

Activator Puts The Brakes On Cancer

University of California, Berkeley (UC Berkeley)



As a kid, James Allison loved to figure out how things worked.

“I wanted to be the first person on the planet to know something before anyone else,” says Allison, who prepared for a life of discovery by pursuing a bachelor’s degree in microbiology and a doctorate in biological sciences.

After 20 years of intense laboratory research studying the body’s immune system, he got his wish.

Using Allison’s pioneering work, the biotechnology company, Medarex, in partnership with Bristol-Myers Squibb, developed Yervoy, the first drug ever shown to significantly improve overall survival for patients with advanced metastatic melanoma, the deadliest form of skin cancer.

“Twenty-five percent of patients treated with Yervoy are still alive four-and-a-half years later, We can’t call it a cure, but what we’re seeing is a durable response.

James Allison

Melanoma: Rare but Lethal

Melanoma, the most dangerous form of skin cancer, is caused by uncontrolled growth in pigment-producing skin cells.

Highly curable in the early stages, melanoma can often be surgically removed. However, the disease is more likely than other skin cancers to metastasize, or spread to other parts of the body, making treatment more difficult. In the late stages of metastatic melanoma, the average survival rate is just six months.

According to the American Cancer Society (ACS), melanoma accounts for less than 5 percent of all skin cancer cases, but the vast majority of skin cancer deaths. The ACS estimates that in 2012, 76,250 Americans will be diagnosed with melanoma, and 9,180 will die from the disease.

“Metastatic melanoma is one of the most aggressive forms of cancer and, despite the rising incidence, no new treatments had been approved in more than a decade before Yervoy,” says Sarah Koenig, spokesperson for Bristol-Myers Squibb.

Harnessing the Immune System

Unlike chemotherapy, which treats the tumor directly, Yervoy is part of an emerging class of treatments known as immunotherapy, which harnesses the body’s own immune system to fight tumors.

In a healthy immune system, foreign bacteria and viruses as well as transformed cancer cells bear molecular structures called antigens that identify them to the immune system as dangerous. A type of immune cell called the T-cell plays a key role in the body’s defensive response to these dangers. However, T-cells attack antigen-bearing targets only when given a green light to do so. To prevent the body from attacking its own normal cells, the immune system has a series of checkpoints that operate like traffic lights, sending signals that either activate or inhibit T-cells.

As a professor in the Division of Immunology and director of the Cancer Research Laboratory at the University of California, Berkeley (UCB), Allison devoted himself to studying the immune response to cancer — and how the disease proliferates by selectively suppressing T-cell activation.

In 1995, he showed that a checkpoint molecule called cytotoxic T lymphocyte antigen-4 (CTLA-4) puts the brakes on T-cell responses. Block CTLA-4, theorized Allison, and the immune system could be activated, unleashing a robust antitumor response. In preclinical experiments, he successfully demonstrated that he could bind a special type of protein called a monoclonal antibody to CTLA-4, preventing it from interfering with T-cell activation.

Finding a Commercial Partner

For help in the patenting process and finding a commercial partner, Allison turned to UCB’s Office of Intellectual Property (IP) and Industry Research Alliances. It turned out to be a long and winding road to commercialization.

“In the early ‘90s, companies were not interested in commercializing IP rights due to lack of what’s known as ‘proof of clinical mechanism,’” says Carol Mimura, Ph.D., assistant vice chancellor, IP and Industry Research Alliances. “As a university without a medical school, we couldn’t advance the opportunity beyond preclinical stages, but we took a risk on pursuing a broad patent portfolio because Dr. Allison convinced us that we had a world-changing opportunity.

“Essentially, we were betting on Dr. Allison and his research team, just as a venture capitalist bets on the management team of a startup company,” explains Mimura.

The technology was originally licensed to NeXstar Pharmaceuticals, which merged with the biopharmaceutical company, Gilead Sciences Inc. Gilead sublicensed the rights to Medarex, which developed a human monoclonal

antibody and began testing in partnership with Bristol-Myers Squibb. Bristol-Myers Squibb acquired Medarex in 2009.

