Research and Development Program Update

December 1, 2015

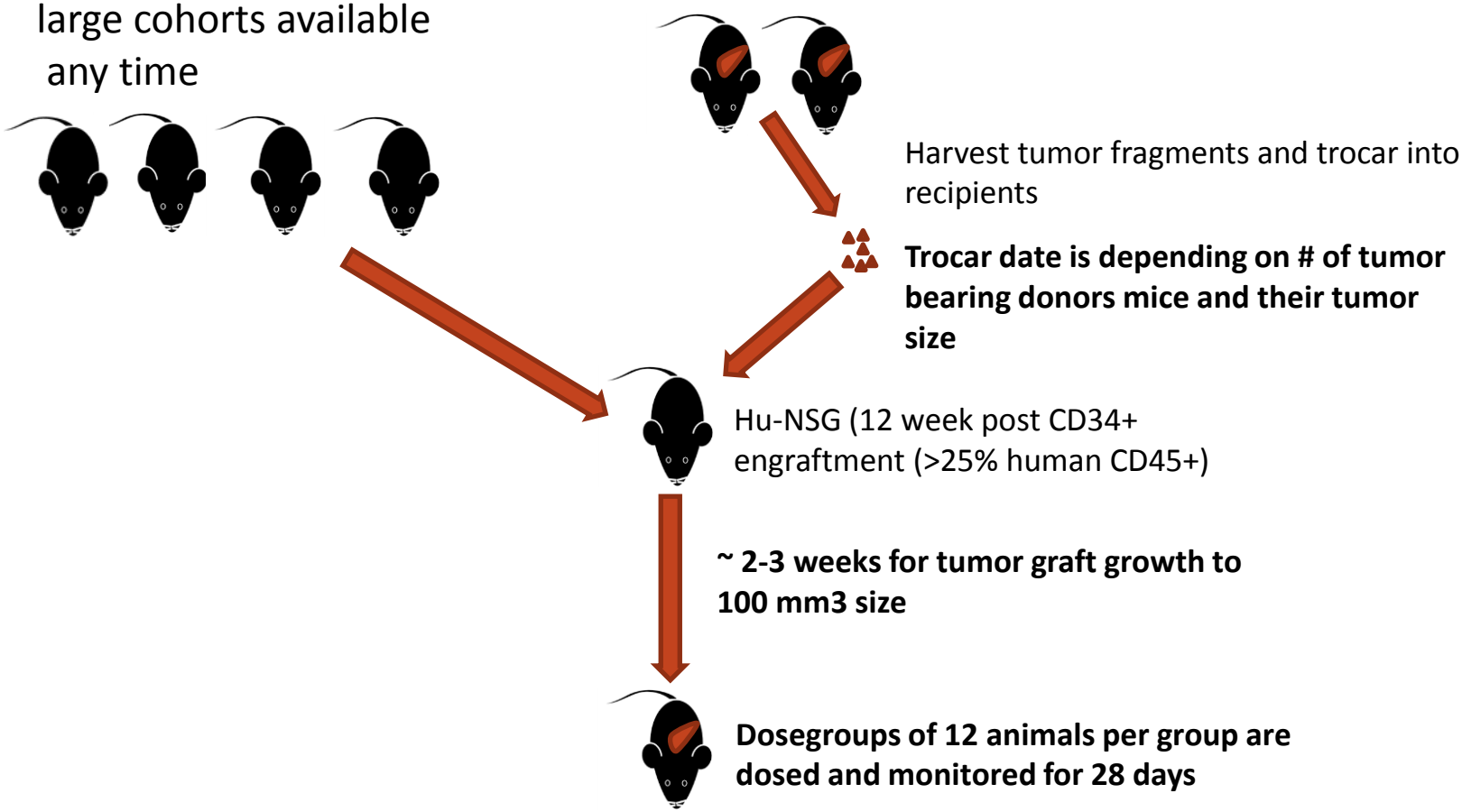
Agenda

- Preclinical animal model studies
- Ex vivo lung biopsy studies

Hu-NSG PDX study outline (Lung LG1306)

