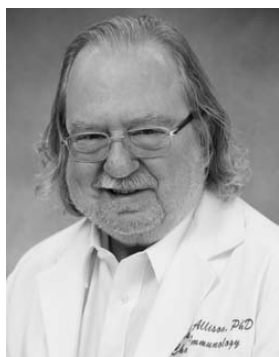


JAMES ALLISON
"Raising the Tail"



CHAPTER ONE

James Allison, Ph.D.

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"I proposed treating cancer by ignoring it." —J. ALLISON

James P. Allison was born in 1948, in Alice, Texas.

"Alice—it's a very small town," intones Allison, in his comfortably worn Texas drawl. "It's got tall boots and mesquite, and cactus, and a lot of cows. Maybe it's hard to find on a map if you don't know ... It's near Palito Blanco and Freer, if that helps."

A nice place to grow up, but Alice is a strange place to take a shine to science. "I was lucky," Allison is quick to acknowledge, "My dad was a country doctor, so through him I got to see medicine and science, and I also had some pretty good schoolteachers that recognized something [in me]."

These early champions got Allison into special academic programs, and he would spend his summers from the eighth grade on in one science program or another at the University of Texas at Austin. The teachings, and the teachers, made their mark on the scientist-to-be.

"There were two teachers, actually," Allison recalls. "One was Ernestine Glossbrenner. She was my eighth grade algebra teacher and she was very supportive." The other teacher provided both positive and negative reinforcement: "Larry O'Rear. He was my physics and chemistry teacher, except he was complicated because he was a Church of Christ lay minister, and he made absolutely sure that no evolution was taught in the school."

This set up an intractable conflict for Allison. "I'd learned about evolution on my own, and since they didn't teach it in biology class I refused to take high school biology." This decision did not sit well with the school board. "It caused quite a rile," says Allison. "But I told them, teaching biology without evolution is like teaching physics without Newton; I don't see how you can

do it. So, they came around." Allison was allowed to take biology by correspondence from UT Austin.

Defender of the Faith

Years later, Allison was called upon again to champion the cause of science education: "So, by this time I'd finished my Ph.D., done a postdoc, and had come back to live in Austin and I get this call." His old eighth grade math teacher, Ernestine Glossbrenner, was now in the Texas legislature and serving on the Education Committee, and she had a problem. "She said there's this crazy guy named Mike Martin who introduced a bill to require teaching of Creation Science in the schools, and you've got to come down and help."

Representative Glossbrenner remembered Allison's run-in with the school board and hoped that he would be willing to stand once again in defense of science. He accepted. Allison would debate Martin in front of a committee of the Texas legislature.

"Martin started in with stuff like, 'If you put a Ford in a field it just rusts, it don't turn into a Cadillac.' That was the level of discourse. So my attitude was, okay, Mr. Martin, you tell me how you can use your creation science to explain how bacteria become resistant to antibiotics. You use your creation science to tell me how a tumor cell escapes the body's immune system. Use your science to explain *anything*. Tell me, give me an example of what you can use your creation science to predict, because science isn't about an incomplete fossil record, it's about predicting things."

As the debate went on Martin tipped his hand to his real concern: There was a secular humanist conspiracy to suppress creationist thought.

Allison bristled, and drove his point home. "I said, no, creation science lost out in the free marketplace of ideas because it's not useful."

He then turned the tables on Martin, pointing out how others in the past have tried to contort science for political or religious reasons. For instance, said Allison, for many years the Soviets emphasized Lamarck over Darwin because Lamarck advocated the inheritance of acquired characteristics, which is more consistent with the socialist/Marxist idea of the perfectibility of man.

"Martin got so flustered by what I said that in his rebuttal time all he could do was keep denying he was a communist. Luckily, I won the debate, and they killed the bill. It was a lot of fun."

Scientist, Know Thyself

From eighth grade on, Allison knew he wanted to be a scientist. "My dad still wanted me to be a doctor, so when I started college I was pre-med," says

Allison. But it didn't last very long. "It quickly dawned on me that the pressures of making decisions, day-to-day decisions that affect people's lives and, you know, you've got to be right. You can't be wrong." A scientist, on the other hand, is expected to be wrong most of the time. That's intrinsic to the journey; most experiments fail. "As a scientist you only have to be right sometimes. I liked that a lot more."

The choice of what sort of scientist to be was not quite so direct, but Allison again let his nature guide him: He likes puzzles; he likes taking things apart. "I was actually trained as a biochemist, not as an immunologist, but I just got interested in immunology." He was fortunate enough to encounter his third mentor. "As an undergrad I took a course taught by a very good, very charismatic professor named Bill Mandy."

