# A dormant danger:

## New therapies target a ubiquitous pathogen known as cytomegalovirus

By Nala Rogers





The promise of organ and tissue transplantation has become more fully realized in the last two decades. Since 1990, the yearly number of organ transplants in the US has nearly doubled, according to the Virginia-based United Network for Organ Sharing. At the same time, preliminary data from the Center for Blood & Marrow Transplant Research, a collaboration between National Marrow Donor Program and the Medical College of Wisconsin with coordinating centers in Milwaukee and Minneapolis, suggests that stem cell transplants from donors have shot up more than fourfold over the same period. But as transplants increase, so too does the threat from a virus that lurks in the bodies of most people.

Cytomegalovirus, or CMV, usually lies dormant, kept in check by the immune system. But when the immune system is suppressed, as it is in transplant recipients who receive drugs with this effect, the virus can reactivate. Moreover, more types of patients are now receiving transplants, says Roy Chemaly, a virologist at the University of Texas MD Anderson Cancer Center in Houston. "We're becoming a little bit more aggressive in transplanting elderly people, or patients at high risk with relapse of their leukemia," Chemaly says. "They are more heavily immunosuppressed. That's why they get into more trouble with infection."

The problem therein is that the type of CMV that infects humans is hard to study and hard to treat. This version of the virus doesn't infect other species, so there are no good animal models. A few existing drugs can quell active infections because they can stop the replicating form of the virus. But the virus will go dormant and hide, making it seemingly impossible for drugs to expunge it from the body completely. Moreover, the drugs available to treat CMV have dangerous side effects, so doctors must balance the risk from the virus with the risk from the medications themselves.

Thankfully, a wealth of new treatments for CMV is on the horizon. At least three drugs against the virus are in late-stage clinical development, each with a promising safety profile, and many companies are working on vaccines. Safer treatments could let doctors treat patients sooner, before the virus can cause harm.

### A catching virus

CMV is ubiquitous. Between 0.2% and 2% of infants in the developed world are born with it, and about a quarter of infected newborns suffer damage such as hearing loss[1]. But those who escape early infection usually catch the virus later from bodily fluids such as urine or saliva, and then carry it for the rest of their lives. Fifty to 80% of people are infected in the US by the age of 40, according to the US Centers for Disease Control and Prevention (CDC), and they show no symptoms as long as their immune systems are strong.

"Most of us who are CMV positive have a fairly deep and robust repertoire of T cell responses that maintain the virus under wraps," says Cameron Douglas, a virologist at Kenilworth, New Jersey–based Merck who is working on a CMV drug candidate called letermovir. "But once you remove that control by making the patients immunosuppressed, that is a means by which the virus can escape its cage."

The risk for transplant patients depends on the type of transplant and on whether the patients and donors already have latent infections. Without antiviral drugs, more than half of those in high-risk groups—for example, CMV-seronegative patients receiving lung transplants from seropositive donors—will develop detectable levels of replicating CMV in their blood. CMV makes people more vulnerable to other infections, and it increases the risk of transplant rejection. If left unchecked, it destroys organs.

The infection is so common and so dangerous that doctors treat many solid organ transplant patients prophylactically, while the virus is still dormant. But the most widely-used drugs, ganciclovir and its oral prodrug form valganciclovir, are toxic to bone marrow. For hematopoietic stem cell transplant patients, this can be a disaster, potentially preventing the transplanted cells from producing new blood cells. The only other effective drug is highly toxic to kidneys. Because the treatments are so dangerous, doctors usually wait to treat hematopoietic stem cell transplant recipients until the virus can be detected in the blood. By then, the virus may have already made people vulnerable to other infections or transplant rejection.

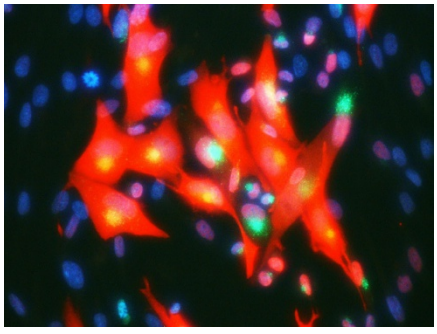
## A trio of treatments

Chimerix's CMV drug candidate, brincidofovir, is a DNA polymerase inhibitor that has shown activity against a wide range of DNA viruses, including CMV, adenovirus, and herpes simplex. This broad-spectrum action is important, says Chimerix spokesperson Joseph Schepers, because immunosuppressed patients often suffer from multiple infections at once. Chimerix has completed enrollment in two phase 3 brincidofovir trials, one to prevent CMV in stem cell transplant patients, and the other to treat adenovirus infections.

