

T-cell Exhaustion in Leukemia Relapse Post Allogeneic Stem Cell Transplantation

Hong Zheng, M.D., Ph.D.

Assistant Professor of Medicine

Penn State Hershey Cancer Institute

Penn State University College of Medicine

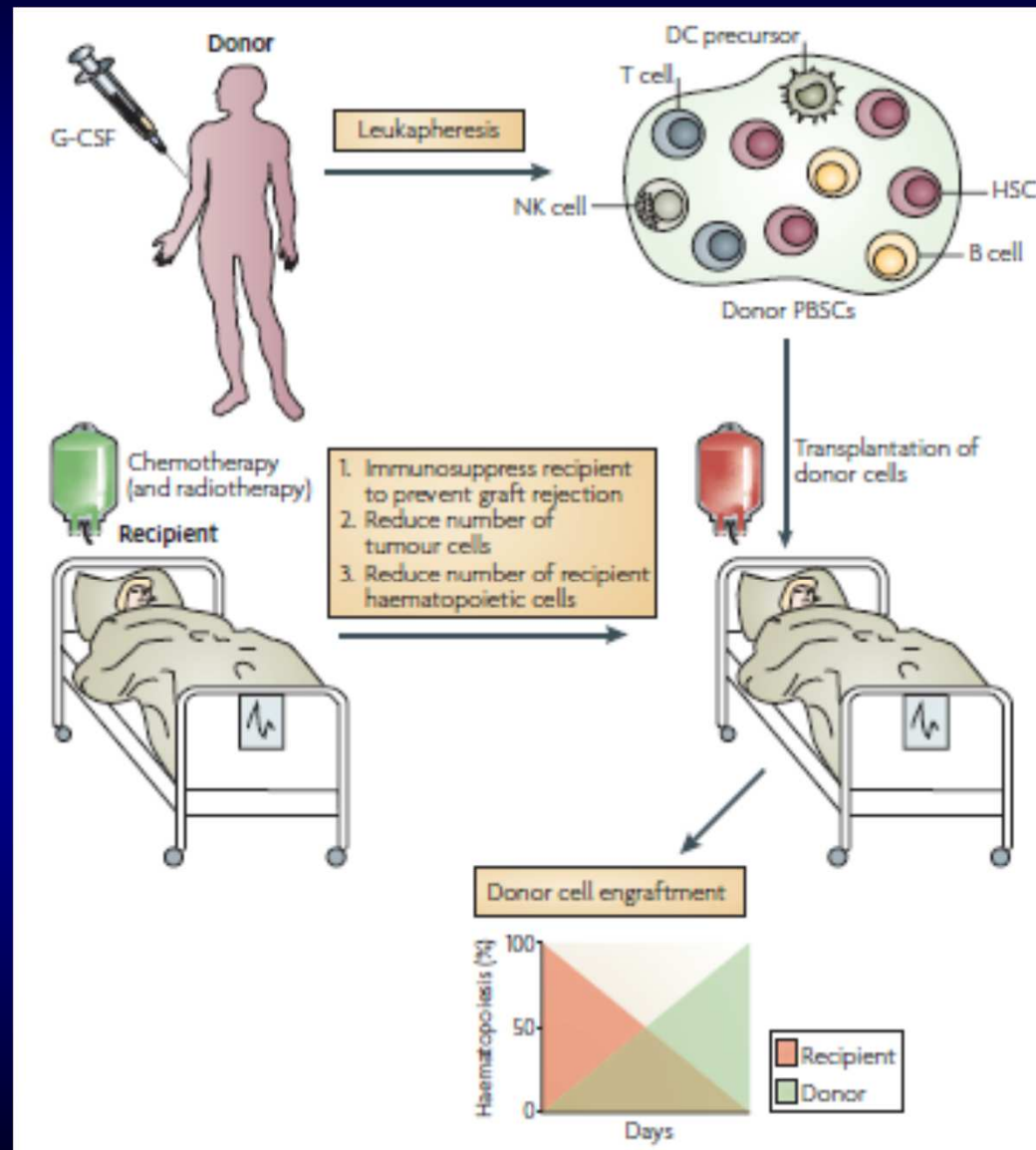
Presenter Disclosure Information

Hong Zheng M.D., Ph.D.

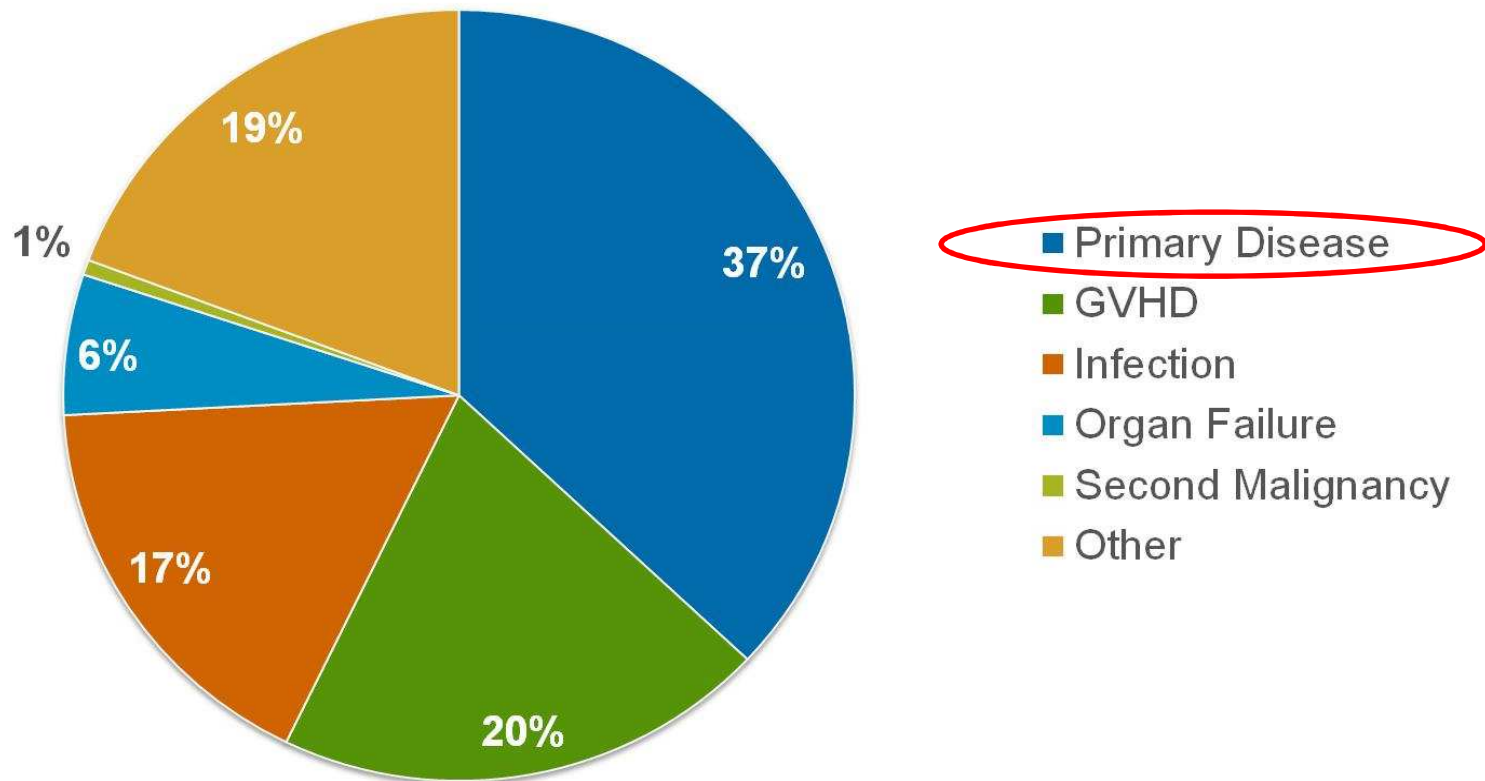
The following relationships exist related to this presentation:

