Name	KATE NANETTE BISHOP
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	2008

Career History

1998-2002: PhD in Virology - National Institute for Medical Research/UCL
2002-2004: Post-doctoral Research Fellow, King's College London
2004-2008: Royal Society Dorothy Hodgkin Fellow, King's College London
2008-2014: Wellcome Trust Career Development Fellow and Programme Leader (Track) National Institute for Medical Research
2017-present: Senior Group Leader, Francis Crick Institute

Major Awards, Honours and Prizes

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

2016 – 2019: Co-organiser of British Microbiology Society Annual Conference
2016: Co-organiser of Cold Spring Harbor Retroviruses Meeting
2015 – 2019: Virology Division Committee Member, British Microbiology Society
2015 – present: Editorial board for Virology
2014 – present: Editorial board for Peer J
2014 – present: Member of AcademiaNet

Lab Name	***Retroviral Replication Laboratory***

Research programme and achievements

Over 37 million people are infected with HIV and there is no cure, no vaccine and a high economic burden associated with current drugs. Hence, retroviral infection is a major global health issue. My research interest is centred on understanding how retroviruses replicate in cells, which underpins investigations into eradicating HIV reservoirs as well as providing novel targets for HIV therapies. Somewhat surprisingly, there are still many gaps in our knowledge of retroviral replication events and in particular, of the host proteins involved. As obligate intracellular parasites, retroviruses are required to make numerous interactions with cellular proteins in order to complete each replication step. Additionally, they must avoid or overcome cellular proteins that inhibit their replication. As such, retroviruses can give us unique insight into the molecular biology of the cell, and reveal fundamental cellular processes beyond those involved in infection control.

My specific research aims are: (i) to elucidate the function and cellular interactions of viral proteins that are essential for early retroviral replication events and (ii) to identify and characterise the action of cellular proteins that restrict infection during early replication. Within this theme, my research programme is divided into three separate but inter-related projects that collectively will help to decipher the early stages of retroviral replication:

Project 1: Investigating the function of the p12 protein of MLV in early replication
Our studies on p12 have identified two new functions for this retroviral protein during early post-entry replication of MLV. We established that an N-terminal domain of p12 binds the viral capsid protein (CA) and stabilises the viral core. We hypothesise that p12 binds within a pocket on the surface of the CA lattice that is common to all retroviral CA shells, including HIV, and that CA stability and uncoating (breakdown of the viral core) are regulated by binding to this pocket. Additionally, we have demonstrated that a C-terminal motif in p12 directly binds to chromatin to tether the viral pre-integration complex to the host cell DNA, revealing a role for CA in MLV integration. The function of CA and CA-binding factors in HIV-1 integration is currently hotly debated (see below) and p12 provides an excellent model and a novel angle to study this problem. We are currently investigating how p12 binding stabilises CA lattices, and the timing of CA release from pre-integration complexes relative to DNA binding and integration.

Project 2: Investigating the role of capsid in HIV-1 early replication
The relationship between uncoating and other early replication events such as reverse transcription, the trafficking of the core to the nucleus, nuclear entry and integration of HIV is currently unclear. We were the first to demonstrate that HIV-1 uncoating is triggered by a specific step of reverse transcription, and to suggest possible mechanisms that drive the uncoating process. Our current work extends these findings and shows that infections of viruses with hyperstable cores are inhibited at a much later replication step. Therefore, we are collaborating with Crick experts in cryo-electron microscopy to visualise uncoating intermediates that have proved elusive to this point. We are also exploring the localisation of CA during infection and the interactions between CA and cellular factors that are important for replication.

Project 3: Investigating how Vpx and Vpr enhance HIV replication
SAMHD1 is a cellular protein that restricts HIV replication. We have mapped the features of SAMHD1 required for this restriction and established the mechanism of SAMHD1 regulation in cells. This has allowed us to propose a model for SAMHD1 antiviral activity that we have recently refined. Additionally, we have studied the effects of SAMHD1 on nucleoside analogue drugs and have shown that targeting SAMHD1 may enhance particular cancer therapies. We are currently collaborating with GSK in this area. Furthermore, we have uncovered the molecular details of how retroviral Vpx proteins counteract SAMHD1 by directing its degradation. We are now extending our investigations to lentiviral Vpr proteins. Vpr is a paralogue of Vpx, whose function is currently unknown but it is able to cause cell cycle arrest and may interfere with DNA repair.

