

Restoring immune function of tumor-specific CD4⁺ T cells during recurrence of melanoma

with anti-PD-L1 and anti-LAG-3 combination therapy.



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*In ancient Roman religion and mythology, Janus (Latin: Janus – Gateway or Door) is the god of beginnings and transitions. He is usually a two-faced god **since he looks to the future and the past**. The month of January was named in honor of Janus by the Romans: Thus a doorway to the new year.*

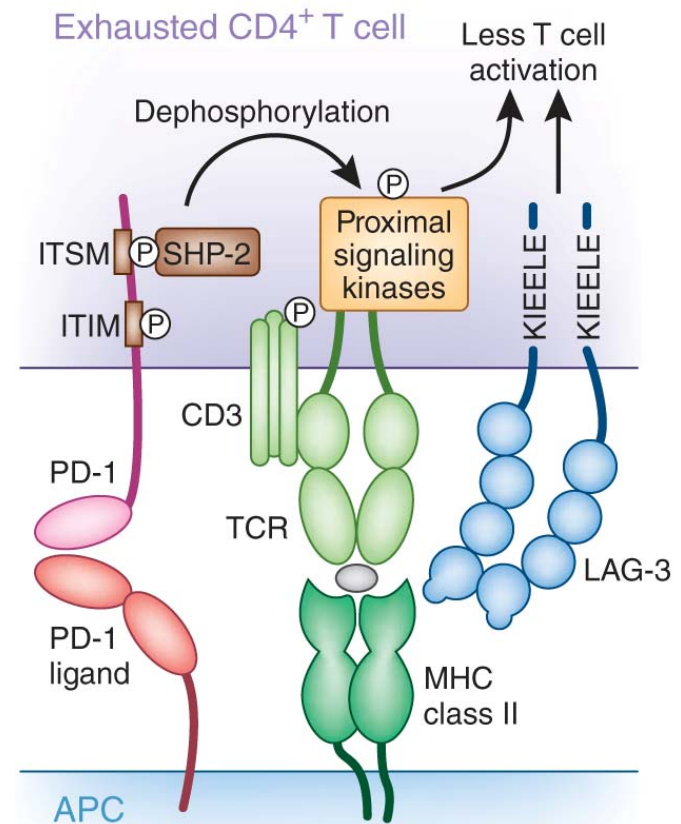
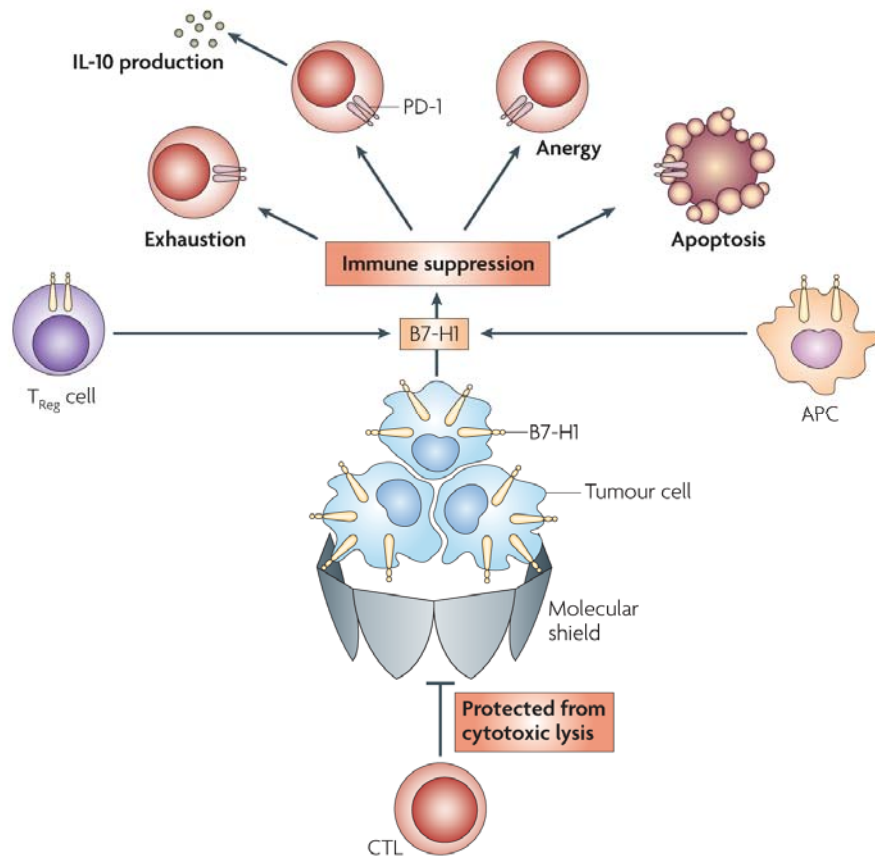
Presenter Disclosure Information

