

## Introduction

*“It works where nothing worked before.”*

—GORDON FREEMAN, PH.D., DANA-FARBER CANCER INSTITUTE

The way we treat cancer is about to change forever. This revolution—and it is precisely that—was sparked not by the invention of a new drug but by the advent of an entirely new way of thinking about and managing cancer patients. Going forward, doctors will not use pharmaceuticals to attack a tumor, at least not directly. Rather, the oncologist will treat the patient's *immune system* with a drug, thereby enabling it to track down and destroy the cancer.

This new branch of medicine is called immuno-oncology (IO), and to date the results from using this approach to treat cancer are without precedent.

In brief, immuno-oncology is based on the idea that, just like with any bacterial or viral infection, the human immune system is capable of recognizing, attacking, and killing tumor cells. This realization is not exactly new; what is new is that the immune system's potential for ridding the body of cancer is now being deliberately employed.

A bit of history: In the early 1900s a renowned surgeon from New York City named William Coley read about the case of a cancer patient who came down with a near-fatal, postoperative infection. That event was routine enough, but what made the case provocative was that the patient not only survived the infection, but that shortly thereafter all his remaining inoperable tumors disappeared. Coley was particularly struck by this history because he had recently operated on a patient with a very similar cancer—a patient that came through surgery with flying colors without ensuing infection, only to later die of the residual cancer that the surgery failed to remove.

After seeking out and finding a number of cases where tumors spontaneously regressed after the patient experienced a bout of infection, Dr. Coley explored and expanded on these findings and went on to develop a related cancer treatment, a bacterial preparation later dubbed “Coley's Toxins.”

Unfortunately, the Toxins were only marginally effective. No one had any idea how they actually worked—if they worked at all—and after the introduction of radiotherapy, Coley's Toxins eventually fell out of favor.

Fast-forward to the early 1980s, when a researcher—another surgeon, named Steve Rosenberg (Chapter 13)—was heralded for treating cancer with a drug called IL-2, a drug that is natural to the human body and is a critical component of the immune system. Using massive amounts of this substance, Dr. Rosenberg was able to cure a number of patients with a variety of tumor types. Unfortunately, however, the treatment was highly toxic and, like Coley's Toxins, only effective in a limited number of patients. And again, the precise way the drug worked was largely unknown.

For years thereafter, the field of IO languished.

Then came “ipi.”

In 2011, a drug called ipilimumab (“ipi” for short) became the first IO agent approved by the U.S. Federal Drug Administration (FDA), thereby setting off the current IO revolution. In the pivotal clinical trial that led to ipi's approval, patients with advanced melanoma—patients with only months, if not weeks, to live—were surviving for years after being treated. In describing some of these patients, oncologists are now even using the word “cured.”

In 2014, two more IO drugs were approved: nivolumab and pembrolizumab. One of the patients to receive the latter drug—a patient that otherwise would almost certainly have already died of metastatic melanoma without this treatment—is former President Jimmy Carter. As of this writing, Carter is alive, well, and tumor-free.

This is not hyperbole. This is real.

Unlike previous attempts at IO, scientists know exactly what these two drugs are doing and, in general, that knowledge has been put to work discovering other agents and approaches that enhance the patient's immune system.

This is just the beginning. IO is here. Many hundreds of patients have already had their lives extended using this new therapeutic approach. Very soon, that number will be in the tens of thousands.

## *Overview*

*“Behind the scenes they just whispered, ‘Ah, I don't believe it.’”*

—DIMITRI GABRILOVICH, PH.D., PROFESSOR OF TUMOR IMMUNOLOGY, THE  
WISTAR INSTITUTE

The IO revolution almost didn't happen. The foundational idea that the immune system could even see a cancer cell, let alone kill it, was to many an anathema. Prominent researchers—highly intelligent men and women—gave the idea a great deal of thought and concluded quite simply that the

underlying scientific principles were flawed, and that the approach would never work.

Coley's Toxins had failed. IL-2 was too toxic. Cancer vaccines that made perfect scientific sense on paper were relentlessly ineffective in the clinic. There were some very dark opinions about this technology and for some very good reasons. By the mid-1990s, the anti-IO bias was so strong that researchers who were actually making substantive progress in their work could not convince their peers that their data was real.