CD34+ engrafted Hu-NSG large cohorts available any time

NSG PDX tumor bearing mice



Harvest tumor fragments and trocar into recipients

Trocar date is depending on # of tumor bearing donors mice and their tumor size

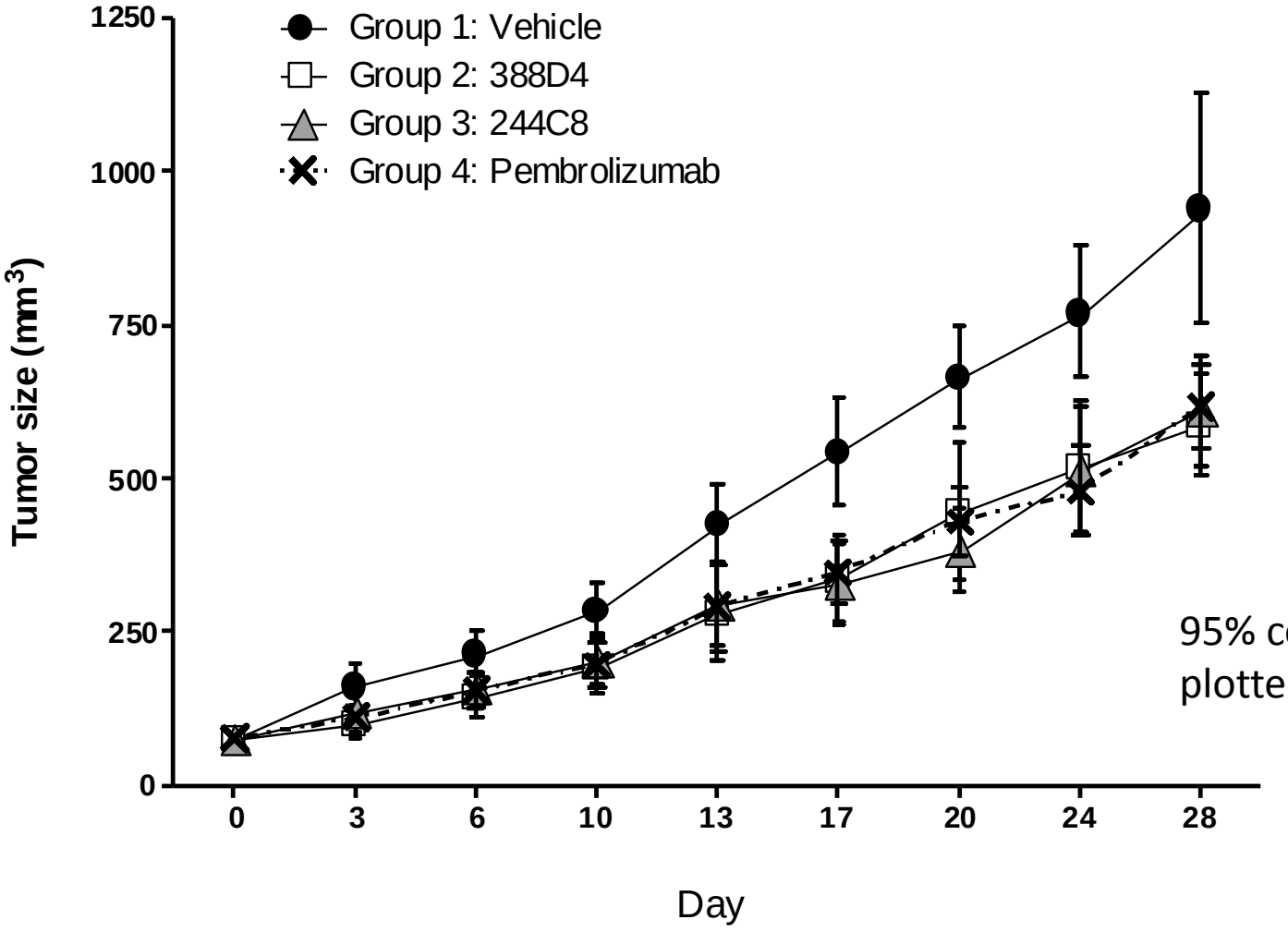
Hu-NSG (12 week post CD34+ engraftment (>25% human CD45+)

~ 2-3 weeks for tumor graft growth to 100 mm3 size

Dosegroups of 12 animals per group are dosed and monitored for 28 days

Study performed by Jackson Labs

Tumor Growth (Mean)



