

The aim of this clinical study was to investigate the effect of nebulised GSK1995057 on pulmonary and systemic inflammation and cell injury in an *in vivo* human model of lung injury induced by inhaled lipopolysaccharide (LPS).

**Methods** Healthy subjects were enrolled in a double-blind, placebo-controlled study and randomised to nebulised GSK1995057 or placebo (1:1) administered 1 hour prior to LPS inhalation. Measurements were performed in bronchoalveolar lavage (BAL) fluid obtained at 6 hours after LPS challenge (7 hours after dosing) and in serum obtained over 24 hours post dosing of GSK1995057. The primary endpoint was BAL neutrophil count at 6 hours post LPS exposure. Data are geometric mean (95% CI).

**Results** Thirty-seven healthy subjects were enrolled. One subject in the placebo group was excluded from the analysis of BAL markers as the BAL was technically poor. Pre-treatment with inhaled GSK1995057 significantly reduced pulmonary and systemic markers of inflammation. In addition, there was a reduction in pulmonary vWF reflecting reduced endothelial cell injury/activation (Table 1). The prevalence of LPS-induced clinical symptoms (e.g. fever, nausea) was also lower in GSK1995057 treated subjects compared with placebo treated subjects. There were no serious adverse events related to study drug.

**Conclusion** This is the first report that inhalation of a novel human antibody fragment directed against the TNFR1 receptor attenuates mechanisms implicated in the pathophysiology of ALI. GSK1995057 may be a potential therapy for ALI.

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**Abstract S94 Table 1. Effect of GSK1995057 on markers of pulmonary and systemic inflammation.**

BALF	Placebo (n = 18)	GSK1995057 (n = 18)	% reduction	P-value
PMN (10 <sup>4</sup> cells/ml)	6.5 (4.5, 9.4)	4.5 (2.89, 6.89) 3.8 (2.8, 5.3)*	31(41) <sup>†</sup>	0.17(0.03) <sup>†</sup>
IL-1b(pg/ml)	6.8(4.3, 10.4)	1.4 (1.0, 2.1)	79	<0.0001
IL-6 (pg/ml)	386.1(277.5, 537.4)	169.4 (111.2, 257.9)	56	0.003
IL-8 (pg/ml)	332.1(254.6, 433.2)	117.5 (82.5, 167.54)	65	<0.0001
MIP1alpha (pg/ml)	133.7(87.2, 205.1)	15.6 (8.3, 29.1)	88	<0.0001
MCP-1 (pg/ml)	799.4 (591.6, 1080.2)	159.5(101.9, 249.5)	80	<0.0001
vWF (ng/ml)	12.8(9.2, 17.9)	8.1(6.1, 10.8)	37	0.04

Serum	Placebo (n = 19)	GSK1995057 (n = 18)	% reduction	P-value
CRP (g/ml)**	55.2(31.0, 98.4)	12.0 (6.6, 21.8)	78	0.0007
OSM (pg/ml)***	20.7(13.4, 32.0)	7.5(4.8, 11.7)	64	0.002

\*PMN data with subject classified as biological outlier (>3 x inter quartile range outside the upper quartile) removed.

<sup>†</sup>% Reduction and statistical significance for BALPMN data with biological outlier excluded.

\*\* CRP data taken at 24h post GSK1995057 dosing. Data are adjusted means with baseline and time effects considered.

\*\*\*OSM data taken at 6h post LPS inhalation. Data are adjusted means with baseline and time effects considered.

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#### EXPLOITING THE IMMUNOREGULATORY ROLE OF SIGLEC-E VIA SIALIC ACID-FUNCTIONALISED NANOPARTICLES AS A NOVEL APPROACH FOR THE TREATMENT OF ACUTE LUNG INJURY

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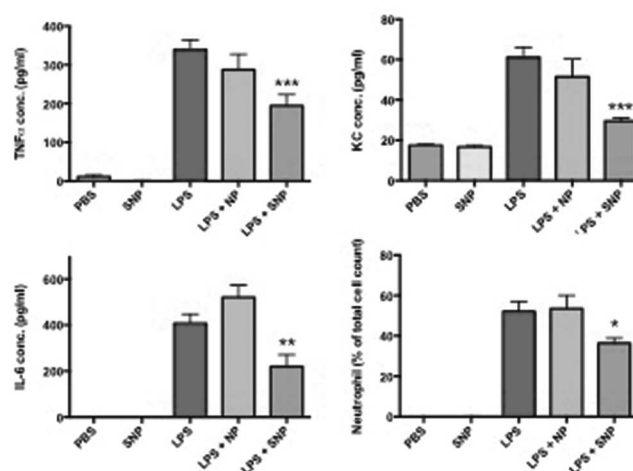
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Acute Lung Injury (ALI) is a life-threatening disorder underpinned by dysregulated inflammatory cascades, with resultant injury to lung architecture. Currently, provision of supportive care represents the mainstay of treatment for ALI and novel anti-inflammatory therapeutic strategies are urgently required. We have developed a polymeric nanoconstruct surface-functionalised with sialic acid targeting moieties (SNP), exploiting the anti-inflammatory effects arising from the targeted engagement of Siglec-E receptors on activated macrophages, with potential therapeutic utility in ALI.

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles of uniform size distribution (approximately 150nm in diameter) were synthesised in accordance with a salting-out formulation. Intratracheal instillation of 20µg lipopolysaccharide (LPS) was utilised as a model of ALI in C57BL/6 mice, co-administered with 1µg SNP or non-functionalised nanoparticles (NP). Bronchoalveolar lavage (BALF) samples were collected 24 hours after treatment for analysis by enzyme-linked immunosorbent assay (ELISA).

As exemplified in Figure 1., intratracheal instillation of SNP significantly attenuated BALF levels of pro-inflammatory TNF and IL-6 cytokines, in addition to the neutrophil chemoattractant KC. Moreover, BALF differential cell counts revealed a decrease in neutrophil numbers upon treatment with SNP under LPS-induced pro-inflammatory conditions. Further analyses addressing the therapeutic utility of SNP have been undertaken, including lung wet/dry ratios, histology and toxicological evaluation, with promising outcomes.

This research clearly demonstrates the ability of SNP to diminish the inflammatory response in a murine model of LPS-induced ALI. Considering that chemoattractants and cytokines are key mediators in the pathogenesis of ALI, these results substantiate the credibility of this nanoscaffold as a therapy for ALI. Ultimately, we aim to progress this modality to a human setting, specifically analysing its effects on alveolar macrophages isolated from human volunteers, before advancing to a human *ex vivo* lung perfusion model.



**Abstract S95 Figure 1. Therapeutic efficacy of SNP in a murine model of LPS-induced ALI (\* p < 0.05, \*\*p < 0.001, \*\*\*p < 0.001 compared to LPS control, as established by one-way ANOVA and Tukey post-hoc test).**

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#### SIMVASTATIN AS AN ADJUVANT THERAPY FOR INFECTION AND SEPSIS—IN-VITRO AND IN-VIVO STUDIES SUGGEST PRE-EMPTIVE / EARLY THERAPY IN THE ELDERLY

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