No Relationships to Disclose

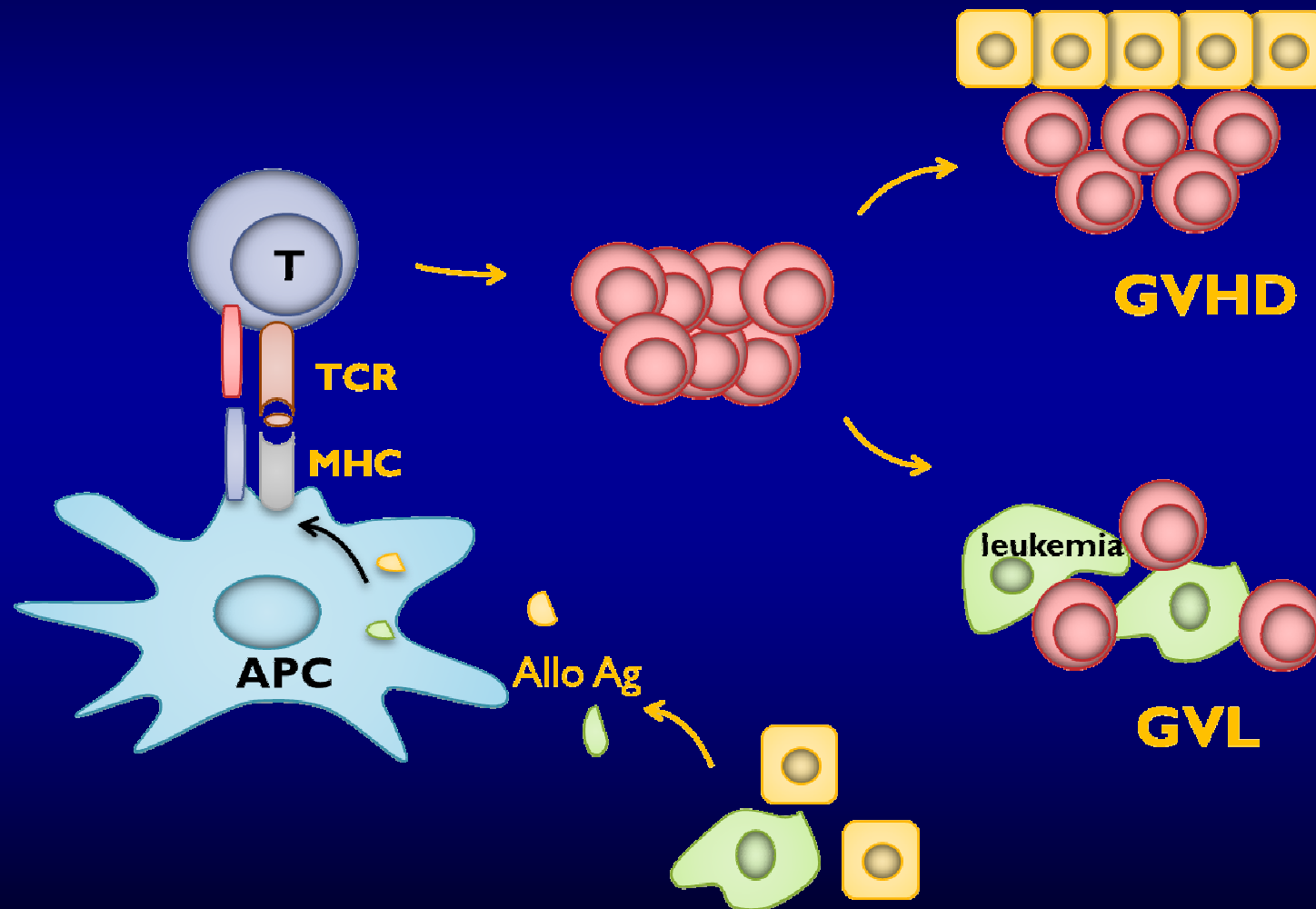
Allogeneic Stem Cell Transplant



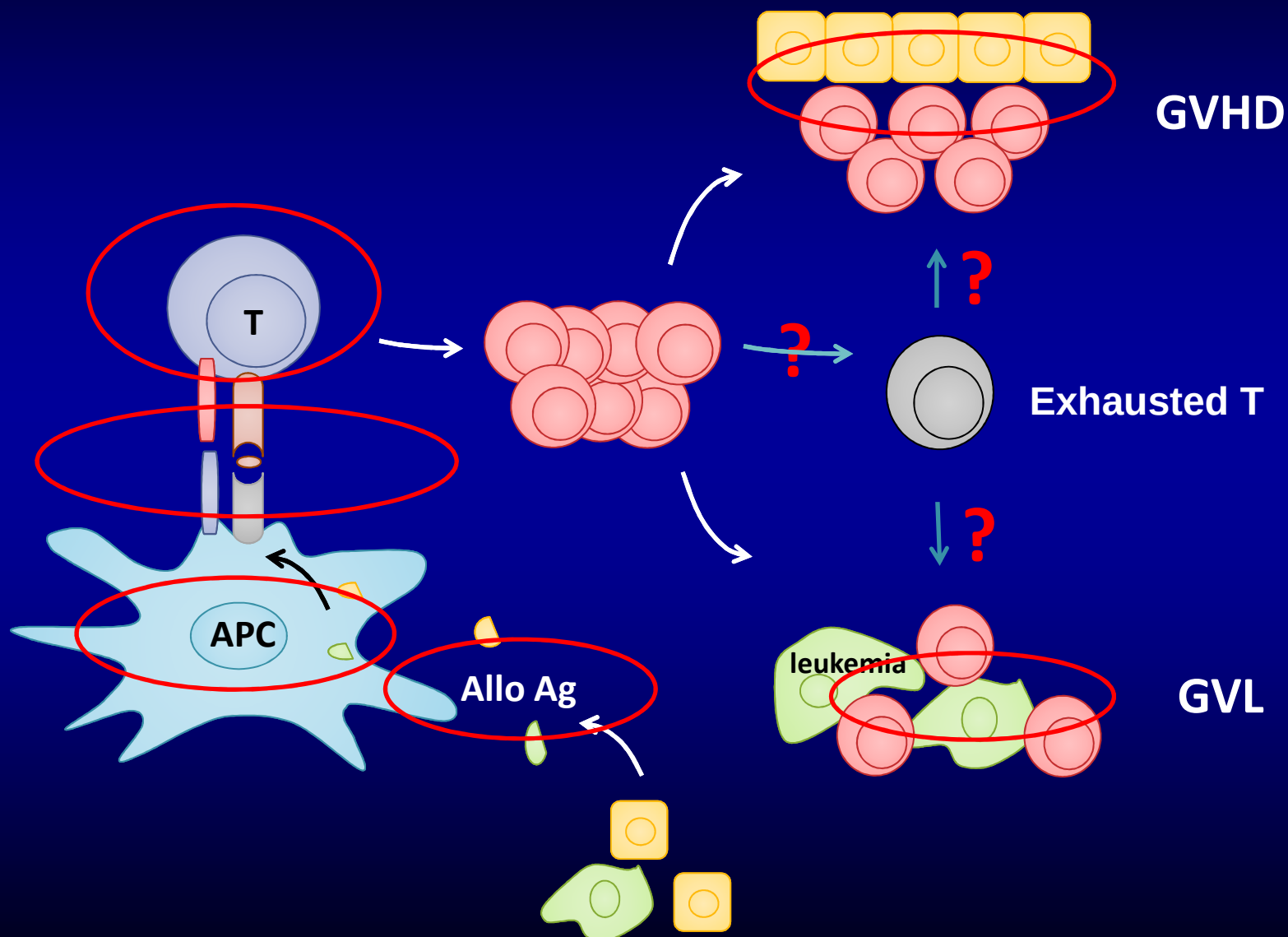
Causes of Death after Unrelated Donor Transplants done in 2011-2012



