relationship between lung function and fungal sputum culture in patients with severe asthma.

Methods We recruited 126 patients attending a tertiary referral centre with a diagnosis of asthma and 18 healthy volunteers. 93% of patients were on GINA treatment step 4 or higher. At a single stable visit subjects underwent: spirometry with reversibility to 200 μg salbutamol; sputum fungal culture and a sputum cell differential count; skin prick testing to both common aeroallergens and an extended fungal panel (+ve ≥3 mm); specific IgE to *Aspergillus fumigatus* by CAP (positive >0.35 kU/l). Fungi were identified by morphology and species identity confirmed by sequencing regions of the nuclear ribosomal operon.

Results Patients had a mean age of 56 years (21–84 years); 48% were males with median ICS dose of 800 μg Fluticasone equivalent. 60% were atopic to common aeroallergens, 45% were IgE sensitised to one fungal allergen and 27% to ≥2 fungal allergens. 64% of patients cultured a mould in their sputum, 7% more than one species. This compared with three healthy subjects (17%) culturing any mould ($p<0.01$). *Aspergillus* species were most frequently cultured (n=58) followed by *Penicillium* species (n=15) and *Thermoascus* species (n=2), others (n=8). Four fungal genera were cultured from healthy volunteers sputum,-*Aspergillus*, *Penicillium, Coprinus* and one other. Post bronchodilator FEV_1% predicted was 71% in those with a positive fungal culture vs 84% in those who were culture negative, ($p<0.01$). There were no differences in the sputum cell differential between culture positive and negative patients.

Conclusions In addition to IgE fungal sensitisation, sputum culture focused towards detection of moulds is frequently positive and associated with impaired post-bronchodilator FEV1. Colonisation of the airways with mould in asthma could be responsible for the development of fixed airflow obstruction.

S137 THE AT-RISK REGISTERS IN SEVERE ASTHMA (ARRISA) STUDY: A CLUSTER-RANDOMISED CONTROLLED TRIAL IN PRIMARY CARE

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Objectives To evaluate the effectiveness of using electronic registers to identify and improve management of high-risk asthma patients in primary care.

Design Cluster-randomised controlled trial with stratification by high/low deprivation scores and 1-year follow-up.

Participants 29 GP practices in Norfolk, UK with suitable software systems used electronic searches and clinical knowledge to identify 911 patients aged 5+ years at high risk from their asthma as defined by British asthma guidelines (severe asthma plus adverse psychosocial characteristics, including poor adherence).

Intervention Intervention practices established registers of high-risk asthma patients and used an electronic alert to identify these patients at all practice encounters. This allowed reception staff to prioritise appointments and facilitate patient access to clinicians and clinical staff to review patients' asthma at all opportunities. Practice staff received a 1-h tailored training session on the use of alerts and actions to be taken from a GP (MN) and nurse (JW). Control practices continued with routine care.

Outcomes A composite measure of moderate–severe exacerbations (primary outcome, see Abstract S137 Table 1 for definition), disaggregated exacerbation-related events, consultations and medications (secondary outcomes) were derived from anonymous clinical data extracted from practice-based patient records for the year before and after implementation of registers.

Abstract S137 Table 1

Events per person per year	Intervention (N=14 pracs, 457 patients)	Control (N=15 pracs, 454 patients)	Rate ratio (95% CI)	p Value
Median (IQR) rate of moderate–severe exacerbations (composite of below*)	1 (2)	0 (2)	1.21 (0.95 to 1.55)	0.13
No. (%) of patients hospitalised for asthma*	15 (3.3)	29 (6.4)	0.52 (0.28 to 0.98)	0.04
No. (%) of patients attending A&E for asthma*	29 (6.4)	37 (8.2)	0.73 (0.41 to 1.30)	0.28
No. (%) of patients attending out-of-hours for asthma*	26 (5.7)	32 (7.1)	0.84 (0.46 to 1.51)	0.56
No. (%) of patients prescribed courses of oral prednisolone for exacerbations*	247 (54.1)	213 (46.9)	1.24 (0.99 to 1.54)	0.06
No. (%) of patients prescribed nebulised short-acting β-agonists	36 (7.9)	63 (13.9)	0.56 (0.37 to 0.84)	0.005
Median (IQR) no. inhaled short-acting β-agonists prescribed	6 (10)	7 (12)	1.03 (0.89 to 1.19)	0.70
Median (IQR) dose of inhaled corticosteroids prescribed (μg/day)	658 (1036)	658 (1036)	1.14 (1.00 to 1.30)	0.04
Median (IQR) no. inhaled long-acting β-agonists prescribed	8 (9)	6 (9)	1.24 (1.08 to 1.42)	0.003
Median (IQR) no. primary care consultations for any reason	9 (11)	8 (11)	1.08 (0.93 to 1.25)	0.34
No. (%) of patients who 'did not attend' primary care consultations for any reason	81 (17.7)	102 (22.5)	0.53 (0.31 to 0.90)	0.02

