

Presenter Disclosure Information

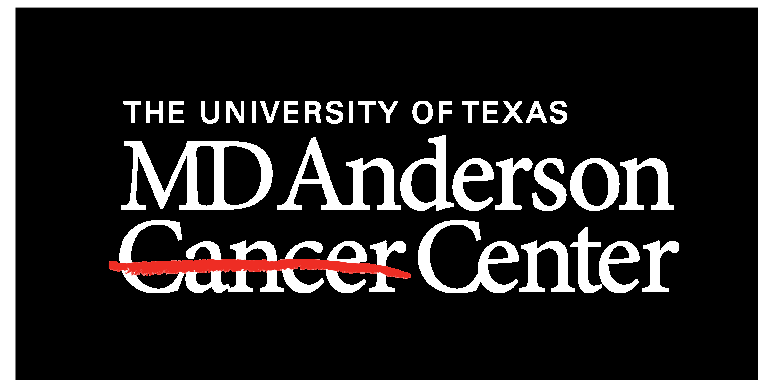
Cara Haymaker

The following relationships exist related to this presentation:

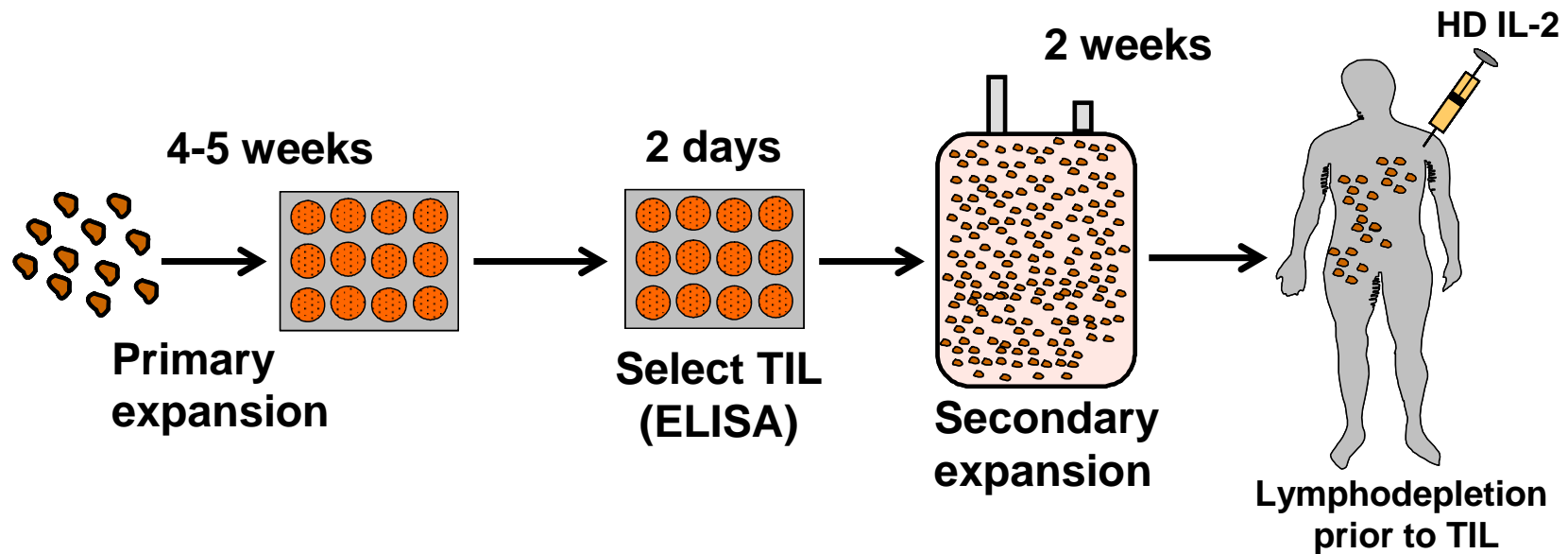
No Relationships to Disclose

Uncovering a novel function of BTLA in tumor-infiltrating CD8⁺ T cells

Mentorship: Dr. Laszlo Radvanyi
Department of Melanoma Medical Oncology,
University of Texas MD Anderson Cancer Center



Current TIL Therapy Regimen



- **45-50% response rate for stage IIIc-IV melanoma**
- **Up to 20% complete response rate (NCI)**
- **Up to 20% of patients have ≥ 4.5 -year survival (MDACC)**
- **Multiple centers worldwide have TIL programs currently**

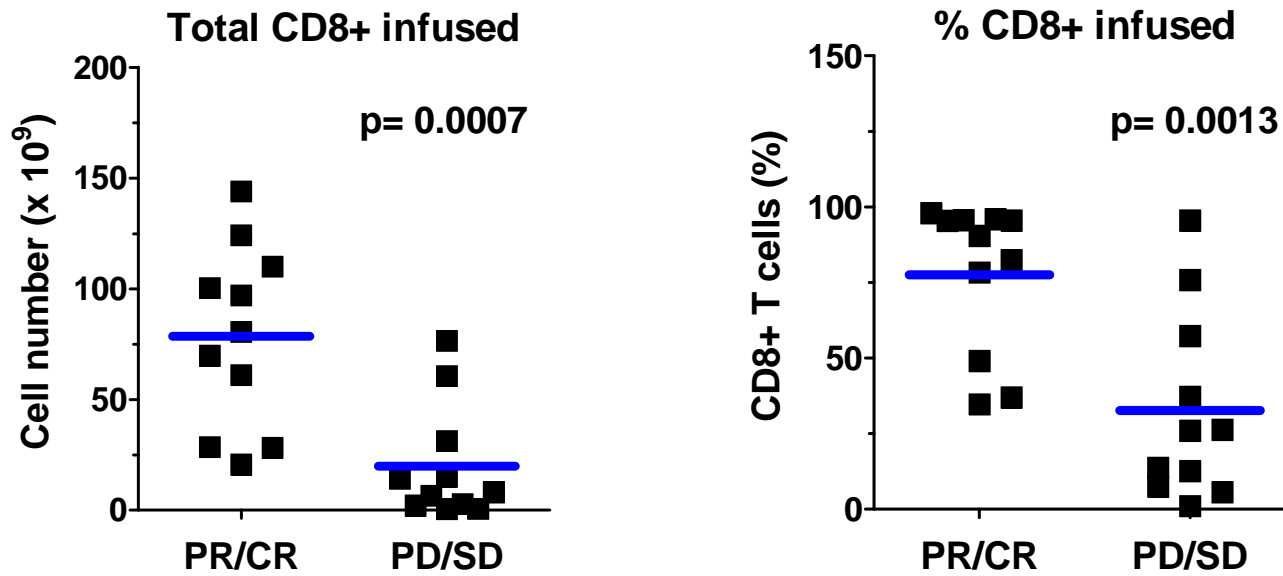
Which biomarker could help us select “better” cells for TIL ACT?

*¹Radvanyi et al., *Can Res* 2012

*²Besser et al., *Clin Can Res* 2010

*³Dudley et al., *J Clin Oncol* 2005

CD8⁺ TIL are critical!