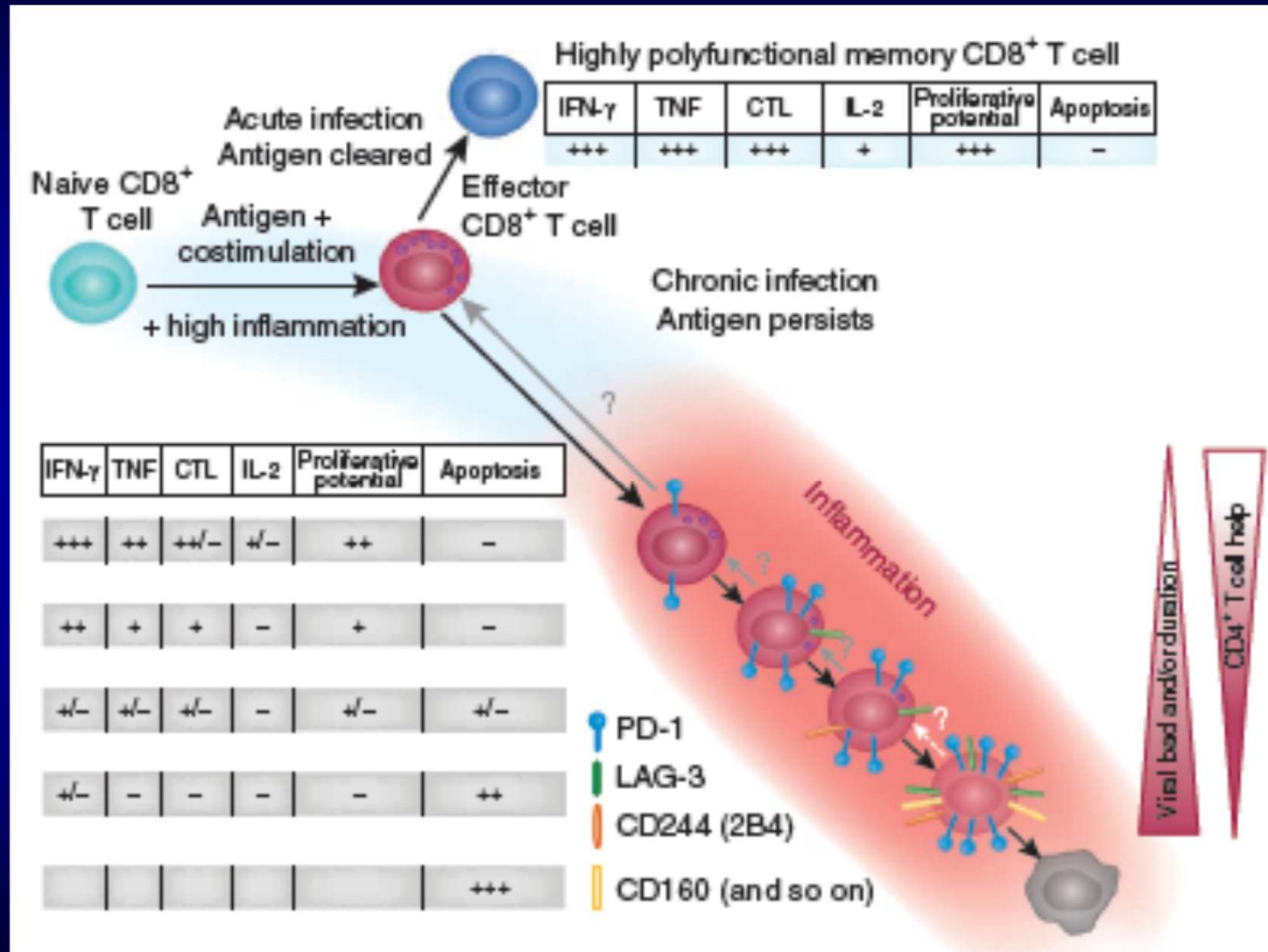
Graft versus Leukemia (GVL) and Graft versus Host Disease (GVHD)



Strategies to Enhance GVL Without Causing GVHD

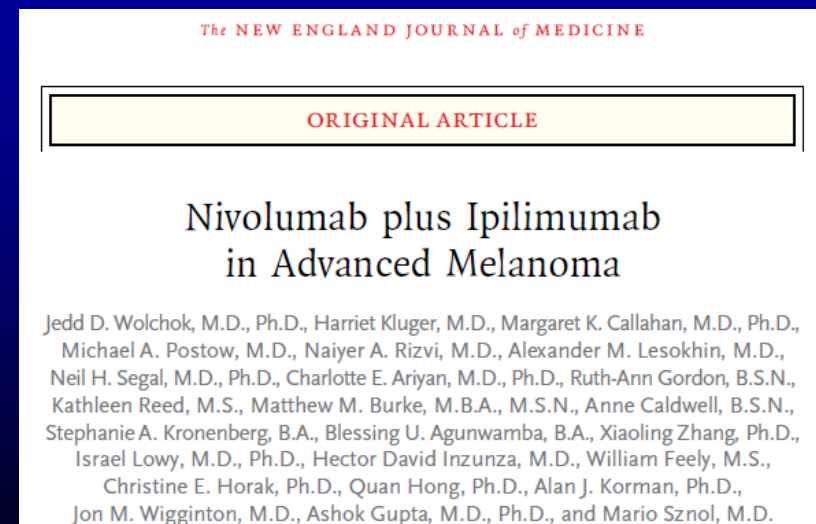
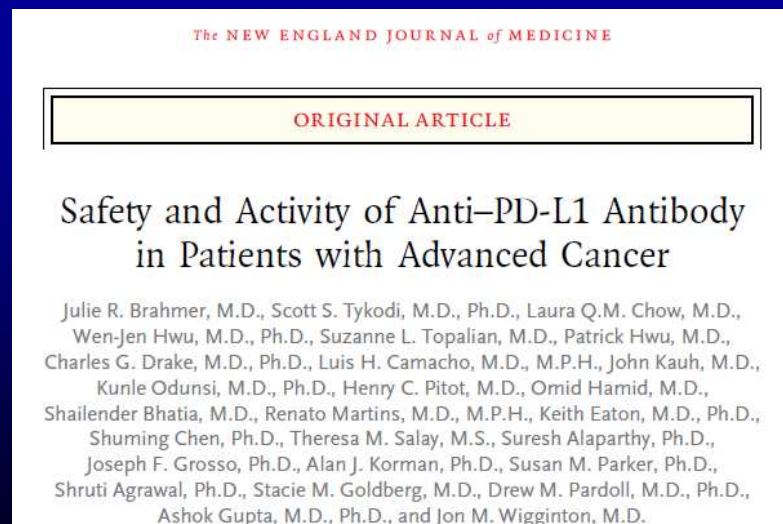
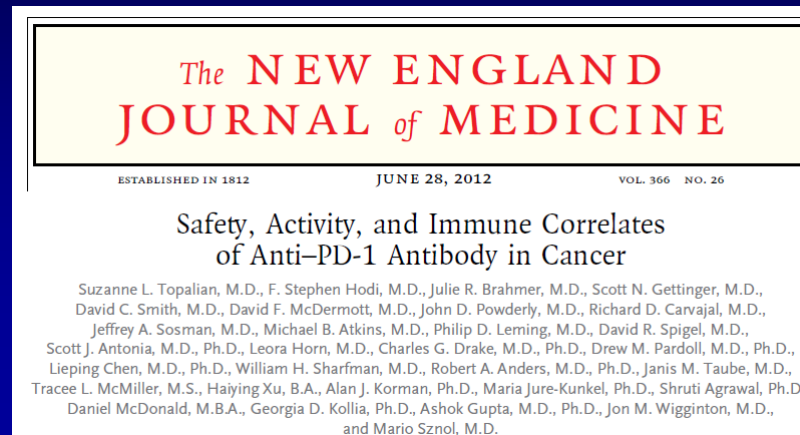


T cell Exhaustion



Wherry EJ, Nature Immunol 2011

Targeting PD-1/PD-L1 for cancer therapy



Targeting PD-1 in AML therapy?

- Blockade of PD-1 pathway improves relapse-free survival in animal AML models.

Zhou Q et al., Blood 2011

- Gene expression of PD-L1 and PD-L2 are up-regulated in leukemia blast of MDS and AML patients.

Yang H et al., Leukemia 2013

- miHA-specific T cells express elevated PD-1 in a CML-AP and a AML patient post DLI. *In vitro* blockade of PD-1/PD-L1 pathway increased function of T cells from AML patients.

