Author's Reply

We entirely agree that humans are, theoretically, the best system in which to study human disease. To some extent, the problem with mouse modeling is even worse than Drs Menache and Keogh claim: Not only do mice have different responses to pulmonary vascular stress than do humans, but different strains of mice have rather different responses compared to each other, on both a physiologic and molecular level.^[1] Moreover, I doubt even the most optimistic mouse modeler believes that any of the dozens of substances that reverse monocrotaline-related pulmonary arterial hypertension (PAH) are likely to be directly relevant to human disease.^[2]

This is not, however, a reason to abandon mouse modeling. The problem is that there are a great many questions that simply cannot be effectively studied in humans. For instance, the largest expression array study performed directly on lungs from humans with pulmonary hypertension found that of 14,000 genes with detectable levels of expression; 13,889 had significant changes.^[3] The signal of etiologic change was overwhelmed with the noise of damage associated with end-stage disease. It is not possible to study initiating events in idiopathic pulmonary hypertension in humans; even with the best registries of not-yet-affected mutation carriers, conversion to disease is so slow that recruitment goals could not practically be met. There are also a great many experiments in gene-gene interaction, especially where these meet

physiologic consequences, which simply cannot be studied in humans.

How, then, are we to make progress, when experiments cannot be done in humans, and we cannot trust the results from mice? The answer is, thoughtfully. As Drs Keogh and Menache point out, genes do not work individually or in linear pathways, but rather in networks. We can use mice to work out the links in these networks, while understanding that the relative strengths of the connections are different in humans and in mice (and likely different from human to human, as well). We can use mice to understand how local and circulating stem cells or transdifferentiation or proliferation of local cells contribute to remodeling, while understanding that the proportions of these cells are likely different in humans. Most of all, we need to understand that the origins of disease in mice are designed to be simple, where in humans they are inevitably multifactorial and complicated by environment and the continued course of disease.

In summary, we entirely agree with Drs Keogh and Menache that use of mouse models is fraught with scientific peril. Our goal in drafting our review was to help the community think more critically about how best to approach this peril.

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