Rational combination of cancer therapies with PD1 axis blockade

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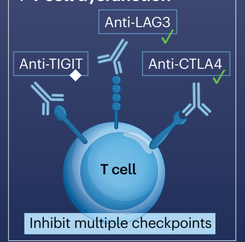
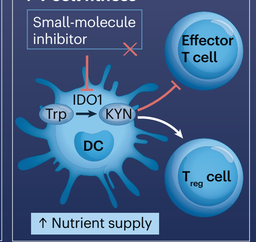
Technological advances have increased our mechanistic understanding of cancer–immune interactions and enabled the discovery of treatments that promote anti-tumour immunity, with ICB of the PD1–PDL1 interaction being a prime example. However, for most advanced cancers, the benefit of single-agent therapy is limited by mechanisms within the TME that curtail effective immune responses. Therefore, many clinical trials are ongoing to combine PD1 axis blockade with other therapies, most often conventional chemotherapy or radiotherapy. Here, we highlight combinations with new therapeutic targets and modalities. Importantly, the number of potential combinations is far greater than the number of patients available for clinical trials, resulting in missed possibilities, clinical failure, unnecessary side effects, inadequate patient recruitment and financial setbacks. It is crucial that therapies are combined in a more rational manner, translating fundamental biological insights and mechanistic understanding.

Reinvigorating effector T cell responses

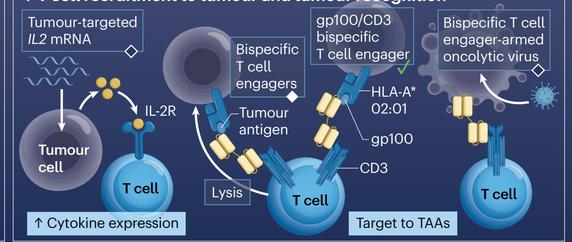
↓ T cell dysfunction



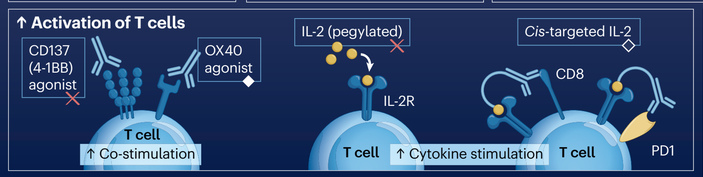
↑ T cell fitness



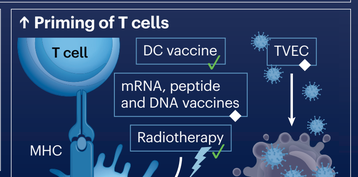
↑ T cell recruitment to tumour and tumour recognition



