

“DARTMOUTH HAS A LONGER HISTORY THAN MOST ACADEMIC INSTITUTIONS IN CONDUCTING RESEARCH IN ANTIBODY THERAPEUTICS, AND THAT’S SOMETHING SPECIAL.”

Immunology colleagues (left to right) Steve Fiering, Mary Jo Turk, Randy Noelle, and Charles Sentman in Turk’s lab at the Norris Cotton Cancer Center. (photo by Jon Gilbert Fox)



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# BUILDING ON HISTORIC STRENGTHS

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BY SUSAN GREEN

Whether defending our bodies against pathogens that can cause infections or mutations that lead to cancer, our powerful immune system identifies these invaders and mobilizes a controlled response to kill the offending cells.

Although malignant cells are recognized, and an attack launched, the system on its own is unable to overcome the local immunosuppressive environment generated by the tumor.

**S**cientists have been discussing and experimenting with tumor immunotherapy for more than 100 years with varying degrees of success. Immunologists now believe and have evidentiary support that the immune system can be harnessed to treat cancer by reversing malignant cells' ability to suppress the immune system's response, making cancer cells more vulnerable.

"For immunotherapy to be successful, it needs to disrupt a very complex balance between stimulatory and suppressive blood cells that participate in immune responses, and break through the immunosuppressive environment tumors generate to shield themselves from immune attack," says Steven Fiering, PhD, a professor of microbiology and immunology at the Geisel School of Medicine.

Immunotherapy is now the most promising method of treating cancer, and Fiering is among the more than 20 researchers affiliated with Norris

Cotton Cancer Center's Immunology and Cancer Immunotherapy Program, which spans seven departments at Geisel and Dartmouth's Thayer School of Engineering.

The program has a strong and impressive heritage. And given the relatively small size of the college and medical school, there are a surprising number of investigators who have long been conducting immunotherapy research, putting Dartmouth on the map early. Rich in multiple resources, it is this historic interdisciplinary approach that sets Dartmouth apart from other academic immunotherapy programs and enables investigators to move quickly in taking research from the lab to the clinic—a legacy initiated by Medarex.

"Nearly everybody working in immuno-oncology knows about Medarex," says Mary Jo Turk, PhD, co-director of the Immunology and Cancer Immunotherapy Program. "Dartmouth has a longer

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history than most academic institutions in conducting research in antibody therapeutics, and that's something special.”

Back in the late 1980s, Geisel immunology researchers Mike Fanger, PhD, and Paul Guyre, PhD, founded Medarex—a biopharmaceutical company that developed monoclonal antibodies to the T cell checkpoint proteins CTLA-4 and PD-1. By blocking the checkpoint proteins, these antibodies enable T cells to attack and destroy cancer cells. Checkpoint proteins control and regulate immunity and immune response.

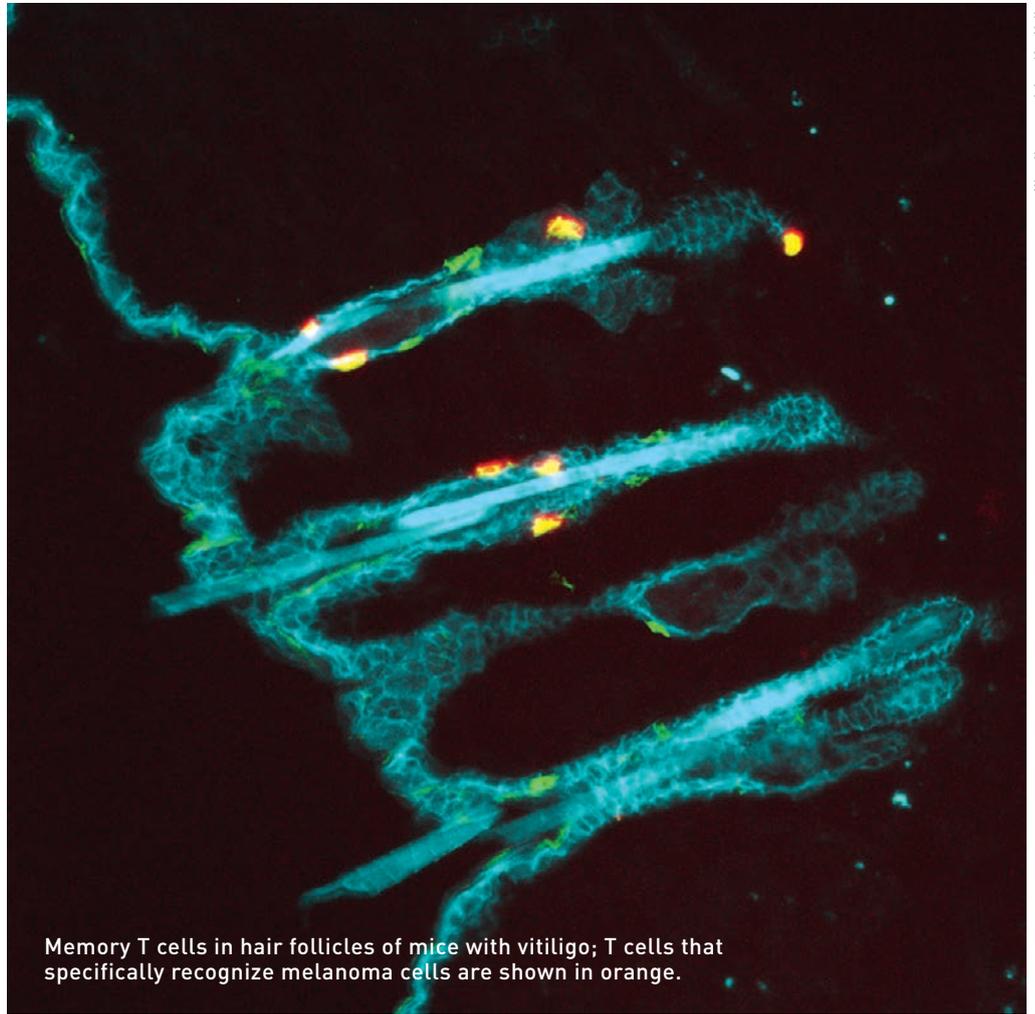
As reported in the September 2017 *New England Journal of Medicine*, the combined use of these antibodies, now approved by the Food and Drug Administration (FDA) and owned by Bristol-Meyers Squibb, result in a 58 percent, 3-year survival for advanced melanoma; survival prior to 2014 ranged from 20 – 38 percent.