Norde WJ et al., Cancer Research 2011

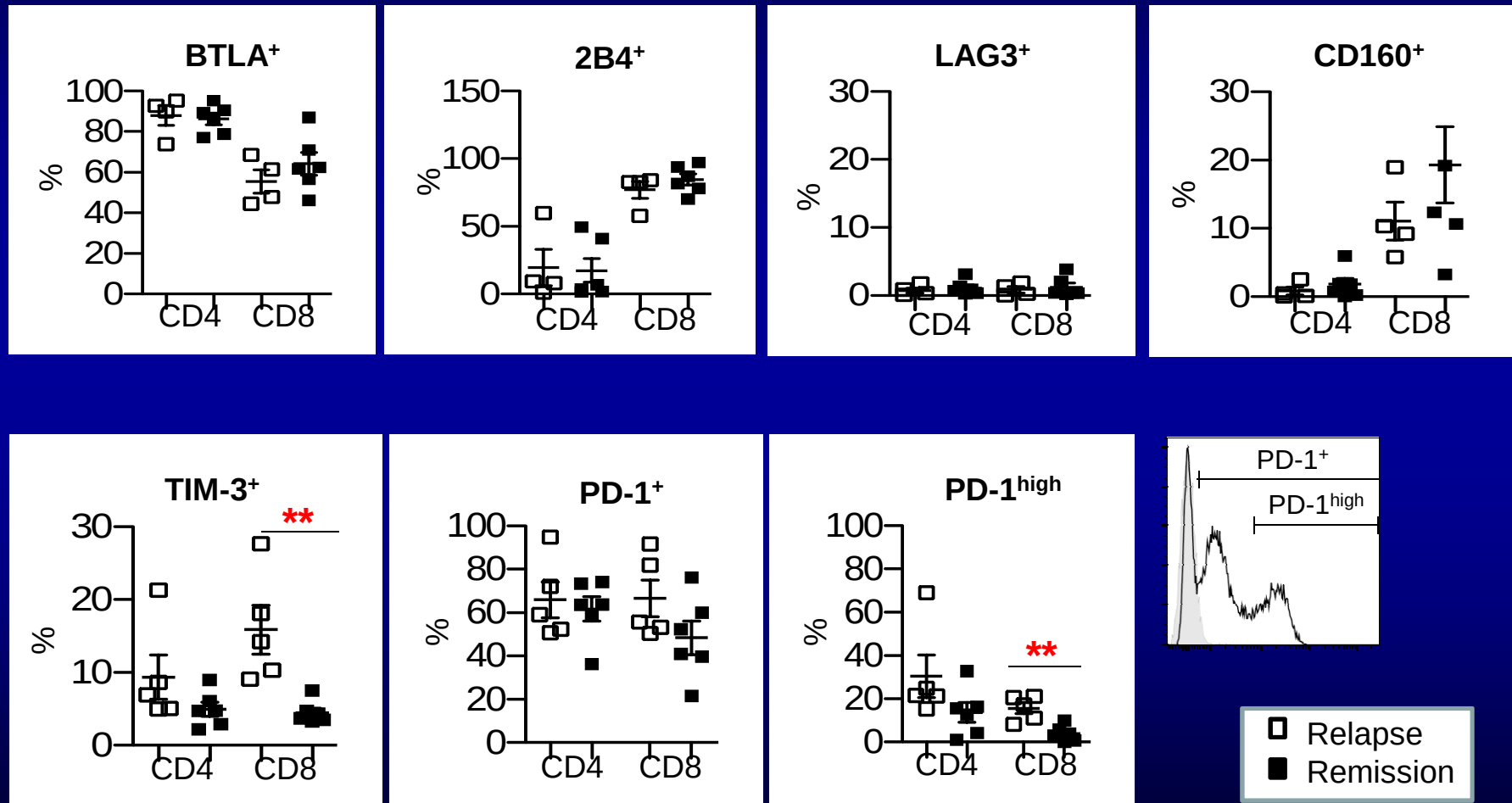
Hypothesis

- T cell exhaustion may contribute to GVL failure and leukemia relapse post alloSCT.
- Targeting key mediators of T cell exhaustion can be a promising leukemia therapeutic.

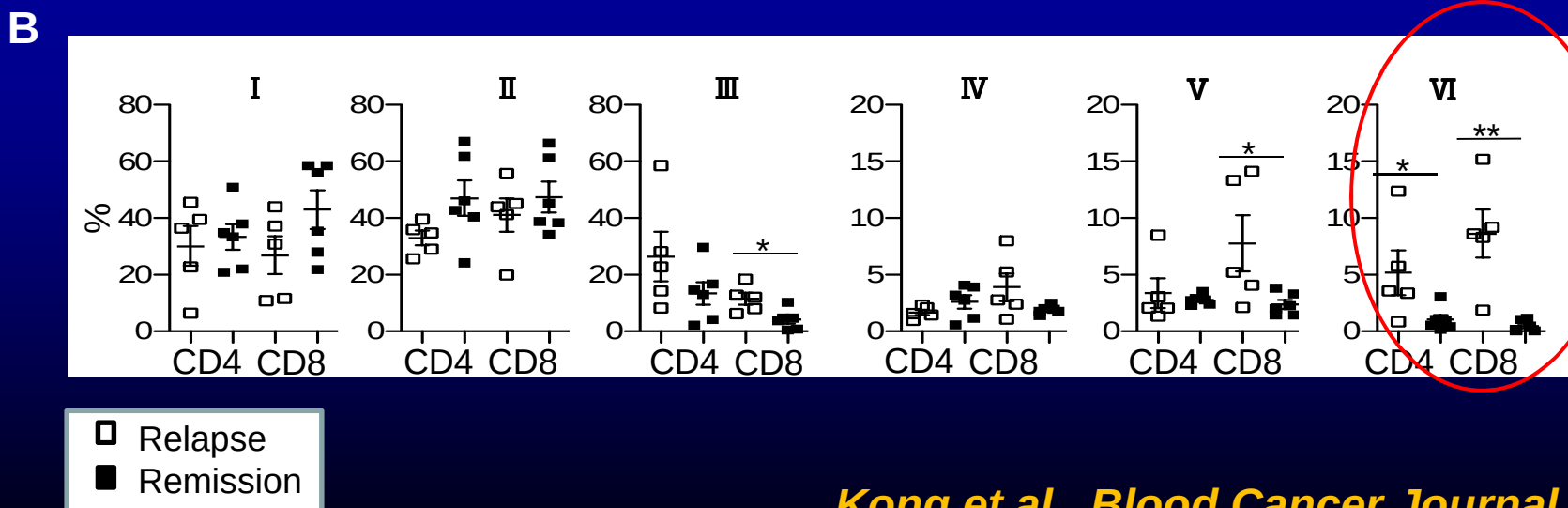
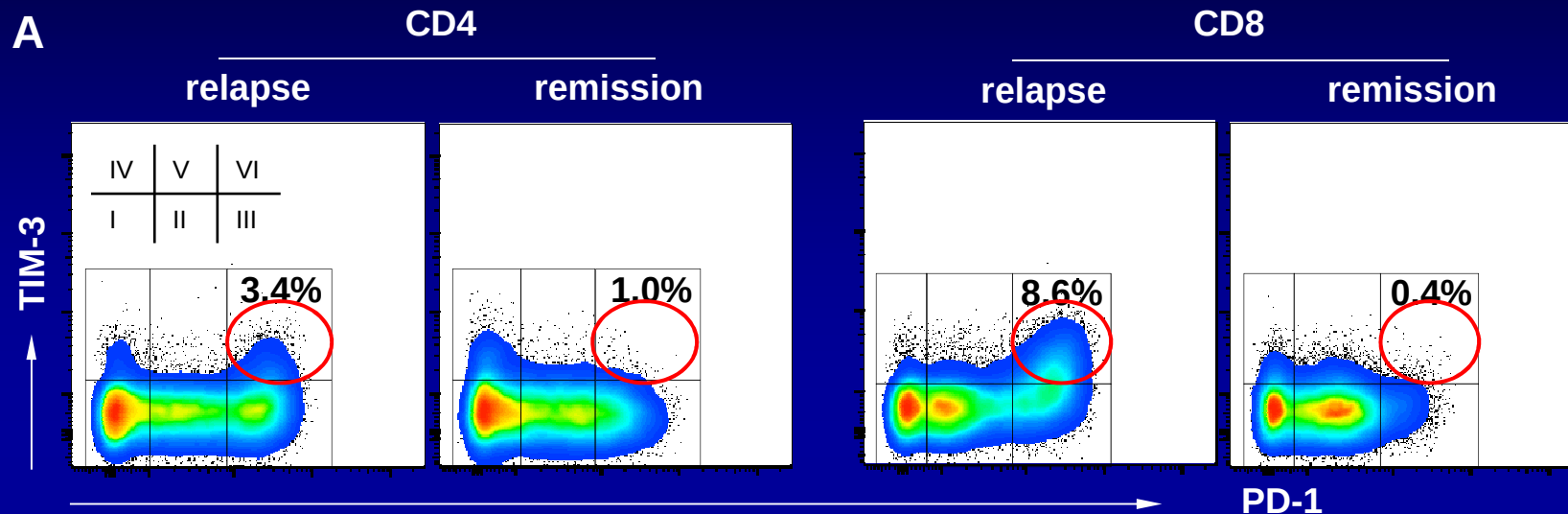
Clinical characteristic of patients

Patient	Age	Sex	Donor	Conditioning	GVHD prophylaxis	Disease status	Collection time
01	48	M	MUD/PB	Ablative Bu/Cy	MTX, ATG, Tacrolimus	Remission	6months
02	58	M	MUD/BM	Ablative Bu/Flu	MTX, ATG, Tacrolimus	Remission	6 months
03	68	F	MMUD/PB	Non-ablative Bu/Flu	MTX, Tacrolimus	Remission	3 months
04	45	M	MUD/PB	Ablative Bu/Flu	MTX, Tacrolimus	Remission	5 months
05	68	F	MSD/PB	Non-ablative Bu/Flu	MTX, Tacrolimus	Remission	4 months
06	67	F	MSD/PB	Non-ablative Bu/Flu	MTX, Tacrolimus	Remission	3 months
07	59	M	MSD/PB	Non-ablative Bu/Flu	MTX, Tacrolimus	Relapse	4 months
08	52	M	MSD/PB	Ablative Bu/Flu	MTX, Tacrolimus	Relapse	6 months
09	64	F	MUD/PB	Non-ablative Bu/Flu	MTX, Tacrolimus	Relapse	5 months
10	53	F	MUD/PB	Ablativ Bu/Flu	MTX, Tacrolimus	Relapse	3 months
11	47	M	MSD/PB	Ablative Bu/Cy	MTX, Tacrolimus	Relapse	2 months

