Arresting Cancer

Binding Key Proteins to Arrest Cancer

Most things in life could benefit from some extra engineering, from the cupholders in your car to the latest mission to Mars. Dr. Vern Schramm, Chair and Merns Professor of Biochemistry, brings that notion of precision engineering to the war on cancer.

Dr. Schramm’s targets are proteins called enzymes, which are churned out according to the genetic instructions in a cell. Each of these enzymes controls (or “catalyzes”) a specific chemical reaction, which in turn influences how cells grow, function and, in some cases, become cancerous. His approach is to develop drugs to strategically lock up key enzymes: he builds a better monkey wrench—to throw into the machinery.

Take the enzyme called PNP (for purine nucleoside phosphorylase). PNP is crucial for the survival of T cells, a category of white blood cells, that are an essential part of the human immune system. Some cancers, as well as many autoimmune diseases, are caused by excessive levels of T cells. In psoriasis, inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis, T cells misdirect their attacks. “T cells recognize foreign invaders and kill them,” says Dr. Schramm. “So if they start to react against your own tissues, whether in your joints or skin or your gut, you get a variety of these inflammatory symptoms.” Even worse, in T-cell leukemia and T-cell lymphoma, T cells multiply out of control. “You fill up with T cells and die,” he says.

Meanwhile, an exceptionally rare disease that is the polar opposite of these cancers may, paradoxically, point to an answer. Worldwide, about 50 babies have been born with what is known as a PNP deficiency. They lose their T cells at an early age, with devastating effect. “They’re born perfectly normal,” explains Schramm. “But at about one or two years old, their T cells disappear, which is a very bad thing. Most of these babies used to die from secondary infections, primarily viral infections.” Luckily, however, there now exists an effective treatment in which doctors replace the missing protein. But the babies’ predicament got researchers to thinking: perhaps the disease, with its paucity of T cells, could somehow serve as a model for the treatment of the cancers and other conditions in which T cells run amok. In other words, the deliberate inhibition of PNP, the enzyme that keeps T cells going, might be a therapy for T cell cancers.

PNP, however, is a difficult enzyme to inhibit chemically, because of its abundance and ubiquity in the body. “If you look in the patent literature,” says Dr. Schramm, “there are 33 patents by seven drug companies that have tried to do the same thing and weren’t able to do it.” That difficulty was an opportunity for Dr. Schramm and his colleagues to employ their “precision engineering.” They’ve now designed a molecule that inhibits PNP about 1000 times better than any of the previously patented compounds. Einstein has licensed the inhibitor, dubbed Immucilin, to a biotechnology company, which completed animal trials in the past year and is poised to start the first human trials. “This compound looks as though it really might work,” says Dr. Schramm.

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based on something called the "transition state" of the enzyme. To explain the concept, Dr. Schramm sounds like a verbally coherent Yogi Berra. "You can think of the enzyme as a catcher's mitt," Dr. Schramm says, "and the molecule it works on"—called the substrate—"as the baseball. In the first step, the ball goes into the mitt, and you know that if you don't clutch your fingers around it, the ball will pop right out again. It's the same way in an enzyme. Many times the substrate hits the pocket and flies right out again. Usually, though, the enzyme will close around the substrate in the same way as a catcher's fingers will close over a baseball. The transition state is analogous to when that ball is being held tightly."

The technology at Dr. Schramm's disposal allows him to determine what the substrate-enzyme system looks like when the substrate is bound tightly by the enzyme in the transition state. (No small feat, because that state lasts only about one-tenth of one-trillionth of a second.) He then designs a chemical, called an inhibitor, that is structurally similar to the bound substrate; a well-designed inhibitor will cause the enzyme to close tightly around it. And an enzyme closed tightly around an inhibitor molecule is an enzyme that cannot accept an actual substrate molecule: the enzyme is effectively blocked from acting. "The practical effect is to make inhibitors that are extremely powerful," says Dr. Schramm.

He and his colleagues are now applying this design principle to other inhibitors that could be important for cancer treatment. "Our general program," he notes, "is to pick an interesting enzyme target, solve the transition state of the enzyme, use that as a blueprint to make powerful inhibitors, and then test those inhibitors in biological systems."

One such interesting enzyme target is MTAP (with the daunting biochemical name 5'-deoxy-5'-methylthi-oladenosine phosphorylase). MTAP plays a role in the production of polyamines, chemicals that coat and protect DNA, the genetic component of a cell. Rapidly multiplying cancer cells require large amounts of polyamines to coat their ever-replicating DNA. Therefore, stemming the production of polyamines is known to prevent the progression of, for example, prostate cancer. But the existing inhibitors of polyamine production have nasty side effects. (For example, one that is used to treat head and neck tumors causes deafness.) The trick then is to target an enzyme that is part of the polyamine production line and that has absolutely no other function. MTAP is such an enzyme, and Dr. Schramm and his colleagues have an inhibitor for it.

Another project involves harnessing the lethal power of a toxin called ricin, extracted from castor beans. This approach has caught the attention of everyone from cancer researchers to KGB assassins (who actually used it). "It turns out that a milligram will kill a horse," says Dr. Schramm. "If you get one molecule of that toxin in a cancer cell, it will kill the cell. So the idea is to take that toxin, attach an antibody that will recognize cancer cells, and inject it in a patient. It'll bind to a cancer cell, be absorbed, and kill the cancer cell specifically."

Such guided-missile medications exist, and patients have been treated with them on an experimental basis. "There have been some remarkable remissions with this therapy," says Dr. Schramm. "However, the side effects are very bad." The problem, of course, is that not all of the deadly ricin is taken up only by cancer cells, leaving some ricin free to destroy healthy cells throughout the body.

Dr. Schramm is therefore working on a "rescue therapy" to be administered shortly after the ricin-based drug. In this strategy, a patient would receive a dose of ricin-modified antibodies that find and bind rapidly to cancer cells, which absorb the toxin. Then, before ricin did its damage to healthy cells, the remaining lethal molecules circulating in the body would be neutralized by the rescue therapy. Dr. Schramm's idea is to design a transition-state inhibitor of ricin to use as the antidote, in the hope that it would prove specific enough and strong enough to shut down the deadly toxin before it harms more than cancer cells. The first generation of these inhibitors has already been made in his laboratory.

The utility of Dr. Schramm's approach is endless. He foresees a future where researchers will intimately know all human enzymes—from their function and role in disease to the structure of their transition states—allowing scientists to engineer inhibitors for any of them. "The evolution of genomics into protein structure and into mechanism," Dr. Schramm says, "gives us tremendous power to develop new drugs and to intervene in cancer as well as other diseases."