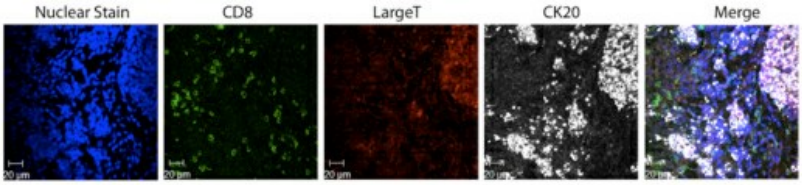
Tumour virus pathogenesis



Group leader: Professor David J Blackbourn

Overview

Tumour viruses account for up to 15% of human cancers globally, equating to 1.5 million cases annually. We study these viruses to investigate virus-host interactions, especially at the level of escape from the immune response, to learn about the role and mechanisms of anti-viral immunity.

Our research group

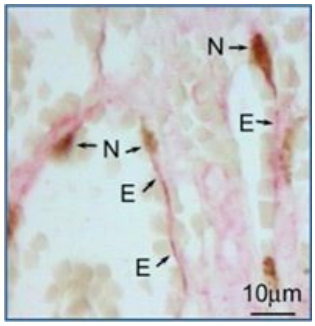
The model virus for our work is Kaposi's sarcoma herpesvirus (KSHV). It causes Kaposi's sarcoma, the leading cancer of sub-Saharan African men and AIDS patients. It also causes primary effusion lymphoma. Approximately one quarter of the genes of KSHV have immune regulatory potential and we study them. We also have research interests in Merkel cell polyomavirus (MCV) and its role in causing Merkel cell carcinoma.

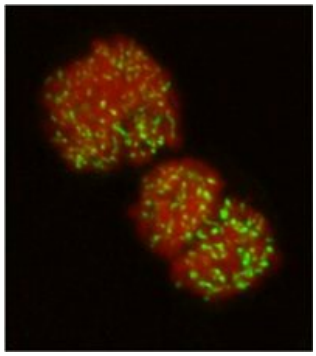
The major aim of our KSHV programme is to understand how this oncogenic human herpesvirus has evolved over ~80 million years to regulate intracellular innate immune pathways of its host. These studies increase our understanding of human immunity. Pathways of particular interest to the lab include the interferon response and Toll-like receptor sensing (see Current Projects).

Innate responses can define the quality and quantity of adaptive responses. Hence, the potential for increased understanding of innate immune pathways to resolve clinical problems and improve health care is a tangible goal for various clinical conditions. Besides the virus-associated malignancies, these conditions include infectious diseases, cancer and allergic and autoimmune diseases. Indeed, discovery of new classes of immune modulators based on viral immune evasion strategies may have therapeutic or prophylactic potential.

In other studies of MCV, we are characterising the tumour microenvironment and determining the factors that regulate its composition. These studies could lead to immunotherapeutic interventions to improve this and other diseases.

We frequently have opportunities to join the team. If you are interested in working or studying with us, please get in touch (**d.j.blackbourn@ bham.ac.uk (mailto:d.j.blackbourn@bham.ac.uk)**).





Left:KSHV infection (brown stain) in the nucleus (N) of Kaposi's sarcoma tumour cells (E). Right: KSHV infection of primary effusion lymphoma (PEL) cells: the KSHV protein LANA is stained green and the cellular DNA red.

Current projects

Open all sections

Interferon interactions
KSHV is unique among viruses that infect humans in that it encodes a family of four homologues of the cellular interferon regulatory factors (IRF) that are referred to as viral (v) IRFs. We have shown that one of these four proteins, vIRF-2, inhibits the type I interferon immune response at the levels of IRF-3-driven transactivation and ISGF-3 activity. We are investigating the molecular mechanism/s by which this inhibition occurs. Likewise, we are studying vIRF-4 modulation of the interferon response.

