries A. M. Feyen, Arne A. N. Bruyneel, Karl J. Okolotowicz, Daniel A. Ryan, Kevin J. Sampson, Franck Potet, Alex Savchenko, Jorge Gómez-Galeno, Michelle Vu, Ricardo Serrano, Alfred L. George, Jr., Robert S. Kass, John R. Cashman and Mark Mercola. Reengineering of an antiarrhythmic drug guided by patient-derived hiPSC-cardiomyocytes. *Cell Stem Cell*.

Media contacts: To arrange on-site, phone, or Skype interviews with the researchers involved in this study, please contact John Cashman at (858) 458-9305 / JCashman@hbri.org or Mark Mercola at Sanford-Burnham-Prebys Medical Discovery Institute at 858-795-5242 or Stanford University at mmercola@stanford.edu

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About Human BioMolecular Research Institute
The Human BioMolecular Research Institute is a non-profit research institute conducting basic research focused on unlocking biological and chemical principles related to diseases of the human brain, cardiovascular disease and cancer. The Institute conducts fundamental studies of central nervous system disorders, heart disease and cancer including stem cell approaches and translates findings into new drug development to address human illness. In addition, the institute promotes scientific learning through community service and public access by disseminating information and sharing research with collaborators, colleagues and the public. For more information, visit us at www.HBRI.org.

About Sanford Burnham Prebys Medical Discovery Institute
Sanford Burnham Prebys Medical Discovery Institute (SBPMDI) is dedicated to discovering the fundamental molecular causes of disease and devising the innovative therapies of tomorrow. The Institute consistently ranks among the top five organizations worldwide for its scientific impact in the fields of biology and biochemistry (defined by citations per publication) and

currently ranks third in the nation in NIH funding among all laboratory-based non-profit research institutes. SBPMDI utilizes a unique, collaborative approach to medical research and has established major research programs in cancer, neurodegeneration, diabetes, and infectious, inflammatory, and childhood diseases. The Institute is especially known for its world-class capabilities in stem cell research and drug discovery technologies. SBPMDI is a U.S.-based, non-profit public benefit corporation, with operations in San Diego (La Jolla), California and Orlando (Lake Nona), Florida. For more information, news, and events, please visit us at http://www.sbpdiscovery.org.

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