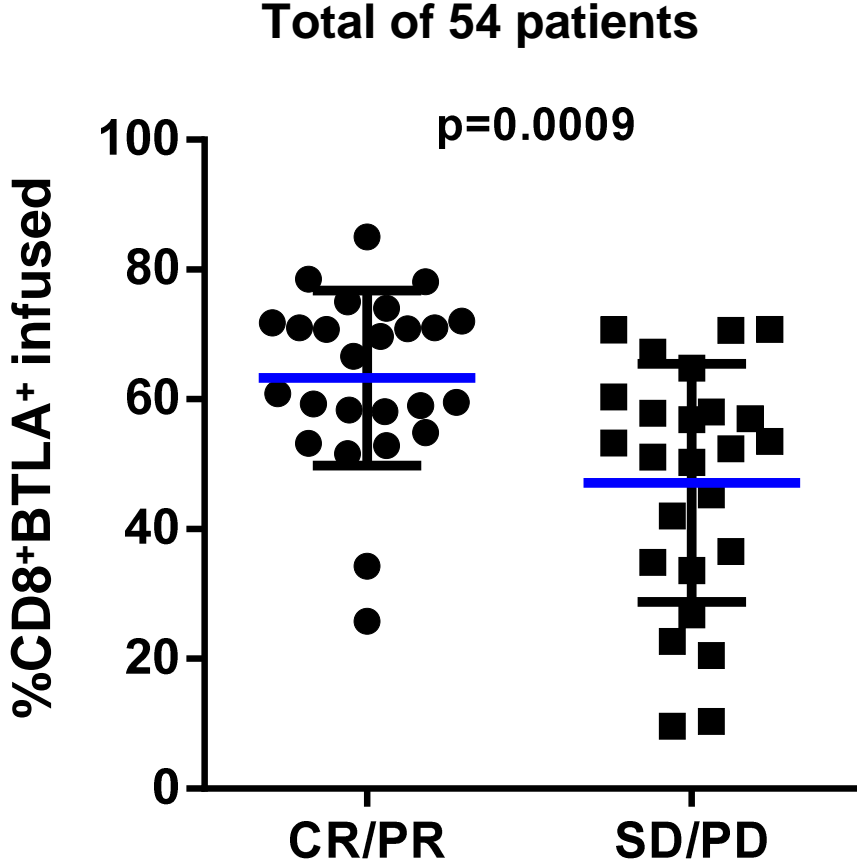
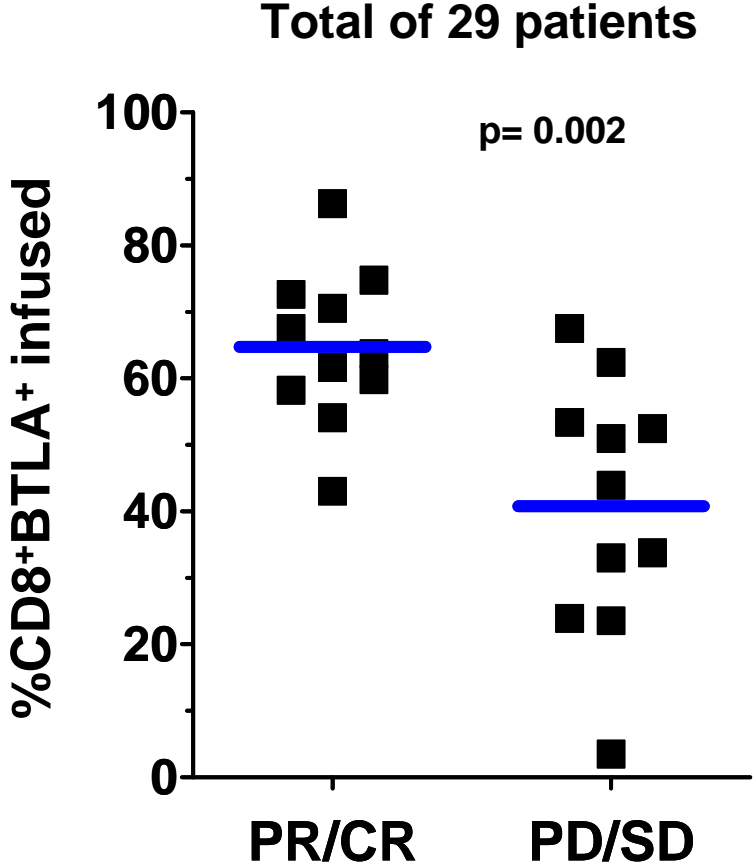


Negative costimulators and their ligands on tumor cells or tumor stroma

Receptor (T-cell)	Ligand (Tumor)
PD-1	PD-1L/B7H1 PD-L2/B7DC
TIM3	Galectin 9
BTLA	HVEM
Lag3	HLA class II (DR)

Hypothesis: Higher Inhibitory receptor expression by CD8⁺ TIL confers worse patient prognosis after ACT

BTLA Expression by CD8⁺ TIL Correlates with a Better Clinical Response

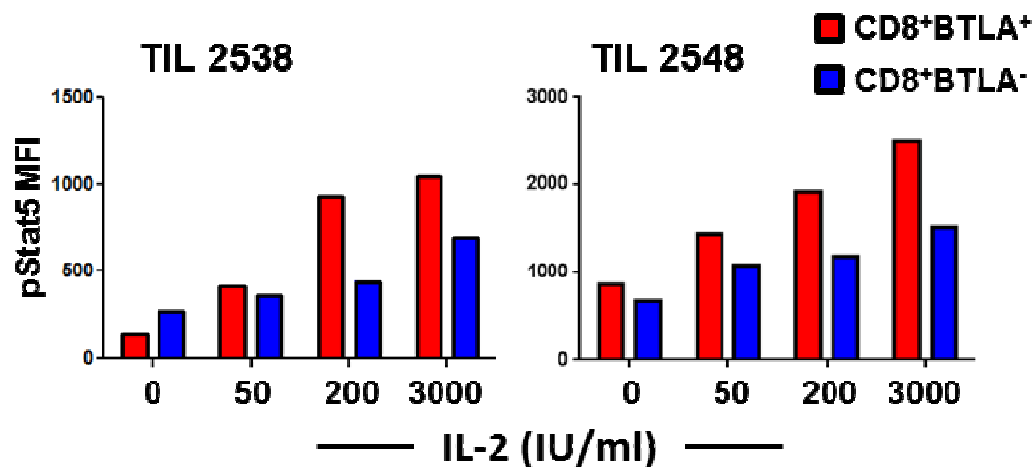
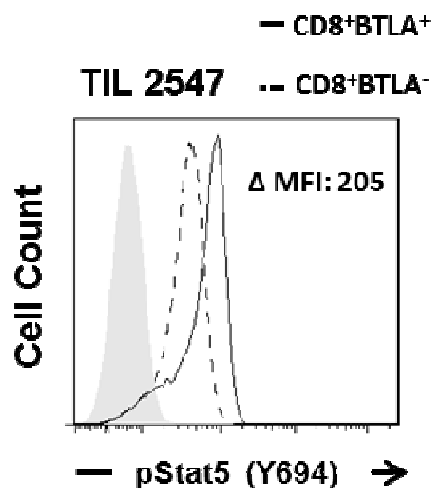
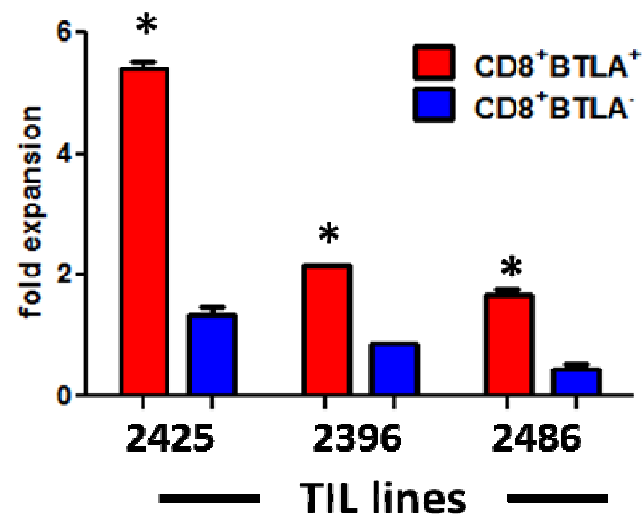
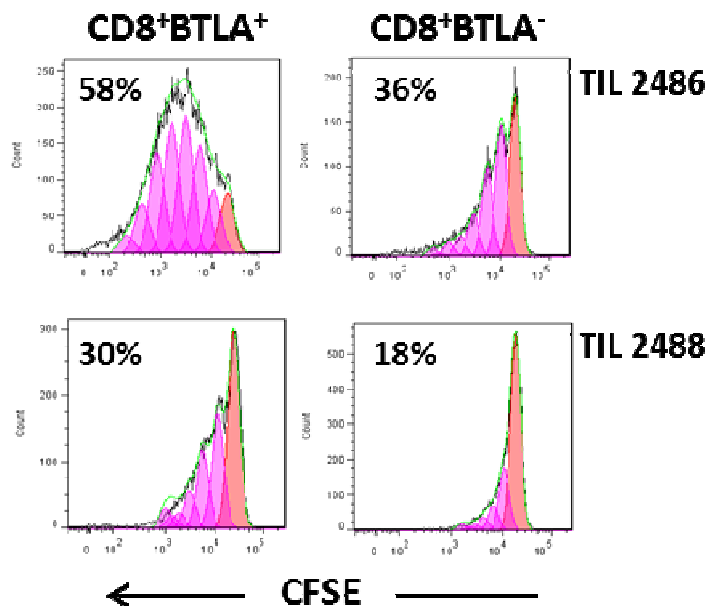


