Novel drug could treat long COVID and prevent re-infection

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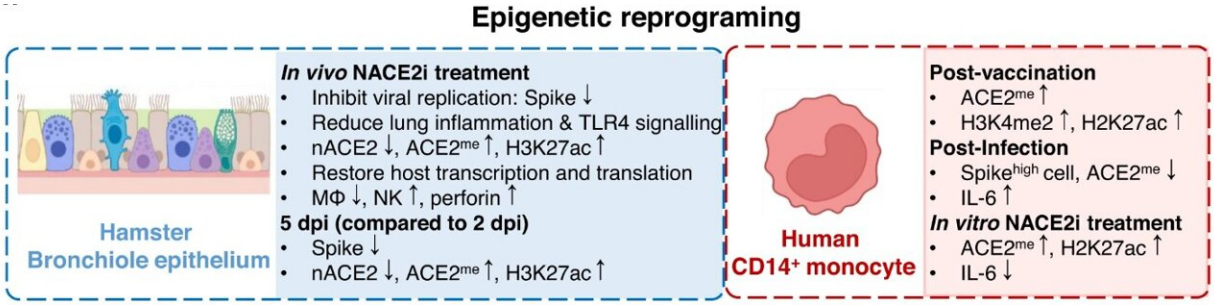

Graphical overview of epigenetic reprograming in hamster bronchiolar epithelium and human CD14$^+$ monocytes. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-39341-4

A new drug developed by QIMR Berghofer could transform the treatment of COVID-19 by potentially protecting against infection by any SARS-CoV-2 variant and reversing the persistent inflammation that is a major driver of debilitating long COVID.

The findings of the second major study demonstrating the pre-clinical effectiveness of the peptide-based drug, NACE2i, have been published in the journal *Nature Communications*.

Epigeneticist and co-lead author, Professor Sudha Rao who heads QIMR Berghofer's Gene Regulation & Translational Medicine Group, said the

drug was tested repeatedly by independent laboratories using a variety of pre-clinical models.

"The results of this second major study are really exciting. It shows our drug, NACE2i, stops the virus replicating and protects against re-infection," Professor Rao said. "We believe it could be a highly promising adjuvant to boost the effectiveness of existing vaccines providing long-lasting protection against any variant of the virus that tries to enter the cells.

"The other major discovery is that we uncovered the pathway that the virus uses to induce the persistent inflammation which causes organ damage found in long COVID. This study shows our drug prevents that inflammation and even repairs damaged lung tissue in pre-clinical models. It is both a prevention and a treatment."

Over the course of the pandemic, hundreds of millions of people have been infected with SARS-CoV-2 which has claimed many millions of lives. New variants continue to emerge contributing to ongoing waves of infection.

Long COVID is thought to affect between 10% and 20% of those infected with COVID-19. Debilitating long-term symptoms include fatigue, breathlessness and brain fog. It is a significant global health burden affecting everyday functioning, with many sufferers unable to work or carry out household tasks.

"We want to help patients. This is why we work in science. We are really proud of what we have achieved here. We are confident NACE2i is a potential treatment for long COVID that will relieve those debilitating symptoms and revive immune function," Professor Rao said.

The first major study by the QIMR Berghofer research team in 2021

showed the SARS-CoV-2 virus hijacks the ACE2 receptor on the cell's surface and draws it into the nucleus or control center of the cell, triggering a process that is essential for the virus to replicate.

NACE2i works by reprogramming the hijacked ACE2 receptor which disarms the virus and stops it replicating. The reprogrammed ACE2 receptor is returned to the cell surface where it acts as a lock that prevents the virus from entering the cell. This process also reverses the inflammation COVID-19 causes in the lungs.

First author and QIMR Berghofer Research Officer Dr. Wen Juan Tu said it was very exciting to see NACE2i repairing damaged lung tissue in pre-clinical models. "The images are really remarkable. In the damaged lung, you see it is missing the surface layer of the lung bronchiole area. After treatment with NACE2i, the lung is restored to normal function with a healthy surface layer," Dr. Tu said.

The QIMR Berghofer researchers have also developed a biomarker blood test to detect the presence of the protective ACE2 receptor layer around cells. They tested this in human blood samples and found it was lacking in patients who had repeated COVID-19 infections. The study found NACE2i restored this biomarker of protection.

Immunologist and co-lead author Professor Nabila Seddiki who is Research Director of Immunology & Infectious Diseases Commissariat à l'Energie Atomique (CEA), Paris-Saclay University and INSERM in France tested NACE2i in their pre-clinical COVID-19 models.

"When we looked at the results it was very clear the peptides were inhibiting inflammation in our SARS-CoV-2 models which was really great to see. We have been working together for a long time with each of us bringing our own expertise to the work and that's how we have achieved what we have," Professor Seddiki said.

The next step is to begin clinical trials of NACE2i.

More information: Wen Juan Tu et al, In vivo inhibition of nuclear ACE2 translocation protects against SARS-CoV-2 replication and lung damage through epigenetic imprinting, *Nature Communications* (2023). DOI: 10.1038/s41467-023-39341-4

Provided by QIMR Berghofer