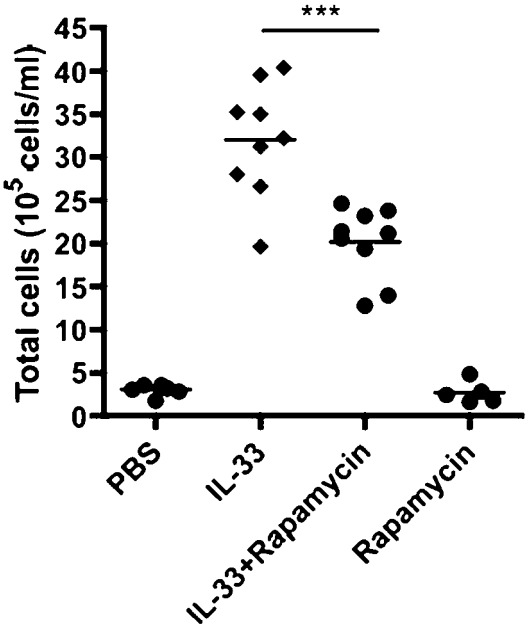
subpopulation of lineage negative innate cells that respond to IL-33 and IL-2.[2] Rapamycin is a macrolide antibiotic that allosterically blocks mTOR, a serine-threonine kinase involved in numerous cellular signalling pathways.

Aim To determine the role of mTOR in IL-33-induced airway inflammation and the effect of rapamycin on IL-33-induced nuocytes in the lung.

Method BALB/c mice were treated with 1 μg of IL-33 intranasally for 5 consecutive days in the presence or absence of rapamycin. Bronchoalveolar lavage (BAL) for cellular and cytokine analysis was performed. Fluorescence-activated cell sorting (FACS) of lung digests were analysed for intracellular IL-5 and cell surface markers.

Results IL-33 induced profound airway cellular infiltration noted in the BAL that was significantly inhibited by rapamycin. Cytokine levels from BAL fluid were also significantly reduced in mice treated with IL-33+ rapamycin. FACS analysis of lung digests demonstrated that IL-33 induced the expansion of lineage negative cells, in keeping with a population of nuocytes, which were the main source of IL-5 in the lung. Furthermore, this population of cells was suppressed by rapamycin.

Discussion Intranasal IL-33 drives mTOR-dependant airway inflammation. Nuocytes are the main source of IL-5 in IL-33-driven airway inflammation. Rapamycin inhibits the production of IL-5 and IL-13 in vivo as well as the expansion of nuocytes in the lung.



Abstract S35 Figure 1 BALB/c mice were treated intranasally with 1 μg IL-33 in the presence or absence of 1 mg/kg rapamycin for 5 consecutive days. The mice were sacrificed on day 6 and BAL total cell counts were performed. ***=p<0.001.

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S36 THE ADHESION RECEPTOR CADM1 PROMOTES HUMAN MAST CELL VIABILITY

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Introduction and Objectives Cell adhesion molecule 1 (CADM1) contributes to cell–cell adhesion, proliferation and adhesion-induced degranulation in human lung mast cells. Previously we found that it is expressed as three alternatively spliced isoforms (major SP4 and SP1, and minor SP6) in human lung mast cells (HLMCs) and only SP4 in the cell line HMC-1, originating from mast cell leukaemia. Here we investigated the role of CADM1 in the viability of HLMCs and HMC-1.

Methods Modulation of CADM1 expression was investigated using adenoviral delivery in both HMC-1 and HLMCs. Cell viability in the absence of survival factors was determined by measuring cell numbers and caspase-3/7 activity.