Continuing in Medarex's footsteps, several Dartmouth investigators are leading the way in important immunology discoveries by either founding a company to further develop their discovery or working with a corporate partner to do so.

“We are certainly continuing to pioneer immunotherapy projects,” Turk says. “For example, Randy Noelle's lab discovered a new immune checkpoint inhibitor (an immune system protein), VISTA. And Charles Sentman designed a new type of Chimeric Antigen Receptor (CAR) T cell. These new forms of immunotherapy are thought of as the next big step in cancer treatment.”

Noelle, the Thomas S. Kosasa, MD, Professor at Geisel, is the chief scientific officer and co-founder of ImmuNext, which is embedded within the Cancer Center. The company develops immunotherapy compounds for treating cancer and autoimmune diseases—their checkpoint regulator anti-VISTA is now in clinical trials. Another significant discovery from Noelle's lab is the natural CD40 ligand, CD154, which together plays a central role in controlling the immune system. CD40L is a monoclonal antibody that suppresses the “activity of a cellular pathway that is overactive in many autoimmune diseases” and is in preclinical development. ImmuNext is partnering with Johnson & Johnson to run the clinical trials.

Though other researchers are also working on CAR T cells, Sentman, a professor of microbiology and immunology at Geisel, has designed something entirely new. “Charles has created CAR T cells that are potent against several different types of cancer,” Turk explains. “And he's taken a slightly different approach by partnering with Celdara Medical to bring the



Memory T cells in hair follicles of mice with vitiligo; T cells that specifically recognize melanoma cells are shown in orange.

therapies to clinical trial.”

Celdara Medical, based in Lebanon, NH, is dedicated to helping investigators secure the funding and partners they need to translate academic science innovations into medicines, and both Fanger and Guyre are affiliated with the company.

Sentman's genetically manipulated antigen T cells are designed to recognize tumors in colorectal, ovarian, bladder, triple-negative breast and pancreatic cancers, myeloid leukemia, and multiple myeloma—and kill them. Using a patient's own T cells, the receptors are engineered on the surface of the cells, multiplied, then introduced back into the patient. The cells appear to continue their attack after treatment ends.

Applying engineering's practical problem-solving approach to immunology, Sentman and Thayer's engineers are tinkering with CAR T cell proteins to improve their performance. Turk says using engineering principles to create smarter cell therapies is the next wave in immunotherapy research.

Five years ago there was doubt about the effectiveness of immunotherapy and whether or not it may have advantages other therapies lacked. Since then, with more therapies gaining FDA approval, immunotherapy has become mainstream.

In treating melanoma, for example, antibodies to PD-1, a checkpoint protein on T cells, were approved by the FDA in 2014. “These two monoclonal antibodies that target either PD-1 or PD-L1 can block this binding and boost the immune

response to cancer cells and have shown impressive results,” Turk says. “In patients with metastatic melanoma there had been nothing for them, but now they can receive anti-PD-1 and get durable results.”

Though it achieves impressive results, immunotherapy shouldn’t be taken lightly, patients still get sick—they don’t lose their hair, but once you take the brakes off the immune system to attack malignant cells many patients develop autoimmune conditions. In the case of melanoma, patients may also develop vitiligo, a depigmentation disease.

“What is happening is the T cells attacking a melanoma arising from the pigment cells in the skin can’t differentiate the normal melanocytes and thus kills them too, creating blotches of skin without pigment,” Turk explains. “Serendipitously modeling this condition in mice, we noticed that one of our treatments resulted in mice growing white hair, and using that model we recently discovered a new type of T cell called a resident memory T cell. These cells have very long lives and can continue to kill cancer cells.”