PD-1 and TIM-3 are enhanced in patients with leukemia relapse

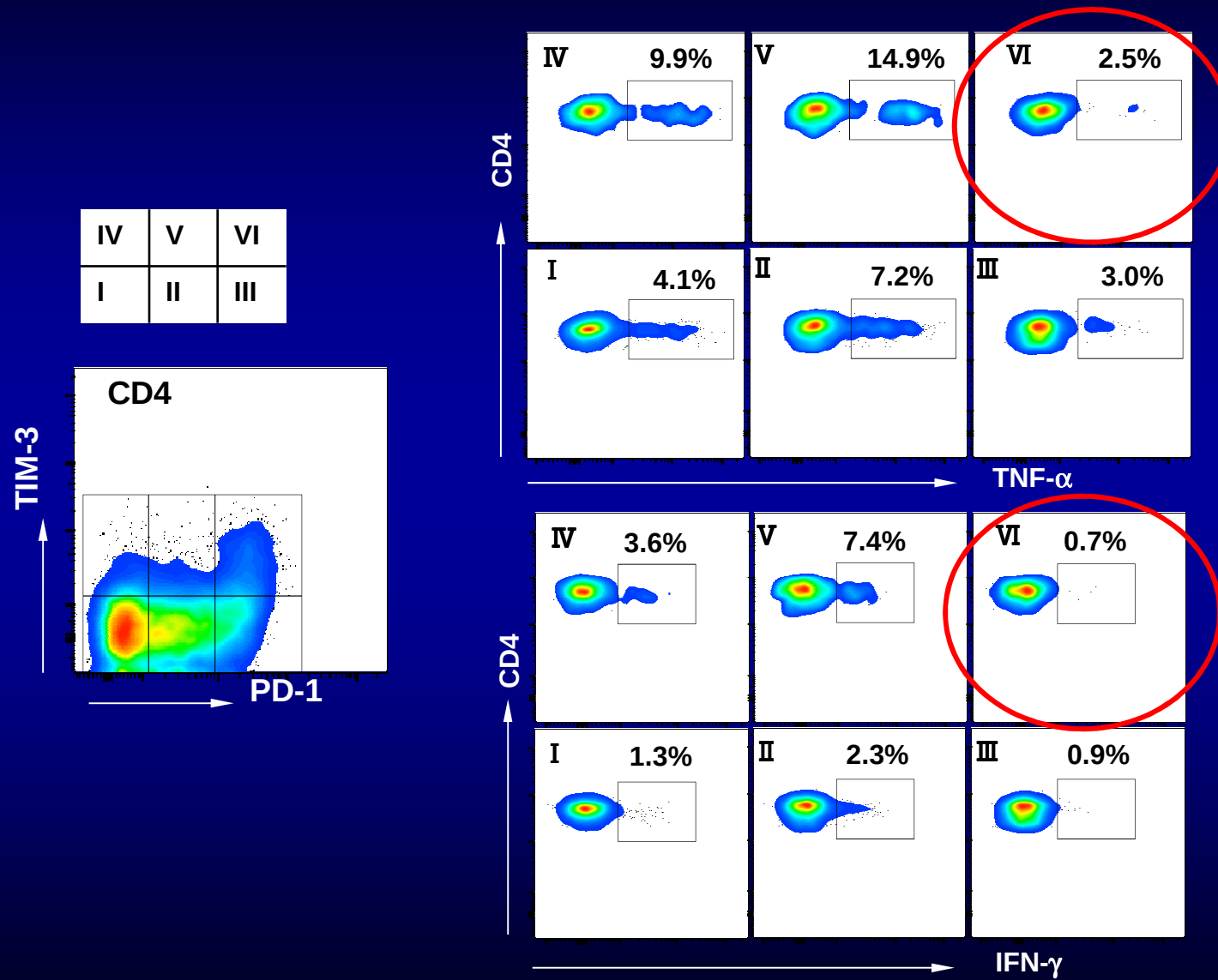


PD-1^{hi} TIM-3⁺ cells associate with leukemia relapse post allSCT

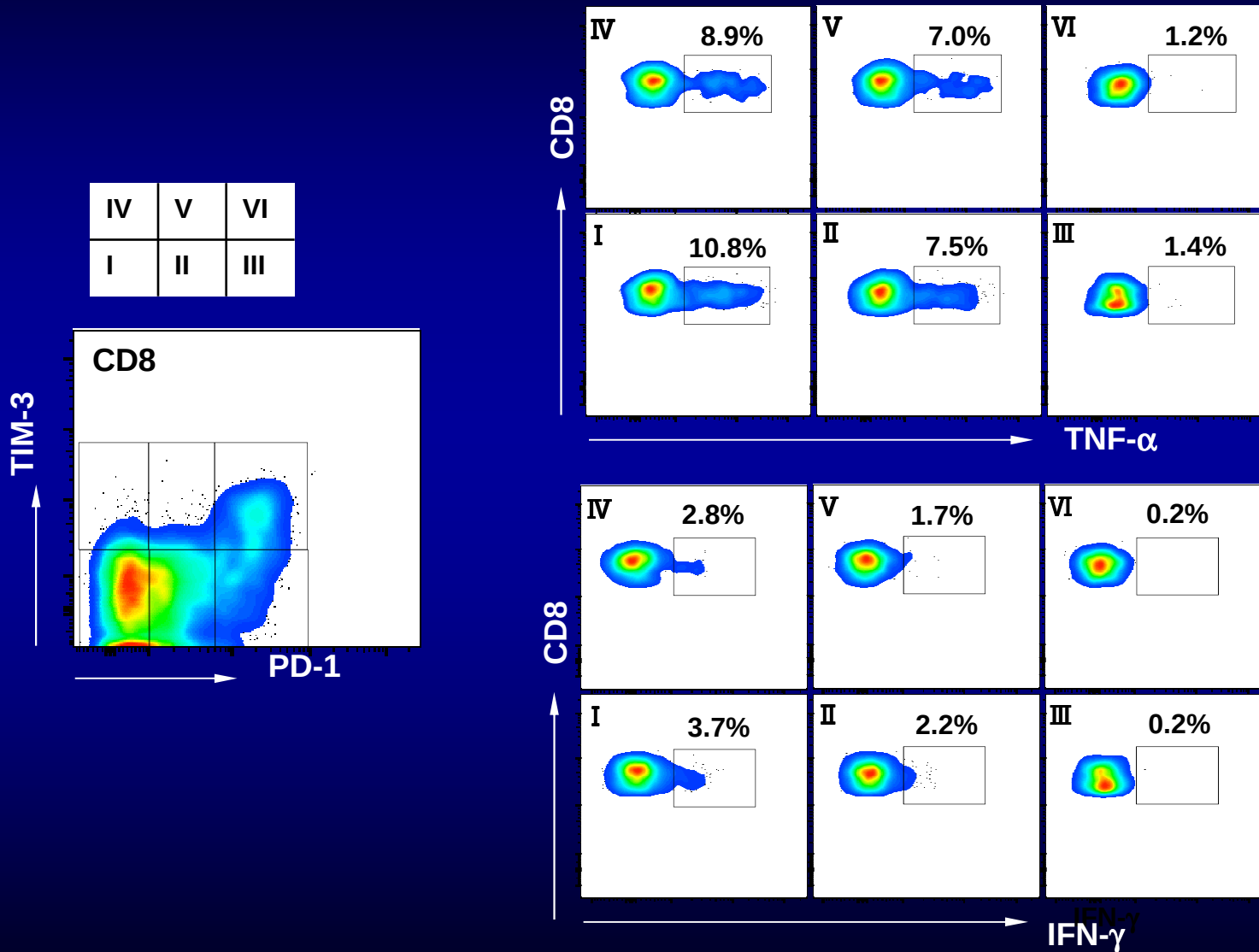


Kong et al., Blood Cancer Journal, 2015

PD-1^{hi} TIM-3⁺ cells produce less cytokines (CD4)



