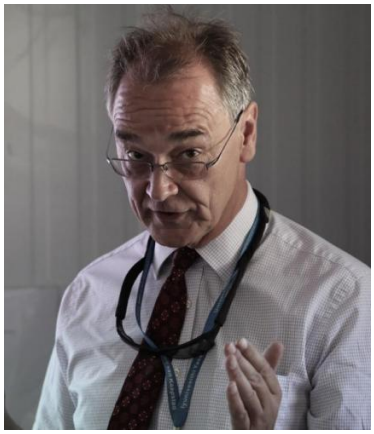
Name	ROBERT WILKINSON
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	2007



Career History

10/2017 11/2017 Fellow Academy of Science of South Africa
05/2017 06/2017 F Med Sci Academy of Medical Sciences
05/1990 07/2003 M then FRCP Royal College of Physicians
10/1993 03/1997 PhD University of London
02/1989 06/1989 DTM&H Royal College of Physicians London
08/1984 06/1987 BM BCh University of Oxford

07/2007 present Professor Imperial College London
04/2016 present Group Leader Francis Crick Institute
12/2008 present Hon Professor Univ Cape Town
09/2016 present Hon Professor University College London
08/2007 03/2016 Programme Leader NIMR
12/2004 12/2008 Hon Ass Professor Univ Cape Town
10/2004 07/2007 Wellcome Snr Fell Imperial College London
10/2001 09/2004 Wellcome Adv Fell Imperial College London
11/2000 07/2004 Hon Cons Infect Dis North West Lond Hosp NHS Trust
10/2000 09/2001 Wellcome Train Fell Imperial College London
10/1999 09/2000 SpR in Infect Dis North West Lond Hosps NHS Trust
10/1997 09/1999 Wellcome Train Fell Case Western Reserve University, OH
10/1993 09/1997 MRC Clin Scientist Clinical Sciences Centre, London
08/1991 07/1993 Registrar Northwick Park Hospital
08/1989 07/1991 Snr House Physician Lothian Health Board
02/1989 07/1989 Snr House Physician Hosp for Tropical Diseases, London
08/1988 01/1989 Snr House Physician North Manchester General Hospital
02/1988 07/1988 House Physician Oxford Hospitals
08/1987 01/1988 House Surgeon York District Hospital

Major Awards, Honours and Prizes

Membership of external committees, editorial boards, review panels, SABs etc

Member, Peer Review College, Wellcome October 2012-December 2016
Associate Editor, International Journal of Tuberculosis and Lung Disease 2008-2018
Section Editor and member of Editorial board, Tuberculosis, July 2009-2018
Editorial board, European Journal of Immunology, June 2016-

Lab Name	*Tuberculosis Laboratory*

Research programme and achievements

I am a Physician Scientist with significant external appointments at Imperial College London and at the University of Cape Town where I direct that institution's Wellcome Centre for Infectious Diseases Research in Africa. This provides access to substantial numbers of tuberculosis and HIV-tuberculosis co-infected persons in proximity to sophisticated clinical research facilities, giving us a globally-unparalleled ability to phenotype accurately. The role of the allied Crick programme is to understand pathogenesis and thereby improve prevention and treatment, and there is particular emphasis on multi-omic analysis which the Crick is very well-provisioned to provide and interpret.

The programme renewed in 2017 was substantially directed to the role of immunopathological inflammation in tuberculosis, in particular in understanding and managing the HIV-tuberculosis associated immune reconstitution inflammatory syndrome (TB-IRIS), and on the modulatory effects of corticosteroid therapy. Since that time we received results and materials from a placebo-controlled randomised controlled trial in 268 patients at risk of TB-IRIS and found adjunctive steroids reduce the frequency of TB-IRIS by 30% (paper 2). In a reverse translational approach we are using the stored materials arising to dissect the mechanism by which corticosteroids prevented inflammation, and expect this to illuminate pathways that could be targeted by more specific and powerful adjunctive immunotherapies. We were first to definitively show this syndrome is associated with a cytokine release syndrome that arises as a consequence of activation of both canonical and non-canonical inflammasomes (paper 5). The general relevance of this work is increased by the recent finding that corticosteroids also reduce immunopathology and thus death associated with severe COVID-19 infection.

A second major area of activity is in understanding and preventing the progression of early tuberculosis infection as this is key to global elimination. In particular we have pioneered the novel use of high resolution functional and anatomical imaging to benchmark risk of progression (paper 4). Downstream multi-omic analysis has thereby implicated a previously unsuspected role for complement activation in the very earliest stages of progression (paper 5). We are pursuing these findings in much larger clinical studies. In work not directly related to the Crick programme, but nevertheless of potentially very great significance in reducing the 1.6 million annual deaths due to tuberculosis, I also collaborated with industry and thereby contributed as co-senior author to a report of a novel tuberculosis vaccine (GSK biologicals M72AS01E) that reduces the risk of progression of tuberculosis by around 50% (publication 1).

