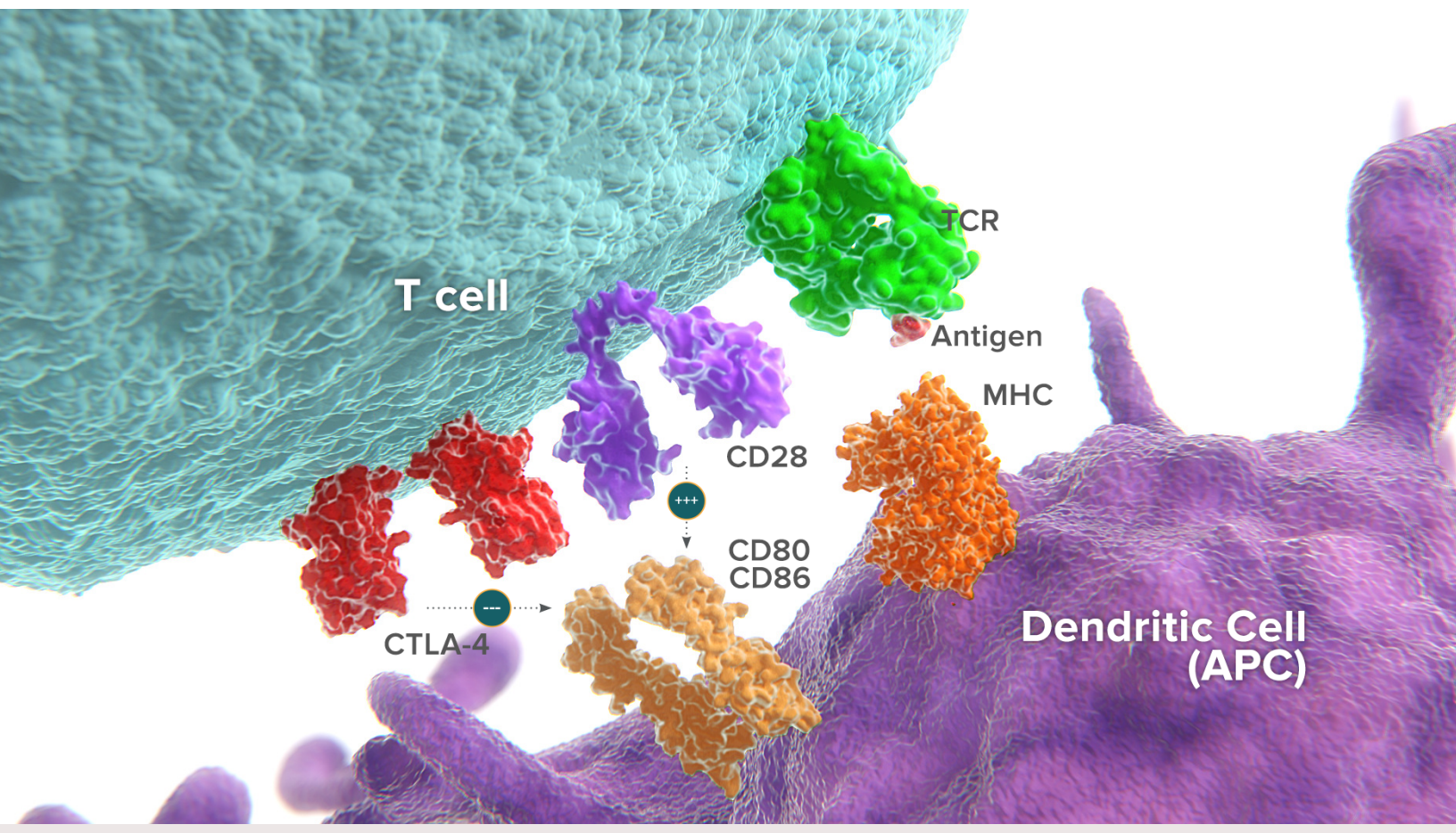
Bristol Myers Squibb™

Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4)

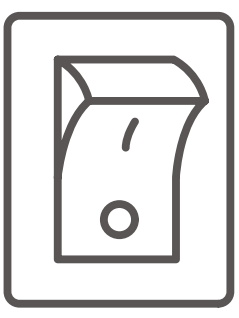


CTLA-4 and its Role in the Immune Response

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is an **immune checkpoint receptor** which is found on the surface of activated T cells.[1,2]

CTLA-4 serves as one of the immune system's "off" switches – slowing down or stopping an immune response. When CTLA-4 binds to its ligand on antigen-presenting cells (APCs), **T cell activation is inhibited and preserves balance** when the immune system is overactive.[3,4,5]

