

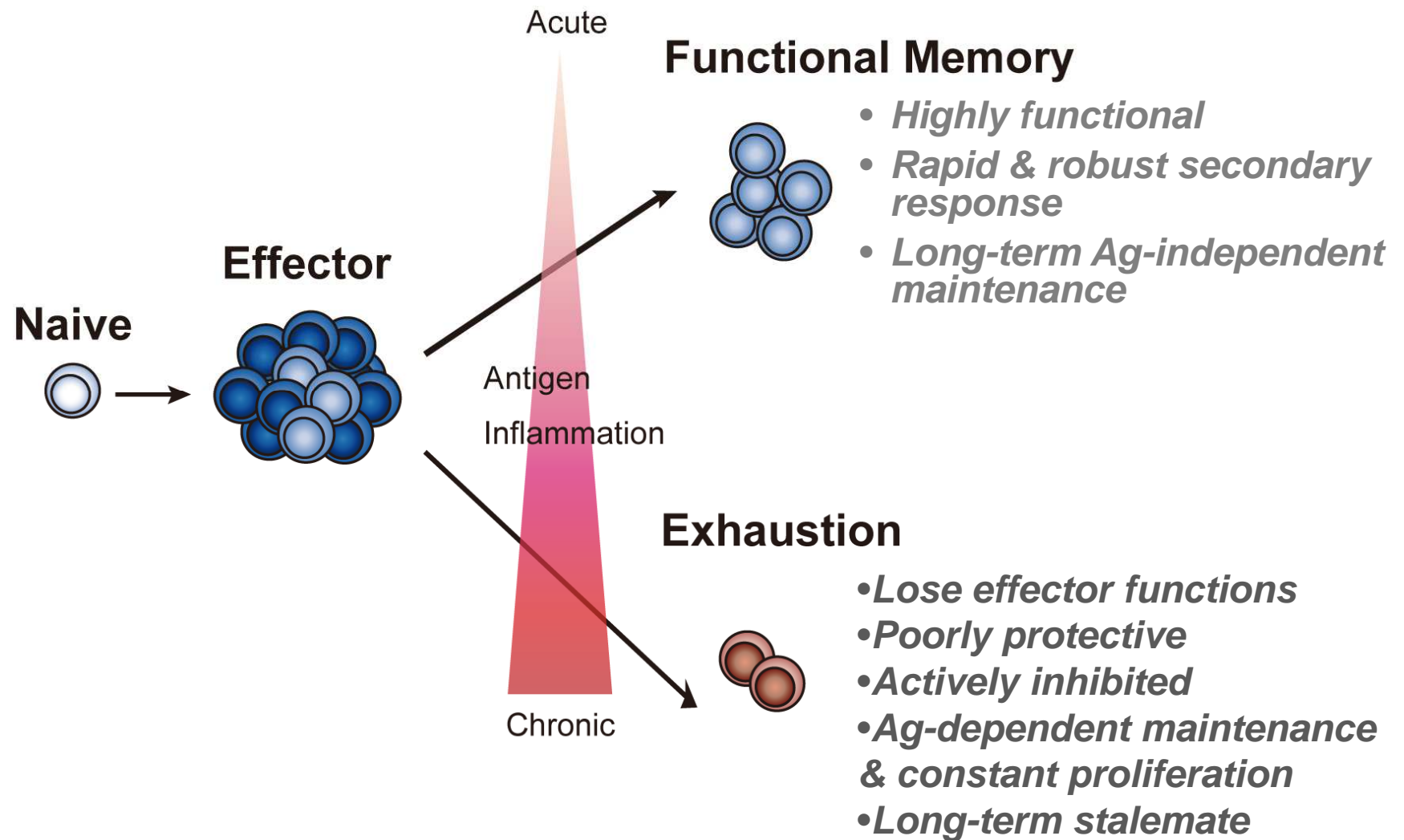
# Mechanisms and Biomarkers of CD8 T Cell Exhaustion

*SITC2014*

E. John Wherry  
Institute for Immunology  
Department of Microbiology  
University of Pennsylvania  
Philadelphia, PA

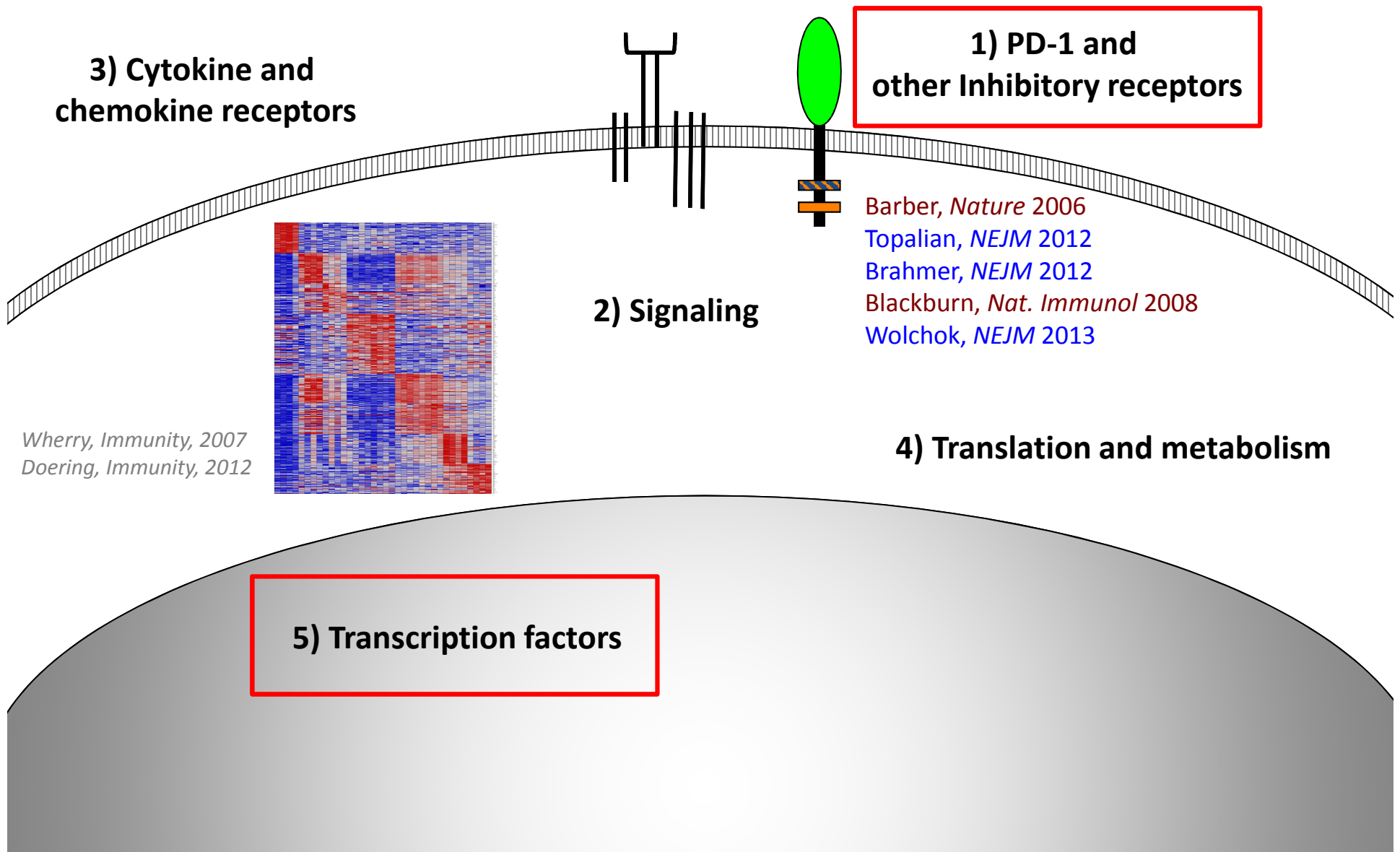
*Disclosures: Genentech/Roche (Patent Licensing Agreement); Surface Oncology (SAB).  
Merck, Janssen/J&J, Ono, BMS (Sponsored research and/or consulting).*