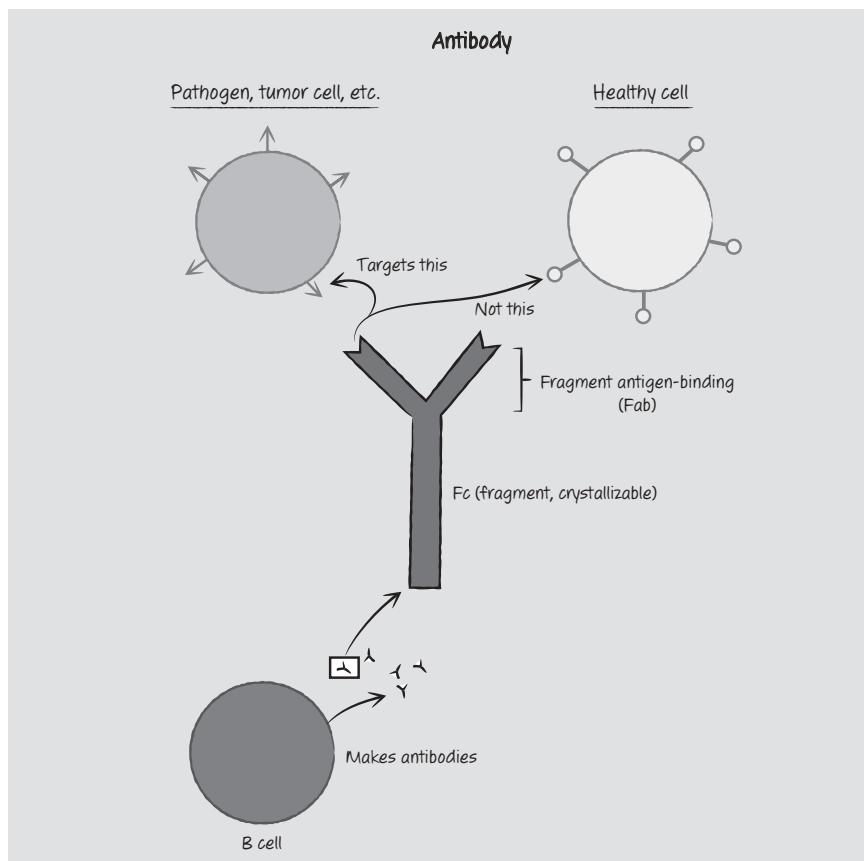
T cells had recently been discovered, but Mandy himself didn't believe they were relevant. "He liked B cells; he was an antibody guy all the way through." (Antibodies come from B cells: see below.) Nevertheless, the entire topic was compelling to Allison. "The idea that you could have these cells going around in your body, traveling through the lymph nodes, communicating with the other cells and tissues in your body and protecting you from most anything that comes along, even things that might not have existed before, and then somehow do that without killing you? I just thought that was a fascinating biological issue."

The Journey to Ipilimumab

After completing his training, Allison began his research in earnest as a faculty member for the University of Texas M.D. Anderson Cancer Center, initially working out the protein structure of the T-cell antigen receptor

Antibodies are large proteins generated by the B cells of the immune system in response to recognizing a given antigen. Antibodies are extremely diverse in the range of what they can recognize. In fact, B cells are able to manufacture antibodies in well over a billion "flavors." Each "flavor," each antibody, is very specific and usually will only recognize and bind to one particular type of antigen—not unlike finding the single archnemesis in a vast and highly varied mob.

An antigen is any distinctive tiny aspect—organic or otherwise (it could even be plastic)—that an antibody can recognize. A prime example of an antigen is pollen. Products said to be "hypoallergenic" contain very few antigens, and as such should be ignored by your immune system.



(TCR; see Mak, Chapter 11). "That's the switch, the ignition switch that turns on T cells," he explains. When a T cell encounters an antigen that matches up with its TCR, the TCR activates. "I was interested in general in how you regulate T cells," those cells being the assassins of the immune system. "How do you turn them on? How do you stop them?"

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Ten years and countless experiments later, Allison came across a second activating pathway, a co-stimulatory signal beyond the coupling between TCR and antigen that is essential for an effective immune response. He thought of it this way: If the TCR–antigen interaction is the ignition, then this second signal was the accelerator, revving the engine, driving the T cell onward to fully engage (and kill) its target.

“It was a big mystery as to what that signal, that molecule was, but it was known to be present on very specialized cells called dendritic cells.” (See Steinman, Chapter 10.) These are the cells that tip off T cells to the presence of a tumor antigen. The tumor doesn’t do this; the dendritic cell does. The co-stimulating moiety Allison was working with is now known as CD28 (cluster of differentiation 28).