Paul Andrew Antony

The following relationships exist related to this presentation:

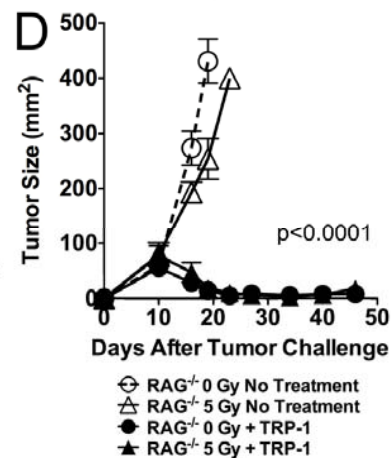
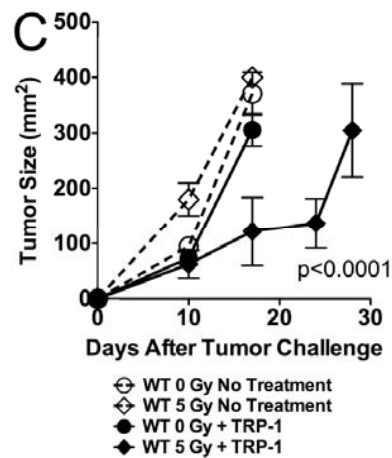
No relationships to disclose

PD-L1 and LAG-3 in immunobiology



Naive tumor-specific CD4⁺ T cells differentiated in vivo eradicate established melanoma

Ying Xie,² Akgül Akpınarlı,⁶ Charles Maris,⁷ Edward L. Hipkiss,⁷ Malcolm Lane,³ Eun-Kyung M. Kwon,² Pawel Muranski,⁸ Nicholas P. Restifo,⁸ and Paul Andrew Antony^{1,2,4,5}



- Cancer **recurrence is a significant health problem**. Most notably, when cancer recurs after an initial treatment, it is usually therapy resistant, more aggressive, and has a higher potential to metastasize.

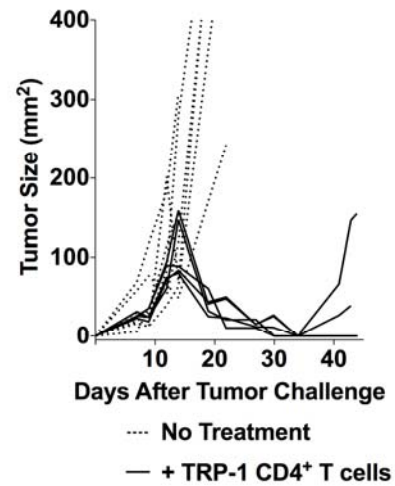
- We developed a **preclinical mouse model of cancer recurrence** that despite initial tumor regression after a successful immunotherapy approximately 50% of tumors relapsed mimicking the clinical course of many solid tumors.