*1Radvanyi et al., *Can Res* 2012

Analysis of CD8⁺BTLA⁺ TIL Approach

1. IL-2 responsiveness of CD8⁺BTLA⁺ TIL
2. Phenotypic analysis of BTLA⁺ and BTLA⁻ TIL
3. In vivo tracking of CD8⁺BTLA⁺
4. BTLA signaling

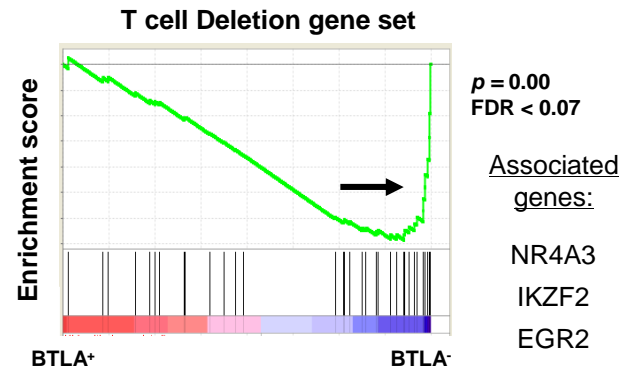
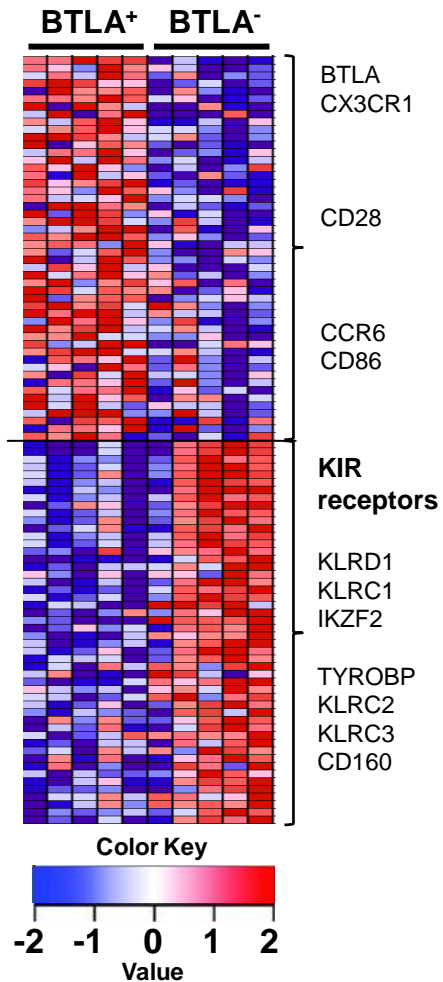
CD8⁺BTLA⁺ TIL are more responsive to IL-2



Analysis of CD8⁺BTLA⁺ TIL Approach

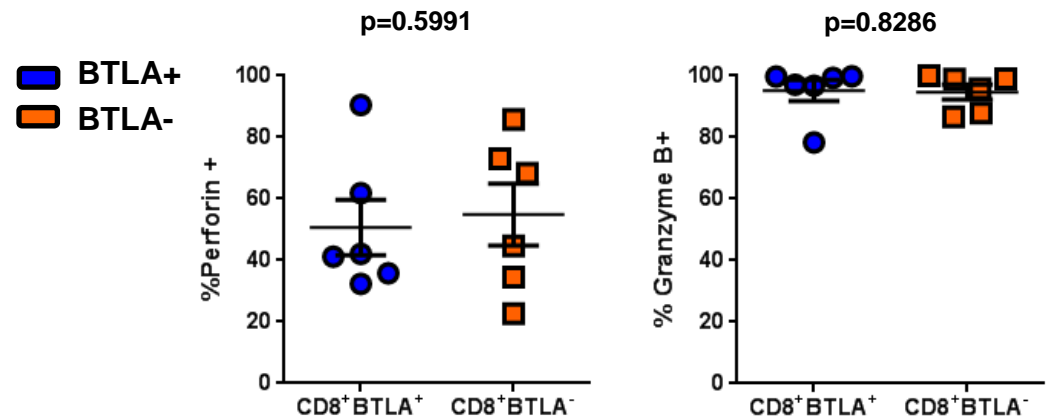
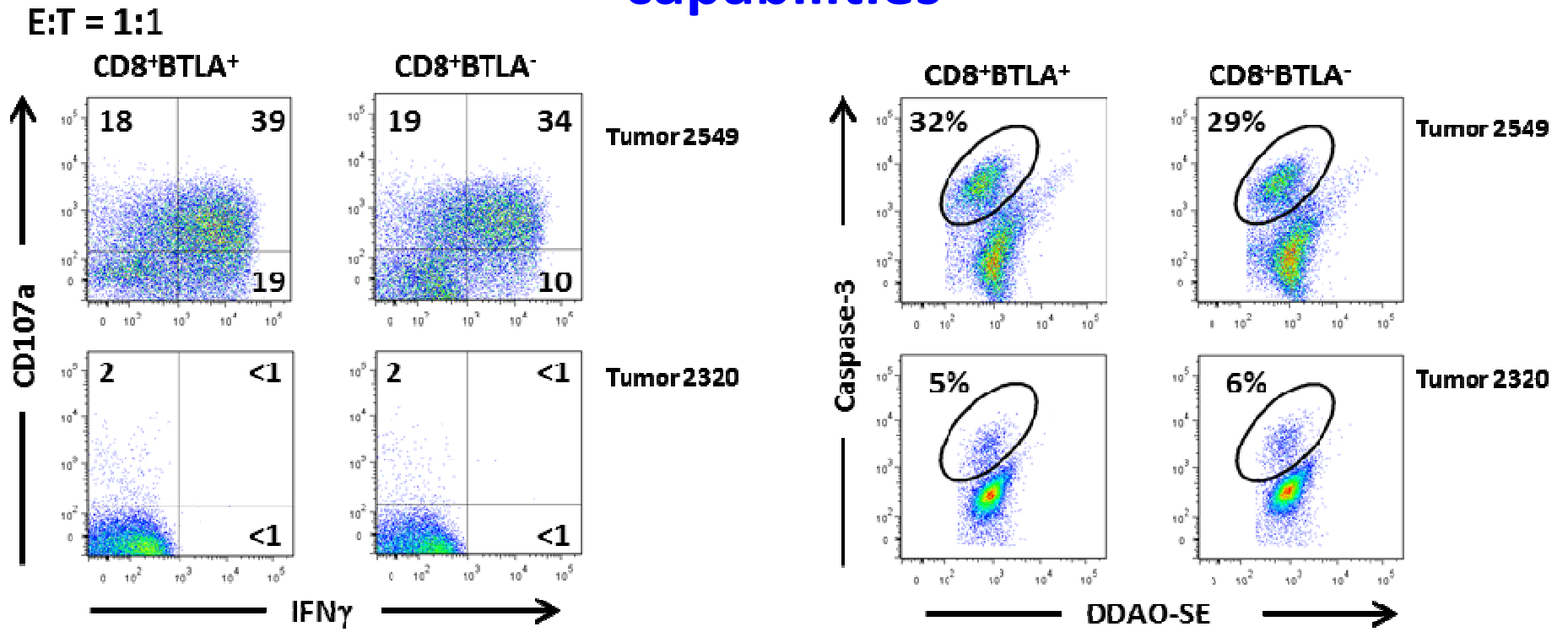
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CD8⁺BTLA⁺ TIL have a “younger” and more activated phenotype



Flow cytometry analysis				
	CD8 ⁺ BTLA ⁺	CD8 ⁺ BTLA ⁻	p value	n
% CD28	61.1 ± 6.2	45.2 ± 6.9	***0.0008	22
% PD-1	42.2 ± 4.1	29.3 ± 3.4	***0.0001	42
% TIM-3	21.7 ± 7.1	13.2 ± 4.8	* 0.015	7
CD25 MFI	1499 ± 434.8	881.8 ± 260.3	**0.005	28
% CD25	28.7 ± 3.4	24.7 ± 3.9	0.114	28
% CD27	33.4 ± 4.5	36.2 ± 4.6	0.4628	22
% KIRs	0	4.1 ± 5.1	0.29	3

