CHECK

James Allison of MD Anderson Cancer Center in Houston has figured out how to defeat cancer at its own game.
How an iconoclastic cancer researcher gamed the immune system and unleashed a potent new weapon against the disease.

By the middle of her senior year at West Virginia University, Sharon Belvin knew something was wrong. The slim, blond 22-year-old was growing increasingly short of breath during her daily runs, but doctors couldn't pinpoint the cause. Then, shortly before graduation, she discovered a hard lump beneath her left collarbone. A biopsy identified it as melanoma — the deadliest form of skin cancer, killing 10,000 Americans annually. Worse, a CT scan showed masses scattered throughout her chest. Belvin faced a crushing prognosis: For Stage IV metastatic melanoma, average survival is measured in months.

Still, she was determined to fight. In May 2004, she returned home to New Jersey, married her high school sweetheart and started chemotherapy at Memorial Sloan Kettering Cancer Center in New York City. The treatment caused debilitating nausea and neuropathy, but the shadows on her scans continued to multiply. That December, Belvin's oncologist informed her that the cancer had spread to her brain.

After surgeons used radiation to burn away the tumor, she was switched to interleukin-2, a naturally occurring protein that, in high doses, sends the body's immune defenses into overdrive. Although IL-2 triggers remission in a small percentage of patients, its side effects are often horrific. Belvin endured violent vomiting, peeling skin and episodes of delirium, but she didn't get better. As the cancer filled her chest cavity with fluid, her hope began to drain away.

That's when the oncologist told her about a clinical trial just getting underway, of a medication called ipilimumab. The drug's mechanism of action was entirely new: Instead of attacking cancer cells (like chemo), or indiscriminately revving up the immune system (like IL-2), ipilimumab blocked a single receptor on one type of immune cell.

"Would you like to try it?" the doctor asked.

"The choice was to do nothing and die, or take a chance," Belvin recalls. "It was the easiest decision I ever had to make."

In September 2005, she received the first of four 90-minute infusions, spread over a 12-week period. The only adverse effect was a daylong spell of shaking and sweating. Soon, she felt well enough to walk her dog again. Her tumors were shrinking dramatically, and they kept doing so for months after her final session.
By September 2006, they'd vanished. After declaring Belvin in remission, the oncologist introduced her to the man behind ipilimumab, immunologist James P. Allison. Belvin burst into tears. Then she hugged him so hard, she nearly knocked off his glasses.

MOON SHOT MAN

That was Allison's first encounter with a patient whose life he'd helped to save, and he still chokes up when he recalls the moment. Over the past decade, he's been the recipient of many such embraces — as well as an array of honors, including the 2015 Lasker-DeBakey Clinical Medical Research Award, often a precursor to a Nobel Prize. The class of medications that he conceived, known as immune checkpoint inhibitors, works counterintuitively. By turning off one of the immune system's built-in safeguards, the inhibitors allow T cells — the system's foot soldiers — to attack tumors more effectively.

"Jim's work has really allowed immunotherapy to become a game changer for patients with cancer," says Elizabeth Jaffee, deputy director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Since approving ipilimumab five years ago, the Food and Drug Administration has OK'd two similar drugs — pembrolizumab and nivolumab — for melanoma and certain lung cancers. Dozens more are in development. At oncology conferences, speakers use the phrase "paradigm shift" when discussing these therapies.

Checkpoint inhibitors already produce unprecedented rates of long-term remission for a handful of hard-to-treat cancers, but their potential is even greater: Because such drugs modify the body's response to cancer, rather than the cancer itself, they could theoretically be effective against almost any kind of malignancy.

Allison's brainchild — and the pioneering research that led to its birth — has brought him a renown that's rare among his peers. "He's one of our rock stars," says Jaffee. Yet at 67, he remains true to his bar-band roots — literally. Allison has played in blues-rock groups since his 20s, and he currently fronts an all-cancer-researcher combo called the Checkpoints. Round-faced and rotund, with long, gray hair and a scruffy beard, he blows harmonica and contributes occasional vocals, belting out classics like "Big Boss Man" in a gravelly baritone.