“We messed around with that a little bit,” says Allison, “but when we cloned CD28 we encountered another molecule that had already been discovered called CTLA-4” (cytotoxic T-lymphocyte-associated protein number 4—i.e., the fourth one discovered). Little was known about this molecule at the time except for a few tantalizing clues: It was not produced in resting T cells, but only in T cells that had been activated, and CTLA-4 appeared to bind the same ligands as CD28: the ligands known as B7-1 and B7-2 found on dendritic cells. A competing laboratory demonstrated that the CTLA-4 receptor bound the ligand more tightly than did CD28. Given this relationship, that group proposed that CTLA-4 was another co-stimulatory molecule.

Ligands are the mates of receptors—like two good friends—and like friends, when ligand and receptor get together, they do something. Generally, when a ligand (often in the form of a protein) binds its partner receptor (often located on the surface of a cell) this coupling turns some process in the cell on or off.

“[The other laboratory] was working in human cells. We were a little behind, but we cloned the mouse gene and made antibodies to the gene product,” says Allison. Interestingly, this work was being mirrored by Jeff Bluestone at the University of Chicago (Chapter 21). “Both Jeff and I independently came to the conclusion that CTLA-4 was not another gas pedal, if you will, but was actually a negative regulator in opposition to CD28: a brake.”

Further investigation indicated that the other group had misinterpreted a key observation: They had concluded that the antibody they were using was an agonist, based on an observed increase in T-cell activity, “But really what it was is that they were blocking the negative signal.” Thus, instead of stimulating new activity, the antibody was restoring existing activity by blocking an inhibitory effect.

Aha!

“The “aha” moment, at least with respect to cancer, came after I started thinking about how tumors just can’t give that second [i.e., activating] signal.”

Allison reasoned thusly: The immune system has a number of built-in mechanisms to prevent autoimmunity: the attack on healthy cells by the immune system. One such mechanism is cross-priming, the process whereby the cellular debris of a dying cancer cell—DNA and all—induces an inflammatory response that summons cells of the immune system to clean up the debris.

Discrete bits of the cellular debris—the unique tumor antigens—can then be processed by the antigen-presenting cells, like dendritic cells (DCs), and “presented” (i.e., displayed) on their cell surface for recognition and targeting by T cells. T cells that recognize the specific tumor antigen being presented will bind to the dendritic cell where the second signal is then given, stimulating the full-blown immune response.

Note: The activity of DCs is more commonly related to the process of toleration—to avoid autoimmunity—not T-cell activation. Thus, the efforts of many in this book are directed at the more difficult task of ramping up the activation of T cells.

“Once fully activated, the T cell will kill, and continue to kill without further instruction. That's how it works,” says Allison. Yet, this proclivity to kill strongly implies that there is an intrinsic mechanism in T cells that can at some point end the carnage, because an unbridled immune response can kill you.

But what was the mechanism?

“Everybody had been concentrating on this process where you get the T-cell receptor signal, and then a co-stimulatory CD28 signal, and then this whole cascade of cell cycle progression and expression of cytokines: all these positive things,” says Allison. “But what wasn't realized, what even I didn't realize for a little while, was that this all starts a negative program as well by inducing the CTLA-4 gene, and that's what's going to eventually turn the system off.” CTLA-4, it was theorized, serves as a “checkpoint” to limit the immune response.

Evidence supporting this “off switch” checkpoint hypothesis was provided by a rather simple experiment. “We knocked out the CTLA-4 gene in a mouse and found that without it these mice die when they're about three weeks old. They just fill up with T cells because they can't stop an immune response.”

Based on these observations, Allison thought, what if activated T cells could actually detect tumors, but the tumor cells themselves were capable of suppressing an otherwise robust immune response? The next logical step for Allison was to try to remove this inhibition. “I figured, let's just disable the brakes by making an antibody that prevents CTLA-4 from binding its ligands, and then we can just keep the immune system running as long as we want.”

It worked: An aha! moment built of incremental progress, but an aha! nonetheless.

Nearly Lost in Translation

At the aha! time, however, Allison was not working on the problem of eliminating tumors. “I always wanted to do something about cancer. I’ve lost a lot of family members to cancer, and I’ve had prostate cancer myself, but that wasn’t why I was doing these experiments. I was doing these experiments to learn how the T cells work, and only after that did I ask the question, ‘What have we learned that we can use to treat disease?’”

Allison had learned that T cells could be activated fully through precise mechanisms to kill tumor cells until such time as they are instructed not to. Tumor cells on the other hand, via CTLA-4 signaling, had the ability to instruct T cells to stop the attack. Therefore, clinical translation would be simple: It didn’t matter what kind of cancer it was. It didn’t matter what the antigen was. All one needed to do was release the brake by inhibiting the CTLA-4 checkpoint.