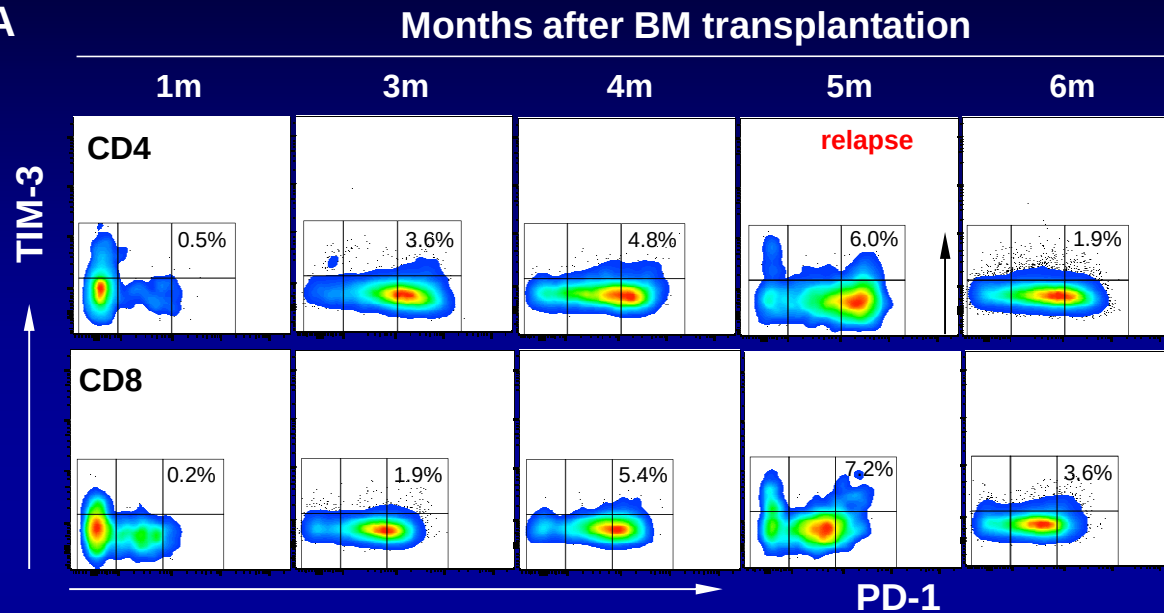
PD-1^{hi} TIM-3⁺ cells produce less cytokines (CD8)



