# Patient-derived Lung-on-Chip model replicates Interleukin-2 – induced vascular leak syndrome

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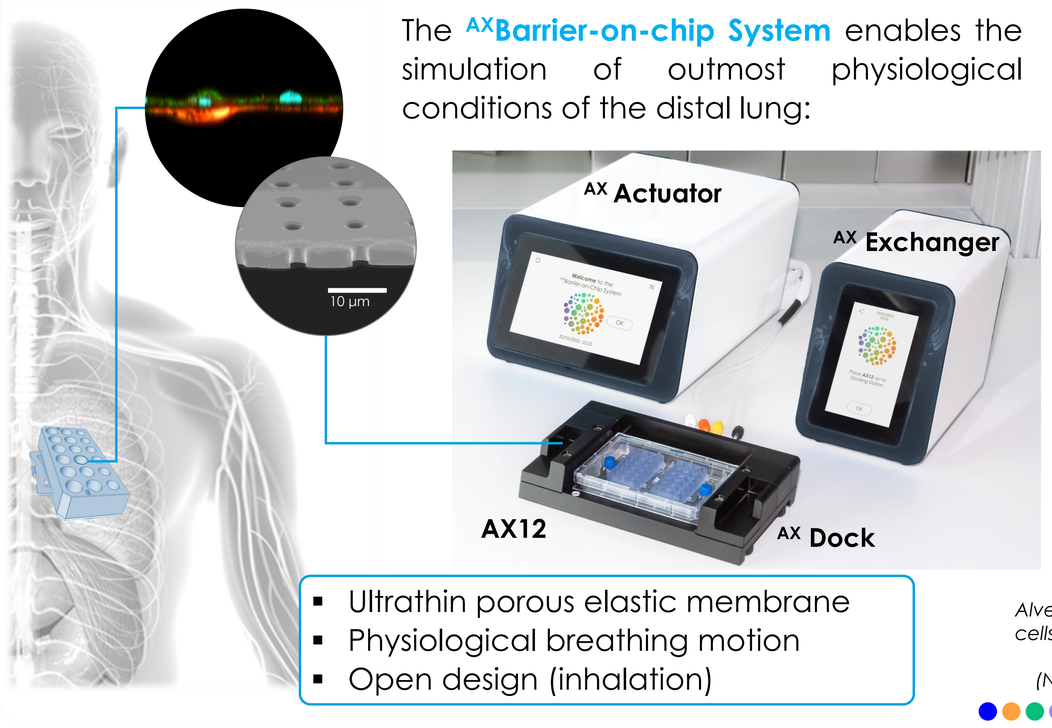
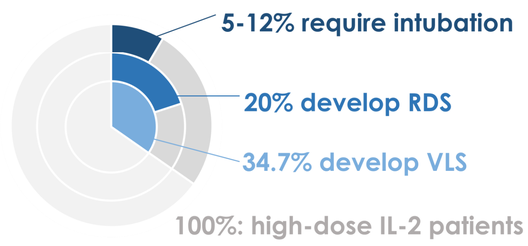
## A patient-derived Lung-on-Chip for immunotherapy safety assessment



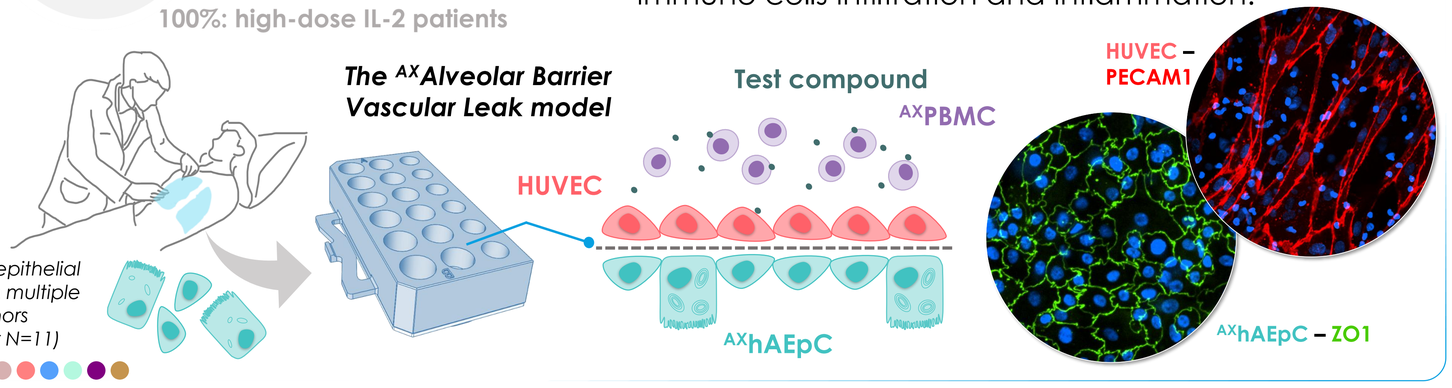

The **AXBarrier-on-chip System** enables the simulation of outmost physiological conditions of the distal lung:

- Ultrathin porous elastic membrane
- Physiological breathing motion
- Open design (inhalation)

Preclinical in vitro and animal models used for assessment of drug safety often fail to predict complications in humans, especially when the drug in question targets the immune system such as in cancer immunotherapy.

