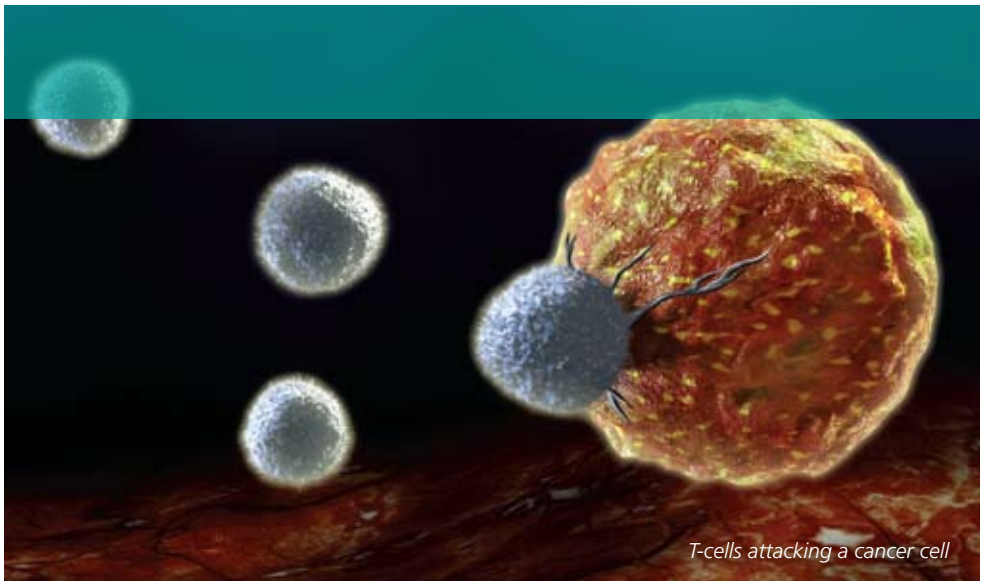
CAR research SPEEDS AHEAD



T-cells attacking a cancer cell

Automobiles are made in factories in Detroit and around the world to meet the demand of people who want to drive in style. So why are scientists in laboratories competing to invent new cars? The cars they are working on are chimeric antigen receptors (CARs). These CARs are genetically attached to the surface of T-cells, which are circulating immune cells that protect the body from infection. CARs are engineered to persuade the T-cells to seek out certain proteins. All cells have proteins specific to the cell type. B-cells, including CLL cells, express a number of proteins on their surface such as CD19, CD20 and CD23.

CLL is a type of B-cell malignancy. The first CARs being used to target B-cell malignancies have been programmed against the surface protein CD19. These CD19-specific CARs have been investigated extensively over the last few years. You likely have seen news coverage of positive results from the University of Pennsylvania study led by Drs. Carl June and Bruce Levine.

This CAR has proven successful with dramatic initial responses in three CLL patients. Both healthy and malignant B-cells express CD19, so the healthy cells are also targeted by this CD19-specific CAR. The depletion of healthy B-cells is being counteracted with IVIG therapy. Results from the UPenn study are still preliminary and more data is needed to determine duration of response. CLL Global has supported other research projects of Drs. June and Levine, but not the recently publicized research.

A number of other CLL Global investigators have also been developing the CAR concept, including collaborators at Baylor College of Medicine in Houston, Texas with Dr. Gianpietro Dotti being the principal investigator. CLL Global grant recipient Dr. Renier Brentjens at Memorial Sloan-Kettering is also currently evaluating a CAR against CD19. Dr. Laurence Cooper in collaboration with Drs. William Wierda, EJ Shpall, Chitra Hosing at MD Anderson Cancer Center, and Tom Kipps at University of California, San Diego (UCSD), are developing a CAR to recognize and respond to the ROR1 protein, which is relatively unique to CLL. There are also several other medical research centers around the country exploring variations of CARs.

A number of years ago, Drs. Kipps and Wierda discovered the ROR1 molecule on CLL cells while conducting gene therapy studies. ROR1 is a protein which is normally expressed on cells before birth but is switched off at approximately the time of birth. Because of its exclusive expression on the surface of CLL cells, ROR1 is a reasonably specific target for immune therapy. Subsequently, Drs. Kipps and Wierda have collaborated with Dr. Cooper and the other investigators at MD Anderson mentioned above to initiate a clinical trial to test the ROR1-specific CAR *(see interview with Dr. Cooper on page 3)*.

