suggesting a mechanism for the crosstalk between BMP and GCN2.

Conclusion We have discovered in *Drosophila* that GCN2 activation modulates BMP signalling. This effect is mediated, at least in part, by the downstream transcription factor ATF4, which inhibits the phosphorylation of MAD (insect SMAD1). Our findings indicate that this pathway is conserved between insects and mammals and this model may shed light on the pathogenesis of PAH and PVOD.

S87 DEFICIENCY OF TOLL-LIKE RECEPTOR 3 (TLR3) EXACERBATES PULMONARY HYPERTENSION IN MICE

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Introduction The mechanisms regulating aberrant vascular remodelling in pulmonary arterial hypertension (PAH) are poorly understood and treatments targeted at halting or reversing this process are lacking. Toll-like receptor 3 (TLR3) is a viral sensor and more recently has been established as a sensor of endogenous damage signals, responding to mRNA released by damaged cells. TLR3 signalling induces pro- and anti-inflammatory cytokine production and regulates inflammation-associated apoptosis and tyrosine kinase signalling. In a model of systemic arterial injury, TLR3 signalling was shown to modulate neointimal remodelling in a protective manner. TLR3 is also expressed in pulmonary artery smooth muscle (PASMCs) and endothelial cells (PAECs). We therefore hypothesised that TLR3 would play roles in pulmonary vascular remodelling.

Methods TLR3-deficient (TLR3−/−) or wild-type C57BL/6 (WT) mice were exposed to hypoxia (10% Oxygen) and given Sugen 5416 (weekly 20 mg/kg subcutaneous injections) or maintained in normoxic conditions for 3 weeks. Haemodynamic (cardiac catheterisation and echocardiography) and histological assessments were performed after 3 weeks. Human PASMCs were serum-starved before stimulation with PDGF or poly(I:C) and proliferation was assessed after 72 hours.

Results TLR3−/− mice developed a markedly exaggerated phenotype of PAH in response to Sugen/Hypoxia with increased right ventricular systolic pressures (WT 51.6 mmHg ± 4.6 vs. TLR3−/− 73.0 mmHg ± 6.8; $p < 0.05$, mean ± SEM, n = 6), increased muscularisation of small pulmonary arteries and reduced right ventricular cardiac output (WT 424.2 RVUmin-1 ± 84.2 vs. TLR3−/− 283.3 RVUmin-1 ± 18.4, mean ± SEM, min n = 6) after 3 weeks. Poly(I:C) suppressed PDGF-induced PASMC proliferation in a dose-dependent manner.

Conclusions We have shown that mice deficient in TLR3 develop a markedly exaggerated haemodynamic pulmonary hypertension phenotype and human PASMC proliferation is suppressed by the TLR3 ligand, poly(I:C). Together these data imply that TLR3 signalling in disease mediates a protective phenotype in keeping with that observed in systemic vascular remodelling, and identify a protective pathway potentially amenable to therapeutic targeting.

Tuberculosis: From Screening to Side Effects

S88 NEITHER UK TUBERCULOSIS INFECTION TESTING GUIDELINE APPEARS COST-EFFECTIVE IN A CONTEMPORARY HIV INFECTED POPULATION

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UK guidelines advise testing for latent tuberculosis infection (LTBI) in people with known HIV. Both National Institute for Health and Care Excellence (NICE) 2011 and 2016, and British HIV Association (BHIVA) guidelines use targeted testing, in comparison to those from other countries, notably the United States. None of these have been compared for cost-effectiveness in a contemporary HIV population.

Abstract S88 Table 1 Costs for selected strategies, discounted cost/case prevented and cost/QALY gained compared to no testing and last (non-dominated) strategy

Strategy	Total cost of strategy per 10,000 people living with HIV	Cases TB prevented (discounted)	QALYs gained compared to no testing (discounted)	Cost/case averted	Cost/QALY compared to no testing	Incremental cost/QALY compared to last strategy
BHIVA 2011	£749,274	2.28	1.28	£21,371	£37,952	EXTENDED DOMINANCE
TST in BA	£749,660	3.9	2.09	£12,566	£23,429	£23,429
TST in BA and MI	£761,797	4.49	2.43	£13,614	£25,218	EXTENDED DOMINANCE
NICE 2011	£788,037	1.11	0.63	£78,429	£139,281	DOMINATED
IGRA in BA	£812,048	6.83	3.85	£16,314	£28,971	EXTENDED DOMINANCE
IGRA in BA and MI	£865,959	9.06	5.1	£18,250	£32,410	EXTENDED DOMINANCE
IGRA in all	£1,056,702	10.17	5.72	£35,030	£62,209	EXTENDED DOMINANCE
NICE 2016	£1,058,522	10.17	5.72	£35,234	£62,571	DOMINATED
TST&IGRA in all	£1,219,154	10.99	5.88	£47,166	£88,139	EXTENDED DOMINANCE
TST&IGRA&CXR&IS in all	£1,999,789	20.58	10.44	£63,142	£124,393	EXTENDED DOMINANCE

BA - Black African, BHIVA – British HIV Association, CXR – chest X ray, IGRA – Interferon-gamma release assay, IS – induced sputum, MI – middle [TB] incidence countries, NICE – National Institute of Health and Care Excellence, QALY – Quality adjusted life year, TB – tuberculosis (includes active disease and subclinical tuberculosis cases), TST – tuberculin skin test.