# T cell exhaustion



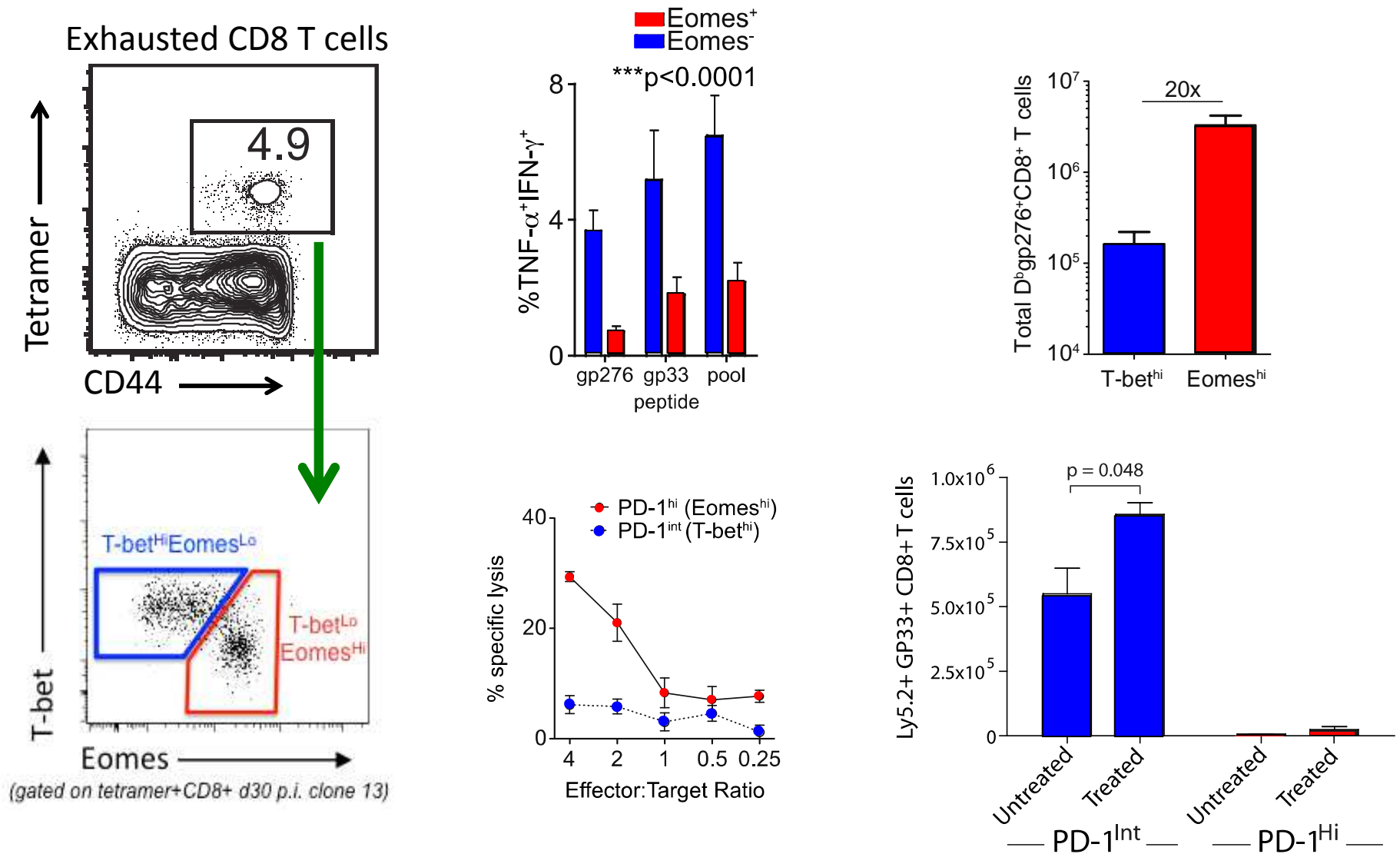
***Exhaustion is common in infections and cancer in mice as well as humans***

# Molecular Basis of CD8 T Cell Exhaustion: Mouse studies lead to clinical trials

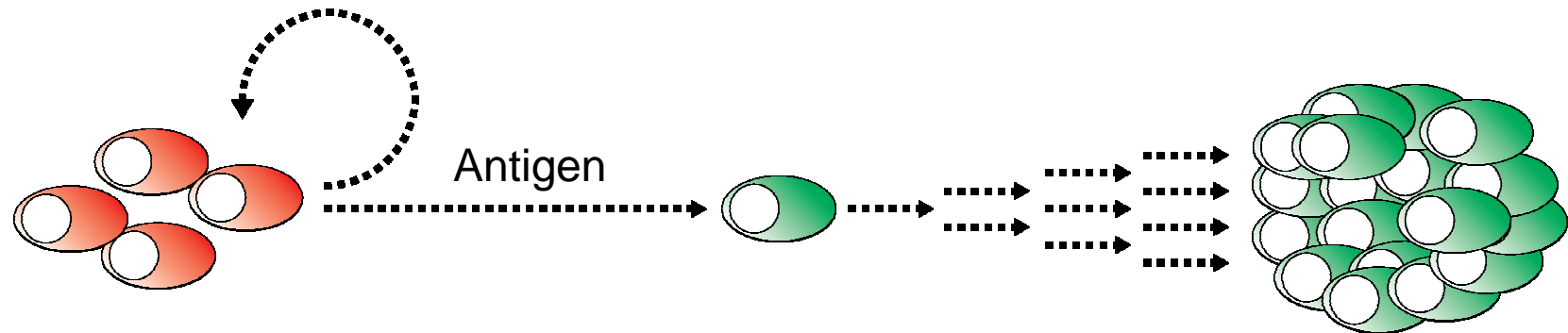


- 1) *Subsets of exhausted T cells*
- 2) *Exhaustion without PD-1*
- 3) *Immune biomarker of reversal of  
T cell exhaustion*

# Subsets of exhausted CD8 T cells during chronic infection



# Maintenance of CD8 T cells during chronic infection



Eomes  
**T-bet**

- PD-1<sup>Int</sup>
- Better cytokine producers (slightly)
- Retain some proliferative capacity
- “Centrally” located
- Depleted by prolonged infection
- Respond to PD-1 blockade

**Eomes**

T-bet

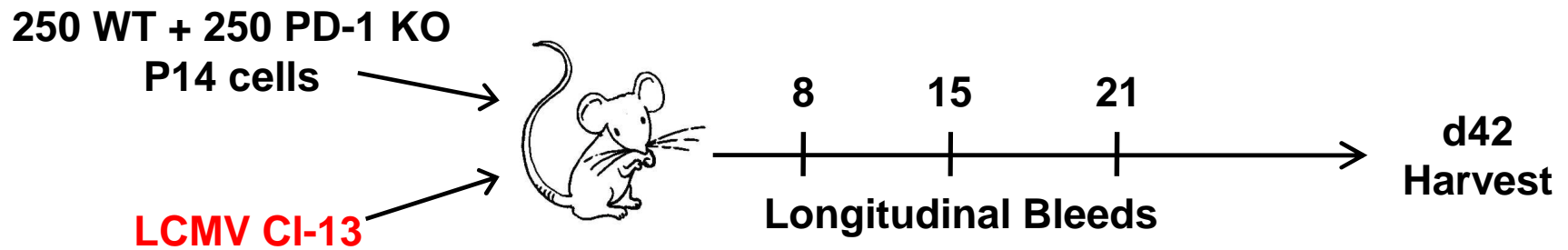


- PD-1<sup>Hi</sup> + other IR
- Better cytotoxicity
- Terminally differentiated
- Short half-life
- Peripheral localization
- Non-reversible