Restoring Immune Function of Tumor-Specific CD4⁺ T Cells during Recurrence of Melanoma

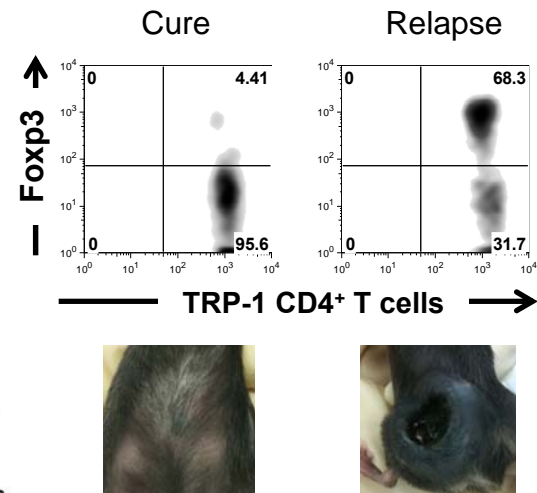
Stephen Goding,* Kyle Wilson,[†] Ying Xie,[‡] Kristina Harris,* Aparna Baxi,[†]
Akgul Akpınarli,[§] Amy Fulton,* Koji Tamada,[¶] Scott E. Strome,^{†,||,#,*} and
Paul Andrew Antony^{*,†,#,*}

Foxp3⁺ T_{reg} cells increase during relapse of melanoma

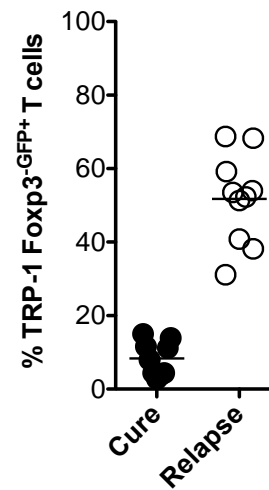
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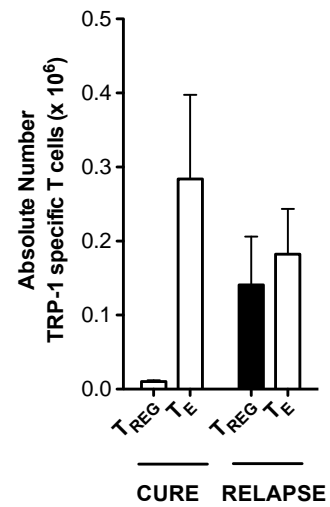
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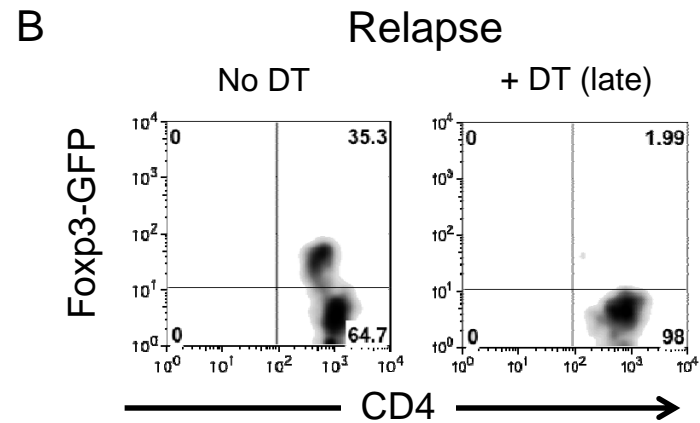
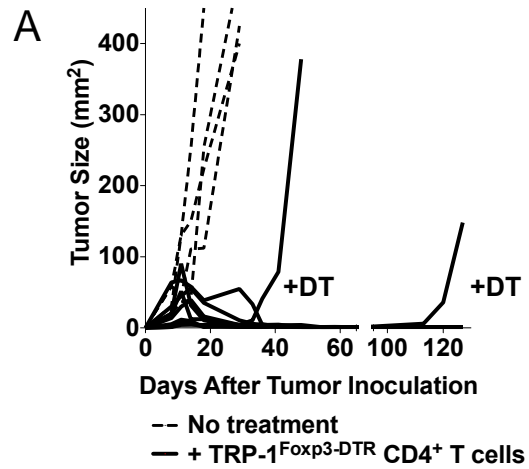


