Targeting GITR in cancer immunotherapy

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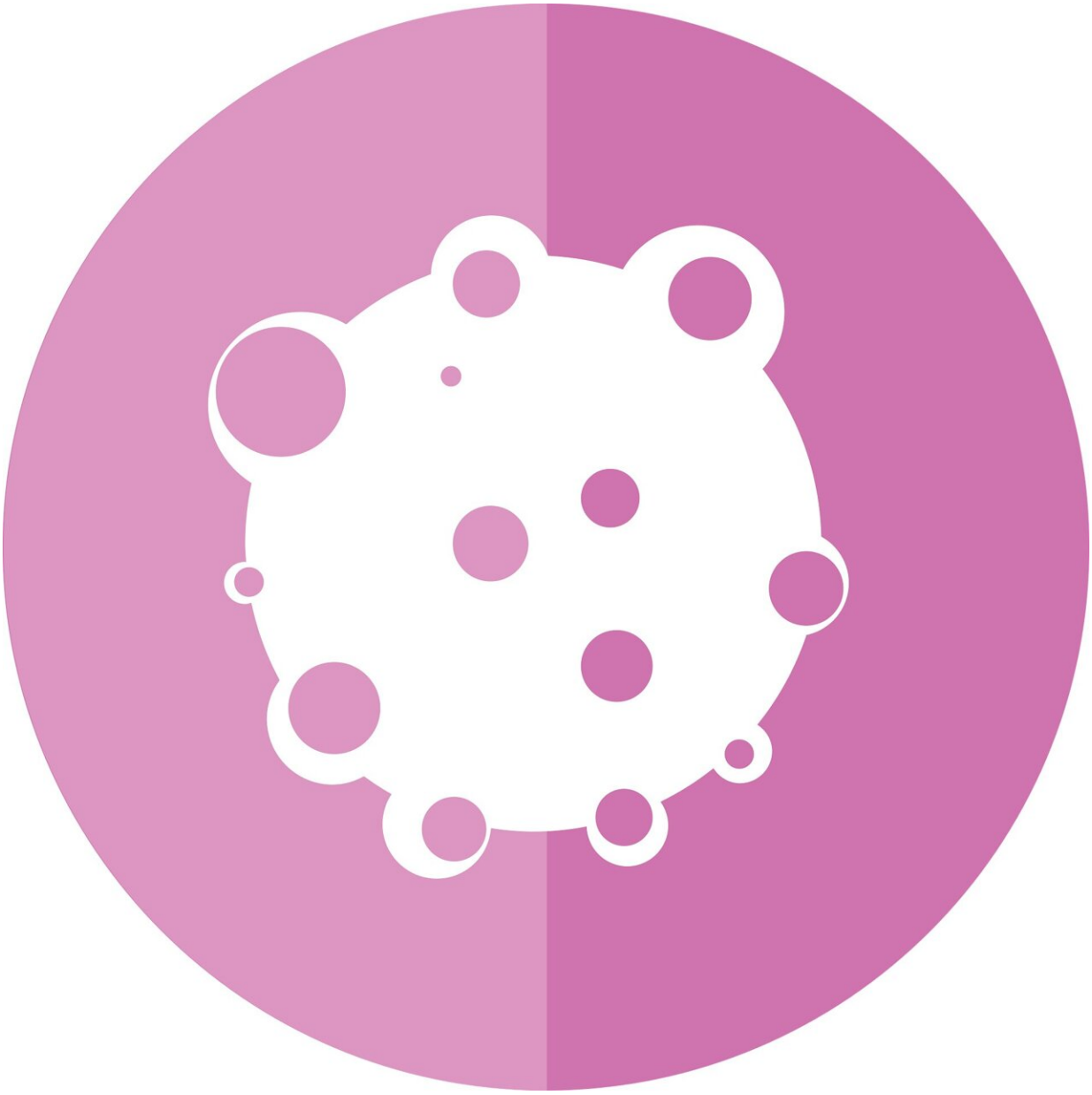

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A new research perspective titled "Targeting GITR in cancer immunotherapy—there is no perfect knowledge" has been published in *Oncotarget*.

In this new perspective, researchers Diwakar Davar and Roberta Zappasodi from the University of Pittsburgh Medical Center (UPMC), University of Pittsburgh, Weill Cornell Medical College, and Weill Cornell Graduate School of Medical Sciences discuss the glucocorticoid-induced TNFR-related protein (GITR), belonging to the TNFR superfamily (TNFRSF) and stimulating both the acquired and innate immunity. GITR is broadly expressed on immune cells, particularly regulatory T cells (Tregs) and natural killer (NK) cells.

"Given its potential to promote T effector function and impede Treg immune suppression, GITR is an attractive target for cancer immunotherapy," the authors state.

Preclinically, GITR agonists have demonstrated potent anti-tumor efficacy singly and in combination with a variety of agents, including PD-1 blockade. Multiple GITR agonists have been advanced into the clinic, although the experience with these agents has been disappointing. Recent mechanistic insights into the roles of antibody structure, valency, and Fc functionality in mediating anti-tumor efficacy may explain some of the apparent inconsistency or discordance between preclinical data and observed clinical efficacy.

Overall, the clinical results obtained so far with GITR agonist agents have demonstrated specific immune effects in the expected immune cell populations based on preclinical studies. However, these effects have not produced substantial therapeutic activity in human cancer patients. A maturing understanding of the immune responses to GITR agonism in

human cancer has clarified novel issues specific to drug development in this space including Ab structure (monospecific and bispecific mAbs and co-stimulatory GITR ligands), Ab valency, and Fc functionality.

"This improved understanding of the immune responses to GITR agonism in patients should be kept in consideration for the design of novel rational combinations or treatment regimens in earlier disease settings where immunotherapy is gradually becoming the treatment of choice," say the researchers.

More information: Diwakar Davar et al, Targeting GITR in cancer immunotherapy—there is no perfect knowledge, *Oncotarget* (2023). DOI: 10.18632/oncotarget.28461

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