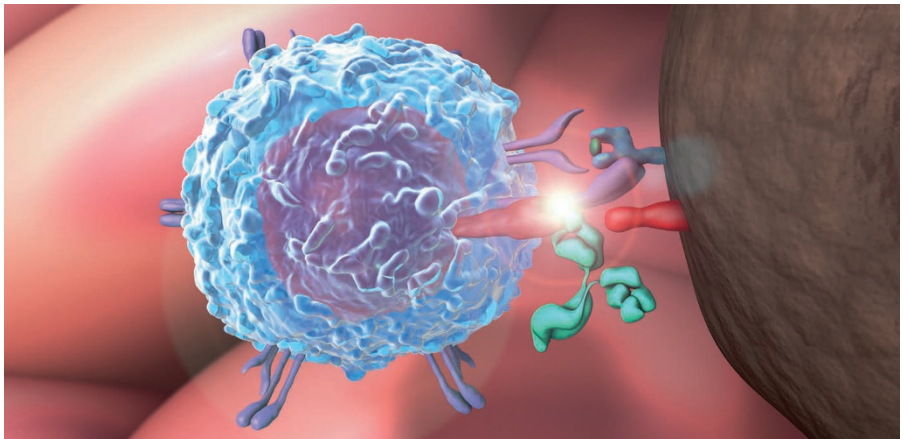

The blockade of immunological checkpoints can activate immune cells to kill tumor cells and is showing promising results in the clinic. Here, a therapeutic antibody is targeting the inhibitory PD-1–PD-L1 axis to promote a cytotoxic T cell response to a tumor. Image credit: Nucleus Medical Media/Nature Publishing Group.

MILESTONE 14

War-winning weapons

Monoclonal antibody technology (MILESTONE 9) has provided high-precision weapons with which to fight cancer with minimal collateral damage. The timeline of cancer immunotherapy reflects the search for the right targets that these weapons must hit to end this war with a victory.

Signaling pathways deregulated in cancer cells have been a target long pursued, initially by pharmacological means and then with monoclonal antibodies. Pioneering work by Michael Shepard, Dennis Slamon and colleagues in the 1990s resulted in the monoclonal antibody trastuzumab (Herceptin), which blocks Her2, a growth-factor receptor amplified in approximately 15–30% of breast cancers. In a fraction of Her2-positive patients, trastuzumab reduces the risk of relapse, extends survival and potentiates the efficacy of chemo- and immunotherapies, although resistance eventually develops.

In addition to modulating receptor-ligand interactions, antibodies can induce target-cell lysis by antibody-dependent cell-mediated cytotoxicity. This strategy has been used in the treatment of blood cancers with the antibody CAMPATH-1H, which targets the mature lymphocyte antigen CD52 (MILESTONE 11). Another landmark addition to the arsenal, developed by Lee Nadler, Nabil Hanna, Antonio Grillo-López and colleagues, was the antibody rituximab, directed against the B cell–lineage marker CD20. Since the approval of rituximab in 1997 by the US Food and Drug Administration, death rates from non-Hodgkin lymphomas have undergone a remarkable decrease. This approach, which eliminates both cancer cells and normal cells that express CD20, is well tolerated in B cell malignancies. However, it is difficult to apply to solid tumors, which arise mainly from essential cell types. Rather than being the cancer cells themselves, the Achilles' heel of solid tumors has turned out to be their supply lines. Targeting angiogenesis has proven effective across multiple tumor types. In 1993, Napoleone Ferrara and colleagues showed that antibody to the vascular growth factor VEGF can inhibit tumor growth in mice, which paved the way to its humanized (MILESTONE 12) version bevacizumab (Avastin). Avastin was approved by the US Food and Drug Administration in 2004 for the treatment of metastatic colorectal cancer and is currently used in combination treatments for cancer.

Although tumor-specific T cells have been known since the late 1970s, realization of their therapeutic potential came only two decades later, with the understanding that the magnitude and duration of T cell responses are regulated by activatory (so-called 'co-stimulatory') and inhibitory ('checkpoint') signals conveyed by receptors of the CD28 family. These receptors, their ligands and the T cell subsets that express them became the targets that have made monoclonal antibodies therapy a ground-breaking success.

The triggering of CD28 by B7 ligands is the second, essential signal required for T cell activation, along with the antigen-recognition signal delivered through the T cell antigen receptor. In 1994–1995, the CD28-related receptor CTLA-4 emerged as a negative regulator of T cell activation. In 1996, a seminal paper by James Allison's group then showed that antibody to CTLA-4 enables mice to reject solid tumor grafts. As turned out later, in addition to blocking CTLA-4 signaling, the antibody ipilimumab (directed against CTLA-4) deletes CTLA-4-positive immunosuppressive T cells by antibody-dependent cell-mediated cytotoxicity. Ipilimumab has afforded unprecedented life extension to some patients with melanoma; this has redefined clinical success as overall survival rather than progression-free survival and has heralded a new era in cancer therapy.

Another checkpoint receptor, PD-1, was cloned and characterized by Tasuku Honjo's team in 1992. Later, the Lieping Chen laboratory demonstrated that its ligand, PD-L1, is upregulated in tumors and disables or kills tumor-specific lymphocytes. Whereas CTLA-4 inhibits the activation of naive T cells, PD-1 elicits negative feedback in effector T cells. Although blockade of CTLA-4 allows the activation of T cells in lymph nodes, PD-1–PD-L1 signals then disarm T cells once they migrate into the tumor, which probably contributes to the failure of CTLA-4 monotherapy in many patients. Combined blockade of CTLA-4 plus PD-1 (or PD-L1) greatly increases the efficacy of such therapy and is now the standard for melanoma immunotherapy.

Immunology research has identified targets, and biotechnology has provided the weapons with which to hit them with minimal collateral damage; this has tipped the balance toward winning the war on cancer for an increasing number of patients. This interdisciplinary alliance continues to advance cancer therapies by targeting other immunosuppressive molecules and combining blockade of immunological checkpoints with chemotherapies, vaccines and engineered T cell approaches. It will definitely score more victories in the near future.

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ORIGINAL RESEARCH PAPERS Brunet, J. F. *et al.* A new member of the immunoglobulin superfamily—CTLA-4. *Nature* **328**, 267–270 (1987) | Walunas, T.L. *et al.* CTLA-4 can function as a negative regulator of T cell activation. *Immunity* **1**, 405 (1994) | Leach, D. R. *et al.* Enhancement of antitumor immunity by CTLA-4 blockade. *Science* **271**, 1734–1736 (1996) | Ishida, Y. *et al.* Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J.* **11**, 3887–3895 (1992) | Dong, H. *et al.* B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. *Nat. Med.* **5**, 1365–1369 (1999) | Dong, H. *et al.* Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion. *Nat. Med.* **8**, 793–800 (2002) | Hodi, F. S. *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* **363**, 711–723 (2010) | Maloney, D. J. *et al.* IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma, *Blood* **90**, 2188–2195 (1997)