CTLA-4 and its Role in Cancer



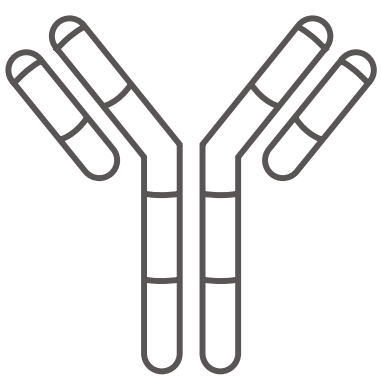
In cancer, tumor cells use the CTLA-4 pathway to decrease T cell activation, proliferation and effector function – **effectively turning "off" the immune response.**[6,7]

CTLA-4 signaling in cancer also **diminishes the ability of memory T cells to sustain an immune response,** damaging the body's ability to provide long-term immunity.[6,7]

Optimizing CTLA-4 Blockade

CTLA-4 blockade as a therapeutic mechanism **has been clinically validated as monotherapy** or in combination with other anti-cancer agents.[8,9]

Researchers are **investigating several approaches** to build upon the established mechanism of CTLA-4 blockade **to further improve the risk/benefit profile** and broaden the understanding of its mechanism.



One approach aims to regulate the degree of immune activity **using non-fucosylated antibodies to enhance Fc receptor binding**. This modification was developed to increase the effects of CTLA-4 blockade and enhance intratumoral regulatory T cell depletion.

- Poor prognosis in various cancers is associated with **the presence of Tregs.**[10,11]
- Preclinical models have shown that a non-fucosylated anti-CTLA-4 **can improve cytotoxic T cell activation and antitumor activity.**[12]

Another approach uses pro-antibodies to improve CTLA-4 blockade specificity **by reducing antibody binding outside of the tumor microenvironment**, sparing healthy tissues.[13,14]

- These antibodies may be primarily active at the tumor site because **they have been masked with a peptide that is removed by enzymes** that are either highly expressed by or only present on tumor cells.[13]
- Preclinical data indicate that **limiting antibody binding to the tumor microenvironment may prevent the immune system from attacking healthy cells,** yet still enable an antitumor response.[14,15]

Novel approaches for optimizing CTLA-4 blockade's ability to restore the immune response are currently under investigation.

1. Perkins D, Wang Z, Donovan C, et al. Regulation of CTLA-4 expression during T cell activation. J Immunol. 1996;156(11):4154-4159.
2. Le Mercier I, Lines JL, Noelle RJ. Beyond CTLA-4 and PD-1, the generation Z of negative checkpoint regulators. Front Immunol. 2015. doi:10.3389/fi mmu.2015.00418.
3. Walunas TL, Lenschow DJ, Bakker CY, et al. CTLA-4 can function as a negative regulator of T cell activation. Immunity. 1994;1(5):405-413.
4. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity. 1995;3(5):541-547.
5. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol. 2016;39(1):98-106.
6. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol. 2016;39(1):98-106.
7. Chambers CA, Sullivan TJ, Truong T, Allison JP. Secondary but not primary T cell responses are enhanced in CTLA-4-defi cient CD8+ T cells. Eur J Immunol. 1998;28(10):3137-3143.
8. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus Ipilimumab in untreated melanoma. NEJM. 2015;372:2006-2017.
9. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. NEJM. 2010;363:711-723.
10. Saito T, Nishikawa H, Wada H, et al. Two FOXP3+CD4+ T cell subpopulations distinctly control the prognosis of colorectal cancers. Nat Med. 2016;22(6):679-684.
11. Tao H, Mimura Y, Aoe K, et al. Prognostic potential of FOXP3 expression in non-small cell lung cancer cells combined with tumor-infi ltrating regulatory T cells. Lung Cancer. 2012;75(1):95-101.
12. Selby MJ, Engelhardt JJ, Quigley M, et al. Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. Cancer Immunol Res. 2013;1(1):32-42.
13. Chen I-J, Chuang C-H, Hsieh Y-C, et al. Selective antibody activation through protease-activated pro-antibodies that mask binding sites with inhibitory domains. Sci Rep. 2017;7(1):11587. doi:o10.1038/s41598-017-11886-7.
14. Tuve S, Chen B-M, Liu Y, et al. Combination of tumor site–located CTL-associated antigen-4 blockade and systemic regulatory T-cell depletion induces tumor-destructive immune responses. Cancer Res. 2007;67(12):5929-5939.
15. Fransen MF, van der Sluis TC, Ossendorp F,