activator Forskolin and the phosphodiesterase 4 (PDE4) inhibitor Roflumilast (all 1μm, 3d) was evaluated. IL-1β (2ng/ml, 24hr) was used for cyclooxygenase 2 (COX-2) induction. α-smooth muscle actin (α-SMA, a myofibroblast marker), COX-2, EP2, EP4 and β_2-receptor expression was analysed by Western blotting and immunocytochemistry, respectively. Adenylyl cyclase mRNA was measured by qPCR and cAMP was measured by radioimmunoassay.

Results F-IPF showed increased α-SMA and collagen expression and repressed COX-2 expression compared to F-NL. PGE_2 treatment prevented TGF-β1-induced α-SMA expression and COX-2 repression in F-NL, which was mimicked by β_2-agonists and Forskolin. PGE_2 also reduced α-SMA expression and increased COX-2 expression in F-IPF despite that it induced significantly less cAMP than in F-NL But this effect on F-IPF was not mimicked by β_2-agonists and Forskolin as they induced even less cAMP than PGE_2 in these cells. TGF-β-treated F-NL also produced less cAMP than untreated cells in response to these cAMP. stimulants. However, the expression of EP2, EP4, β_2-adrenoceptors and adenylyl cyclase isoforms was similar in F-NL and F-IPF. Furthermore, combination of PGE_2 with Roflumilast showed greater effect than PGE_2 alone on α-SMA reduction and COX-2 expression in F-IPF and F-NL, whereas Roflumilast alone had no effect.

Conclusions cAMP is a key anti-fibrotic regulator of myofibroblast differentiation. However, cAMP production in myofibroblasts is defective, probably due to increased degradation by PDE4.

S130 EXOGENOUS MACROPHAGES ARE RETAINED IN MOUSE LUNGS AFTER INJURY AND TARGET THERAPEUTIC TRANSGENES TO THE INJURED LUNG PARENCHYMA

doi:10.1136/thoraxjnl-2012-202678.135

K McNulty, EK Sage, R Alexander, CJ Scotton, SM Janes. *University College London, London, UK*

Introduction Pulmonary fibrosis evolves in response to epithelial injury in a number of lung diseases, and carries a poor prognosis; novel therapies are urgently needed. The epithelial mitogen keratinocyte growth factor (KGF) has been shown to prevent fibrosis in a number of animal models however its therapeutic utility is limited by its short half-life. There is a growing interest in cell therapy approaches, and we hypothesised that macrophages could be used as vehicles to target KGF therapy to injured lung.

Methods Lentiviral vectors expressing luciferase, KGF and GFP (control) were generated and used to transduce the IC-21 macrophage cell line. Appropriate transgene expression was confirmed. KGF macrophages were co-cultured with primary mouse tracheal epithelial cells in a proliferation bioassay. Luciferase-expressing macrophages were tracked longitudinally using bioluminescence imaging after oropharyngeal delivery to the lungs of mice given bleomycin to induce injury, or saline control. Immunostaining was used to localise macrophages within lung sections. KGF and GFP-macrophages were delivered during bleomycin-induced lung injury; endpoint measures included lung histology, micro-CT analysis, and quantification of inflammatory cell infiltrates, vascular leak, lung collagen by HPLC, and inflammatory and fibrotic mediators by ELISA and qPCR.

Results Exogenously delivered macrophages were retained in the lungs of bleomycin-injured mice, but not uninjured controls, when given during either the inflammatory or fibrotic phases of injury, and localised to injured lung parenchyma. KGF-transduced macrophages induced proliferation of mouse tracheal epithelial cells during co-culture, but delivery to bleomycin-injured mice was not associated with overall improvements in endpoints when delivered during either the inflammatory or fibrotic phases of injury. Delivery of macrophages *per se* was associated with an increase in inflammatory mediators consistent with classical M1 macrophage activation, which may have off-set any beneficial effects of KGF-transduced macrophages.

Conclusions Exogenously delivered macrophages are preferentially retained in injured lung and show potential as vehicles to target therapeutic transgenes by localising to damaged areas. Whilst KGF-transduced macrophages induced epithelial proliferation *in vitro*, any protective effects *in vivo* may have been negated by the exacerbatory effects of macrophage delivery. Future work will determine whether *ex vivo* manipulation of macrophage phenotype can confer therapeutic benefit.

