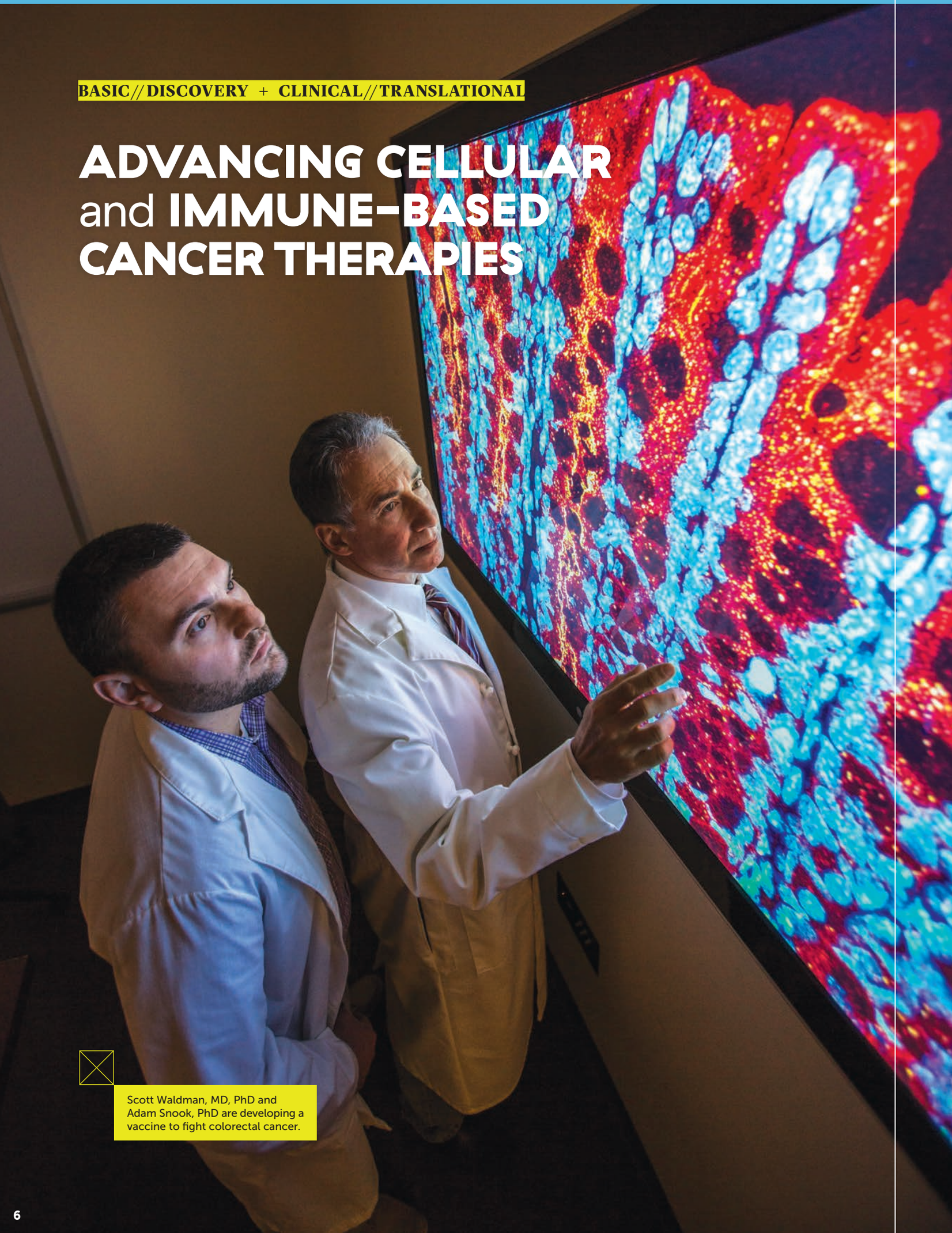
BASIC // DISCOVERY + CLINICAL // TRANSLATIONAL

ADVANCING CELLULAR and IMMUNE-BASED CANCER THERAPIES



Scott Waldman, MD, PhD and Adam Snook, PhD are developing a vaccine to fight colorectal cancer.

THE NCI-DESIGNATED SIDNEY KIMMEL CANCER CENTER (SKCC) is the heart of Jefferson's broad-based cancer research program. SKCC investigators are currently pursuing hundreds of basic science, translational and clinical studies on cancer cell biology and signaling, molecular biology and genetics, and specific diseases ranging from brain cancer to uveal melanoma. Among the most exciting efforts are partnerships between SKCC basic scientists and clinician-researchers to both advance new immune-based therapies and continuously improve current approaches.

