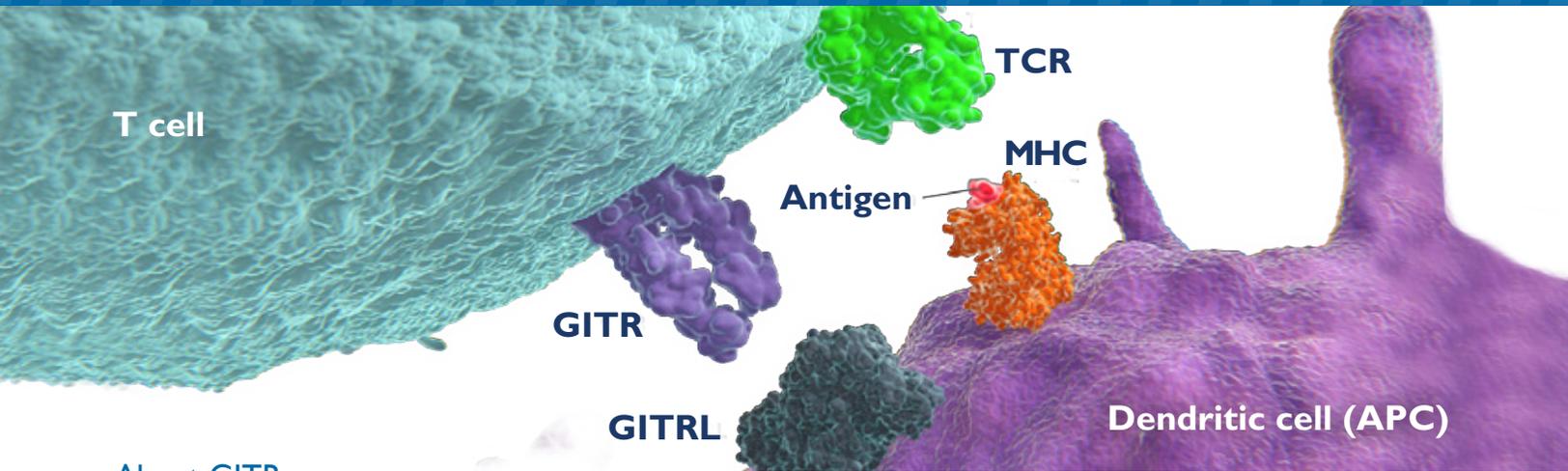


Glucocorticoid-Induced TNFR-Related Protein (GITR) Immune Pathway



About GITR

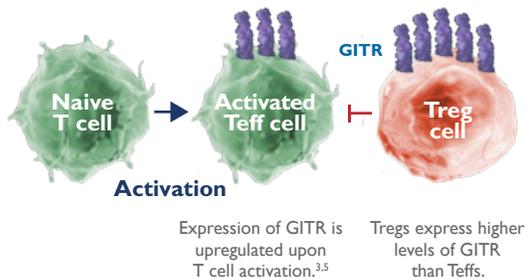
Glucocorticoid-induced TNFR-related protein (GITR) is a costimulatory activating receptor on the surface of T cells and other immune cells that functions to energize T cell responses to antigens.^{1,2} As a member of the tumor necrosis factor receptor (TNFR) super family of costimulatory receptors, GITR interacts with its ligand, GITRL, on neighboring immune cells.

GITR and Immune Function

Downstream effects of GITR activation through ligand interaction are dependent on cell type:

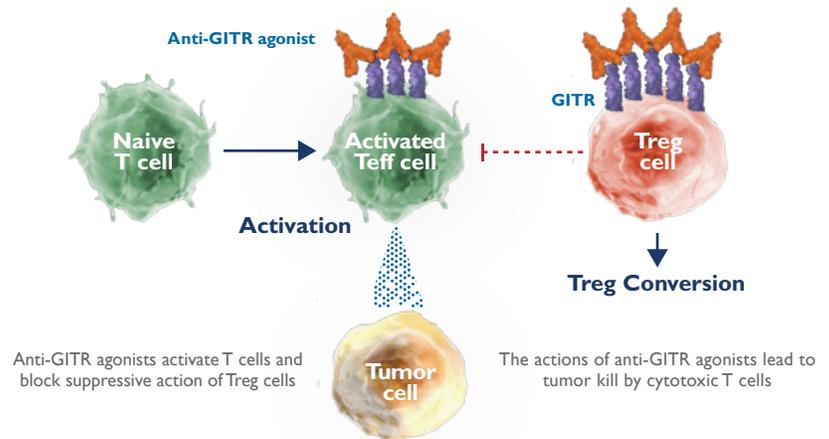
- On T effector cells (Teff), GITR signaling enhances survival and proliferation, thereby increasing cancer-killing activity^{1,3}
- On T regulatory cells (Treg), GITR signaling blocks the suppressive abilities of Tregs, further enhancing cytotoxic T cell function⁴

Overall, GITR activation serves to boost the immune system's ability to respond to threats, leading to potent anti-tumor immunity.



GITR and Cancer

In preclinical studies, activation of GITR signaling through an anti-GITR agonist enhances immunity through the activation of cytotoxic T cells and inhibition of immune-suppressive Treg activity.



Interactions with Other Pathways

By energizing the immune system, GITR signaling may synergize with other pathways to promote enhanced tumor killing activity.^{7,8}

The GITR pathway is just one of many immune pathways under investigation at Bristol-Myers Squibb. Learn more about our work in immuno-oncology by visiting:

<https://iopathway.web.bms.com>

¹Gurney AL, Marsters SA, Huang A, et al. Identification of a new member of the tumor necrosis factor family and its receptor, a human ortholog of mouse GITR. *Curr Biol*. 1999;9(4):215-218. ²Hanabuchi S, Watanabe N, Wang YH, et al. Human plasmacytoid dendritic cells activate NK cells through glucocorticoid-induced tumor necrosis factor receptor-ligand (GITRL). *Blood*. 2006;107(9):3617-3623. ³Tone M, Tone Y, Adams E, et al. Mouse glucocorticoid-induced tumor necrosis factor receptor ligand is costimulatory for T cells. *Proc Natl Acad Sci U S A*. 2003;100(25):15059-15064. ⁴Shimizu J, Yamazaki S, Takahashi T, et al. Stimulation of CD25+CD4+ regulatory T cells through GITR breaks immunological self-tolerance. *Nat Immunol*. 2002;3(2):135-142. ⁵Knee DA, Hewes B, Brogdon JL. *Eur J Cancer*. 2016;67:1-10. ⁶Cohen AD, Schaer DA, Liu C, et al. Agonist anti-GITR monoclonal antibody induces melanoma tumor immunity in mice by altering regulatory T cell stability and intratumor accumulation. *PLoS One*. 2010;5(5):e10436. doi:10.1371/journal.pone.0010436. ⁷Lu L, Xu X, Zhang B, et al. Combined PD-1 blockade and GITR triggering induce a potent antitumor immunity in murine cancer models and synergizes with chemotherapeutic drugs. *J Transl Med*. 2014;12-36. ⁸Mitsui J, Nishikawa H, Muraoka D, et al. Two distinct mechanisms of augmented antitumor activity by modulation of immunostimulatory/inhibitory signals. *Clin Cancer Res*. 2010;16:2781-2791.