infection. Both pathogens target macrophages by evading innate immune recognition or intracellular killing. Since macrophages play a key role in inflammatory responses and their resolution, we tested the hypothesis that HIV-1 infection of macrophages may modulate inflammatory responses to co-infection with Mtb contributing to the immunopathogenesis of active tuberculosis (TB).

Methods Innate immune responses to Mtb were assessed in human macrophages with and without productive HIV-1 infection using genome-wide transcriptional profiling. Array data were validated by quantitative PCR and correlated with protein secretion in cell culture supernatants. The effects of Mtb co-infection on HIV replication were assessed by ELISA. The mechanisms underlying the observed phenotype were examined by Western immunoblotting and using selective inhibitors of innate immune signalling pathways.

Results HIV-1 infection of monocyte-derived macrophages leads to sustained, exaggerated pro-inflammatory responses to Mtb co-infection, including cytokines and chemokines that may recruit and activate further inflammatory leucocytes, and matrix metalloproteinases which play a role in tissue destruction. This phenotype is associated with rescue of HIV-1 replication following early repression in response to Mtb. Our data suggest that augmented inflammatory responses to Mtb result from deficient induction of anti-inflammatory interleukin-10 in HIV-1 infected cells. None of these changes were evident in HIV-1 infected macrophages co-infected with *Streptococcus pneumoniae*, and the specificity of the effect in Mtb co-infection was mirrored by lower IL-10 and higher pro-inflammatory IL-1β in respiratory samples from HIV-1 infected patients with pulmonary TB compared to non-tuberculous respiratory infection. Complementation of deficient IL-10 responses to Mtb in HIV-1 infected macrophages reverses the exaggerated pro-inflammatory phenotype. HIV-1 infection attenuates phosphorylation of p38 and ERK1/2 in mitogen activated kinase pathways involved in IL-10 induction downstream of TLR2 and dectin-1 receptor stimulation. IL-10 production in HIV-1 infected cells is also inhibited in response to zymosan stimulation of these pathways. Inhibition of virus maturation with HIV-1 protease inhibitors, does not affect attenuation of IL-10 responses.

Conclusions Deficient induction of homeostatic IL-10 and consequent augmentation of pro-inflammatory responses may contribute to the immunopathogenesis of active TB and propagation of virus infection in HIV-1/Mtb co-infection.

S131 HUMAN MACROPHAGE MODEL OF BIOMASS SMOKE EXPOSURE SHOWS IMPAIRED INGESTION OF *STREPTOCOCCUS PNEUMONIAE*

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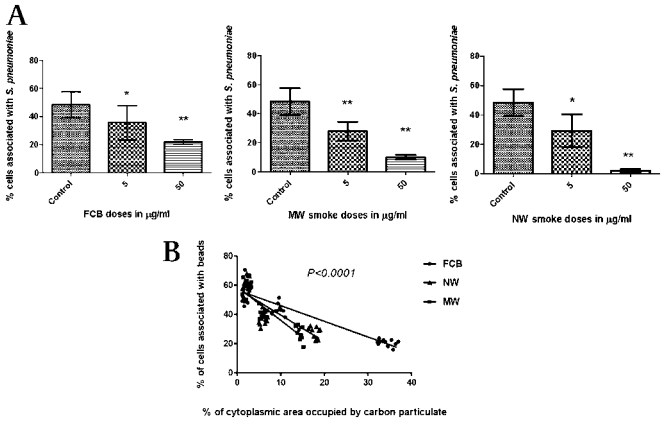
Background Three billion people worldwide, primarily in less economically developed countries use biomass fuel (BMF) as their main source of household energy. In children, the risk of pneumonia is increased by exposure to BMF smoke by a factor of 1.8. In adults, an epidemiological association between acute pneumonia and outdoor air pollution and tobacco smoke exposure has been demonstrated but there are no data confirming an association between pneumonia and BMF smoke exposure. Few mechanistic studies have been performed in humans investigating the association between BMF exposure and *S pneumoniae*. This work aimed to assess the phagocytic ability of particulate matter (PM) challenged macrophages on fluorescent labelled beads and *S pneumoniae*.

Methods In order to model BMF exposure, monocyte derived macrophages (MDMs), from 12 day old buffy coats, were challenged with different types and doses of PM (fine carbon black (FCB), Malawi wood and Norwegian wood). The percentage area of the macrophage cytoplasm that PM occupied (PM load) was calculated using image analysis software (Image SXM). The ability of PM challenged MDMs to phagocytose fluorescent labelled beads and *S pneumoniae* was assessed by counting the beads / bacteria associated with MDMs, using fluorescent microscopy.