By combining biochemistry, virology and cell biology, and a successful, long-term collaboration with structural biologists, my lab has been able to reveal novel interactions between retroviruses and their hosts. Furthermore, we have learnt much more about how our own cells work. In the future, we aim to increase our fundamental knowledge of both retroviral replication as well as host cell biology, in order to identify ways to protect ourselves from retroviruses and viral infections in general.

Research outputs

Wanaguru M, Barry DJ, Benton DJ, O'Reilly NJ, Bishop KN. (2018) *Murine leukemia virus p12 tethers the capsid-containing pre-integration complex to chromatin by binding directly to host nucleosomes in mitosis*. PLoS Pathog. 14(6):e1007117. DOI: 10.1371/journal.ppat.1007117
In this paper, we determined that the retroviral p12 protein directly binds to host chromatin to tether the pre-integration complex to DNA ready for integration. This study also revealed that the capsid protein is an important component of this complex and is essential for this stage of viral replication.

Ordonez P, Kunzelmann S, Groom HC, Yap MW, Weising S, Meier C, Bishop KN, Taylor IA, Stoye JP. (2017) *SAMHD1 enhances nucleoside-analogue efficacy against HIV-1 in myeloid cells*. Sci Rep. Feb 21:7:42824. DOI: 10.1038/srep42824
This study showed that SAMHD1 could influence the activity of several nucleoside analogue drugs used as antiviral or cancer therapies, either by directly degrading them, or through degradation of competing canonical nucleotides and thus raising the drug effective concentration. This suggested that manipulation of SAMHD1 activity may be useful in combination with existing cancer therapies.

Cosnefroy O, Murray PJ, Bishop KN. (2016) *HIV-1 capsid uncoating initiates after the first strand transfer of reverse transcription*. Retrovirology 13(1):58. DOI: 10.1186/s12977-016-0292-7
In this report, we identified for the first time a stage in reverse transcription that triggers uncoating (breakdown) of HIV-1 cores, a highly controversial area of retrovirology. This in turn suggested possible mechanisms for uncoating and also reopened the long unresolved debate about the location of reverse transcription in the cell.

Arnold LH, Groom HC, Kunzelmann S, Schwefel D, Caswell SJ, Ordonez P, Mann MC, Rueschenbaum S, Goldstone DC, Pennell S, Howell SA, Stoye JP, Webb M, Taylor IA and Bishop KN. (2015) *Phospho-dependent Regulation of SAMHD1 Oligomerisation Couples Catalysis and Restriction*. PLoS Pathog 11(10):e1005194. DOI: 10.1371/journal.ppat.1005194
This study explained the mechanism of SAMHD1 regulation by phosphorylation/ tetramerisation and correlated restriction activity with the capacity of SAMHD1 to form long lived, stable tetramers. These data form the basis of the prevailing model for SAMHD1 restriction of HIV-1 where dNTP-stabilised SAMHD1 tetramers deplete and maintain low levels of dNTPs in the non-permissive cells resistant to HIV-1 infection.

Schwefel D, Boucherit VC, Christodoulou E, Walker PA, Stoye JP, Bishop KN and Taylor IA. (2015) *Molecular determinants for recognition of divergent SAMHD1 proteins by the lentiviral accessory protein Vpx*. Cell Host & Microbe 17:489-99. DOI: 10.1016/j.chom.2015.03.004
This combined virological and structural study revealed how different lineage Vpx proteins are able to target different regions of SAMHD1, whilst still binding to the DCAF1 adaptor to recruit SAMHD1 to the Cullin 4A/E3 ligase complex for degradation. The work provides the first description of how lentiviral accessory proteins employ differing strategies to subvert and inactivate the cell's viral defence system.