TrIFIC 2

Modulating Cell Death Pathways in Pulmonary Aspergillosis

Applications are invited for a Cystic Fibrosis Trust funded 3-year PhD studentship. This studentship is integral to a major Strategic Research Centre in Fungal Immunotherapy (TrIFIC) made to Imperial College London collaborating with the University of Manchester, University of Exeter, University of Massachusetts and Radboud University Nijmegen. The overall aim of the SRC is to systematically define the underlying mechanisms of inflammation in pulmonary aspergillosis in the context of cystic fibrosis. This will enable development of immuno-diagnostic tests to identify which patients will benefit from targeted immunotherapies that can be repurposed in CF-related fungal disease.

We are seeking a highly motivated student to join the opportunistic pathogens group led by Dr Darius Armstrong-James within the MRC Centre for Molecular Bacteriology and Infection within the Faculty of Medicine of Imperial College London at the South Kensington Campus in collaboration with Dr. Anand Shah (National Heart and Lung Institue and Royal Brompton Hospital), and Professor Frank van der Veerdonk (University of Nijmegen, the Netherlands)

Pre-clinical data indicate that CF leads to a hyper-inflammatory cell death response to A. fumigatus. Treatment of Aspergillus-infected CF macrophages with 'necroptosome' inhibitors blocked cell death and restored apoptotic anti-inflammatory responses. Inflammasome inhibition with the clinically licensed IL-1 receptor blocker Anakinra ameliorated inflammation and enhanced fungal clearance in murine CF-related aspergillosis. Furthermore, levels of sputum HMGB1, a key necrotic cell death marker, are predictive of increased mortality in CF patients.

To further characterize cell death pathway activation, the student will assess inflammasome and necroptosome activation in sputum as well as in PBMC response assays in CF patients with pulmonary aspergillosis. As cell death inhibitors are in clinical studies for a range of inflammatory diseases (e.g. GSK2982772), we will further assess their therapeutic utility in vitro in macrophage/PBMC Aspergillus infection assays, correlate findings in primary epithelial cell-macrophage co-culture models, and further explore the importance of key pathways for outcome from A. fumigatus infection in our CF animal models. These studies will define the degree of inflammasome/necroptosome activation in the host and how it relates to disease severity.

Dr Darius Armstrong-James (http://www.imperial.ac.uk/people/d.armstrong), Dr. Anand Shah (MRC CARP, School of Public Health, Imperial) and Professor Frank van der Veerdonk (https://www.radboudumc.nl/en/people/frank-van-de-veerdonk) are the academic supervisors.

To apply: please send a single PDF document including a one-page cover letter discussing research interest and experiences, a two-page CV, a copy of transcripts, and contact information of two references to Dr Armstrong-James (d.armstrong@imperial.ac.uk) with subject line "CF_PhD_App" before the **closing date of 31st July 2019**. Successful students will be expected to begin the PhD in October 2019.

The studentship is open to UK, EU and overseas nationals, includes payment of home/EU fees and a stipend for 3 years starting at £22,278 per annum in October 2019. Overseas students are expected to cover the difference between the home/EU and overseas fee.

Applicants must have a first or upper second-class BSc degree from a UK University, or the overseas equivalent, in a relevant area of immunology, biochemistry, chemistry or microbiology. A Master's degree in one of the above fields and/or experience in immunology would be advantageous. Applicants are also required to meet Imperial College's English language requirements: http://www.imperial.ac.uk/study/pg/apply/requirements/english

Subject areas:

Fungal immunopathogenesis
Macrophage cell biology
Confocal immunoflourecent imaging
Cell death inhibition
Animal models

References:

1. Human NK Cells Develop an Exhaustion Phenotype During Polar Degranulation at the Aspergillus fumigatus Hyphal Synapse. Santiago V, Rezvani K, Sekine T, Stebbing J, Kelleher P, Armstrong-James D. Front Immunol. 2018 Oct 22;9:2344. doi: 10.3389/fimmu.2018.02344. eCollection 2018.

2. Ibrutinib blocks Btk-dependent NF-kB and NFAT responses in human macrophages during Aspergillus fumigatus phagocytosis. Bercusson A, Shah A, Warris A, Armstrong-James D, Blood. 2018 Jul 18. pii: blood-2017-12-823393. doi: 10.1182/blood-2017-12-823393. [Epub ahead of print]

3. Armstrong-James D, Brown GD, Netea MG, Zelante T, Gresnigt MS, van de Veerdonk FL, Levitz SM. Immunotherapeutic approaches to treatment of fungal diseases. Lancet Infect Dis. 2017 Dec;17(12):e393-e402. doi: 10.1016/S1473-3099(17)30442-5. Epub 2017 Jul 31. Review. PubMed PMID: 28774700.

4. Shah A, Kannambath S, Herbst S, Rogers A, Soresi S, Carby M, Reed A, Mostowy S, Fisher MC, Shaunak S, Armstrong-James DP. Calcineurin Orchestrates Lateral Transfer of Aspergillus fumigatus during Macrophage Cell Death. Am J Respir Crit Care Med. 2016 Nov 1;194(9):1127-1139. PubMed PMID: 27163634; PubMed Central PMCID: PMC5114448.

5. Herbst S, Shah A, Mazon Moya M, Marzola V, Jensen B, Reed A, Birrell MA, Saijo S, Mostowy S, Shaunak S, Armstrong-James D. Phagocytosis-dependent activation of a TLR9-BTK-calcineurin-NFAT pathway co-ordinates innate immunity to Aspergillus fumigatus. EMBO Mol Med. 2015 Mar;7(3):240-58. doi: 10.15252/emmm.201404556. PubMed PMID: 25637383; PubMed Central PMCID: PMC4364943.