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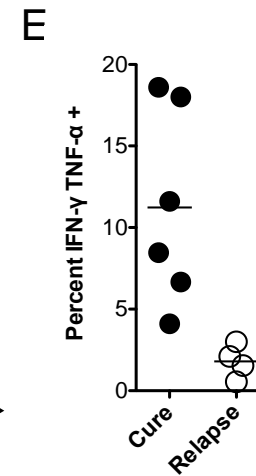
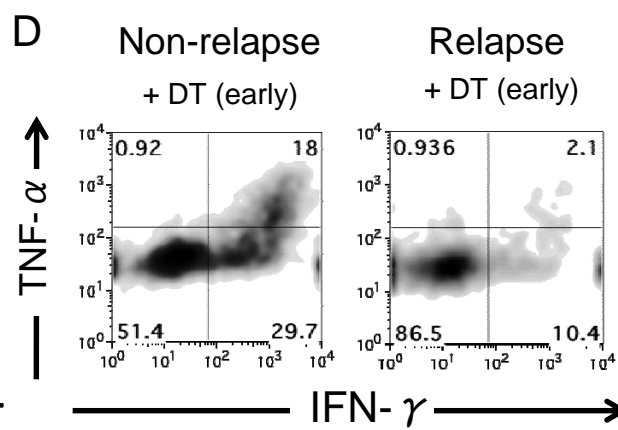
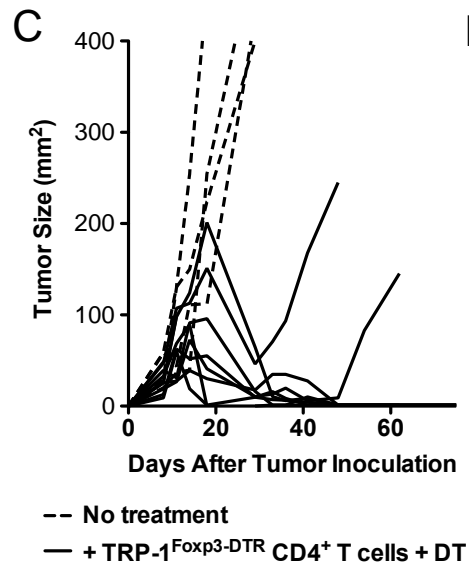