In his day job, at the University of Texas MD Anderson Cancer Center in Houston, Allison serves as chair of the immunology department, deputy director of the David H. Koch Center for Applied Research of Genitourinary Cancers and executive director of the immunotherapy division of the Moon Shots Program, a multidisciplinary effort tackling cancer mortality. In his cluttered office, a Willie Nelson poster hangs amid the diplomas and trophies — a memento of a long-ago jam with the master. In conversation, Allison can seem shy and distracted until he gets onto a topic that excites him. Then, his eyes sparkle, and the words come at warp speed.

"I just like to have fun with it," he says when asked about his music, and he speaks of his scientific pursuits in almost identical terms. As with any good bluesman, however, Allison's sense of fun is informed by tragic experience. To grasp the passion that drives his work, it helps to glimpse the pain that shaped his youth.

CONFRONTING CANCER AT AN EARLY AGE

Allison grew up in the small oil town of Alice, Texas, the youngest of three brothers. His father was a country doctor, his mother a homemaker. She was seriously ill for several years, but no one mentioned that she had lymphoma until shortly before she died — with Allison, who was 11, holding her hand. "I saw the burns on her neck from radiation treatment," he recalls, "but I didn't know what they were. Back then, people didn't talk about cancer."

Over the next few years, Allison watched an uncle die of melanoma, and another of lung cancer. Meanwhile,
he began showing an obsessive interest in science — as well as a rebellious streak. He got in trouble for talking out of turn and playing hookey. When he learned that his high school biology teacher refused to teach evolution for religious reasons, he boycotted the class. A counselor suggested he take a correspondence course from the University of Texas instead. Studying solo in a room near the gym, Allison stoically bore the taunts of jocks and coaches.

He graduated early, at 16, and enrolled at UT Austin as a premed. Soon, though, he realized that he didn’t want to follow in his father’s footsteps. “I thought how scary it was to be a physician and have someone’s life in your hands,” he says. “In medicine, you have to be right all the time. In science, you learn by being wrong.” He wound up with a bachelor’s degree in microbiology, and he went on to earn a Ph.D. in biological science.

Allison didn’t set out to be a cancer researcher; he dreamed of solving some of the basic mysteries of biochemistry. But in graduate school, when he was assigned to tinker with the formulation of a common chemotherapy for leukemia, his family history prompted him to try an experiment of his own, one that would deeply influence his career direction. Allison wondered what would happen if he injected mice with tumors after they were cured. To his astonishment, the animals didn’t get leukemia again. Somehow, he surmised, their immune systems had learned to kill the tumors.

By 1973, when Allison finished his doctorate, the mechanics of immunity were somewhat better understood than in Coley’s day. For example, researchers had recently identified T lymphocytes, white blood cells that destroy pathogens in several distinctive ways. Each T cell, scientists believed, was programmed to recognize a particular snippet of protein, or peptide, unique to invaders such as bacteria, viruses or tumor cells. These bits of protein are categorized as antigens, substances capable of triggering an immune response. When a T cell detects one, it morphs into a fighting machine, zapping invaders with lethal chemicals, multiplying into an army of identical killers or signaling other immune-system troops to join the attack. Yet exactly how T cells are activated remained largely a matter of conjecture.

Those leukemia-resistant mice spurred Allison to explore the immune system’s uncharted territory. He did a postdoctoral fellowship in molecular immunology at the Scripps Clinic and Research Foundation in La Jolla, Calif. Then, in 1977, he headed back to Texas, as an assistant biochemist at MD Anderson’s new Cancer Center Science Park in Smithville.

One of immunology’s great unknowns was how T cells recognized the antigen that marked an invader for destruction. Researchers presumed that each T cell bore a receptor on its surface, shaped to fit a foreign peptide like a lock fits a key. But no T cell antigen receptor (TCR) had yet been identified.

