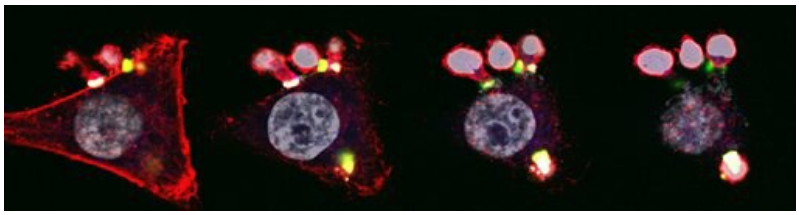
EBV persistence and lymphomagenesis



Group lead: **Martin Rowe (/staff/profiles/cancer/rowe-martin.aspx)**

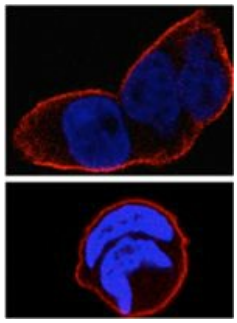
Overview

Epstein-Barr virus (EBV) is carried by the vast majority of all adults worldwide as an asymptomatic infection. Although ubiquitous and mostly harmless, EBV is the prototypic human tumour virus, and is associated with at least 10 different types of cancer. We are studying how this potentially dangerous virus successfully establishes persistent asymptomatic infections in most people, and how perturbations of the virus:host balance may give rise to virus-associated lymphomas.

Our research group

The EBV research team led by Professor Rowe is located in the School of Cancer Sciences. The team consists of both basic scientists and clinician scientists, with several strong collaborative links locally, nationally and internationally. The aim of our research is to better understand EBV persistence and pathogenesis, which will ultimately facilitate the design of rational anti-viral therapies.

We use a range of methodologies, including the generation of recombinant EBVs to examine the role of individual viral promotors and genes in the context of virus infections. For the ectopic expression of individual viral genes in cells or shRNA-induced knockdown of specific genes, we use transfection of bacterial plasmid vectors and transduction with retroviral/lentiviral vectors. We study global transcription changes induced by virus infection, and apply a range of biochemical, cellular, and immunological techniques to study the molecular mechanisms underlying viral gene function.



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Current projects

How does EBV establish latency in memory B cells?

(**Bell (/staff/profiles/cancer/bell-andrew.aspx)** , **Rickinson (/staff/profiles/cancer/rickinson-alan.aspx)** , Rowe)

One of the unresolved mysteries of EBV biology is that despite all B cell subsets apparently being equally infectable with the virus in vitro, analysis of the blood of healthy carriers of reveals that the virus is exclusively in memory B cell subsets and not in transitional or naïve B cells. By resolving this fundamental paradox, we anticipate learning more about the processes that aberrantly lead to B cell lymphomagenesis, e.g. Post-transplant lymphoma, Burkitt lymphoma and Hodgkin lymphoma, all of which demonstrate post-germinal centre B cell markers.

The molecular mechanisms of EBV infection of different cell types

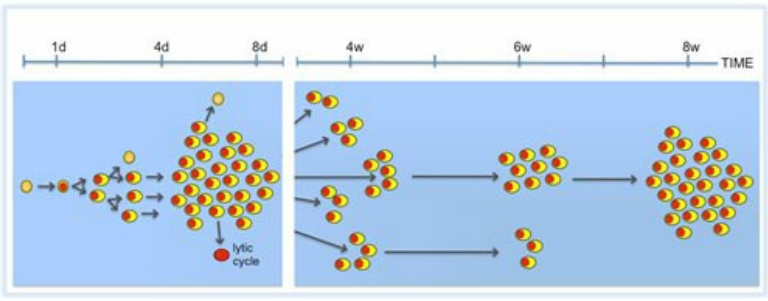
(**Shannon-Lowe (/staff/profiles/cancer/shannon-lowe-claire.aspx)** , Rowe)

EBV establishes latency in the B lymphocyte compartment, and many of the EBV-associated tumours are of B cell origin. Nevertheless, EBV-positive tumours of other cell types have been identified, most notably nasopharyngeal carcinoma which is one of the commonest forms of cancer in SE Asia. In addition to B cell and epithelial tumours, other malignant and pre-malignant diseases are characterised by the presence of EBV in NK cells or T cells. Whilst the molecular mechanisms involved in the infection of B cells are well characterised, infection of other cell types is under-researched to date. Dr Shannon-Lowe is leading the efforts of our group to understand how EBV infects epithelial cells, NK cells and T cells.

Mechanisms of malignant cell transformation by EBV

(Tierney, Bell, Shannon-Lowe, Rowe)

EBV is the most potent known transforming agent for human cells. Experimental infection of B cells in culture results in efficient cellular transformation and the establishment of continuously growing lymphoblastoid cell lines (LCLs). This transformation is driven by the expression of a limited set of 'latent' viral genes, through mechanisms that are partly understood. These LCLs are a good model for EBV-positive lymphomas that can arise in immunosuppressed transplant patients. However, most other EBV-positive malignancies express only a small subset of these transformation-associated latent genes; here there appears to be a greater cooperation between the expressed viral genes and the occurrence of cellular mutations. Our group is working to elucidate the respective roles of viral genes, cellular genes/mutations, and stromal environment in the malignant transformation of different cell types.



The interaction of the virus with the host immune system

(Zuo, Rickinson, Rowe)

It has long been recognised that infected people generate potent anti-viral immune responses. The specificity and effectiveness of CD4 and CD8 T cell responses to EBV have been extensively studied by the Rickinson group. It is evident that for the virus to persist asymptomatically in infected hosts, an equilibrium must be established between the immune responses of the host and immune evasion by the virus. The Rowe group is identifying viral genes that actively interfere with antigen presentation to immune T cells, and charactering their molecular mechanisms.

Recent publications

- Fox CP, *et al*: A novel latent membrane 2 transcript expressed in Epstein-Barr virus-positive NK- and T-cell lymphoproliferative disease encodes a target for cellular immunotherapy. ***Blood*** 2010, 116(19):3695-3704
- Shannon-Lowe C, and Rowe M: Epstein-Barr Virus Infection of Polarized Epithelial Cells via the Basolateral Surface by Memory B Cell-Mediated Transfer Infection. ***PLoS Pathog*** 2011, 7(5):e1001338.
- Zuo J, et al: Epstein-Barr virus evades CD4 T cell responses in lytic cycle through BZLF1-mediated downregulation of CD74 and the cooperation of vBcl-2. ***PLoS***

Pathog 2011, 7(12):e1002455.

- Heath E, et al: Epstein-Barr virus infection of naive B cells in vitro frequently selects clones with mutated immunoglobulin genotypes: implications for virus biology.***PLoS Pathog*** 2012, 8(5):e1002697.
- Schmitz R, et al: Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. ***Nature*** 2012, doi:10.1038/nature11378

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