Current, effective therapies are not without risk. Therefore it would be a major advance if the immune system could be educated to be more proficient in killing CLL cells and prevent recurrence. Patients have been waiting for a specific therapy which does not damage the rest of the body for as long as cancer has been treated. CARs may or may not be the Holy Grail in eliminating CLL, but they most certainly will be part of the answer. : :

Driving CARs

TO THE FOREFRONT OF THERAPY

Dr. Laurence Cooper is Chief of Pediatric Cell Therapy at MD Anderson Cancer Center. In addition to caring for young patients undergoing hematopoietic stem-cell transplantation, he supervises a laboratory that develops and implements new immune-based therapies. He and his collaborators have combined gene therapy and immunology to adapt T-cells to target cancerous cells. Clinical trials infusing these T-cells are now under development.

HOW WAS THE POWER OF T-CELLS DISCOVERED?

Hematopoietic stem-cell transplantation (HSCT, formerly referred to as bone marrow transplantation) uses stem cells from either a matched donor or from a patient's own cells. What we have observed from stem cell transplantation is that donor-derived T-cells are able to sniff out friend from foe in the transplant recipient and are capable of killing off remaining malignant cells.

We therefore asked, "What can we learn from HSCT going forward to avoid the problems of toxicities, costs, etc.?" One answer is to give just the T-cells and strip away everything else. To do this, we have learned how to trick the T-cells and engineer them to have targeted specificity to only recognize malignant cells.

HOW DO YOU TRICK THE T-CELLS?

We insert chimeric antigen receptors (CARs) to tell the T-cells what to target. CARs are similar to antibodies. Antibodies have one end that binds to a molecule (antigen) on the malignant cells. The other end of the antibody recruits immune cells that eliminate the malignant cells. However, these antibodies have to interact with the patient's immune system which is compromised by their disease and/or chemotherapy, especially in patients with CLL.

What we are doing now has been decades in the making. Dr. Zelig Eshhar from the Weizmann Institute in Israel discovered that just the antigen binding domain of an antibody, what we call the CAR, can be stitched onto the surface of a T-cell. The external portion of the CAR is on the lookout for antigens. The attached portion of the CAR causes the T-cell to proliferate, to make cytokines which contribute to an inflammatory response, and importantly to kill. Infusion of the T-cells genetically modified to express a CAR provides the patient with everything they need: the power of antibodies to detect malignant cells with the ability of T-cells to eliminate malignant cells.

Over the years we have improved upon the CAR design to fully activate a T-cell and to take on all of the T-cell properties. We are currently using CARs to target CD19 and ROR1. One trial using a CD19-specific CAR for patients with B-cell malignancies is actively accruing at MD Anderson.

WHY WERE CD19 AND ROR1 CHOSEN TO BE TARGETED?

CD19 is a protein expressed on B-cells, which are cells in the immune system that make antibodies. CLL is a disease arising from malignant B-cells. For the first trial, T-cells will be taken from the patient prior to HSCT and genetically modified to introduce the CD19-specific CAR. Patients will undergo an autologous HSCT (meaning they receive their own stem cells) and then receive their modified T-cells.

So patients get a bonus. As they receive the HSCT, they also benefit from the CD19-specific T-cells trying to eradicate their disease.

The ROR1-specific CAR is in collaboration with Dr. Tom Kipps at UCSD and Dr. Bill Wierda at MD Anderson. In Dr. Kipps' lab an observation was made that ROR1 is expressed only on the malignant B-cells of CLL. We hope that by making a CAR specific to ROR1 that the specificity is redirected to just the malignant B-cells, unlike the CD19-specific CAR which targets both healthy and malignant B-cells.

WHEN WILL ROR1 EXPRESSING CARS BE TESTED IN PATIENTS?

We are gearing up right now to put the trial through the regulatory process with Dr. Wierda and Dr. Kipps. We know that the CAR works, we know how to get the CAR into T-cells and we know how to maneuver through the regulatory pipeline. We are still working on the manufacturing procedures to grow ROR1-specific T-cells in high enough numbers so that they are effective when given back to the patient. This is a solvable problem, but it is going to take some more work. I expect that we will submit the trial for approval in the fall with hopes of opening early next year. Initially the trial will only be open at MD Anderson, and then we anticipate opening the trial on the West coast to accommodate the needs of Dr. Kipps' patients.