*“Michel [Sadelain; Chapter 17] pulled me into his wonderfully cramped conference room and showed me the data that was emerging, and I almost fell off my chair. My first reaction was that it was probably not true.”*

—JOSE BASELGA, M.D., PH.D., PHYSICIAN-IN-CHIEF, MEMORIAL SLOAN  
KETTERING CANCER CENTER, NEW YORK

But the data kept coming, and among those that were previously skeptical there were some converts. They remained doubtful, but at least they were listening, and waiting.

They were waiting for the clinical trial results.

When the first of the IO drugs finally emerged from animal testing and made it to the clinic—a drug called tremelimumab—some patients (a very few) began to respond. It wasn't great, but it was something. However, the drug had some serious potential side effects, and as the clinical trials progressed the general lack of efficacy became clear. The company developing this innovative IO agent pulled the plug, and that was that.

Yet at almost the exact same time another company's IO drug, a drug of very similar design to the one that failed, was also in clinical trials. Preliminary results for that drug, ipilimumab, were also iffy, but ipi had three distinct advantages.

1. The person who discovered ipi was a highly persuasive, charismatic man who would not take no for an answer.
2. The clinician to first use ipi in a clinical trial had the rare ability to listen closely to his patients—in particular, to one patient who, despite having test results that showed the drug was failing, *said he felt better*.
3. And finally, ipi had a corporate champion: someone within the pharmaceutical company realized the drug was actually working, but he and his team would have to utterly rethink and rewrite the gold standard criteria used throughout the world to verify statistically that a cancer drug was

actually effective. It was a monumental argument to be made, and they made it.

In short, the IO revolution is the doing of some very special people: a determined bunch, if not actually fanatical, because they had to be—because no one else believed in them.

This book is their story.

Based entirely on interviews with the investigators, this book is the story of the IO pioneers. It is a book about failure and resurrection, redemption and success. It is a book about science—about discovery, intuition, and cunning. It is a peek into the lives and thoughts of some of the most gifted medical scientists on the planet.

What this book is *not* is a science textbook. Nor is it, frankly, a rigorously vetted record of exactly who did what, when, where, and how, crammed full of supporting citations (though there is just a bit of that). Rather, this is a life book. This technology is saving, and will save, hosts of lives. Therefore, this book is a celebration of the living—the living, breathing, thinking, charming, arrogant, funny, obstinate, spiteful, joyous, drinking-too-much, not-drinking-nearly-enough stellar human beings who have dedicated their lives to making cancer immunotherapy happen.

Finally, the book is not just about IO. Along the way of the story's telling there will be issues raised—problems in the scientific community like gender, politics, and funding. There will be anecdotes—nuggets found along the road like “Tales from the Dark Night” (advice on how not to give up when it's all going wrong), or a discussion of art history, or the Six-Day War, or Stalin, or Les Paul guitars, or dolphins or chickens or *Star Trek*.

It is a book about people—a surprisingly small group of people who are, in fact, a very tight, fiercely bright, packed-with-passion family.

They just happen to be scientists.



### *Reading Notes*

- This is not a single narrative. The technologies of cancer immunotherapy are greatly varied, and the stories of their discovery are often as unique as the technologies themselves. Some discoveries may indeed overlap with others in time, space, and personnel, but many others do not. Chapters set off by themselves are just that: stand-alones that tell a single story. As such, these unique contributions can be read in almost any order.
- There is one chapter that does not read like the rest: the story of Ralph Steinman (Chapter 10). This singular exception to the book's overall design is

because, of all the scientists highlighted herein, Dr. Steinman is the only one no longer with us. Although there are many deserving IO innovators that could have been included posthumously, when the idea for the book was first conceived it was decided that the telling of the stories would be left to those who are still here to tell them. That said, Dr. Steinman's contribution to the field is so central to so many of the other technologies described that his exclusion from the book would have been unconscionable.

- There are hand-drawn illustrations facing most of the chapter title pages. Many of the scientists profiled for this book drew these cartoons (that's what scientists call such diagrams: cartoons).

The images are not meant to be particularly instructive or even dutifully detailed, as they were done on the fly—most were executed in front of me in a matter of minutes—and were not intended to further my personal scientific education. They are simply a quick peek of what was in the scientist's mind at the time when the cartoon was requested.

Please look upon them as fan autographs, if you will, gifted to me by my favorite stars.