We sought to determine the cost-effectiveness of each UK guideline from an NHS perspective, plus alternatives, using prospective data.

All patients with a new HIV diagnosis attending an ambulatory HIV clinic, plus a sample of those with known HIV were approached; and offered a symptom questionnaire, chest radiograph (CXR), tuberculin skin test (TST), blood interferon gamma release assay (IGRA) and induced sputum for mycobacterial culture (IS). The uptake and results were used to calculate the cost-effectiveness of thirty different testing strategies using univariate, multivariate and probabilistic sensitivity analyses (PSA).

219 subjects, representative of the total clinic population, took part. 73% were male, 28% black African and 95% on antiretroviral therapy (ART). During testing, 2 cases (0.9%) of subclinical TB and 14 (6%) of LTBI were detected. Half the patients with LTBI completed preventive treatment. Over a median of 28 months follow up, no new cases of active TB were identified.

When compared to no testing, only three of the thirty strategies were below the maximum NICE threshold for cost-effectiveness <£30,000/QALY gained. Testing black Africans with just TST or IGRA cost £23,429/QALY and £28,971/QALY respectively, whilst testing black Africans plus those from countries with a TB incidence of >20/100,000 ('middle incidence', MI) cost £25,218/QALY and £32,410/QALY using TST alone or IGRA alone respectively. NICE, BHIVA, or more extensive strategies, were not cost-effective. (Table)

Using PSA, no testing was most likely cost-effective up to £30,000/QALY.

In a contemporary HIV population with very high uptake of ART, neither current UK guideline is cost-effective. Testing black Africans, or black Africans and people from middle TB incidence countries appear at best marginally cost-effective. Future UK guidance needs to reflect changing health demographics, improved outcomes for people in HIV care, and clinical pragmatism.

S89 THE USE OF TUBERCULOSIS CHEMOPROPHYLAXIS IN PATIENTS OF RENAL REPLACEMENT THERAPY

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Introduction Individuals with end stage renal disease (ESRD) undergoing renal replacement therapy (RRT) are at increased risk of tuberculosis (TB). Timely identification and treatment of latent TB infection (LTBI) reduces the risk of progression to active disease. Diagnosing LTBI is challenging in ESRD as standard tests, such as the tuberculin skin test (TST) and Interferon Gamma Release Assay (IGRA) are less reliable. Although TB guidelines exist for ESRD they acknowledge a lack of evidence base and are limited in their scope.

This study aimed to establish the current LTBI screening and treatment practice in patients of RRT in a central London teaching hospital with the hypothesis that there would be a varied approach with overall low levels of screening.

Methods New starters on haemodialysis (HD) in the year 2010 were identified from computerised renal databases and information collected on; demographics, renal diagnosis, co-morbidities, dialysis attributes, TB risk factors, screening methods and LTBI treatment. All patients were followed for a period of 5 years to establish the rate of active TB after commencing RRT. Screening was considered to have taken place if any of the following were performed irrespective of symptoms of active disease; TST, IGRA, radiography specifically to investigate for TB or documented risk stratification.

Results Of the 331 eligible patients only 77 (23.2%) received screening. In those who were screened, 13 (16.9%) were diagnosed with active TB equating to an incidence of 3927/100,000, 37 (48.1%) with latent TB and 27 (35.1%) with neither. Risk factor stratification was the commonest modality of LTBI identification although there were a wide variety of approaches. Chemoprophylactic treatment regimes were non-standardised and often based on clinical experience rather than guidelines. Of those with active infection, disease developed most commonly within the first year of starting HD.

Conclusion High rates of active TB occur mainly within the first year of RRT. There is a lack of a uniform approach to detecting and treating LTBI in this population currently. Risk stratification and the use of immunological tests may offer the most sensitive approach to screening ESRD and within the first year of RRT.

S90 THE NATURE AND DURATION OF SYMPTOMS AND TIME TO STARTING TREATMENT COMPARING OLDER WITH YOUNGER PULMONARY TUBERCULOSIS PATIENTS

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Introduction and objectives In 2013, Public Health England (PHE) reported that 39% of pulmonary tuberculosis (TB) patients >65 years old started treatment >4 months after symptom onset compared to 25% of patients aged 15–44 years. A longer symptomatic period, particular if smear positive, may result in increased transmission and poorer treatment outcomes. We investigated age-related differences in symptom duration and time to starting TB treatment in a large UK cohort of TB patients.

Methods The cohort comprised patients on the London TB register (LTBR) who were treated at Northwick Park Hospital between 2002–2015. Patients aged >65 years were compared with a random sample of patients aged 18–40 years, with respect to symptoms, symptom duration at presenting to secondary care and time to starting treatment after presenting to secondary care.

Results 357 patients over 65 and 517 younger patients were identified. Demographics for the total number of patients are included in Table 1. Data were available for 489 of the younger group and 73 of the older group. 26 of the >65s (35.6%) and 9 (1.8%) of the 65s were diabetic.

Conclusions This study has identified that a potential cause for a delay in diagnosis in the elderly may be related to the decreased frequency of 'classical' TB symptoms in those >65 years of age. Clinicians need to be vigilant despite the lack of these symptoms.

Median duration of symptoms was twice that in older patients versus younger patients (90 days versus 45) with a longer time to starting treatment (7 days versus 2). The total duration (in months) from symptom onset was also higher at 3 months versus 2 months. A higher proportion of older patients (32%) started treatment greater than 4 months from symptom onset compared to 13.1% in younger patients.