95% confidence interval plotted

Study Observations

- End of study tumor biopsies collected and analyzed
- Low TIL % in tumors
  - <1% TIL in tumors
  - Suggests narrow dynamic range for immuno-modulation
- Unclear if myeloid functionality in hu-NSG model
  - Kinetics of engraftment may not recapitulate biology of myeloid cells
  - Newer NSG-SGM3 model thought to rectify this

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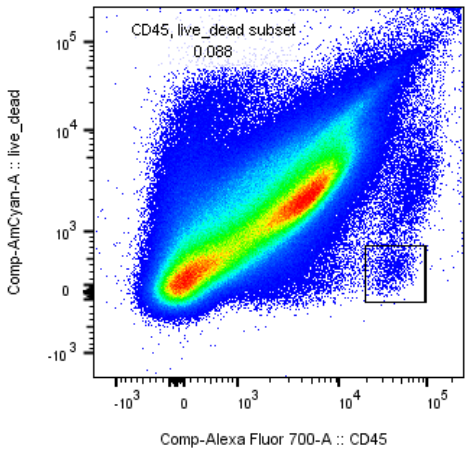
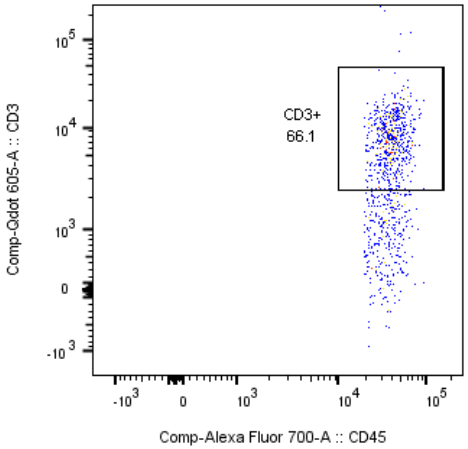
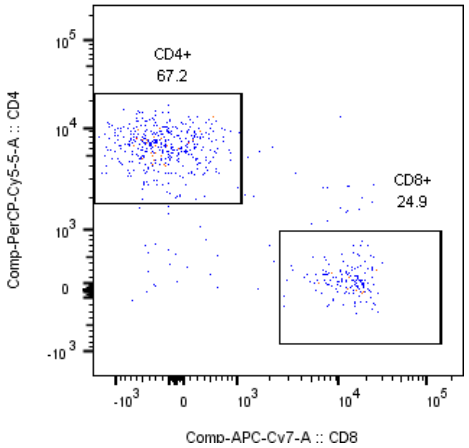
T Cell Infiltration from hu-NSG/PDX Tumors

