Lost in translation

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Pulmonary hypertension is a fascinating and yet challenging disease that continues to be associated with significant risk of death despite several advances in its medical management during the past 1 or 2 decades. The absence of a pulmonary hypertension cure is due in part to the lack of proper understanding of the pathophysiology of this disease and also in part to the fact that this is a heterogeneous disorder that is multifactorial, and the therapy success and consequently prognosis therefore vary with the type and extent of the disease and related cardiac, pulmonary, and systemic problems.¹⁻³ The World Health Organization has recently updated the classification of pulmonary hypertension to 5 groups: pulmonary arterial hypertension, secondary to left heart disease, secondary to primary lung disease, secondary to thromboembolism, and, finally, of unclear multifactorial origins in association with hematologic, oncologic, systemic, or metabolic illnesses.⁴ This classification serves to underscore the heterogeneity of this disease and the multitude of factors that are potentially involved in its pathophysiology. Although the second type, that associated with left heart disease, is among the most common, it still does not necessarily represent a uniform group, and the sequelae of systolic left heart dysfunction may differ from those of diastolic dysfunction or of obstructive valvular lesion. In addition, some argue that pulmonary hypertension from pulmonary venous occlusive disease falls more into the first classification of patients, those with pulmonary arterial hypertension.

Several inherent issues related to disease incidence and heterogeneity naturally limit the ability to conduct research to study pulmonary hypertension. Similar to other conditions, a lot of advancements in our knowledge of the pathophysiology of pulmonary hypertension and development of novel therapeutic strategies have relied on translational research to create animal models. There have been dozens of animal models that have been developed to create neointimal lesions that mimic various pulmonary hypertension groups. Those experimental models have included chronic hypoxia, chemically or surgically induced (eg, pneumonectomy); in addition

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Central Message

Translational research with animal models is necessary to understand the pathophysiology of left heart-associated pulmonary hypertension and to study novel therapeutic options.

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to overexpression, knockout, and various other models that aimed to simulate different types of pulmonary hypertension, more so pulmonary arterial hypertension and that associated with lung disease.¹⁻³ Creation of pulmonary hypertension models related to left heart disease has been challenging; the attempts have included pulmonary artery banding (used to study mainly the effect on the right side of the heart), aortopulmonary shunt, aortic banding, and pulmonary venous banding.^{1-3,5,6} Although those various models were fruitful to a certain extent, all were associated with several drawbacks that hampered their utility in investigational research.

In search of a useful “ideal” left heart-associated pulmonary hypertension model, Fujimoto and colleagues⁷ from Japan have created an interesting animal model with laboratory rats, the basis for their featured research article in the current issue of the *Journal*. Through a left thoracotomy, they created left atrial obstruction with a metal clip. The rats were followed up with serial echocardiography, cardiac catheterization, and, finally, organ excision and various histopathologic, DNA microarray and real-time polymerase chain reaction examinations. Relative to a control group of rats that underwent sham operation, the rats with clips placed showed evidence of an increased left atrial inflow gradient that was associated with increased systolic right heart

pressure, increased diastolic left and right heart pressures, increased pulmonary venous wall thickness, medial but not neointimal hypertrophy of the pulmonary arteries, enhancements of transforming growth factor- β and endothelin-1 protein expressions. Fujimoto and colleagues⁷ concluded that this novel feasible rat model might be used for further study of the pathophysiology of and potential therapy for left heart-associated pulmonary hypertension.

This article by Fujimoto and colleagues⁷ is very stimulating and seems to be the closest we get to an ideal left heart-associated pulmonary hypertension model. It may be more practical than another nice piglet model that was described by the Toronto group in this *Journal* as well.^{5,6} No doubt we will continue to rely on translational research for a better understanding of this disease and will discover novel therapeutic interventions that could alter the unfavorable prognosis of this challenging disease. Nonetheless, resemblance to a real-life pathology that is so variable and so complicated is doubtful, and several questions remain. Can a single model fit all forms of this heterogeneous disease? Can we ever recreate a process that might have started during fetal development? Can we extrapolate any of the findings from various animals to

human beings? And how can we cross the bridge from translational research to clinical application? The task is challenging; however, the prize is extraordinary, and any step forward is treasured.

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