“Two startup companies took the risk of performing lengthy and expensive R&D [research and development] for more than a decade on an unproven opportunity,” Mimura says of NeXstar and Medarex. “Entrepreneurship and dogged determination resulted in a product that the pharmaceutical industry was able to take to the finish line.”

In clinical trials, the antibody — named ipilimumab — added months to the survival rates of patients with advanced melanoma, something no other drug had been able to achieve. Based on the results of a randomized, double-blind Phase III study, the drug was fast-tracked and approved from the U.S. Food and Drug Administration in March of 2011.

“Yervoy provided a critical missing piece to the cancer immunotherapy armamentarium and was a game-changer not only for melanoma patients who desperately needed new treatment options, but also for the entire field of cancer immunotherapy,” says Jill O’Donnell-Tormey, Ph.D., CEO and director of scientific affairs for the Cancer Research Institute in New York. “We expect Yervoy and other types of treatments that block the immune system’s ‘off switches’ will potentially help patients with any type of cancer, and if used in combination with cancer vaccines or conventional cancer treatments, could help a much larger percentage of patients.”

Unleashing T-Cells on Cancer

To date, more than 10,000 cancer patients have received Yervoy in clinical trials to treat advanced melanoma and other types of cancer, either alone or in combination with other drugs. Immunotherapy is a key area of focus at Bristol-Myers Squibb, which is also testing the use of Yervoy to treat specific prostate cancers and both small-cell and non-small-cell lung cancer.

“This treatment is unique in that it recruits the immune system to fight the cancer,” says Mimura. “It’s also nonspecific to a given tumor type. Clinical trials are now under way for prostate, breast, lung and other cancers.”

Allison says that unlike other drug therapies, which have short half-lives, T-cells, once activated, stay in the body for decades or maybe even a lifetime.

“One of the reasons so-called miracle drugs don’t work is because they only last in the system a short amount of time, and 85 percent of the time the cancer comes back because you can’t get every cancer cell,” says Allison. “If you try to kill cancer, it’ll beat you every time because it mutates.”

Over the years, Allison has had the opportunity to meet several patients who, thanks to Yervoy, have survived much longer than expected.

“I met a woman who participated in our very first clinical trial 12 years ago,” he says. “That’s one of the hallmarks of immunotherapy. Once it works, it’s permanent.”

Funding Fundamental Research

Mimura and Allison say the success of Yervoy underscores the importance of conducting and funding basic research.

“Dr. Allison transformed the field of immunology and achieved clinical success by performing basic research on T-cells,” says Mimura. Adds Allison, “It’s satisfying that I could come up with this only by getting under the hood and seeing how things work.”

According to Mimura, both federal dollars — through National Institutes of Health — and later, private funding from the Howard Hughes Medical Institute, played critical roles in Allison’s discovery.

“We hit several valleys between federal grants that could have spelled death for the project,” she says. “A vital \$50,000, no-strings-attached grant from Michael Milken’s CaP CURE (now the Prostate Cancer Foundation) provided Dr. Allison’s laboratory with much-needed bridge funding at a very critical time.”

The tenacity of everyone involved paid off when it came time to negotiate a drug royalty monetization agreement with Bristol-Meyers Squibb: UCB received an upfront payment of \$87.5 million — the biggest win to date for the university’s IP office — with the possibility of additional future payments if sales achieve certain pre-specified levels. The university directed funds toward a myriad of scientific research needs, from faculty retention, new biology teaching labs and equipment for the cancer research lab to a new building devoted to stem cell research.

Today, Allison is chair of the Immunology Program at the Sloan-Kettering Institute in New York City, where he is working side by side with physicians to increase the number of patients who respond to Yervoy by combining it with other cancer treatments.

“I believe we can increase survival rates by using cancer treatments that shrink the tumor, and then coming in behind them and taking the brakes off the immune system,” he says. “It’s just a matter of finding the appropriate pairing of therapies.”

Allison’s lifelong quest for new discoveries also continues: He’s currently on the hunt for other molecules that interfere with the body’s natural immune response.

“I’m proud to have turned a scientific finding into something that benefits a lot of people,” he says. “I hope to do it again.”

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