Name	ANNE O'GARRA
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	2001

Career History

1978-1980: BSc. Microbiology/Biochemistry (First Class Honours) University of London
1980-1983: PhD in Microbiology, MRC National Institute for Medical Research (NIMR)
1983-1987: Postdoctoral Fellow Division of Immunology, MRC NIMR
1987-1991: Senior Research Associate, DNAX Research Institute (now Merck), CA, USA
1991-2001: Staff Scientist/ Senior Staff Scientist/ Principal Staff Scientist, DNAX, USA
2001-2015: Head, Division of Immunoregulation, MRC NIMR, Mill Hill, London
2015-2019: Associate Research Director, and Senior Group Leader, The Francis Crick Institute (stepped down as Associate Res Director, June 2019, to focus on human TB research)
2015 - Present: Senior Group Leader, Laboratory of Immunoregulation & Infection, The Francis Crick Institute.

Major Awards, Honours and Prizes

1992-2002: 2nd of Highly Cited Authors in Immunology (ISI Science Indicators).
2005: Election as Fellow of the Academy of Medical Sciences, UK
2006: Election as an AAAS Fellow, in the Section on Medical Sciences, USA
2008: Election as Fellow of The Royal Society, UK
2009: Election to EMBO membership

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

Editorial Boards:
2004-present: Editorial Board (Academic Editor): Journal of Experimental Medicine
2015-2017: Editorial Board, Annual Reviews Immunology, USA

Scientific Advisory Boards (SAB) and panels:
2005-present: SAB & Member of Board of Directors, Keystone Conferences, USA
2017-present: SAB Global Health Institute, EPFL, Lausanne, Switzerland
2018-present: SAB, Kennedy Institute of Rheumatology, University of Oxford.
2018-present: SAB, MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, University of Oxford
2018-present: SAB, National Research Foundation, Singapore
2019-present: Pasteur Scientific Council
2018-2020: Jury for the Sanofi-Institut Pasteur awards, France
2012-2016: Jury, Novartis Prizes for Immunology
2019-present: Council, International Cytokine & Interferon Society
2010-2013: Royal Society Sectional Committee 7 (SC7) Panel
2016-2019: Royal Society Sectional Committee 7 (SC7) Chair

Lab Name	*Immunoregulation and Infection Laboratory*

Research programme and achievements

The Laboratory of Immunoregulation and Infection has a major focus on transcriptional regulation of cytokines, essential for protection against infection, and their regulation by the cytokine IL-10 to prevent collateral damage from an immune response to pathogens and pathobionts. We also continue to study the immune response in tuberculosis (TB), in both mouse models and human disease.

Tuberculosis remains a major cause of death from infectious disease, with 1.5 million deaths in 2018, but diagnosis remains difficult. Moreover, a third of the world is estimated to have been infected by *Mycobacterium tuberculosis*, although most remain asymptomatic or latent, with 10% progressing to active TB, although the host factors determining outcome to infection are unknown. New approaches are needed for TB diagnosis, to determine early which individuals will progress to TB disease, and also to identify the host factors determining the outcome to *M. tuberculosis* infection.

Our identification of a blood neutrophil-driven type I interferon (IFN) -inducible transcriptional signature of active TB, absent in the majority of latently exposed asymptomatic individuals and healthy controls, has now been widely reproduced. We recently demonstrated immunological heterogeneity in the blood transcriptome of a cohort of recent TB contacts. A small proportion expressed a persistent TB signature and subsequently progressed to active TB disease. The composition of this initial blood transcriptional signature in TB progressors suggested a host response evolving towards active disease. Additionally, 50% of contacts who were sensitised to *M. tuberculosis* infection but did not progress to disease exhibited a similar, but not identical, blood signature that was transient and resolved within three months.