*How does PD-1 regulate subsets of exhausted CD8 T cells?*

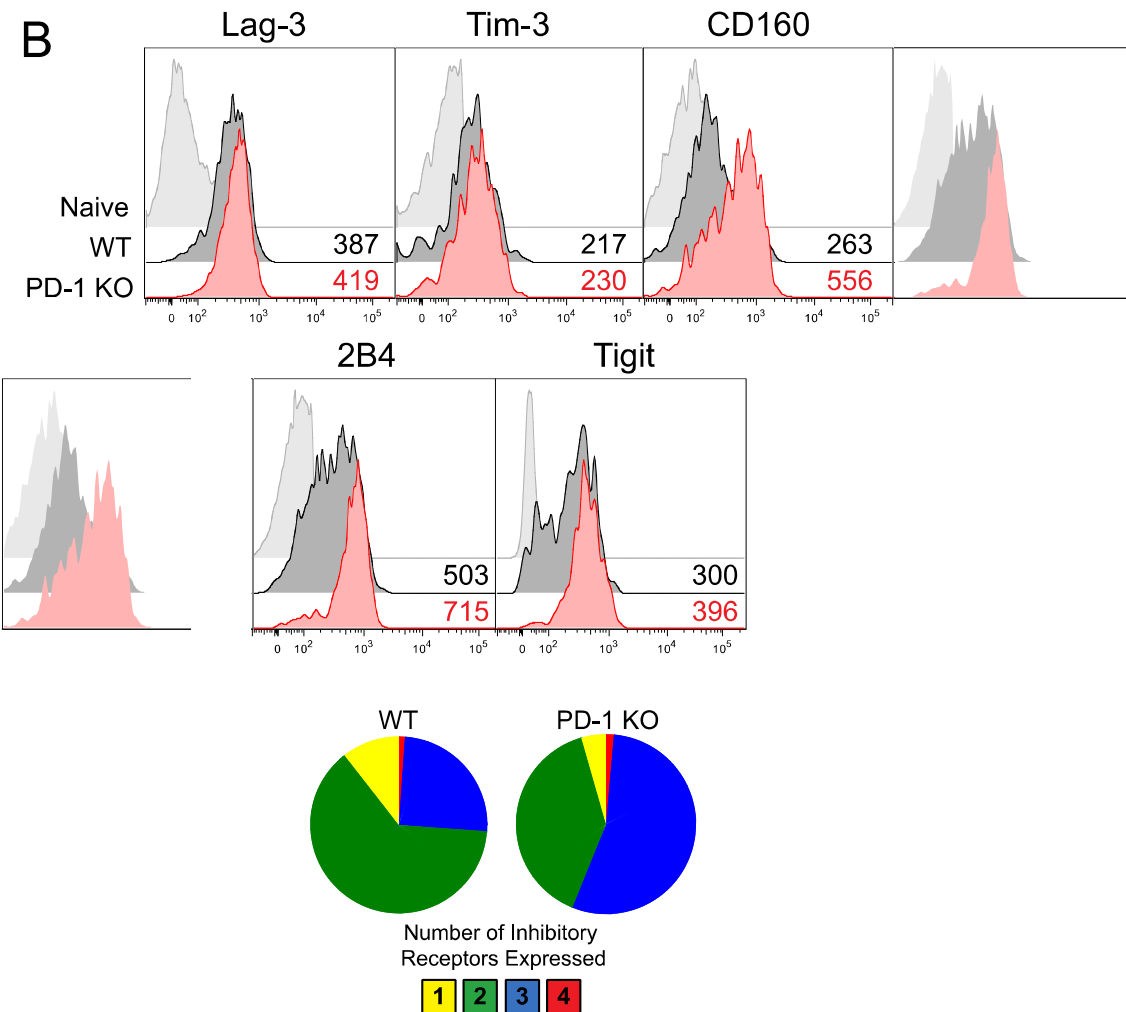
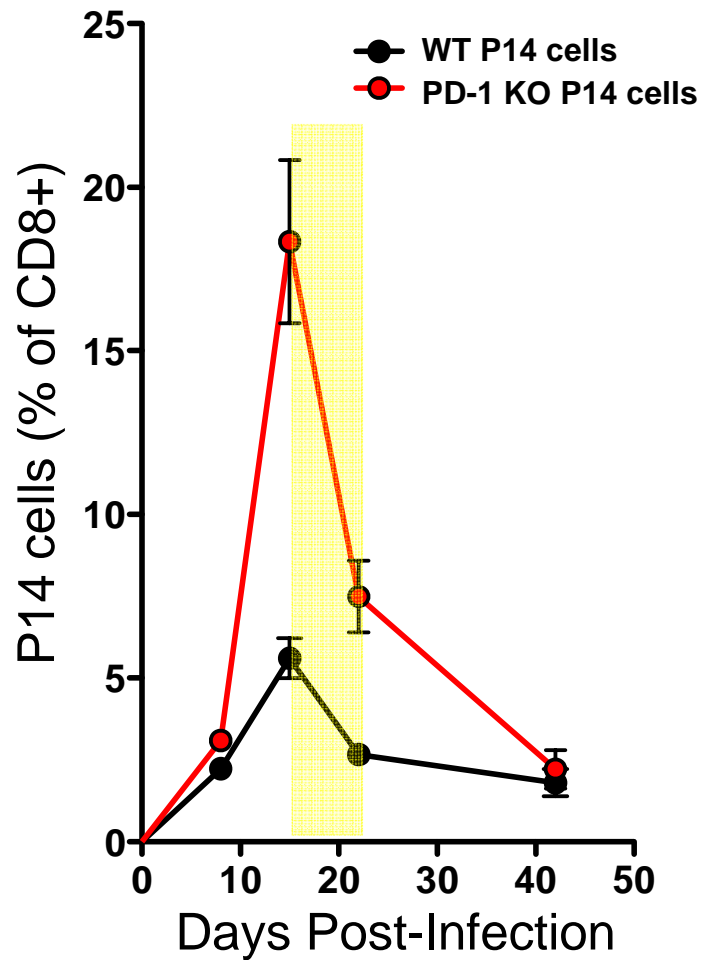
***Does PD-1 cause exhaustion?***

# Can T cell exhaustion occur without PD-1

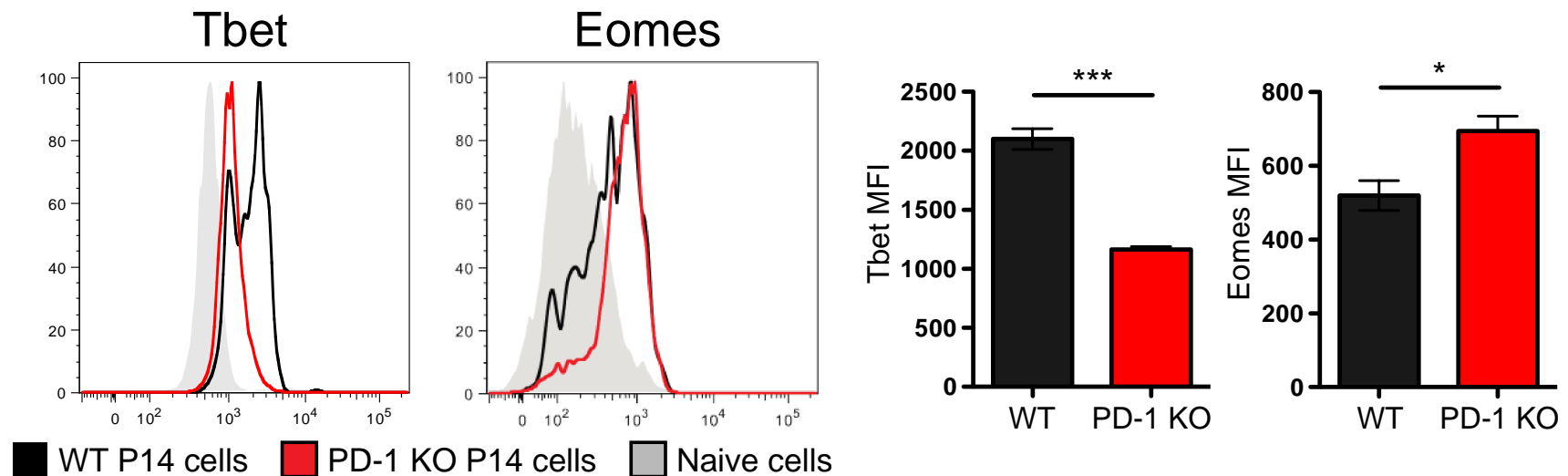




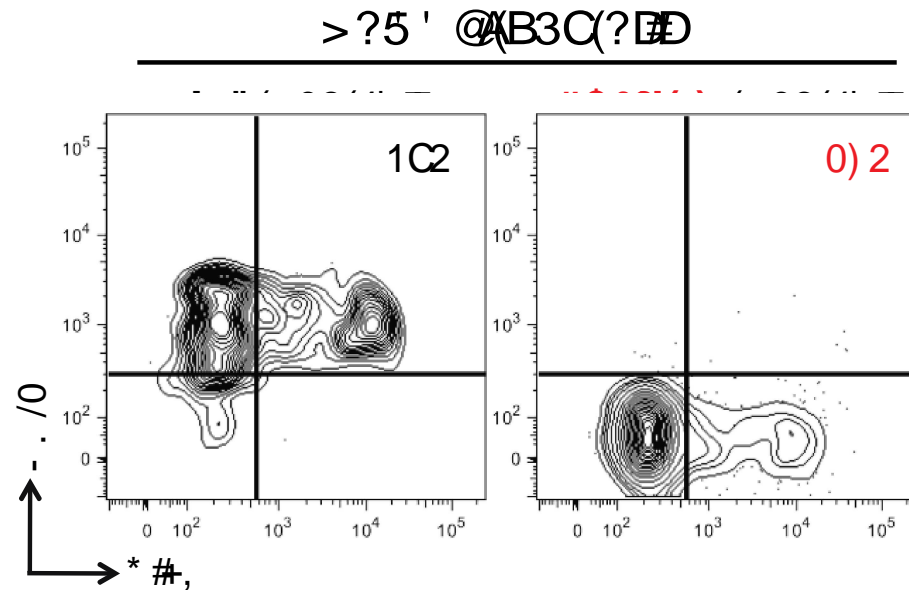
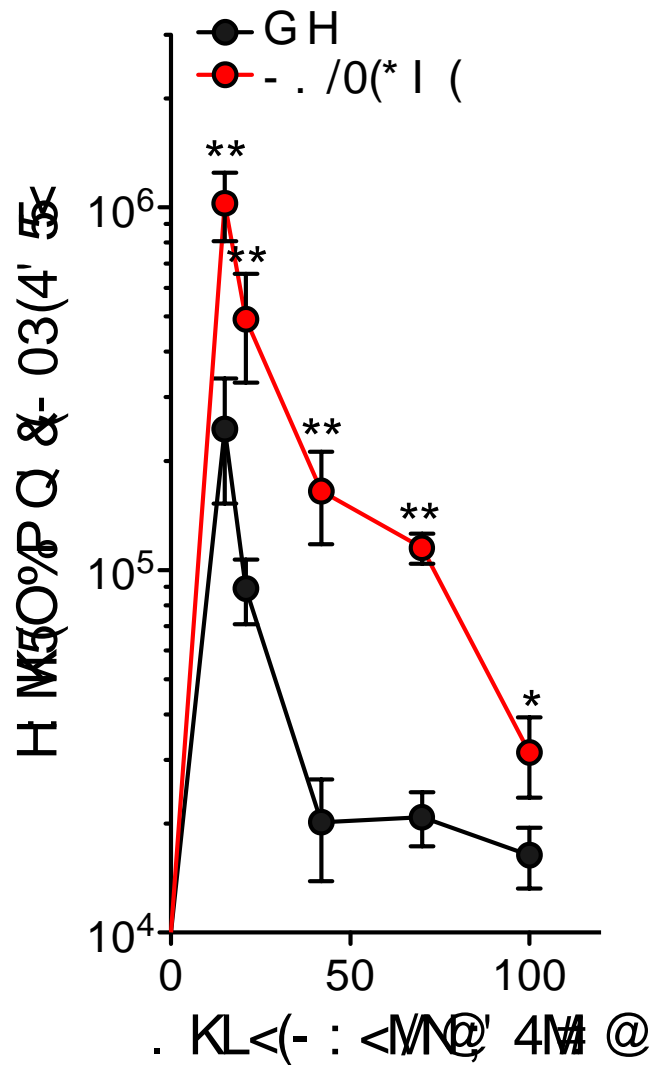
# PD-1 KO P14 cells Outnumber WT P14 cells during Chronic Viral Infection