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The notion of harnessing immune defenses to fight cancer dates back to the 1890s, when a New York surgeon named William Coley learned that some patients with sarcomas went into remission after contracting a Streptococcus infection. It seemed the body’s attack on the microbes wiped out the tumors as well. Coley began inoculating cancer patients with the same strain of strep; a few died of the infection, but others emerged tumor-free. When he switched to dead bacteria, patients’ survival rates improved. Coley’s Toxin, as it became known, was widely used for 40 years. But its results were unpredictable, and the concept of cancer immunotherapy fell out of favor as the field focused on chemotherapy and radiation. Although a few scientists continued to probe the potential of immune-based approaches, their work was mostly ignored.

Allison decided to go hunting. If a TCR was a hidden lock, he reasoned, the logical way to find it was to fashion a key and poke around until something clicked. The kind of key he had in mind had only recently been developed: a monoclonal antibody. Researchers had discovered how to custom-manufacture antibodies — naturally occurring molecules that target specific antigens — through cloning. These designer antibodies could be used, among other things, to detect and manipulate cellular receptors.

Allison began by injecting a mouse with lymphoma tumors to trigger an immune response. He and two colleagues then used spleen cells from the animal to grow 43 cell lines. Next, Allison’s team exposed the cell lines to the mouse tumors. One of the 43 began producing a new protein, which the researchers took to be an antibody to
the tumor antigen. Chemical analysis showed that its structure resembled that of a protein found on T cells.

In 1982, Allison published a paper in The Journal of Immunology suggesting "the possibility" that the look-alike protein on T cells might be a TCR. Soon afterward, other researchers confirmed that it was. Armed with his first big discovery, Allison won a full professorship at the University of California, Berkeley, where he became co-chair of the department of molecular and cell biology and director of the cancer research lab.

KILLING A KILLER

Over the next few years, immunologists learned that it took more than an encounter between a TCR and an antigen to trigger a T cell's killer mode. In the late 1980s, researchers began to suspect that a second signal, from an unidentified player, was required before activation could occur. It was Allison's team that identified a T cell protein called CD28 as the crucial co-stimulator — the gas pedal to the TCR's ignition switch.

But controversy arose in 1991, when a team led by pharmaceutical researcher Peter Linsley identified another protein molecule, CTLA-4, which closely resembled CD28 and was found only on activated T cells. Linsley theorized that CTLA-4 was another co-stimulator. Immunologist Jeff Bluestone, at the University of Chicago, disagreed: His experiments suggested that CTLA-4 subdued T-cell activation. Allison, using different methods, came to a similar conclusion. The molecule seemed to function as a checkpoint, turning off the T cell after a period of activity — perhaps to prevent collateral damage to healthy tissue.

That got Allison thinking about the disease that took his mother. Why didn't the immune system nip every cancer in the bud? Sometimes, he speculated, it was because CTLA-4 deactivated T cells before they could finish off a clump of tumor cells. If that were the case, simply stomping on the gas, with immune stimulators such as Coley's Toxin, or the IL-2 initially used to treat Sharon Belvin, would be of limited use. Inhibiting the checkpoint — releasing the T cell's metaphorical brakes — might be a more productive approach, Allison thought.

In 1995, Allison's team created a monoclonal antibody designed to block the CTLA-4 receptor, effectively shutting down the checkpoint. They injected it into tumor-bearing mice. In the untreated control group, the animals died; in the treated group, 90 percent rejected their tumors and survived. "It was too good to be true," Allison later wrote. "I didn't believe the initial results." He repeated the experiment. For two weeks, the tumors in all the mice continued to grow, and Allison braced himself for disappointment. Then the tumors in most of the treated mice again melted away.

Allison's team went on to test anti-CTLA-4 against a variety of cancers, both alone and in combination with vaccines and chemotherapy. The responses continued to be encouraging — and enduring. Because the checkpoint inhibitor targeted T cells rather than tumor cells, cancers didn't readily respond by mutating and developing resistance, a common problem with chemotherapy. Meanwhile, each mouse retained an immunological memory of the tumor it had vanquished, which curbed recurrence.

