SARS-CoV-2: Uncovering the evolutionary secrets of its spike

CoSeC
Computational Science Centre for Research Communities

Dr. Antoni Wrobel, a postdoctoral Research Fellow in Steve Gamblin's lab at The Francis Crick Institute, London, won 2nd place in the 2021 CoSeC Impact Award for his work on SARS-CoV-2. Antoni and colleagues studied the structure and function of the spike protein of the coronavirus responsible for the COVID-19 pandemic. This work continues to increase an understanding of the origin of the pandemic and the importance of newly emerging variants, and their potential impact on the human population.

Background

To infect an individual cell a virus must attach itself to a specific site (a 'receptor') on the outer surface of a cell membrane, and fuse its own outer membrane with that of the bound cell leading to the inclusion of its genetic material into the cell.

In the case of the SARS-CoV-2, its surface is covered in spike proteins responsible for binding to a specific receptor on the host cell known as 'ACE2'.

Once bound, the virus needs to fuse with the membrane of the host cell. This leads to release of the viral genetic material into the cell and allows the virus to replicate within the cell.

.The field of structural biology focuses on understanding the structure/function relationships of biological materials such as proteins; for SARS-CoV-2 elucidating the structure of the spike protein alone, and when bound to the receptor provide a mechanistic insight into how the spike recognises the receptor site on the host's cell.

Ultimately, this can inform understanding of the origin of the pandemic and the importance of newly emerging variants, but first several challenges need to be overcome.

Challenges

The major challenge is understanding why SARS-CoV-2 was able to achieve a level of **transmissibility and infectivity** that resulted in a pandemic. What are the properties of this virus that facilitate the attachment, fusion and inclusion of genetic material in the host cell? Additional challenges lay in gaining a greater understanding of: **related animal viruses and** their receptor-binding properties; and how the virus benefits from **evolving new variants in the human population.**

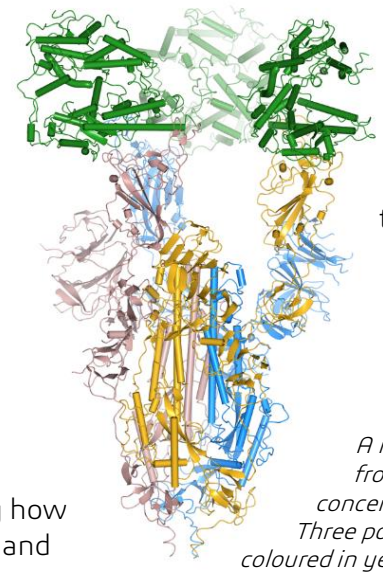
Finally, the important challenge of **communicating the science** of the pandemic-related research to a range of audiences at a level that is sufficiently informative to encourage people to understand science and therefore seriousness of the situation, without causing widespread panic and alarm.

Antoni's role in addressing the challenges

Dr. Wrobel together with Dr. Donald Benton in Steve Gamblin's lab and many other colleagues* and collaborators* within The Francis Crick Institute investigated the structure of the spike protein from SARS-CoV-2, its variants, and related viruses. Employing the software of the CCP-EM suite, they were among the first groups to produce an almost complete spike structure at high resolution. They then showed how the spike undergoes a series of conformational changes upon binding to its receptor ACE2, and suggested how this could prime it for subsequent fusion with the host cell.

Antoni and colleagues then explored the evolution of the SARS-CoV-2 spike comparing it to spikes of related coronaviruses isolated from bats and pangolins, and were the first to conclude that the Pangolin-CoV spike was much better in binding to the human receptor than the Bat-CoV most closely related to SARS-CoV-2, RaTG13. They also provided a structural explanation for the emergence of one of the first SARS-CoV-2 variants D614G, from which all the variants of concern such as alpha, beta, and delta subsequently evolved.

Their work continues in understanding how SARS-CoV-2 evolved to infect humans and how it currently evolves in the human population through newly emerging variants.



A molecular model of the trimeric spike from the SARS-CoV-2 alpha variant of concern in complex with its receptor ACE2. Three polypeptide chains of the spike are coloured in yellow, blue, and goldenrod and each of them engages one molecule of ACE2, each coloured in green. Image generated using CCP4MG Software.

Dr. Wrobel and colleagues communicated their findings to the benefit of the diverse community of researchers working on SARS-CoV-2 as well as influencing pandemic policy makers. In addition, they helped the general public to understand the role of basic science during the pandemic, and engaged school students to encourage career-interest in the biological sciences.

CoSeC's Impact

> My entire research revolves around solving protein structures and elucidating their functions, which is only possible thanks to the software tools built by the CCP4 and CCP-EM communities. By being a part of these communities, attending the meetings, and being exposed to the science discussed there, I was able to progress from my crystallographic background to using their software to determine the cryo-EM structures of the spike proteins we studied.
>
> Dr. Antoni Wrobel

CCP4 is the Collaborative Computational Project: Software for Macromolecular X-Ray Crystallography; and **CCP-EM**: Electron Cryo-Microscopy. Together they

- support and train users and developers of the CCP4 and CCP-EM software;
- hold workshops and courses for students, early career researchers, and project leaders;
- provide a national and international community hub

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