# PD-1 KO P14 cells Have Altered Expression of Tbet and Eomes during Chronic Infection

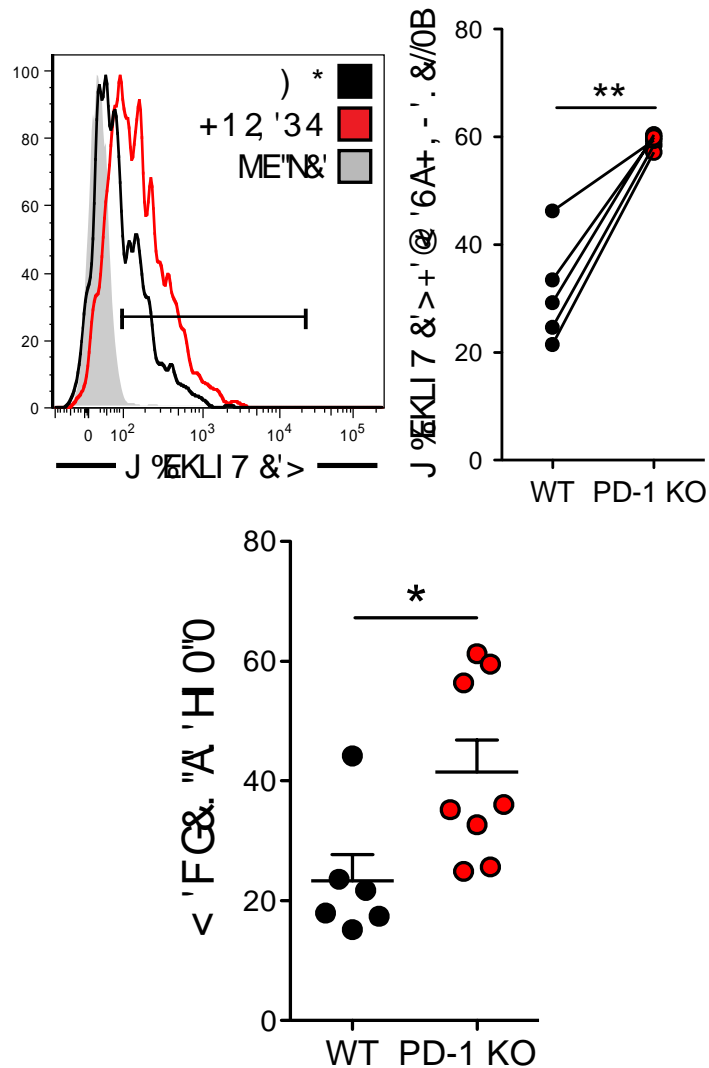


# Greater attrition of exhausted CD8 T cells in the genetic absence of PD-1

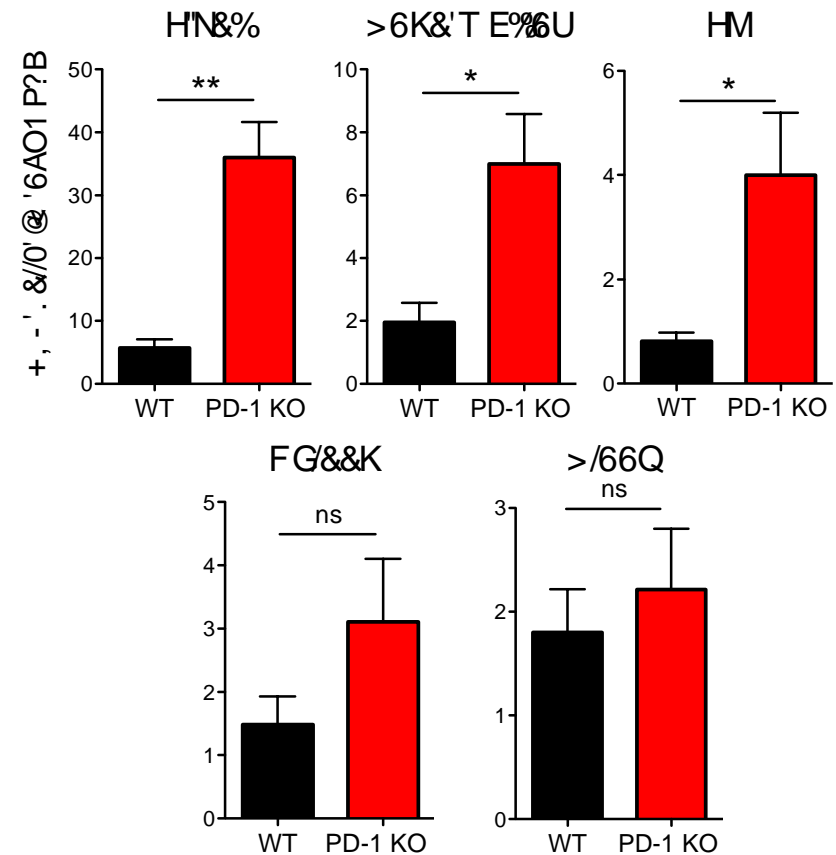


# Enhanced cytotoxicity and peripheral tissue localization without PD-1

## Cytotoxicity



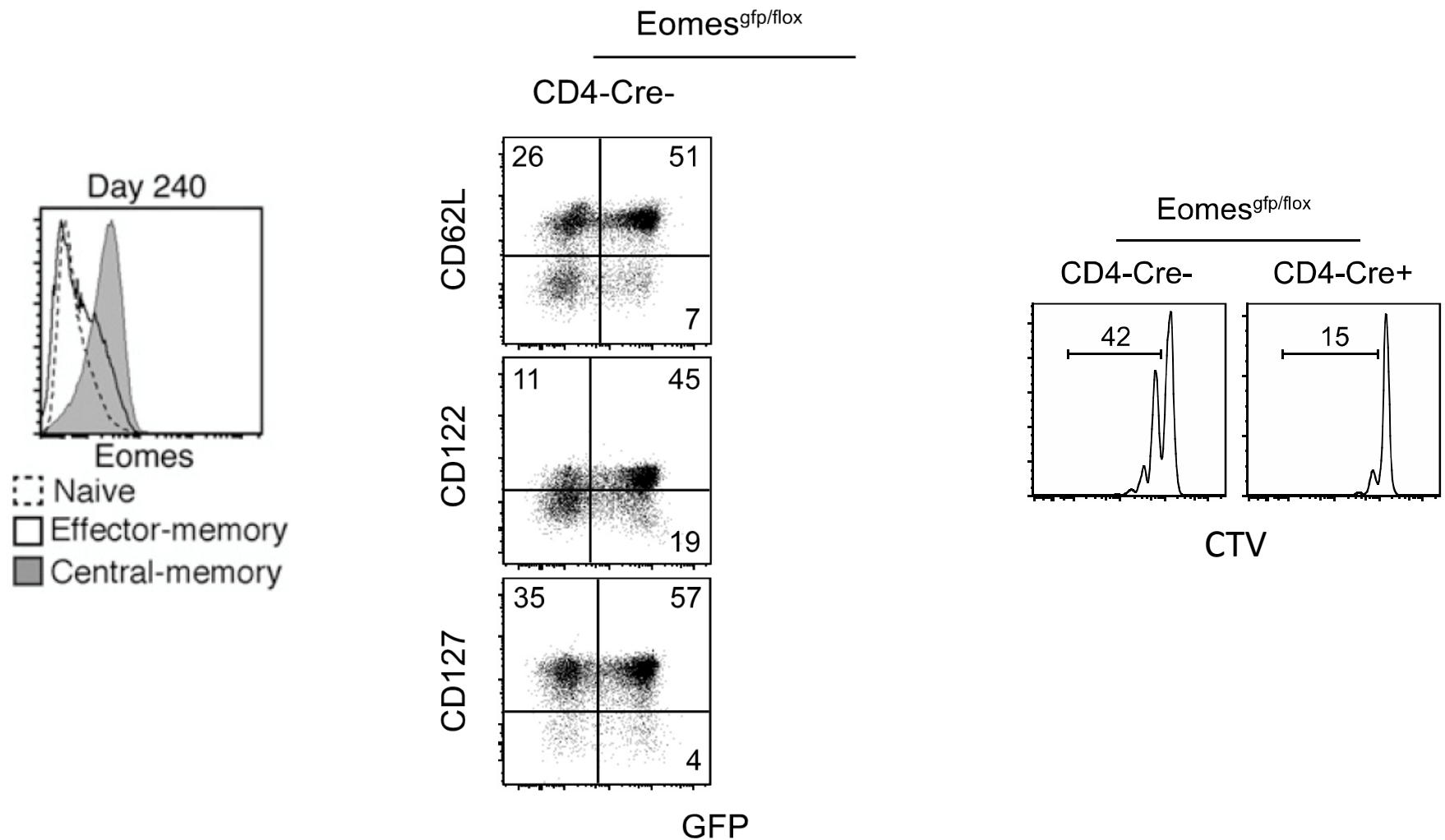
## Tissue localization



\*\*\*Similar results with PD-1 pathway blockade

- **Loss of PD-1 → initial proliferative benefit, but cells rapidly skew towards terminal exhaustion**
- **Removing PD-1 fosters the Eomes<sup>Hi</sup> subset with enhanced tissue distribution and killing**
- **How to use this information to inform human checkpoint blockade therapy?**
- **Eomes<sup>Hi</sup>PD-1<sup>Hi</sup> subset**

