

<b>Name</b>	IAN A TAYLOR	
<b>Position</b>	Senior Group Leader	
<b>Year joined (Crick or founder institute)</b>	2001	

### Career History

1988- 1992: University of Portsmouth, PhD in Biophysics  
 Supervisor: Professor G. G. Kneale  
 Thesis title: Biochemical Characterisation of the Type I DNA Modification Methylase, EcoR124I  
 1992- 1995: University of Portsmouth, Postdoctoral Fellow  
 Project: Biophysical studies of type I restriction/modification systems  
 1995- 2000: NIMR, Postdoctoral Fellow  
 Project: Structural studies of Cell-cycle regulatory proteins.  
 2000- 2001: University of Oxford, Postdoctoral Fellow  
 Project: Structural studies of the anaphase promoting complex

### Major Awards, Honours and Prizes

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

2020; Member of assessment panel, HCERES review of the Institute for Structural Virology, Grenoble, France.  
 2016-present; Member of Crick Africa Network Steering committee

### Lab Name

***Macromolecular Structure Laboratory***

### Research programme and achievements

Despite many years of progress, HIV infection and AIDS still remain global health concerns. HIV-1 is presently incurable, there is no vaccine and the economic burden of current drug regimens is significant. Therefore, research into HIV-1 and other retroviruses has the goal of furthering our understanding of retrovirus biology with a view to disease eradication but also the development of antiviral compounds and new drug strategies for HIV-1 intervention. To this end, my research is focused on three key areas of retrovirus research; the retroviral capsid and post entry capsid-associating restriction factors, restriction of HIV-1 replication by SAMHD1 and lentiviral accessory proteins, viral countermeasures that evade host-cell defences.

Research into retroviral assembly and post-entry restriction factors has focused on the retroviral core, specifically the capsid protein (CA) and its interaction with host cell restriction factors Trim5 $\alpha$ , TrimCyp, Fv1 and Mx2. We have employed structural biology methods - X-ray crystallography, solution and solid-state NMR and cryo-electron microscopy - to determine the structures of restriction factors and individual CA proteins, but also to visualise CA assemblies and analyse their interaction with restriction factors,

---

other viral components and small molecules. These studies aim to provide a full description of the intermolecular interactions required for capsid assembly, and the molecular details of the capsid interaction with restriction factors and drugs. Longer term, we aim to translate this research into development of antiretroviral compounds that act through interaction with capsid, to work alongside existing reverse transcriptase, protease and integrase inhibitors.

Other restriction factor research is focussed on SAMHD1, a dNTP triphosphohydrolase that inhibits HIV-1 replication through depletion of the cellular dNTP pool. SAMHD1 also maintains normal cellular dNTP homeostasis, and controls the efficacy of nucleotide-based antiviral and chemotherapies. Its mutation is a cause of dNTP imbalance, genome instability and human disease. SAMHD1 nucleotide binding, quaternary structure and phosphorylation all contribute to allosteric regulation and catalysis. We have employed structural, enzymological and nucleotide analogue studies to determine the mechanism of allostery and catalysis and how they impact on HIV-1 restriction, normal cellular dNTP homeostasis and drug metabolism together with the dynamics of SAMHD1 quaternary structure. One longer-term goal is to draw on these studies to prepare small molecule activators or inhibitors of SAMHD1 that can be employed in SAMHD1-targeted anti-HIV-1 and anticancer therapies.

To counter the inhibition by restriction factors, lentiviruses express the accessory proteins Vpr and Vpx, which disable cellular defence mechanisms through reprogramming of the substrate adaptor DCAF1, recruiting restriction factors to the Cul4 E3 ubiquitin ligase to be tagged for degradation. SAMHD1 is the target for Vpx, and some Vpr proteins from Simian Immunodeficiency Viruses (SIVs) also target SAMHD1. However, in other lentiviruses, including HIV-1, the Vpr target is unclear. We have undertaken, virological, cell biological, biophysical and structural studies focused on Vpx(r)-DCAF1-SAMHD1 complexes to determine the structural basis of these host-pathogen interactions at a molecular level. These studies have been expanded into other Vpr proteins and their cellular targets and in the longer-term, these structural data will guide experimentation into a new class of small molecule “therapeutic disrupters” that work through inhibiting Vpx(r)-DCAF1 interactions, preventing the recruitment of host-cell defence proteins for degradation and exposing the virus to the effects of restriction factors.