Results Increasing the PM dose was associated with a decrease in the percentage of cells associated with *S pneumoniae* (Abstract S131 figure 1A) and beads. The same result was observed when the average number of *S pneumoniae* (or beads) within cells was used as the outcome measure. With all three PMs used, a lower PM load was correlated with a higher capacity to phagocytose *S pneumoniae* and beads. Malawi wood and Norwegian wood impaired MDMs phagocytic ability more than FCB (Abstract S131 figure 1B).



Abstract S131 Figure 1 (A) Comparison of percentage of cells associated with *S pneumoniae* with 3 different types of particulate matter. (B) Comparison between the percentages of cells associated with *S pneumoniae* and cytoplasmic area occupied by PM and three different types of PM (FCP, Norwegian wood and Malawi wood).

Conclusions Our data demonstrate that MDMs exposed to PM have impaired ability to phagocytose beads and *S pneumoniae* and that wood smoke exposed MDMs had a greater phagocytic impairment than FCB. These observations support an association between BMF smoke exposure and pneumonia. Our model enables further work to be carried out on the dose-response of smoke exposure and pneumococcal disease as well as into the pathogenesis of increased susceptibility to pneumococcal infection in BMF exposed individuals.

S132 INVESTIGATING THE ROLE OF PELLINO1, AN E3 UBIQUITIN LIGASE, IN MODULATING SIGNALLING PATHWAYS CONTROLLING THE INFLAMMATORY RESPONSE

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Viruses, such as Rhinovirus, are a major cause of asthma exacerbations. Pellino1 was identified as an interleukin 1 receptor associated kinase binding partner and has shown to act as an E3-ubiquitin ligase that is involved in Lysine-63 polyubiquitination of interleukin 1 receptor associated kinase 1/4 and RIP1, which are key mediators of the Toll-like receptor and interleukin 1 receptor (IL-1R) signalling pathways. As such, these pathways are implicated in responses to both bacterial and viral infections. However, the functional importance of Pellino proteins in regulating immune responses and their role in airway inflammatory diseases is yet to be

elucidated. We hypothesised that Pellino1 would play a critical role in regulating the inflammatory response in the lung airway epithelium. Pellino1 was knocked down in the human bronchial airway epithelial cell line BEAS2B and primary human bronchial epithelial cells (PBECs) using targeted siRNA. Knockdown of Pellino1 at the transcriptional level was measured using qPCR. Pellino1 knockdown cells were stimulated with Toll-like receptor/IL-1R agonists or the natural pathogen rhinovirus 1B (RV1B) and cytokine release was measured using ELISA. Signalling pathways were explored by western blotting.Pellino1 was expressed in BEAS2B and primary bronchial epithelial cells. Pellino1 mRNA transcript level was knocked down by 78% in BEAS2B and 94% in PBECs. Pellino1 knockdown led to reduced IL-8 generation in response to IL-1ß and a viral mimic Poly (I:C) stimulation in BEAS2B, however RANTES production was unchanged. In contrast to the BEAS2B, the primary bronchial epithelial cells exhibited preserved IL-1 signalling. However, these cells also showed a reduction in IL-8 production in response to both Poly (I:C) stimulation and RV1B infection. Pellino1 knockdown had no effect on the interferon-stimulated gene RANTES production. Pellino1 knockdown leads to reduced IL-8 production in response to a viral mimic Poly (I:C) in lung airway epithelial cells and RV1B in PBECs. These data indicate that Pellino1 regulates proinflammatory responses in airway epithelium and may be a feasible target to downregulate neutrophillic airway inflammation while retaining antiviral immunity, which would be highly beneficial in the treatment of chronic airway inflammatory disorders such as asthma and COPD. These studies were supported by an MRC/Asthma UK PhD studentship.

ILD: clinical studies

S133 THE ASSESSMENT OF HEALTH RELATED QUALITY OF LIFE IN INTERSTITIAL LUNG DISEASE WITH THE KING'S BRIEF INTERSTITIAL LUNG DISEASE QUESTIONNAIRE (K-BILD)

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Introduction The King's brief interstitial lung disease questionnaire (K-BILD) is a recently developed and validated 15 item HRQOL questionnaire comprising of 3 health domains (psychological, breathlessness and activities, and chest symptoms) and an overall HRQOL score. We set out to evaluate HRQOL in a large group of patients with interstitial lung diseases (ILD's) and determine the factors that influence it.

