Name	PETER CHEREPANOV
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	2011

Career History

1995-2000: PhD, University of Leuven, Belgium
2000-2003: Postdoctoral fellow, University of Leuven, Belgium
2003-2005: Postdoctoral fellow, Dana-Farber Cancer Institute, USA
2005-2009: Senior Lecturer, Imperial College London
2009-2011: Reader in Virology, Imperial College London
2011-present: Professor in Virology, Imperial College London

Major Awards, Honours and Prizes

Fleming Prize Lecture, Society for General Microbiology, Harrogate, UK, Apr 12, 2011

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

Lab Name	***Chromatin Structure and Mobile DNA Laboratory***

Research programme and achievements

The focus of our research is retroviral replication and host-pathogen interactions, in particular those involved in HIV entry and DNA integration. Our main techniques are cryo-electron microscopy and X-ray crystallography, which allow us to determine three-dimensional structures of viral components, as well as cellular factors that enable or counteract viral replication.

Integrase is an essential retroviral enzyme that forms the intasome at the termini of linear viral DNA and then inserts them into a host cell chromosome. Replication via a stable proviral form is the unique property that allows HIV and other retroviruses to establish life-long persistent infections. Integrase is essential for retroviral replication and, as such, is an important target for the development of anti-HIV/AIDS therapeutics.

In the past five years we made seminal contributions to understanding the mechanism of retroviral DNA integration. We determined the first structure of the intasome belonging to *Lentivirus,* the retroviral genus that includes HIV. Surprisingly, the structure revealed an extended protein scaffold comprising 16 integrase subunits. We dissected the molecular interactions involving two key viral factors (integrase and the viral structural protein Gag) with the basic repeat unit of chromatin, the nucleosome. For example, we discovered that the intasome locally remodels the nucleosomal structure, literally peeling DNA off the histone octamer surface. More recently, we explained the mode of action of the advanced

clinical integrase strand transfer inhibitors Dolutegravir and Bictegravir and the mechanism of HIV resistance to this drug class via mutations in the integrase active site. The interactions with magnesium ions, which are nearly covalent in nature, are partly responsible for the extraordinary tight binding of the strand transfer inhibitors. Our results revealed that the chink in the armor of this drug class, exploited by the virus, is the extreme sensitivity of metal ions for the precise geometry and electronic properties of the ligand chelating cluster. The intasome structures determined in our laboratory are used by pharmaceutical companies to develop this important class of antiretroviral drugs.

Recent research uncovered an array of innate immunity mechanisms employed by host organisms to impede pathogen replication and the specific countermeasures the latter evolve to circumvent host restriction. One such axis of antagonism involves the human transmembrane protein SERINC5, which when incorporated into budding HIV-1 virions, can potently inhibit their subsequent entry into host cells. In addition, SERINC5 strongly enhances the ability of antibodies to neutralize the virus. Using cryo-EM we were able to determine three-dimensional structures of two members of the SERINC protein family, revealing a novel protein fold comprising ten transmembrane helices. Guided by the structure, we dissected the critical regions of SERINC5 that contribute to its antiviral activities. The mechanism of HIV-1 restriction by the SERINC family of proteins remains one of the hottest topics in the field and is our next goal.

Research outputs

Cook, N.J., Li, W., Berta, D., Badaoui, M., Ballandras-Colas, A., Nans, A., Kotecha, A., Rosta, E., Engelman, A.N. and Cherepanov, P. (2020) *Structural basis of second-generation HIV integrase inhibitor action and virus escape*. Science 367, 806-810. DOI : 10.1126/science.aay4919
HIV integrase inhibitors represent some of the most impactful antimicrobial inhibitors. The second-generation drugs display improved barriers to the emergence of resistance, which spearheaded their worldwide rollout. Yet not even the most advanced compounds are immune to viral resistance. Our results explained the mechanism of viral resistance associated with the most common drug resistance mutations. Furthermore, we established the key difference between the first and second-generation strand transfer inhibitors, which will inform further development of this drug class.

Pye, V.E., Rosa, A., Bertelli, C., Struwe, W.B., Maslen, S.L., Corey, R., Liko, I., Hassall, M., Mattiuzzo, G., Ballandras-Colas, A., Nans, A., Takeuchi, Y., Stansfeld, P.J., Skehel, J.M., Robinson, C.V., Pizzato, M. and Cherepanov, P. (2020) *A unique bipartite structural organisation defines the SERINC family of HIV-1 restriction factors*. Nat. Struct. Mol. Biol. *27*, 78-83. DOI: 10.1038/s41594-019-0357-0
In this work we determined the structure of SERINC5, a potent HIV-1 restriction factor and discovered a novel transmembrane protein fold. The work has important implications for understanding the antagonistic host-virus interactions and for the development of future antiviral therapies.

Ballandras-Colas, A., Maskell, D.P., Serrao, E., Locke, J., Swuec, P., Jonsson, S.R., Kotecha, A., Cook, N.J., Pye, V.E., Taylor, I.A., Andresdottir, V., Engelman, A.N., Costa, A. and Cherepanov, P. (2017) *A supramolecular assembly mediates lentiviral DNA integration*. Science 355, 93-95. DOI: 10.1126/science.aah7002
Lentiviral IN proteins are notoriously poorly behaved *in vitro*, and the HIV1 intasome has eluded structural biologists for over two decades. Prior research resulted in a collection of partial crystal and NMR structures that did not explain how lentiviral integrase synapses viral DNA ends. This paper described the first structure of the lentiviral intasome, solving the long-standing mystery and reconciling years of HIV-1 integrase structural biology and biochemistry.

Lesbats, P., Serrao, E., Maskell, D.P., Pye, V.E., O'Reilly, N., Lindemann, D., Engelman, A.N. and Cherepanov, P. (2017) *Structural basis for spumavirus Gag tethering to chromatin*. Proc. Natl. Acad. Sci. U.S.A. 114, 5509-5514. DOI: 10.1073/pnas.1621159114

Spumaviruses are being developed as vectors for gene therapy applications, but how these retroviruses select genomic locations for integration remains unknown. Here we used X-ray crystallography to visualise the interaction between the spumaviral Gag protein and a nucleosome. We showed that this interaction is essential for the observed distribution of spumavirus integration sites in various human cell types. Thus, despite stark differences in the mechanistic details of spumavirus and orthoretrovirus replication strategies, both retroviral subfamilies depend on their structural proteins to locate optimal integration sites.

Maskell, D.P., Renault, L., Serrao, E., Lesbats, P., Matadeen, R., Hare, S., Lindemann, D., Engelman, A.N., Costa, A. and Cherepanov, P. (2015). *Structural basis for retroviral integration into nucleosomes*. Nature 523, 366-369. DOI: 10.1038/nature14495

Prior to this work there was no structural information on how the retroviral integration machinery engages its natural target, the nucleosomal DNA. Moreover, our structure was the first to illustrate nucleosome flexibility facilitating a biological process, and therefore had important implications for the wider field of chromosome biology.