# Eomes is normally associated with functional Central Memory T cells



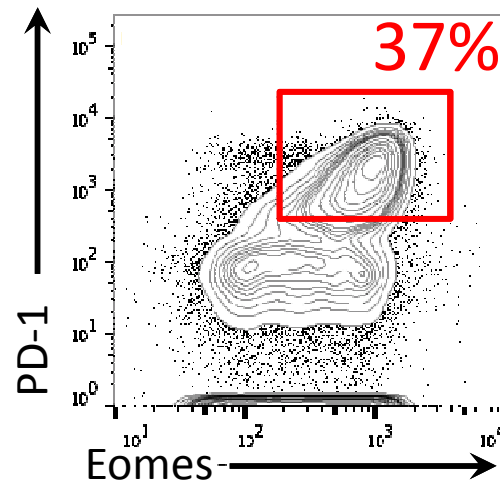
Banerjee, *J* 2010

Paley, *JLB* 2012

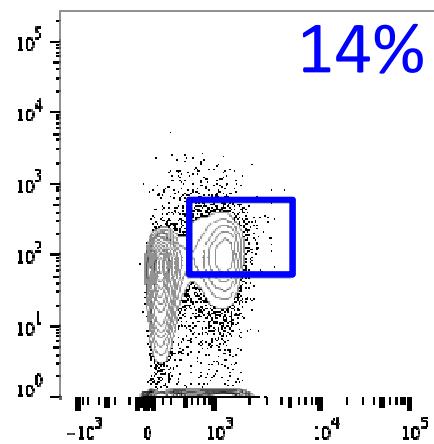
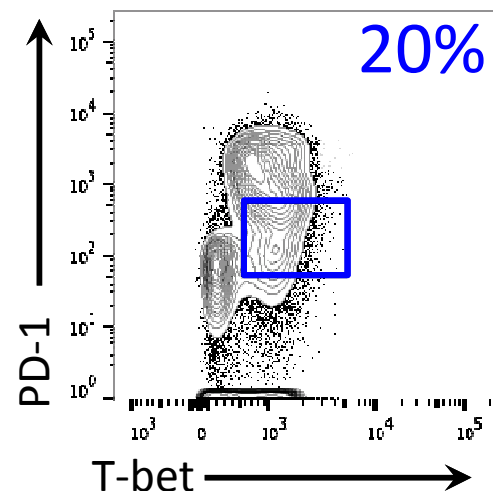
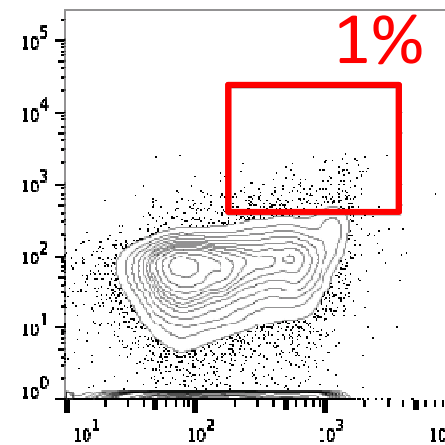
Zhou, *Immunity* 2010

