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Immunotherapy: It Takes a Village

Drew Pardoll

Abeloff Professorship in Oncology, Cancer Immunology and Hematopoiesis Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, School of Medicine, Baltimore, MD 21287, USA. dpardol1@jhmi.edu

Abstract

We in the cancer immunology and immunotherapy community are thrilled that *Science* named “Cancer immunotherapy” as 2013’s Breakthrough of the Year (J. Couzin-Frankel, 20 December 2013, p. 1432). The rapid succession of clinical successes by blocking antibodies to two immune checkpoints, CTLA-4 and PD-1, and by chimeric antigen-receptor-transduced T cells, shows the power of basic immunology when translated to therapy. As such, I write to acknowledge some of the key scientists whose basic discoveries paved the way for the clinical successes outlined in the Breakthrough issue.

CTLA-4 was originally cloned by Pierre Goldstein (1). Peter Linsley later demonstrated that its ligands were B7.1 and B7.2, in fact the same as for the T cell costimulatory receptor CD28 (2, 3). On the basis of in vitro studies, Jeffrey Bluestone first suggested that, in contrast to CD28, CTLA-4 was an inhibitory receptor (4). A year later, concurrent with similar in vitro findings from Jim Allison (5), Arlene Sharpe and Tak Mak independently proved CTLA-4’s inhibitory function in genetic knockout mice (6, 7). These discoveries paved the way for Allison’s seminal work demonstrating in murine tumor models that CTLA-4 blockade induced antitumor responses, supporting its subsequent clinical development.

An independent sequence of discoveries paved the way for the clinical development of PD-1/PD-L1 pathway blockers. Almost 10 years after the cloning of PD-1 by Tasuku Honjo (8), Gordon Freeman demonstrated that its major ligand was another B7 family member (9) that had been identified a year earlier by Lieping Chen (10). This ligand-receptor pair was also an immune “checkpoint” but biologically very different from CTLA-4. Chen went on to show that many human tumors up-regulate PD-L1 (11), commonly as an adaptive response to γ -interferon produced by antitumor T cells (12). He also showed that expression of PD-L1 in cancer cells conferred immune resistance that could be abrogated by antibodies that blocked the PD-L1/PD-1 interaction, leading to tumor regression in mouse models (11).

The origin of chimeric antigen receptors dates back to work by Zelig Eshhar (13), who first demonstrated that transduction of T cells with chimeric genes encoding single-chain antibodies linked to a transmembrane region and an intracellular domain. The intracellular domain, encoding the signaling adaptor for the T cell receptor, was discovered by Larry Samelson and Richard Klausner (14). It could redirect T cell killing to cells expressing the antibody’s cognate antigen.

Eventually, millions of cancer patients will benefit from these immunotherapies and will hopefully be reminded by their physicians that they are the fruits of decades of basic immunology research, which must continue to be supported.

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Women in Engineering

M. Klawe's Book Review about *Girls Coming to Tech!* by Amy Sue Bix (14 March, p. 1201) recounts the challenges faced by women who pursued engineering before the 1970s. The topic elicited personal accounts, including one by the woman shown in the Review's photo. See the comments below and at www.sciencemag.org/content/343/6176/1201.full.

I was delighted to see myself pictured in your article, at 17 and with a slide rule. My years at MIT were full of memorable ups and downs. Though our numbers were small, there were more women who loved math and science than I had ever known before. I met many of my closest friends and colleagues during those years. I am now in my 43rd year as a professor at Northeastern University, where I was one of the founders of the College of Computer and Information Science.

—Harriet Fell

While reading the text, some memories came to me. In 1990, during an interview for work experience, a director of an international company told me “your CV is very good technically speaking, but you have a problem: You are a woman.” However, today I am very happy with my engineering work.

—Vania Salvini