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Response to Letter regarding article,"Orai1 channel inhibition preserves left ventricular systolic function and normal Ca^{2+} handling after pressure overload"

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We thank Dr Mehmood for his interest in our study in which we reported the cardioprotective effect of Orai1 inhibition after pressure overload in mice. Dr Mehmood nicely draws attention to the fact that several clinically used drugs inhibit Orai1-mediated Store-Operated Ca^{2+} Entry (SOCE) at therapeutically-achievable concentrations for leflunomide and teriflunomide or at higher dose for more SOCE-selective inhibitors such as lansoprazole, tolvaptan and roflumilast(1). We agree that this is potentially important and worthy of further consideration alongside other efforts to achieve benefit from Orai1 suppression. Various selective Orai1 inhibitors have been developed, such as AnCoA4, CM2489 and CM4620, and clinical trials are on-going with such agents(2). While we are positive about Dr Mehmood's perspective, we caution that potential concerns or limitations may need to be overcome. The potency of these drugs for inhibiting Orai1 and not Ca^{2+} signaling mediated by Transient Receptor Potential Canonical (TRPC) channels, for example, is required. Indeed, we identified JPIII as a potent and selective Orai1 inhibitor with improved physico-chemical characteristics for *in vivo* usage and showed that it possesses good efficacy, safety and pharmaceutical characteristics in mice. We therefore have proof-of-concept that *in vivo* selective Orai1 blockade with JPIII, without obvious systemic side effects, might provide a new efficient therapy by preserving normal Ca^{2+} handling and improving left ventricular function at adult stage even if increased cardiac mass occurs(3). By contrast, *in vivo* inhibition of TRPCs avoids the development of the cardiac hypertrophy(4). The concept of preserving or preventing pathological hypertrophy is still controversial and some reports showed that hypertrophy blockade may be detrimental(5). Therefore, we prefer to consider selective Orai1 inhibitors as potentially beneficial inotropic agents.

We agree that efforts to repurpose clinically-used drugs for heart failure should be considered and we will progress such studies when we are in a position to do so after the Covid-19 shutdown of our research facilities and when funding for such work is in place. This could be an important shortcut to new important therapies. In addition and in parallel, we encourage continued efforts to further understand Orai1 inhibition in the heart and its relevance to people. It is also important to properly understand the risks of potential adverse effects, especially given the associations of genetic disruption of *ORAI1* with immune suppression. Key next steps include the need for extensive follow-up to confirm the benefit of *in vivo* Orai1 inhibition by JPIII and its new, further improved analogues, after pressure overload

over long time periods and to test such agents in preclinical models of other heart failure etiologies like myocardial infarction and type I and II diabetes. We plan such studies and hope to report on them in the not-so-distant future.

Disclosures Statement: None

References

1. Rahman, S., and Rahman, T. (2017) Unveiling some FDA-approved drugs as inhibitors of the store-operated Ca(2+) entry pathway. *Sci Rep* **7**, 12881
2. Stauderman, K. A. (2018) CRAC channels as targets for drug discovery and development. *Cell Calcium* **74**, 147-159
3. Bartoli, F., Bailey, M. A., Rode, B., Mateo, P., Antigny, F., Bedouet, K., Gerbaud, P., Gosain, R., Plante, J., Norman, K., Gomez, S., Lefebvre, F., Rucker-Martin, C., Ainscough, J. F. X., Kearney, M. T., Bruns, A. F., Shi, J., Appleby, H. L., Young, R. S., Shawer, H. M., Debant, M., Gomez, A. M., Beech, D. J., Foster, R., Benitah, J. P., and Sabourin, J. (2020) Orai1 Channel Inhibition Preserves Left Ventricular Systolic Function and Normal Ca(2+) Handling After Pressure Overload. *Circulation* **141**, 199-216
4. Eder, P. (2017) Cardiac Remodeling and Disease: SOCE and TRPC Signaling in Cardiac Pathology. *Adv Exp Med Biol* **993**, 505-521
5. Crozatier, B., and Ventura-Clapier, R. (2015) Inhibition of hypertrophy, per se, may not be a good therapeutic strategy in ventricular pressure overload: other approaches could be more beneficial. *Circulation* **131**, 1448-1457