Depletion of Foxp3⁺ T cells does not prevent or treat relapse

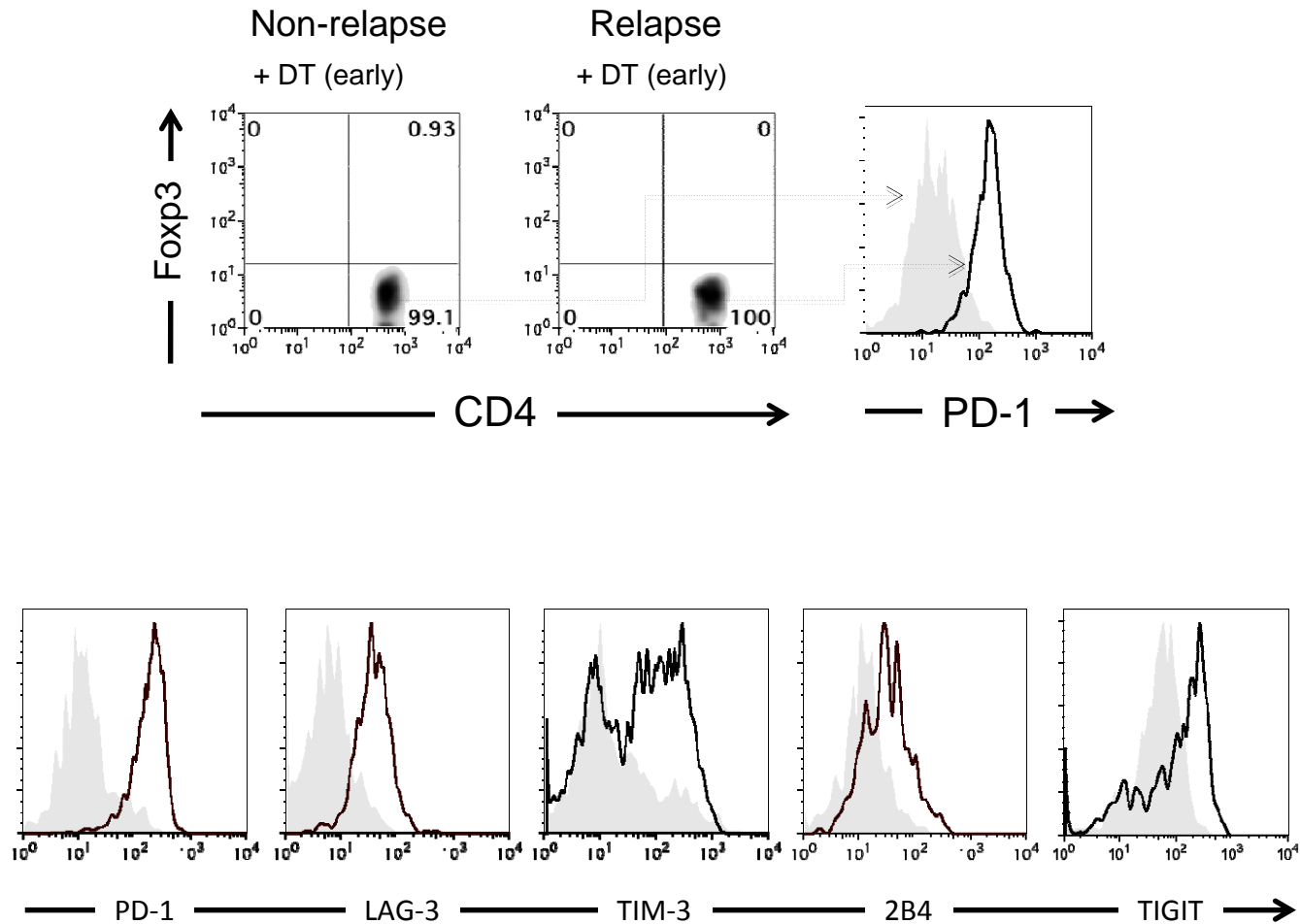
