Combating cancer with the body's own defenses

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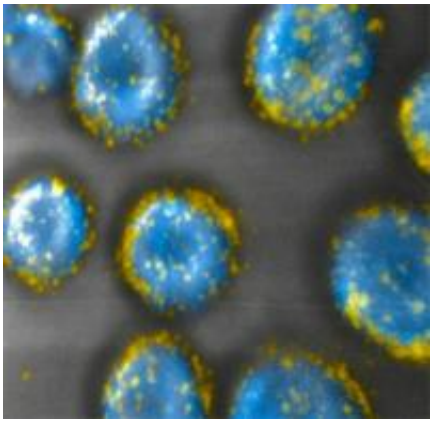

MIT engineers have developed a way to attach drug-carrying pouches (yellow) to the surfaces of cells. Image: Darrell Irvine and Matthias Stephan

In the past 40 years, scientists have learned a great deal about how cells become cancerous. Some of that knowledge has translated to new treatments, but most of the time doctors are forced to rely on standard chemotherapy and radiation, which can do nearly as much damage to the patients as they do the tumors. This series looks at targeted treatments that are on the horizon, and what needs to be done to make them a reality.

When a virus invades the human body, the immune system springs into action. Specialized cells called killer T cells roam the body, identifying and killing infected cells, with help from countless other cells and molecules.

Cancer biologists have long been intrigued by the prospect of harnessing those T cells to attack tumors, either to supplement or replace traditional chemotherapy. Using T cells to wipe out tumor cells could avoid the side effects often seen with chemotherapy.

“It has great potential,” says Jianzhu Chen, an MIT biology professor working on T-cell therapies for cancer. However, success has been limited, he says, because the exquisite coordination needed to launch a T-cell attack has proven difficult to replicate.
MIT engineers have developed a way to attach drug-carrying pouches (yellow) to the surfaces of cells.Image: Darrell Irvine and Matthias Stephan

Scientists at the National Cancer Institute have had some striking successes treating melanoma with T-cell therapy, but so far it has been much less effective against other cancers. According to Chen and other researchers investigating T-cell therapy, several challenges remain: getting viable T cells from the patient, engineering them to target tumors, and making sure the T cells stay alive once re-injected into the patient.

Billions of T cells flow through the average person’s bloodstream at any given time, each specialized to recognize different molecules. When a T cell encounters a cell that has a foreign molecule on its surface — indicating it has been infected — it kills the cell and starts multiplying rapidly, creating an army of T cell clones all specialized to hunt down and destroy infected cells.

Like infected cells, tumor cells have surface proteins that are not found on healthy cells, but those proteins do not seem to provoke T cells to attack. To generate T cells suitable for cancer therapy, researchers need to remove T cells from the patient and program them to attack a specific tumor molecule.

T-cell generation

Those T cells can be obtained either from the patient's blood or from the tumor itself. To have any effect, vast numbers of tumor-specific T cells are needed — up to a trillion. After removing T cells from the body, researchers treat them with growth factors called cytokines, which stimulate the cells to multiply.

Generating enough T cells this way can take weeks, and T cells from cancer patients with suppressed immune systems don't proliferate very well, making it impossible to generate enough cells.

Those T cells also have to be engineered to target specific molecules, such as HER2, a protein found on breast cancer cells. However, just recognizing those proteins is not enough to stimulate T cells. The proteins must be displayed with cell-surface molecules known as MHC. Tumors have very low levels of MHC, making it easier for them to evade T-cell attack.

To get around that problem, some researchers have engineered T cells that express antibodies; these antibodies recognize foreign molecules and are normally found on a different type of immune cell called B cells. Antibodies do not require MHC stimulation, so T cells expressing them can become activated more easily. Several clinical trials using this approach are now underway.

Staying alive

Another obstacle is keeping the T cells alive once they are returned to the patient. Most T cells have a short lifespan, so after weeks of manipulation in the lab, they may die soon after they enter the patient. Furthermore, the tumor itself creates an environment very hostile to T

cells. This is why most clinical trials for T cell therapy have “failed miserably,” says Chen. “After the T cells are transferred back, most of them simply die.”

His lab is now trying to figure out how tumor cells suppress T-cell function, in hopes of finding ways to reactivate the T cells.

Researchers at the National Cancer Institute, who have had some success treating melanoma with T cells, “primed” their patients by destroying most of their existing T cells with chemotherapy, making way for the new cells to proliferate. Giving patients large doses of growth factors called cytokines also helps, but those can have severe side effects, including heart and lung failure, when given in large doses.

Darrell Irvine, MIT associate professor of biological engineering, and postdoctoral fellow Matthias Stephan recently developed a new approach that could avoid those side effects. They engineered T cells with tiny pouches that can carry cytokines, which are gradually released from the pouches, enhancing the longevity of the T cells that carry them.

In a study published in the journal *Nature Medicine* in August, Irvine and Stephan used their modified T cells to treat mice with lung and bone marrow tumors. Within 16 days, all of the tumors in the mice treated with T cells carrying the drugs disappeared. Those mice survived until the end of the 100-day experiment, while mice that received no treatment died within 25 days, and mice that received either T cells alone or T cells with injections of cytokines died within 75 days.

They are now working on ways to more easily synthesize the pouches at a large scale, so they can be tested in humans, using materials that would be more likely to get FDA approval.

A time-consuming process

Despite the obstacles remaining, many cancer researchers still believe T-cell therapy is a promising approach. “The major advantage of T cells is that unlike chemotherapy and radiation, there’s very little toxicity associated with them,” says Cliona Rooney, a professor in the Center for Cell and Gene Therapy at Baylor College of Medicine.

Rooney and colleagues have developed T cells to treat lymphoma associated with Epstein-Barr virus, including Hodgkin’s and non-Hodgkin’s lymphoma. These studies have demonstrated that even small numbers of T cells can be effective if they proliferate inside the patient’s body, and as few as 20 million cells have produced complete regression of relapsed lymphomas in around 60 percent of patients.

One potential drawback to widespread use of T-cell therapy is that while engineering the cells has become easier, it’s still a time-consuming process, says Rooney. “It’s not off-the-shelf,” she says. “We have to make T cells for every patient. It’s not so much a drug as a procedure, which must be personalized for every patient.”

Though that could be expensive, she expects it will be comparable to traditional cancer treatment options, because hospitalization and side effects will be reduced.

In some cases, T-cell therapy might be most beneficial when used in combination with other treatments. Stephan believes T-cell therapy could produce better results if patients received it right after having surgery to remove the bulk of the tumor, to clear out any residual cancer cells. "Ongoing T cell therapy clinical trials enroll primarily late-stage cancer patients with well-established relapsing tumors as a final experimental treatment option,” he says. “T cell therapy could reveal its full potential when combined with surgery in newly diagnosed patients.”