Finally, Progress in Pulmonary Hypertension Associated with Heart Failure with Preserved Ejection Fraction

The complexity, nonlinearity, adaptability, and compartmentalization of the biological systems have led biologists in recent years to expand on the results of molecular biology, using high-throughput approaches, complex computational methods, and systems biology approaches. In the field of pulmonary hypertension (PH), we have seen significant progress in dissecting the molecular mechanisms, mostly after gene discoveries in patients with familial PH and careful hypothesis-driven investigations in animal models of the disease. However, with the expanded understanding of PH in humans and the refined World Health Organization (WHO) classification of PH, recognition of the limitations of traditional animal models has increased, leading to greater efforts to molecularly characterize human samples and to search for novel models that better mimic the human subphenotypes of PH.

In this issue of the *Journal*, two articles, by Kelly and colleagues (pp. 488–496) and Meng and colleagues (pp. 497–505), tackle PH associated with heart failure with preserved ejection fraction (PH-HFpEF), an increasingly important syndrome commonly accompanied by other features of the metabolic syndrome (1–3). Despite its prevalence and the fact that it is an important cause of mortality and morbidity, PH-HFpEF has so far lacked a specific therapy, an animal model, and a central molecular hypothesis connecting the systemic features with the development of PH. In the two articles in this issue of the *Journal* (1, 2), the authors use an elegant approach of screening susceptibility among various strains of inbred mice to develop a novel mouse model of PH-HFpEF and to identify a potential novel molecular regulator mechanism underlying this syndrome. Both investigations are based on the results of an initial exposure of 36 different mice strains to 20 weeks of a high-fat diet and studying their susceptibility to PH.

In the first article, Meng and colleagues (2) identify the AKR/J strain as a strain that developed the combination of cardiovascular changes, PH, and right and left ventricular hypertrophy, and attributes of the metabolic syndrome including obesity, glucose intolerance, insulin resistance, and hyperlipidemia. Using detailed cardiovascular phenotyping methods, they suggest convincingly that this is a novel model for a PH-HFpEF mouse model, which in many ways is comparable to human WHO group 2 PH. They also demonstrate a therapeutic response (decreased pulmonary artery pressures) after ongoing supplementation of nitrite and metformin.

In the second article, Kelly and colleagues (1) apply network analysis to mouse genome-wide association study results to identify human-relevant PH genes. They identify single nucleotide polymorphisms that associate with elevated right ventricular systolic pressures in mice and then filter them on the basis of their connection to the human PH interactome (4). They focus on the epidermal growth factor receptor (*Egfr*) as the "highest-rank" candidate gene. They also show that *Egfr* messenger RNA and protein expressions are increased in the mouse strain that developed PH-HFpEF (AKR/J) compared with a mouse strain that did not (C57BL/6J).

The two articles should lead to significant progress in our understanding and management of WHO group 2 PH. First, they generate the first human-relevant mouse model of PH-HFpEF. It is difficult to overestimate the impact of the availability of a well-characterized validated model on a disease area. Using a human-relevant mouse model, scientists can implement advanced genetic manipulation of key regulatory molecules, identify key pathways, and potentially test novel interventions. This is, we think, a critical first step toward having a PH-HFpEF–specific therapy and is thus a major breakthrough. Second, although there may be additional findings hiding in the genome-wide association study results, *Egfr* is definitely a good starting point. *Egfr* is a very appealing target because of the availability of multiple small molecule inhibitors and because it is known to regulate pulmonary artery smooth muscle cell growth and proliferation. Although the results of studies of *Egfr* in animal models of PH and human pulmonary arterial hypertension have not been consistent (5), the current studies suggest that *Egfr* should be evaluated as a therapeutic target for PH-HFpEF.

We believe that the results reported in the two articles are of the highest importance to the field of pulmonary hypertension, but we do want to note that the observations described in both articles were derived from male mice only. In 2014, after reports that male animals were used more frequently in preclinical research, the National Institutes of Health, as part of its plan to enhance scientific rigor and reproducibility, announced a requirement to ensure sex and sex inclusion compliance in clinical research (6). This was not an expression of "political correctness," but a recognition of the importance of sexual dimorphism, defined as phenotypic differences between sexes that occur in addition to differences in the sexual organs. In the context of the two articles, sexual dimorphism has been observed in humans and laboratory animals predisposed to the metabolic syndrome (7), heart disease (8), and PH (9). Male bias has been reported to be common in cardiovascular research in particular (8). The failure to study both sexes in experiments involving laboratory animals is often cited as one of the reasons why drugs that look so promising in preclinical trials fail in humans (10). Considering the impressive success of the approach the authors took, it would be worthwhile to complete the same set of experiments in female animals, to allow generalizing of the results to both men and women.

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In conclusion, Kelly and colleagues (1) and Meng and colleagues (2) should be commended for making a significant contribution to the field of PH-HFpEF, an increasingly common and poorly understood syndrome that currently lacks a specific pharmacologic intervention. Overcoming the lack of a model mimicking the human disease, and reigniting interest in a well-characterized therapeutic pathway, could lead to the repositioning of well-characterized drugs from the field of cancer to PH-HFpEF. The availability of the authors' complete data set, with their detailed phenotyping information, should also drive the study of PH forward, because alternative analytical approaches may identify additional targets and pathways. Improved human tissue availability, mainly through the National Heart, Lung, and Blood Institute–funded Pulmonary Vascular Disease Phenomics consortium (11), a multicenter effort to collect samples of 1,500 patients in the five WHO PH groups, will enhance the feasibility of identifying more human-relevant targets and will accelerate discovery. In the past 2 decades, most of the therapeutic progress has been made in patients with WHO group 1 PH. On the basis of the two articles in this issue of the *Journal*, we believe a path for similar success has been opened in PH-HFpEF. ■

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