Curiously, Turk and her team noticed that mice with vitiligo generated resident T cells able to fight off aggressive melanoma. Those without vitiligo did not. There is now evidence that humans can also generate these cells. “This changed the way we look at where T cells need to be, and began thinking that they need to get into tissues, rather the bloodstream.”

Turk and Christina Angeles, MD, a surgical oncologist at Dartmouth-Hitchcock Medical Center, are collaborating on a clinical study to discover why patients who develop vitiligo during treatment for melanoma have such a good prognosis, and to identify the super-charged T cells responsible.

Immunotherapy differs from chemotherapy in that it is systemic—meaning treatments are not focused on directly killing the cancer cells, Fiering says, but on enabling the immune system to kill the cancer cells. With solid tumors, it is the metastatic disease that kills the patient, not the existing tumor.

This is an important distinction for Fiering. “My approach is to take identified tumors protected by the local

immunosuppression and inject stimulatory reagents directly into them—in situ vaccinations,” he says. “Injecting a high concentration reagent that’s systemically quite low and safe to generate an immune response to attack the tumor may expand the T cell mediated response.”

Fiering says there are now more tumor specific immune cells able to potentially find metastatic disease and eliminate it. “This could work with some of the other therapies such as checkpoint blockade so we have more T cells recognizing the tumor and generating a better response with lower levels of checkpoint antibodies.

“It’s a bit of a different idea,” he admits, “but I’m convinced this is something that can be used in combination with other immunotherapies—locally treating an identified tumor to stimulate both the local and systemic response against the cancer.”

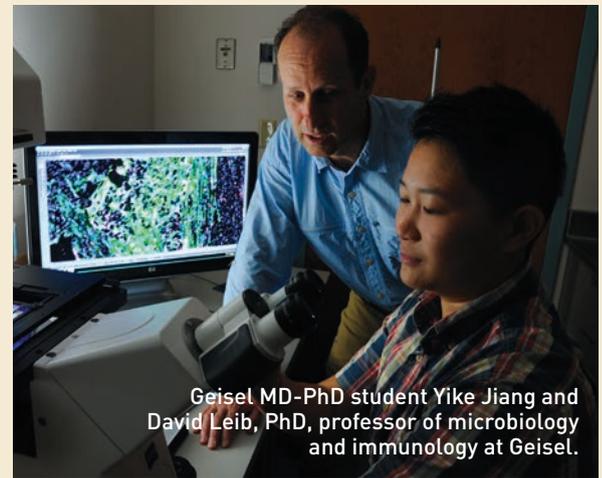
That immunotherapies themselves are likely to become combinatorial is something beginning to take root. “As treatment becomes more complex it also becomes more personal,” Fiering says. “Bringing different approaches together in a way that is effective, inexpensive, and dependable becomes the question.”

Yet despite exponential growth in immunotherapy, it is impossible to predict which patients will respond favorably to which immunotherapies—some patients simply can’t tolerate T cells attacking normal tissue and they develop autoimmunity. But that uncertainty may be changing. Identifying biomarkers for those likely to benefit from treatments is now an area of research interest.

“We may never be able to cure cancer—and I don’t think we have enough experience with immunotherapy to really talk about a cure—because no matter how good we get we will lose patients whose immune systems are compromised,” Fiering notes. “But now that we have more treatments, cancer is closer to becoming a manageable disease with patients living longer lives.”

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SUSAN GREEN IS SENIOR WRITER FOR  
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Geisel MD-PhD student Yike Jiang and David Leib, PhD, professor of microbiology and immunology at Geisel.

## DARTMOUTH TOPS THE IVY LEAGUE IN NATURE’S 2017 INNOVATION INDEX

Dartmouth ranks highly in a new measure of the impact of academic research on global innovation, according to the *Nature Index 2017 Innovation* supplement. The index examines how often research articles from top science journals are cited in third-party patents around the world.

Dartmouth ranks 20th among the top 200 institutions surveyed in the index, and is the only Ivy League institution in the top 20. Rankings are based on the number of scientific papers that lead to patents owned by entities other than the university itself.

“It’s a small college, but there are those that cite her,” says Dean Madden, PhD, Dartmouth’s vice provost for research and professor of biochemistry and cell biology at the Geisel School of Medicine. “The nice thing about this methodology is that it focuses on the role of basic research, published in the peer-reviewed literature, as a source of innovation in the long term. Too often, we assume that fundamental and applied research are siloed—papers vs. patents—but they’re not.”

The index aims to help show the social benefits of research. “This analysis comes at a time when following the transfer of scientific knowledge into industry and the economy is a growing priority for governments and research funding agencies—for them, the need to demonstrate that publicly funded science is being used for society’s benefit is paramount,” says David Swinbanks, founder of the Nature Index.

As an example of how academic institutions help transfer scientific knowledge into industry and the economy, *Nature Index 2017 Innovation* profiled Geisel’s Michael Sporn, MD, an emeritus professor of pharmacology and medicine, whose research between 1959 and 2006 has frequently been cited in patents, which have in turn led to numerous drugs in clinical development for cancer, fibrosis, and other diseases.

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