Depletion during



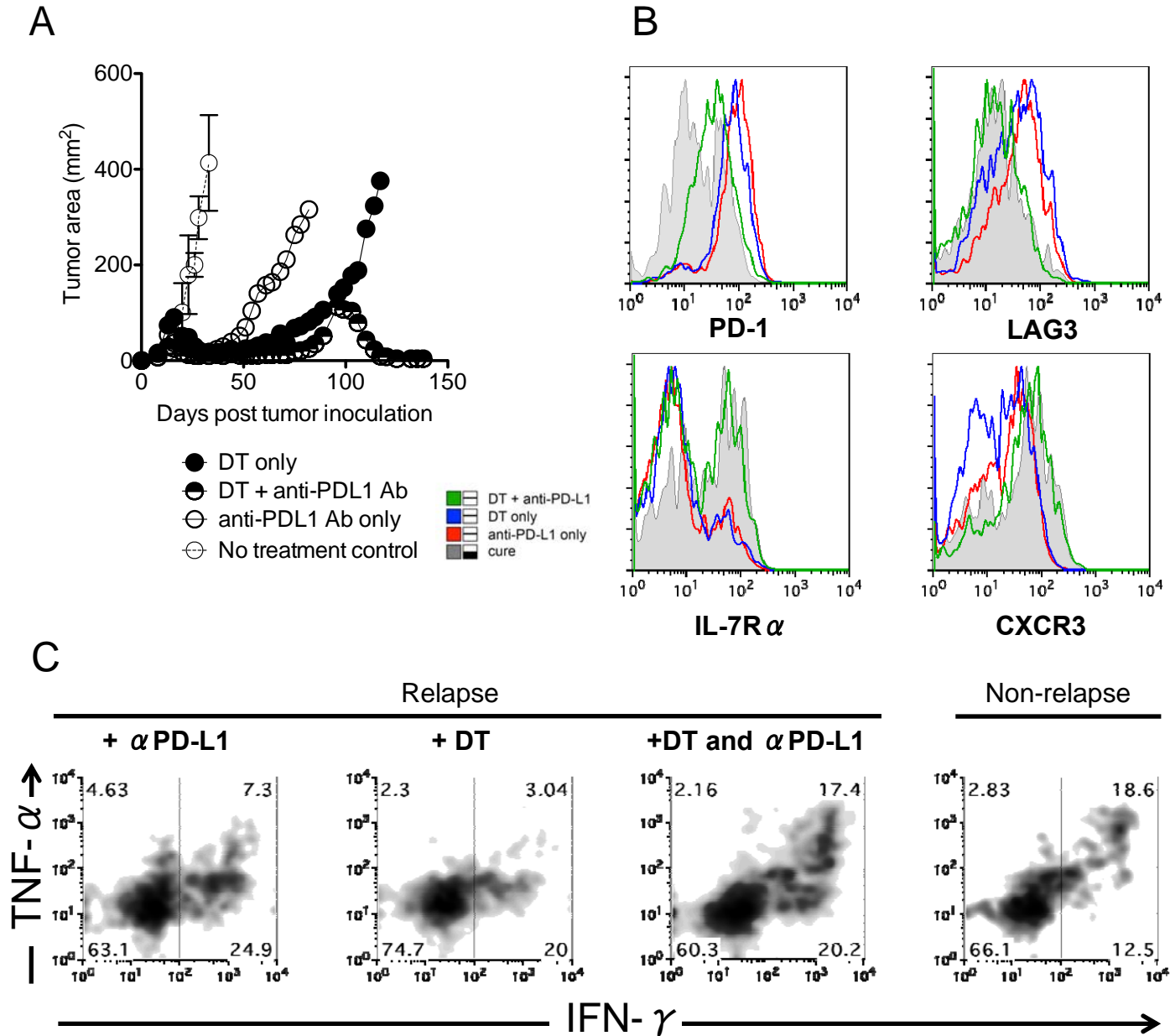
Depletion before



