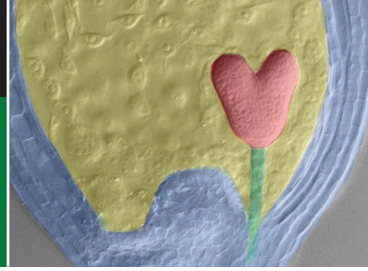

LETTERS

edited by Jennifer Sills

Immunotherapy: It Takes a Village

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 upregulate 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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theBUZZ

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

CREDIT: AAAS

A New Threat to European Vultures

A DECADE AGO, DICLOFENAC WAS FOUND TO be responsible for the collapse of the Indian vulture populations (*1*). Banning its use and that of related anti-inflammatory nonsteroidal drugs allowed the beginning of a population recovery (*2*). However, Europe may now face a similar threat, as the Spanish government in 2013 licensed the use of both dolofenac and diclovet, veterinary drugs that contain 50 mg/ml of diclofenac, mainly for pig and cattle farming.

Since 2000, the bovine spongiform encephalopathy (BSE) crisis has put European vultures at risk. With the recent implementation of the European Regulations (*3*) and the Royal Decree 1632/2011 (*4*), which provide Spain with a legal framework for increasing food availability for carrion-eating birds, it appeared that the vultures were finally getting a reprieve. Until the regulations were approved, carcasses had to be taken to vulture feeding sites or destroyed. Now animals that die in grazing fields can be left for vultures as well, after being checked for disease. Although we are optimistic about the effects of these regulations, the benefits would be limited by the use of diclofenac.

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4. Royal Decree 1632/2011 of 14 November, regulating the feeding of certain wildlife species with animal by-products not intended for human consumption (www.boe.es/aeboe/consultas/bases_datos/doc.php?id=BOE-A-2011-18536)[in Spanish].

India Puts Informed Consent on Camera

IN ITS LATEST INITIATIVE TO STRENGTHEN THE regulation of clinical trials, the Indian government is now requiring clinical trial investigators to document the informed consent process through audiovisual recording (*1*). The government took this step in response to a Supreme Court order requiring clinical trials in India to incorporate audiovisual as well as written informed consent as a prerequisite to enrollment of potential study participants. The Central Drugs Standard Control Organization has issued a draft guideline describing these procedures (*2*).

The informed consent process in developing countries is largely focused on complex written documentation consisting primarily of the literal translation of consent forms designed for other countries (*3*). Rather than truly informing the trial participants, the primary purpose seems to be providing legal protection to the investigators. Audiovisual documentation of oral consent has been shown to be a valid instrument for populations with limited understanding of trial

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elements (*4*). For those who are illiterate or otherwise unfamiliar with the process, it is difficult to establish voluntary participation based on standard written consent procedures (*4*). Audiovisual recording can also serve as an oversight mechanism for the ethics committees and drug regulators.

In response to the new requirements, concerns have been raised about the lack of clarity regarding operational issues, scope of guidance, maintenance of confidentiality, escalated trial costs, and sociocultural barriers to effective implementation in India (*5*). Although these initial concerns seem to be valid, further clarification is expected to address the uncertainties facing the clinical researchers and sponsors.

The present legislation is intended to improve the quality, reliability, and transparency of informed consent process; enhance investigator accountability; and restore public trust in clinical trials. However, as is true for any alternative strategy, audiovisual recording of trial consent needs to be examined and monitored, and its effectiveness in addressing one of the fundamental requirements of ethical research needs to be assessed.

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CORRECTIONS AND CLARIFICATIONS

This Week in Science: "Immune variation" (7 March, p. 1055). M. N. Lee *et al*. analyzed expression of genes from 534 healthy subjects, rather than 30. The HTML and PDF versions online have been corrected.

News of the Week: "Threat of H10N8 surfaces" (7 February, p. 583). The H10N8 flu virus has been identified in China, but not in Taiwan.

Reports: "Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice" by S. Giovanoli *et al*. (1 March 2013, p. 1095). Joram Feldon was awarded grants from the Swiss National Science Foundation (SNSF) and ETH Zurich, as well as a National Alliance for Research on Schizophrenia and Depression Distinguished Investigator grant. The HTML and PDF versions online have been corrected.

Reports: "Writing about testing worries boosts exam performance in the classroom" by G. Ramirez and S. L. Beilock (14 January 2011, p. 211). The authors discovered minor mistakes in the formula used to calculate response time and in the formula used to calculate high demand problem accuracy and response time for a single subject in the unrelated writing condition. Correcting these mistakes did not in any way change the significance or interpretation of the results; however, the relevant statistics in the main text and the supplementary materials and the relevant supplementary tables have been corrected.

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the past 3 months or matters of general interest. Letters are not acknowledged upon receipt. Whether published in full or in part, Letters are subject to editing for clarity and space. Letters submitted, published, or posted elsewhere, in print or online, will be disqualified. To submit a Letter, go to www.submit2science.org.