The New York Times

11 THINGS WE'D REALLY LIKE TO KNOW

How Can We Unleash the Immune System?

Although immunotherapy can work wonders for cancer, it does not help everyone, side effects can be fierce, and costs are high. But the field is young.

By Denise Grady

Nov. 19, 2018

Cancer has an insidious talent for evading the natural defenses that should destroy it. What if we could find ways to help the immune system fight back?

It has begun to happen. The growing field of immunotherapy is profoundly changing cancer treatment and has rescued many people with advanced malignancies that not long ago would have been a death sentence.

"Patients with advanced cancer are increasingly living for years not months," a recent editorial in the journal JAMA said. It added that longer survival means that health workers in just about every specialty — not just oncologists — will be taking care of people who are living with cancer or recovered from it.

Immunotherapy accounts for much of the progress. Still, it does not help everyone, side effects can be ferocious, and so can the expense.

Overall, immunotherapy works in fewer than half of patients — but it can bring remissions that last years.

Is this as good as it gets? Probably not. The field is still young, hundreds of clinical trials are underway and basic researchers are trying to find ways to fine-tune the treatments they have already developed, as well as find new ones.

So far, the two main forms of immunotherapy approved by the Food and Drug Administration for cancer are drugs called checkpoint inhibitors and CAR-T cells. Both involve a workhorse of the immune system — T-cells, a type of white blood cell whose job is to kill cells that have turned malignant or become infected with viruses.

But scientists are also trying to open a whole new avenue of immunotherapy, one that focuses not on T-cells, but on another part of the immune system, a white blood cell called a macrophage.

Macrophages gobble up and destroy microbes and other foreign substances, but cancer cells can evade capture by flipping an "off" switch on the macrophage. The malignant cells carry a protein that researchers call a "don't eat me" signal, which shuts down the macrophages.

In an early phase study, published this month in The New England Journal of Medicine, researchers tested 22 patients with lymphoma that had resisted other treatments. They gave the patients a standard drug combined with an experimental one that blocked the "don't eat me signal." (Forty Seven, the maker of the experimental drug, helped pay for the study.)

The cancer shrank in 11 patients, and disappeared completely in eight. Side effects were minor, especially compared to those from other forms of immunotherapy, the study authors said.

They caution that the research is early and needs to be validated. But other researchers are exploring the same approach in different cancers, including multiple myeloma.

"The concept, if it holds true, is really quite profound," said Dr. Alexander M. Lesokhin, an oncologist at Memorial Sloan Kettering Cancer Center in New York who is doing similar research but was not involved in the recent study. "It could be pretty extraordinary."

For one of the patients in the study, the results were pretty extraordinary. Michael Stornetta, 71, has had a disease called follicular lymphoma for about five years, and several different treatments had failed to control it. He entered the study about a year ago at Stanford University, one of 10 centers involved.

“The lab rats, I consider myself one,” he said. “It’s very gratifying to know I’m able to do this and hopefully this drug becomes very successful in treating other types of cancer, including the kind I have. I feel like I’m kind of giving something back to humanity.”

At the start of the trial, 10 to 15 spots lit up on his PET scan, indicating cancer.

Now, he said: “When I look at the new scan, they’re gone, except for one tiny spot, and they don’t think it’s cancerous, maybe just a residue of dead cancer.”

He is still being treated, and will probably continue it for a total of two years.

“I don’t know that I’ll ever be able to say I’m 100 percent cancer free, but I know the results are certainly pointing in that direction. Whether it comes back or not, who knows? I’m gratified to know it’s where it is right now.”

The work on macrophages and T-cells is based on the same underlying idea: Cancer sometimes tricks these defenders, by flipping an “off” switch that the body normally uses to keep immune cells from attacking healthy tissue.

Checkpoint inhibitors block the “off” switch, freeing T-cells to go after cancer. The first such drug, ipilimumab (brand name Yervoy) was approved in 2011; the next, nivolumab (Opdivo) in 2014; and since then about a half-dozen more have come to market.

Two researchers who identified checkpoints on T-cells, and whose work led to the checkpoint inhibitors, shared this year’s Nobel Prize in Physiology or Medicine.

One of them, James Allison, from the M.D. Anderson Cancer Center in Houston, said the next steps are to discover ways to make immunotherapy work for more patients.

Medical teams are already chipping away at that goal, in part by combining checkpoint inhibitors with each other, or with standard chemotherapy. In recent months, medical journals have reported that these multiple treatments have considerably prolonged survival in patients with very aggressive cancers: melanoma that had spread to the brain and a hard-to-treat type of breast cancer called triple negative.

Similar studies are examining other diseases. At M.D. Anderson, one is even testing two checkpoint inhibitors plus chemotherapy in people with acute myeloid leukemia.

CAR-T cells involve a much more complex treatment, in which millions of a patient’s T-cells are extracted from blood, genetically reprogrammed to attack a particular target on cells, multiplied and then dripped back into the patient’s vein. This is the treatment that, while still experimental at Children’s Hospital of Philadelphia in 2012, saved a 6-year-old with advanced leukemia, Emily Whitehead. Now 13, in eighth grade, Emily is still in good health.

Sometimes called “living drugs,” two CAR-T treatments were approved in 2017 for certain types of leukemia and lymphoma. Both products have unpronounceable names: tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta). Kymriah is the commercial version of Emily’s treatment.

Researchers are testing the CAR-T treatments in other blood cancers and trying to expand their uses and their power by programming them to attack a broader range of targets on cells. So far, they have not worked against so-called solid tumors like breast or colon cancer, but scientists haven’t given up yet.

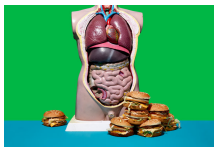
More things we’d really like to know

When Will We Solve Mental Illness? Nov. 19, 2018

How Long Can People Live? Nov. 19, 2018

Will We Ever Cure Alzheimer's? Nov. 19, 2018

Why Are We Still So Fat? Nov. 19, 2018



Why Don't We Have Vaccines Against Everything? Nov. 19, 2018

Denise Grady has been a science reporter for The Times since 1998. She wrote "Deadly Invaders," a book about emerging viruses. @nytDeniseGrady

A version of this article appears in print on Nov. 19, 2018, on Page D5 of the New York edition with the headline: 4. How Can We Unleash the Immune System?