

Better Living Through Viruses

Chicken Soup for the Cell

Drug-induced side effects are taking over. Pay attention to the prime-time commercials for even half an hour and you'll hear about more side effects than solutions. The problem is not necessarily the drug molecules, but the way they are introduced to the body—inoculation. Matt Francis, assistant professor of chemistry at Berkeley, has big plans about how to make inoculation go more smoothly and is applying this idea to powerful anti-cancer drugs.

Most drugs are either taken orally or injected. Either way, the drug molecules enter the bloodstream, flooding the patient's body and visiting every tissue. The drugs can potentially interact with every type of tissue, helping one portion of the body while hurting another. This lack of specificity (e.g. for cancer) is the origin of the depressed red blood cell count, irritability, nausea, and hair loss that chemotherapy patients endure.

If drugs could be concentrated in the sick portion of the body—in the tumor—these side effects would virtually disappear. Doses could decline because instead of throwing drugs at every organ in the body the treatment would be tactical, constrained to one area. This is the goal of the Francis lab, and they draw inspiration from an unlikely source: viruses.

The idea is to use viruses as a scaffold, attaching drugs and other molecules to their surfaces. There are three problems to overcome with this approach, explains graduate

student Ernest Kovacs. The first is actually attaching a drug or any other molecule to the virus. The second is that for the drug to be useful the virus particle has to find a tumor, and the third problem is that the virus has to survive the patient's immune response long enough to deliver its payload.

The Francis lab has been working to attach foreign molecules to the surface of a virus called bacteriophage MS2. Why this one in particular? "There are several reasons," says Kovacs. Among these, "its known crystal structure provides excellent guidance for our selective chemical modifications."

A virus is a combination of a capsid (a shell made mostly of protein) and a genome (DNA or RNA coiled inside). Capsids are typically made of hundreds of protein molecules, each of which is a combination of amino acids, like colored beads arranged on a string. Coil the amino acid strands to make a protein, stack the proteins to make a capsid. It would be difficult to get anywhere on a chemical problem like this without a crystal structure, a map of where the different amino acids lie.

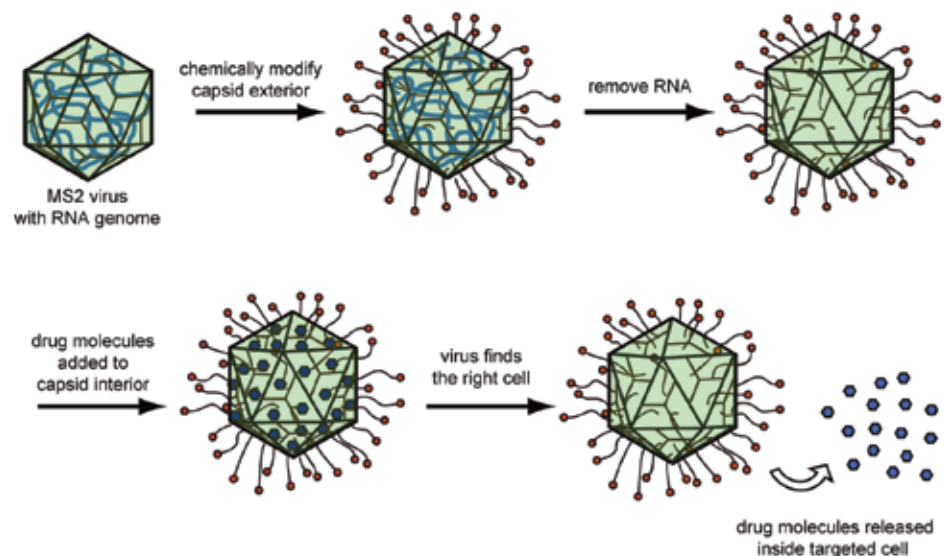
Each amino acid can react chemically, bonding to a foreign molecule. Francis, Kovacs, and their coworkers have been perfecting the

chemistry that enables them to remove the viral genome, then attach any molecule they desire to either the inner or outer surface of the capsid. This flexibility enables the placement of drugs on the inside, and camouflage against the immune system on the outside.

Kovacs is now teaching the viruses to target tumors. He points to a messy workbench enclosed under a glass safety hood. Today, he is working on synthesizing viruses that have folic acid bound to their exteriors because most types of cancer cells have a gigantic number of folic acid receptors on their surfaces—many more than healthy, normal cells. Bacteriophage MS2 has 180 proteins in its capsid ("180 times the chemistry," he grins), which should lead to a huge concentration of drug-carrying viruses in tumors.

Francis and his students can bind whatever drug they wish to a viral capsid, they understand how to make the virus target cancer cells, and they think they also have a way to get a patient's immune system to ignore the virus.

Even though bacteriophage MS2 is harmless to humans—it won't infect our cells—the immune system will destroy it. Poly-(ethylene glycol), PEG,



RIGHT: The process of turning MS2 into a lean, mean, drug-delivering machine

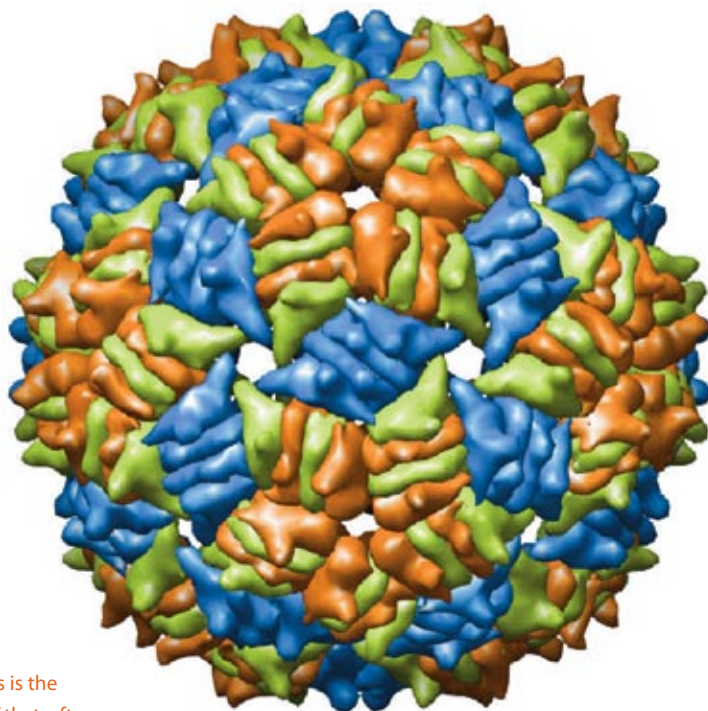
is a polymer that acts like camouflage. It dissolves in water, making it easily deliverable throughout the body and, most importantly, your immune system can't make antibodies for PEG. This means that, unlike the viruses that cause diseases, your body will never gain immunity to a PEG-coated virus.

So the game plan is: bind drugs, folic acid, and PEG to the outside of bacteriophage MS2, try it out on real tumors, and if all goes well, go to the FDA for approval. This scheme could save the lives of millions of cancer patients, and reduce the miserable side effects that come with chemotherapy.

MARK ABEL is a graduate student in chemistry.

Want to know more?

Check out the Francis lab on the web: www.cchem.berkeley.edu/francisgrp



This virus is the "syringe" that, after modification, will stealthily deliver drugs to targeted tissues.

MS2 CAPSID IMAGE COURTESY UCSF/ CREATED WITH THE UCSF CHIMERA VISUALIZATION PACKAGE FROM THE RESOURCE FOR BIOCOMPUTING, VISUALIZATION AND INFORMATICS AT THE UNIVERSITY



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