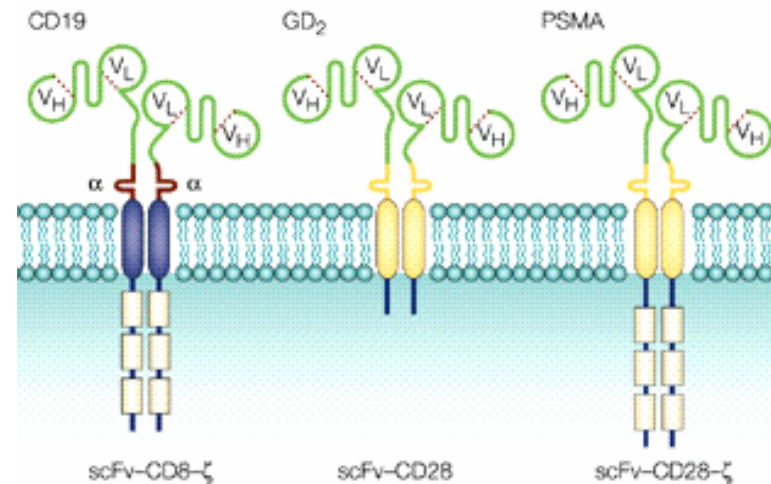


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Co-stimulation of tumour-reactive T cells *in vivo*. **a** | Tumour-reactive T cells receive signals in response to presentation of tumour antigens by professional antigen-presenting cells (APCs) — that is, dendritic cells, B cells and macrophages. These APCs present both major histocompatibility complex (MHC)-peptide complexes and B7 to T cells (cross-priming). When engaging tumour cells, the T cells engage their T-cell antigen receptor (TCR), but not CD28. In normal cells, CD28 binds to B7 to provide the co-stimulatory signal. The lack of co-stimulatory signaling by cancer cells prevents a T-cell anti-tumour response in cancer patients. **b** | Transduction of tumour cells with the co-stimulatory ligand B7 enables tumour cells that also express the appropriate MHC-peptide complex to act as APCs, and to activate T cells through the TCR. Although this approach is useful in promoting *in vitro* T-cell expansion, this strategy is hampered by the difficulty to transduce tumour cells *in vivo*. **c** | Bystander co-stimulation can be provided in *trans*. In this case, the tumour cell presents the MHC-peptide complex to the TCR, while another cell presents the co-stimulatory signal (B7) to CD28 on the T cell. The effectiveness of this co-stimulatory approach remains to be established. Various cell types could serve, in principle, as bystander co-stimulatory cells. **d** | Antigen-dependent co-stimulation is provided by engagement of a tumour antigen-specific co-stimulatory receptor. One signal is provided by the tumour antigen, in the context of MHC, through the endogenous TCR, and the second co-stimulatory signal is provided by the chimeric receptor (scFv-CD28), which recognizes another tumour antigen but signals through the CD28 cytosolic domain. This approach requires T-cell transduction and MHC-peptide-complex presentation by the tumour cell. **e** | MHC-independent, tumour-antigen-dependent, monoreceptor-mediated T-cell activation and co-stimulation. Both the antigen signal and the co-stimulatory signal are provided by a single chimeric receptor. In this case, the scFv portion of the receptor interacts with the tumour antigen, and signals through the CD28 ζ cytosolic domain. Recent studies have shown that such receptors can induce both cytolysis and T-cell proliferation in primary T cells. This approach requires T-cell transduction and is applicable to MHC-negative tumour cells, unlike **a–d**. (Nature Reviews, 2003, 3, pp 35-45)



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Figure 2. Examples of chimeric antigen receptors. Chimeric antigen receptors (CARs) engage cell-surface molecules by means of Ig–Ag (immunoglobulin–antigen) interactions and transmit activation signals via their cytoplasmic domain. CARs enable non-HLA-restricted antigen recognition by T cells. The nature of the activation signal depends on the composition of the transmembrane and cytoplasmic regions within the CAR. Primarily investigated in T cells, CARs might also function in natural-killer (NK) cells, B cells or granulocytes, depending on their signaling domain. Many CARs interact with antigen through scFvs — the antigen-binding regions of Ig that consist of rearranged heavy (V_H) and light (V_L) chains linked by a short peptide linker. The CD8/ ζ fusion receptor engages HLA class I molecules. The CARs that are shown in the figure specifically bind antigen CD19, the GD_2 ganglioside and prostate-specific membrane antigen (PSMA). They incorporate various portions of the B-cell antigen receptor (light green), T-cell-receptor–CD3 complex (ivory), CD8 α (brown), FcR γ (blue ITAM domains) and CD28 (yellow) cytoplasmic activation domains (blue ovals). The P28 ζ receptor (far right) which recognizes PSMA, includes signaling domains from both CD28 and CD3 ζ . (Nature Reviews, 2003, 3, pp 35-45)

