Dankesrede

von

Prof. Dr. Carl H. June

anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter- Preises

2015

in der Paulskirche Frankfurt am Main

14. März 2015

Es gilt das gesprochene Wort

Ladies and gentlemen and esteemed members of the committee, I would like to thank Prof. zur Hausen as chairman of the scientific Council, and Prof. Birgitta Wolff, and members of the selection committee. I apologize in advance that I must give my remarks in English.

First of all I would like to say that it is a wonderful honor to receive the Paul Ehrlich prize. There is a pleasing symmetry with this that I would like to point out. Paul Ehrlich is known for many seminal advances from his research but perhaps best known is that he popularized the concept of a "magic bullet". Monoclonal antibodies are best known as the magic bullets of the immune system, and these were invented by Kohler and Milstein in the 1970s. The CAR T cells that my group has developed are also based on monoclonal antibody technology, so it can be said that there is a direct lineage from the work first conceptualized by Ehrlich to the CAR T cell therapies that my group are now using for patients with cancer.

The therapy that we have developed is called CAR T cells. CAR in this case stands for chimeric antigen receptors. T cells are white blood cells that are normally involved in the protection against viral infections. As such they have long lifespans compared to other cells found in the blood that live for only a few days to weeks. T cells can have lifespans for your entire life, providing an explanation for the longevity and durability of the effects of vaccines and cancer immunotherapy.

My particular training in cancer therapy began during a postdoctoral fellowship at the Fred Hutchinson cancer center in Seattle. There I saw the early bone marrow transplants that were done for leukemia. Until recently that was the only curative form of therapy for leukemia. In the case of a bone marrow transplant a patient receives new T cells from a donor, often a brother or sister, and it is those T cells from the donor that eradicate the last leukemia cells in patients and keep them in remission. Our goal with CAR T cells is to replace the need for bone marrow transplants, and to engineer the patient's own T cells so they can become cancer-killing CAR T cells.

Next I'll describe the process of CAR T cell therapy, a process that can be divided into five steps. First the patient donates blood which contains the patient's T cells. We then infect the T cells with a modified form of the HIV virus in order to genetically engineer the patient's T cells, so they will permanently express the CAR molecule. Then the cells are grown in the laboratory for about a week and frozen. At the end of the process, the CAR T cells are returned to the patient and infused as a simple blood transfusion that takes about five minutes. Once infused, the CAR T cells leave the blood after a few minutes and begin their role as "hunter cells", patrolling the body for tumor cells.

Next I would like to describe what a chimeric antigen receptor is. The CAR is a small protein that has two domains. On the outside of the cell is a recognition domain which is comprised of a monoclonal antibody fragment, that is, as I mentioned previously, a direct descendent of the "magic bullet" that Paul Ehrlich described more than 100 years ago. The second domain of the CAR is inside the T cell, and this domain controls decisions that the CAR T cell makes. When the monoclonal antibody domain of the CAR binds to a tumor cell it sends signals to the inside of the CAR T cell to tell the T cell to make two decisions. First it will tell the T cell to kill the leukemia cell, and secondly it will tell the CAR T cell to divide and make more CAR T cells. It is not uncommon to find in patients that 1 CAR T cell can generate more than 10,000 descendants. Thus CAR T cells are the first example of "living drugs"; they persist in patients for years and do not have to be given recursively as in the case with normal drugs. In addition, CAR T cells are the first example in medicine of the use of "synthetic biology". Synthetic biology is an emerging discipline in science with the objective to create non-natural

molecules that may have enhanced functional properties compared to those that evolved through natural or Darwinian selection. In this case the synthetic aspect of the CAR T cell is the chimeric antigen receptor, a molecule that does not exist in nature.

We began to work on CAR T cells back in the 1990s and the first patients treated with CAR cells had HIV infection. In those initial studies we found that it was safe to infuse the CAR T cells in patients with HIV infection and that the CAR T cells could persist for at least a decade in those patients.

Then about 15 years ago we began to develop CAR T cells for cancer therapy. We first made a CAR T cell that would bind to and kill leukemia cells, and tested those in mice with experimental leukemia. Our first cancer patients given these leukemia-specific CAR T cells had advanced chronic lymphocytic leukemia, a form of leukemia that is not curable without a bone marrow transplant. The first patients were treated in July 2010 and all three of the first three patients treated had remarkable responses, with between three and 7 pounds of tumor that was eradicated within weeks following infusion of the CAR T cells. Now, more than four years later the patients remain in remission with no evidence of leukemia.

In 2012 we began to treat patients with acute leukemia, a much more rapidly lethal form of leukemia. We wrote protocols for both adult and pediatric patients with acute leukemia. As it happened, the first patient that we treat was Emily Whitehead, a six-year-old with relapsed and very advanced leukemia that was refractory to all forms of chemotherapy. She had a remarkable response and was in complete remission within three weeks after infusion of the CAR T cells. Her story was featured on the front page of the New York Times and has been chronicled in several films, including a three-minute documentary entitled Fire with Fire. She is now nine years old, remains free of leukemia and has returned to a normal life.

We have since treated more than 50 children with acute lymphoblastic leukemia and have observed a 90% complete remission rate, a response rate that is unprecedented in previous clinical trials. In 2012, Novartis licensed the technology that was developed in my laboratory for CAR T cells and Novartis is now conducting multicenter trials across the United States in acute lymphoblastic leukemia. We have had patients travel from Germany in order to receive CAR therapy in Philadelphia. And Novartis has been in discussions with officials here at the Paul Ehrlich Institute in order to open the trial in Germany; this is expected to occur within the next year, so that CAR T cell therapy will become available in Europe as well as the United States. Novartis expects to submit for commercial approval to the US FDA in 2016 so that CAR therapy will become generally available for both adult and pediatric patients who have acute leukemia. Thus the first form of gene transfer therapy with engineered cells will likely be with CAR T cells.

To date there have been two forms of toxicity with the CAR T cell therapy. First the CAR T cells kill the normal B cells as well as the leukemia cells that exist in the patients. This is because the normal B cells have the same target as the leukemia cells. B cells are the type of immune cell that normally make antibodies for us. Fortunately, the B cell functions can be replaced by antibody infusions, given in the form periodic gamma globulin infusions; thus, this is not a serious toxicity. The other toxicity is called cytokine release syndrome, and this can be serious. This is manifest by the occurrence of fever and chills in patients, and can progress to life-threatening organ toxicity. The syndrome always occurs when the CAR T cells are proliferating and killing the cancer cells. In fact if the patient does not get a fever, this is regarded as a “bad sign” as those patients do not enter remission and do not benefit

from the therapy. The fever is due to the factors that the CAR T cells make when they are killing the cancer cells. Cytokine release syndrome only occurs in patients who have very large amounts of tumors, and therefore, if the therapy can be given earlier in the course of the cancer, cytokine release syndrome does not occur.

Finally I am often asked as to whether CAR therapy will work in other forms of cancer, beyond leukemia. In the laboratory our experimental models have shown that CAR T cells can kill nearly all forms of cancer cells, at least in petri dishes. Pilot trials are just beginning in patients with solid cancers. Our initial trials are in patients with brain cancer, pancreatic cancer, and ovarian cancer. Over the next several years investigators in the field will test CAR T cells in nearly every form of cancer. Indeed, it is likely that CAR T cells will be used in combination with the checkpoint therapies that Prof. Allison has described, as in our preclinical laboratory experiments, the two forms of therapy are synergistic when given together. In both cases, CAR therapy and checkpoint therapy, the treatments enhance the function of T cells.