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: Ianus – 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

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• 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 Akpinarli,§ Amy Fulton,* Koji Tamada,¶ Scott E. Strome,†,‖,#,,** and Paul Andrew Antony*,†,#,**
Foxp3⁺ T_{reg} cells increase during relapse of melanoma

A

B

C

D

Cure

Relapse

TRP-1 CD4⁺ T cells

Foxp3

TRP-1 specific T cells (x 10⁶)

% TRP-1 Foxp3⁺ T cells

CURE RELAPSE

Foxp3+ T_{reg} cells increase during relapse of melanoma.
Depletion of Foxp3⁺ T cells does not prevent or treat relapse

A. Depletion during

B. Relapse

C. Depletion before

D. Non-relapse

E. Percent IFN-γ⁺ TNF-α⁺
Cells from relapsing mice, in the absence of $T_{\text{reg}}$ cells, are exhausted.
Blockade of anti-PD-L1 and depleting Treg cells treats relapse

A

Tumor area (mm²)

Days post tumor inoculation

- DT only
- DT + anti-PDL1 Ab
- anti-PDL1 Ab only
- No treatment control

B

PD-1

LAG3

IL-7R α

CXCR3

C

Relapse

- + αPD-L1
- + DT
- +DT and αPD-L1

Non-relapse

TNF-α

IFN-γ
Blockade of anti-PD-L1 and depleting $T_{\text{reg}}$ cells treats relapse
Combination therapy with Anti-PD-L1 and anti-LAG-3 therapy

A

+ DT  + α PD-L1  +DT and α PD-L1  Cure

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LAG-3

B

Days post tumor inoculation

Anti-PD-L1 and anti-LAG-3
No relapse
No therapy
No therapy at relapse

C

+ α PD-L1 + α LAG-3 No therapy

Foxp3 CD4
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 $T_{\text{reg}}$ cell mediated suppression or simultaneous blockade of LAG-3 to restore immune function of tumor-specific T cells.

Therefore chronic exhaustion and $T_{\text{reg}}$ 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.
Acknowledgements

Lab
• Stephen Goding, PhD- Post doctoral fellow
• Kyle Wilson, BA – MD, PhD graduate student

Previous fellows
• Ying Xie, PhD- post doctoral fellow

Collaborators
• Kristina M. Harris, PhD
• Amy Fulton, PhD
• Koji Tamada, MD
• Scott E. Strome, MD

Grants/Support
K22 NCI Career Award
DOD Cancer Idea Award
Melanoma Research Foundation
DOD post doctoral award
Harold Lloyd Charitable Trust
ACS internal grant