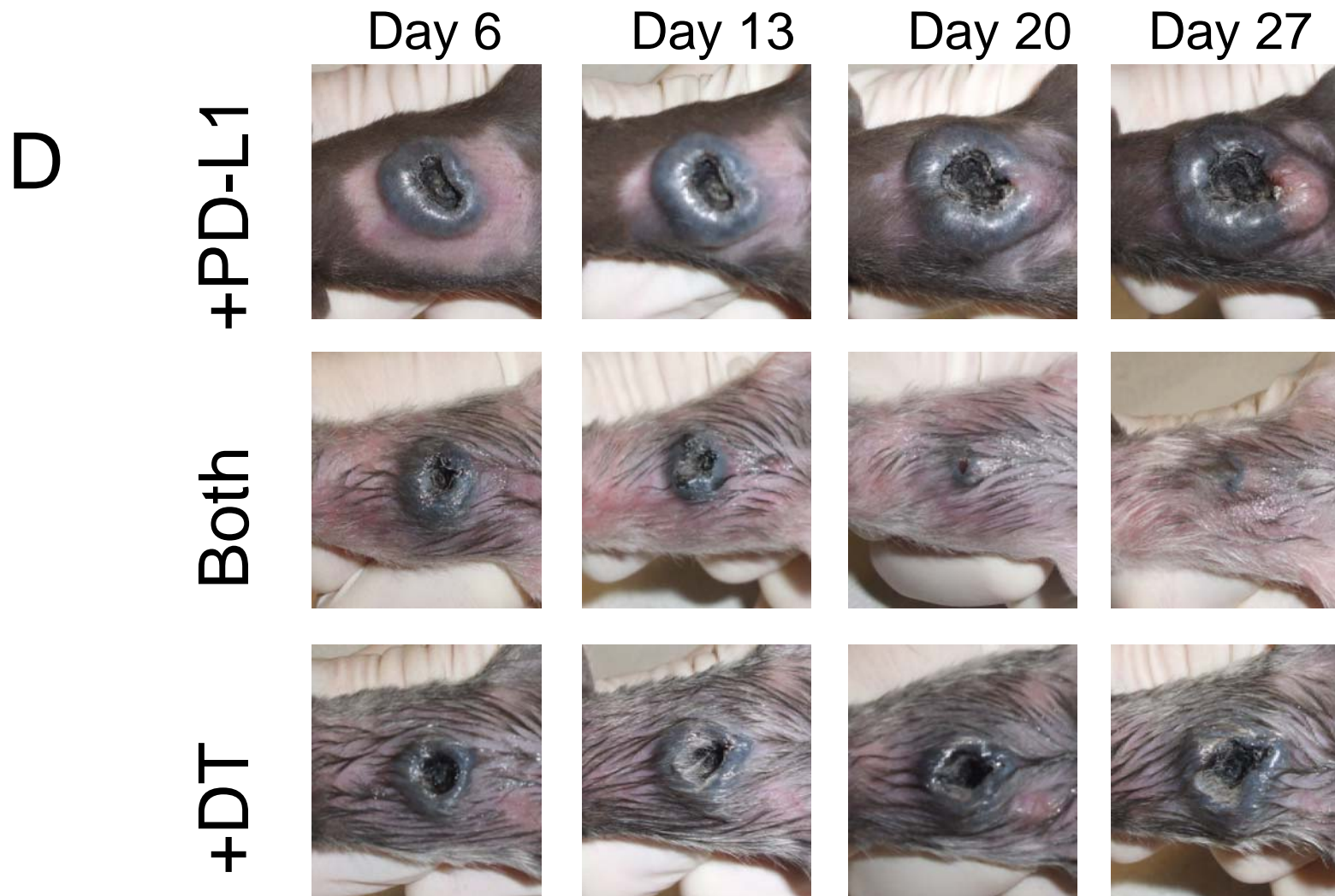
Cells from relapsing mice, in the absence of T_{reg} cells, are exhausted