Occupational lung disease

S131 IDENTIFYING OCCUPATIONAL ASTHMA AMONG A COHORT OF CLEANERS IN THE NORTH EAST ENGLAND

doi:10.1136/thoraxjnl-2012-202678.136

[1]S Alfajjam, [2]C Stenton, [1]T Pless-mulloli, [1]D Howel. *[1]Institute of Health and Society, Newcastle Upon Tyne, United Kingdom; [2]NHS Foundation Trusts, Newcastle Upon Tyne, United Kingdom*

Introduction We have demonstrated a prevalence of asthma of 14% in a survey of 1400 UK hospital and university cleaners, and an estimated incidence of asthma of 3.3/1000 person-years. 26% of cleaners reported work-related symptoms. We have explored the possibility that these cleaners have occupational asthma using serial measurements peak expiratory flow (PEF) and airway responsiveness.

Objectives To identify occupational asthma in a cohort of cleaners.

Methods A respiratory symptom questionnaire was distributed among 1400 cleaners working in three local hospital trusts and two universities. Airway responsiveness (PD20) was measured in those with asthma symptoms using a methacholine challenge test. Those with measurable airway responsiveness (PD20 <1600ug) were invited to undergo a repeat measurement away from work and to carry out serial PEF measurements that were analysed for a work-related effect using OASYS (Burge, Pantin et al. 1999).

Results 557 (40%) returned the questionnaire and 167 reported respiratory symptoms. Of these, 56 (33.5%) attended for methacholine challenge testing. 26 (46%) had quantifiable results.

12 subjects underwent serial PD20 measurements at and away from work. Overall, there were no significant changes in airway responsiveness. Geometric mean PD20 at work was 193 ug and away from work was 254 ug (t=0.6; p=0.5). 5 cleaners showed a 3-fold or more increase in PD20 away from work raising the possibility of significant changes in those individuals.

10 subjects completed serial peak expiratory flow measurements. The mean OASYS score was 1.97. One subject had a score of > 2.5 suggesting a work related effect.

Conclusion Although the prevalence of asthma symptoms in our cohort is consistent with other epidemiological evidence showing a 1.5 to 2.0 fold risk of asthma, we found little evidence of occupational asthma using conventional clinical diagnostic tests in this group. The findings are consistent with the hypothesis that cleaners develop their asthma in an unusual way, possibly though a low dose irritant mechanism.

Burge, P.S., C.F.A. Pantin, et al. (1999). "Development of an expert system for the interpretation of serial peak expiratory flow measurements in the diagnosis of occupational asthma." Occupational and Environmental Medicine **56**(11): 758–764.

S132 CHRONIC BRONCHITIS, PULMONARY FUNCTION, AND OCCUPATIONAL EXPOSURE IN FRAMINGHAM HEART STUDY

doi:10.1136/thoraxjnl-2012-202678.137

SY Liao, X Lin, DC Christiani. *Harvard School of Public Health, Boston, United States*

Introduction Occupational exposure to dust, gases and fumes has been associated with chronic airway disease or poor lung function in several workforce based studies. However, workforce studies may underestimate such associations because of healthy worker effect confounding bias. We conducted a community-based study that used a more generalised populations of individuals and less susceptible to healthy worker effect. We investigated the associations between the self-reported occupational exposure and chronic bronchitis, as well as pulmonary function testing.

Methods The study population is the Third-Generation cohort from Framingham Heart Study with a total of 3,894 participants. We used participants' examination of FEV1, FEV1/FVC, chronic bronchitis (based on self reported symptoms) as outcomes. Occupational exposure was assessed by self-reported exposure to vapours, gas, dust, or fumes at work. Gender, age, height, pack-years, and smoking status were used as covariates in our analysis. We used linear mixed effect models for continuous outcomes and generalised estimating equations for dichotomous outcomes due to the family structure.

Results There are 1,745 participants reporting occupational exposure at work and 2,149 participants reporting no occupational exposure. The association of occupational exposure on the FEV_1 and FEV_1/FVC was not significant in this cohort. However, self-reported occupational exposure was associated with a risk of chronic bronchitis after controlling for covariates (OR 1.55, 95% CI 1.19 to 2.01). Current smoking was associated with a greater risk of chronic bronchitis after controlling for covariates (OR 3.20, 95% CI 2.37 to 4.32). Those with combined occupational and smoking exposure had a 5 fold increased risk of chronic bronchitis compared those with neither occupational nor smoking exposure.

Conclusions Occupational exposure is significantly associated with chronic bronchitis. In addition to preventing smoking exposure, preventive strategies should be taken by clinicians and health policy-makers to reduce occupational exposures in workplace.