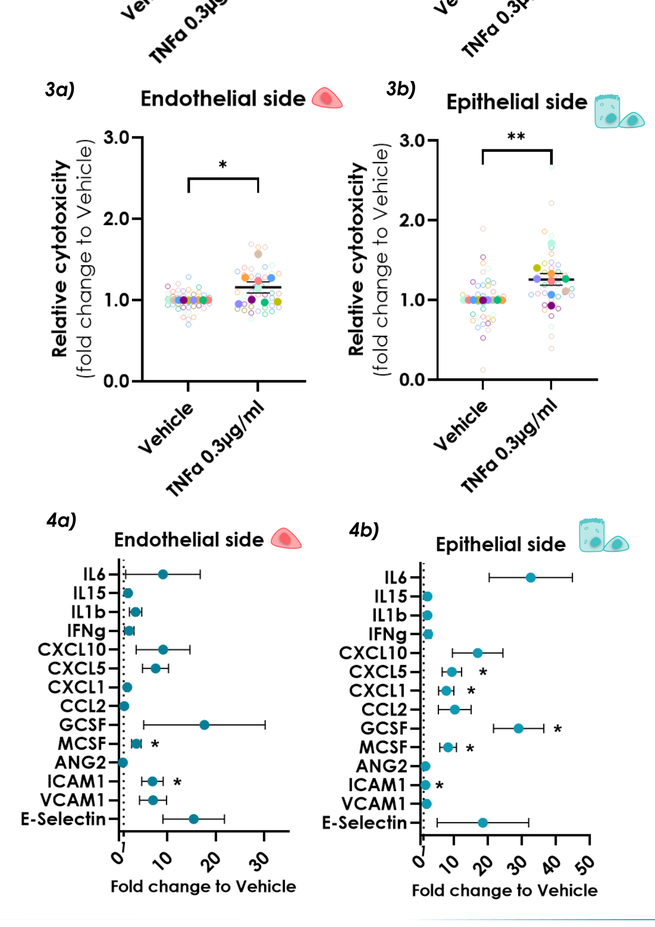



Adverse events can occur in the lungs, where drugs such as the first approved immunotherapy **Interleukin-2** (IL2, Proleukin®) have led to unwanted side effects. In fact, approx. 1/3 of the patients under IL2 therapy develop **vascular leak syndrome (VLS)**, characterized mainly by lung edema, immune cells infiltration and inflammation.



