combination screening with TST or IGRA should be considered. There remains a need for a robust national screening strategy that promotes the detection of latent as well as active tuberculosis.

**David Thomas, Miles Jarvis, Alan Williams**

Royal Bournemouth and Christchurch Hospitals NHS foundation Trust, Department of Thoracic Medicine, Royal Bournemouth Hospital, Bournemouth, UK

**Correspondence to** David Thomas, Royal Bournemouth and Christchurch Hospitals NHS foundation Trust, Department of Thoracic Medicine, Royal Bournemouth Hospital, Castle Lane East, Bournemouth BH7 7DW, UK; david.thomas@rbch.nhs.uk

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## Authors' response

We welcome the correspondence[1 2] relating to our recent editorial[3] and thank the authors for their interest.

Mr Thomas from the Royal Bournemouth Hospital presents two interesting local audits. The first highlights the possibility of wasted resources in screening individuals identified by the Port Health Control Unit as having an abnormal chest x-ray. The second demonstrates the potential shortcoming in the NICE guidelines, which can lead to an underidentification of latent tuberculosis (TB) infection. We share Mr Thomas's concerns, particularly on this latter point.

Dr Pareek and colleagues from Imperial College and the Health Protection Agency show that the NICE guidance is often not followed and that it is TB services which serve the areas with the highest TB burden which appear least likely to undertake screening for latent TB infection. This latter finding is, we would argue, unsurprising when resources are as scarce as they are in TB services. Those in high burden areas will be concentrating on 'fire fighting'—treating those cases of actual disease which actually do arise, with little or no time left for detecting latent infection and preventing the emergence of new active cases. This is likely to be a funding issue. Even in 2001, only one in six of high TB burden districts met minimum staffing recommendations.[4] Despite the DH funding template produced in 2007, this is widely ignored by primary care trusts as 'not applying to them', continuing the under-resourcing of TB services in many high (and some low) burden districts.

These authors also highlight the deviation from the NICE guidance in the latent TB infection screening methods employed, and we agree that there is a need for effective national coordination. They agree with our arguments regarding the need to change policy and we too feel that there is a need for an expanded evidence base to determine the most effective structure for the future. We also agree on the need for health economic analysis in these cost-constrained times. We understand that this will be provided in the updated economic appraisal of this area, which should be part of the revised NICE TB guidelines in January 2011, and believe it will be fully supportive of our case.

**John C Moore-Gillon,[1] Peter D O Davies,[2] L Peter Ormerod[3]**

[1]Department of Respiratory Medicine, St Bartholomew's and Royal London Hospitals, London, UK; [2]Department of Respiratory Medicine, Cardiothoracic Centre, Liverpool, UK; [3]Department of Respiratory Medicine, Royal Blackburn Hospital, Lancashire, UK

**Correspondence to** John C Moore-Gillon, Barts and the London NHS Trust, St Bartholomew's Hospital, London EC1A 7BE, UK; john.mooregillon@btinternet.com

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## Sarcoidosis is a Th1/Th17 multisystem disorder: wider implications

Facco *et al* demonstrated elevated levels of T helper 17 (Th17) cells in the peripheral blood and in the bronchoalveolar lavage of patients with active sarcoidosis; increased expression of interleukin 17 (IL-17) and *IL-23R* in lung and lymph node specimens was also noted.[1] These results suggest a role for the IL-23/Th17 inflammatory axis in the pathogenesis of sarcoidosis.

Crohn's disease (CD) is a severe inflammatory bowel disease (IBD). Many components of the IL-23 pathway (*IL23R*, *IL12B*, *STAT3*, *JAK2*, *TYK2*) are true IBD susceptibility genes, suggesting a crucial role for this pathway in maintaining intestinal immune homeostasis.[2]

We recently reported the development of multisystem sarcoidosis in two CD patients who had received maintenance therapy with natalizumab, a selective adhesion molecule inhibitor that prevents lymphocyte migration to the gut.[3] We hypothesised that natalizumab may have contributed to the development of the disease by allowing dysregulated lymphocyte trafficking to the respiratory mucosa and other extraintestinal mucosal surfaces in genetically predisposed individuals.

Complex disease genetics has been revolutionised by the advent of genome-wide association (GWA) studies. Shared susceptibility genes between IBD and other immune mediated/inflammatory disorders (ankylosing spondylitis, psoriasis, systemic lupus erythematosus, rheumatoid arthritis, asthma, atopic dermatitis, coeliac disease, multiple sclerosis, type 1 and type 2 diabetes mellitus, mycobacterial disease) have already emerged, paralleling the reported epidemiological evidence.[4] A combined analysis of a limited (100 kb) GWA study in CD and sarcoidosis identified a common susceptibility locus on 10p12.2 (but not at GWA levels of significance).[5]

We feel that this recent publication provides further intriguing evidence of common immunopathogenic pathways between CD and sarcoidosis. Ongoing research into common pathways and susceptibility regions between these two granulomatous conditions is essential, with further exploration of the IL-23/Th17 axis looking increasingly like a good starting point.

