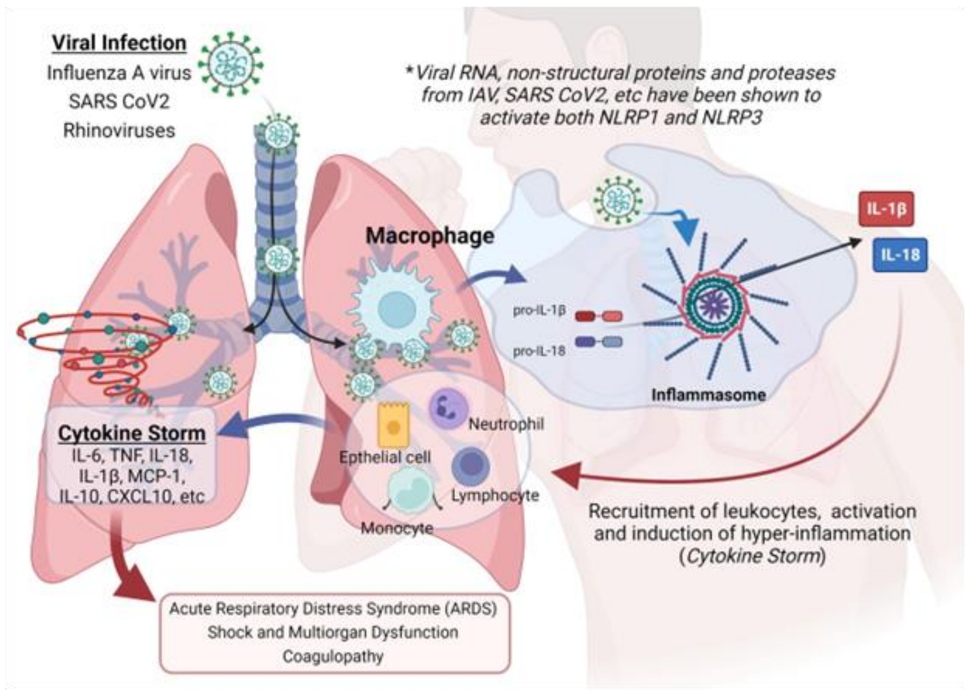
ADS032, a novel dual NLRP1/3 inflammasome inhibitor for the treatment of lung inflammation



Introduction

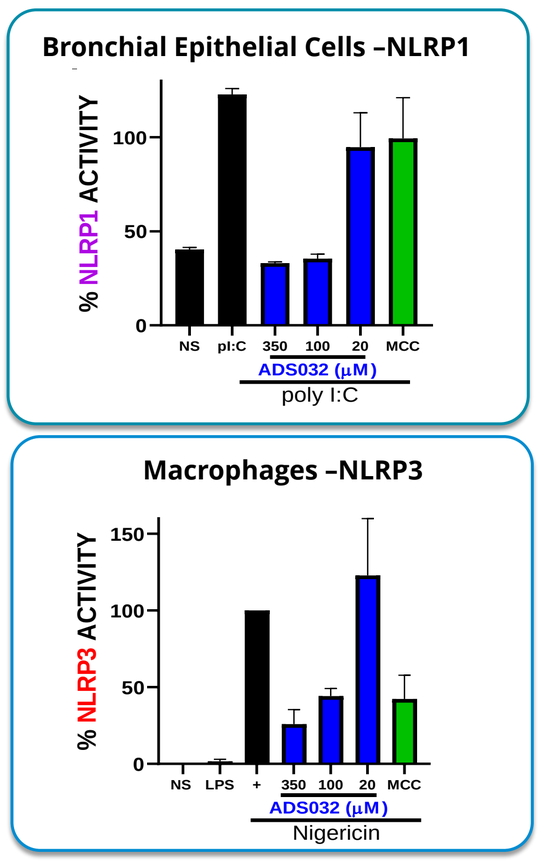
Inflammasomes are multiprotein complexes that sense host dysbiosis due to both endogenous and external triggers. When activated, they process IL-1β and IL-18 to their active, proinflammatory forms.

