between Trx and MIF in adults with SIRS/sepsis. (Leaver 2009) Furthermore Trx was shown to inhibit the secretion of MIF in THP-1 cells (Tamaki 2006). The aim of this study was to determine the effect of exogenous Trx on the release of MIF and for comparison IL-8 and IL-10 from primary human monocytes at baseline and following stimulation with lipoteichoic acid (LTA) or lipopolysaccharide (LPS).

**Methods** Monocytes were extracted from whole blood of healthy volunteers using Percoll gradients and MACS columns. Monocytes ($1\times10^6$ cells/ml) were pre-incubated with Trx (0.1—10 000 nM) for 24 h followed by treatment (24 h) with medium alone, LPS 1 μg/ml, LTA 10μg/ml. MIF, IL-8 and IL-10 concentrations in cell supernatants were determined by ELISA.

**Results** Following incubation with Trx there was no significant change in MIF release from monocytes. By contrast, LPS and LTA significantly ($p<0.01$) induced MIF from base line. When monocytes were treated with LPS (Abstract S51 Figure 1) or LTA following pre-incubation with Trx, MIF release was significantly less than the theoretical additive effects of the two treatments alone. By contrast, although Trx significantly induced IL-8 and IL-10, Trx did not modulate LPS or LTA induced cytokine release.

**Conclusion** Trx reduced MIF release following stimulation with LPS and LTA. Extracellular Trx exerts an anti-inflammatory effect in this model. The Trx/MIF axis should be explored as a potential route for therapeutic intervention in patients with sepsis.

## S52 THE ROLE OF THE RECEPTOR FOR ADVANCED END PRODUCTS (RAGE) IN ACUTE LUNG INJURY (ALI)

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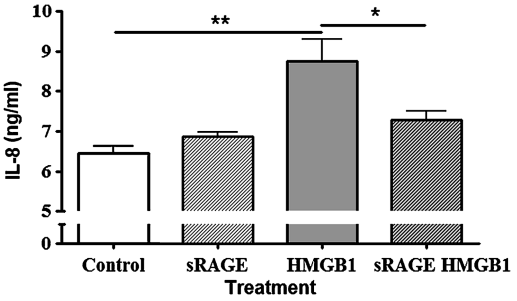
**Introduction** RAGE is expressed by both alveolar epithelial and endothelial cells. The receptor can bind to pro-inflammatory ligands, including HMGB1 which is elevated in ALI. RAGE negative mice show a reduced inflammatory response when challenged with LPS. We hypothesised that RAGE activation in the pulmonary circulation propagates inflammation in ALI and that soluble RAGE (sRAGE) can act as a scavenger receptor, reducing RAGE-mediated inflammation.

**Aim** To investigate HMGB1 RAGE-dependent activation of pulmonary microvascular endothelial cells, and resultant production of inflammatory cytokines and tissue-destructive proteases in a model of ALI.

**Methods** Primary HPMECs (human pulmonary microvascular endothelial cells) were stimulated with clinically relevant concentrations of HMGB1. MAPK phosphorylation was assessed by Western Blot. Supernatants collected at 72 h were analysed by ELISA for IL-8, Tissue Inhibitors of Metalloproteinases (TIMPs)-1 and -2. Experiments were repeated both with a RAGE-blocking antibody and in the presence of sRAGE.

**Results** HMGB1 increased phosphorylation of ERK1/2 at 15 min and p38 at 30 min after stimulation HMGB1 increased IL-8 secretion (from 6.46 ng/ml to 8.75 ng/ml, $p<0.01$) and significant decrease in TIMP-1 secretion (from 19.79 ng/ml to 16.9 ng/ml, $p<0.05$) at 72 h. MAPK activation, IL-8 increase and TIMP-1 decrease was significantly reversed in the presence of sRAGE ($p<0.05$) (Abstract S52 Figure 1). Incubating cells with a RAGE blocking antibody inhibited MAPK phosphorylation by HMGB1.

**Conclusions** Data suggest that RAGE ligation leads to an increase in pulmonary endothelial cell activation and IL-8 release. *In vivo* this would increase inflammatory cell influx into the pulmonary environment, propagating inflammation. This is combined with a decrease in TIMP protection potentially increasing degradation of the basement membrane by functionally unopposed proteinases.




Abstract S52 Figure 1 sRAGE and HMGB1 were used at 1 μg/ml. Statistics are one way ANOVA with Tukey post test. *$p<0.05$, **$p<0.01$.

That these changes can be partially rescued using sRAGE shows that it could potentially decrease inflammatory damage in ALI.

## S53 NANOPARTICLES CAUSE PULMONARY INFLAMMATION THROUGH IL-1α AND PARTIAL ACTIVATION OF THE NLRP3 INFLAMMASOME

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Nanoparticles are increasingly used in various fields, including biomedicine and electronics. Their size and physical characteristics allow them to easily access the cytosol of tissue or immune cells. Although inorganic metal oxide nano-$TiO_2$ is believed to be biologically inert, an emerging literature reports increased incidence of respiratory diseases in exposed people. Here, we show that instillation of nano-$TiO_2$ induces lung inflammation which is strongly suppressed in IL-1R- and IL-1α-deficient mice. They have drastically reduced neutrophil recruitments in the alveolar space, together with lung inflammatory cytokine productions. Surprisingly, the NLRP3 inflammasome complex seems to be only partially involved. Nlrp3-, ASC- or Casp-1-deficient mice show only a slight reduction in pulmonary inflammatory response. IL-1β-deficient mice exhibit decreased inflammation parameters that are less pronounced than IL-1α-deficient mice. *In vitro* experiments show that primary pulmonary epithelial cells cultured in presence of nano-$TiO_2$ are able to produce KC and IL-1α, but not IL-1β, to initiate inflammation. In conclusion, it appears that nanoparticles-mediated inflammation is highly dependent on IL-1α and to a less extend on the NLRP3 inflammasome/IL-1β axis. Collectively, these data demonstrate that the expending use of nano-$TiO_2$, e.g. in cosmetics, may present a health hazard and should be taken under consideration, a situation reminiscent of inflammation provoked by asbestos exposure.

# Orphan lung diseases

## S54 CHARACTERISING SARCOIDOSIS USING A WEB-BASED REGISTRY: A PILOT STUDY

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**Introduction and Objectives** Sarcoidosis is a chronic multisystem disorder of unknown cause. Demographic and phenotypic characteristics have not been comprehensively studied in Britain.