Glioblastomas are aggressive brain tumors—and very hard to eliminate completely. However, a glioblastoma combination immunomodulatory vaccine approach developed by Jefferson researchers is now progressing into a phase II trial. The immunomodulatory vaccine product is notable for its initial success with a tumor type where previous immunotherapy approaches have failed.

Created by **David Andrews, MD**, professor of neurosurgery, and **D. Craig Hooper, PhD**, professor of cancer biology, the vaccine employs a patient's own tumor cells collected during surgical removal of the primary brain tumor. The researchers treat those cells with an antisense oligodeoxynucleotide (AS-ODN) containing immunostimulatory motifs. The AS-ODN works against a receptor shown to drive tumor growth and metastasis and the activity of tumor-promoting, anti-inflammatory macrophages. Next, the cells are loaded into a dime-sized diffusion chamber with additional AS-ODN, and the contents are irradiated. The chamber is then implanted under the patient's skin, allowing antigens produced by the cells and the AS-ODN to diffuse into the body to stimulate pro-inflammatory tumor-immune cells and boost anti-tumor immunity.

New Colorectal Cancer Vaccine

A new Jefferson-developed colorectal cancer vaccine also shows great promise. The adenovirus vector vaccine works by prompting an immune response specifically to a colorectal cancer tumor antigen called guanylyl cyclase (GUCY2C), first identified by **Scott Waldman, MD, PhD**, Samuel M.V. Hamilton Professor of Medicine. Developed by Dr. Waldman and **Adam Snook, PhD**, assistant professor of pharmacology and experimental therapeutics, the vaccine combines a GUCY2C molecule with a molecule that boosts the anti-tumor activity of CD8 positive cytolytic T lymphocytes. GUCY2C is expressed by cells lining the intestine and by at least several types of cancer cells; but, because the vaccine is injected into arm muscle, it does not come into contact with healthy intestinal cells.

In a phase I clinical trial, patients' blood showed markers of immune activation, suggesting that the vaccine could train the immune system to attack colon cancer cells that had spread before surgical removal. In pre-clinical mouse studies, the vaccine reduced the formation of colon cancer metastases in the lungs by >99% percent and more than doubled survival time. The researchers—who are preparing for phase II trials of the vaccine—recently found that GUCY2C is also expressed by gastric, esophageal and pancreatic cancer cells. They will pursue opportunities to test the vaccine with those cancers as well.

GUCY2C is also the target of a new CAR-T-based immunotherapy for colorectal cancer that Drs. Snook and Waldman have developed. The therapy—which engineers and re-infuses patients' own immune cells to target only the tumor—is preparing to enter phase I trials. Previously, a human-ready version of the therapy proved successful in killing tumors and preventing metastatic growth in mice—more than quintupling survival in cases with advanced lung metastases. Notably, there were no off-target or adverse effects of the treatment, which has been a major problem for other CAR-T cancer therapies.

Two–Step Approach

A unique approach to bone marrow transplant (BMT) involving half-matched (haploidentical) donors and higher-risk patients has proven as effective as transplants that use traditional, fully-matched donors. And continuing improvements in the procedure are driving even better results for patients. The "two-step approach"—developed by **Neal Flomenberg, MD**, professor of medical oncology—has been used in more than 300 procedures involving half-matched donors since 2006. Until recently, Jefferson was the only institution in the nation using the two-step approach.

In traditional BMT, chemotherapy (and, sometimes, radiation therapy) is administered before the patient receives an infusion containing both T-cells and stem cells in a single step; then immunosuppressive drugs are used to prevent or limit the otherwise overwhelming immune response that results in graft-versus-host disease (GVHD). In the two-step approach, after half the chemotherapy is administered, just donor T-cells are infused; two days later, the remaining chemotherapy is administered. (As a result, the cells spurring GVHD are eliminated, which lessens the need for a close HLA match.) Finally, an infusion of highly purified stem cells is given.

The two-step approach's benefits for patients are significant: less-aggressive regimes of immune-suppressant drugs; reduced incidence of GVHD; and engraftment of donor cells that occurs more quickly than with a traditional approach. Perhaps most significantly, the process and time needed to find a donor are reduced—a huge factor since approximately only 30 percent of patients will have a family member who is a full match. In addition, Dr. Flomenberg's approach gathers donor cells differently: rather than extracting stem cells from bone marrow, they are harvested from the donor's blood. It is less painful and less risky for donors, and enables the physicians to better standardize the number of cancer-fighting T-cells and stem cells (which replenish depleted blood supply) given the patient. ■

The glioblastoma and colorectal cancer vaccines reflect one facet of Jefferson's expansive basic science and translational research on vaccines. See *Vaccines Fighting Viruses and Cancer* on page 18 for a broader look at that work.