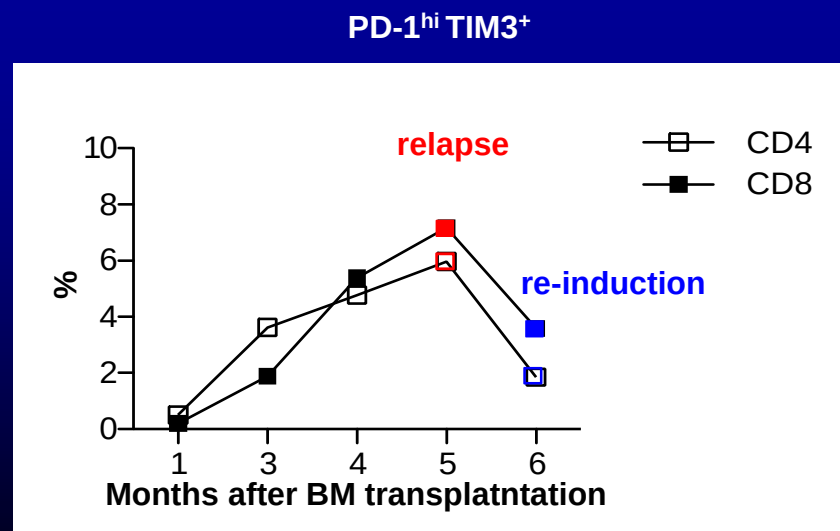
Kong et al., Blood Cancer Journal, 2015

Increase of PD-1^{hi} TIM-3⁺ cells predict leukemia relapse

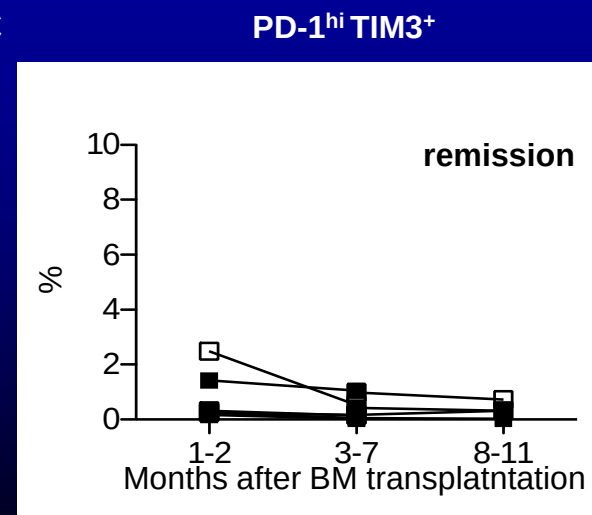
A



B

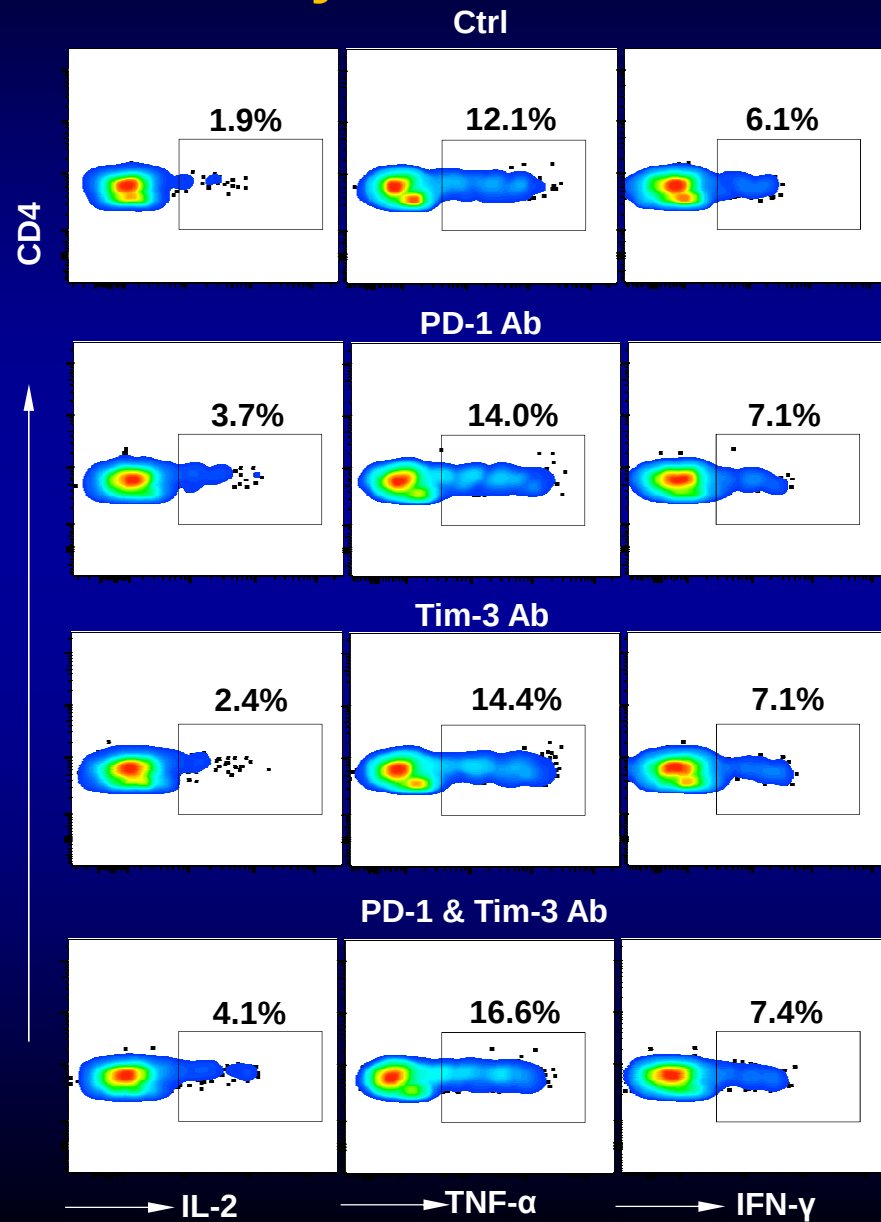


C



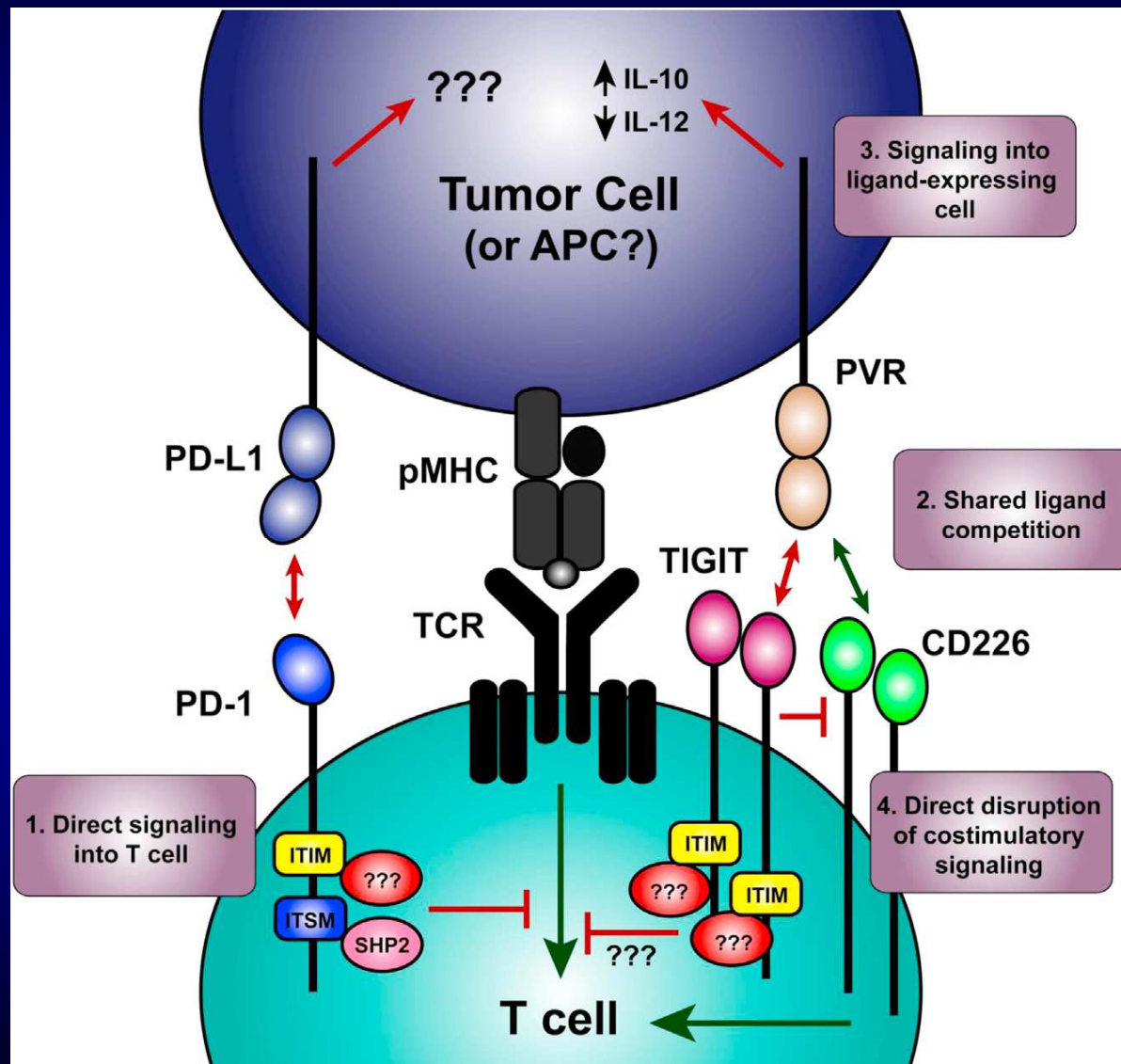
Kong et al., Blood Cancer Journal, 2015

Blockade of PD-1 and TIM-3 show moderate increase of cytokine release



Kong et al., Unpublished data

TIGIT (T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain)



TIGIT in Tumor immunity

Cancer Cell Article

The Immunoreceptor TIGIT Regulates Antitumor and Antiviral CD8⁺ T Cell Effector Function

Robert J. Johnston,¹ Laetitia Comps-Agrar,² Jason Hackney,³ Xin Yu,¹ Mahrugh Huseni,⁴ Yagai Yang,⁵ Summer Park,⁶ Vincent Javinal,⁵ Henry Chiu,⁷ Bryan Irving,¹ Dan L. Eaton,² and Jane L. Grogan^{1,7}

¹Department of Cancer Immunology

²Department of Protein Chemistry

³Department of Bioinformatics and Computational Biology

⁴Department of Oncology Biomarker Development

⁵Department of Translational Oncology

⁶Department of Translational Immunology

⁷Department of Biochemical and Cellular Pharmacology

Genentech, 1 DNA Way, South San Francisco, CA 94080, USA

*Correspondence: grogan.jane@gene.com

<http://dx.doi.org/10.1016/j.ccell.2014.10.018>

RESEARCH ARTICLE

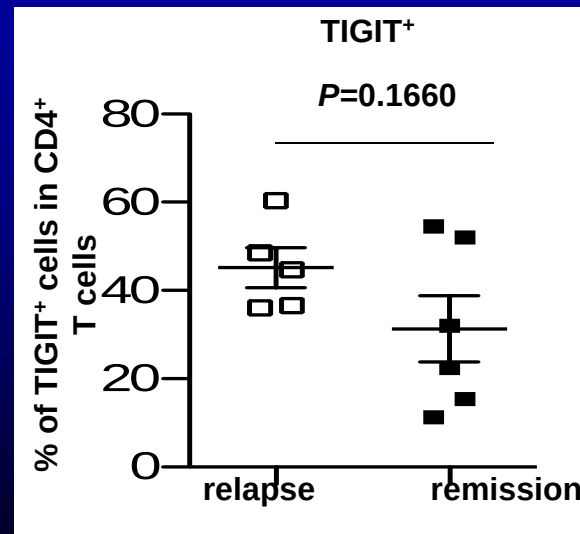
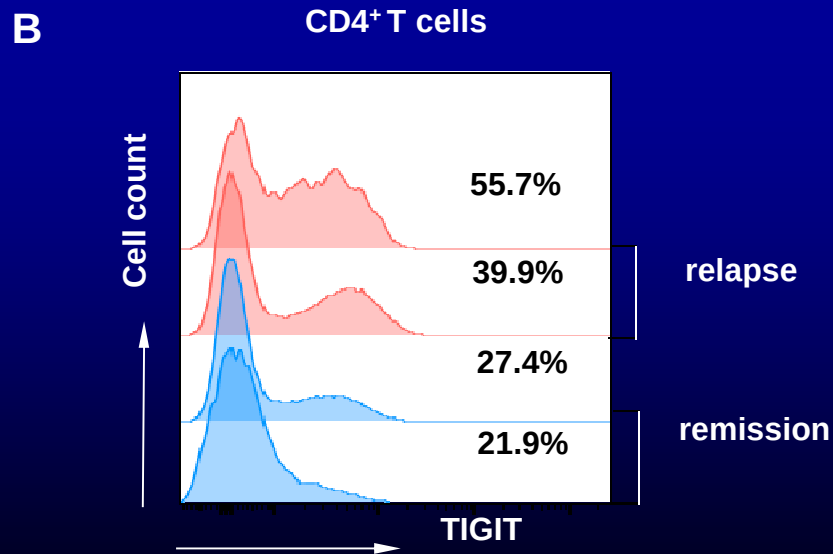
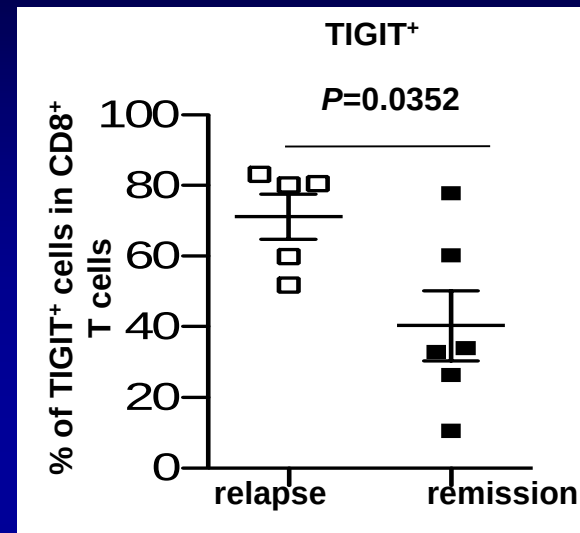
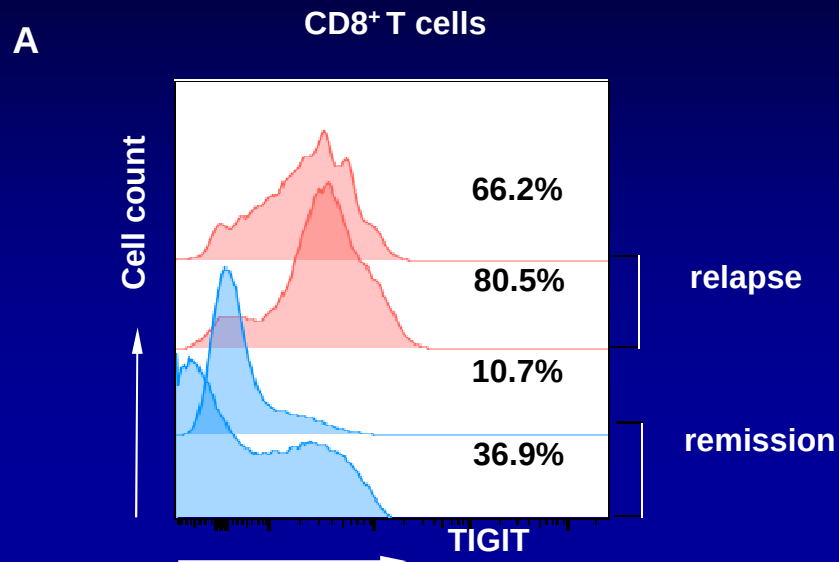
The Journal of Clinical Investigation

