The next pandemic: Firebreaks and host-directed therapies

By Anette Breindl

Specific therapies against a new disease take time to develop. But there are methods that can speed up that development – and in the meantime, there are ways to make do with what's already in the cupboard.

In the case of SARS-CoV-2, research projects that got off the ground in response to SARS and MERS have enabled rapid trial entry of repurposed antivirals.

Screening efforts led to the identification of remdesivir (GS-5734, Gilead Sciences Inc.) and Aluvia (lopinavir/ritonavir, Abbvie Inc.) as repurposing candidates.

Though HIV drug Aluvia fell flat in its initial coronavirus clinical trial, it is one of the options being tested in the SOLIDARITY trial, a large WHO trial that is looking at several drugs that might have repurposing promise. SOLIDARITY is testing Aluvia, remdesivir, the malaria drug chloroquine/hydroxychloroquine, and interferon-beta.

Repurposing from one pandemic to the next can shorten the development timeline, but, ideally, such efforts could identify truly broad-spectrum candidates.

A January publication in *Science Translational Medicine* by scientists from the University of Leeds, for example, reported that in an animal study, a topical TLR7 agonist applied to the skin after an experimental version of a mosquito bite activated skin macrophages and blunted systemic infection with a range of arboviruses.

The arbovirus family comprises major public health threats, including dengue, Zika virus and chikungunya, also termed "break-bone fever."

Arboviruses are already responsible for millions of infections annually, and climate change has expanded the range of its mosquito hosts. According to the WHO, "in 2007 [chikungunya] transmission was reported for the first time in Europe, in a localized outbreak in northeastern Italy. There were 197 cases recorded during this outbreak and it confirmed that mosquito-borne outbreaks by [the mosquito *Aedes] Albopictus* are plausible in Europe." France, too, has reported locally acquired cases since.

Because arboviruses are genetically very diverse, broad-spectrum drugs or vaccines that target the virus are challenging to develop. "By defining and targeting a key aspect of the innate immune response to virus at the mosquito bite site, we have identified a putative new strategy for limiting disease after infection with a variety of genetically distinct arboviruses," the Leeds team wrote.

Identifying broad-spectrum drugs is a place where artificial intelligence (AI) approaches may shine. While screening for repurposing drugs via wet lab techniques is increasing in scale, AI has the potential to scan very large literature sets for indications that a drug might be effective against multiple viruses.

Firebreak for break-bone fever

A complementary approach is to use what are arguably the most specific weapons in the therapeutic arsenal, antibodies, but administer them in new ways.

In September 2019, Moderna Therapeutics Inc. reported positive results of a phase I trial testing the delivery of mRNA-1944 for the anti-chikungunya antibody CHKV-24 in 22 healthy volunteers.

The trial marked "the first systemic mRNA therapeutic to show production of a secreted protein in humans," the company wrote.

mRNA-1944 is being developed with grant funding from the Defense Advanced Research Projects Agency (DARPA). In a DARPA podcast, project manager Amy Jenkins explained that giving mRNA rather than the antibody itself is a faster route to deployment.

In the 2014 Ebola epidemic, successful antibody production in mammalian cells took between 10 and 24 months. "That was much too long for rapid response," she said.

By administering the mRNA rather than the antibody itself, "the person can become the bioreactor. So the thought is for this coronavirus outbreak, we may be able to actually manufacture antibodies in anywhere from four to eight months."

In a pandemic, she said, such antibodies could be preventively administered to individuals who are at high risk of exposure, such as health care workers, ideally providing protection for several months.

"In many cases we think of them as a firebreak," she said. "You give it to people so that they don't get sick."

Immunotherapies

In addition to interferon-beta in the SOLIDARITY trial, several immunotherapies are also being tested for their ability to prevent COVID-19 from progressing to its most severe form.

As with other pathogens, including SARS and the 1918/1919 pandemic flu, the damage done by the virus can be eclipsed by an inflammatory response that can lead to acute respiratory distress syndrome (ARDS), sepsis and organ failure.

In COVID-19 patients with hyperinflammation, multiple inflammatory cytokines are elevated, including IL-6.

Direct IL-6 inhibitors Actemra (tocilizumab, Roche Holding AG) and Kevzara (sarilumab, Sanofi SA) as well as indirect inhibitor Jakafi (ruxolitinib, Novartis AG) are all currently in clinical trials for their ability to stave off hyperinflammation.

A form of cytokine release syndrome is also a major toxicity of CAR T-cell therapy, though the two forms of cytokine storm have significant differences, Michael Gantier told *BioWorld*.