It was a provocative idea and it was not well received. “Ever since Nixon declared the ‘War on Cancer’ and the DNA sequencers came along everybody said, ‘We’re going to sequence, we’re going to learn everything about cancer cells, and we’re going to beat cancer by learning what causes it,’” says Alison. This translated to the therapeutic revolution of so-called “targeted therapy” and at the time, the targeted approach was considered to be the way to the Promised Land. “And here I was saying you don’t need to characterize every cancer cell, you don’t need to know what causes cancer. The immune system doesn’t know if it’s a kidney cancer, lung cancer, prostate cancer; the immune system doesn’t know if it’s caused by RAS [a mutated protein] or mutant epidermal growth factor receptor or anything. It just knows it shouldn’t be there.”

“The immune system doesn’t know if it’s a kidney cancer, lung cancer, or prostate cancer . . . It just knows it shouldn’t be there.”

The second radical notion suggested by Allison’s approach was not to treat the tumor directly at all. “I proposed treating cancer by ignoring it,” says Allison, proudly. “I said, instead, treat the immune system. That was the idea: just let the immune system rip.” In other words, remove the inhibitory factors and allow the immune system to finish its job (with the caveat that the immune system knows the cancer is there, an issue addressed in other chapters).

It was a simple idea, with data to back it up, but there was still a lot of convincing to do. Allison spent the better part of two years making the rounds of

pharmaceutical and biotech firms, and the negative feedback was largely the same. First, that this drug was not a small molecule, which would be greatly preferred by drug companies (antibodies are huge and expensive to make), and second, this drug was a form of immunotherapy, an approach that had been disqualified by previous attempts.

Counterarguments were presented. There was a lot of fruitless back and forth, and a near miss: “There was a preexisting patent that Bristol-Myers Squibb had filed,” Allison recalls, “But they got the biology backwards: they said it was a positive [i.e., activating] molecule.” Allison had the mechanism right and developed a sound intellectual property position from that perspective, but it was still an uphill battle to get anyone to take notice. “Finally, this little company called Medarex expressed interest. They had a mouse that had some immunoglobulin genes replaced with human and so they could make totally human antibodies from the start, so I said okay.”

Note: “Humanized” antibodies are produced by genetically engineered mice and can be safely administered to people.

A Phase I trial was performed with humanized CTLA-4 antibodies. Typically, a Phase I study only generates data regarding dosage and toxicity of the treatment, not the treatment's efficacy. “Well, there were three objective responders in that trial, and one of them was a patient on that trial I met during her 10th annual checkup at UCLA after being cured. She's now 14 years out.” Allison smiles as big as a Texas sky.

A Rose by Any Other Name, and the Latest Gig

How do they come up with these drug names? No one knows. “When we first started working on it, it was called MDX [Medarex]-010,” says Allison. Then, for reasons not given, the FDA named it ipilimumab. “It was kind of a letdown. I mean, I was at Berkeley at the time, so I suggested they at least put an ‘H’ in front of it—you know, *Hippi*-limumab—but I guess they didn't think that name had enough gravitas for a cancer drug.”

Although Allison failed to influence the FDA regarding the drug's new name, he had better luck in naming his blues band: It's called, appropriately, The Checkpoints. “Everybody in the band is an immunotherapist,” says Allison. “You know Patrick Hwu (Chapter 15), head of melanoma at M.D. Anderson? He's the keyboard player, and Tom Gajewski, from the University of Chicago (Chapter 24) is the lead guitar player and he really holds the band together.” Other band members include lead singer, Rachel Humphrey (Chief Medical Officer, CytomX Therapeutics), drummer Dirk Spitzer (instructor in the Department of Surgery at Washington University School of

Medicine in St. Louis), and on bass, John Timmerman (Associate Professor of Medicine, David Geffen School of Medicine, Los Angeles). Jim Allison plays the harmonica.

“We play every year at ASCO (American Society of Clinical Oncology), and we play at the Society for Immunotherapy of Cancer meeting too. The last three years we played at the House of Blues in Chicago and sold out the room.”

Not too shabby for an inquisitive boy from a little town called Alice.



The Checkpoints, the Society for Immunotherapy of Cancer's house band, performing on June 4, 2017. Band members (*left to right*) Ferran Prat, M.D., Ph.D.; Jason Luke, M.D.; Tom Gajewski, M.D., Ph.D.; Rachel Humphrey, M.D.; Jim Allison, Ph.D.; John Timmerman, M.D.; Brad Reinfeld; and Patrick Hwu, M.D. Heard but not seen is drummer Dirk Spitzer, Ph.D. (Reproduced, with permission. © Society for Immunotherapy of Cancer.)