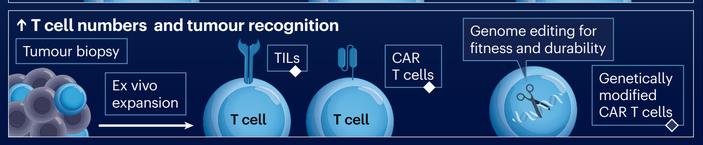
↑ Activation of T cells



↑ Priming of T cells

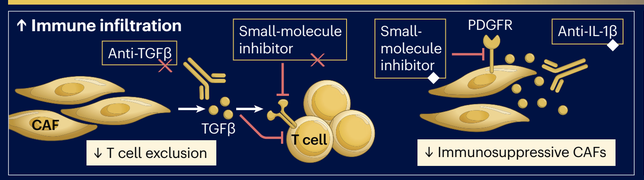


↑ T cell numbers and tumour recognition

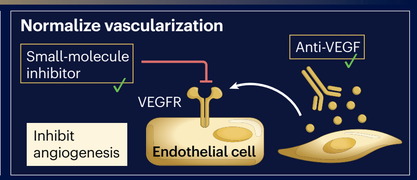


Manipulating the tumour microenvironment and stroma

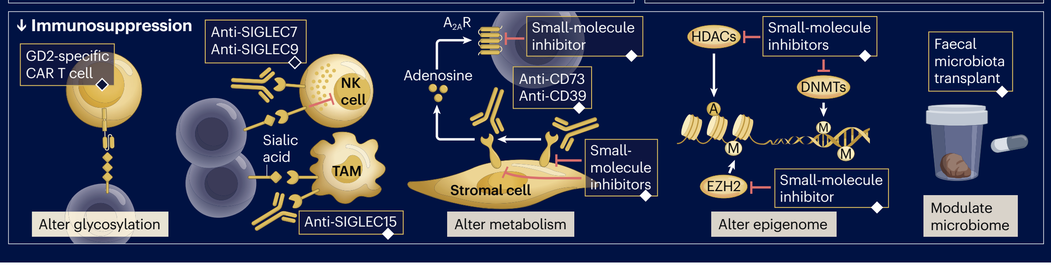
↑ Immune infiltration

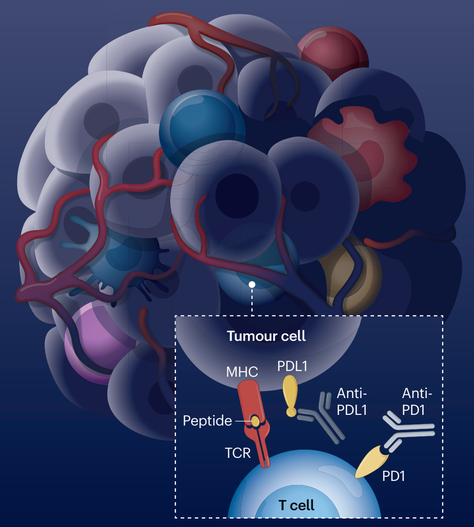


Normalize vascularization



↓ Immunosuppression





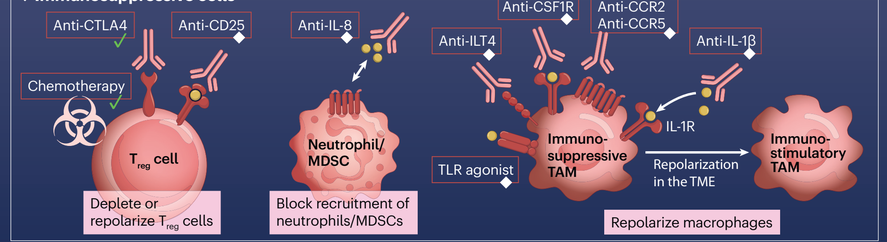
Rational combination principles

Immunotherapies show remarkable clinical benefit in some patients with cancer, but lack of therapy response and on-treatment resistance remain complex problems for many patients. The response to ICB can fail in several ways — for example, at the level of effector T cells ($CD4^+$, $CD8^+$ and γδ T cells); suppression of $CD8^+$ T cells by other immune cells such as T_{reg} cells or neutrophils and macrophages; lack of tumour recognition by T cells; or T cell-suppressive factors in the TME. This poster illustrates approaches in each of these four categories that can be combined with PD1 axis blockade. The justification for treatment combinations is to establish cooperative or synergistic clinical benefits, based on the simultaneous targeting of different signalling pathways in cancer cells, immune cells or other cells of the TME. Existing treatments of proven benefit also qualify for combining with ICB. The term 'rational' is used for treatment combinations in a broad sense, and includes innovative preclinical concepts, clinical trials, as well as US Food and Drug Administration-approved treatments. Representative, but not exhaustive, examples are shown. Note that not all combinations that seem rational are successful, for several reasons including incomplete mechanistic insight and tumour heterogeneity.

