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LETTER TO THE EDITOR

Prof. Cristobal dos Remedios and the Sydney Heart Bank: enabling translatable heart failure research

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Thanks in large part to the pioneering efforts of Prof. Cristobal dos Remedios and the Sydney Heart Bank (SHB), accessible donor and diseased human heart tissue has become a valuable research tool in understanding the complex molecular nature of heart failure (HF). Of the over 130 studies using tissue from the SHB, the vast majority of them focus on characterizing various aspects of HF tissue compared with donor tissue (Li et al. 2019). As a result of the SHB and Dr. dos Remedios' achievements, we now know more about the complex genomic, proteomic, phosphoproteomic, and functional details of human HF than ever before (dos Remedios et al. 2017).

The ultimate hope shared by Prof. dos Remedios and all his collaborators is that our increased understanding of the molecular mechanisms underlying HF will guide the development of novel HF therapies. As is well known, current HF therapies focus on downstream targets such as cardiac conduction pathways, blood pressure regulation, and neurohormonal signaling. These therapies may elicit adverse side effects that hurt patient quality of life without significantly improving long-term prognosis. For many cardiomyopathies, the most promising next-generation therapies rely on inotropic small molecules that interact with sarcomeric proteins to alter cardiac force generation and contractile dynamics (Hwang and Sykes 2015). Doing so allows small molecule inotropes to precisely target the root of HF and to potentially sidestep many adverse side effects.

Even though these inotropes promise to improve on many of the shortcomings of conventional HF therapy, their development has been slow and costly. Many HF drug candidates fail in the final phases of clinical trials after billions have been spent on research and development (Scannell et al. 2012; Hay et al. 2014). While the exact cause for these high failure rates is complex and is the topic of many review articles, heavy reliance on animal models of HF in preclinical trials is likely to contribute, at least in part (Milani-Nejad and Janssen 2014; Ahmad et al. 2019). Thanks again to the SHB, researchers can avoid the translational challenges of using animal models posed by their physiological and pathophysiological differences while reflecting the genetic variability in human populations by supplementing animal model data with human tissue data (Milani-Nejad and Janssen 2014; dos Remedios et al. 2017).

By testing small molecule HF drug candidates on human heart fiber preparations, preclinical studies can describe a wide range of potential drug effects on key functional and kinetic contractile parameters. These parameters may identify important drug mechanisms along with potential in vivo implications before beginning in vivo testing. In addition, the intact lattice structure of the myofibril helps maintain important cooperative cross-bridge behaviors (Holmes et al. 2020). For example, we used the stretch activation response to study the effects of the myosin activator omecamtiv mecarbil (OM) on the cooperative on and off rates of myosin cross-bridges in both a murine model of HCM and in human tissue supplied by the SHB (Mamidi et al. 2015). The results indicated possible OM-induced changes to diastolic and systolic performance during cardiac function in vivo (Mamidi et al. 2019). Our subsequent study investigating the dose-dependent effects of OM showed a decreased response in human HF versus human donor tissue and highlights the need to study drug effects in diseased tissue (Mamidi et al. 2017). Force-velocity and force-power experiments can further help by reflecting how a drug changes the heart's power profile against different levels of preload (Hanft and McDonald 2019).

Because of the SHB and Prof. dos Remedios, researchers around the globe have the capabilities to contribute highly translatable research to solving the global HF problem using human cardiac tissue. And as the SHB continues to increase its number of available hearts, the variety of hearts, and the

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level of and genomic detail included with each heart, the potential role of the SHB and Prof. dos Remedios' crowning career legacy in preclinical studies will only increase (dos Remedios et al. 2017; Li et al. 2019). We hope that more researchers will take advantage of this potential to continue making advances in finding a true HF cure.

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