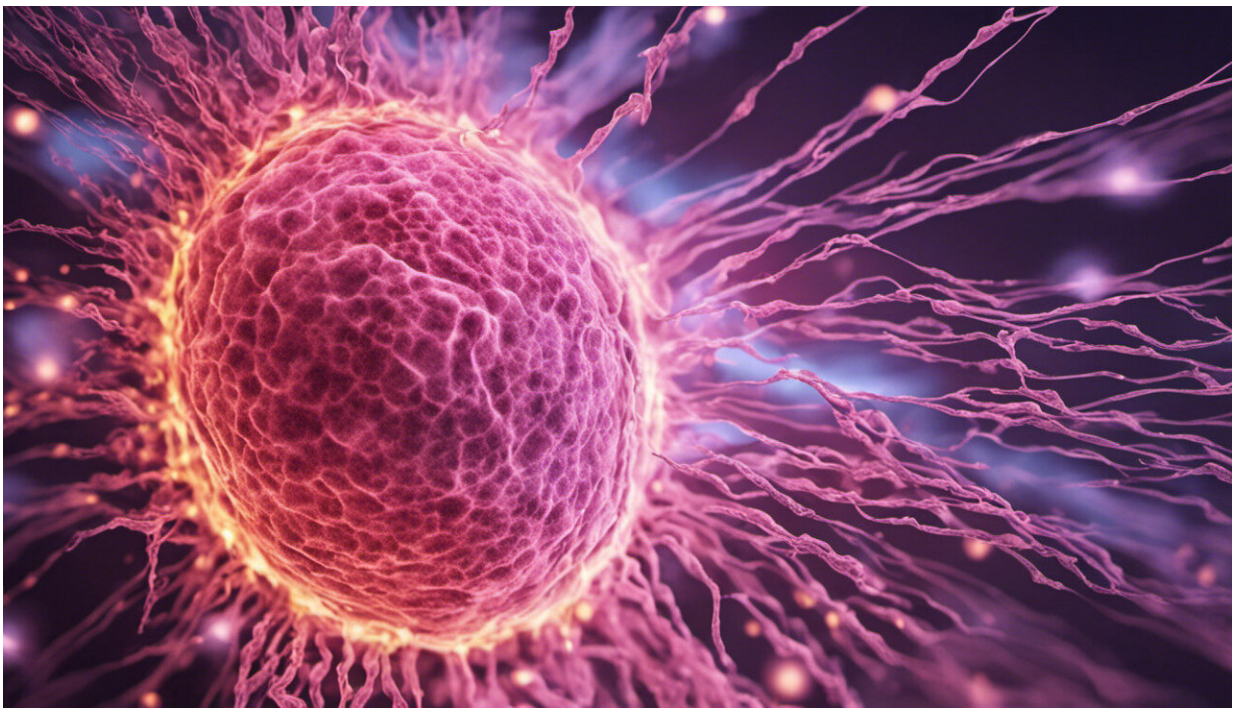
Combination radiation with immunotherapy shows promise against 'cold' breast cancer tumors

September 25 2023



Credit: AI-generated image (disclaimer)

Researchers at Weill Cornell Medicine have discovered that radiation therapy combined with two types of immunotherapy—one that boosts T cells, and another that boosts dendritic cells—can control tumors in preclinical models of triple negative breast cancer, a cancer type that's

typically resistant to immunotherapy alone. Immunotherapy activates the body's own immune system to fight cancer but isn't effective for difficult-to-treat "cold" tumors, like this.

The findings were published Aug. 24 in *Nature Communications*. Though radiation therapy has previously been combined with T-cell boosting immunotherapy, it rarely succeeds in eliminating cold tumors. The new, preclinical study found that activating another type of immune cell called a dendritic cell, in addition to the other two approaches, produced a synergistic effect that elicited tumor regression.

"I think this is quite exciting," said principal investigator Dr. Sandra Demaria, professor of radiation oncology at Weill Cornell Medicine and pathologist at NewYork-Presbyterian/Weill Cornell Medical Center, who conducted the research under the auspices of the Department of Radiation Oncology. "There is so much room for improvement to provide more effective therapeutic options, especially for patients with cold tumors."