# Can Eomes<sup>Hi</sup>PD-1<sup>Hi</sup> cells be used as a surrogate of changes in exhausted T cells?

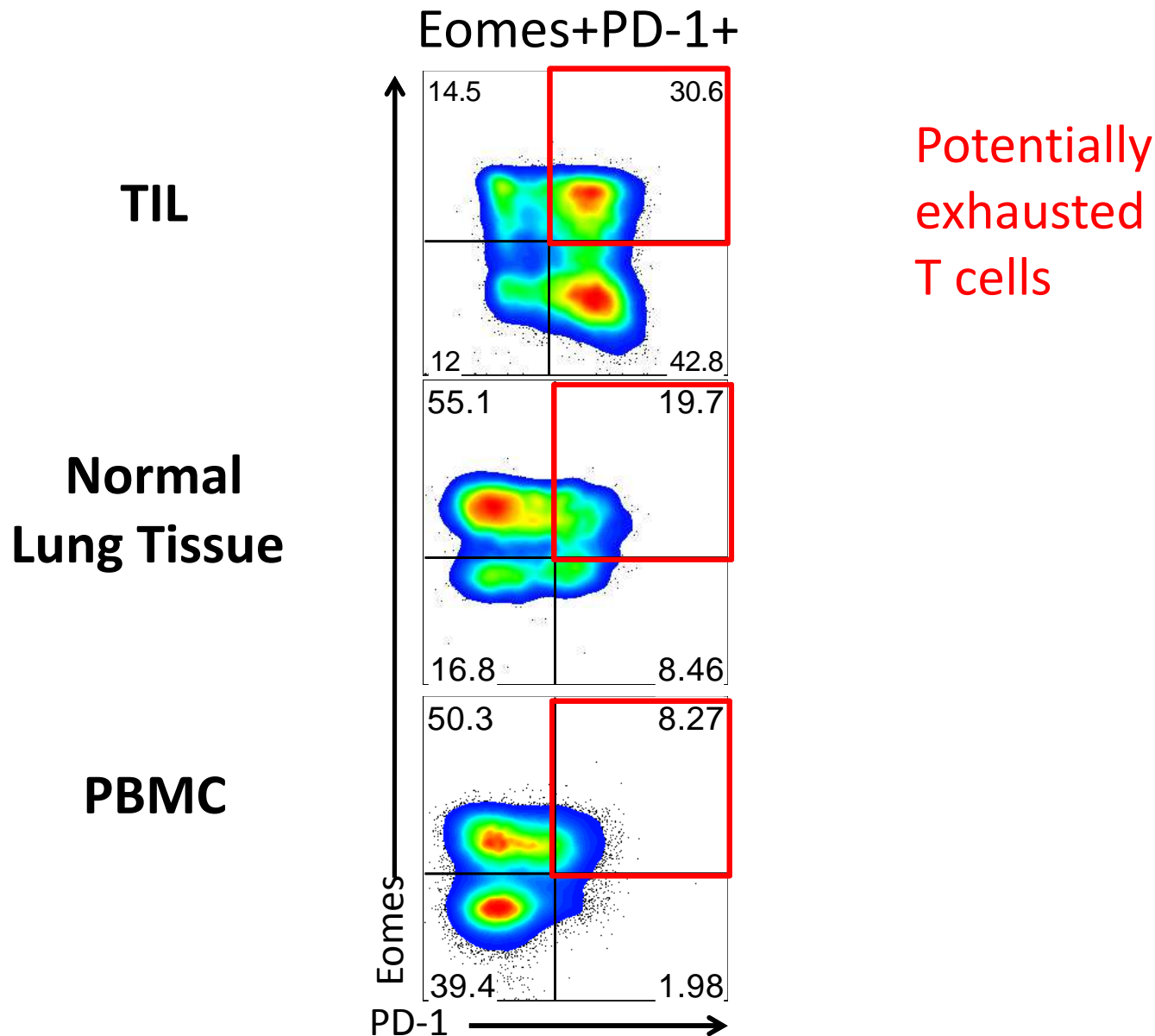
## Chronic Infection



## Memory

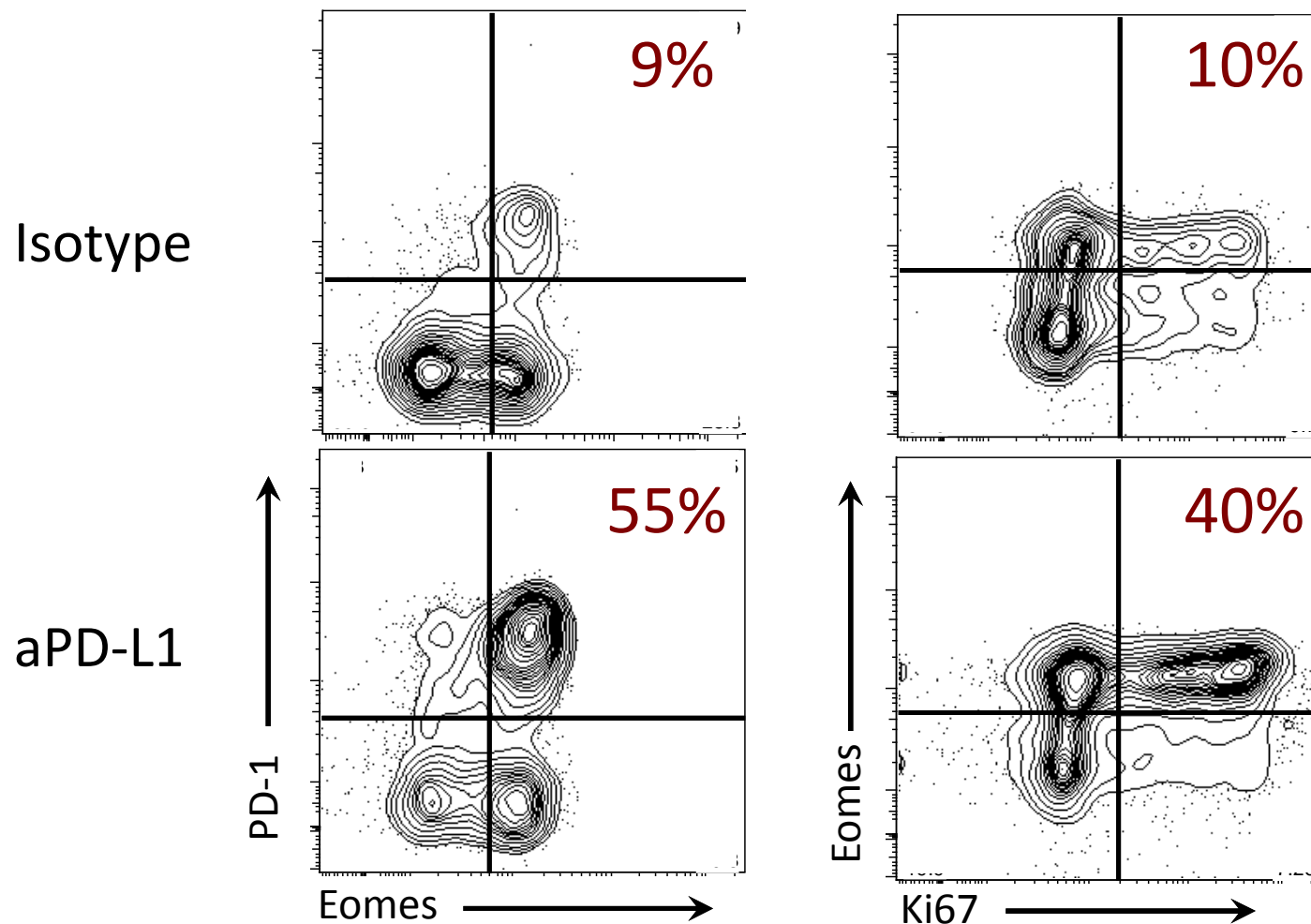


# T-bet and Eomes Expression in Human Tumor Tissue





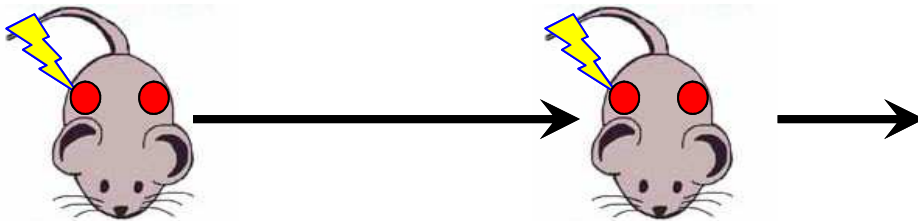
# Can Eomes<sup>Hi</sup>PD-1<sup>Hi</sup> cells be used as a surrogate of changes in exhausted T cells?



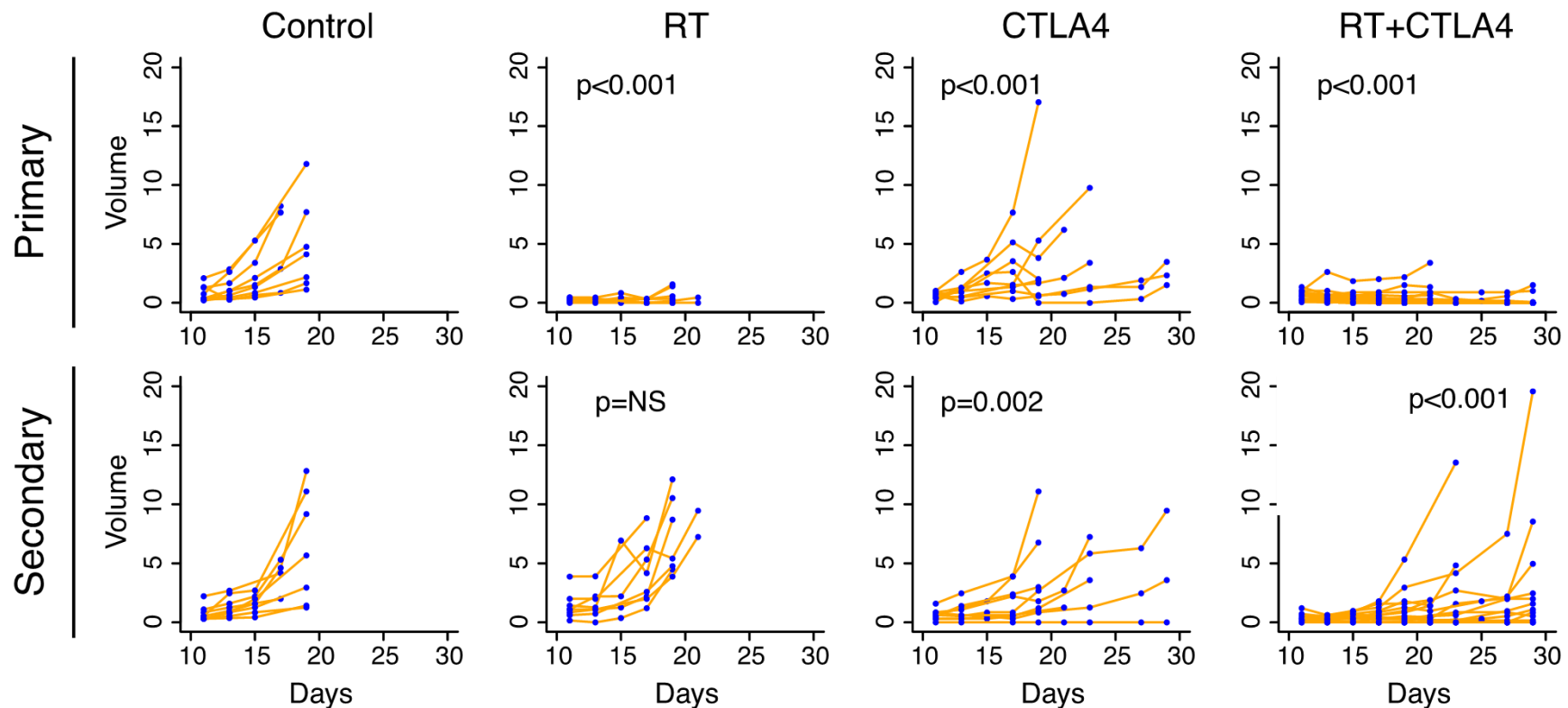
LCMV clone 13 after 2 weeks of aPD-L1  
Spleen  
Gated on CD8+

Pam Odorizzi / Kristen Pauken

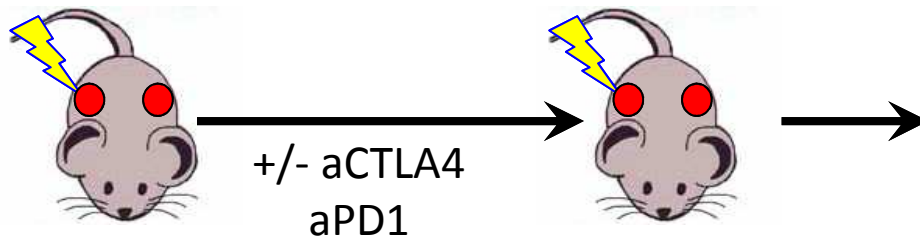
# A model for testing Eomes<sup>Hi</sup>PD-1<sup>Hi</sup> cells as a surrogate for immunotherapy



- Effect on unirradiated tumor
- Combination of Rad + anti - IRs “RadVax”
- Immune parameters
- Reversal of Exhaustion signatures