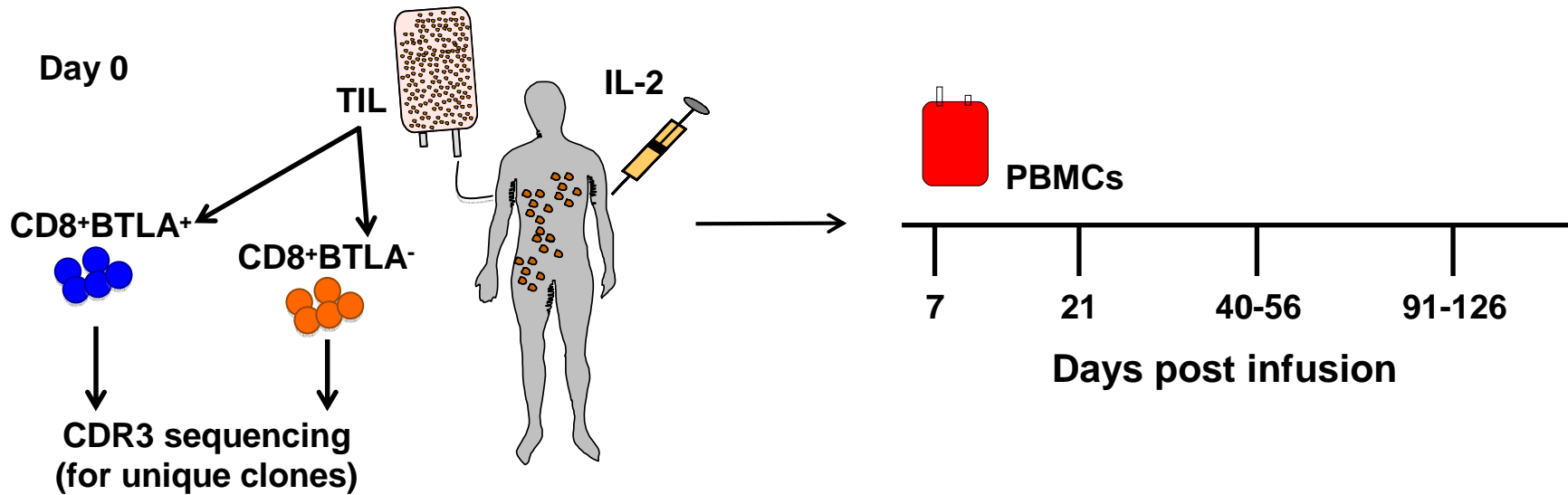
CD8⁺BTLA⁺ and CD8⁺BTLA⁻ TIL have similar cytotoxic capabilities



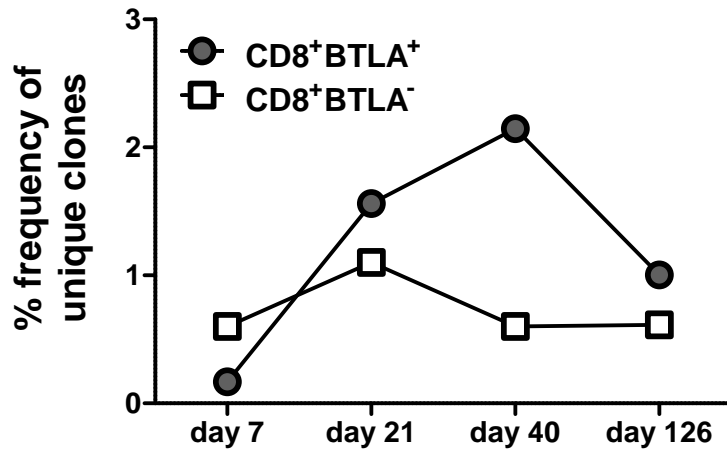
Analysis of CD8⁺BTLA⁺ TIL Approach

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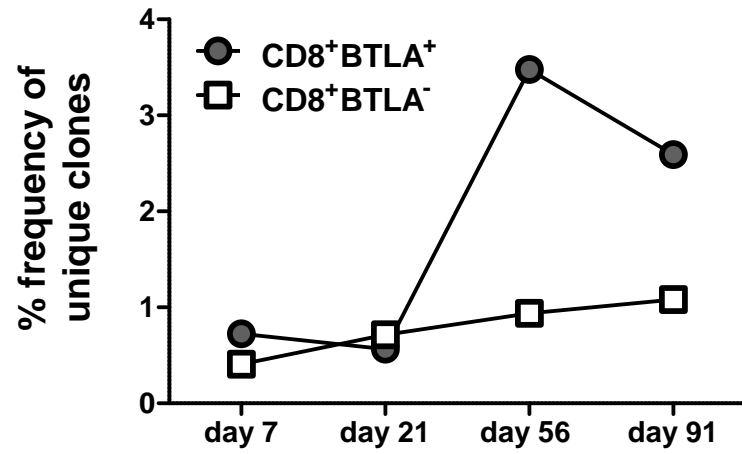
CD8⁺BTLA⁺ TIL expand and persist in treated patients



TIL 2498



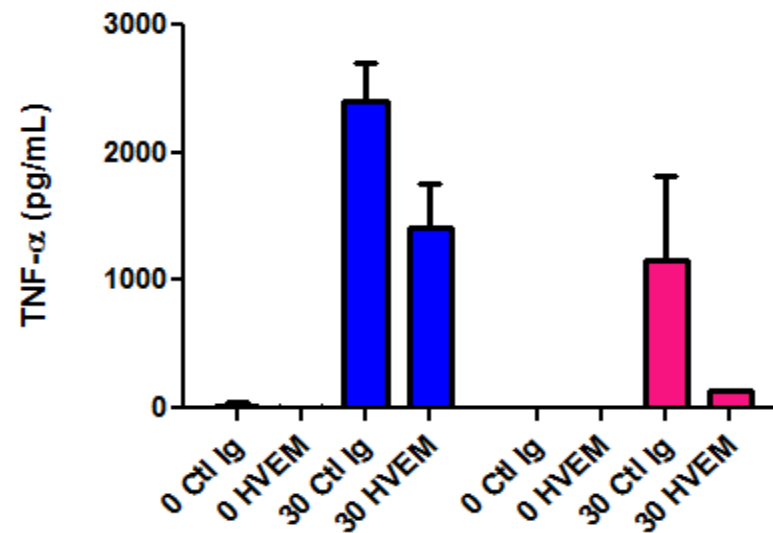
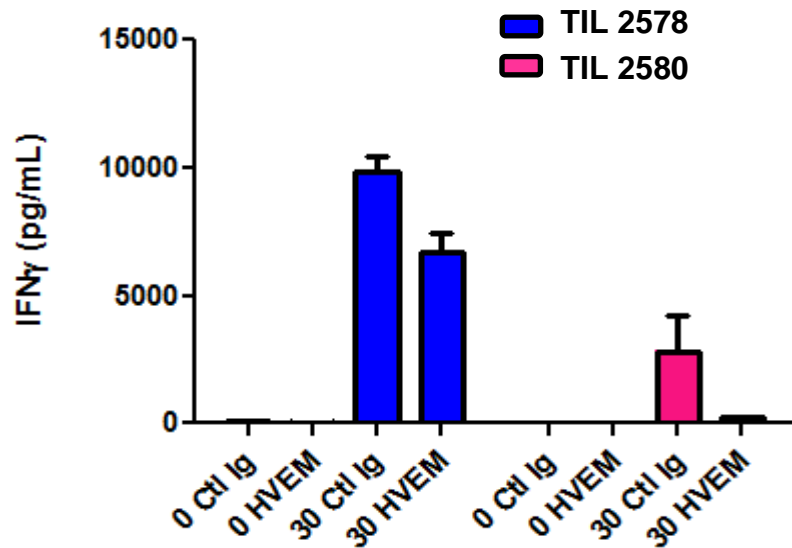
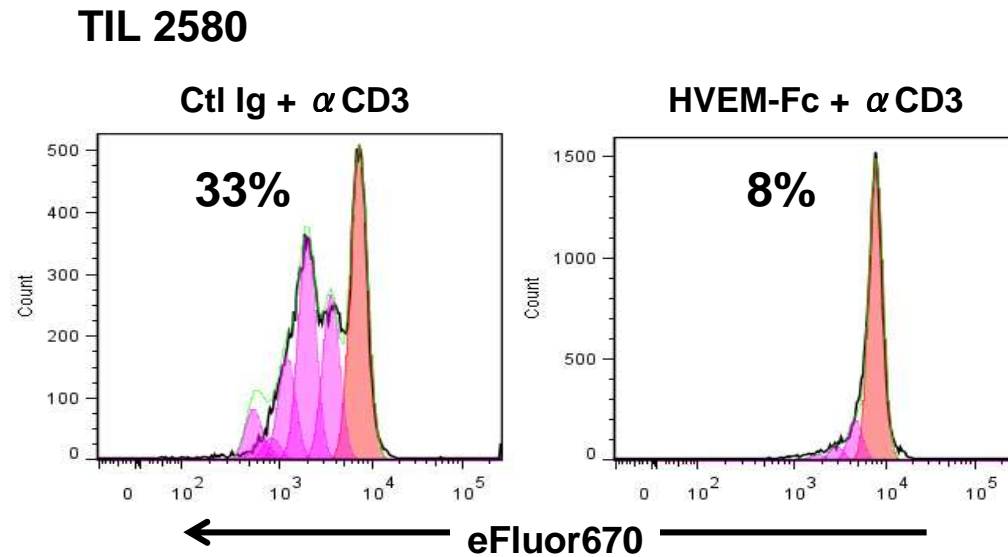
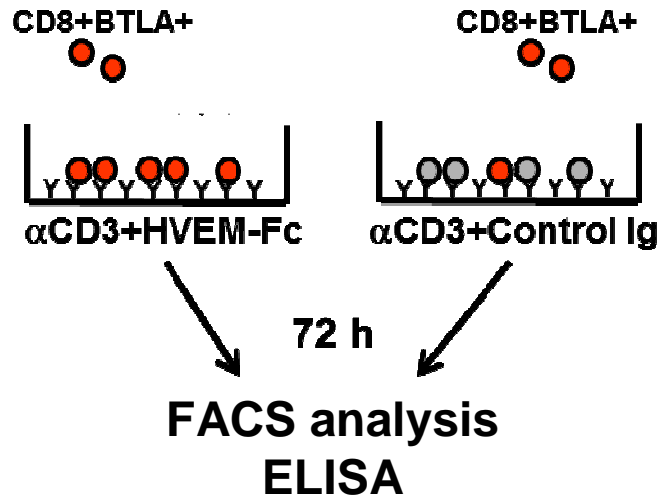
TIL 2496



