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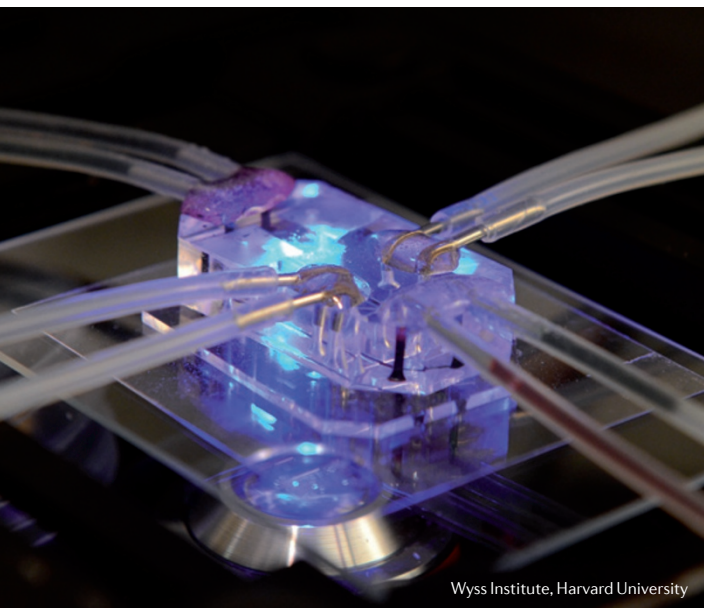
LUNG DISORDERS

A new model and modulator of pulmonary oedema

Pulmonary oedema is characterized by the accumulation of intravascular fluid in the alveolar air spaces and interstitial tissues of the lung, and can occur following disorders such as heart failure or renal disease, or as a result of drug toxicity.

Together, two complementary studies published in *Science Translational Medicine* have identified a new microdevice model — termed 'lung on a chip' — of pulmonary oedema, and identified a blocker of transient receptor potential cation channel vanilloid 4 (TRPV4) that inhibits pulmonary oedema in animal models.

In the study by Huh and colleagues, the authors built on previous work that had engineered the 'lung on a chip' device (which was shown to reconstitute the alveolar–capillary interface of the human lung and mechanically 'breathe') by investigating whether the device could mimic pulmonary oedema and be used to test pharmaceutical agents. To develop a drug toxicity-induced model, they perfused interleukin-2 (IL-2) — which can cause dose-limiting pulmonary oedema when given therapeutically — through the microvascular channel of the device. This caused leakage of liquid across the endothelial lining of the microvascular channel and into the previously air-filled alveolar compartment, which compromised oxygen transport. Moreover, this was exacerbated in the presence of breathing motions, showing that the device could mimic the clinical situation.



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Further work showed that IL-2 caused pathological changes in the integrity of the pulmonary barrier and that the mechanical forces generated by breathing acted synergistically with IL-2 to enhance the opening of cell–cell junctions in the epithelial and endothelial monolayers.

Next, they investigated whether the microdevice could be used to test compounds that might prevent vascular leakage induced by IL-2. Administration of angiopoietin 1 (which is known to stabilize endothelial intercellular junctions) in the microvascular channel inhibited vascular leakage and prevented paracellular gap formation. Because stimulation of TRPV4 can cause vascular leakage in the lung, and because TRPV4 is activated by mechanical distortion of endothelial cells, the authors also examined the effects of a novel TRPV4 blocker, GSK2193874. This compound inhibited the increase in vascular permeability induced by IL-2.

The study by Thorneloe and colleagues first showed that TRPV4 is more highly expressed in the pulmonary vasculature of patients with heart failure than in healthy controls. They then established that TRPV4 mediates the formation of pulmonary oedema in response to high pulmonary venous pressure in isolated mouse lungs, and that GSK2193874 could inhibit this pulmonary oedema. Similar effects were seen in canine lungs using GSK2263095 — an analogue of GSK2193874 that has enhanced potency for canine TRPV4.

The authors next evaluated the effect of GSK2193874 in rodent models of pulmonary oedema induced by heart failure. Pretreatment of mice with GSK2193874 for 5 days before myocardial infarction and treatment for 2 weeks afterwards inhibited the resultant pulmonary oedema. The TRPV4 blocker also improved systemic arterial oxygenation and reduced left ventricular dilation, but had no significant effects on survival. In models of established pulmonary oedema, GSK2193874 (given orally for 1 week, beginning 1 week after myocardial infarction) resolved oedema but did not significantly improve systemic arterial oxygenation or ventricular dilation.

Together, these studies identify a new disease model for assessing agents for the treatment of pulmonary oedema, and suggest that TRPV4 blockers might be such a class of agents with therapeutic potential.

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ORIGINAL RESEARCH PAPERS Huh, D. *et al.* A human disease model of drug toxicity-induced pulmonary edema in a lung-on-a-chip microdevice. *Sci. Transl. Med.* **4**, 159ra147 (2012) | Thorneloe, K. S. *et al.* An orally active TRPV4 channel blocker prevents and resolves pulmonary edema induced by heart failure. *Sci. Transl. Med.* **4**, 159ra148 (2012)