In 2009, Mario Sznol, MD, Professor of Medicine (Medical Oncology) and Co-Leader of the Cancer Immunology Research Program, walked across the hall to the office of Scott Gettinger, MD, Professor of Medicine (Medical Oncology), and made a suggestion. Dr. Gettinger listened and thought, ‘He’s lost his marbles.’ Dr. Sznol wanted Dr. Gettinger to put a few of his lung cancer patients onto a new clinical trial testing another attempt at immunotherapy.

Then, as now, lung cancer killed more people in the United States than any other type of cancer, and it killed them fast. Dr. Gettinger had devoted himself to lung cancer patients and was always looking for better ways to treat them. Nothing really worked, including previous forms of immunotherapy, so he was deeply skeptical of Dr. Sznol’s suggestion. On the other hand, when your patients are likely to die within six months without some kind of miracle, why not take a shot at a miracle? Dr. Gettinger agreed to put a few patients on the trial.

Dr. Sznol, on the other hand, had believed in the potential of immunotherapy for more than two decades, ever since his fellowship at Mount Sinai in New York, where he saw some of the first patients successfully treated for melanoma and kidney cancer with a new immunotherapy called interleukin-2 (IL-2). From Mount Sinai he went to the NCI, where he studied new immunotherapy agents.

“The studies done early on at the NCI provided proof of concept for immunotherapy,” he said, “even though IL-2 only worked with melanoma and kidney cancer. But there was the promise that if we could figure out why, we could translate that into other diseases.”

Dr. Sznol had been following the work of an immunobiologist at the Mayo Clinic named Lieping Chen, MD, PhD, now the United Technologies Corporation Professor in Cancer Research and Professor of Immunobiology, Dermatology, and Medical Oncology at Yale. Dr. Chen had shown that several types of cancer expressed molecules, later called PD-1 and...
Bob’s Story

In 2006, life was good for Bob Amendola, his wife, and their two young children. “We had a normal life, career was going well, everything was as planned,” he said. “Then I fell sick in 2006. I had metastatic lung cancer. It had spread to his lymph nodes, esophagus, and brain. I oncologist gave me about six months to reduce your cancer and recommended palliative care.”

Mr. Amendola had other ideas. He looked into the eyes of his oncologist and said, “I’m not going anywhere. You will not see me to go out together.” His story spread after several years of palliative care, which included chemotherapy, in addition to radiation and surgery. After he was exhausted and nauseated, he was still able, eventually the treatments were not effective. Amendola reached out to his oncologist and asked for help. However, his oncologist sent him to Dr. Scott Gettinger.

In early 2012, Mr. Amendola joined Dr. Gettinger’s trial of a new immunotherapy drug in metastatic lung cancer. Mr. Amendola enrolled in Dr. Gettinger’s “we’re going to go out together” doc. At that time, there was no drug to treat lung cancer. When he started the trial, he noticed the staff was very kind and seemed to be looking after him. Mr. Amendola was encouraged by Dr. Gettinger to keep going. On a Friday afternoon, he had a follow-up CT scan where his tumor size was looking better. The week after his blockage was reduced by a bit and his treatment went on with a PAH, medicine. Mr. Amendola was going down the right path. He believed his oncologist, but his tumor was shrinking at a good pace. “As you can imagine,” Mr. Amendola said, “my family and I were jumping for joy.”

Within a few months, Mr. Amendola’s scans showed no signs of cancer. “Because of immunotherapy,” he said, “I am cancer free today and get to do the things I love to do and I have a normal life.” Eight years later, his semi-annual scan remains clean.

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PD-L1, that destroyed T cells and thus boosted tumor growth. Dr. Smith’s enrollment grew in 2002 after Dr. Chen published data showing that when PD-1 and PD-L1 were blocked, the immune system became active and attacked cancer. In 2009, now at Yale, Dr. Smith noticed that the first small trial of Dr. Chen’s new anti-PD-1 compound, called nivolumab, had shown encouraging results in several cancers, including melanoma. By 2010, he began planning a trial at Yale for patients with melanoma. A lung cancer patient also had responded well, and so Dr. Smith tapped into Dr. Gettinger’s interests.

The following years would be packed with revolutionary developments in immunotherapy, the decade’s biggest story in cancer treatment. Yale scientists have played leading roles in that story. In December 2009, Dr. Chen’s clinical trial treated the first patient in the world to receive a combination of nivolumab and ipilimumab, a CTLA-4 antibody. The results were amazing. About 70 percent of the patients benefited. In more than half of them, the tumors shrunk by 40 percent.

Meanwhile, Dr. Gettinger had put a few patients into a small trial using nivolumab against non-small cell lung cancer. He was pessimistic. Everybody in the trial had already failed on multiple therapies and had a prognosis of three to six months. The following years would be packed with revolutionary developments in immunotherapy, the decade’s biggest story in cancer treatment. Yale scientists have played leading roles in that story. In December 2009, Dr. Chen’s clinical trial treated the first patient in the world to receive a combination of nivolumab and ipilimumab, a CTLA-4 antibody. The results were amazing. About 70 percent of the patients benefited. In more than half of them, the tumors shrunk by 40 percent.