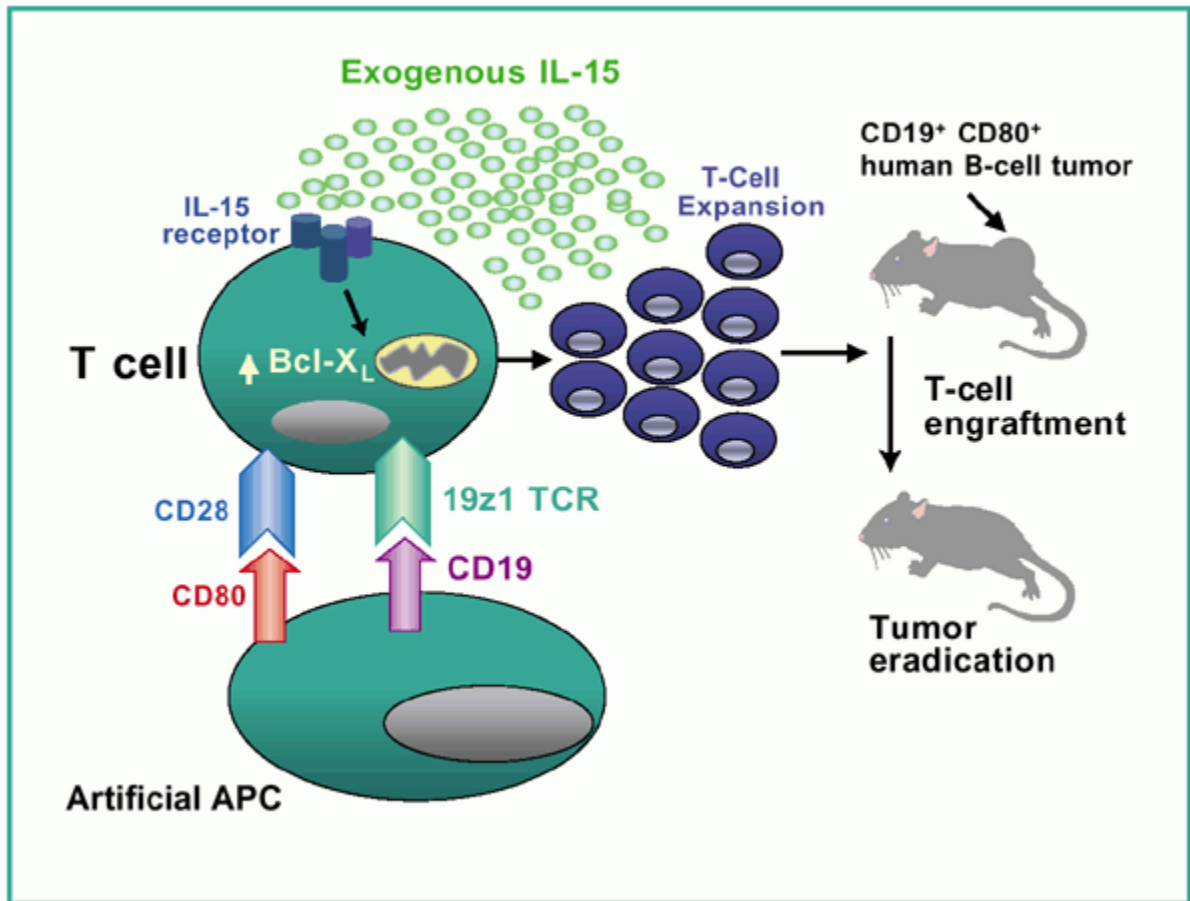


Figure 3: The tumor-killing T cell.

To destroy B-cell tumors, Dr. Sadelain’s group first transduced human peripheral blood T cells with an artificial T-cell receptor (19z1) specific for CD19, an antigen present on B-cell tumors. They expanded T cells in IL-15 in the presence of artificial APCs expressing CD19 and the co-stimulatory molecule CD80 (B7.1). IL-15 upregulates expression of the mitochondrial anti-apoptotic protein Bcl-X_L, promoting T-cell survival. CD80 signals through the T-cell receptor CD28 to provide the vital second signal for T-cell activation. Both IL-15 and CD80 are essential for the resultant 1,000-fold T-cell expansion. Adoptive transfer of CD8⁺ 19z1⁺ T cells results in eradication of the CD80⁺ CD19⁺ human B-cell tumor burden in SCID-beige mice. In contrast, replacement of IL-15 with exogenous IL-2 results in modest T-cell expansion without Bcl-X_L induction, followed by cell death. Furthermore, IL-2-expanded T cells cannot eradicate tumors *in vivo*. (Nature Medicine 9,257-258 (2003))