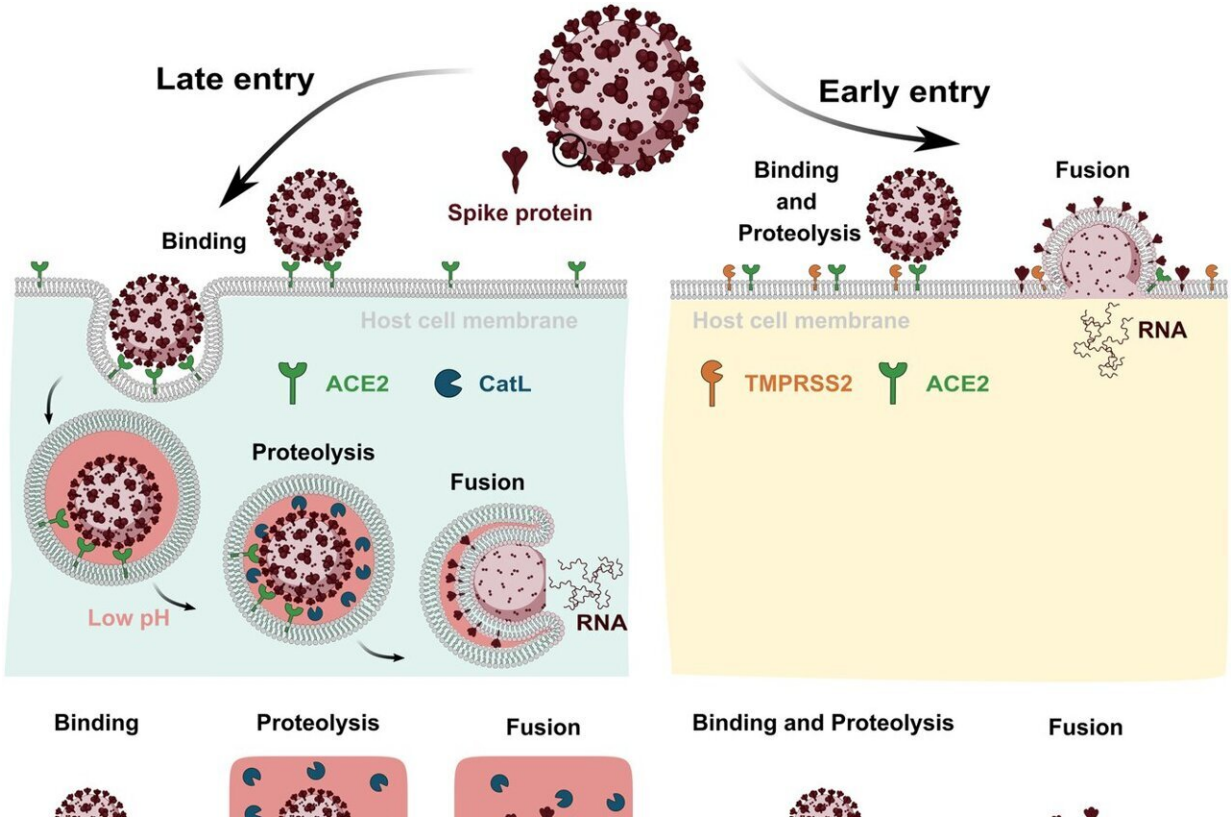
Bio-based tool quickly detects concerning coronavirus variants

July 8 2024, by David Nutt



SARS-CoV-2 entry pathways and the components needed to recapitulate these entry routes in an in vitro platform. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-49415-6

Cornell researchers have developed a bioelectric device that can detect and classify new variants of coronavirus, and potentially other viruses,

such as measles and influenza, to identify those that are most harmful.

The sensing tool uses a cell membrane, aka biomembrane, on a microchip that recreates the cellular environment for—and the biological steps of—infection. This enables researchers to quickly characterize variants of concern and parse the mechanics that drive the disease's spread, without getting bogged down by the complexity of living systems.

