ex vivo lung perfusion perfusate during the recovery of severely injured lungs may also prove to result in positive outcomes.

Despite the promising findings of their study, further examination of this therapeutic drug needs to be performed in different animal models (preferably a large animal transplant model) to evaluate its preclinical potential within a more translational setting. Furthermore, although the dosing of NSA was arbitrarily set based on previously published literature, the optimal dose and timing of administration are the next step toward optimizing this therapeutic strategy.

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Commentary: A journey of a thousand miles begins with a single step

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Ischemia-reperfusion injury (IRI) remains the leading cause of primary graft dysfunction in lung transplantation and is considered the most important risk factor in early morbidity and mortality.¹ One of the prevailing features of IRI is necroptosis, a recently recognized category of cell death. Traditionally, cell death has been divided into controlled, programmed cell death (apoptosis), and accidental cell death (necrosis). Necroptosis displays features of both: the initiation of necroptosis is tightly regulated, and necroptotic cells trigger a strong inflammatory response.

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CENTRAL MESSAGE

Necroptosis is a promising new therapeutic target for reducing ischemia-reperfusion injury in lung transplantation.

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Necroptosis has been described as a relevant factor in a variety of diseases.^{2,3}

In this issue of the *Journal*, Ueda and colleagues⁴ report on the efficacy of necrosulfonamide, a mixed-lineage kinase domain-like protein inhibitor, in a rat pulmonary ischemia-reperfusion injury model. The number of

necroptotic cells in the lungs was significantly decreased in the necrosulfonamide study group. This resulted in less inflammation, improved oxygenation, and better lung compliance.

We would like to congratulate Ueda and colleagues on this well-conducted study and the excellent results. The authors come from a well-known lung transplant center, which is highly acknowledged for its work in basic research.

“A journey of a thousand miles begins with a single step” is a famous quote from the Chinese philosopher Lao-Tze. Ueda and colleagues have successfully made this first step, but many more must follow before necrosulfonamide can be implemented in the clinical routine. The results of this study are intriguing; however, there is one major limitation: the rat hilar clamp model, which served as the basis of all experiments. A hilar clamp model only partly resembles the complex changes a donor organ undergoes during lung transplantation (eg, damage related to donor brain death, prolonged cold ischemic time, immunologic aspects). Therefore, it is imperative to confirm the effect of necrosulfonamide in a rat/mouse transplantation model. Then a large animal model, such as a porcine single lung transplantation model, has to follow. This step is critical, because a considerable number of promising agents targeting IRI have failed the transfer from small to large animal models.

Anticipating the far end of this “road of a thousand miles”, necrosulfonamide could be tested in human donor

lungs not suitable for lung transplantation. This approach is increasingly used to assess new therapeutics and their effect on human tissue without the risk of harming a patient.^{5,6} Only when this last milestone has been passed successfully, necrosulfonamide can be introduced in the clinical routine.

Thus, the road ahead is terribly long—but then again, without this important first step made by Dr Ueda and colleagues, the goal of treating IRI will always remain elusive.

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