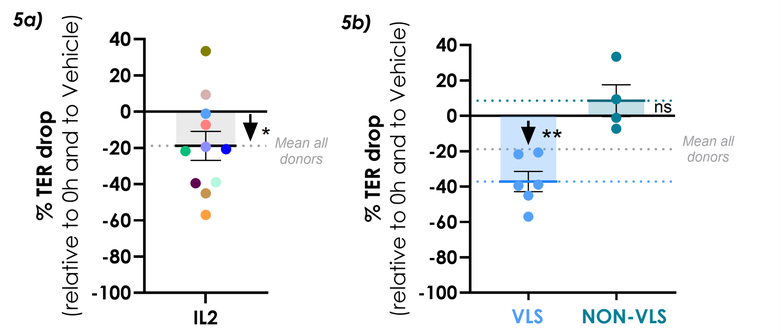

## Model validation

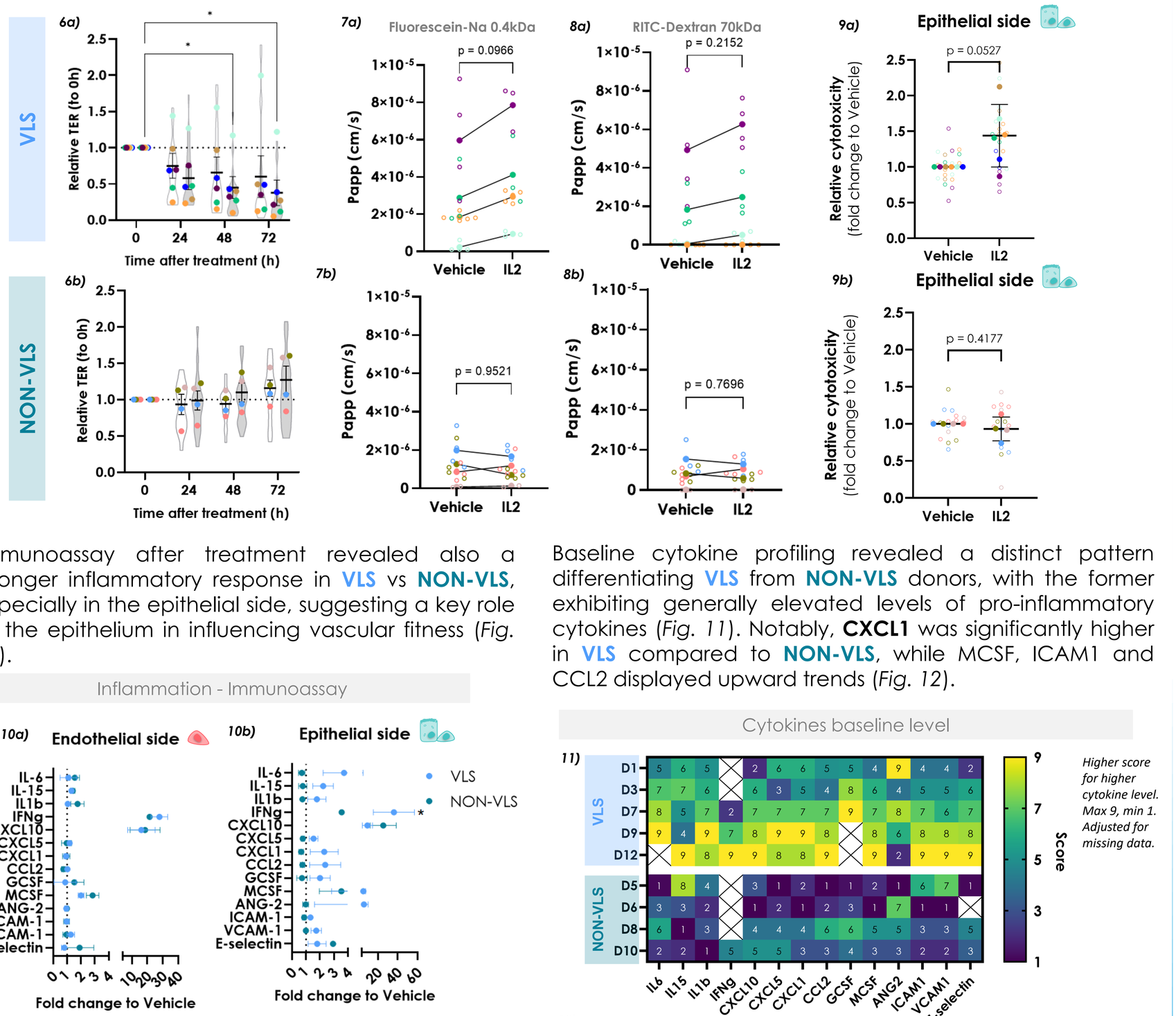
The *AXAlveolar Barrier Vascular Leak model* was first evaluated with TNFa, as inducer of cytokines storm and VLS. Under these conditions, the model successfully reproduced VLS hallmarks across the 9 tested donors (*Fig. 1-4*):




## IL2-induced vascular leak syndrome & patient variability

Treatment with Interleukin-2 (Proleukin®) across 11 donors resulted in varying degrees of barrier disruption. Based on the relative TER reduction at 72 hours, donors were stratified into two groups: **VLS** and **NON-VLS** (*Fig. 5*).
These groups exhibited distinct profiles in TER, permeability, and cytotoxicity assays. Notably, features characteristic of VLS were exclusively observed in the **VLS** group (*Fig. 6-9*).




Immunoassay after treatment revealed also a stronger inflammatory response in **VLS** vs **NON-VLS**, especially in the epithelial side, suggesting a key role of the epithelium in influencing vascular fitness (*Fig. 10*).




Baseline cytokine profiling revealed a distinct pattern differentiating **VLS** from **NON-VLS** donors, with the former exhibiting generally elevated levels of pro-inflammatory cytokines (*Fig. 11*). Notably, **CXCL1** was significantly higher in **VLS** compared to **NON-VLS**, while MCSF, ICAM1 and CCL2 displayed upward trends (*Fig. 12*).




## Conclusions

These results highlight the **predictive potential** of the *AXAlveolar Barrier Vascular Leak* model, which reliably replicates the healthy alveolus, its impairment upon IL2 treatment, and notably, the **patient-to-patient variability observed in the clinics**. This model could thus contribute significantly to advancing cancer immunotherapy drug development by facilitating the selection of drugs with a more favorable benefit-risk ratio.

**Abbreviations:** AXhAEpC: human alveolar primary epithelial cells HUVEC: human umbilical vein endothelial cells AXPBMC: peripheral blood mononuclear cells **TER**: transbarrier electrical resistance