The team's paper, "Recreating the Biological Steps of Viral Infection on a Cell-free Bioelectronic Platform to Profile Viral Variants of Concern," was published July 3 in *Nature Communications*. The co-lead authors are postdoctoral researchers Zhongmou Chao and Ekaterina Selivanovitch.

"In the news, we see these variants of concern emerge periodically, like delta, omicron and so on, and it kind of freaks everyone out. The first thoughts are, 'Does my vaccine cover this new variant? How concerned should I be?'" said Susan Daniel, the Fred H. Rhodes Professor in the Robert Frederick Smith School of Chemical and Biomolecular Engineering in Cornell Engineering, and the paper's senior author. "It takes a little while to determine if a variant is a true cause for concern or if it will just fizzle out."

Daniel's group developed the platform with a team from the University of Cambridge led by professor Róisín Owens. Daniel and Owens first collaborated almost a decade ago on an effort to put biomembrane patches on electronic devices as a way to conduct toxicology measurements—a precursor to the new platform.

While plenty of biological elements have been put on microchips, from cells to organelles and organ-like structures, the new platform differs from those devices because it actually recapitulates the biological cues and processes that lead to the initiation of an infection at the cellular

membrane of a single cell. In effect, it fools a variant into behaving as if it is in an actual cellular system of its potential host.

Studying viruses in cellular systems is exponentially difficult. Not that designing the biomembrane platform was simple.

"In order to recreate the complex process of infection outside of a cell, you need to know what the essential biological elements and cues are," Daniel said. "You also have to know how to fabricate these microelectrodes and put these tiny membrane patches on them. It's quite tricky to get them to lay down onto that little microelectrode patch in just the right way. That may be perhaps the hardest part, honestly."

The researchers worked with the Cornell Nanoscale Facility to fabricate the microelectrode arrays, which resemble tiny gold-patterned spiders, and each electrode pad was coated with a cell membrane. A membrane sample from, say, a lung cell, is placed on the microelectrode and then the virus is added. If the virus detects the desired receptor on that patch, it will bind. The biosensor measures how the electrical resistance changes as the variant interacts with the membrane host layer and attempts to deliver its genome across the host cell membrane so it can release its instructions on the other side.

"There could potentially be a correlation between how well a variant can deliver its genome across the biomembrane layer and how concerning that variant can be in terms of its ability to infect humans," Daniel said.

"If it's able to release its genome very effectively, perhaps that's an indicator that a variant of concern should be something we should monitor closely or formulate a new vaccine that includes it. If it doesn't release it very well, then maybe that variant of concern is something less worrisome.

"The key point is we need to classify these variants quickly so we can make informed decisions, and we can do this really fast with our devices. These assays take minutes to run, and it's 'label-free,' meaning you don't actually have to tag the virus to monitor its progress."

Because the researchers are able to faithfully recreate the biological conditions and cues that activate a virus, they can also change those cues and see how the virus responds.

"In terms of understanding the basic science of how infection occurs and what cues can assist or hinder it, this is a unique tool," Daniel said. "Because you can decouple many aspects of the reaction sequence, and identify what factors promote or impede infection."

The platform can be tailored for other viruses, such as influenza and measles, so long as the researchers know what cell type has the propensity to be infected, as well as what biological idiosyncrasies allow a specific infection to flourish. For example, influenza requires a pH drop to trigger its hemagglutinin, and coronavirus has an enzyme that activates its spike protein.

"Every virus has its own way of doing things. And you need to know what they are to replicate that infection process on chip," Daniel said. "But once you know them, you can build the platform out to accommodate any of those specific conditions."

Co-authors include doctoral student Ambika Pachaury; and Konstantinos Kallitsis and Zixuan Lu of University of Cambridge.

More information: Zhongmou Chao et al, Recreating the biological steps of viral infection on a cell-free bioelectronic platform to profile viral variants of concern, *Nature Communications* (2024). DOI: 10.1038/s41467-024-49415-6

Provided by Cornell University