Summary
In-patient ratios of two protein biomarkers found in blood serum (CSF1R for SA and S100A8/A9 for TB) can provide excellent differential diagnosis of Sarcoidosis versus Tuberculosis, with potential for development into a low-cost, reliable ELISA-based diagnostic test.

Background
Pulmonary Sarcoidosis (SA) is a chronic inflammatory disease with no known aetiology that often results in a skin rash, shortness of breath and a persistent cough. A major clinical problem in hospitals is the diagnosis of sarcoidosis because the disease shares symptomatic, radiological and immune-pathological features with the more common disease, Tuberculosis (TB), which results from infection by Mycobacterium tuberculosis and affects a third of the world’s population. As Sarcoidosis is unresponsive to Tuberculosis therapy, a rapid and affordable diagnostic test which could discriminate between the two conditions would dramatically improve time to diagnosis and treatment for individuals with either condition.

Specific signatures derived from the blood are highly attractive as non-invasive, rapid and affordable tests to support diagnosis of disease. The distinct biochemical make up of granulomas in TB and SA can be revealed through Endobronchial ultrasound-guided transbronchial needle aspiration and this has improved diagnosis in mediastinal disease. The biochemical profiles derived from these distinct granulomas are found in the sera and indicate that serum proteomic profiles may be able to distinguish SA and TB. However, currently no biomarkers are available that provide a highly sensitive and specific clinical test. Methods of diagnosis currently require an invasive biopsy and the histological identification of distinct cellular features, processes that come with attendant risks and costs.

Technology
- Using high-resolution mass spectrometry, the inventors quantitatively assessed serum profiles of people suffering from pulmonary forms of both SA and TB
- Proteomic screening identified 5 proteins that were

Quick Info
- A current clinical challenge is to differentiate between SA and TB
- Serum proteomic profiles may hold the key
- A novel highly specific SA biomarker, CSFR1, has been identified
- In-patient ratios of CSFR1:S100A8/A9 (SA:TB biomarkers) provide high diagnostic accuracy
- A simple ELISA-based test has been developed and validated

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The protein CSF1R was found to be highly specific to SA and has not been reported as a serum marker for SA previously.

The in-patient ratio of SA biomarker (CSF1R) and TB biomarker (S100A8/A9) provided high diagnostic accuracy when explored by ELISA methods (AUC = 0.96) (Fig. 1a).

A simple ELISA-based test has been developed that correlates well with MS data (Fig. 1b).

This method appears to be more sensitive compared to transcriptomic signatures from whole blood.

The CSFR1/S100A8/A9 marker pair shows better differentiation when compared to a pair of markers composed of a known sarcoidosis marker (Chitotriosidase-1) and a known tuberculosis marker (Matrix metalloproteinase-9).

Applications

The inventors have demonstrated that the serum proteome reflects the necrotic status often observed only through biopsy in SA and TB, which can provide diagnostic value in these clinically similar pulmonary diseases. The enhanced ability to differentiate these diseases would dramatically improve time to diagnosis and treatment for individuals with either condition. The use of a blood test for diagnosis would avoid invasive biopsy procedures, benefitting both patients and healthcare providers. ELISA tests provide rapid, inexpensive, and safe means of conducting serologic investigations. Furthermore, the technology lends itself towards development of similar ELISA-based tests, for example utilising other SA-specific or TB-specific biomarkers.

Team

The technology was developed Dr Robert Parker, a Research Associate in Professor Ajit Lalvani’s group and Dr Muhunthan Thillai, a Consultant Physician at Royal Papworth Hospital who specialises in sarcoidosis and other interstitial lung diseases. Professor Ajit Lalvani is Chair of Infectious Diseases, National Institute of Health Research Senior Investigator and Wellcome Senior Clinical Research Fellow at Imperial College London, as well as the Founding Director of the Tuberculosis Research Centre. He is Co-Chair of Respiratory Infections at the National Heart and Lung Institute and Honorary Consultant Physician at Imperial College London and Imperial College Healthcare NHS Trust.

Intellectual Property

The technology is protected by a patent application (Priority Patent Application Number: 1719853.2)

Relevant publications

https://www.imperial.ac.uk/people/a.lalvani/publications.html

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Fig 1: Using the normalised in-patient ratio of CSF1R and S100A8/A9 a simple diagnostic test was developed which a) provided a ROC AUC of 0.96 using ELISA to differentiate SA and TB and b) correlated well with MS data.