Adoptive Cell Therapies: One Cancer at a Time

After completing medical school and a general surgery residency at the University of Missouri, Kansas City, Christian Hinrichs, M.D., planned on doing cancer research at the start of his fellowship at Roswell Park Cancer Institute in 1996. However, a detour sent him into surgical oncology, and Hinrichs only returned to his research interests through a subsequent surgical oncology fellowship at NCI. Then, cancer had an unexpectedly personal impact on Hinrichs' career when an ocular melanoma compromised his eyesight and cut short his potential as a surgeon. Undeterred, Hinrichs shifted his focus to internal medicine as a resident at George Washington University and a medical oncology fellow in CCR. Now a Lasker Clinical Research Scholar in CCR's Experimental Transplantation and Immunology Branch, he is using his knowledge of cancer immunotherapies to help patients with metastatic cancers caused by the human papilloma virus (HPV).

During my surgical oncology fellowship, I worked in the laboratory of Nicholas Restifo, M.D., Senior Investigator in CCR's Surgery Branch. The branch was studying the use of adoptive cell transfer (ACT) for melanoma. In ACT, cancer-killing immune cells are harvested from the patient's tumor, grown outside the body, and then reintroduced. These lymphocytes (T cells) carry receptors which allow them to identify abnormal cells and other threats to the body that express specific protein markers, or antigens. We were expanding populations of the native tumor infiltrating lymphocytes (TIL) from patients and we were trying to engineer T cells with receptors designed to recognize specified antigens found on the melanoma cells. Unfortunately, antigens are rarely found exclusively on cancer cells and one of the key toxicities we were seeing in our melanoma protocols was the destruction of normal tissues that also contained melanocytes, e.g., the skin, eyes, and ears.

TIL for HPV

When I began my own research as a CCR Investigator, I had already thought a lot about the kinds of tumor antigens we could use for ACT that would be effective against cancers, while sparing more normal tissue. Although most cancers are caused by mutations of genes found

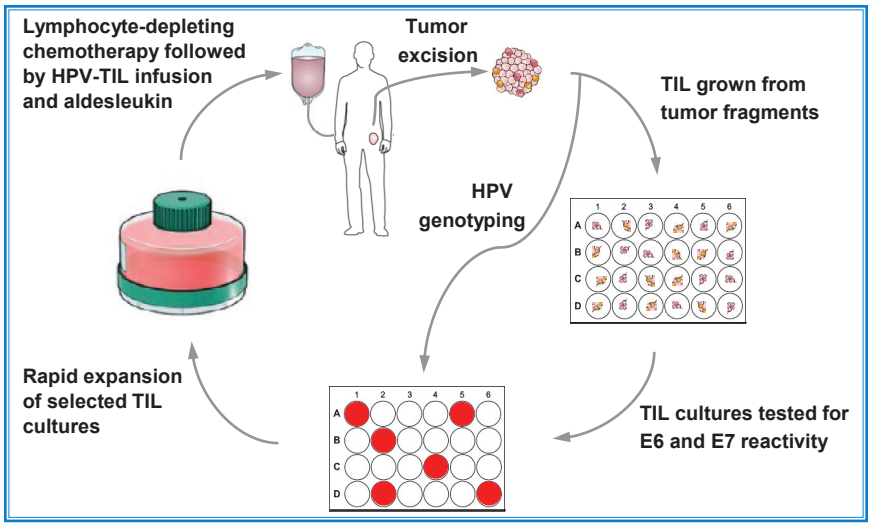
(Photo: R. Baer)

Christian Hinrichs, M.D.

normally in the body, some are caused by viruses, which introduce oncoproteins. Certain strains of HPV (HPV-16 and HPV-18), for example, cause cervical cancers as well as oropharyngeal, anal, vulvar, vaginal, and penile cancers. Although cervical screening and now anti-HPV vaccines may one day make these cancers obsolete, cervical cancer alone causes 4,000 deaths per year in the United States. Like many cancers, once cervical cancers reach advanced stages, they do not respond well to chemotherapy.

In 2012, we opened a protocol to treat women with cervical cancer, using essentially the same procedures that were initially pioneered for metastatic melanoma, but with an added layer of complexity. We tested our TIL cultures for reactivity to specific HPV antigens (E6 and E7) and selectively expanded the most HPV-reactive populations before reintroducing them into patients.

