Name	JONATHAN STOYE
Position	Senior Group Leader International Activities Ambassador
Year joined *(Crick or founder institute)*	1989

Career History

1981: PhD, Basel University, Switzerland
1982- 1989: Research Associate, Tufts University School of Medicine, Boston, USA.
1989- present: MRC-National Institute for Medical Research; Francis Crick Institute

Major Awards, Honours and Prizes

2017 Elected Fellow of the Royal Society

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

Member, MRC Infections and Immunity Board (2017-present)
Member, Covid-19 MRC Agile Review Panel (2020-present)
Member, Journal of Virology editorial board (1994-present)
Member, Royal Society Section Committee 7

Lab Name	***Retrovirus-Host Interactions Laboratory***

Research programme and achievements

Throughout evolutionary history, eukaryotes have been subjected to genetic assault by a variety of different retroelements capable of inserting their genomes into those of their hosts. Some of these elements (such as retroviruses like HIV-1) also cause harm by non-integrative mechanisms. As a consequence, a number of intrinsic defence mechanisms have evolved to neutralise these retroelements; in turn, viral countermeasures have developed. My interests span various aspects of the ensuing genetic to and fro. Specifically, we study:

A. **Mechanisms for preventing infection**
   Still our prime focus is the restriction gene Fv1, arguably the prototypic restriction factor and first identified in my lab, and other host factors that bind to the capsid core of newly infecting viruses, blocking an early step in the viral life cycle. We would like to understand the long-term survival of these factors and the principles underlying virus recognition. Recently we have shown that maintenance of the Fv1 open reading frame requires continued selection, implying an on-going series of virus infections reaching back millions of years. We have shown the presence of Fv1 in a wide variety of Muridae and identified variants with the ability to restrict five different genera of retroviruses carrying CA proteins with very different primary sequences. This has prompted us, in collaboration with the group of Ian

Taylor, to examine the 3D structures of CA from retroelements with increasing divergence from modern day retroviruses. We have demonstrated significant structural conservation in the capsid core of all retroelements, including those of yeast and *Drosophila*, and this may explain why a limited number of sequence changes in Fv1 can allow restriction of viruses showing 90% sequence divergence. We are currently collaborating with a group in the USA to study copy number control of Ty1 elements in yeast which appears to operate by a mechanism closely resembling Fv1 restriction of murine leukemia virus (MLV). We anticipate that these comparative approaches will shed further light on the mechanism of Fv1 action.

We also study the restriction factor SAMHD1 which we have shown to act on retrovirus replication by reducing intracellular dNTP pools with consequent effects on reverse transcription (collaborations with Kate Bishop and Ian Taylor). Lentiviruses encode a handful of accessory proteins capable of targeting potential restriction factors for destruction by the cellular proteasomes. Probing the interaction between one such protein, Vpx, SAMHD1 and cellular ubiquitinating enzymes has revealed how lentiviral accessory proteins have been retargeted during virus evolution to deal with different host proteins. Our studies have also highlighted the key role played by SAMHD1 as a regulatory enzyme in cell metabolism. We are currently seeking to identify small molecules targeting SAMHD1 function in high throughput screens.

B. **Mechanisms for silencing insertions.**

Cells possess several mechanisms for silencing inserted retroelements. One of these is the HUSH system which silences gene expression by a mechanism involving the spread of H3K9me3 marks on integrated transgenes. We are examining how this system acts on newly integrated viruses. In addition to its effects on SAMHD1, Vpx can also act to prevent HUSH silencing by a mechanism seemingly involving degradation of one or more HUSH components by proteasomes. We are examining the hypothesis that this represents a further example of accessory protein retargeting to cause degradation of a factor inhibiting virus expression, mediated by hijacking of the cellular pathway for proteolysis.