S133 COPD, OCCUPATION AND QUALITY OF LIFE AMONG RESIDENTS OF A HISTORICALLY INDUSTRIALISED AREA

doi:10.1136/thoraxjnl-2012-202678.138

LGB Lewis, A Darby, J Waterhouse, D Fishwick. *Sheffield Teaching Hospitals, Sheffield, United Kingdom*

Introduction COPD is known to significantly affect health and quality of life, and is increasingly recognised to have a significant contribution from occupational exposures, particularly vapours, gases, dusts and fumes (VGDF). However, there is a paucity of evidence exploring the relationship between exposure to VGDF at work and health-related quality of life.

Methods A random selection of adults aged over 55 years in the Sheffield area of the UK were mailed a self-completed questionnaire (including questions on respiratory symptoms and physician-diagnosed disease, smoking and occupational history); responders were invited to perform lung function (FEV_1 and FVC), and to complete the EQ-5D-3L quality of life instrument. A measure of socioeconomic deprivation (SED), using the proportion of individuals within a participants postal code receiving income support, was also collected.

Results Out of 4000 questionnaires, 2001 were returned. From these, 623 provided further data as detailed above. 57% were male, 62% had been, or were, smokers, 24% had a physician diagnosis of COPD and 62% reported having been exposed to VGDF in the past. In univariate analysis those with COPD were more likely to be older, have smoked, been exposed to VGDF and have a lower quality of life (all $p<0.001$). A history of exposure to VGDF was associated with a lower quality of life ($p<0.001$). Both VGDF exposure and COPD were associated with greater levels of SED ($p<0.001$). A linear regression analysis was performed using the EQ_5D summary index as the dependant variable and age, gender, SED, smoking status, physician diagnosed COPD and percentage predicted FEV_1 and VGDF exposure as independent variables. Female gender, greater SED, VGDF exposure and physician diagnosed COPD were identified as predictors of reduced quality of life (as measured by EQ-5D VAS and summary index scores).

Discussion These results support the link between COPD and reduced quality of life, and additionally provide evidence to link occupational exposures to VGDF to a reduction in quality of life. These findings are of significance to health care professionals and policy makers, given future expectations for longer working lives.

S134 COMPARISON OF SPECIFIC INHALATION CHALLENGE (SIC) WITH OASYS ANALYSIS OF SERIAL PEF ANALYSIS IN THE DIAGNOSIS OF OCCUPATIONAL ASTHMA

doi:10.1136/thoraxjnl-2012-202678.139

VC Moore, PS Burge. *Birmingham Heartlands Hospital, Birmingham, England*

Aims to compare Specific inhalation challeng (SIC) with serial measurements of PEF in the diagnosis of occupational asthma Methods; All workers having SIC with occupational agents over a 3 year period were included. Their serial PEF records made during exposure to the suspected agents where analysed using Oasys software. Positive records were those with any of the following; Oasys score >2.5; ABC score ≥15litres/min/hr or timepoint ≥1 non-waking reading Results; 211 challenges were done in 51 workers. 45/51 kept serial PEF records suitable for Oasys analysis. SIC and Oasys analysis were concordant in 17/45 (38%), particularly those exposed to isocyanates or metal-working fluids. SIC was positive in 5 workers with equivocal Oasys analysis in line with its known sensitivity of c70–80%. 12 workers had negative or non-asthmatic SIC responses with positive Oasys analysis. Further investigation showed that occupational asthma was the most likely diagnosis. Negative SIC responses were due failure to identify the correct causative agent or problems with reproducing the work exposures. This was a particular problem with cleaning agents where a protein source may be needed to convert chlorine-releasing agents to chloramines (as shown in swimming pool asthma). Nine workers had equivocal challenges and clearly positive Oasys analysis, helping to clarify the diagnosis in this group, again non-standard agents were common in this group.

Conclusion SIC and serial PEF analysis are complementary methods for validating a diagnosis of occupational asthma. SIC has particular problems when methods of exposure for newer agents have not been fully developed, Oasys analysis lacks sensitivity when current specificity is fixed at >90%.

Abstract S134 Table 1

	Oasys		
SIC	**Positive**	**Equivocal**	**Negative**
Positive	16	5	0
Equivocal	9	1	1
Rhinitis etc	5	0	0
Negative	7	1	1

S135 ASTHMA, OCCUPATION AND QUALITY OF LIFE IN A HISTORICALLY INDUSTRIALISED AREA OF THE UNITED KINGDOM

doi:10.1136/thoraxjnl-2012-202678.140

LGB Lewis, A Darby, J Waterhouse, D Fishwick. *Sheffield Teaching Hospitals, Sheffield, United Kingdom*

Introduction Whilst harmful inhaled workplace exposures are known to be associated with either the development or aggravation