Of the nine women we treated on this protocol initially, three saw their tumors shrink. In one patient, the response was only partial and lasted for three months. But, the other two patients remain cancer free to this day (see "Going Home to Kansas," in this issue). We have since treated a total of 29 patients with HPV-related cancers with TIL. It has taught us some important concepts, namely that immunotherapy can mediate complete regression of cervical cancer. This is the most compelling evidence to date that cellular therapy can cause complete regression of an epithelial cancer. The trial numbers are small, so we cannot accurately assess the overall response rate. Fundamentally, TIL is also limited because we have to do surgery before we can even make a cell product for these patients. And once we do, the cell products are quite variable. For example, some cells are very reactive against HPV antigens, while others are completely unresponsive. We cannot control whether the patient has reactive cells, but our data indicates that the degree of reactivity of a patient's cells is related to the success of the procedure.



(Figure: C. Hinrichs, CCR)

Outline of first HPV-TIL protocol. A tumor is selected, excised, and split into tiny fragments which are grown in individual wells of cell culture plates. After initial expansion of two to three weeks, individual TIL cultures are tested for HPV-type specific E6 and E7 reactivity. Selected TIL cultures (red wells) are further expanded using a rapid expansion protocol. Expanded TIL are administered to patients, who have first been treated with lymphocyte-depleting chemotherapy to "clean the immunological slate" and allow the TIL to dominate.

Engineering Better T Cells

As part of our protocol, we not only wanted to assess the potential of TIL therapy for HPV-related cancers, we also wanted to study the populations of T cells in patients that were reactive against HPV. Our hope was that we could identify a good T-cell receptor that could be used to engineer lymphocytes extracted from patients' blood to respond to their tumors, thereby avoiding the issues associated with isolating TIL. In one of our patients who responded well to the TIL therapy, we identified a T-cell receptor against the E6 protein of HPV-16.

Armed with the genetic sequence for this receptor, we have now begun a protocol to treat patients whose tumors were caused by the HPV-16 strain, without having to surgically extract cells in the hope that they contain reactive TIL. Instead, we can use leukapheresis to extract lymphocytes from the blood, engineer those lymphocytes with the T-cell receptor sequence, and expand the cells. Leukapheresis can be performed at any medical center that already handles hematopoietic stem cell transplants. The leukapheresis product can be shipped to a commercial facility for genetic engineering then returned to the medical center to be given to the patient. However, at this stage, we

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(Photo: R. Baer)

Arrica Wallace and Christian Hinrichs, M.D., discuss her scans.

can only treat patients that 1) have the HPV-16 strain (65 percent of cervical cancers, 70 percent of oropharyngeal cancers, and 90 percent of anal cancers) and 2) are immunologically matched to the original T-cell receptor donor (HLA-A2, about 40–50 percent of Caucasians).

Patients are always very excited to see their cells infused, but it is actually kind of anticlimactic for me. I think what is important is seeing the scans when they come back for their first follow-up appointment. Patients return six weeks after the cell infusion; and, if the treatment is going to work, we usually see some shrinkage. However, at the first visit, it can still be difficult to tell if the treatment is working. We really only understand how well the cells are working after the second, third, or even fourth monthly visit.

From Clinic to Laboratory

I see my patients in clinical trials and I cover the medical oncology service for two weeks each year; the rest of my time is in the laboratory. I have four people working directly with me and two additional cell processing technicians who work in my lab. The Experimental Transplantation and Immunology Branch is developing a critical mass of cell therapy researchers, e.g., Jim Kochenderfer, M.D., who works on very similar approaches but for hematological cancers, and Luca Gattinoni, M.D., who works at a more basic science level. The three of us have a similar interest in cellular therapies; and Luca and I have a joint lab meeting and joint journal clubs.

I mostly work with human cells, studying why treatments work in some patients and not in others, trying to discover new T-cell receptors for gene therapy-based approaches, and investigating ways to improve the function of the T cells that we give to patients. Projects in my lab include efforts to delineate the landscape of T-cell responses against tumor antigens in the patients with cervical cancer who we have treated successfully. We are also working to identify new T-cell receptors that can be used to treat patients with HPV-related cancers and other types of cancer. Finally, we are seeking to improve

