Name	CAETANO REIS E SOUSA
Position	Senior Group Leader Assistant Research Director
Year joined *(Crick or founder institute)*	1998

Career History

1992: DPhil, Oxford University
1993- 1998: Postdoc, NIH, USA
1998- present: Imperial Cancer Research Fund -> London Research Institute -> Francis Crick Institute
2013- present: Professor of Immunology, Imperial College

Major Awards, Honours and Prizes

2019: Bial Award in Biomedicine
2019: Fellow of The Royal Society
2017: The Louis Jeantet Prize for Medicine
2014- present: Highly Cited Researchers list (Thomson Reuters editions)
2009: Officer, Ancient Military Order of Sant'lago da Espada (from Portuguese Republic)
2008: Liliane Bettencourt for Life Sciences Award (Fondation Bettencourt-Schueller)
2006: Member, European Molecular Biology Organisation
2006: Fellow, The Academy of Medical Sciences

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

Panels
2021 – present Member, Wellcome Trust Expert Review Group 4 (Immunology in Health & Disease)
2015 - 2018 Member, CRUK New Investigator Committee
2015 - 2018 Chair (2016, 2018) or Shadow Member (2015, 2017), ERC Consolidator Grants Evaluation Panel LS6 - Immunity and Infection

Scientific Advisory Boards
2020 - present Bicara Therapeutics
2020 - 2024 Center for Microbes, Development and Health, Institut Pasteur of Shanghai
2020 - present Bicycle Therapeutics
2020 - present Champalimaud Foundation, Lisbon
2019 - present Sosei Heptares
2019 - 2021 U19 Systems Immunology, Harvard
2016 - present EtheRNA
2016 - 2018 Tusk Therapeutics
2015 - present iMM Lisboa
2015 - 2018 PROCROP EU Consortium
2014 - 2018 DCBIOL (Institut Curie, Paris/CIML, Marseille)
2013 - present Centre d'Immunologie de Marseille-Luminy (CIML)

Editorial Boards
2019 – present Current Research in Immunology
2016 - present Cell Stress
2015 – present Immunology-Microbiology Section, Oncotarget
2013 – present Genes and Immunity
2012 - present F1000 Research
2012 - present OncoImmunology
2012 - 2016 Clinical and Experimental Medicine
2011 - 2017 Frontiers in Antigen Presenting Cell Biology
2011 - 2017 Frontiers in Molecular Innate Immunity
2011 - 2017 Scientific Reports
2010 - present The EMBO Journal
2009 - present European Journal of Immunology (Executive Committee 2010-2016)

Lab Name	***Immunobiology Laboratory***

Research programme and achievements

The Immunobiology Laboratory studies receptors and signalling pathways that mobilise dendritic cells (DC) and other cell types in response to infection, injury or cancer. In a related programme, the laboratory studies DC heterogeneity and ontogeny.

In the last five years, the Immunobiology Laboratory continued earlier work on cell-intrinsic immunity to RNA viruses to show that antiviral RNA interference, an ancestral form of antiviral defence, is conserved in mammals but masked by the effects of interferons, cytokines elicited by the innate immune response to the virus. In a distinct line of investigation, the lab continued its studies of the Syk-coupled C-type lectin receptor, DNGR-1. This receptor was previously found by the lab to be used by the cDC1 subset of DCs to detect F-actin exposed by cells undergoing necrosis, which suggested that extracellular recognition of cytoskeletal components is an evolutionarily ancient means of detecting tissue damage. Consistent with that notion, the lab found that extracellular □-actinin, an actin-binding protein, elicits a response in *Drosophila melanogaster* akin to tissue injury. To further understand the role of extracellular actin recognition, the lab solved the structure of the DNGR-1/F-actin complex and went on to show that the association of F-actin with myosin II greatly potentiates DNGR-1 triggering through ligand cross-linking. The lab then validated the importance of F-actin detection and a pH-induced conformational change in DNGR-1 allowing cDC1s to extract antigens from cell corpses for presentation to $CD8^+$ T cells, a process termed cross-presentation. More recently, the lab discovered the cell biological basis for DNGR-1-dependent cross-presentation by finding that the receptor signals via Syk to induce rupture of phagosomes that contain internalised dead cell debris. This allows wholesale access of antigens associated with cell corpses to the endogenous MHC class I presentation pathway of cDC1s.

Cross-presentation can contribute to immunity to cytopathic viruses and to cancer. In the context of the latter, the lab found that DC activation and immune control can be subverted by prostaglandin E_2 produced by tumour cells. Prostaglandin E_2 also suppresses accumulation of cDC1s in tumours, which led the lab to discover that cDC1 infiltration of cancers is driven by chemokines produced by intratumoural innate lymphocytes such as NK cells.

Independently of its presence and function in differentiated cDC1s, DNGR-1 is also expressed by mouse DC precursors and, in earlier work from the lab, was used to fate-map those cells *in vivo*. In an extension of that work, the lab more recently described the clonal organisation of DCs in tissues and characterised an infection-driven acute recruitment to affected tissues of DC precursors originating from bone marrow. In parallel work, the lab characterised the ontogeny of mouse and human DCs using both *in vitro* cultures and humanised mice.