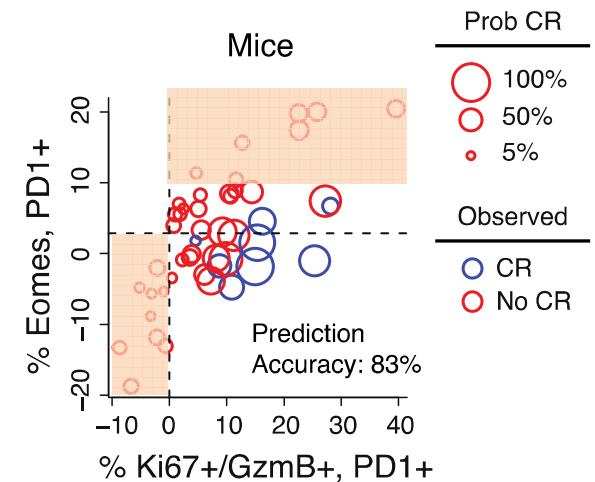
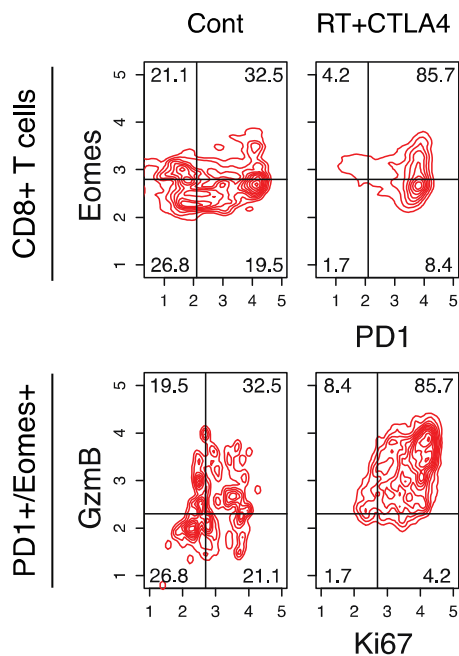
# A model for testing Eomes<sup>Hi</sup>PD-1<sup>Hi</sup> cells as a surrogate for immunotherapy



- Immune parameters
- Reversal of Exhaustion signatures
- Are Eomes+PD-1+ cells a surrogate of response to immunotherapy

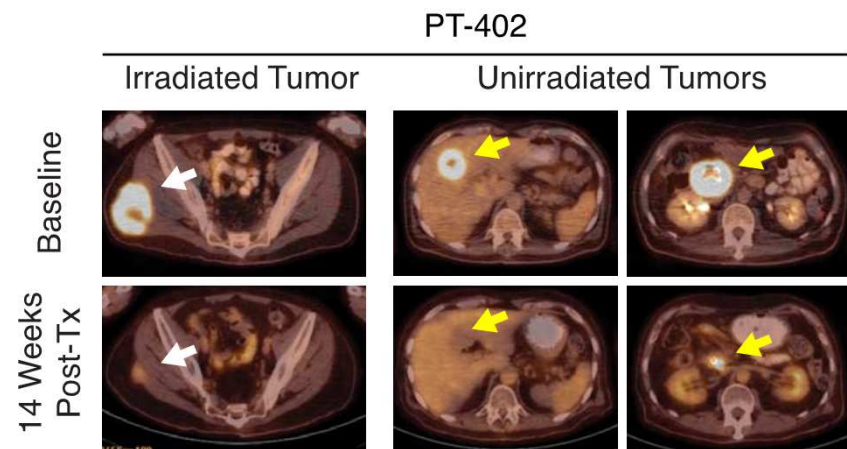
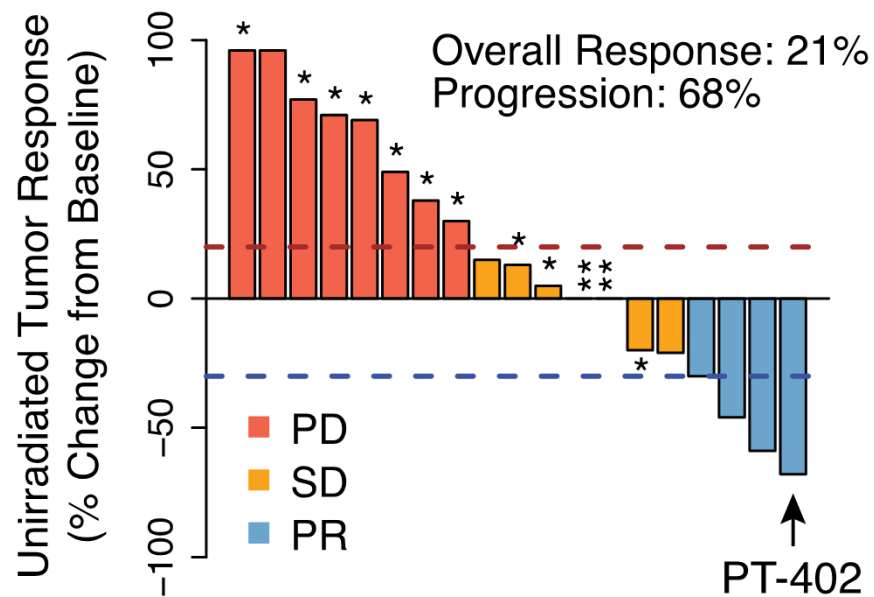
Sensitive or resistant tumors

B16



# What about humans?

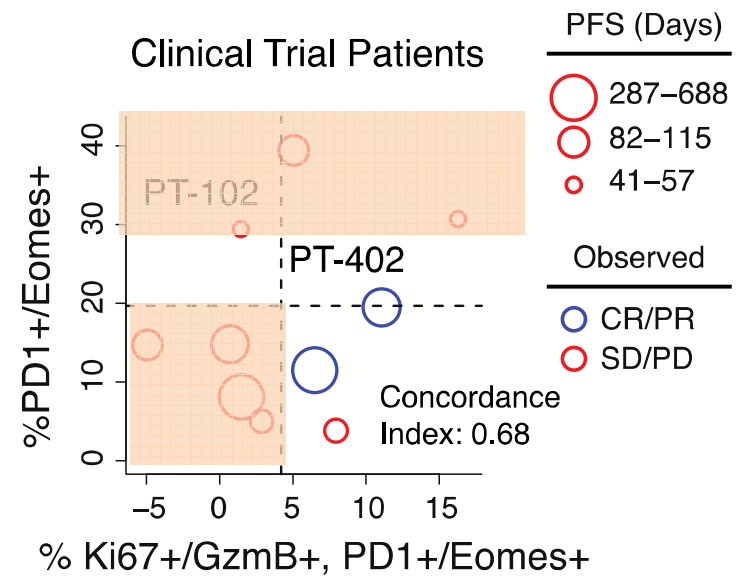
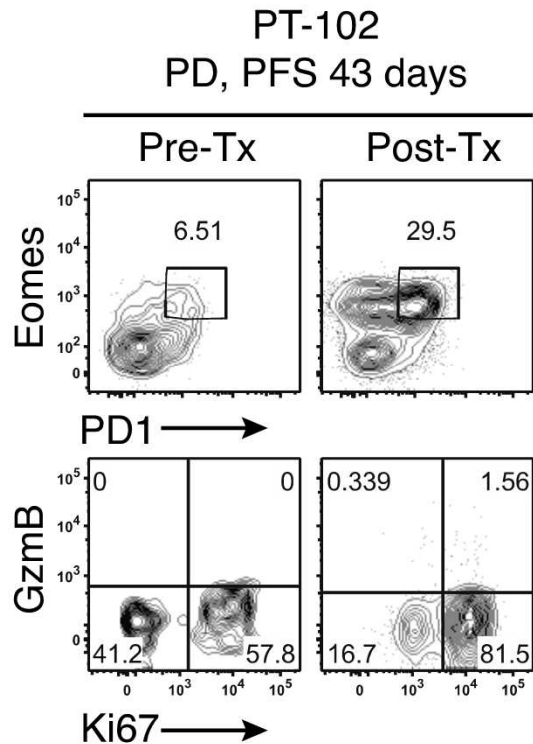
19 patients treated with “RadVax”  
4 PR, 2 SD



2-3 cycles of hypofractionated radiation to index site  
4 cycles of Ipilimumab  
RECIST and FDG-PET