Mouse infection models have been used to study the host response to *M. tuberculosis*, but their validity in revealing determinants of human tuberculosis (TB) resistance and disease progression has been heavily debated. We have now shown that the modular transcriptional signature in the blood of TB susceptible C3HeB/FeJ mice infected with a clinical isolate of *M. tuberculosis* resembles that of active human TB disease, with dominance of a type I interferon response and neutrophil activation and recruitment, providing a tractable model to study targets and mechanisms underlying TB pathogenesis. Notably, the blood signature of active disease shared by mice and humans was also evident in latent TB progressors before diagnosis, suggesting that these responses both predict and contribute to the pathogenesis of progressive *M. tuberculosis* infection. Conversely, resistant but not susceptible strains of mice showed increased lung B cell, natural killer and T cell effector responses in the lung upon infection, suggesting that early local immune responses are critical determinants of outcome from infection.

We will identify the early immune events in the airways of human contacts of TB patients and determine host factors that determine outcome of control of progression to active TB disease. We will in parallel study these early airway events in TB resistant and susceptible mice to identify targets that parallel the host factors determining outcome in human TB, so as to test and identify the early local pathways and mechanisms that determine protection or pathogenesis in TB.

Underpinning our research in TB we continue to define the molecular mechanisms for induction of IL-10 versus inflammatory cytokines in immune cells. We have shown that

type I IFN acts as a transcriptional regulator of *Il10* mRNA in *M. tuberculosis* infected or TLR4 stimulated macrophages and continue to identify this in-depth in both *in vitro* and *in vivo* systems. In T cells, we have demonstrated that although the transcription factor c-Maf plays a dominant role in regulation of *Il10* both *in vitro* and *in vivo,* c-Maf exerts context-specific effects in different diseases *in vivo,* through its regulation of other pathways and transcription factors. We continue to study regulation of *Il10* and proinflammatory cytokines *in vivo* by c-Maf and other candidate transcription factors, to determine the mechanisms of their context specific effects on the immune response to intracellular (Th1)-type pathogens and pathobionts, relevant to other intracellular infections such as TB.

Collectively, our studies highlight the complex role of cytokines in protecting or promoting infectious diseases, and we continue to dissect mechanisms underlying their expression and function in this context. We additionally continue to study the diverse roles of type I IFN in the regulation of cytokines in the immune response to *M. tuberculosis,* to provide valuable information for the development of immunomodulatory treatments. We have confirmed the reproducibility of our blood-based transcriptional signature to characterise the immune response determining the outcome of *M. tuberculosis* infection, and to develop tools to support diagnostics and treatment monitoring of TB.

Research outputs

Moreira-Teixeira, L., Redford, P.S., Stavropoulos, E., Ghilardi, N., Maynard, C.L., Weaver, C.T., Freitas do Rosario, A.P., Wu, X., Langhorne, J., and O'Garra, A. (2017) *T Cell-Derived IL-10 Impairs Host Resistance to Mycobacterium tuberculosis* Infection. J Immunol 199, 613-623. DOI: 10.4049/jimmunol.1601340
This manuscript showed that the T-cell derived suppressive cytokine IL-10 limits the protective immune response to *M. tuberculosis* infection. In the absence of IL-10, decreased bacterial loads correlated with early increased influx of Th1 cells into the site of infection and enhanced production of IFN-γ, indicating that IL-10 contributes to TB pathogenesis.

Gabryšová, L., Alvarez-Martinez, M., Luisier, R., Cox, L.S., Sodenkamp, J., Hosking, C., Pérez-Mazliah, D., Whicher, C., Kannan, Y., Potempa, K., Wu, X., Bhaw, L., Wende, H., Sieweke, M.H., Elgar, G., Wilson, M., Briscoe, J., Metzis, V., Langhorne, J., Luscombe, N. M. and O'Garra, A. (2018) *C-Maf controls immune responses by regulating disease-specific gene networks and repressing IL-2 in CD4+ T cells*. Nature Immunology 9(5):497-507. DOI: 10.1038/s41590-018-0083-5
We show T cell-specific deletion of c-Maf leads to reduced levels of the suppressive cytokine Il10 gene *in vivo* and and thus increased collateral damage in mouse models of malaria and allergy. Conversely, in an autoimmunity model, T cell-specific deletion of c-Maf, although reducing *Il10* expression, had a protective effect. Analysis of complex gene regulation networks revealed that c-Maf is a central regulator of gene expression in $CD4^+$ T cells, explaining its context-specific effects in autoimmunity. Such genomics approaches aid understanding of the complexity of the immune response, and how context-specific activation of transcription factors regulates diverse functions in immunity.

