Title: CD27 Agonism Enhances Long-Lived CD4$^+$ T Cell Vaccine Responses Critical for Anti-Tumor Immunity

Keywords: Breast cancer, CD27, cancer vaccine, CD4$^+$ T cells.

Abstract:

Patients with metastatic breast cancer were vaccinated with dendritic cell (DC) vaccines targeting HER2, and all seven survived >18 years. PBMC analysis revealed HER2-specific CD27$^+$ memory CD4$^+$ and CD8$^+$ T cells, suggesting that CD27 signaling supports durable immune memory. We tested this by combining an anti-CD27 agonist antibody (Varlilumab) with a HER2 vaccine, which enhanced HER2-specific responses, particularly long-lived CD4$^+$ memory T cells detectable up to 300 days post-vaccination. Transient CD27 agonism was observed in CD4+ T cells by scRNAseq and resulted improved tumor control (~40% regression) compared to vaccine alone (~6%), and synergy with PD-1 blockade led to complete tumor rejection in ~90% of mice. CD4$^+$ T cells were essential for this effect, as shown by depletion and adoptive transfer experiments, while CD8$^+$ T cells played a less critical role. These findings demonstrate that antigen-specific huCD27$^+$ CD4$^+$ T cells are key effectors of vaccine-induced immunity and support CD27 agonism as a promising strategy to enhance therapeutic cancer vaccination.

One Sentence Summary: CD27 signaling is essential for CD4$^+$ T cell activation during vaccination and enable robust and long-lasting anti-tumor responses, which are independent of CD8$^+$ T cells, but can also enhance their function.