NLRP3, one of the most studied inflammasomes, is a key inflammation mediator in the dendritic compartment of innate the immune system (macrophages, neutrophils). Excessive NLRP3 inflammasome activation is linked to the pathophysiology of a broad range of respiratory inflammatory diseases. These include silicosis, influenza, SARS-Cov-2 and cystic fibrosis.

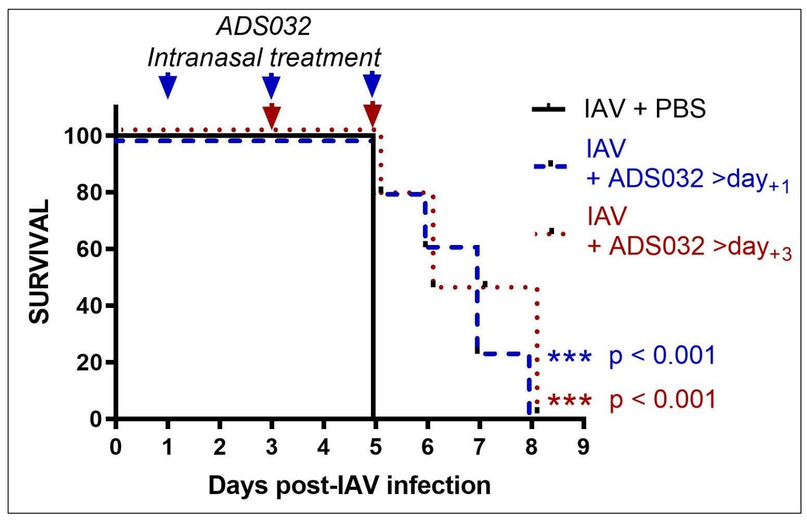
NLRP1, present in barrier-type cells such as bronchial epithelial cells, has more recently emerged as an additional driver of inflammation in respiratory disease. Triggers of NLRP1 activation include viral proteases and viral dsRNA.

Given this prominent role in diseases by both NLRP1 and NLRP3, there is considerable interest in targeting both to ameliorate overt respiratory inflammation. To date, pharmacological targeting of inflammasomes has focused primarily upon NLRP3 activity, however, until now there has not been a specific inhibitor described for NLRP1.

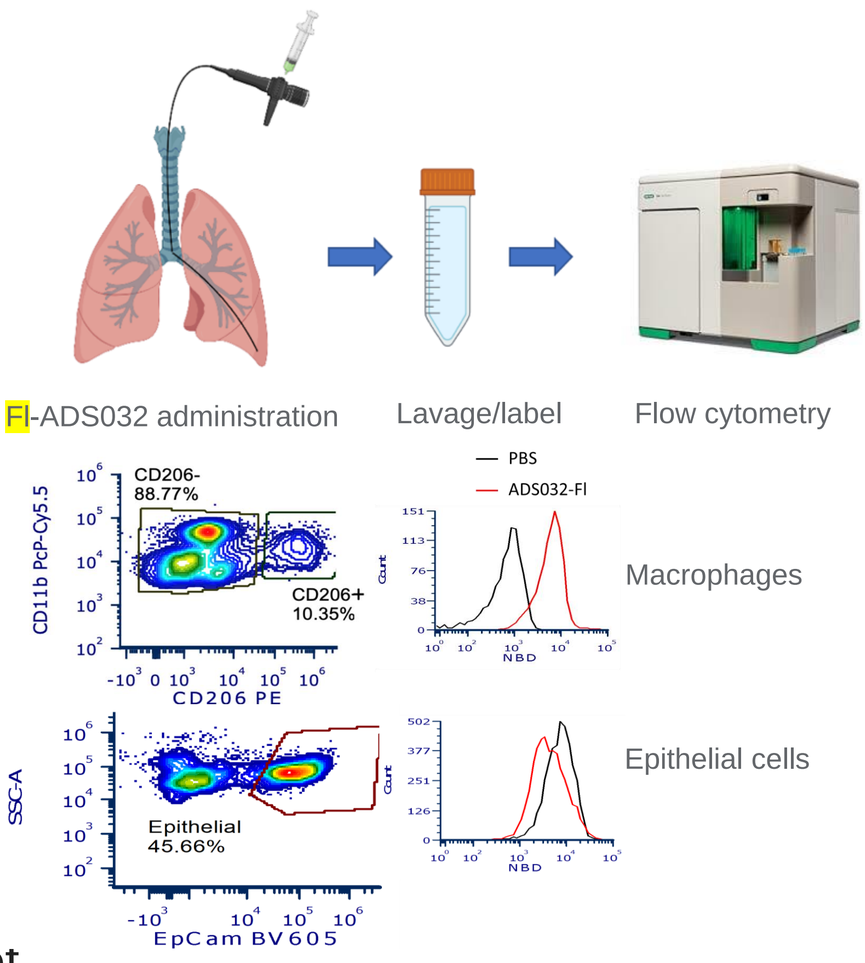
ADS032 represents the first small molecule inhibitor that specifically binds to and inhibits the activation of both NLRP1 and NLRP3. ADS032 is being developed as an inhaled delivery to the lung.



