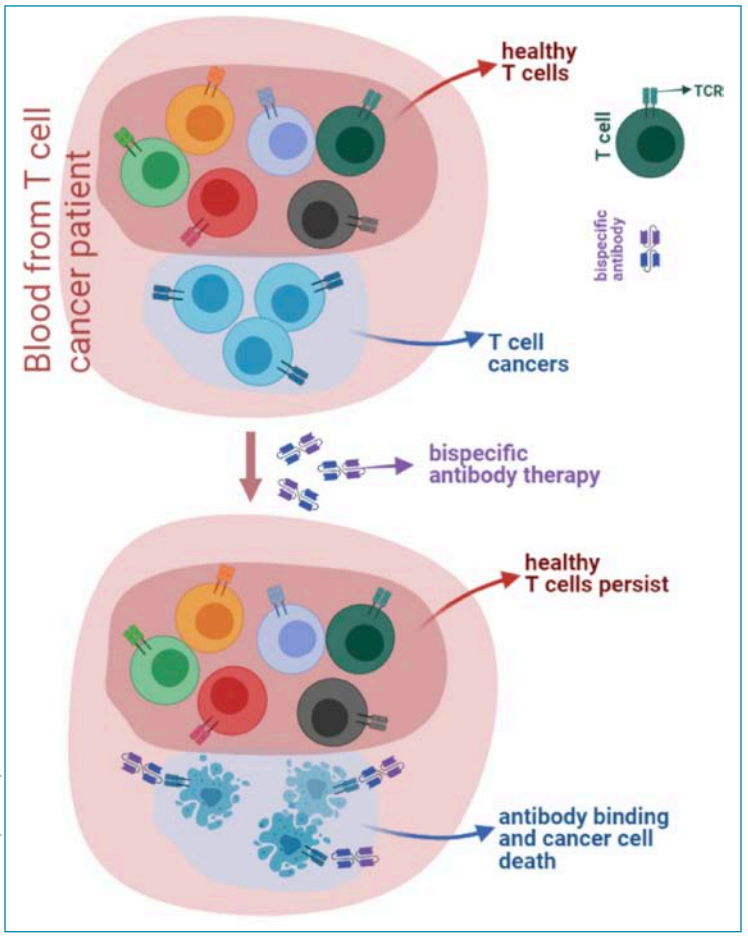
Advances in Off-the-Shelf Immunotherapy: Expert Discussion

BY DIBASH KUMAR DAS, PHD

Immunotherapy, especially immune cell-based therapy, has revolutionized cancer treatment strategies. Traditionally, patients have been restricted to four treatment possibilities: surgery, chemotherapy, radiation, and targeted therapy. However, the holy grail for researchers and physicians has always been to develop alternative strategies that would leverage a patient's own immune system to recognize and attack cancerous cells.

As immunotherapy continuously evolves, immunologists have discovered a new type of protein-based methodology which could lead to the possibility of highly effective generic or "off-the-shelf" immunotherapies that could be used in multiple patients, unlike the highly personalized approach of engineered immune cell therapies (*Cancer Sci* 2019; doi: 10.1111/cas.13892).



Suman Paul, MBBS, PhD

Figure A: Blood from a patient with T-cell cancer harbors both healthy T cells and cancerous T cells. The bispecific antibodies bind only to the T-cell receptor (TCR) sequence that is displayed by the cancerous T cells causing cancer cell death. The bispecific antibodies do not bind the TCR sequence in healthy T cells and as a result the healthy T cells persist.

These off-the-shelf protein-based treatments, known as bispecific T-cell engaging antibodies, are engineered to use one of their arms to tightly bind cancer-related peptides and with the other recruit a T-cell to destroy the peptide-presenting cell (*Pharmacol Ther* 2018; https://doi.org/10.1016/j.pharmthera.2017.08.005). T-cell cancers (T-cell leukemias and lymphomas) are a diverse group of diseases that encompasses about 15 percent of non-Hodgkin lymphomas and 20 percent of acute lymphoblastic leukemias (ALL) (*Blood Adv* 2020; doi: 10.1182/bloodadvances.2020001822).

