


Name	PETER B. ROSENTHAL	
Position	Senior Group Leader	
Year joined (Crick or founder institute)	2005	

Career History

1982 – 1986 Harvard College B.A. Physics cum laude
 1987 – 1996 Harvard University Ph.D. Biophysics
 1996 – 1997 Harvard University Postdoctoral fellow
 1997 – 1999 MRC Laboratory of Molecular biology Human Frontiers Long Term Fellow
 1999 – 2001 MRC Laboratory of Molecular biology Agouron Institute Fellow
 2001 – 2004 MRC Laboratory of Molecular biology Investigator Scientist

Major Awards, Honours and Prizes

Human Frontier Science Program Long-Term Fellowship

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

Chair, Advisory Committee, World Wide Protein Databank, 2019-
 Chair, Collaborative Computational Project for Electron Microscopy (CCP-EM), UK 2016-

Lab Name

Structural Biology of Cells and Viruses Laboratory

Research programme and achievements

Our research applies electron cryomicroscopy to study high-resolution biological structure from the molecular to the cellular scale. Our main focus is the structural study of lipid-enveloped viruses in order to understand key steps in virus infection. We study the structural organisation of influenza virus to understand how protein and membrane interactions drive virus assembly. Influenza virus enters cells by binding cell surface receptors and, following receptor-mediated endocytosis, fuses with the endosome membrane. We image dynamic structural changes in the hemagglutinin glycoprotein (HA) and ultrastructural changes in the virus as a whole to understand the mechanism of HA-mediated membrane fusion. We are also interested in related, integrated studies of retrovirus structure. We use electron cryotomography to image high-resolution cell architecture as well as structural information on protein complexes *in situ*. In this area, our main focus is understanding how von Willebrand factor, a glycoprotein with roles in haemostasis, inflammation, and thrombosis, is packaged in storage granules (Weibel-Palade bodies) for acute exocytic release following vascular injury. We also develop experimental and computational methods to improve structure determination by cryomicroscopy in order to extend the range of its application in biology. We lead a UK consortium to develop methods for cryo-EM structure validation.

The main achievements of the laboratory since 2015 are as follows:

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- Imaging the fusion of influenza virus with liposome targets at low pH by electron cryotomography revealing structural intermediates of HA and their interaction with membranes.
 - Single particle cryomicroscopy resolved changes of the influenza HA glycoprotein at the low pH of membrane fusion, identifying structural intermediates including a dilated arrangement of the membrane distal domains and a 150 Å long extended coiled-coil intermediate at high-resolution.
 - Structure of full-length HA solubilised in detergent by single particle cryomicroscopy revealing the structure of the transmembrane region which plays roles in assembly and membrane fusion.
 - First structure of a capsid assembly from an endogenous retrovirus (HML2), the first atomic resolution structure of any retroviral shell, showing principles by which a single capsid protein can form closed assemblies consisting of pentamers and hexamers.
 - Electron cryotomography of Weibel-Palade bodies, storage granules for von Willebrand factor, in intact endothelial cells identified novel CD63-containing intraluminal vesicles that are released as an exosome during Weibel-Plade body exocytosis.

In our future work, (1) we plan to extend our understanding of the mechanism of HA-mediated membrane fusion by higher resolution studies of influenza HA intermediates to understand their interaction with membranes and to directly image viral membrane fusion in cells (2) we will determine the integrated structure of foamy viruses, a subfamily of *Retroviridae*, which infect a wide range of mammalian hosts. We will perform cryotomography of prototype foamy virus and sub-tomogram averaging of the surface glycoprotein and capsid cores to high-resolution (3) we will extend structural studies of cellular architecture including mammalian filopodia and the structure of von Willebrand factor in Weibel-Palade bodies by cryotomography and sub-tomogram averaging and (4) we will develop new methods for validating cryo-EM maps obtained by single particle analysis and sub-tomogram averaging which are now urgently required following advances in cryomicroscopy.