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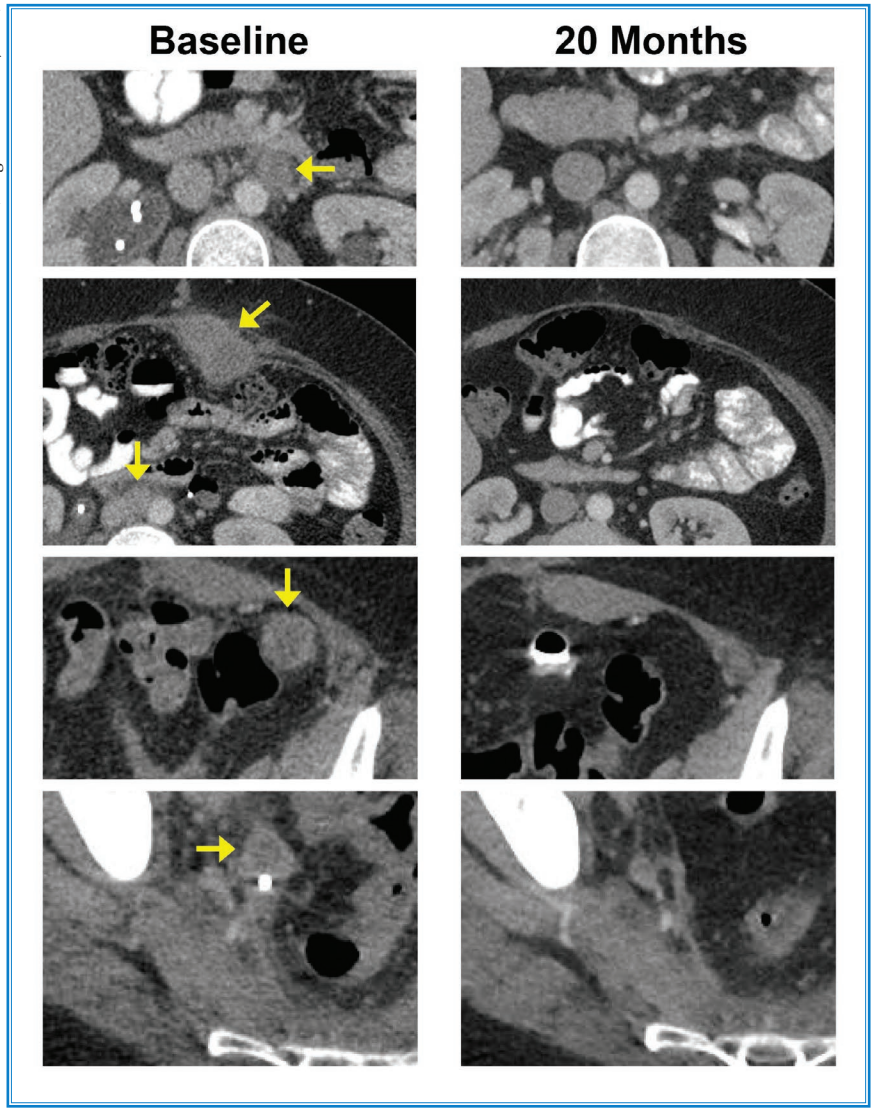
the function of therapeutic T cells, either by increasing expression of stimulatory genes or by decreasing expression of inhibitory genes.

We are also looking at the tumor side of the equation to understand better how tumors might evade our treatments. Tumors can lose expression of molecules that are needed for recognition by the immune system. They can also produce molecules that inhibit T cells, like PD-1. Understanding these factors can help us to select patients who are most likely to respond to treatment and to design rational combination therapies.

As it stands right now, it is proving difficult to get a single therapy to work in many different kinds of cancers, especially in the realm of solid tumors or epithelial cancers. It might be that we do not find a single magic bullet, a highly effective cellular therapy that can be broadly applied to different types of cancer; rather, we may move forward in increments, where we find a target for a particular type of cancer that makes sense, works well, and has low toxicity. And then, we repeat the process for the next type of cancer or even a particular subset of a type of cancer. Instead of looking for one target expressed by all cancers and targeting that, I think we will make more progress by finding a really good target in a smaller subset of cancers.

For the kind of research I do, working with complex cell therapies, there is no other center in the world that can do it as well as the NIH Clinical Center. It is the mission of the Clinical Center to do these kinds of cutting-edge clinical trials that would be very difficult to conduct elsewhere, with high impact and important laboratory science. We need to be able to move between patient protocols and research into the cellular mechanisms associated with patient outcomes. I cannot imagine doing that more efficiently anywhere else.

(Image: C. Hinrichs, CCR)



Computed tomography (CT) images of a 36-year-old patient with adenocarcinoma (HPV-18+) before and after treatment with adoptive cell transfer immunotherapy.

To learn more about Dr. Hinrichs' research, please visit his CCR website at https://ccr.cancer.gov/Experimental-Transplantation-and-Immunology-Branch/christian-s-hinrichs.