Analysis of CD8⁺BTLA⁺ TIL Approach

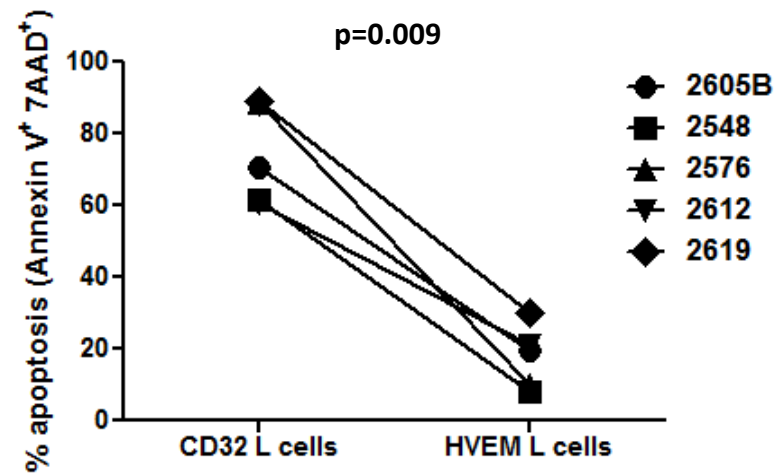
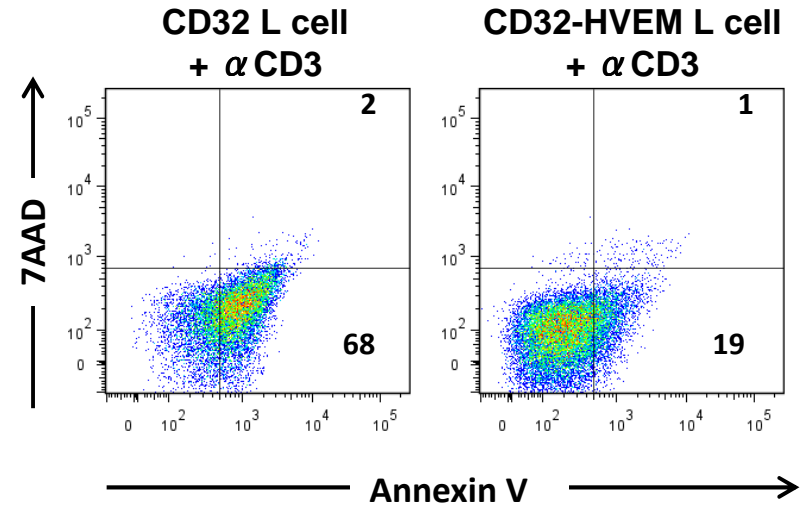
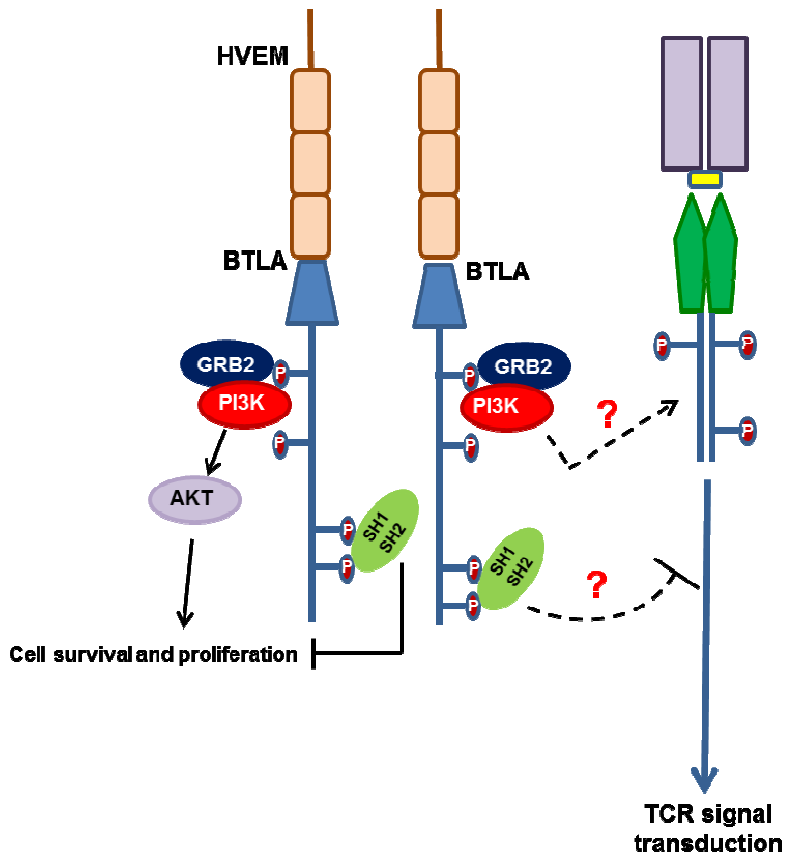
1. IL-2 responsiveness of CD8⁺BTLA⁺ TIL
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Inhibitory Role of BTLA signaling