ADS032 blocks activation of NLRP1 and NLRP3 in human bronchial cells and macrophages



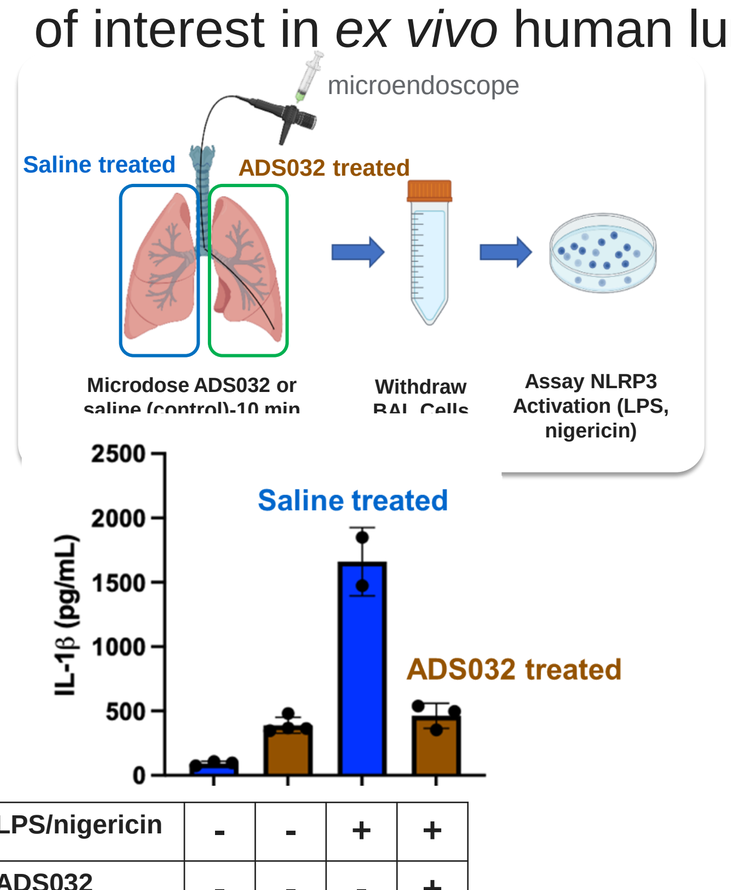
ADS032 efficacy in a murine model of pandemic influenza infection, improving survival and decreasing immune cell infiltrate



Labelled ADS032 enters target cells of interest in *ex vivo* human lungs

Summary

Direct binding of both NLRP1 and NLRP3 ▪ *Demonstrated by direct competition and binding: MS analysis*
NLRP1 and NLRP3 inhibition ▪ *Demonstrated in human bronchial epithelial cells and human alveolar macrophages*
Intranasal delivery in mice ▪ *Well tolerated, no induction of inflammation* ▪ *Demonstrates efficacy in various lung inflammatory models (flu, silicosis)*
Instillation delivery in *ex vivo* human lungs ▪ *Drug rapidly taken up in both immune and epithelial cells* ▪ *Inflammasome inhibition demonstrated*
Pilot toxicology in rats ▪ *SC (7 day), PO and IV delivery of high doses well tolerated* ▪ *Rapid systemic clearance demonstrated*



LPS/nigericin	-	-	+	+
ADS032	-	-	-	+

ADS032 reduces NLRP3-mediated inflammation in *ex vivo* human lungs

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