Name	RUPERT BEALE
Position	Clinical Group Leader
Year joined *(Crick or founder institute)*	2019

Career History

Jan 2019 -	Clinician Scientist Group Leader, Francis Crick Institute. Honorary Consultant Nephrologist Royal Free Hospital
2015-2019	MRC Clinician Scientist Fellow; Division of Virology, Department of Pathology, University of Cambridge. Honorary Consultant Nephrologist, Addenbrooke's Hospital.
2014	Consultant Nephrologist, Royal Free Hospital
2009-2014	Visiting researcher in the laboratory of Dr Felix Randow, MRC Laboratory of Molecular Biology, Cambridge
2007-2014	Clinical Lecturer in Renal Medicine and Immunology, University of Cambridge; honorary specialty registrar Addenbrooke's and Ipswich Hospitals
2006-2007	SHO rotation in Medicine, Addenbrooke's Hospital, Cambridge
2005-2006	PRHO rotation, Cambridge and Ipswich
2004	MB BChir, University of Cambridge
2001-2004	PhD, MRC Laboratory of Molecular Biology, Cambridge; DNA sequence specificity of APOBEC family deaminases, supervised by Professor Michael Neuberger (as part of MB/PhD programme)
1996-2000	BA Natural Sciences, Class I, University of Cambridge

Major Awards, Honours and Prizes

2020	Fellow of the Royal College of Physicians
2015	MRC Clinician Scientist Fellowship

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

UK Government Covid advisory bodies:
Chair of Universities Testing Expert Panel (Cabinet Office/DfE)
Member of PHE Serology Working Group (Subgroup of SAGE)
Member of Advisory Group for Antibody Testing (DHSC)
Member of Higher Education Project Board for Mass Testing (DfE)
Chair of Trial Steering Committee, PROTECT-V (Prophylaxis for patients at risk of Covid-19 infection in vulnerable population)

Lab Name	***Cell Biology of Infection Laboratory***

Research programme and achievements

Research overview:
Our cells can detect infection by looking for non-self molecular structures, such as bacterial cell walls. Viruses transmit between similar organisms, taking all their structural components from their hosts. They therefore present few targets for host cells to detect. Viruses must hijack the cell to produce progeny, and this results in disturbed homeostasis. Cells therefore also detect perturbed physiology as a potential sign of infection. How this happens, and how the cell responds to these perturbations are the focus of my research.

My lab is particularly interested in what happens to cells when they cannot maintain pH gradients. These gradients are maintained by proton pumps, complicated and energetically expensive molecular machines. Viruses such as influenza and coronaviruses encode channels that allow protons to escape compartments that would normally be acidic. This triggers an inflammatory response, and also a response that looks similar to autophagy. By combining information from genetic screens we discovered that the proton pumps themselves recruit the autophagy machinery under these circumstances. We are trying to work out what this means for the cell and what this means for viruses. The evidence so far points to modulation of antiviral and inflammatory responses – the responses that determine the outcome of severe viral infections such as Covid-19.

Achievements:
Discovered (with the Florey group) the basis for triggering 'non-canonical' autophagy in response to disrupted pH gradients during viral infection. This requires the autophagy protein ATG16L1 to interact with the vacuolar ATPase via its C-terminal WD40 domain (Fletcher et al. 2018, Ulferts et al. in press).

Set up simple cell culture models of SARS-CoV-2 infection that are widely used within the Crick, underpinning live virus neutralisation assays and small molecule inhibitor screens. Helped establish the SARS-CoV-2 diagnostic pipeline at the Crick and provided critical data to inform public health responses (Ambrose et al., Houlihan et al., Hellewell et al., 2020).

Future directions:
The unexpectedly beneficial effect of corticosteroids on survival in oxygen-dependent Covid patients underlines how little we really understand inflammatory responses to infection. Corticosteroids are an exceptionally blunt implement in therapeutic terms, but have proved highly effective. In the case of SARS-CoV-2, this targeting of the host response has proved more useful than targeting the virus itself.
The focus of my research in the next few years will be to try to understand the mechanisms that underly inflammatory and other potentially maladaptive responses to infection, using clinical observations as well as advances in molecular virology to inform the design of experimental models. We intend to discover how viral ion channels (viroporins) such as influenza M2 and SARS-CoV-2 E trigger inflammation, and how this is related to the 'non-canonical' autophagy phenomena that they also trigger and which we have partly characterised. We are also interested in how certain genes implicated by GWAS studies as important for host responses to viral infection (including autophagy genes) might impinge on inflammatory responses at both a cell biological and whole organism level. Understanding these processes better may ultimately enable us to escape the dichotomy of targeting either host response or the virus itself by focussing on the most important host:pathogen interaction.

Research outputs

Fletcher K*, Ulferts R*, Jaquin E, Veith T, Gammoh N, Aresteh JM, Mayer U, Carding SR, Wileman T, Beale R†, Florey O†. (2018) *The WD40 domain of ATG16L1 is required for its non-canonical role in lipidation of LC3 at single membranes*. EMBO J 37(4):e97840. DOI: 10.15252/embj.201797840
We showed that multiple forms of so called 'non-canonical' autophagy depend on a different domain of ATG16L1 than canonical autophagy. This important mechanistic advance paved the way for paper 2, and a further manuscript (not yet available as pre-print) shows this depends on an interaction with the vacuolar ATPase.

Durgan J, Lystad A, Sloan K, Carlsson S, Wilson M, Elena Marcassa, Ulferts R, Webster J, Lopez-Clavijo A, Wakelam M, Beale R, Simonsen A, Oxley D, Florey O. (2021) *Non-canonical autophagy drives alternative ATG8 conjugation to phosphatidylserine.* Molecular Cell 81, 9: 2031 – 2040. DOI: 10.1016/j.molcel.2021.03.020
Oliver Florey's lab went on to show that non-canonical lipidation includes phosphatidylserine rather than just phosphatidylethanolamine. We provided evidence (in collaboration) that ATG4D recycles this conjugate.

Catherine F Houlihan, Nina Vora, Thomas Byrne, Dan Lewer, Gavin Kelly, Judith Heaney, Sonia Gandhi, Moira J Spyer, Rupert Beale, Peter Cherepanov, David Moore, Richard Gilson, Steve Gamblin, George Kassiotis, Laura E McCoy, Charles Swanton, Crick COVID-19 Consortium; Andrew Hayward, Eleni Nastouli, SAFER Investigators. (2020) *Pandemic peak SARS-CoV-2 infection and seroconversion rates in London frontline health-care workers*. Lancet 396(10246):e6-e7. DOI: 10.1016/S0140-6736(20)31484-7.
This important paper showed very high levels of infection amongst healthcare workers in a local hospital. It has influenced government policy – asymptomatic healthcare workers are to be screened as per our recommendation (announced October 12th).

Ambrose K, Beale R and many others in the Crick Covid-19 Consortium. (2020) *Scalable and robust SARS-CoV-2 testing in an academic center*. Nat Biotechnol 38, 927-931. DOI: 10.1038/s41587-020-0588-y
Along with many others I helped design and implement the Crick testing pipeline. My particular responsibility was the initial viral inactivation and RNA preservation step.

Houlihan CF, Beale R. (2020) *The complexities of SARS-CoV-2 serology*. Lancet Infect Dis 20(12), 1350 – 1351. DOI: 10.1016/S1473-3099(20)30699-X
This commentary arose from my work advising both PHE and the Department of Health and Social Care on serological testing.