CROSSTALK

Rebuttal from Krishna C. Penumatsa, Rod R. Warburton, Nicholas S. Hill and Barry L. Fanburg

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The remarks that Dr Vitali makes regarding the use of SuHx mice as a preclinical animal model of pulmonary arterial hypertension (PAH) are good ones. However, the question of what criteria are needed to make the animal model representative of PAH is an old one. Gomez-Arroyo *et al.* (2012) addressed this extensively and Dr Vitali adds to those criteria the need to show persistence of pulmonary hypertension (PH) as opposed to reversal of the PH and accompanying effects after removal of the hypoxic exposure. However, the most compelling feature of the SuHx model is the presence of PH marked by increased right ventricular (RV) systolic pressure produced by hypoxia and accentuated by Sugen 5416. It also appropriately reflects the accepted mechanisms of glycolytic shift and hypoxia-inducible factor-dependent signalling that occur in PAH (Chan & Rubin, 2017). The general gestalt from accumulation of multi-study data is that the presence or absence of RV failure is mainly a reflection of degree and duration of PH, and identification of RV hypertrophy as noted by Ciuclan *et al.* (2011) in mouse studies may be sufficient.

The use of rodents as models of human disease has been previously questioned (Maarman *et al.* 2013; Perlman, 2016). Yet, the general perception is that, although admittedly imperfect, these models are useful for testing preclinical therapeutics and gaining insights into pathobiology of human disease. Dr Vitali references a review article by de Jesus Perez (2016) where it is stated that therapies successful in animal models have failed to reverse PAH in humans; however, most of the PAH therapies available commercially today have been tested successfully in animal models first.

Dr Vitali's argument hinges on the notion that an animal model of PAH must manifest features of severe disease including RV dysfunction or failure and progressive arteriopathy. But these have never been established as essential features of an animal model of PAH and the argument ignores several advantages of the SuHx mouse over other models she mentions; i.e. simplicity, greater severity than hypoxia alone and lending itself to much easier genetic manipulation than the more robust rat SuHx model. Furthermore, the susceptibility of mice to pulmonary hypertensive stimuli varies by strain (Nadziejko *et al.* 2007), and it is possible that SuHx administered to a susceptible mouse strain will manifest the features that Dr Vitali desires. The SuHx model in mice is not perfect, but it is good enough to serve a role in preclinical studies for the foreseeable future.

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Additional information

Competing interests

No competing interests declared.

Author contributions

All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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