FAQS

Dr. William Wierda, Associate Professor of Medicine in the Department of Leukemia at MD Anderson, is actively exploring immune therapy approaches for CLL. Below he provides answers to some common questions about CARs.

ARE THERE SPECIFIC CONCERNS YOU WILL BE WATCHING FOR IN THE CLINICAL TRIALS?

A trial using a CD19-specific CAR is currently being conducted by Dr. Carl June at the University of Pennsylvania for B-cell malignancies. One of the observations from his trial is that patients with CLL benefited from the T-cell infusion! *(Note: these results were widely reported in the media.)* However, the healthy B-cells of patients disappear after this therapy as CD19 is expressed on both malignant cells and normal B-cells. You can live without B-cells for a certain amount of time because we can replenish antibodies with intravenous immunoglobulin (IVIG) therapy. Nonetheless it would be better for the patients if we could just restrict the killing to the malignant B-cells, and this is why the ROR1-specific CAR is worth testing.

> "The hope is that one day… patients can eliminate their disease with just an injection of T-cells."

Also, the CAR-modified T-cells are quite potent. When infused into the patient, these T-cells disseminate throughout the body and when they bind to CD19 they can simultaneously become activated. Patients consequently can experience side effects such as fever and shakes. The ability to manage these types of infusion-related toxicities is important. Fortunately, we are able to learn from Carl's [Dr. June's] experiences and adapt our trials accordingly.

IS THERE POSITIVE DATA FROM ANY OF THE CAR TRIALS WHICH HAVE BEEN CONDUCTED?

There is a lot. Trials infusing CAR-modified T-cells are taking place all over the world for various disorders. There is one published case report from the NCI, and Dr. June has promising preliminary data from his trial using CD19-specific T-cells.

IS THERE AN IDEAL PATIENT GROUP YOUR RESEARCH WILL BENEFIT?

Initially these trials are only open to patients with aggressive diseases refractory to other treatments or at high risk for relapse. If everything goes well, the goal is for all CLL patients to benefit from T-cell therapy. The hope is that one day this approach can replace HSCT and even chemotherapy, so patients can eliminate their disease with just an injection of T-cells.

AS A PEDIATRIC PHYSICIAN, WHAT IS YOUR INTEREST IN STUDYING CLL, WHICH IS CONSIDERED AN "ELDERLY DISEASE"?

I have witnessed the power of T-cell therapy and one of the more compelling areas to try it is the field of CLL. These patients are burdened by this chronic illness and often cannot receive a HSCT for one reason or another; they are too old or too sick. With the ability to harness a patient's T-cells and redirect the specificity, we are now capable of creating a targeted therapy that can benefit CLL patients today and can be applied to treat diseases of malignant B-cells in children tomorrow.

WHAT IS YOUR MOTIVATING FACTOR TO CONTINUE RESEARCHING?

The belief that I can make a difference is what keeps me going. I know I can help patients if I innovate and work hard. : :

WHEN WILL CARS BE WIDELY AVAILABLE TO ALL PATIENTS?

Significant work is still needed on CAR research and clinical application before this becomes a treatment that can be generally applied to patients. When we know it is safe and know how best to give it to patients, it will become generally available. Because it involves taking the patients' own T-cells and modifying them to express the CAR gene, patients' cells must be manipulated in highly specialized laboratory facilities. The logistics and implementation of this is very different from a pill or IV medication that can be dispensed by a pharmacy.

WHEN WILL CARS RECEIVE FDA APPROVAL?

It will probably take several years of clinical testing. Many variables go into FDA approval: pharmaceutical companies have objectives and agendas; feasibility can be an issue; and short and longer term safety must be assessed; etc. CARs are a highly specialized treatment which must be done at a specialized center. Experimental therapies - and this is very experimental therapy - do not usually get special treatment from the FDA just because they look promising or make big headlines.

HOW DO I FIND OPEN CAR TRIALS?

There are several groups around the country studying CARs. There is limited published information thus far, indicating that this is early in clinical development. Currently, the best way to determine if there are open clinical trials testing CARs is to search via www.clinicaltrials.gov. For clinical trials, most patients will probably have to be previously treated or refractory to standard treatments before they are eligible. : :