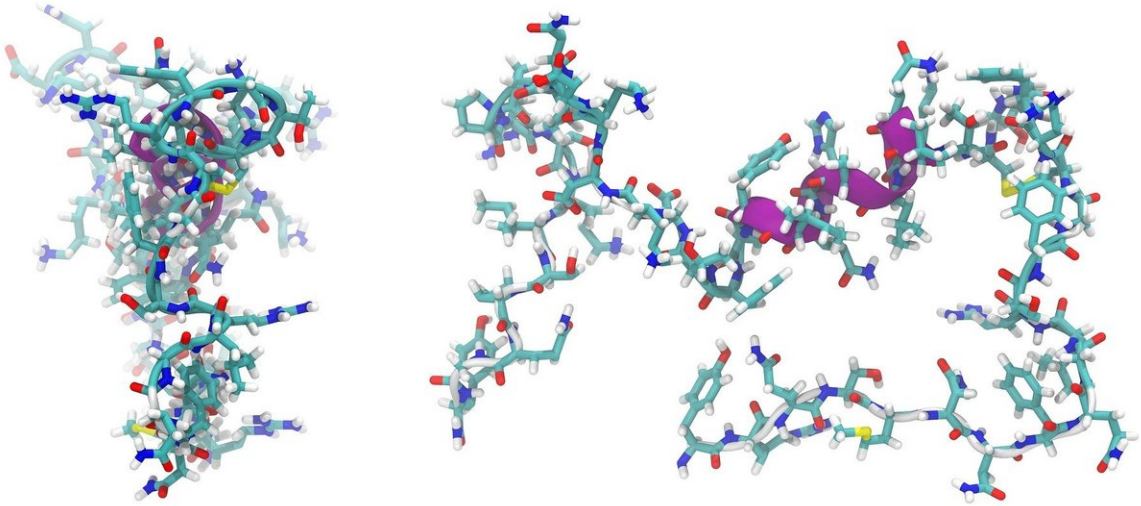
Bioengineer aims to turn nature's virus fighters into powerful drugs

May 24 2021, by Andrew Myers



Credit: CC0 Public Domain

Among the powerful biochemicals of the human immune system, peptides are one of the best.

Most commonly found in the places where microbes love to take root—mucous membranes of the eye, mouth, nose and lungs—they're known to kill all sorts of tiny invaders, such as viruses, bacteria and fungi.

Given their power, one might think peptides would represent promising drug treatments, perhaps even a cure, for many infectious diseases. But, alas, they are fundamentally flawed: They are vulnerable to a myriad of enzymes whose job is to rapidly break them down in a way that robs them of their therapeutic properties.

"Because of their vulnerability to enzymatic breakdown, peptides are not ideal drugs. They're expensive to produce, and yet they must be given in large doses because they disintegrate so quickly," said Annelise Barron, an associate professor of bioengineering at Stanford School of Engineering.

But, as Barron describes in the journal *Pharmaceuticals*, she and a team of collaborators have now created peptide-like molecules—which she calls 'peptoids'—that could circumvent peptides' shortcomings and turn these new molecules into the basis for an emerging category of antiviral drugs that could treat everything from herpes and COVID-19 to the common cold. Although Barron cautions that years of development and testing remain before these peptoid-based drugs will make it to market, results to date are extremely encouraging.

A better backbone

Peptoids are among a class of biochemicals known as 'biomimetics'—molecules that mimic the behavior of biological molecules, but with certain key advantages.

Their real-world counterparts, the peptides, are composed of series of bioactive amino acids, known as side chains, bonded in a specific sequence to a long-chain scaffold, known as the peptide backbone. The result is a little like a biomolecular charm bracelet. Unfortunately, the bonds that hold the all-important charms in place are too easily dissolved in the body by the enzymes known as proteases, which digest proteins.

When peptides dissolve, their powers vanish.

Peptoids, however, are engineered for durability. Their strength derives from their structure, which is like, and yet fundamentally different from, that of peptides. By altering the underlying backbone and strengthening the bonds that hold the charms in place, Barron's team has created a way for these antiviral agents to retain the powers that peptides lose when they are degraded by proteases.

"We are excited that our peptoids show great potential as novel antivirals," Barron said.

Upside potential

In their study, Barron and team chose to focus on the herpes virus, which is most notable for causing cold sores around the mouth, sexually transmitted infections and even certain forms of blindness. If contracted later in life, herpes can be particularly devastating to its host. Herpes virus brain infections also are associated with Alzheimer's disease, an active area of research.

The team reviewed a number of prospective peptoids, beginning with a library of 120 molecular structures—which were at that point just chemical symbols on a page. Based on preliminary experiments, they narrowed these to 10 promising candidates, which her team synthesized. Barron then worked with professor Gill Diamond (University of Louisville) to test her newly minted molecules not just for their effectiveness against the herpes virus, but also for their effect on healthy human cells from the exterior surface of the mouth—known as the oral epithelium.

As expected, some of the peptoids showed no effect against the virus. Others were active, but harmful to healthy host cells. But a precious

handful of five peptoids proved worthy of additional study. In the end, two hit the sweet spot—defanging the herpes virus while not harming epithelial cells. One of the candidates, in fact, showed "complete" effectiveness against the virus, and that has Barron excited about the possibilities for treating herpes and, perhaps, beyond.

Bursting the bubble

The peptoids work by disrupting the virus's encapsulating outer membrane. This protective bubble is key to any virus's ability to insinuate itself into healthy tissues and distribute its harmful DNA into human cells, leading to infection.

"Peptoids destroy the membranes, not just of herpes but other viruses as well. This should give them wide applicability, perhaps even against certain deadly viral infections that currently have no cure," Barron said.

Barron has since sent samples of peptoids to infectious disease labs around the world asking them to test these new structures against a host of virulent strains, most notably the SARS-CoV-2 virus that causes COVID-19, but also more familiar viruses like influenza and rhinovirus, the culprit behind the common cold.

"The early reports from my collaborators are very encouraging," Barron said. "Because our peptoids mimic a very specific human broad-spectrum antiviral peptide—cathelicidin LL-37—we weren't surprised that they work, but still absolutely delighted to see these results coming in from all around the world."

More information: Gill Diamond et al, Potent Antiviral Activity against HSV-1 and SARS-CoV-2 by Antimicrobial Peptoids, *Pharmaceuticals* (2021). DOI: 10.3390/ph14040304

Provided by Stanford University