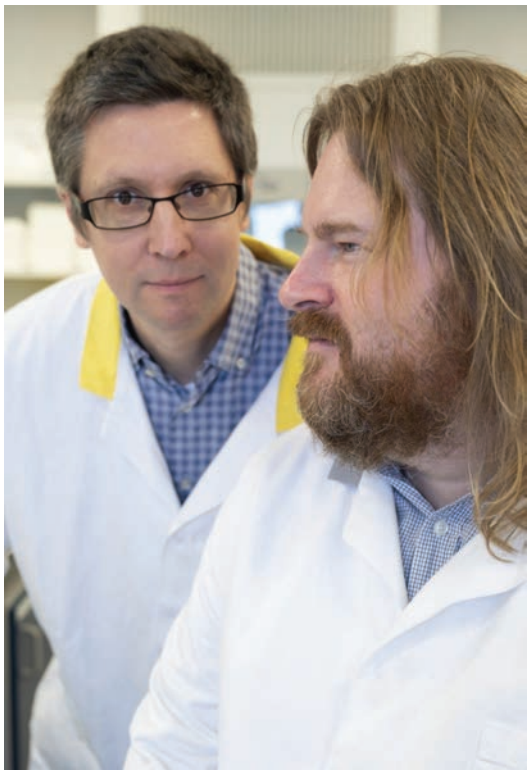
The E484K mutation - a 'backdoor' to undoing vaccine efforts

Professor Martin Michaelis and Dr Mark Wass

As we are seeing many novel Covid-19 variants around the world, Professor Martin Michaelis and Dr Mark Wass of University of Kent's School of Biosciences explain why this may be happening and what these new variants may mean:



Professor Martin Michaelis (left) and Dr Mark Wass School of Biosciences (Credit: University of Kent)

'After almost a year, in which SARS-CoV-2, the coronavirus that causes COVID-19, has not seemed to change its properties, troubling new variants of the virus seem to have only emerged in the last few weeks.

'Although viruses like SARS-CoV-2 have high mutation rates, they may not change their features until there is a substantial selection pressure that favours new variants. One such selection pressure is caused by an increasing level of immunity in a population. Hence, it is no surprise that novel variants are found in places with high levels of COVID-19 spread or COVID-19 vaccination programmes, such as the UK, Brazil and South Africa.

'Many of the new variants have mutations in the Spike (S) protein, the SARS-CoV-2 surface protein that mediates virus entry into host cells. The Spike protein is a main target of our defensive antibodies generated against infection. Current vaccines use different approaches to present the Spike protein to the immune system, so vaccine-mediated immunity is exclusively targeted towards the Spike protein, which is likely why we are now seeing these mutations.

'Thus, it is probable that the novel variants are due to the selection pressure associated with increased levels of immunity provided by previous COVID-19 infections and vaccines. Many of the new variants harbour E484K mutation in the Spike protein, a mutation that is anticipated to reduce the protection gained from vaccination or previous infections.

'The South African B.1.135 variant carries the E484K mutation, and the Novavax vaccine was much less effective in South Africa than in the UK. In Manaus in Brazil, there is a new surge in COVID-19 cases, although more than three quarters of the population have already been infected. P.1, a new variant also harbouring E484K, may be partly responsible.

'P.1 and P.2, another novel Brazilian E484K variant, have both been associated with re-infections of individuals who previously had COVID-19. Most recently, E484K mutations have also been found in Kent and other places in the UK. The emergence of such cases also in the UK raises concerns that the spread of E484K variants may reduce the protection provided by our current vaccine programmes.

'We can already see that increased immunity from vaccinations and previous infections causes a selection pressure resulting in new SARS-CoV-2 variants that can bypass this pre-existing protection. Our vaccination efforts will be substantially complicated by this.

'New variants carrying E484K mutations clearly confirm that vaccination campaigns alone will not solve all our COVID-19 problems and further measures will be required. Only the combination of low COVID-19 numbers and broad vaccination campaigns will enable disease control, as the risk of new variants drops with reduced virus spread and replication.'

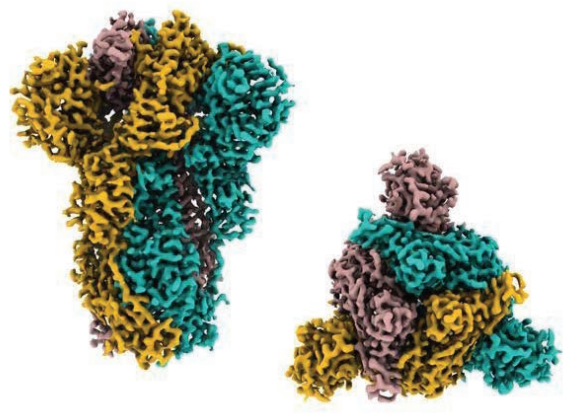
Professor Michaelis and Dr Wass run a joint computational/ wet laboratory. Dr Wass is a computational biologist with expertise in structural biology and big data analysis. Professor Michaelis' research is focused on the identification and investigation of drugs and their mechanisms of action, with a focus on cancer and viruses. With regard to viruses, Professor Michaelis and Dr Wass work on virus-host cell interactions and antiviral drug targets. In the cancer field, they investigate drug resistance in cancer. In collaboration with Professor Jindrich Cinatl (Goethe-University, Frankfurt am Main), they manage and develop the Resistant Cancer Cell Line (RCCL) Collection, a unique collection of 2,000 cancer cell lines with acquired resistance to anti-cancer drugs. They are also interested in meta-research that investigates research practices in the life sciences.

Could Pangolins cause Coronavirus Infections in Humans?