---

## Research outputs

**Morris ER, Caswell SJ, Kunzelmann S, Arnold LH, Purkiss AG, Kelly G, Taylor IA. (2020) *Crystal structures of SAMHD1 inhibitor complexes reveal the mechanism of water-mediated dNTP hydrolysis*. Nat Commun 11: 3165. DOI: [10.1038/s41467-020-16983-2](https://doi.org/10.1038/s41467-020-16983-2)**

This ground-breaking structural and biochemical study determined the precise chemical mechanism of metal-water mediated SAMHD1 catalysis and provided the molecular details of SAMHD1 inhibition by nucleotide-based compounds. The study revealed how SAMHD1 both down-regulates cellular dNTP and decreases the efficacy of nucleoside-based anti-cancer and anti-viral therapies, paving the way for rational design of future SAMHD1 inhibitors.

**Cottee MA, Letham SC, Young GR, Stoye JP, Taylor IA. (2020) *Structure of Drosophila melanogaster ARC1 reveals a repurposed molecule with characteristics of retroviral Gag*. Sci Adv 6: eaay6354. DOI: [10.1126/sciadv.aay6354](https://doi.org/10.1126/sciadv.aay6354)**

In this structural/evolutionary study, we determined the crystal structure of neuronal protein dARC, which is essential for memory and learning, and examined its relationship with the capsid of retroviruses and retrotransposons. The study revealed that ARC proteins that arose as a result of the exaptation of ancient retrotransposon Gag genes have retained the basic building block structure and can assemble into shells with the

---

---

overall architecture seen in spuma- and orthoretroviruses. Nevertheless, through adaptation, their original viral genome packaging function has been repurposed to now enable encapsidation and transfer of genetic information across synapses in the brain.

**Acton O, Grant T, Nicastro G, Ball NJ, Goldstone DC, Robertson LE, Sader K, Nans A, Ramos A, Stoye JP, Taylor IA\*, Rosenthal PB\*. (2019) *Structural basis for Fullerene geometry in a human endogenous retrovirus capsid*. Nat Commun 10: 5822. DOI: [10.1038/s41467-019-13786-y](https://doi.org/10.1038/s41467-019-13786-y)**

This study used combined structural methods of solution NMR, X-ray crystallography and Cryo-EM to examine the capsid of the human endogenous retrovirus HERV-K. We determined the high-resolution structures of four classes of Fullerene CA-assemblies that demonstrated how invariant CA pentamers combine with plastic CA hexamers to build the polyhedral structures that define the retroviral core. The study also revealed how adaptability and symmetry breaking of intra- and interprotomer CA-CA interactions combine to accommodate the variable curvature of the CA shell.

**Arnold LH, Groom HCT, Kunzelmann S, Schwefel D, Caswell SJ, Ordonez P, Mann MC, Rueschenbaum S, Goldstone DC, Pennell S, Howell SA, Stoye JP, Webb M, Taylor IA\*, Bishop KN\*. (2015) *Phospho-dependent regulation of SAMHD1 oligomerisation couples catalysis and restriction*. PLoS pathogens 11(10): e1005194. DOI: [10.1371/journal.ppat.1005194](https://doi.org/10.1371/journal.ppat.1005194)**

This structural, biochemical and virological study revealed the tetramerisation /phosphorylation dependent mechanism of SAMHD1 regulation. These data form the basis of the prevailing model for SAMHD1 restriction of HIV-1 where dephosphorylation switches housekeeping SAMHD1, found in cycling cells, to a high-activity stable tetrameric form that depletes and maintains 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, Taylor IA. (2015) *Molecular Determinants for Recognition of Divergent SAMHD1 Proteins by the Lentiviral Accessory Protein Vpx*. Cell host & microbe 17(4): 489-499. DOI: [10.1016/j.chom.2015.03.004](https://doi.org/10.1016/j.chom.2015.03.004)**

This study revealed the crystal structure of a molecular complex containing the lentiviral accessory protein Vpx, a component of the human cellular degradation machinery DCAF1, and a C-terminal region of the anti-HIV-1 restriction factor SAMHD1. The structure combined with our previous 2014 publication provides the explanation of how lentiviral accessory proteins can use different modes of action to subvert the cell's normal protein degradation pathway to inactivate the viral defence system.

---