Results See Abstract S137 Table 1 for results of unadjusted analyses. After adjustment for relevant covariates at baseline similar effects were observed but only the effect on nebulised β-agonists prescriptions remained significant.

Conclusions Use of at-risk registers had no significant effect on the overall rate of moderate–severe exacerbations. However, they were associated with increases in prescriptions of oral steroids, inhaled steroids and long-acting β-agonists, coupled with reductions in asthma hospitalisations, prescriptions of nebulised short-acting β-agonists and in failures to attend primary care appointments. Together these are suggestive of improved asthma management in the intervention group.

Mechanisms of fibrosis in respiratory disease

S138 CLARA CELLS INHIBIT ALVEOLAR EPITHELIAL WOUND REPAIR THROUGH A TRAIL-DEPENDENT APOPTOSIS MECHANISM

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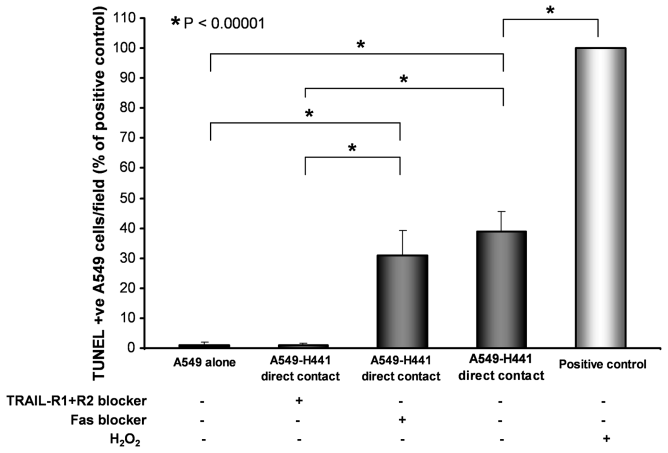
Introduction Alveolar bronchiolization, a hyperproliferation of ciliated and non-ciliated (Clara) bronchiolar cells and their extension into the alveolar region, is a common feature of idiopathic pulmonary fibrosis. The role of this bronchiolization process in alveolar wound repair is controversial. Clara cells are also believed to be progenitors for ciliated bronchiolar epithelium but their influence in repair processes is unclear.



Abstract S138 Figure 1 H441 direct contact induced apoptosis in A549 cells through TRAIL-R1+R2 (10 µg/ml each) blockade. Fas blocker (10 µg/ml) failed to block direct cell contact- induced apoptosis. In positive control, apoptosis was induced with 200 µM H2O2. Negative control was represented by A549 cells cultured alone in monolayer.

Methods Using an in vitro wound repair model we explored the interaction of human Clara cells (H441 cell line) and type II AEC (A549 cell line). A transwell co-culture system was developed to determine the direct contact effect of densely populated Clara cells on wounded AEC monolayers.

Results In serum-free media, lone H441 cell wound repair was higher than equivalent A549 cells, despite the fourfold slower doubling time of H441 cells. Serum-free conditioned media obtained from unwounded and wounded H441 monolayers did not show any significant influence on A549 wound repair. However, in a direct contact co-culture A549-H441 cell model significant inhibition of A549 wound repair ($p<0.005$) was observed. Interestingly, H441 migration into the injured A549 layer was seen after 24 h; with a significant proportion of migrated H441 cells found at the wound margins. Coupled to this migration we observed a 50% reduction in A549 cell number at the wound margins. TUNEL assay detected about 40% A549 apoptosis in juxta-wound monolayers in A549-H441 direct contact ($p<0.00001$). This direct contact-induced apoptosis was significantly blocked by TRAIL-R1 and R2 combined receptor blockers ($p<0.00001$); whereas, Fas blocker failed to block this apoptosis.