CME/NCPD

A study by researchers at Johns Hopkins University offers an emerging method to achieve off-the-shelf protein-based immunotherapeutic for treating T-cell cancers. As reported in *Science Translational Medicine*, researchers tested an approach to determine whether a CD3 bispecific T-cell-engaging antibodies (BsAb) could deplete T-cell malignancies while safeguarding healthy T cells (2021; doi: 10.1126/scitranslmed.abd35950).

The αβ T-cell receptor (TCR) is expressed on normal and cancerous T cells. Each T cell expresses a distinctive TCR β chain generated from one of 30 TCR β chain variable gene families (TRBV1 to TRBV30), wrote the authors. To establish proof of concept, the team hypothesized that bispecific antibodies targeting a single TRBV family member expressed in malignant T cells could stimulate extermination of these cancer cells, while conserving healthy T cells that express any of the other 29 possible TRBV family members.

The findings revealed that generated BsAb targeting TRBV5–5 (α-V5) or TRBV12 (α-V12) explicitly depleted appropriate malignant T-cell lines and patient-derived T-cell leukemias in vitro, and resulted in significant tumor regressions in mouse models of human T-cell cancers. Furthermore, the TRBV-directed therapies preserved most healthy human T cells.

Oncology Times recently chatted with Suman Paul, MBBS, PhD, Assistant Professor of Oncology at Johns Hopkins University, to discuss their recent work and the impact of off-the-shelf immunotherapy for patients with cancer.

Oncology Times: *What can highly effective "off-the-shelf" immunotherapy mean for patients with cancer?*

Paul: "Immunotherapy is a broad term that encompasses multiple agents. In solid tumor patients, immunotherapy usually refers to checkpoint blocking antibodies, such as nivolumab or pembrolizumab. In hematologic malignancies, immunotherapy may involve chimeric antigen receptor (CAR) T-cell therapy that targets specific proteins on the surface of cancer cells. The CAR T cells have to be engineered for each patient and the process of producing the CAR T cells takes 2-4 weeks.

"Alternatively, immunotherapy may involve the use of pre-made antibodies that target cell-surface proteins on cancer cells. Such pre-made antibodies are sometimes called "off-the-shelf" as they are ready to use, and patients can avoid the time delay that is associated with manufacturing CAR T-cell products.

"Several such off-the-shelf immunotherapies are available for the treatment of patients with B-cell leukemias and B-cell lymphomas. Rituximab targeting the cell-surface protein CD20 may be considered one of the earliest example of off-the-shelf immunotherapy and has revolutionized the treatment of B-cell leukemias and lymphomas.

"And newer bispecific antibodies such as blinatumomab and mosunetuzumab have shown impressive response rates and improved survival when compared with traditional treatment regimens. These antibodies can be considered as highly effective off-the-shelf immunotherapy in hematologic malignancies. However, quite a few cancers, including T-cell leukemia and T-cell lymphomas, lack such immunotherapeutic antibodies; as a result, we have much fewer treatment options available for these patients."

Oncology Times: *The findings in these studies describe a CD3 BsAb that uses T-cell receptor–specific antibodies to selectively eliminate T-cell malignancies. What excites you most from the findings of this study?*

Paul: "We are excited about two important implications of this study. First, the bispecific antibodies can target any T-cell receptor (TCR) that shares the same TCR sequence. As a patient's T-cell leukemia or lymphoma cells share the identical TCR sequence, antibodies bind and kill only the T-cell leukemia or lymphoma cells. And as most normal T cells express different TCR sequences, antibodies do not affect most of the normal T cells (see Figure A). This is important as humans need the normal T cells to provide protection against bacteria, viruses, and other pathogens. The ability to selectively kill T-cell leukemia and lymphoma cells is a major step forward in the field and provides a path towards developing highly effective off-the-shelf immunotherapy for these patients. We are hoping that these bispecific antibodies will improve outcomes in patients with T-cell cancers.