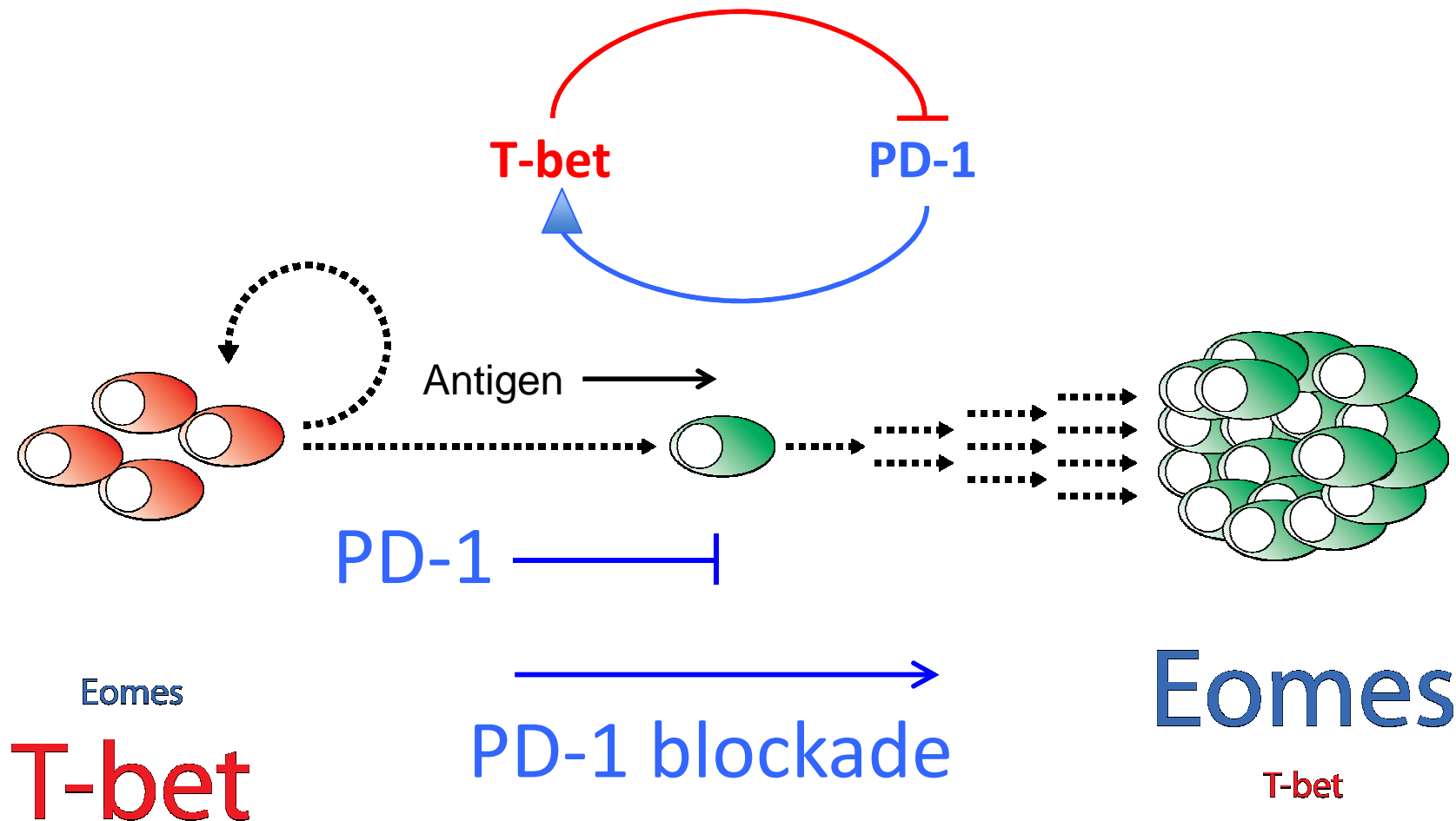
Twyman-Saint Victor, Rech, Pauken, Minn, Vonderheide

# What about humans?



# Changes in PD-1, T-bet and Eomes accompany subset conversion during chronic infection

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# Key Points

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- T cell exhaustion is clinically relevant
- Mouse models have been key to dissecting exhaustion
- Inhibitory receptors play a key role and are important therapeutic targets, but exhaustion can occur without PD-1
- T-bet and Eomes control a proliferative hierarchy in exhausted T cells → dissecting the mechanisms informs human clinical trials
- *Changes in Eomes<sup>Hi</sup>PD-1<sup>Hi</sup> exhausted cells correlate with response to immunotherapy → T-bet<sup>Hi</sup> progenitors may be the underlying mechanism*

# Acknowledgements

## Wherry lab

Mohammed Ali  
John Attanasio  
Bertram Bengsch  
**Shawn Blackburn**  
Travis Doering  
Sarah Henrickson  
Ramin Herati  
Alex Huang  
Jonathan Johnnidis  
Makoto Kurachi  
**Pam Odorizzi**  
**Michael Paley**  
Olesya Palko  
**Kristen Pauken**  
Erietta Stelekati  
Vesko Tomov  
Laura Vella

## UPenn

**Andy Minn**  
**Christina Twyman**  
**Bob Vonderheide**  
**Andrew Rech**  
**Steve Hahn**  
**Amit Maity**  
Lynn Schuchter  
Tara Gangadhar  
Mike Feldman  
George Xu  
Steve Albelda  
Evgeniy Eruslanov  
Sunil Singhal  
Gwenn Danet-Desnoyers

## Other Collaborators

**Steven Reiner**  
**Arlene Sharpe**  
**Gordon Freeman**  
**Nick Haining**  
**Tony Barnitz**

Supported by NIH/NIAID:

AI071309; AI078897; AI105343  
U19 AI083022; U19 AI082639  
Dep. of Radiation Oncology;  
Cancer Research Institute

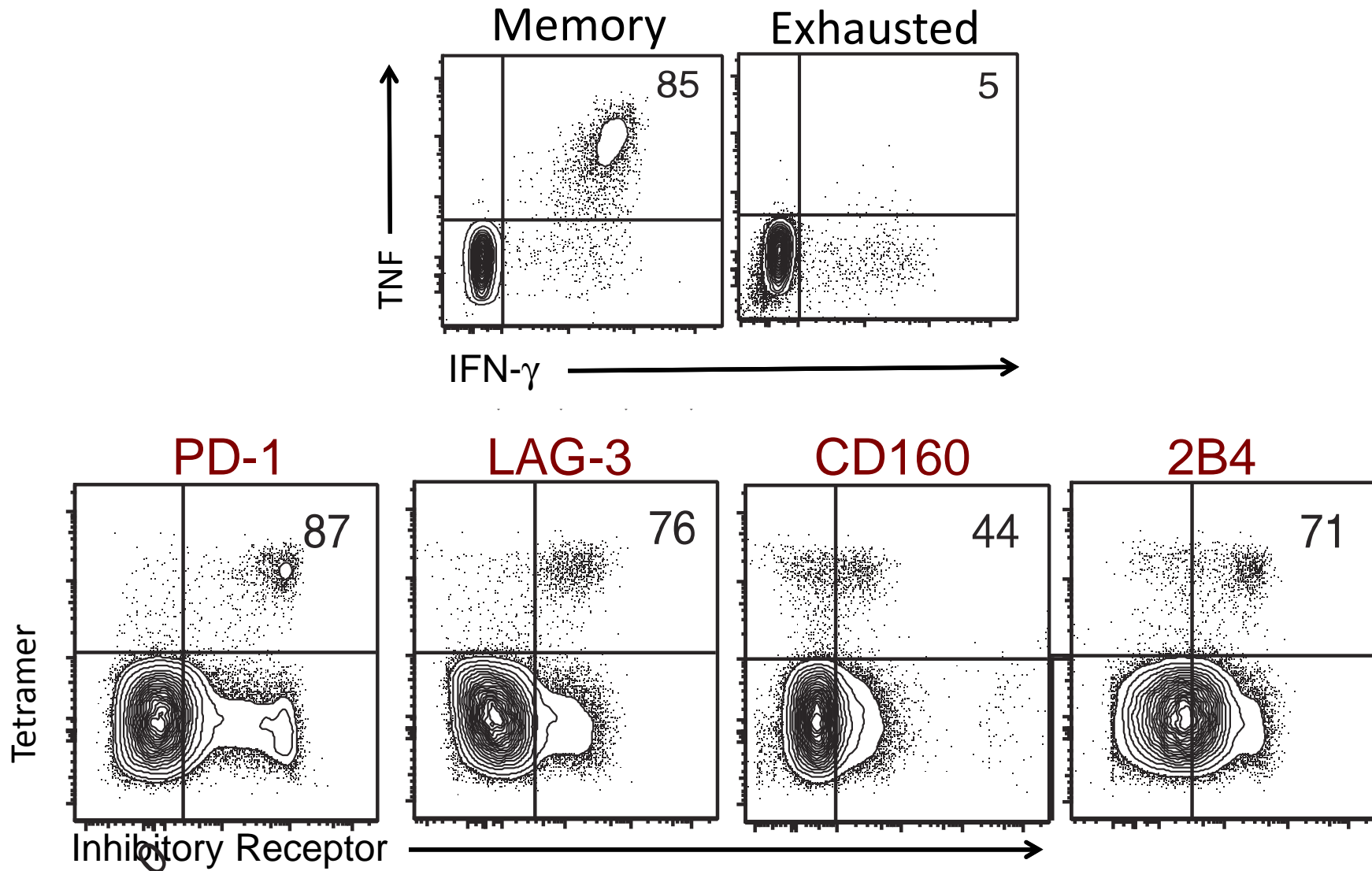


***Institute for Immunology***<sub>24</sub>





# T cell exhaustion



Moskophidis D, *Nature* 1993; Gallimore A, *J Exp Med* 1998; Zajac AJ, *J Exp Med* 1998; Lee P. *Nat Med* 1999; Lechner F. *J Exp Med* 2000; Wherry EJ, *J Virol* 2003; Fuller MJ, *J Immunol* 2004; Barber DL *Nature* 2006; Day CL. *Nature* 2006; Wherry EJ *Immunity* 2007; Blackburn SD *Nat Immunol* 2009; Nakamoto N. *PLoS Pathog* 2009; Wherry EJ *Nat Immunol* 2011