Cytokine release syndrome in CAR T-cell therapy is due to the T-cell activation, while in COVID-19 infection, the cytokine release is a consequence of organ damage due to hypoxia. "In this context it is unlikely that targeted inhibition of IL-6 alone will block the storm which is broadly emerging from the organ [damage]," Gantier said.

Gantier is a research group leader at the Hudson Institute of Medical Research's Centre for Innate Immunity and Infectious Diseases, and has conducted research suggesting that idronoxil, the active ingredient in Australian biopharma Noxopharm's experimental cancer drug Veyonda could inhibit the production of IL-6 "along with that of other key mediators of organ failure," potentially inhibiting the damaging immune response more broadly.

Such broad inhibition is also the goal of inhibiting GM-CSF, another innate immune signaling molecule. "GM-CSF is an initiator, while IL-6 is a prolonger; GM-CSF is earlier in the cytokine cascade and patients are showing it is overactivated," Someit Sidhu, co-founder and CEO of Izana Biosciences Ltd.

Izana, Kiniksa Pharmaceuticals Ltd, and Humanigen Inc. have all supplied anti-GM-CSF antibody drugs on a compassionate use basis and are now testing those antibodies in various trials as well.

Targeting the immune system is the most likely path to drugs that could be useful in future pandemics as well as the current one.

For example, cytokine storm was also a factor in making the 1918/1919 flu pandemic as deadly as it was – though Gantier noted that as with the cytokine storm that occurs as a result of CAR T-cell treatment, there were important differences as well.

"There are many roads to the cytokine storm," he said. "Although the cytokine storm is clearly likely to be important in COVID-19 morbidity, I think it is fair to say it is only part of the equation (and it was probably a more prevalent factor in the flu pandemic, for which the storm was more rapid and toxic in younger individuals who had a sharper response)."

Other approaches are focused on boosting the initial immune response to viral infections. Like cytokine targeting, such approaches may be useful against more than one virus.

Babes in the woods

Another possibility is to supplement, rather than boost, innate immune responses. That approach, too, is being pursued by IDRI, which is coordinating a study of Celularity Inc.'s natural killer (NK) cell-based cell therapy, CYNK-001, for severe cases of COVID-19.

Pluristem Therapeutics Inc., Athersys Inc., Celltex Therapeutics Corp. and Wuhan Hamilton Biotechnology Co. Ltd. are also working on cell therapy products to address respiratory issues.

CYNK-001 is an allogeneic, off-the-shelf NK cell therapy derived from placental hematopoietic stem cells. It is in phase II trials for multiple myeloma and acute myeloid leukemia, and Celularity plans to test it in solid tumors, including glioblastoma multiforme.

IDRI's Casper told *BioWorld* that the lack of pre-existing immunity that allows pandemic diseases to spread so easily has parallels to the situation of a newborn, who has no pre-existing immunity to any diseases yet.

While maternal antibodies are one part of the reason newborns do not universally succumb to the first virus that finds them after birth, innate immunity is another protective mechanism.

NK cells "will hone to the site of infection and kill the virus," Casper said. "The day you are born, they are one of the key defenses," implying they could be a tool for fighting emerging outbreaks with no population-based pre-existing immunity.

Given the enormous costs cell-based therapies such as CAR T cells, there are economic as well as clinical challenges for the scale of pandemic medicine.

But Casper, who has also been a practicing physician at times during his career, has practiced in both Uganda and the Fred Hutchinson Cancer Research Center, giving him experience with both ends of the medical wealth spectrum. And in his opinion, there is a place for cell-based therapies in the pandemic medicine ecosystem.

For one thing, NK cells, which are derived from placental cells, can be more easily acquired and stockpiled.

"Unlike things like CAR T cells, [NK cells] do not have to be donor-specific," he explained. "The thing that makes a lot of these cell therapies so costly is all of the manipulations that have to be done."

The cells, he said, are meant for patients who are hospitalized with moderate disease. And if they manage to forestall worsening of the disease, they will be cost-effective overall: "Where so many of our resources are going right now is to intensive care."

Editor's note: Pandemics come and go, but they keep coming. And so, even as the world grapples with COVID-19, researchers and public health officials are trying to apply its lessons to future outbreaks. Part 4 in tomorrow's issue will look at vaccines: Back to normal won't happen until there is a vaccine. Technology developments during COVID-19 could lead to more rapid deployment of vaccines in future pandemics. Read part 1 focusing on surveillance for the next pandemic and part 2 focusing on diagnostics. BioWorld also has been tracking drugs and vaccines in development for COVID-19.