Structural similarities between SARS-CoV-2 and a pangolin coronavirus found by scientists at the Francis Crick Institute, suggest that a pangolin coronavirus could affect humans although it doesn't rule out that another species may be a carrier of a coronavirus that will jump to humans. While SARS-CoV-2 is thought to have evolved from a bat coronavirus, its exact evolutionary path is still unclear as there are likely many undiscovered bat coronaviruses. Also due to differences between bat coronaviruses and SARS-CoV-2, it is thought that the virus may have passed to humans via at least one other species.

In the study, the scientists compared the structures of the spike proteins found on SARS-CoV-2, the most similar currently identified bat coronavirus RaTG13 and a coronavirus isolated from Malayan pangolins, seized by authorities after being smuggled to China. The pangolin virus was found to be able to bind to receptors from both pangolins and humans, while the bat coronavirus, could not effectively bind with human or pangolin receptors.

Antoni Wrobel, co-lead author and postdoctoral training fellow in the Structural Biology of Disease Processes Laboratory at the Crick, said: "By testing if the spike protein of a given virus can bind with cell receptors from different species, we're able to see if, in theory, the virus could infect this species.



Cryo-EM images of the spike of Pangolin-Cov, showing two different angles (credit: Francis Crick Institute)

"Importantly here, we've shown two key things. Firstly, that this bat virus would unlikely be able to infect pangolins. And secondly that a pangolin virus could potentially infect humans."

The team used cryo-electron microscopy to uncover in minute detail the structure of the pangolin coronavirus' spike protein, which is responsible for binding to and infecting cells. While some parts of the pangolin virus' spike were found to be incredibly similar to SARS-CoV-2, other areas differed.

The work does not confirm whether or not this pangolin virus is definitely part of the chain of evolution for SARS-CoV-2, but does support various possible scenarios for how the coronavirus jumped from bats to humans. One potential route is that SARS-CoV-2 originated from a different, currently unknown bat coronavirus which could infect pangolins and from this species it then moved to humans. Alternatively, RaTG13 or a similar bat coronavirus might have merged with another coronavirus in a different intermediate species, other than a pangolin.

Donald Benton, co-lead author and postdoctoral training fellow in the Structural Biology of Disease Processes Laboratory at the Crick, added: "We have shown that a pangolin virus could potentially jump to humans, so we urge caution in any contact with this species and the end of illegal smuggling and trade in pangolins to protect against this risk."

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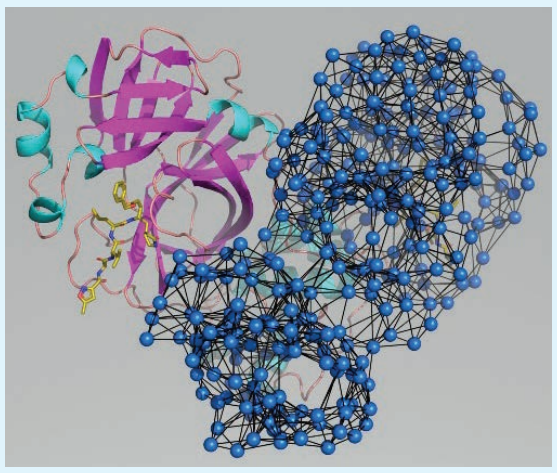
Modelling Highlights Vulnerable Sites on SARS-Cov-2 Protein



Picture credit: University of York

University of York scientists have been able to identify potentially vulnerable sites on a key protein found in coronavirus using computer modelling, paving the way for possible new drug treatments in the future.

The coronavirus responsible for the Covid-19 epidemic deploys dozens of viral biomolecules when it invades host cells with the disease. One of these is a compact protein, the main protease, whose function is critical to the virus. By analysing the structure of the protease using modelling techniques, the scientists have been able to simulate the protein's motions, suggesting sites that might be accessible to new drugs.

The study (1), by Tom McLeish, Professor of Natural Philosophy in the Department of Physics and Igors Dubanevics from the School of Natural Sciences, 'was not related to the current vaccines, which are based on the 'Spike' protein, but is a study of another key protein in the Covid process,' Prof McLeish said. He added: "It is more relevant to potential future drugs than to future vaccines, as the motions of the protein that it uncovers point to new 'sites' on the protein where binding small molecules might disrupt the protein function. The advantage of these sites, and our method in general, is that they are not the 'obvious' ones that compete with the normal binding of the protein, but other sites that can be accessed even when the usual binding sites are occupied."

Igors Dubanevics said: "We have identified promising druggable sites in the main protease via computer simulations and some of them have been supported by the newest studies by other groups. The next logical step would be to investigate the identified sites by conducting biological experiments in a lab.

(1) Published in the *Journal of the Royal Society Interface*.

More information online: ilmt.co/PL/Go30

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Consortium to provide Swifter Pandemic Predictions

UK Research and Innovation (UKRI) is providing funding of £3 million will bring together leading mathematical and statistical modellers from seven UK universities to produce rigorous predictions for the COVID-19 pandemic. The 'Joint UNIversities Pandemic and Epidemiological Research' (JUNIPER) consortium will develop and use bespoke models to provide predictions and estimates on key questions about the COVID-19 pandemic. These results feed regularly into SPI-M, the modelling group that provides evidence to the Scientific Advisory Group for Emergencies (SAGE) and the wider UK government.

The research groups include that of Professor Deirdre Hollingsworth of the Big Data Institute based on the Oxford University Campus. The other universities are the University of Cambridge University of Warwick, University of Exeter, University of Bristol, The University of Manchester and Lancaster University.

They will work closely with many other organisations and research teams active on COVID-19 research including the Alan Turing Institute, the Royal Statistical Society, Health Data Research UK, Public Health England, the Royal Society's 'RAMP' initiative and the Isaac Newton Institute for Mathematical Sciences.

More information online: ilmt.co/PL/lDlo

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Picture credit: Big Data Institute