After publishing his findings in 1996 in Science, Allison went looking for a pharmaceutical company to develop a CTLA-4 inhibitor for humans. He ran into a wall. Since the demise of Coley's Toxin, several types of immunotherapy had showed promise in animal models, only to fail in people. The few that worked either had narrow applications or marginal success rates.

For two years, Allison got nothing but rejections, but his old stubbornness kept him going. At last, a small New Jersey-based company called Medarex said yes.
Its scientists began working with Allison to develop the new medication. And by 2001, ipilimumab was ready for testing.

**TRIALS AND TRIBULATIONS**

In Allison's office, there's a drawing of him playing harmonica, captioned "The Cancer Immunotherapy Clinical Trial Blues." The trials for ipilimumab involved about 5,000 patients who had received the drug. In 2004, Allison moved from Berkeley to Memorial Sloan Kettering to work with the scientists leading the study — including Sharon Belvin's oncologist, Jedd Wolchok. The following year, Allison underwent a prostatectomy for prostate cancer, and his middle brother died of the disease. The return of the family curse underscored the urgency of his research, and made its deliberate pace harder to bear.

At first, the trials went badly. Few patients made progress by 12 weeks, the point at which chemotherapy is usually assessed. But clinicians eventually found that with ipilimumab, many tumors began shrinking later. In fact, ipilimumab proved to be the first medication to significantly expand median survival rates in patients with advanced melanoma — from six months to 11.

More important, nearly a quarter of patients survived for more than three years. Most of that group was still alive a decade later. And although some patients experienced serious side effects, such as colitis or hepatitis, these could usually be controlled with relative ease.

In 2011, the FDA approved ipilimumab for melanoma, and the phama giant Bristol Myers-Squibb — which had acquired Medarex — began marketing it as Yervoy. (Approval was later expanded to non-small-cell lung cancers.) Soon afterward, Allison returned to MD Anderson, lured by the opportunity to launch the center's $30 million Moon Shots immunotherapy research program. He was also attracted by the prospect of working more closely with the program's scientific director, Padmanee Sharma, an oncologist and researcher with whom he'd collaborated in the past. Sharma had developed a new method for studying how tumors with different characteristics respond to different immunotherapies: She would treat patients before their growths were surgically removed, then analyze the tissue in her lab.

"We did some grants together, and then we started going together," Allison recalls. "At some point, we decided we might as well get married." They tied the knot in 2014.

Sharma emigrated from Guyana as a girl; a driven personality formed during early struggles with poverty and a serious injury, along with her obsessive brilliance, made her an ideal match for Allison. "We both live and breathe science and medicine," she says with a laugh. "Jim gives entire lectures on T cells in his sleep."

Since Allison hatched the idea of blocking CTLA-4, several more immune checkpoints have been identified. "What he showed us is turning the immune system on isn't enough; the crucial step is to make sure it doesn't turn itself off," says Antoni Ribas, director of the tumor immunology program at UCLA's Jonsson Comprehensive Cancer Center. "Now we're trying to understand which brakes need to be taken out and which gas pedals stepped on to achieve the maximum benefits."

Pembrolizumab and nivolumab, for example, the newest inhibitors to win FDA approval, target a checkpoint called PD-1, through which tumors can induce a T cell to deactivate. Studies show that PD-1 inhibitors are effective for a larger proportion of melanoma patients than ipilimumab alone — and, in combination with that drug, they achieve a two-year survival rate of 80 percent. More than 500 clinical trials are underway to explore the impact of these and other checkpoint inhibitors on a dozen varieties of cancer, alone or with other immunotherapies, as well as conventional treatments.

For thousands of patients, Allison's passion and persistence have already paid off. "I owe Jim so much," says Belvin, now a personal trainer, health educator and a mother of two. "As far as I'm concerned, he deserves the world."
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