"Second, many autoimmune pathologies are thought to be caused by T cells attacking the patients' own healthy cells resulting in tissue damage. Such autoreactive T cells are have been found in diverse diseases with limited treatment options, including celiac disease, scleroderma, inclusion body myositis, and graft-versus-host disease. And a recent report suggests a role for autoreactive T cells in patients with Alzheimer's disease. The autoreactive T cells are often clonal—that is the autoreactive T cells share the same TCR sequence. So, using methods that are similar to our study, we can design antibodies that only kill the autoreactive T cells and spare the normal T cells, and hopefully provide some benefit in each of the above-mentioned pathologies."

Oncology Times: *What are factors that need to be considered before therapeutic efficacy of this approach can be fully realized?*

Paul: "Our study was conducted in mice that were harboring human T-cell leukemias. These mouse studies are often the very first step in the long process of drug development. For the treatment to work in humans, we will need to conduct early-phase clinical trials to study the behavior/kinetics of the antibodies in humans and to make sure that we are not encountering any major adverse effects.

"Once we have the pharmacokinetics and safety data, additional clinical trials can be planned to actually test the activity of the antibodies in killing T-cell leukemia or lymphoma cells in humans. The median time from drug development to approval is reported to be around 12 years, so it will take a while before these antibodies can be tested in humans."

Oncology Times: *Are there any studies being conducted either in vitro or in vivo to determine if this approach can be combined with other cancer-targeting therapies to yield a superior response?*

Paul: "Combining different forms of immunotherapy, such as antibodies, with other cancer-targeting therapies, such as chemotherapy, have shown benefit in both solid tumors and in hematologic malignancies. However, our particular immunotherapy utilizes the bispecific antibody format, which requires the presence of a healthy T-cell population to achieve its cancer-killing effect.

"Traditional chemotherapies often lower the number of healthy T cells in a patient's blood and as a result may reduce the efficacy of bispecific antibodies. We found that our bispecific antibodies on their own are highly effective in killing the cancerous T cells in mouse models.

"While currently we are not conducting studies to examine the combination approach of bispecific antibodies with chemotherapies, such studies are certainly on the horizon so we can extract the maximum clinical benefit out of these antibodies." OT

Dibash Kumar Das is a contributing writer.

Read This Article and Earn CME or NCPD!

Earn continuing education credit by completing a quiz about this article. You may read the article here or on our website, then complete the quiz, answering at least 70 percent of the questions correctly to earn credit.

CONTINUING MEDICAL EDUCATION INFORMATION FOR PHYSICIANS

Visit **http://CME.LWW.com** for more information about this educational offering and to complete the CME activity. This enduring material is available to physicians in all specialties. Lippincott Continuing Medical Education Institute, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Lippincott Continuing Medical Education Institute, Inc., designates this enduring material for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity. This activity expires September 30, 2023.

The cost of the exam is $10. The payment covers processing and certificate fees.

PROVIDER ACCREDITATION INFORMATION FOR NURSES

Lippincott Professional Development (LPD) will award 1.0 contact hour for this Nursing Continuing Professional Development (NCPD) activity. LPD is accredited as a provider of NCPD by the American Nurses Credentialing Center's Commission on Accreditation. This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749 for 1.0 contact hour. LWW is also an approved provider by the District of Columbia, Georgia, and Florida CE Broker #50-1223. Visit **www.nursingcenter.com** for more information and to complete the NCPD activity.

Fee: $12.95.

Deadline: September 1, 2023

For nurses who wish to take the test for NCPD contact hours, visit www.nursingcenter.com.

Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Summarize recent advances in the study of bispecific T-cell engaging antibodies. 2. Identify the implications of these recent developments for the treatment of patients with cancer or other diseases and for future research.

Disclosure: The author(s), faculty, staff, and planners in any position to control the content of this activity, have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.