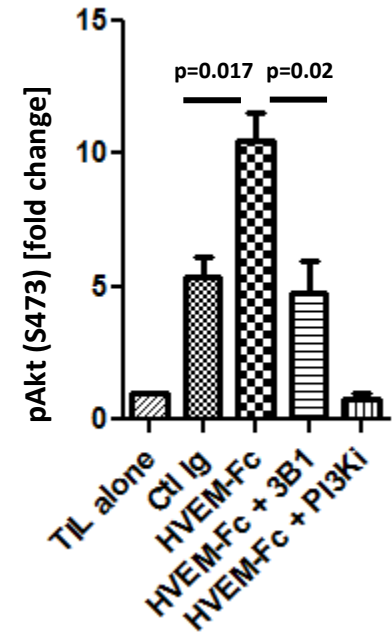
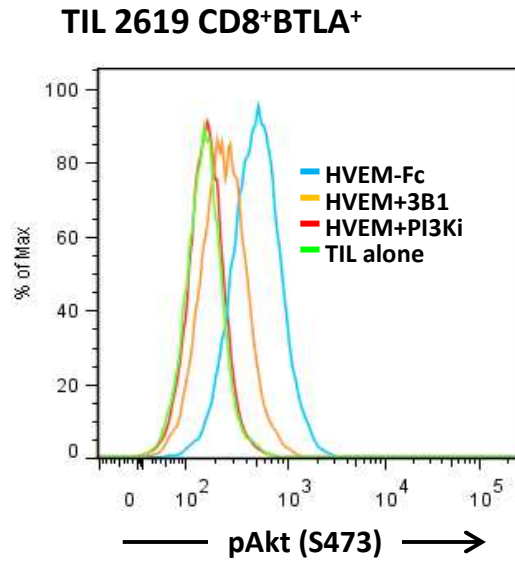
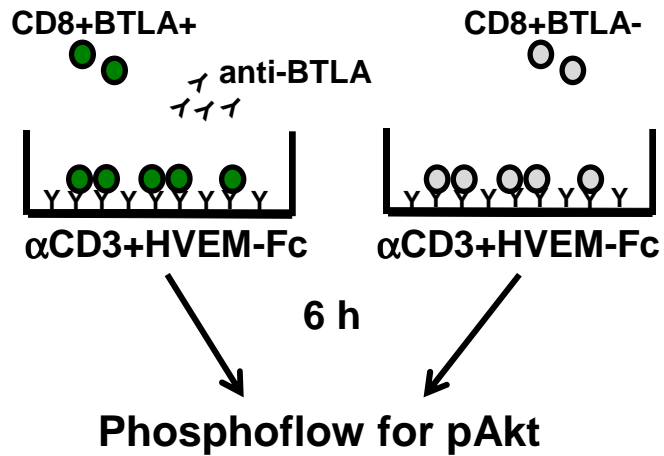


BTLA-HVEM ligation protects TIL from AICD

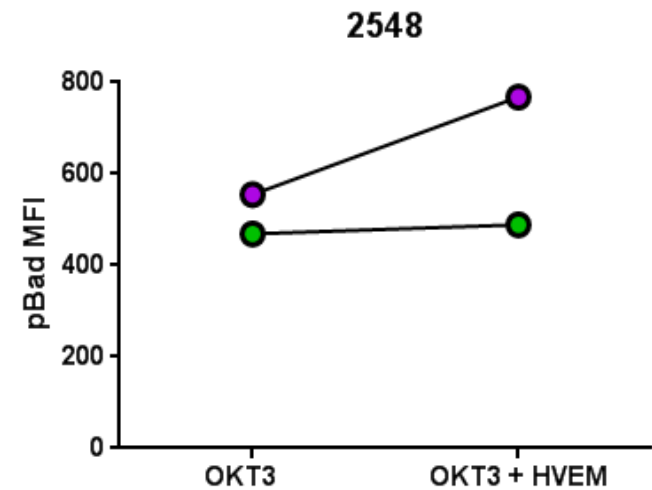
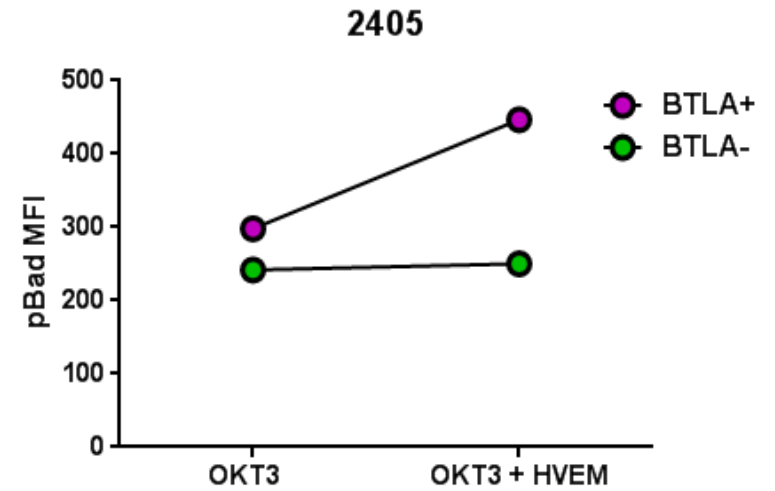
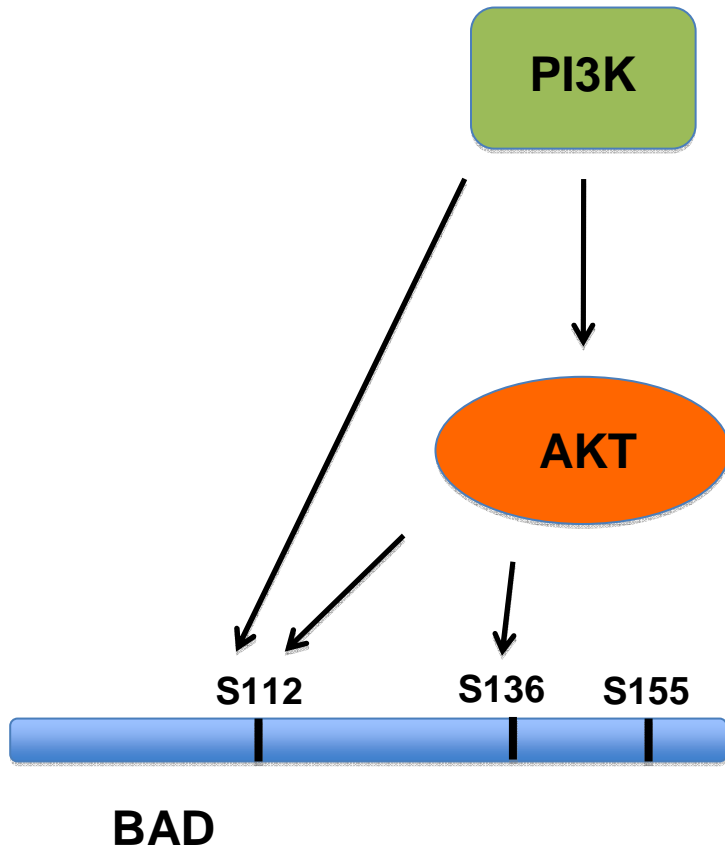
TIL 2605B