Singhania A, Verma R, Graham CM, Lee J, Tran T, Richardson M, Lecine P, Leissner P, Berry MPR, Wilkinson RJ, Kaiser K, Rodrigue M, Woltmann G, Haldar P, O'Garra A. (2018) *A modular transcriptional signature identifies phenotypic heterogeneity of*

***human tuberculosis infection*. Nat Commun 19;9(1):2308. DOI: 10.1038/s41467-018-04579-w**
This study recapitulated our findings of a type I IFN-inducible transcriptional blood signature of active TB, in a new cohort of TB patients in Leicester, and in other published TB cohorts, indicating globally the association of type I IFN-inducible genes with disease susceptibility. Additionally, we demonstrated immunological heterogeneity in the blood transcriptome of a cohort of recent TB contacts in Leicester. A small proportion expressed a persistent TB signature and subsequently progressed to TB disease. These findings provide potential prognostic biomarkers for early detection of TB in asymptomatic individuals, importantly in a low burden TB setting where reinfection is minimal.

Singhania A*, Graham CM*, Gabryšová L*, Moreira-Teixeira L, Stavropoulos E, Pitt JM, Chakravarty P, Warnatsch A, Branchett WJ, Conejero L, Lin JW, Davidson S, Wilson MS, Bancroft G, Langhorne J, Frickel E, Sesay AK, Priestnall SL, Herbert E, Ioannou M, Wang Q, Humphreys IR, Dodd J, Openshaw PJM, Mayer-Barber KD, Jankovic D, Sher A, Lloyd CM, Baldwin N, Chaussabel D, Papayannopoulos V, Wack A, Banchereau JF, Pascual VM, O'Garra A. (2019) *Transcriptional profiling unveils type I and II interferon networks in blood and tissues across diseases*. Nat Commun 10(1):2887. DOI: 10.1038/s41467-019-10601-6
Using advanced bioinformatics approaches, we deciphered the global transcriptional response in the lungs of mice infected or challenged with a broad spectrum of infectious pathogens, including parasites, bacteria, viruses, fungi, or allergens; we also determined to what extent each of these responses is preserved in the blood. We demonstrated a unique global transcriptional signature for each of the different diseases in both lung and blood. The lung transcriptional signatures showed a gradation, ranging from IFN-inducible gene clusters, to those associated with granulocyte/neutrophil/IL-17 dominated genes, to responses dominated by expression of genes encoding T_H2 cytokines, mast cells and B cells.

Moreira-Teixeira,. L*., Tabone, *O., Graham, C.M*., Singhania, A, Stavropoulos, E., Redford, P.S., Chakravarty, P., Priestnall, S., Suarez-Bonnet, A., Herbert, E., Mayer-Barber, K.D., Sher, A., Fonseca, K.L., Sousa, J., Cá, B., Verma, R., Haldar, P., Saraiva, M., and O'Garra, A. (2020) *Mouse transcriptome reveals potential signatures of protection and pathogenesis in human tuberculosis*. Nature Immunology 21, 464-476. DOI: 10.1038/s41590-020-0610-z
We demonstrated that TB susceptible mice infected with a clinical isolate of *M. tuberculosis* have a type I IFN-inducible and neutrophil driven transcriptional signature closely resembling the human disease. The signature was also evident in latent tuberculosis progressors before diagnosis. This suggests that these responses both predict and contribute to the pathogenesis of progressive *M. tuberculosis* infection, providing potential prognostic biomarkers for early detection of TB in asymptomatic individuals. Our identification of a TB-susceptible mouse model that recapitulates the human disease provides a tractable system to further dissect the immune mechanisms underlying protection or pathogenesis resulting from *M. tuberculosis* infection.