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 (10^4 cells/ml)	6.5 (4.5, 9.4)	4.5 (2.89, 6.89) 3.8 (2.8, 5.3)*	31(41)†	0.17(0.03)†
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.
†% 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.

S95 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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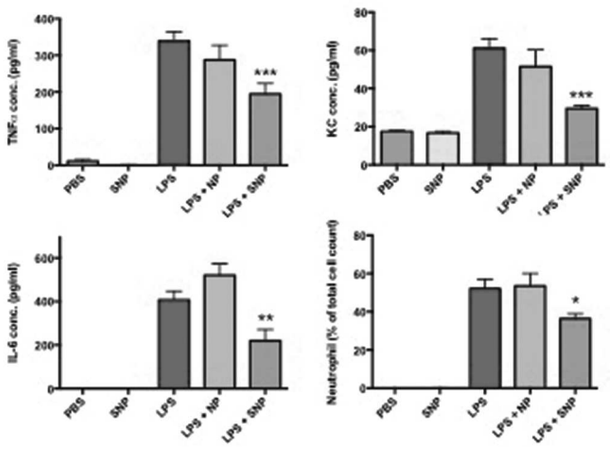
Acute Lung Injury (ALI) is a life-threatening disorder underpinned by dysregulated inflammatory cascades, with resultant injury to lung architecture. Currently, provision of supportive care represents the mainstay of treatment for ALI and novel anti-inflammatory therapeutic strategies are urgently required. 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.

Polylactic-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 Tuley post-hoc test).

S96 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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