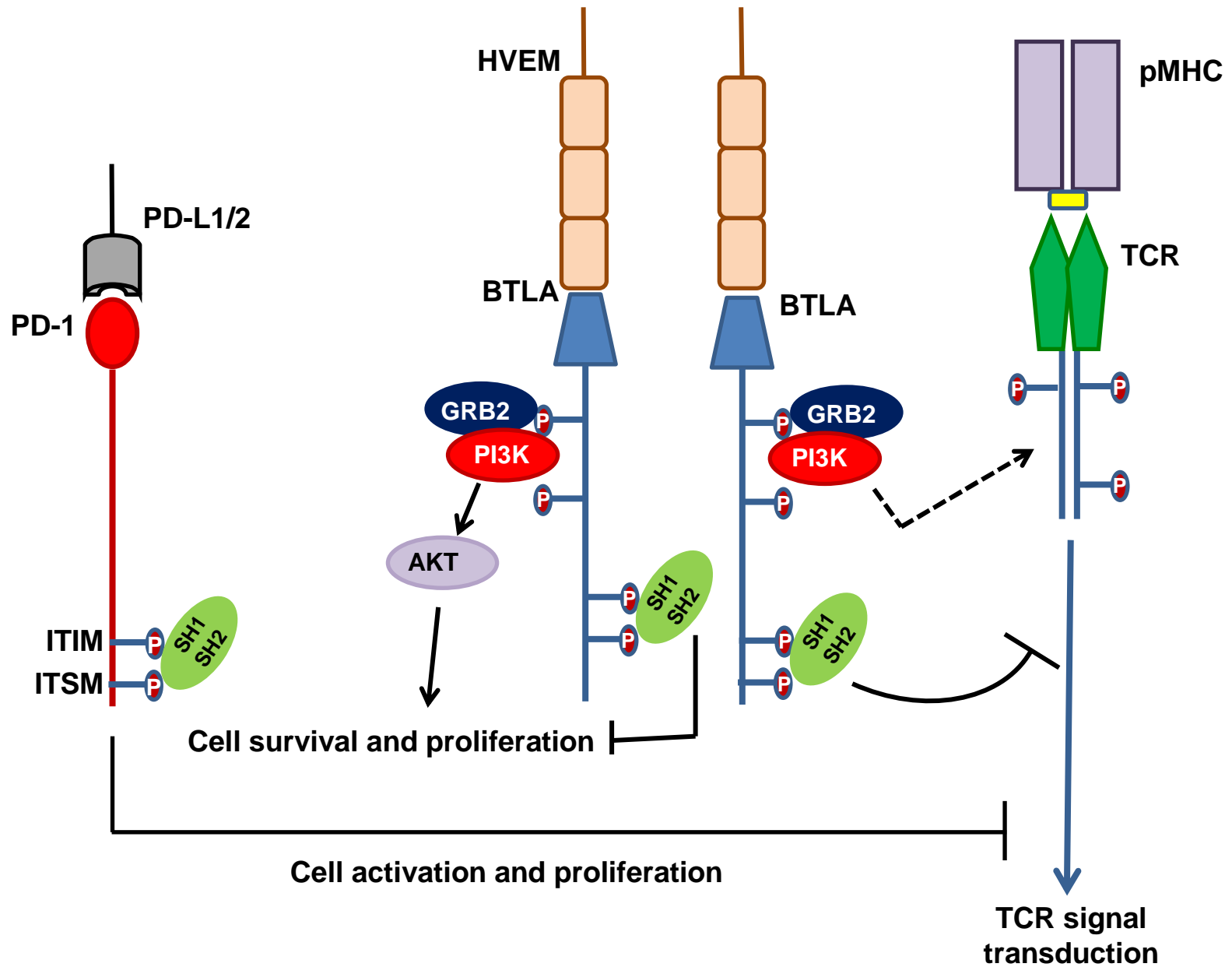
BTLA-HVEM ligation activates pAkt



BTLA-HVEM ligation activates pro-survival molecules

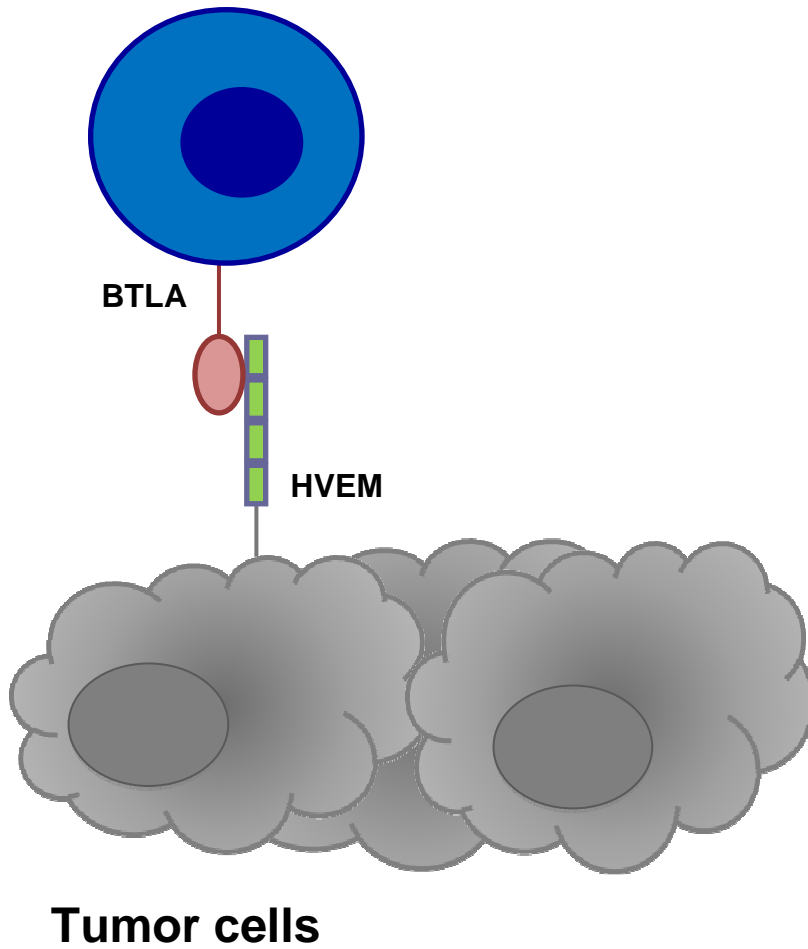


BTLA: A Dual Signaling Molecule



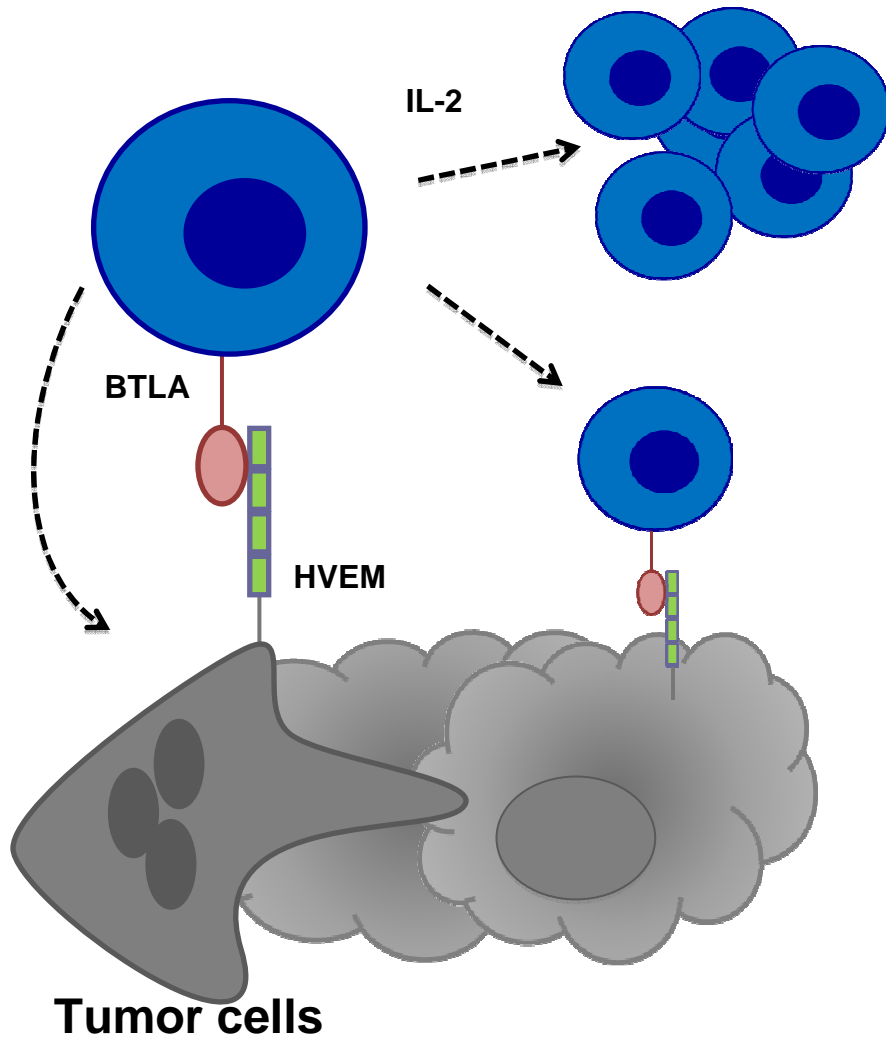
Lessons and Take Home Messages

BTLA+ TIL

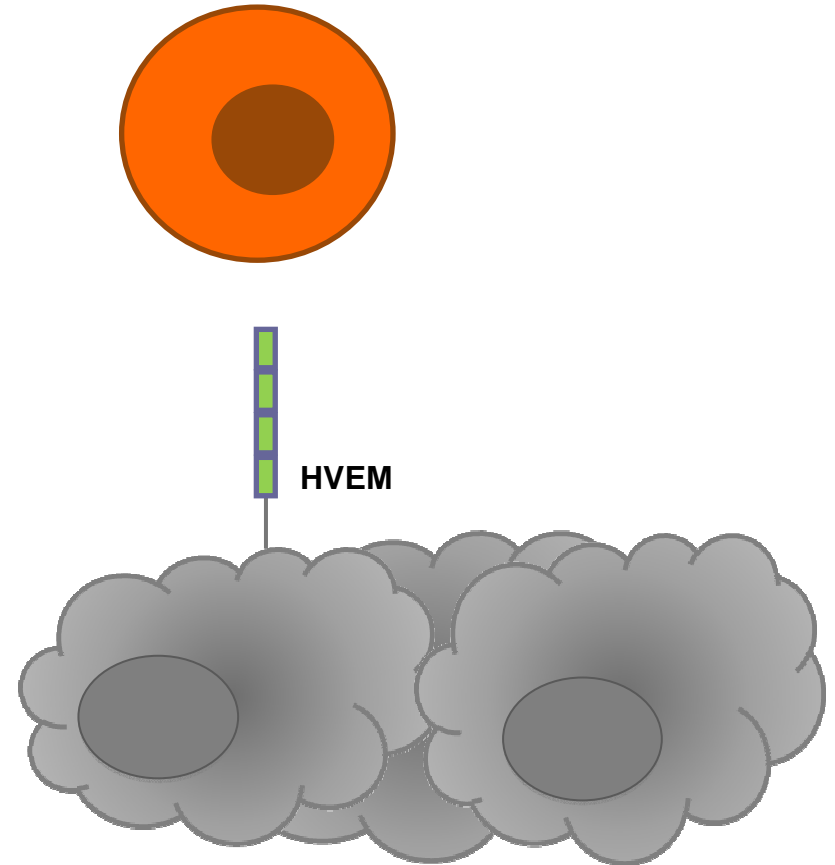


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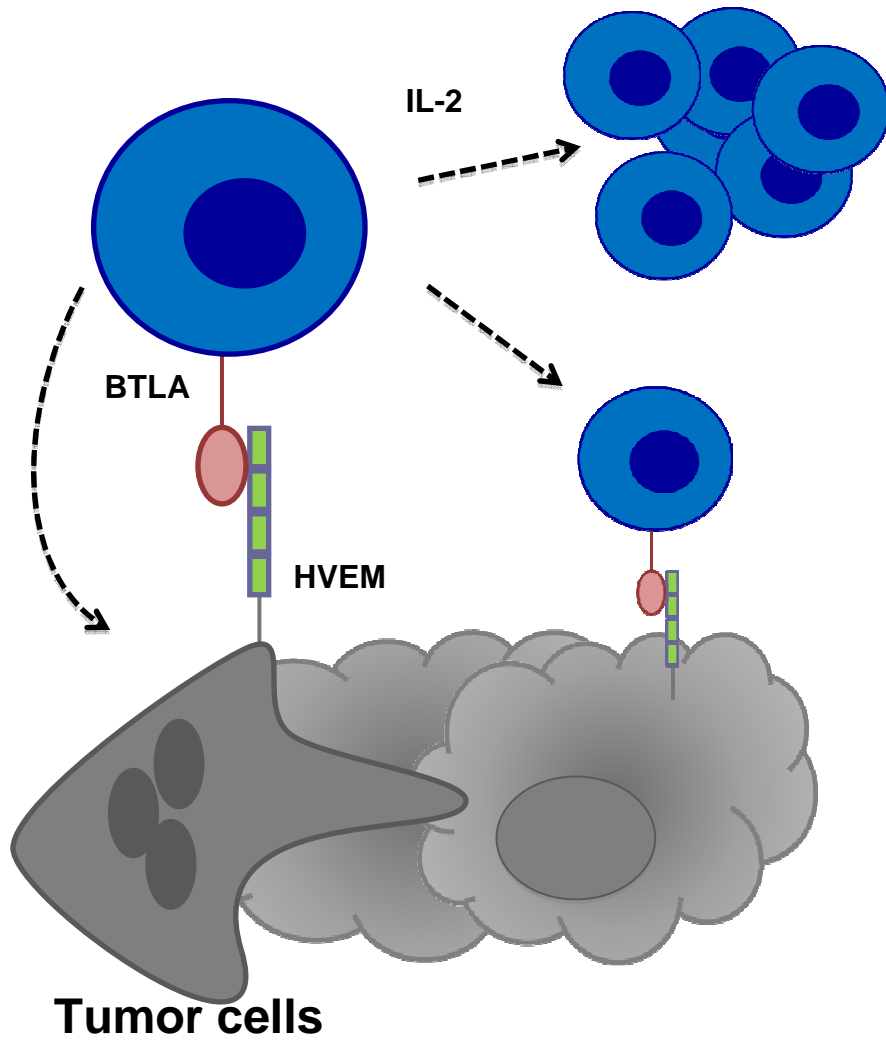


BTLA- TIL

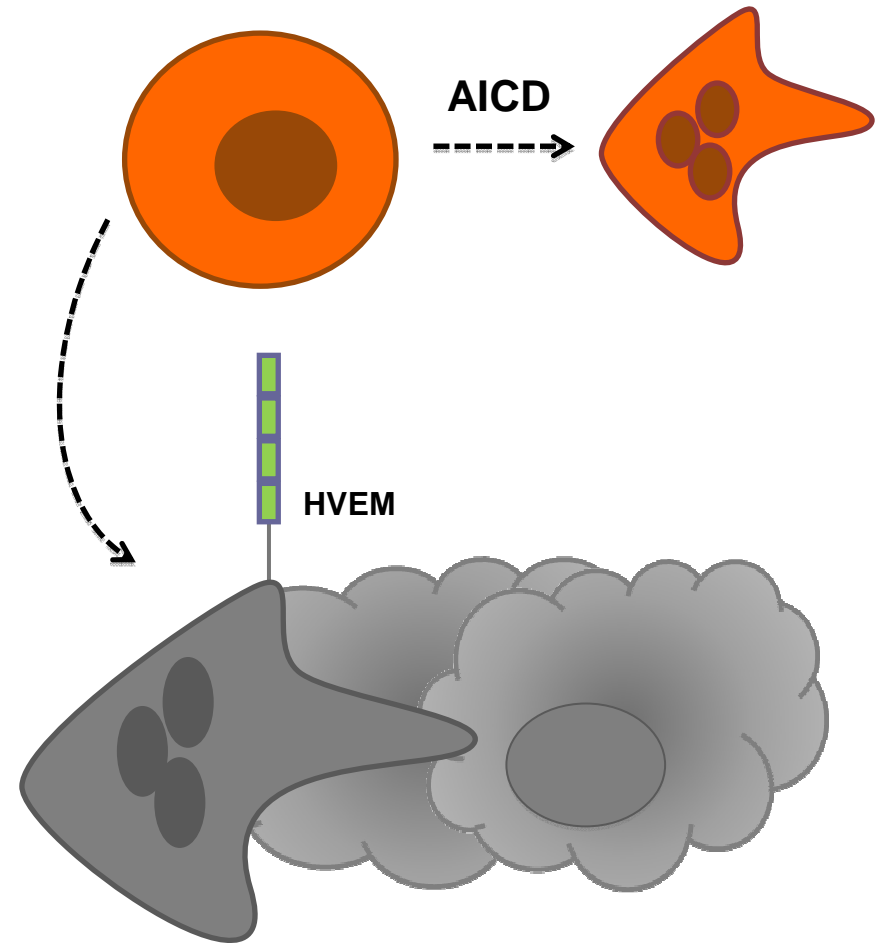


Lessons and Take Home Messages

BTLA+ TIL



BTLA- TIL



Acknowledgments

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- Richard Wu
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- Geok Choo Sim
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- Charuta Kale
- Krit Rittipichai
- Caitlin Creasy

**The Patients
and their Families**

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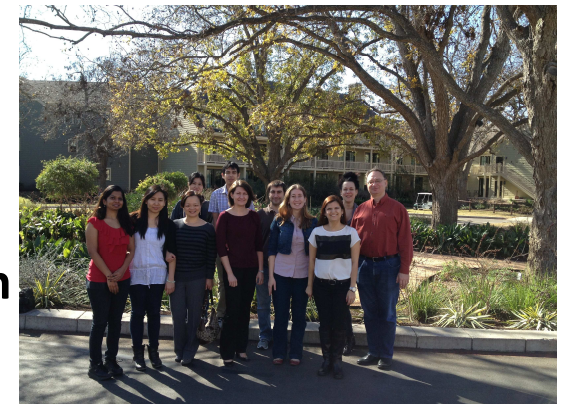
-Ena Wang

-Hui Lui

MDACC TIL Lab

MD Anderson Immune Monitoring Platform

South Campus Flow Cytometry Core



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