TIGIT and PD-1 impair tumor antigen-specific CD8⁺ T cells in melanoma patients

Joe-Marc Chauvin,¹ Ornella Pagliano,¹ Julien Fourcade,¹ Zhaojun Sun,¹ Hong Wang,² Cindy Sander,¹ John M. Kirkwood,¹ Tseng-hui Timothy Chen,³ Mark Maurer,³ Alan J. Korman,³ and Hassane M. Zarour^{1,4}

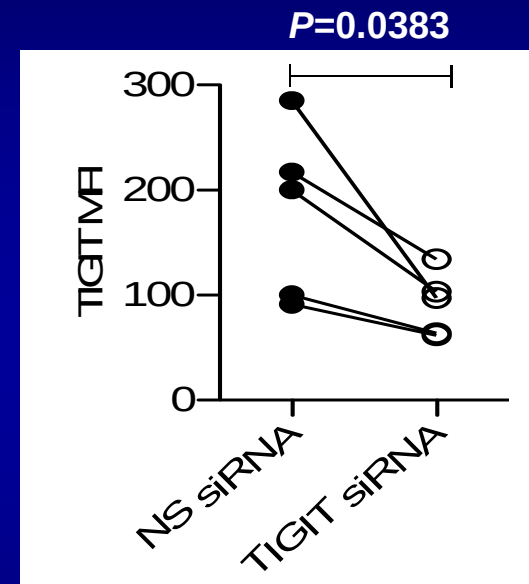
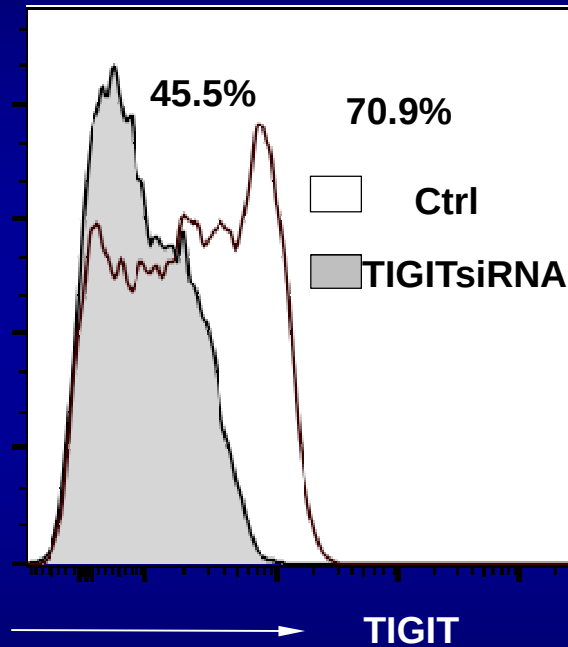
¹Department of Medicine and Division of Hematology/Oncology and ²Department of Biostatistics, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania, USA. ³Biologics Discovery California, Bristol-Myers Squibb, Redwood City, California, USA. ⁴Department of Immunology, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania, USA.

TIGIT is elevated on CD8+ T cells from patients with leukemia relapse post alloSCT



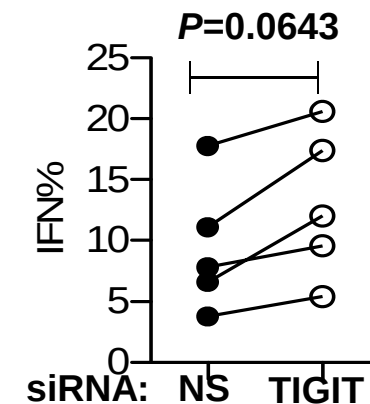
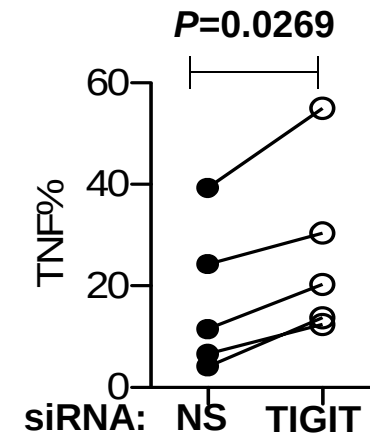
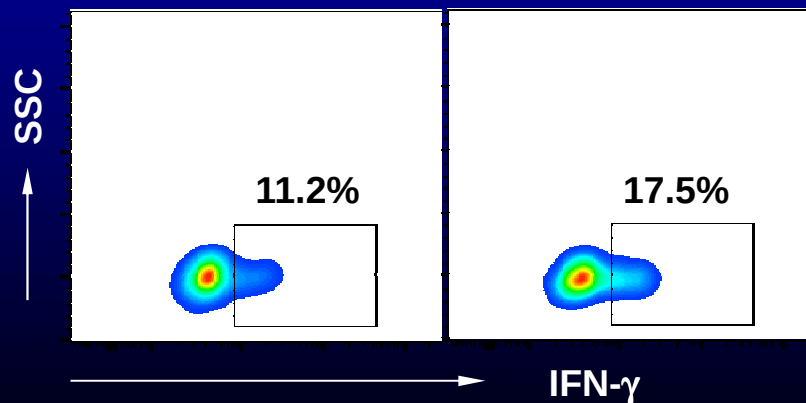
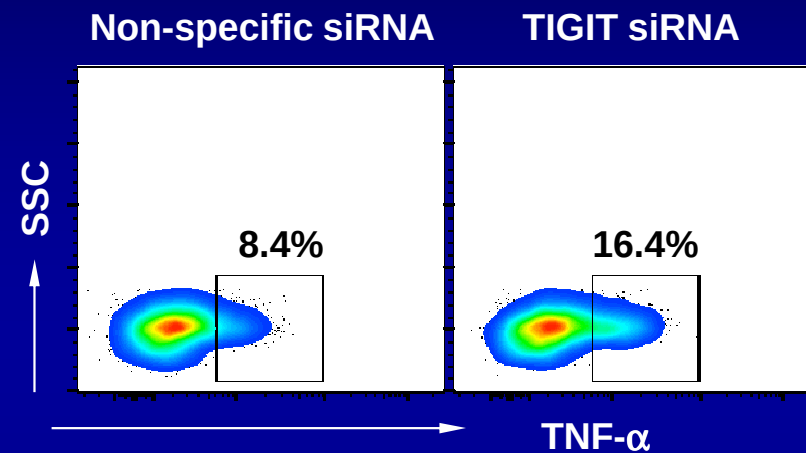
Kong et al., Unpublished data

TIGIT knockdown by siRNA



Kong et al., Unpublished data

TIGIT knockdown enhanced cytokine release by CD8⁺ T cells from AML patients



Kong et al., Unpublished data

Summary

- **PD-1^{hi} TIM-3⁺ T cells are associated with leukemia relapse post alloSCT, and show functional impairment that consistent with exhaustion.**
- **PD-1^{hi} TIM-3⁺ Cells may have predictive value for leukemia relapse post alloSCT.**
- **Elevated TIGIT expression on CD8⁺ T cells correlates with leukemia relapse post alloSCT, TIGIT knockdown increased function of T cells from AML patients.**

Conclusion

- T cell exhaustion associates with AML relapse post alloSCT.
- Combined blockade of inhibitory pathways involved in exhaustion may represent a effective leukemia therapeutic.

Acknowledgment

Penn State Cancer Institute

Laboratory

Yaxian Kong M.D., Ph.D.

Jianhong Zhang M.D.

Liuluan Zhu Ph.D.

Clinic

David Claxton M.D.

Christopher Ehmann M.D.

Witold Rybka M.D.



Todd Schell Ph.D.

**Penn State College of Medicine,
Dept of Microbiology and
Immunology**

**Chinese American
Hematologist and
Oncologist Network**



Funding support

ACS IRG

**The Kiesendahl Endowment Funding
Start-up funds,**

Penn State College of Medicine