Other very severe immunopathological manifestations of tuberculosis affect the central nervous system (meningitis) and heart (pericarditis). Within the last 18 months we have begun work to advance clinical and pathological studies of these conditions. We will extend multi-omic analysis as above to advance knowledge and potentially improve treatments. In addition we have most recently documented common trilateral association of incident SARS-CoV2 and tuberculosis in HIV-1 infected persons in South Africa. A rapidly established prospective hospital-based study of SARS-CoV2 patients in South Africa has recruited ~140 participants with (unlike many clinical studies of SARS-CoV2 hitherto) adequate and appropriate control groups. We hope to conduct multi-omic analysis of materials collected from this study as well.

Research outputs

Tait, D.R., Hatherill, M., Van Der Meeren, O., Ginsberg, A.M., Van Brakel, E., Salaun, B., Scriba, T.J., Akite, E.J., Ayles, H.M., Bollaerts, A., Demoitié, M-A., Diacon, A., Evans, T.G., Gillard M.D., Hellström, E., Innes, J.C., Lempicki, M., Malahleha, M., Martinson, N., Vela, D.M., Muyoyeta, M., Nduba, V., Pascal, T., Tameris, M., Thienemann, F., Wilkinson, R.J., Roman, F. (2019) *Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis*. New England Journal of Medicine 381:2429-2439. DOI: 10.1056/NEJMoa1909953

Among adults infected with *M. tuberculosis*, vaccination with M72/AS01$_E$ elicited an immune response and provided protection against progression to pulmonary tuberculosis disease for at least 3 years. This is the first vaccine against tuberculosis to be shown effective in humans since the advent of BCG in 1921. A product development and further testing plan has recently been agreed and we will contribute to the latter.

Meintjes, G., Stek, C., Blumenthal, L., Thienemann, F., Schutz, C., Buyze, J., Ravinetto, R., van Loen, H., Nair, A., Jackson, A., Colebunders, R., Maartens, G., Wilkinson, R.J., Lynen, L. on behalf of the *PredART* trial team. (2018) *Prednisone for prevention of paradoxical tuberculosis-associated IRIS.* New England Journal of Medicine 379:1915-25. DOI: 10.1056/NEJMoa1800762

Prednisone treatment during the first four weeks after the initiation of antiretroviral therapy for HIV-1 infection resulted in a lower incidence of tuberculosis-associated immune reconstitution inflammatory syndrome than placebo, without evidence of an increased risk of severe infections or cancers.

Esmail, H.E., Lai, R. P-J., Lesosky, M., Wilkinson, K.A., Graham, C.M., Horswell, S., Coussens, A.K., Barry III, C.E., O'Garra, A.,Wilkinson, R.J. (2018) *Complement pathway gene activation and rising circulating immune complexes characterize early disease in HIV associated tuberculosis.* Proc Nat Acad Scis USA 115(5):E964-E973 DOI: 10.1073/pnas.1711853115

This *ex vivo* analysis of materials arising from paper 4 (below) showed that transcripts representing the classical complement pathway and Fcγ receptor 1 were differentially expressed before disease presentation. Our results indicate that levels of antibody/antigen complexes increase early in disease, associated with increased gene expression of receptors that bind them.

Esmail, H., Lai R.P-J., Lesosky, M., Wilkinson, K.A., Graham, C.M., Coussens, A.K., Oni, T., Warwick, J.M., Said-Hartley, Q., Koegelenberg, C.F., Walzl, G., Flynn, J.L., Young, D.B., Barry 3rd, C.E., O'Garra, A., Wilkinson, R.J. (2016) *[^{18}F]-fluorodeoxyglucose combined positron emission and computed tomographic characterisation of progressive HIV-associated tuberculosis*. Nature Medicine 22(10):1090-1093. DOI: 10.1038/nm.4161

This work used high-resolution PET/CT imaging to establish for the first time in humans the existence of a high-risk asymptomatic transition state between latent infection and active disease. The technique is thus a phenotypic benchmark for further Experimental Medicine studies of interventions to prevent progression of asymptomatic subclinical tuberculosis.

Lai, R.P-J., Meintjes, G., Wilkinson, K.A., Graham, C.M., Marais, S., Van der Plas, H., Deffur, A., Schutz, C., Bloom, C., Munagala, I., Anguiano, E., Goliath, G., Maartens, G., Banchereau, J., Chaussabel, D., O'Garra, A., and Wilkinson, R.J. (2015) *HIV-Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome Is*

Characterized by Toll-Like Receptor And Inflammasome Signalling. **Nature Communications 6: 8451. DOI: 10:1038/ncomms9451**
This transcriptomic analysis definitively identified the key immunopathological event in tuberculosis immune reconstitution inflammatory syndrome to be *Mycobacterium tuberculosis* induced activation of the inflammasome attendant on rapid antiretroviral-mediated suppression of HIV-1 replication.