Research outputs

Benton, DJ, Gamblin, SJ, Rosenthal, PB, and Skehel, JJ. (2020) *Structural transitions in influenza haemagglutinin at membrane fusion pH*. Nature, 583: 150-153. DOI: [10.1038/s41586-020-2333-6](https://doi.org/10.1038/s41586-020-2333-6)

The influenza HA is one of two glycoproteins on the surface of influenza virus and mediates receptor binding and membrane fusion during viral entry. Here, we directly image structural transformations in the HA at the pH of membrane fusion and solve the structure of three structural intermediates including a 150 Å-long triple-helical coiled coil of the HA2 transmembrane subunit. This was a long sought-after result but showed new, surprising concerted conformational rearrangements important to the membrane fusion mechanism. This extended to atomic resolution our application of cryo-EM to study the dynamic process of membrane fusion.

Acton, O, Grant T, Nicastro G, Ball NJ, Goldstone DC, Robertson LE, Sader K, Nans A, Ramos A, Stoye JP, Taylor IA and Rosenthal PB (2019). *Structural basis for Fullerene geometry in a human endogenous retrovirus capsid*. Nature Communications, 10(1). DOI: [10.1038/s41467-019-13786-y](https://doi.org/10.1038/s41467-019-13786-y)

Here we determined the structure by single particle cryo-EM of capsid assembly in an endogenous retrovirus. This is the first atomic resolution structure of a closed capsid shell, which in retroviruses packages and protects the genome. By studying 4 different types of symmetric assemblies, we discovered how the underlying Fullerene geometry is achieved by the CA protein forming both pentamers and hexamers and found structural rules by which invariant pentamers and structurally plastic hexamers associate to form the unique polyhedral structures.

Streetley, J, Fonseca, A-V, Turner, J, Kiskin, NI, Knipe, L, Rosenthal, PB and Carter, T. (2019) *Stimulated release of intraluminal vesicles from Weibel-Palade bodies*. *Blood*, 133(25), 2707-2717. DOI: [10.1182/blood-2018-09-874552](https://doi.org/10.1182/blood-2018-09-874552)

Weibel-Palade bodies (WPBs) are secretory granules that contain von Willebrand factor and P-selectin, molecules that regulate haemostasis and inflammation. We used electron cryo-tomography of frozen-hydrated endothelial cells to image the structure of WPBs and VWF in the context of well-preserved architecture and identified internal vesicles as novel structural features of the WPB lumen. By live-cell fluorescence microscopy, we directly observe the exocytotic release of EGFP-CD63 intraluminal vesicles (ILVs) during WPB exocytosis, describing a novel route for release of ILVs during endothelial cell stimulation. Thematically, this reflects our interest in linking molecular and cellular pictures of cell structure and function.

Benton, DJ, Nans A, Calder LJ, Turner J, Neu U, Lin YP, Ketelaars E, Kallewaard NL, Corti D, Lanzavecchia A, Gamblin SJ, Rosenthal PB and Skehel JJ (2018). *Influenza hemagglutinin membrane anchor*. *Proceedings of the National Academy of Sciences of the United States of America*, 115(40), 10112-10117. DOI: [10.1073/pnas.1810927115](https://doi.org/10.1073/pnas.1810927115)

Here we used single particle cryo-EM to solve the structure of the full-length influenza hemagglutinin (HA) in a detergent micelle showing the central triple-helical structure in the membrane as well as flexible linkers between the ectodomain and the transmembrane domain. We also study the HA in complex with a broadly neutralising monoclonal Fab that binds near the ectodomomain membrane anchor junction and restricts flexibility of the TM region. Flexibility is likely important for the structural re-arrangements that mediate membrane fusion and the Fab may neutralize in part by restricting movement of the glycoprotein.

Calder, LJ and Rosenthal, PB (2016). *Cryomicroscopy provides structural snapshots of influenza virus membrane fusion*. *Nature Structural & Molecular Biology*, 23(9), 853-858. [10.1038/nsmb.3271](https://doi.org/10.1038/nsmb.3271)

Influenza membrane fusion mediated by the hemagglutinin (HA) glycoprotein has been a paradigm for membrane fusion by enveloped viruses and also by vesicles in intracellular and neuronal contexts. This study advances our understanding of this process by imaging structural re-arrangements of the HA in the context of membrane transformations by electron cryotomography.