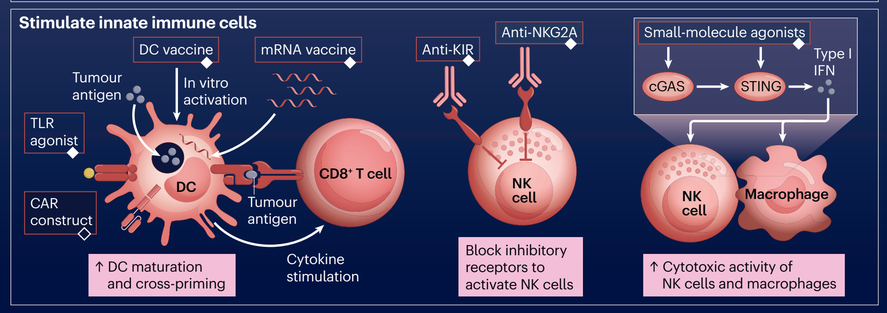
Clinical phase:
✓ Approved ✗ Unsuccessful ◆ Clinical trial ◇ Preclinical concept

Targeting innate immune cells and regulatory cells

↓ Immunosuppressive cells

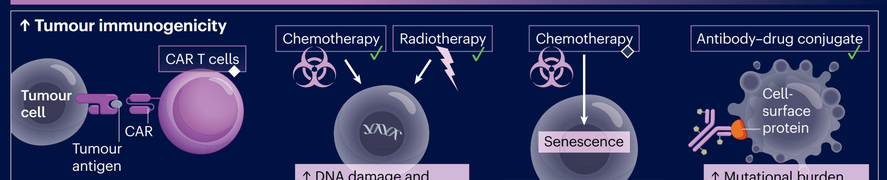


Stimulate innate immune cells

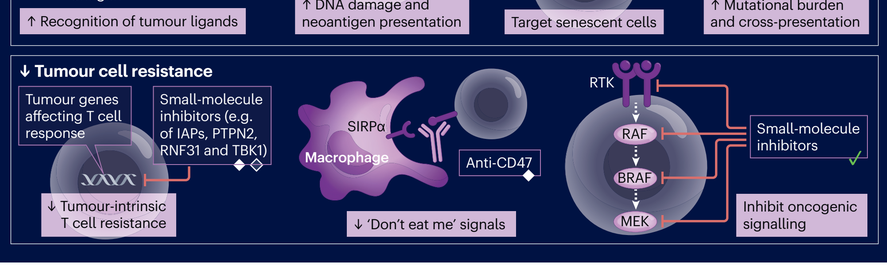


Exploiting cancer cell specificities and dependencies

↑ Tumour immunogenicity



↓ Tumour cell resistance



Abbreviations
$A_{2A}R$, adenosine A_{2A} receptor; CAF, cancer-associated fibroblast; CAR, chimeric antigen receptor; cGAS, cyclic GMP–AMP synthase; CSF1R, colony-stimulating factor 1 receptor; CTLA4, cytotoxic T lymphocyte antigen 4; DC, dendritic cell; DNMT, DNA methyltransferase; EZH2, enhancer of zeste homologue 2; GD2, disialoganglioside; HDACs, histone deacetylases; IAP, inhibitor of apoptosis protein; ICB, immune checkpoint blockade; IDO1, indoleamine 2,3-dioxygenase 1; IFN, interferon; IL-2R, IL-2 receptor; ILT4, immunoglobulin-like transcript 4 (also known as LILRB2); KIR, killer cell immunoglobulin-like receptor; KYN, kynurenine; LAG3, lymphocyte activation gene 3 (also known as CD223); MDSC, myeloid-derived suppressor cell; NK cell, natural killer cell; PD1, programmed cell death 1; PDGFR, platelet-derived growth factor receptor; PDL1, programmed cell death ligand 1; PTPN2A - Receptor-type tyrosine-protein phosphatase N2; RNF31 - E3 ubiquitin-protein ligase RNF31; RTK, receptor tyrosine kinase; SIGLEC, sialic acid-binding immunoglobulin-like lectin; SIRPα, signal regulatory protein-α; STING, stimulator of interferon genes; TAA, tumour-associated antigen; TAM, tumour-associated macrophage; TCR, T cell receptor; TGFβ, transforming growth factor-β; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domains; TILs, tumour-infiltrating lymphocytes; TLR, Toll-like receptor; TME, tumour microenvironment; T_{reg} cell, regulatory T cell; Trp, tryptophan; TVEC, talimogene laherparepvec (genetically engineered herpesvirus); VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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