

AUGUST 15, 2010

A New Lifeline Boosts Therapeutic Cells

Therapeutic cells, such as those implanted in the body to battle cancer or replenish devastated populations of stem cells, may someday be able to carry their own life-support packets.

New research, led by Howard Hughes Medical Institute (HHMI) investigator Darrell J. Irvine, shows how transplanted cells can be loaded with minuscule particles, or nanoparticles, which contain substances that help the therapeutic cells survive and flourish. These tiny packets of drugs may provide more effective support for the therapeutic cells, and cause less harm overall, because doctors might be able to achieve therapeutic effects with smaller doses of medicine.

Details of the research were published online on August 15, 2010, in the journal *Nature Medicine*.

“My laboratory is devoted to figuring out how to deliver drugs and vaccines that better target the immune system,” says Irvine. “We’re trying to learn how to make the immune system mount more effective attacks against cancer and HIV.”

"We're trying to learn how to make the immune system mount more effective attacks against cancer and HIV."

- Darrell J. Irvine

His goal is to create materials that, once in the body, can attract and be taken up by immune cells, and then spur those cells to seek out pathogens or tumor cells. That means fine-tuning the materials themselves, but it also requires a deep understanding of the immune processes that Irvine and his colleagues hope to stimulate.

In one set of experiments reported in *Nature Medicine*, Irvine's group at the Massachusetts Institute of Technology chemically attached the

immune-stimulating molecules, interleukin-15 (IL-15) and interleukin-21 (IL-21), to disease-killing immune cells called T cells. IL-15 and IL-21, which are both in clinical development and not yet approved by the Food and Drug Administration, promote the production and survival of T cells. The scientists packed the interleukins into nanoparticles in a manner very similar to so-called liposomal chemotherapies currently on the market, such as Doxil, which is a drug loaded into a lipid, or fatty, shell. On the outside of their nanoparticle shells, the researchers attached chemical groups that would readily link the nanoparticles to the therapeutic cell.

Their experiments showed that after transfusion into mice with tumors, the nanoparticles helped boost the number of killer T cells available to do battle with cancer. Even without the nanoparticles, this type of treatment, called adoptive T cell therapy, has shown promise in fighting melanoma, and is also being studied in other cancers.

“The issues that still exist are that the T cells may either not survive very well when they’re transferred into the patient, or the tumor itself may be secreting factors that shut down the function of those cells,” Irvine says. IL-15 and IL-21 were selected for use in the nanoparticles because studies suggest the drugs can help T cells avoid such suppression.

But the side effects of interleukins can be severe, even limiting the pool of patients eligible to receive them. “If you can come up with a way that that drug is only getting to the cells that need it, that could make this therapy more effective in more patients,” Irvine says.

The MIT team also used nanoparticles to enhance stem cell survival with TWS119, a type of medicine called a GSK-3 inhibitor. Clinical testing has shown GSK-3 inhibitors promote faster reconstitution of stem cells in animals.

Stem cell transplants are commonly given to patients with blood cancers to repair immune system damage caused by very high doses of chemotherapy and sometimes radiation. Improving delivery of the GSK-3 inhibitor could allow patients’ immune system cells to be restored more quickly.

“It takes months for patients’ immune systems to come back, and during that window of time they’re at severe risk of infection or any other insult related to having a dysfunctional immune system,” says Irvine, an associate professor of materials science and engineering and biological engineering.

Meanwhile, in analyzing the T cells, the researchers found they could load about 100 nanoparticles on each T cell without interfering with the cells’ division, or with their ability to migrate through tissue, find targets in the bloodstream, and kill tumor cells. “If we were interfering with any of those, the whole idea wouldn’t work,” he says.

Both the T cells and stem cells could keep the nanoparticles sitting on their surface—with dividing cells actually splitting up the cargo—an intriguing finding because biologists expect cells to continually turn over their membrane, taking up bits of it and secreting new membrane, Irvine says.

The researchers also studied the activity of nanoparticle-laden T cells in mice that had transplanted melanoma metastases in their lungs and bone marrow. Using bioluminescent T cells, whose glow allows scientists to track their activity, the team could readily see that the interleukin nanopackets were helping the cells reproduce and thrive.

Much additional work will be needed to assess whether this strategy would be effective against human cancers. To start, the research team aims to test its technique in mice that have been engineered to develop tumors over long periods of time, more like cancer develops in humans. “Those tumors are different in many ways; they may be more immunosuppressive than transplanted tumors,” Irvine says.