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# Endothelial eNAMPT amplifies pre-clinical acute lung injury: efficacy of an eNAMPT-neutralising monoclonal antibody

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**Underscoring the therapeutic potential for targeting the eNAMPT/TLR4 pathway in ARDS/VILI, a humanised eNAMPT-neutralising monoclonal antibody (mAb) was highly effective in reducing the severity of ARDS in these dual complementary pre-clinical ARDS models** <https://bit.ly/3ljEhBD>

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## ABSTRACT

**Rationale:** The severe acute respiratory syndrome coronavirus 2/coronavirus disease 2019 pandemic has highlighted the serious unmet need for effective therapies that reduce acute respiratory distress syndrome (ARDS) mortality. We explored whether extracellular nicotinamide phosphoribosyltransferase (eNAMPT), a ligand for Toll-like receptor (TLR)4 and a master regulator of innate immunity and inflammation, is a potential ARDS therapeutic target.

**Methods:** Wild-type C57BL/6J or endothelial cell (EC)-cNAMPT<sup>-/-</sup> knockout mice (targeted EC NAMPT deletion) were exposed to either a lipopolysaccharide (LPS)-induced (“one-hit”) or a combined LPS/ventilator (“two-hit”)-induced acute inflammatory lung injury model. A NAMPT-specific monoclonal antibody (mAb) imaging probe (<sup>99m</sup>Tc-ProNamptor) was used to detect NAMPT expression in lung tissues. Either an eNAMPT-neutralising goat polyclonal antibody (pAb) or a humanised monoclonal antibody (ALT-100 mAb) were used *in vitro* and *in vivo*.

**Results:** Immunohistochemical, biochemical and imaging studies validated time-dependent increases in NAMPT lung tissue expression in both pre-clinical ARDS models. Intravenous delivery of either eNAMPT-neutralising pAb or mAb significantly attenuated inflammatory lung injury (haematoxylin and eosin staining, bronchoalveolar lavage (BAL) protein, BAL polymorphonuclear cells, plasma interleukin-6) in both pre-clinical models. *In vitro* human lung EC studies demonstrated eNAMPT-neutralising antibodies (pAb,

mAb) to strongly abrogate eNAMPT-induced TLR4 pathway activation and EC barrier disruption. *In vivo* studies in wild-type and EC-cNAMPT<sup>-/-</sup> mice confirmed a highly significant contribution of EC-derived NAMPT to the severity of inflammatory lung injury in both pre-clinical ARDS models.

**Conclusions:** These findings highlight both the role of EC-derived eNAMPT and the potential for biologic targeting of the eNAMPT/TLR4 inflammatory pathway. In combination with predictive eNAMPT biomarker and *NAMPT* genotyping assays, this offers the opportunity to identify high-risk ARDS subjects for delivery of personalised medicine.