Another promising candidate, maribavir, was originally developed by Glaxo Wellcome (which later became GlaxoSmithKline) to combat CMV in individuals who had developed full-blown AIDS. But as HIV treatments advanced, symptomatic CMV infections related to AIDS virtually disappeared, prompting the company to stop work on maribavir in 2001. Exton, Pennsylvania-based ViroPharma licensed maribavir in 2003 for development in areas beyond HIV, but the drug failed to meet efficacy endpoints in phase 3 trials with liver and stem cell transplant patients[2,3]. Still, many researchers remain hopeful, believing that the trials used inappropriate endpoints or insufficient dosages[4,5]. Now, the pharmaceutical company Shire, which acquired ViroPharma in 2013, has completed two successful phase 2 trials in stem cell and solid organ transplant patients with active CMV infections. One of the trials focused on treatment-resistant CMV, and found that maribavir was effective even when other antivirals were not, according to Shire spokesperson Elizabeth Kalina. The company is considering launching a phase 3 trial in 2016.

A third drug candidate is letermovir, which Merck licensed from Wuppertal, Germany–based AiCuris after successful phase 2 trials[6,7]. CMV replicates by creating long stringst of DNA containing multiple complete genomes attached head to tail. If letermovir is approved, it would be the first in a new class of drugs that prevents CMV from chopping its long DNA strand into individual genome units, Douglas says. Merck is now testing the drug in a phase 3 trial with stem cell transplant patients.

So far in clinical trials, subjects have suffered few side effects from these three advancing CMV drug candidates. Brincidofovir caused some gastrointestinal upsets, but none of the compounds harmed bone marrow. "Because they don't affect the white blood cell count, they could all potentially be used to prevent CMV in the bone marrow transplant setting, where we have no options," says Deepali Kumar, a transplant infectious disease specialist at the University of Toronto in Canada.



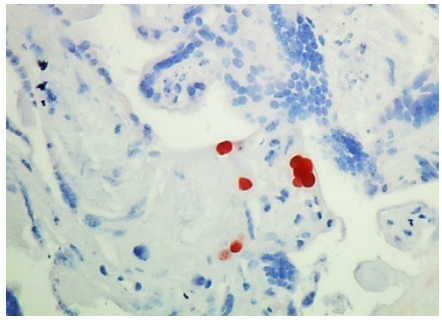
William Rawlinson and Stuart Hamilton

**Red alert:** Connective tissue cells infected with CMV (shown in red).

## Race for a vaccine

Despite the importance of antiviral drugs to treat CMV, the best long-term solution is likely to be a vaccine, says William Rawlinson, a virologist at Prince of Wales Hospital in Randwick, Australia. But vaccine development has proven challenging.

"CMV is a large virus," says Rawlinson. "It has a lot of space in the genome to make genes that are dedicated to getting away from the host immune system. That means it has a lot of mechanisms that you have to get around."



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**Transmission threat:** CMV-infected cells (shown in red) from the placenta of a stillborn infant.

The search has escalated since the US Institute of Medicine (now called the National Academy of Medicine) declared CMV vaccines a priority in 1999, says Stanley Plotkin, emeritus professor of pediatrics at the University of Pennsylvania in Philadelphia and a consultant on numerous CMV vaccine projects. At least nine companies and research groups have CMV vaccine programs, including GSK, Merck, Pfizer, and Sanofi. These groups have developed a wide range of candidates, most of which failed in early clinical trials[8]. Only TransVax, a vaccine composed of DNA plasmids that encode CMV antigens, has made it to the phase 3 trial stage, according to Lisa Damani, a spokesperson for Japan-based Astellas Pharma. Astellas and San Diego–based Vical are currently collaborating on two TransVax trials: a phase 2 trial in kidney transplant patients, and a phase 3 trial in stem cell transplant patients.

Ultimately, having a working vaccine or new antivirals against CMV could make a huge difference. The rise of transplant medicine has left more and more patients battling CMV with weakened immune systems, and clinicians eagerly await new ways to help. "We need vaccines; we need new drugs; we need new diagnostics," says Kumar. "The whole transplant community hopes they will come."

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