Overall, the studies of the Immunobiology Laboratory over the last quinquennium have helped build a global picture of the cells, receptors and signalling pathways that regulate immunity with applications in immunotherapy of cancer and infectious diseases. Future plans follow on directly from those of the past quinquennia. Part of the focus will be innate immune recognition of dead cells and its impact on inflammation, infection and cancer. Another focus will be the development and function of DCs, including how DC progenitors seed tissues and to what extent the latter process is regulated by demand.

Research outputs

Canton, J. et al. (2021) *The receptor DNGR-1 signals for phagosomal rupture to promote cross-presentation of dead-cell-associated antigens*. Nat Immunol 264, 1–14. DOI: 10.1038/s41590-020-00824-x
Immune cells such as type 1 conventional dendritic cells (cDC1) can “eat” (phagocytose) dead tumour or virally-infected cells and present associated antigens to CD8+ T cells to elicit a tumour- or virus-specific cytotoxic T cell response. How antigens from the debris get presented on MHC class I (MHC-I) molecules on cDC1 has long been puzzling as MHC-I normally presents antigens found in the cytosol. Canton et al show that cDC1 use the DNGR-1 receptor to induce phagosomal rupture, releasing the debris-associated antigens into the cytosol. These findings have implications for our understanding and manipulation of immunity to infection and cancer.

Cabeza-Cabrerizo, M., J. van Blijswijk, S. Wienert, D. Heim, R.P. Jenkins, P. Chakravarty, N. Rogers, B. Frederico, S. Acton, E. Beerling, J. van Rheenen, H. Clevers, B.U. Schraml, M. Bajénoff, M. Gerner, R.N. Germain, E. Sahai, F. Klauschen and C. Reis e Sousa. (2019) *Tissue clonality of dendritic cell subsets and emergency DCpoiesis revealed by multicolor fate mapping of DC progenitors*. Sci Immunol 4 pii:eaaw1941. DOI: 10.1126/sciimmunol.aaw1941
Conventional dendritic cells (cDCs) originate from a committed precursor in bone marrow (BM) that exits via the blood as a pre-cDC to seed tissues with the cDC1 and cDC2 subsets. We used a multi-colour genetic tracing mouse model to analyse colonisation of tissues by pre-cDC. We found that cDCs in tissues comprise clones mostly composed of a single cDC subset and that ‘flu infection causes an efflux of pre-cDCs from BM and influx into the lungs. The latter finding indicates that cDCpoiesis is responsive to emergency need, which suggests previously undiscovered communication between tissues and cDC progenitors in BM.

Böttcher, J.P., E. Bonavita, P. Chakravarty, H. Blees, M. Cabeza-Cabrerizo, S. Sammicheli, N.C. Rogers, E. Sahai, S. Zelenay and C. Reis e Sousa. (2018) *NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control*. Cell 172:1022 - 1037. DOI: 10.1016/j.cell.2018.01.004

This work follows on from a paper that we published in 2015 (see below). In the present paper, we showed that cDC1 recruitment and infiltration in several mouse tumour models depends on the chemokines CCL5 and XCL1 produced by NK cells. In human cancers, CCL5/XCL chemokine transcripts correlate with gene signatures for NK cells and cDC1 and predict overall survival in melanoma, head and neck cancer, breast cancer and lung adenocarcinoma. Therefore, our data uncovered a mechanism for cDC1 recruitment into tumours that is translatable to humans and cancer patient survival.

Zelenay, S., A.G. van der Veen, J.P. Böttcher, K.J. Snelgrove, N. Rogers, S.E. Acton, P. Chakravarty, M.R. Girotti, R. Marais, S.A. Quezada, E. Sahai, C. Reis e Sousa. (2015) *Cyclooxygenase-Dependent Tumor Growth through Evasion of Immunity*. Cell 162:1257-1270. DOI: 10.1016/j.cell.2015.08.015

In this paper, we uncovered a potent mechanism of cancer immune evasion, namely cyclooxygenase (COX)-dependent secretion of prostaglandin E_2 (PGE_2) by tumour cells. We further showed that the growth of PGE_2-secreting tumours in mice can be reversed by a combination of checkpoint blockade immunotherapy and COX inhibitors, suggesting that COX inhibition might be a useful addition to both conventional and immune-based therapy of cancer. This paper led to seven clinical trials worldwide to test combinations of prostaglandin E_2 inhibition with checkpoint blockade cancer therapies and resulted in the attribution of the inaugural Bial Prize in Biomedicine 2019 to the authors.

Hanč, P., Fujii, T., Iborra, S., Yamada, Y., Huotari, J., Schulz, O., Ahrens, S., Kjær, S., Way, M., Sancho, D., Namba, K., C. Reis e Sousa. (2015) *Structure of the Complex of F-Actin and DNGR-1, a C-Type Lectin Receptor Involved in Dendritic Cell Cross-Presentation of Dead Cell-Associated Antigens*. Immunity 42:839-849. DOI: 10.1016/j.immuni.2015.04.009

We previously identified DNGR-1 (CLEC9A) as a DC receptor that recognises exposed F-actin and allows for immune responses to dead cells. In this paper, we solved the cryo-EM structure of DNGR-1 bound to F-actin. We identified the key residues involved in binding and show that the latter depends greatly on multimeric interactions that increase receptor avidity. Notably, the binding site was revealed to be a composite of three distinct actin filament subunits explaining why the receptor can only bind to the filamentous form and not to G-actin.