A second silencing mechanism involves the recruitment of Trim28/Kap1 and Setdb1 to ERVs by cellular Krüppel-associated box domain zinc finger proteins (ZFPs) to mediate their silencing by histone methylation. In collaboration with George Kassiotis, we have recently shown that *Gv1*, a murine gene regulating ERV expression in multiple strains of mice, encodes the ZFP *2410141K09Rik* and are exploring its mode of action in greater detail to shed greater light on the roles of ZFPs in controlling ERV expression. Despite control mechanisms of this kind, ERVs can be expressed with a variety of consequences. We therefore continue to explore patterns of ERV expression and their potential roles in normal physiology and pathology.

Research outputs

Young, G. R., M. W. Yap, J. R. Michaux, S. J. Steppan and J. P. Stoye. (2018). *Evolutionary journey of the retrovirus restriction gene Fv1*. Proc Natl Acad Sci., USA. 115:10130-10135. DOI: 10.1073/pnas.1808516115

This manuscript explores the evolutionary history of Fv1, demonstrating that the gene has its origins 45 million ago and thus is much older than previously thought. Modelling studies indicated that the maintenance of the gene's open reading frame for this period of time can only be explained by repeated selection events from waves of retroviral infection throughout murid evolution.

Yap, M. W., G. R. Young, R. Varnaite, S. Morand and J. P. Stoye. (2020). *Duplication and divergence of the retrovirus restriction gene Fv1 in Mus caroli allows protection from multiple retroviruses*. PLoS Genetics. 16(6):e1008471. DOI: 10.1371/journal.pgen.1008471.
It is thought that retroviruses and their hosts are locked in an evolutionary arms race characterised by development and escape from novel restriction mechanisms. This study examines the status of Fv1 in wild populations of mice from Thailand. It describes a gene duplication event allowing selection of simultaneous restriction of two virus genera. It helps to define limits to the range of restriction possible with a single factor.

Ball, N. J., G. Nicastro, M. Dutta, D. J. Pollard, D. C. Goldstone, M. Sanz-Ramos, A. Ramos, E. Müllers, K. Stiornnagel, N. Stanke, D. Lindemann, J. P. Stoye, W. R. Taylor, P. B. Rosenthal and I. A. Taylor. (2016). *Structure of a spumavirus Gag central domain reveals an ancient retroviral capsid*. PLoS Pathogens. 12(11):e1005981. DOI: 10.1371/journal.ppat.1005981.
In contrast to orthoretroviruses, spumaraviruses contain an unprocessed Gag protein. We had previously shown that (i) Fv1 and Trim5 restriction was dependent on an assembled viral core and (ii) that they could restrict spumaviruses. This prompted us to examine the structure of the central domain of the spumavirus Gag protein, revealing a previously unsuspected structural similarity to orthoviral CA implying a common evolutionary origin.

Cottee, M. A., S. C. Letham, G. R. Young, J. P. Stoye and I. A. Taylor. (2020). *Structure of the Drosophila melanogaster ARC1 reveals a repurposed molecule with characteristics of retroviral Gag*. Sci Adv. 6(1):eaay6354. DOI: 10.1126/sciadv.aay6354
A study of a *Drosophila* protein important for learning and memory, derived from an exapted retrotransposon of the Metaviridae family. Its structure is fully consistent with hypothesised roles for ARC1 in packaging mRNA for transfer across synaptic junctions. However, subtle differences between the *Drosophila* and tetrapod proteins suggest independent exaption events. The overall similarity with the CA protein of the Retriviridae provides further evidence for common evolutionary origins of all retroelements.

Ordonez, P., S. Kunzelmann, H. C. Groom, M. W. Yap, S. Weising, C. Meier, K. N. Bishop, I. A. Taylor and J. P. Stoye. (2017). *SAMHD1 enhances nucleoside-analogue efficiency against HIV-1 in myeloid cells*. Sci Rep 7:42824. DOI: 10.1038/srep42824.
A study examining the effects of dNTP depletion by introduced SAMHD1 on the anti-HIV activity of a number of nucleotide analogues that are not normally considered antiretrovirals. It points to the possibility of manipulating the activities of such drugs, not just allowing redirection towards HIV, but also in potentiating anti-cancer effects, by altering SAMHD1 activity.