Commentary: No one drug does only one thing in only one setting

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A well-worn cliché states that no one drug does only one thing. This can be an advantage when the drug's actions are applicable to other pathologies. On the basis of reports of anti-inflammatory and antioxidant actions of the antifibrotic agent pirfenidone, Saito and colleagues¹ conducted a proof-of-concept exploration, reported in this issue of the *Journal*, of the efficacy of pirfenidone in attenuating lung ischemia-reperfusion injury—a different setting that shares some pathophysiology with idiopathic pulmonary fibrosis. With a rodent model of acute single-lung ischemia-reperfusion, Saito and colleagues¹ report that oral pirfenidone pretreatment (1) attenuated loss of compliance, (2) improved arterial oxygenation, (3) reduced perivascular edema and the presence of neutrophils and apoptotic cells, and (4) decreased expression of proinflammatory mediator messenger RNA after ischemia-reperfusion relative to the untreated group. The conclusion that pirfenidone inhibits experimental acute pulmonary ischemia-reperfusion injury is supported by the data.

The study by Saito and colleagues¹ has several strengths. It is innovative, albeit observational. The study was not designed to determine dose-response characteristics, nor to determine mechanisms of action or molecular targets. The end points were relevant to the pathophysiology of pulmonary ischemia-reperfusion injury. The research design appropriately included time-matched sham and control (untreated) ischemia-reperfusion groups. All groups received the vehicle used to dissolve pirfenidone, thereby avoiding any confounding between-group effects attributable to the vehicle itself. Notably, Saito and colleagues¹ measured blood and lung tissue concentration of pirfenidone, demonstrating that oral pirfenidone was systemically present. Key aspects of histologic and messenger RNA data were quantified, to which statistics were applied.

The study by Saito and colleagues¹ also has several weaknesses. Although the rat model is inexpensive and less labor-intensive than larger animal models, rodent inflammatory biology has notable differences from that of other species, which may question rodent data's

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Central Message

The antifibrotic drug pirfenidone has application in lung after ischemic injury because of similarities in the pathophysiology of idiopathic fibrosis.

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applicability to those species. The messenger RNA data could have been further strengthened by measuring respective protein levels in lung tissue. Although Saito and colleagues¹ frequently state that the in vivo ischemia-reperfusion model simulates lung transplantation, flushing and storage solutions with various compositions and temperatures used in transplantation may present a different pathobiology than warm ischemia-reperfusion. Furthermore, it is not clear whether, in practice, efficacy would require administration of pirfenidone to both donor and recipient of the lung transplant.

There are many next steps required to develop pirfenidone for use in lung ischemia-reperfusion injury, least of which is testing in large animal survival studies. But this study of Saito and colleagues¹ is a necessary first step. On the basis of inhibition of proinflammatory mediator and reactive oxygen species² generation by pirfenidone, and the reported direct effects on promoting contractile function,³ pirfenidone may have exciting potential in the heart. Reports suggest pirfenidone is effective in reducing infarct size and fibrosis in myocardial infarction.⁴ Pirfenidone may also be effective as an adjunct to cardioprotective strategies designed to attenuate postcardioplegia pathology. Likewise, pirfenidone may be useful in cardiac transplantation when added to storage solutions and administered after transplant. Pirfenidone may also be applicable in other organ systems that share inflammatory and oxidant mechanisms. The study by Saito and

colleagues¹ is a first step in seeking to broaden applications for pirfenidone to lung protection and beyond.

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