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**C A Parisinos**

Gastrointestinal Unit, Western General Hospital, Edinburgh, UK

**Correspondence to** Constantinos A Parisinos, Gastrointestinal Unit, Molecular Medicine Centre, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK; c.a.parisinos@doctors.org.uk

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## Authors' response

We would like to thank Dr Parisinos for his letter and interest in our study on the role of Th17 cells in sarcoidosis.[1] His recent report on the development of sarcoidosis in two patients affected by Crohn's disease and treated with natalizumab[2] further highlights the indubitable link existing between the immune pathogenesis of the two disorders. In fact, sarcoidosis and Crohn's disease are both characterised by an abnormal cell-mediated immune response to still unknown factor(s) that ultimately leads to granuloma formation and tissue damage. Furthermore, in both diseases Th1 and Th17 cytokines play a crucial role in the development of immune reactions taking place in the involved organs. Interestingly, the presence of IL-17-producing T cells marks out other immune-mediated and chronic inflammatory diseases that have been described to be associated with sarcoidosis, such as systemic lupus erythematosus, autoimmune chronic hepatitis, multiple sclerosis, coeliac disease and ulcerative colitis.

In the cases described by Parisinos *et al*, the use of natalizumab might represent an intriguing therapeutic option for its direct function (ie, the inhibition of the α4-mediated adhesion of leucocytes to their counter-receptors) and even for its effects on T cells, particularly on regulatory T cells (FoxP3 +Tregs), that are expanded by the treatment with natalizumab.[3] This issue raises a number of questions that should be addressed. First, considering that sarcoidosis is characterised by an abnormal expression of Tregs that, from a functional point of view, are unable to totally suppress TNFα and IFNγ secretion and granuloma formation,[4] it remains to be established whether the induction of a strong Treg response may really favour the recovery of the disease. Furthermore, keeping in mind that cytokines that are released during both Crohn's and sarcoid inflammatory processes, such as IL-6, TGF-β and IL-1β, are able to convert naive T cells and/or Tregs into Th17 lymphocytes via STAT3 expression,[5] the effect of natalizumab on Th17 and Treg plasticity has to be tested in both diseases.


**Monica Facco,[1,2] Gianpietro Semenzato,[1,2] Carlo Agostini[1,2]**

[1]Department of Clinical and Experimental Medicine, Hematology-Immunology Section, Padua University School of Medicine, Padova, Italy; [2]Venetian Institute of Molecular Medicine, Padua University School of Medicine, Padova, Italy

**Correspondence to** Carlo Agostini, Department of Clinical and Experimental Medicine, Padua University School of Medicine, Padova, Italy; carlo.agostini@unipd.it



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## GWAS in lung disease

We read with interest the recent article 'Genome-wide association studies in lung disease' by Artigas *et al*.[1] While we agree that a greater understanding of the biological pathways underlying disease development and progression (susceptibility) will be a major outcome from these genetic epidemiological studies, we suggest other benefits may also stem from this research.

The genetics of chronic obstructive pulmonary disease (COPD) and lung cancer represent unique models for the genetics of lung disease because they result in the main from a 'single' measurable and preventable environmental exposure (cigarette smoking). That we can stratify for smoking exposure in these genetic association studies is critical to disease gene discovery and study design, as many of the underlying 'susceptibility genes' only become clinically evident (ie, expressed as disease) after several decades of daily smoking exposure. In studies of lung cancer, where cases and controls are carefully stratified by smoking exposure it appears the genes relevant in smokers are distinct to those in non-smokers.[2 3] When smokers are stratified by smoking exposure and lung function, it appears that genes implicated in lung cancer overlap with those implicated in COPD.[3] This might explain why COPD predates lung cancer in up to 80% of cases, conferring a two- to sixfold greater risk compared with smokers with normal lung function. By stratifying for COPD (lung function), this approach has also identified genes conferring a 'protective' effect in lung cancer (ie, found in healthy or resistant smokers).[3] Until cigarette smoking is eradicated, understanding the biology of resistance to smoking may be of greater clinical relevance than that of susceptibility. Specifically, if the pathogenetic processes that protect smokers from COPD also protect them from lung cancer,[3 4] then chemo-preventive approaches might target these pathways. Of more immediate clinical utility is the use of genetic data (from a cheek swab) to help identify smokers at the greatest risk of COPD and/or lung cancer.[3] To this end, we and others have combined genetic data with known clinical variables (eg, COPD) to develop risk models for lung cancer.[3] Preliminary studies suggest such gene-based risk assessment might help motivate some smokers to quit smoking[3 5] and may help target those most in need of CT screening.[3] We conclude that COPD and lung cancer GWAS studies have much to contribute to respiratory medicine notably the possible basis of differential responsiveness of smokers to smoking exposure, the link between COPD and lung cancer, and the potential to develop new strategies in prevention and early diagnosis.


**Robert P Young,[1,2] Raewyn J Hopkins[1,2]**

[1]School of Biological Sciences, University of Auckland, Auckland, New Zealand; [2]School of Health Sciences, University of Auckland, Auckland, New Zealand

**Correspondence to** Dr Robert P Young, PO Box 26161, Epsom 1344, Auckland, New Zealand; roberty@adhb.govt.nz



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