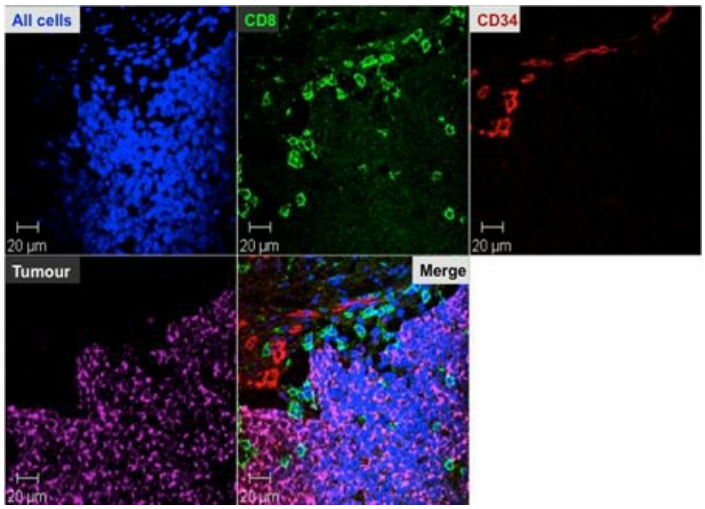
Suppression of T cell responses
We have shown that the vOX2 protein of KSHV inhibits neutrophil function. More recently, we have discovered another vOX2 activity, that of suppressing adaptive immunity, in collaboration with Dr Andrew Hislop (Birmingham). Our work to understand the mechanism behind this activity is ongoing.

Complement modulation
Complement provides a major barrier to virus infection as determined by the number and variety of viruses, including KSHV, that have evolved strategies to evade this immune response. We were the first to publish the functional characterisation of the complement regulatory activity of the KSHV ORF4 protein, that we call KCP. Our studies also reveal this protein participates in KSHV infection of cells.

Modulation of Toll-like receptor signalling
Toll like receptors (TLRs) form one of the very fundamental cellular early warning systems to sense virus infection; they are pattern recognition receptors (PRRs) that detect specific elements of a virus (e.g.- nucleic acid). In this project, we are determining if and how KSHV interacts with TLRs.

KSHV and the DNA damage response
To develop treatments for Kaposi's sarcoma we must understand KSHV replication and transformation. We hypothesise these processes depend on modulation of the DNA-damage response (DDR). This response is the means by which cells react to damage to their DNA. It is now clear that virus infection can activate the DDR, which may be either advantageous or detrimental to viral replication and its modulation can contribute to viral oncogenesis. Together with Dr Roger Grand, we are investigating how KSHV modulates the DDR.

The tumour microenvironment
Merkel Cell Carcinoma (MCC) is an aggressive neuroendocrine skin cancer. Merkel Cell Polyomavirus (MCPyV) is the likely cause. With Dr Neil Steven, we are using multicolour confocal microscopy to characterise the immune microenvironment of MCC in order to understand the factors that make it such an aggressive disease. Therapeutic and prophylactic interventions could then be developed.



Above: : Analysing the Merkel cell carcinoma tumour immune microenvironment by confocal microscopy.

Recent publications

- **Damania, B and D.J. Blackbourn**. Innate Barriers to Viral Infection. *Future Microbiology* 7:1-8, 2012.
- **Butler, L.M., H.C. Jeffery, R.L. Wheat RL, P.C. Rae, H.M. Long, G.B. Nash & D.J. Blackbourn.** KSHV inhibits expression and function of endothelial cell MHC class II via suppressor of cytokine signalling 3. *J.Virol*. 86: 7158-7166, 2012.
- **Misstear, K., S.A. Chanas, S.A.R. Rezaee, R. Colman, A.S. Solovyova, L.L. Quinn, H.M. Long, J.M. Lord, J.A. Gracie, I.B. McInnes, A.D. Hislop and D.J. Blackbourn.** Suppression of antigen-specific T cell responses by the KSHV vOX2 protein and its cellular orthologue, CD200. *J.Virol.* 86: 6246-6257, 2012.
- **Mutocheluh, M., L. Hindle, C. Aresté, S.A. Chanas, L.M. Butler, K. Lowry, K. Shah, D.J. Evans & D.J. Blackbourn.** KSHV vIRF-2 inhibits type 1 interferon signalling by targeting ISGF-3. *J. Gen. Virol.,* 92: 2394-8, 2011.
- **Jackson, B.R., J.R. Boyne, M. Noerenberg, A. Taylor, G.M. Hautbergue, M.J. Walsh, R. Wheat, D.J. Blackbourn, S.A. Wilson, A. Whitehouse.** An interaction between KSHV ORF57 and UIF provides mRNA-adaptor redundancy in herpesvirus intronless mRNA export. *PLoS Pathog*. 2011 Jul;7(7):e1002138. Epub 2011 Jul 21.

Lab publications

- **Pubmed links (http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=PureSearch&db=PubMed&term=Blackbourn%20d)**
- **Global infection - David Blackbourn transcript (http://www.birmingham.ac.uk/accessibility/transcripts/global-infection-david-blackbourn.aspx)**
- **Virology and Bacteriology (http://www.birmingham.ac.uk/staff/excellence/fellows/areas/Virology-and-Bacteriology.aspx)**