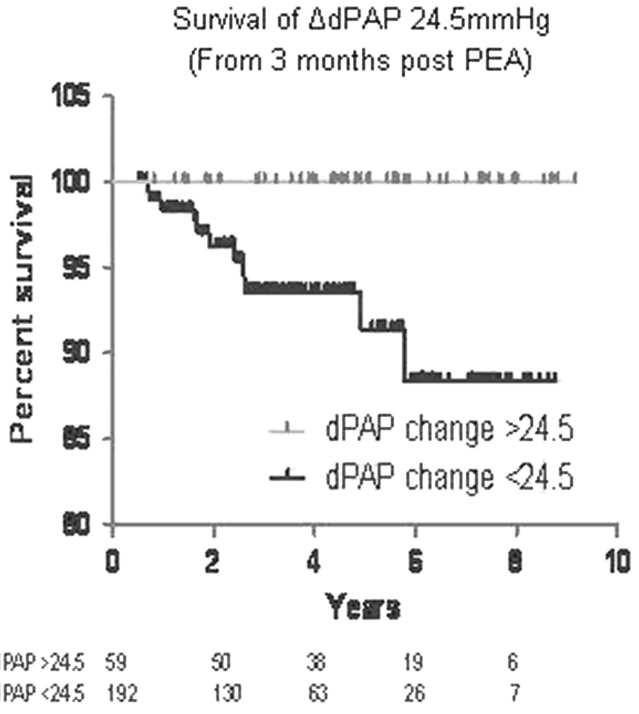

Abstract S100 Figure 1 Survival of ΔdPAP 24.5 mm Hg (From 3 months post PEA).

S101 PRAZIQUANTEL PREVENTS PROGRESSION AND REVERSES PULMONARY HYPERTENSION AND PULMONARY VASCULAR REMODELLING IN A MOUSE MODEL OF SCHISTOSOMIASIS

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Introduction Schistosomiasis is the most common world-wide cause of pulmonary hypertension. Praziquantel is the drug of choice and has been shown to reverse the liver pathology associated with *Schistosomamansoni* in mice. We sought to determine whether praziquantel could reverse established pulmonary vascular remodelling and pulmonary hypertension in a mouse model of *Schistosomamansoni*.

Methods Mice were infected percutaneously with a low dose of *Schistosomamansoni*. At 17 weeks post-infection mice were either sacrificed or received praziquantel by oral gavage or a vehicle control. At 17 or 25 weeks post-infection right ventricular systolic pressure (RVSP) and right ventricular (RV) hypertrophy, liver and lung egg counts were measured. Pulmonary vascular remodelling was assessed by morphometry, following immunohistochemistry. A cytokine array was performed and the degree of infectivity was measured by faecal egg counts.

Measurements and main results At 25 weeks post-infection there was a significant increase in RVSP and RV hypertrophy between infected and control mice, which was reversed by Praziquantel treatment. RVSP was elevated in mice at 25 weeks post-infection but had normalised with praziquantel treatment. There was a significant increase in the muscularisation of small pulmonary arteries following 25 weeks of schistosomal infection, which was prevented by with Praziquantel treatment. Liver, lung and faecal egg counts were elevated following 25 weeks of schistosomal infection and substantially reduced with praziquantel treatment.

Conclusions This study has shown that severe pulmonary vascular remodelling accompanied by an increase in RVSP and RV hypertrophy occurs 25 weeks post-infection in a mouse model of S mansoni infection. Importantly, this study has shown that progression of disease can be prevented by two oral doses of praziquantel. The mechanism thought to underlie the dramatic pulmonary vascular remodelling, is a local increase in inflammatory cytokines.

Acute lung injury: what are the causes?

S102 KGF ENHANCES PULMONARY PRODUCTION OF PRO-EPITHELIAL REPAIR FACTORS IN A HUMAN IN VIVO MODEL OF ACUTE LUNG INJURY

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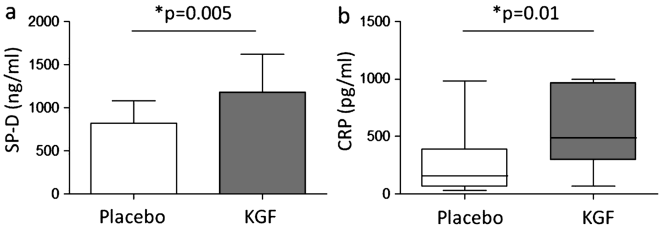
Introduction Keratinocyte Growth Factor (KGF) has been suggested as a possible intervention for acute lung injury. In vitro it enhances epithelial repair. In the human ex vivo perfused lung model KGF supplementation after LPS-induced injury was associated with improved alveolar fluid clearance indicating improved epithelial function. We hypothesised that KGF pre-treatment in the in vivo human LPS model of lung injury would reduce epithelial injury and increase production of mediators that induce epithelial repair.

Methods 36 subjects were randomised to either placebo or recombinant human KGF (Palifermin) 60 μg/kg/day for 3 days prior to inhalation of 50 μg *E Coli* LPS. 6 h after LPS inhalation subjects underwent bronchoalveolar lavage (BAL). BAL concentrations of SP-D, RAGE, MMP-9 and CRP were measured by ELISA. Total protein was measured by Bradford assay. Markers of LPS-induced pulmonary inflammation were measured using multiplex bead array (CXCL8, TNFα, MCP-1, IL-6, MMP-7/-8) or ELISA (HMGB1 and Calgranulin C). Permeability was assessed by BAL IgG:total protein ratio.

Results KGF increased BAL SP-D (Abstract S102 Figure 1A) but not RAGE. KGF increased BAL MMP-9 by 77% (p=0.04). KGF increased BAL IL-6 by 84% (p=0.03) and CRP (Abstract S102 Figure 1B). KGF did not alter BAL total white cell count or neutrophilia, TNFα, CXCL8, MCP-1, HMGB1 or Calgranulin C. KGF did not alter BAL total protein or permeability index. Increased frequency of altered taste or tongue sensation (p=0.01) and of facial erythema (p=0.005) were observed in the KGF-treated group. There were no serious adverse events.



Abstract S102 Figure 1

Conclusion KGF specifically increased the production of several factors that are key for epithelial migration and wound healing including MMP-9 and IL-6, and increased the production of SP-D, a marker of type II alveolar epithelial cell proliferation. Furthermore it increases the production of BAL CRP which in the pulmonary compartment acts as an opsonin, aiding the clearance of apoptotic cells (or bacteria). However, KGF pre-treatment did not alter the inflammatory infiltrate or permeability change in response to inhaled LPS. Data suggest that KGF may promote a healing environment within the damaged alveoli and support further investigation of KGF as a treatment for lung injury.