Conclusion In summary, direct contact of H441 cells induces apoptosis in the A549 monolayers through a TRAIL-dependent mechanism which disrupts wound margin integrity, inhibiting wound repair. This novel observation warrants further exploration of the role of Clara cell-alveolar epithelial cell interaction within the context of aberrant wound repair associated with chronic fibrotic lung disorders.

S139 THE K^+ CHANNEL KCa3.1 IS A NOVEL TARGET FOR THE TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS

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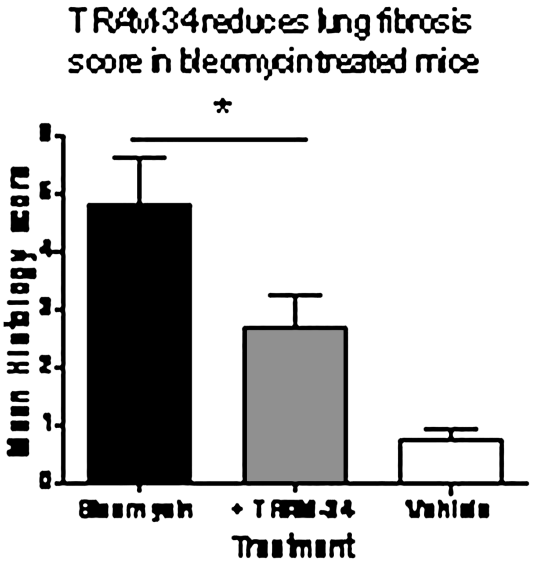
Introduction and objectives Idiopathic pulmonary fibrosis (IPF) is common, largely unresponsive to treatment with a median survival of 3 years. New therapies are urgently required. IPF is characterised by proliferation of pulmonary mesenchymal cells through epithelial mesenchymal transition, resident fibroblast proliferation and circulating fibrocyte recruitment. We have previously demonstrated that the potassium channel $K_{Ca}3.1$ regulates lung mesenchymal cell proliferation, is up-regulated by TGFβ, an important driver of IPF, and is present in fibrocytes in peripheral blood. We tested the hypotheses that $K_{Ca}3.1$ is up-regulated in IPF using the bleomycin-induced pulmonary fibrosis murine model and that $K_{Ca}3.1$ inhibition reduces pulmonary fibrosis.

Methods Prophylactic (Day -3) and daily thereafter, sub-cutaneous TRAM-34, a specific $K_{Ca}3.1$ inhibitor, was administered to C57BL/6 mice later exposed to nasal bleomycin (Day 0) and culled on day +21. Mice exposed to PBS or bleomycin acted as negative and positive controls. The primary endpoint was histological fibrosis score. Inflammation was assessed by bronchoalveolar lavage. Collagen deposition and $K_{Ca}3.1$ expression were assessed by Masson's trichrome staining and qPCR.

Results Bleomycin-induced pulmonary fibrosis characterised by thickened alveolar septae, architectural destruction and collagen deposition. Co-administration of TRAM-34 significantly reduced pulmonary fibrosis (Modified Ashcroft's score +/− SEM: 4.8+/−0.8 bleomycin group vs 2.6+/−0.6 TRAM-34 group: $p=0.02$). Bleomycin increased lung $K_{Ca}3.1$ (55-fold versus PBS control) and collagen Iα mRNA (fourfold) expression ($n=3$ in each case). Mice receiving bleomycin lost more weight (2.39 vs 0 g) and had greater mortality than those co-administered TRAM-34. BAL cellularity did not differ between the groups. Collagen staining was reduced in the TRAM-34 group.

Conclusions $K_{Ca}3.1$ expression is increased in a model of pulmonary fibrosis and inhibition with TRAM-34 significantly improves pathological outcome. The mechanism is likely to involve the modulation of cells involved in the fibrotic process. Previous clinical studies have shown KCa3.1 inhibition to be safe in humans and our study provides a rationale for a clinical trial of $K_{Ca}3.1$ inhibitors in human IPF.



Abstract S139 Figure 1

S140 THE ROLE OF TRANSFORMING GROWTH FACTOR-β ACTIVATED KINASE-1 (TAK-1) IN THE DEVELOPMENT OF AIRWAY FIBROSIS

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Introduction and aims Fibrotic disorders of the lung are characterised by an increase in fibroblast numbers and excessive deposition of extra