Blockade of anti-PD-L1 and depleting Treg cells treats relapse

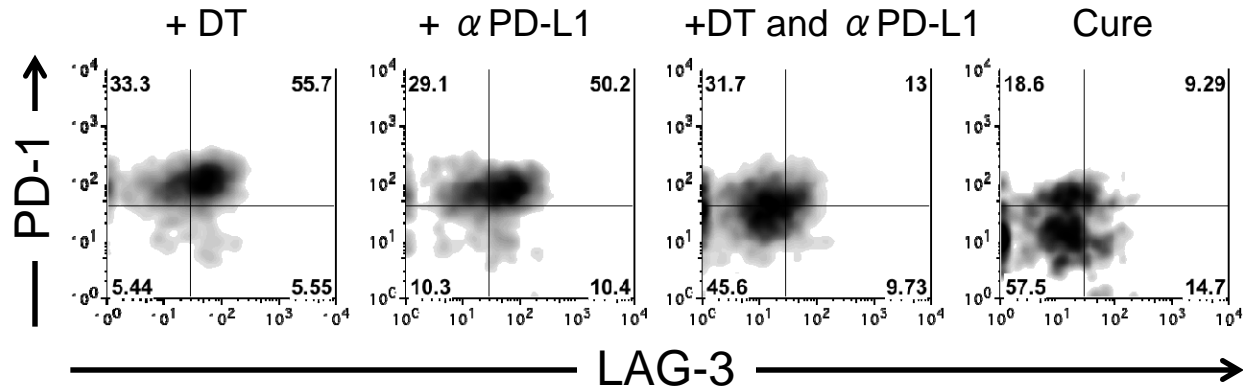


Blockade of anti-PD-L1 and depleting T_{reg} cells treats relapse

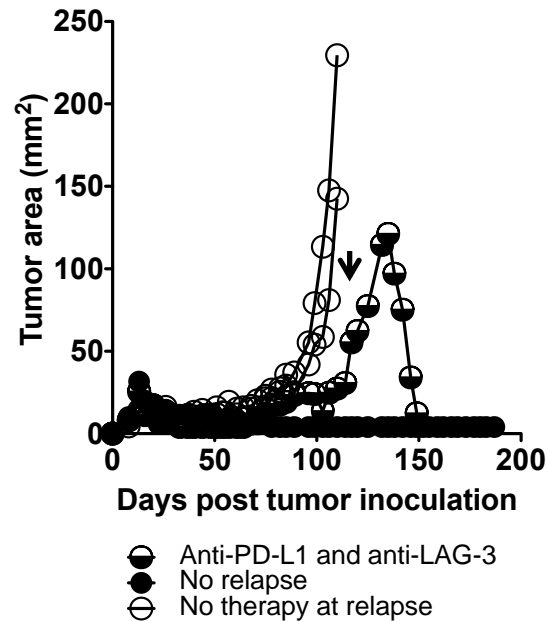


Combination therapy with Anti-PD-L1 and anti-LAG-3 therapy

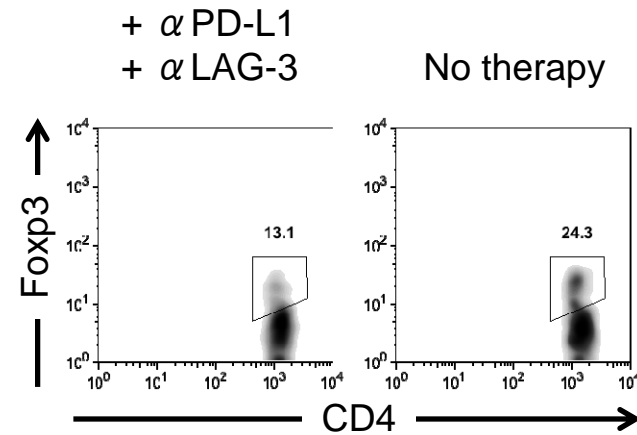
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During recurrence, **Foxp3⁺ tumor-specific CD4⁺ T cells** **represented over 60%** of the tumor-specific CD4⁺ T cells in the host.

However, effector CD4⁺ T cells from relapsing mice also **showed traits of chronic exhaustion** and high expression of inhibitory receptors: PD-1, TIM-3, TIGIT, and LAG-3.

These findings suggest that the PD-1/PD-L1 pathway plays a dominant role in cancer relapse, but resolution of recurring cancer with **PD-L1 blockade requires the absence of T_{reg} cell mediated suppression or simultaneous blockade of LAG-3** to restore immune function of tumor-specific T cells.

Therefore chronic exhaustion and T_{reg} cell mediated suppression are intricately working together to maintain tolerance during recurrence and **combination therapy** appears to overcome this impediment.

This work is in memory of my dear friend **Bernadette A. Estrada** who died from cervical cancer on August 24, 2011. She was one of the first patients to start anti-PD-L1 therapy and dedicated herself to cancer awareness while here at the NIH working with the President's Cancer Panel.





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SCHOOL OF MEDICINE

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