Results Modulation of CADM1 expression in HMC-1 cells and HLMCs by overexpressing SP4 (exon 8/11) and SP1 (exon 8/9/11) and RNA interference was confirmed by FACS and Western blotting. Overexpression of SP4 did not affect HMC-1 viability (105%±7% of original number of cells) or caspase-3/7 activity (7.7±0.2 FU/cell) in IMDM only for 48 h vs GFP-transduced cells, but overexpression of SP1 reduced cell number (66%±1%) and increased caspase-3/7 activity (9.8±0.3 FU/cell). CADM1 knockdown reduced HMC-1 number (71%±2%) and increased caspase-3/7 activity (9.5±0.2 FU/cell) in these conditions. In contrast to HMC-1 cells, overexpression of SP4 in HLMCs enhanced cell survival (39%±3%) in IMDM alone after 72 h compared to non-transduced cells (31%±1%, whereas downregulation of CADM1 reduced cell number to 26%±2%. Caspase3/7 activity was increased in HLMCs with downregulated CADM1 (99±20 FU/cell) compared to SP4-overexpressing and non-transduced cells (40±4 FU/cell and 20±1 FU/cell respectively). HLMCs displayed lower basal levels of Mcl-1, parallelled with lower survival and higher caspase-3/7 activation compared to HMC-1 cells. CADM1 downregulation in HLMCs coincided with decreased basal expression of Kit and Mcl-1.

Conclusions Modulation of CADM1 isoform expression or CADM1 downregulation in HMC-1 cells reduced survival. Conversely, SP4-overexpression or CADM1 downregulation in HLMCs resulted in increased survival or increased cell death, respectively. CADM1 modulation in HLMCs coincided with modulation of proteins related to survival. Hence, CADM1 promotes survival in human mast cells.

S37 MYD88 DEFICIENCY INFLUENCES MURINE TRACHEAL EPITHELIAL METAPLASIA AND SUBMUCOSAL GLAND ABUNDANCE

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Tracheal epithelial remodelling, excess mucus production, and submucosal gland hyperplasia are features of numerous lung diseases, yet their origins remain poorly understood. Previous studies have suggested that NF-?B signalling may regulate airway epithelial homeostasis. The purpose of this study was to determine whether deletion of the NF-?B signalling pathway protein myeloid differentiation factor 88 (Myd88) influenced tracheal epithelial cell phenotype. We compared wild-type and Myd88-deficient or pharmacologically inhibited adult mouse tracheas and determined that in vivo Myd88 deletion resulted in increased submucosal gland number, secretory cell metaplasia, and excess mucus cell abundance. We also found that Myd88 was required for normal resolution after acute tracheal epithelial injury. Microarray analysis revealed that uninjured Myd88-deficient tracheas contained 103 transcripts that were differentially expressed relative to wild-type and all injured whole tracheal samples. These clustered into several ontologies and networks that are known to functionally influence epithelial cell phenotype. Comparing these transcripts to those expressed in airway progenitor cells revealed only five common genes, suggesting that Myd88 influences tracheal epithelial homeostasis through an

extrinsic mechanism. Overall, this study represents the first identification of Myd88 as a regulator of adult tracheal epithelial cell phenotype.

Advances in screening and diagnosis of TB

S38 COMMUNITY-BASED EVALUATION OF IMMIGRANT TB SCREENING USING INTERFERON GAMMA RELEASE ASSAYS AND TUBERCULIN SKIN TESTING: YIELDS AND COST-EFFECTIVENESS

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Background Tuberculosis (TB) notifications in the UK continue to rise due to disease in the foreign-born immigrant population. UK guidelines on immigrant screening have recently been revised but accurate calculation of cost-effectiveness is hampered by a lack of empiric data on the comparative performance of tuberculin skin test (TST) and interferon-γ release-assays (IGRA) in immigrants arriving from countries with varying TB incidence.

Methods Prospective evaluation of TST and two commercially available IGRAs (QuantiFERON Gold in-tube (QFN-GIT) and T-SPOT.TB) in recent immigrants aged =16 years to quantify test positivity, concordance and factors associated with a positive result for all three tests. We computed yields at different incidence thresholds and the relative cost-effectiveness, using a decision-analysis-model stratified by HIV/drug-resistance, of screening using different latent TB infection (LTBI) screening modalities at varying incidence thresholds supplemented with/without port-of-arrival chest radiography.

