Darrell Irvine is focusing his engineer’s mind to boost the body’s defenses against cancer. He’s also working on ways to deliver drugs directly—and only—to the cells that need them.

T-Cell Booster Kits

A bioengineer remolds cell surfaces to prod the immune system.
T cells from the immune system can be removed from a cancer patient, trained in a laboratory dish to recognize and attack tumor cells, and then returned to the patient ready for battle. In some clinical trials, up to 70 percent of patients with advanced melanoma have seen their tumors shrink with this experimental immunotherapy.

These tumor-hunting T cells don’t remain active for long, however, unless the patient receives sustained doses of stimulatory interleukins such as IL-2. These powerful immune stimulants can cause low blood pressure, flu-like symptoms, nausea, diarrhea, and dizziness. For some patients, this adjuvant drug treatment makes T-cell therapy too dangerous.

But what if the T cells could carry their own tiny supplies of interleukins, just enough for their own needs?

HHMI investigator Darrell Irvine has found a way. In his laboratory at the Massachusetts Institute of Technology, he and his colleagues make nanoparticles filled with interleukins and attach these immune “booster kits” to the surface of T cells. They’re so minuscule that 100 booster kits can fit on just 3 percent of the cell’s surface area, where they slowly release their contents to the cell.

By “getting the drug just to the cells that need it,” says Irvine, “we’re looking for the extra nudge that could take immune-cell therapy from working [only] in a subset of people to working in nearly all patients.”

Irvine and postdoctoral research associate Matthias Stephan mounted booster kits containing IL-15 and IL-22 onto T cells extracted from metastatic melanoma tumors implanted under the skin of mice. The T cells were “educated” in laboratory dishes to recognize and destroy the melanoma cells. When infused back into the rodents, the enhanced T cells rapidly proliferated and accurately zeroed in on the metastatic tumors, according to the researchers’ report in the September 2010 Nature Medicine. Importantly, the enhanced cells remained viable longer than untreated T cells and increased the survival rates for the cancer-ridden mice receiving them.

Remodeling the surface of cells with synthetic materials for therapeutic ends reflects Irvine’s merger of materials science and immunology. He studied engineering in college and materials science in graduate school. “I became attracted to life science and problems in medicine, and how someone with an engineering background could have a role in those fields,” he says. In particular, he became fascinated with the immune system and its complex regulatory actions that control the body’s defenses.

Improving Cell Therapy

Irvine found success when he turned a standard approach on its head. For several decades, researchers have explored the possibilities of using cells directly as therapy (stem cell transplants, for example) or as transporters. One research group was developing T cells as vehicles to infect tumors with cancer-killing viruses. “Instead of using the T cell as a ferry for a virus,” Irvine says, “we started thinking about putting synthetic drug particles onto T cells to make them function better.”

First Irvine’s group had to overcome a difficult challenge: because components of the T-cell surface are recycled over periods of hours to days, particles placed on the plasma membrane would rapidly be swept into the cell’s recycling bins and inactivated. After some trial and error, Irvine found he could shackle the booster kits to small reactive sulfur groups, called thiols, which remain stable on the cell surface, allowing the nanoparticles to survive for at least a week. “I think this linkage is somehow stabilizing the material on the surface,” Irvine says.

The bioengineer envisions an array of additional applications. In a related experiment described in the Nature Medicine paper, Irvine attached drug-filled nanoparticles to blood stem cells. When transplanted into mice lacking blood-forming cells, the enhanced stem cells restored the bone marrow more quickly than stem cells without the drug boost. He’d also like to try transporting small molecule drugs such as vaccines or contrast agents into patients. Another possibility is using T cells to carry antiretroviral drugs into the deepest recesses of HIV/AIDS patients’ immune systems.

Transferring cells in and out of the body along with the necessary lab work makes T-cell therapy costly and time-consuming. Ever the engineer, Irvine is brainstorming possible shortcuts, aiming for “strategies where you could deliver drug agents, like interleukins, directly to specific cells within the patient,” he says.

Meanwhile, his group continues to develop the booster kit method, filling the particles with IL-2 and testing them in more clinically relevant melanoma mouse models. The researchers look forward to a day when patients undergoing T-cell therapy may be spared any toxic side effects. • Richard Saltus