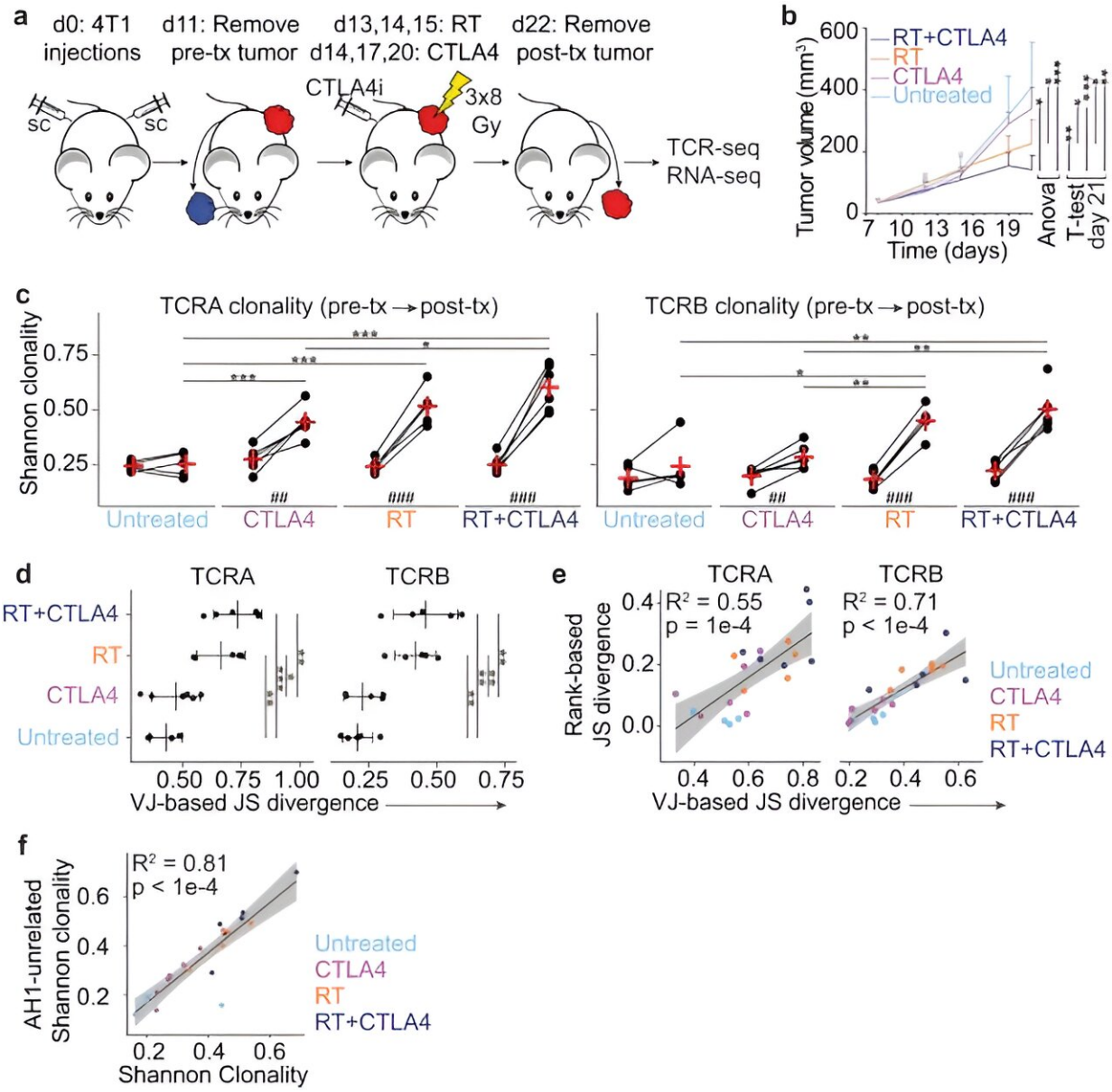
Infiltrating cold tumors

Cold tumors are often referred to as impregnable fortresses that can't be infiltrated by the immune system's T cells, which directly attack viruses, bacteria, as well as cancer cells. That makes them tough to treat with an immunotherapy drug called checkpoint inhibitors. Checkpoints are a safety mechanism on T cells that stop the immune cells from attacking healthy cells, but some cancers use them to hide from the immune system. Taking the brakes off these checkpoints with inhibitors allows the immune system to find and destroy cancer cells.

The team's previous research explored using radiation therapy to "warm up" cold tumors. Radiation directly kills cancer cells and sends out inflammatory signals that attract "killer" T cells. While this approach

activated the immune system, the T cells couldn't overcome the immune suppression of the tumor. They also knew from previous studies that an inhibitor targeting the CTLA4 checkpoint could be combined with radiation to trigger a stronger immune response.

For the new study, the researchers used two preclinical models of triple-negative breast cancer, which is aggressive and difficult to treat. These tumors are resistant to immunotherapy and poorly infiltrated by T cells. While the combination of radiation with CTLA4 inhibition converted cold tumors into T-cell-inflamed tumors, this was not enough to significantly reduce the tumor. They also found that adding a second checkpoint inhibiting immunotherapy did not improve tumor responses. Next, Dr. Demaria and her colleagues decided to look beyond T cells.



Clonal expansion of T cells in 4T1 tumors post-therapy. a Experimental schema for collection of pre- and post-treatment (pre-tx and post-tx) 4T1 tumor tissue (n = 6 biologically independent mice/group were used for panels b–f). b Tumor growth curves; lines and error bars illustrate mean and standard deviation (error bar only shown in one direction for visualization). Statistical significance in tumor volume growth between groups was determined with 2-way repeated measures ANOVA between day 15–21, and t test at day 21, as indicated in the figure. c Shannon clonality of paired pre- and post-tx T cell receptor (TCR) repertoires. Lines indicate paired samples from the same mouse. Red crosses

indicate mean value within group/timepoint. *-*** and ##-### indicate p-values for pairwise and paired t tests, respectively. d VJ-gene based Jensen-Shannon Divergence (JSD) calculated between paired pre- and post-tx TCR repertoires. *-*** indicate p-values pairwise t tests. e Linear regression between ranked and VJ-gene based JSD. f Linear regression between clonality of unmodified (x-axis) and AH1-unrelated (y-axis) TCRB repertoires. For all panels: Tukey's and Holm's method for adjusting p-values corrected for multiple comparison was used for the ANOVA and t tests, respectively; *, ** and ***, and #, ##, ###, and ####, indicate p-values