Results 231 immigrants included; median age 29 (IQR 24–37). TST accepted by 80.9%, read in 93.6%; 30.3% positive. QFN-GIT and T-SPOT.TB positive in 16.6% and 22.5% respectively. Positive TST, QFN-GIT and T-SPOT.TB independently associated with increasing TB incidence in immigrants' countries of origin (p=0.008, 0.007 and 0.01 respectively). Implementing current guidance (depending on test) would identify 98%–100% of LTBI but also require 97%–99% of the immigrant cohort to be tested; raising the threshold to 150/100 000 (includes immigrants from Indian Subcontinent) would identify 49%–71% of LTBI but require half the cohort to be screened. The three most cost-effective screening strategies (which were more cost-effective than current guidance) were: no CXR at port-of-entry and screen with single-step QFN-GIT at 250/100 000 (Incremental cost-effective ratio (ICER) £21 565.3/per case averted), no CXR at port-of-entry and screen with single-step QFN-GIT at 150/100 000 (averted additional 7.8 cases of active TB, ICER of £31 867.1/per case averted) and no CXR at port-of-entry and screen with single-step QFN-GIT at 40/100 000 which averted a further 9.4 cases (ICER £34 753.5/per case averted).

Conclusions Immigrant screening in the UK could cost-effectively and safely eliminate mandatory CXR on arrival by emphasising systematic screening for LTBI with single-step IGRA. An intermediate incidence threshold for screening balances the need to identify as much imported LTBI as possible against limited service capacity.

S39 MIGRATION AND TUBERCULOSIS: THE START OF INTELLIGENT NEW ENTRANTS SCREENING

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Tuberculosis (TB) remains a problem in the UK, and almost three-quarters of active TB cases occur in the non-UK born. Most of these are likely infected abroad and strategies to detect latent TB in this population are being considered. We investigated how soon after arrival into the UK certain groups developed TB and the implications of this for numbers needed to screen and treat. Numbers of migrants arriving in 2005 from the top 6 countries of origin (of TB cases) were obtained from the Labour Force Survey (LFS). National TB surveillance (ETS) provided information on active cases from these countries. Estimates of interferon γ release assay (IGRA) positive cases (20%–28%), IGRA sensitivity (84%), and efficacy (65%) and completeness (85%) of chemoprophylaxis were obtained from Pareek *et al.* (Lancet ID 2011). The Abstract S39 table 1 shows numbers needed to screen and treat to prevent one case of TB developing in the UK in the 5 years after arrival. Numbers were relatively low, especially for Bangladesh and Somalia. The Abstract S39 table 1 also shows time between diagnosis and entry into the UK, which varied between countries of the Indian Subcontinent and sub-Saharan Africa and changed over time. While 45% of cases born in India had been in the country more than 10 years prior to arrival in 2000–2004, this was 32% in 2005–2009. Conversely, 57% of cases born in Zimbabwe were diagnosed within 2 years of arrival in 2000–2004, decreasing to 15% in 2005–2009. The relatively low numbers needed to treat among migrants from these high burden countries provide support for new guidance to expand latent infection treatment. The observed trends and differences in time since entry reflect underlying migration patterns, with higher but decreasing levels of migration from sub-Saharan Africa and an established and ongoing

Abstract S39 Table 1 Estimated numbers needed to screen and treat to prevent a TB case in the 5 years after arrival, and time since entry into the UK of TB cases, England Wales and Northern Ireland

	Estimated numbers needed to screen and treat, based on immigration in 2005					Time between diagnosis and arrival into the UK of TB cases reported in:					
		TB cases 2005–2009		Number per case		2000–2004			2005–2009		
Country of birth—top 6	Immigrants in 2005 *	All	Entry 2005 †	Screen	Treat	0–1 year	2–9 years	10+ years	0–1 year	2–9 years	10+ years
India	41 337	6403	546	163	33	25%	30%	45%	26%	42%	32%
Somalia	10 156	2883	293	75	21	34%	53%	13%	24%	57%	19%
Pakistan	15 533	4336	285	117	23	22%	32%	46%	20%	37%	43%
Bangladesh	3058	1123	101	65	13	24%	31%	45%	21%	38%	41%
Zimbabwe		1097	67	0	0	57%	40%	3%	15%	78%	7%
Nigeria	14 578	810	72	436	122	38%	37%	25%	28%	52%	20%
All countries	405 943	16 652	2130	411	82	29%	36%	35%	23%	46%	31%

*Population which entered the UK in 2005 that remain in the country as at Jan–Mar 2010 (LFS).
†Number of TB cases reported in 2005–2009 that were known to have entered the UK in 2005 (ETS).