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Meanwhile, Dr. Gettinger had put a few patients into a small trial using nivolumab against non-small cell lung cancer. He was pessimistic. Everybody in the trial had already failed on multiple therapies and had a prognosis of three to six months. The first thing he noticed was that patients tolerated the drug well, without side effects. That encouraged him to enroll more patients in 2010. He could hardly believe what he was seeing. Not all patients responded, but some responded dramatically. Tumors shrank and in a few cases, disappeared. “It was like magic,” he explained. The hope for patients with metastatic lung cancer had been close to zero. Among the 125 patients around the world who participated in that early trial, the rate was 16 percent. “That was just incredible,” said Dr. Gettinger. “Since those early trials, the way we treat lung cancer has changed dramatically. Immunotherapy has become the standard for patients with advanced lung cancer, with most patients receiving this as their first-line therapy. No one could have predicted that 10 years ago.”

For Dr. Chen’s melanoma patients who took nivolumab with ipilimumab, the five-year survival rate was even more remarkable, jumping from between five and 10 percent to nearly 50 percent. For patients with advanced melanoma, this combination is now standard treatment.

In fact, immunotherapies have become standard for more than 20 cancers, either in combination with other therapies or as first-line treatment. The field is dominated by six FDA-approved drugs based on Dr. Chen’s original discovery about the PD-1/PD-L1 pathway. Thanks to Drs. Chen, Sznol, and Gettinger, and many other Yale scientists, Sznol has consistently been among the first to offer clinical trials in these breakthrough drugs.
In turn, Yale’s leadership in immunotherapy has attracted more top scientists, including Roy S. Herbst, MD, PhD, Ensign Professor of Medicine, Chief of Medical Oncology at Yale Cancer Center and Smilow Cancer Hospital, and Associate Cancer Center Director for Translational Research. Dr. Herbst arrived in 2011 as a prominent researcher in lung cancer and soon opened the very first trial of another PD-L1 inhibitor, atezolizumab, which has since been approved for use against certain lung, breast, and urothelial cancers. In addition, tissue samples taken from that trial enabled the definition of patterns of immune response and resistance that were later published in the journal Nature.

“Around the same time,” said Dr. Herbst, “we also did the first phase 1 trials of pembrolizumab,” another PD-1/PD-L1 inhibitor now in wide use. “We really were among the first places to do early phase trials in immunotherapy,” said Dr. Herbst. “Not only are we doing the trials,” he noted, “we’re doing the science.” For decades Yale has been distinguished for its basic research in immunobiology. That reputation has grown as Yale’s lab scientists and clinicians have forged strong collaborations in pursuit of translational medicine. “It’s an exciting time at Yale,” said Dr. Gettinger, “with a contagious enthusiasm among basic scientists and clinical investigators to collaborate on efforts to understand sensitivity and resistance to current immunotherapies, and develop the next generation of immunotherapies.”

They all mention that despite the tremendous progress, big challenges remain. Only 15 to 20 percent of patients respond to checkpoint inhibitors. Additionally, some patients have innate resistance to current immunotherapies, while others develop resistance over the course of treatment. Some of these shortcomings will be filled by promising new immunotherapy approaches such as adoptive T cell therapy. Dr. Chen hopes that his new inhibitor, Siglec-15, now in early trials, will target another 20 to 30 percent of cancer patients.

Dr. Herbst thinks science has barely touched immunotherapy’s potential. He envisions a time when every patient will receive a personalized version. “We helped start these therapies and now everyone’s doing it,” he said, “so it’s up to us to figure out what’s next. Through our Lung Cancer SPORE, we recently brought siglec 15 to the clinic, and there will be many more novel therapies. I know Yale scientists in all disciplines and all tumor types will continue to be among the leaders.”

“I’m so lucky I happened to be in the right place at the right time. When you receive that diagnosis, your whole world turns upside down. Dr. Gettinger and Smilow and Dr. Chen turned my world right side up again. They extended my life.”

Maureen O’Grady

In January 2009, at 55, Maureen O’Grady received devastating news. Though a smoker for 16 years, she had given up cigarettes 25 years earlier. But now, an oncologist was telling Maureen that she had metastatic lung cancer with a prognosis of 12 to 18 months to live. He offered to hope. Ms. O’Grady asked a friend whose sister worked at Yale to get her name of the best lung cancer doctor at Smilow. The name that came back was Dr. Scott Gettinger.

Ms. O’Grady saw him in February. “He was invested in me from day one,” she said. “That’s the kind of people they are there. The diagnosis didn’t change, but he gave me a little bit of hope.” Still, her cancer had spread to her liver, adrenal glands, and heart. Those months of chemotherapy didn’t slow it in mid-2010, with few options left, she joined Dr. Gettinger’s clinical trial for a new immunotherapy drug called nivolumab.

Just eight weeks later, all of her tumors were substantially smaller, and they continued shrinking until they finally disappeared from her scans. The study ended after two years. Ms. O’Grady hasn’t taken nivolumab since, nor have the tumors returned in the nearly 10 years since she began her treatment. She has been able to celebrate her wedding anniversaries, the marriages of her two daughters, and the births of four grandchildren.

“Life is in Milford, 10 minutes away from Smilow,” she said, “I’m so lucky I happened to be in the right place at the right time. When you receive that diagnosis, your whole world turns upside down. Dr. Gettinger and Smilow and Dr. Chen turned my world right side up again. They extended my life.”

Maureen O’Grady

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Maureen’s Story