Methods 219 patients with ILD (60 idiopathic pulmonary fibrosis (IPF), 81 connective tissue associated ILD, 23 idiopathic non-specific interstitial pneumonitis (NSIP), 21 hypersensitivity pneumonitis, 10 organising pneumonia, 24 other) attending ILD clinics at King's College and Royal Brompton Hospitals completed the K-BILD. The K-BILD Scores range from 0 to 100, with a higher score representing a better HRQOL. Demographic data, immunosuppressant medication, long-term oxygen therapy use, multi-disciplinary team ILD diagnosis and lung function were recorded.

Results Patients had a mean (SEM) age of 60 (1) years, 75% of patients were Caucasian, 60% were females, mean (SEM) VC% predicted was 80 (24) % and TLCO % predicted was 47 (18)%. HRQOL was impaired in all domains, mean (SEM) scores: psychological 62 (2), breathlessness and activities 43 (2), chest symptoms 67 (2), total 59 (2). There were no significant associations between overall HRQOL and age ($r=-0.007$) or gender ($p=0.13$). There was a modest correlation between HRQOL and lung function (Abstract S133 table 1). HRQOL was significantly lower in IPF patients compared to other ILD's (total score 51 (3) vs 62 (2); $p<0.01$), those with UIP pattern vs NSIP (total score 51 (3) vs 62 (3); $p<0.01$) and those prescribed long-term oxygen therapy (total score 38 (4) vs 63 (2); $p<0.01$). IPF patients prescribed immunosuppressant medication had significantly worse overall HRQOL (48 (4) vs 74 (8); $p=0.02$). There was no significant difference between CTD-NSIP patients compared with idiopathic NSIP (total score 62 (3) vs 62 (5); $p=0.91$).

Conclusions HRQOL is impaired in patients with ILD. The type of ILD, immunosuppressant medication, and lung function all influence HRQOL. This study provides further clinical validation of the K-BILD.

Abstract S133 Table 1 The relationship between the HRQOL assessed with the K-BILD and lung function

	Psychological	Breathlessness and activities	Chest symptoms	Total score
FEV_1 % predicted	r=0.34	r=0.46	r=0.38	r=0.43
	p<0.01	p<0.01	p<0.01	p<0.01
FVC % predicted	r=0.32	r=0.45	r=0.38	r=0.42
	p<0.01	p<0.01	p<0.01	p<0.01
TLCO % predicted	r=0.41	r=0.48	r=0.35	r=0.46
	p<0.01	p<0.01	p<0.01	p<0.01
CPI	r=0.36	r=0.44	r=0.35	r=0.42
	p<0.01	p<0.01	p<0.01	p<0.01

Data shown are Spearman's correlation coefficients.
CPI, Composite physiologic index.

S134 HIGH PREVALENCE OF ISCHAEMIC HEART DISEASE (IHD) IN PATIENTS MEETING CLINICO-RADIOLOGICAL PROFILE FOR IDIOPATHIC PULMONARY FIBROSIS (IPF)

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Introduction IPF and ischaemic cardiac disease may share pathological similarities including aberrant tissue remodelling. Given their recognised heterogeneity, we hypothesised that patterns of IPF (usual interstitial pneumonia, UIP; non-specific interstitial pneumonia, NSIP; indeterminate UIP-NSIP) may inter-relate differently with the prevalence of IHD and associated co-morbidities.

Methods Ethical approval was obtained to identify all cases of IPF undergoing high-resolution CT between 2003 and 2010. Details of cardiac disease and its management (risk factors, drug treatment, coronary angiography and revascularisation) were included. Consensus radiological diagnoses were reached by 2 chest physicians and 2 thoracic radiologists. Comparison of multiple variables was undertaken using logistic regression (STATA V.11).

Results Of 256 potentially suitable cases, 96 fulfilled ascertainment and were consented: 38 (40%) UIP, 44 (48%) NSIP and 14 (16%) indeterminate (INDET) pattern. An inter-observer k coefficient of 0.56 was calculated for radiological agreement. Regardless of morphological pattern, patients with IPF had a significant cardiovascular risk profile. Where present, IHD predated IPF in the majority of cases, with the highest occurrence (58%) in the UIP subgroup. UIP patients were of comparable age, gender frequency, smoking status and had similar rates of major cardiovascular risk factors as NSIP and INDET subjects. Crucially, they were 2.5 times more likely than NSIP patients to have IHD after adjustment for