Vehicle Control

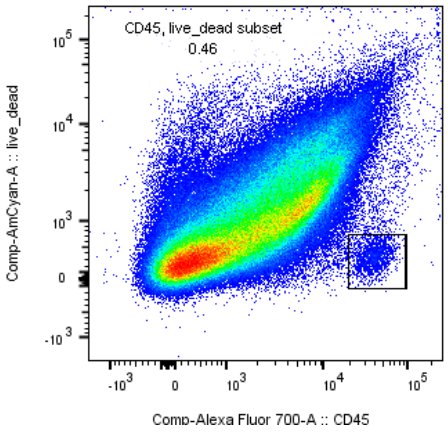


CD3+: Freq. of Total : 0.058

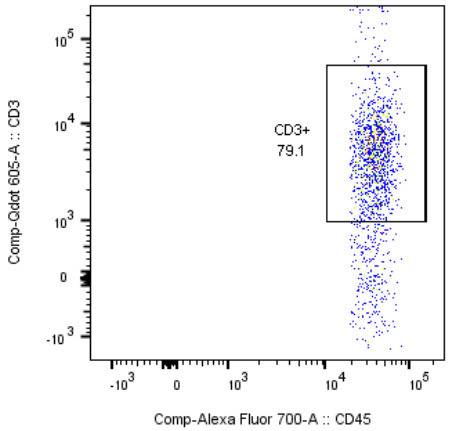


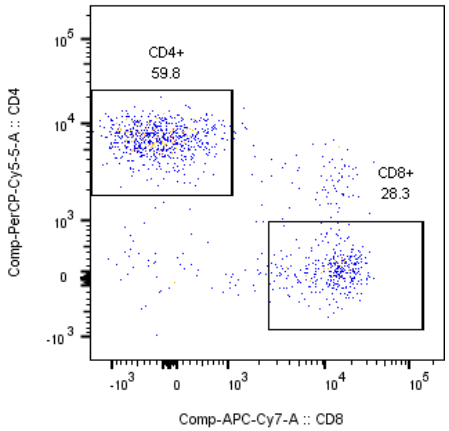


Vehicle Control



CD3+: Freq. of Total : 0.37





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Summary

- Enumeral anti-PD1 antibodies 388D4 and 244C8 demonstrate activity in an accepted *in vivo* model of immunomodulation
  - huNSG lung PDx model used
  - Tumor growth inhibition similar to that observed with pembrolizumab
- Initial characterization of tumor biopsy suggests low levels of TIL infiltration
  - Model has a narrow dynamic range for measuring activity of novel immunomodulators and may not reflect effects on non-T cell compartments

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PD-1 Blockade in NSCLC Tumor Samples

Complex IMR biology

Overview: Data Annotation

- The following slides show data obtained from two different lung biopsies obtained from patients undergoing staging surgeries

- Characterization of baseline IMR expression on TILs:

  - TIM-3^{lo}/TIGIT^{lo} - WD36444

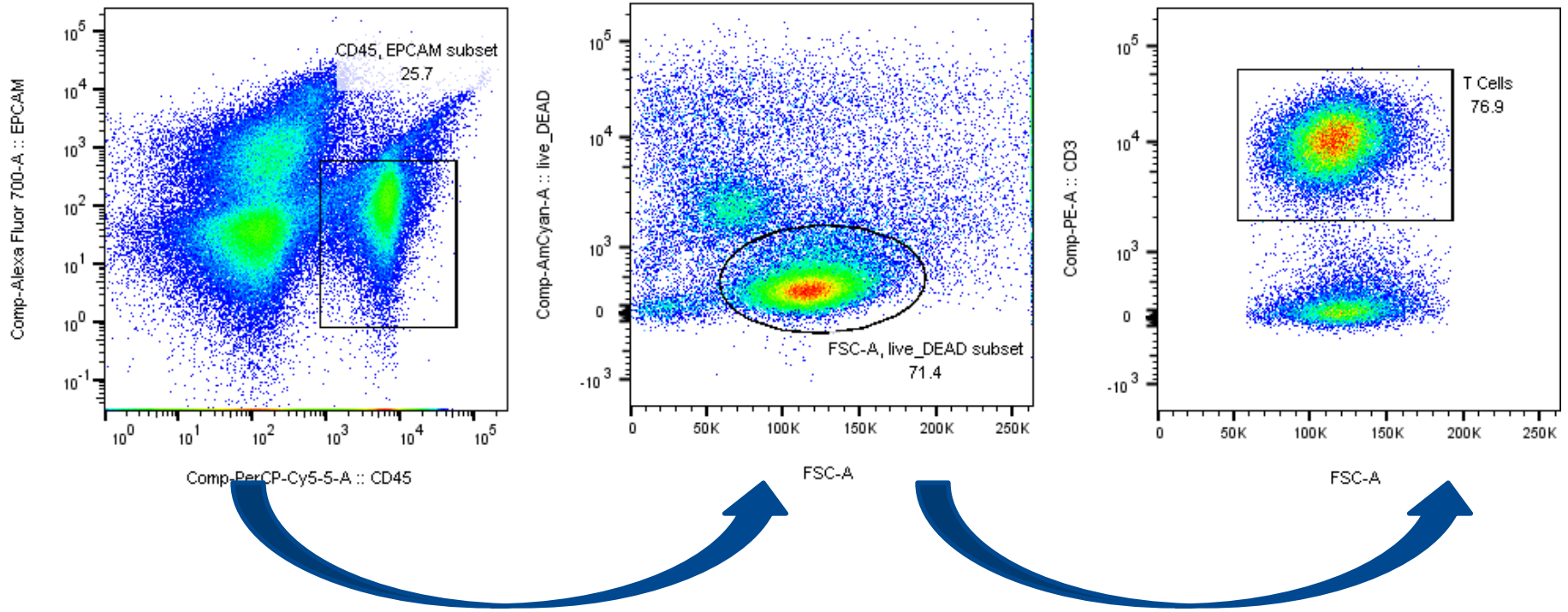
  - TIM-3^{hi}/TIGIT^{hi} - WD36988

NSCLC WD36444 Contains 14% T Cells

CD45+ cells

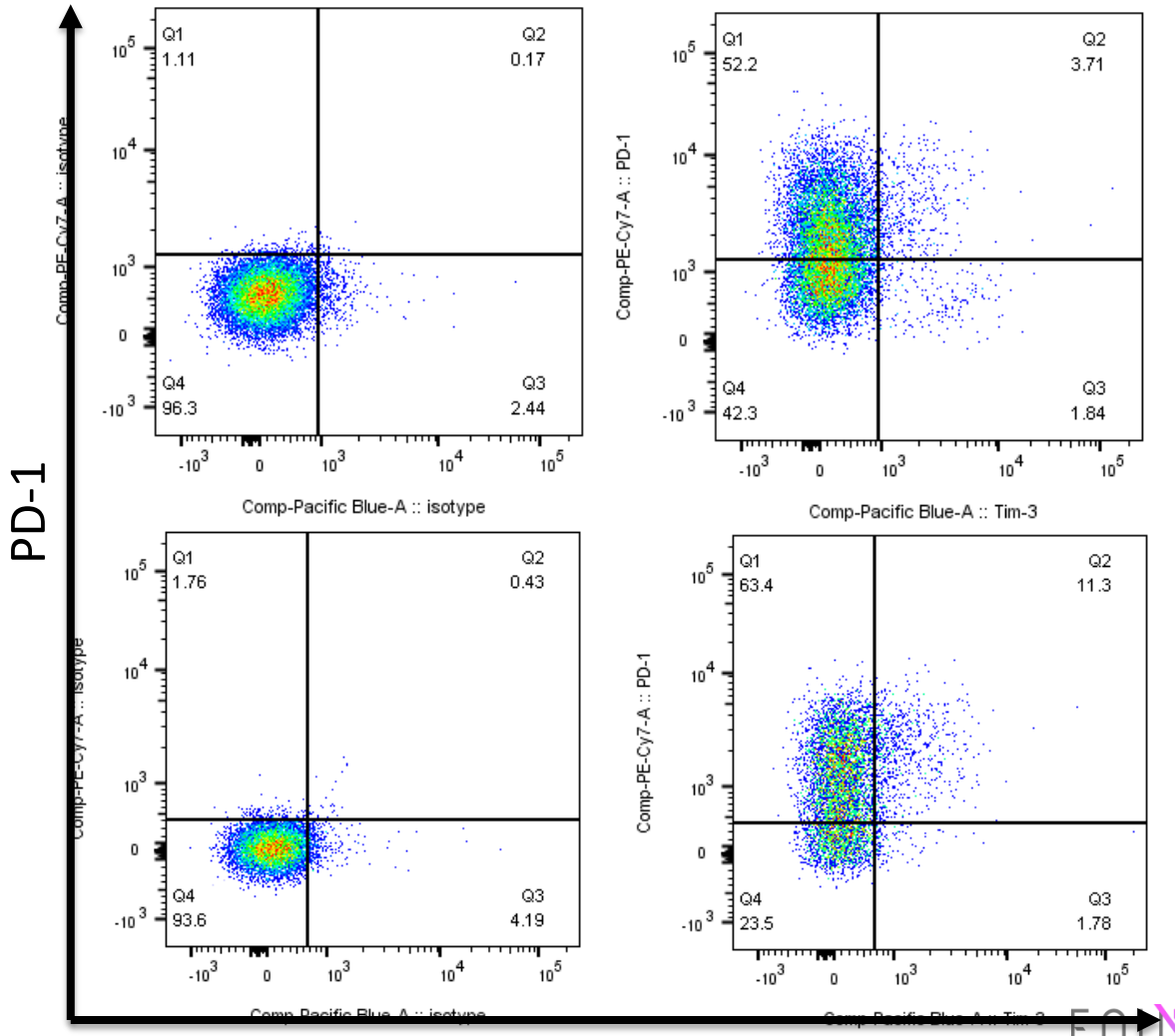
Live/dead cells

T cells



WD36444 CD4 and CD8+ TILS Express PD1^{hi}, but TIM-3^{lo}

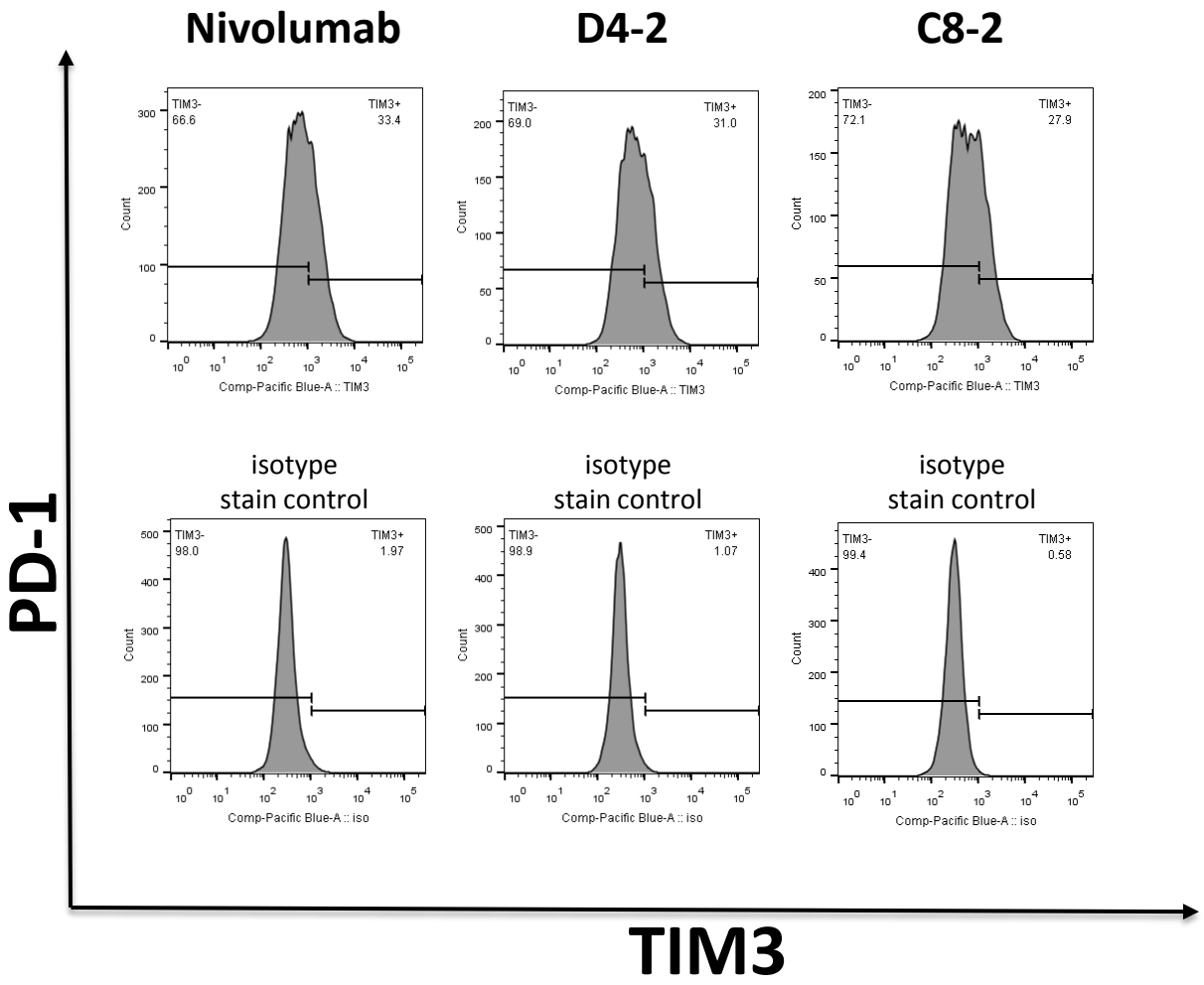
- PD-1 is expressed on 55% of CD4 cells and 75% of CD8 cells
- **TIM-3 is expressed on 5.5% of CD4 cells and 13% of CD8 cells**
- Cells dually expressing both markers are observed



CD4 cells

CD8 cells

Ex Vivo PD-1 Blockade Can Drive Expression of TIM-3 on TILs Derived From Lung Cancer Biopsy



WD-36444

Condition	CD3⁺ Tim-3%
isotype	<1
Nivolumab	31.4
D4-2	29.9
D4-3	34.7
C8-1	39.5
C8-2	27.3
C8-3	42.5

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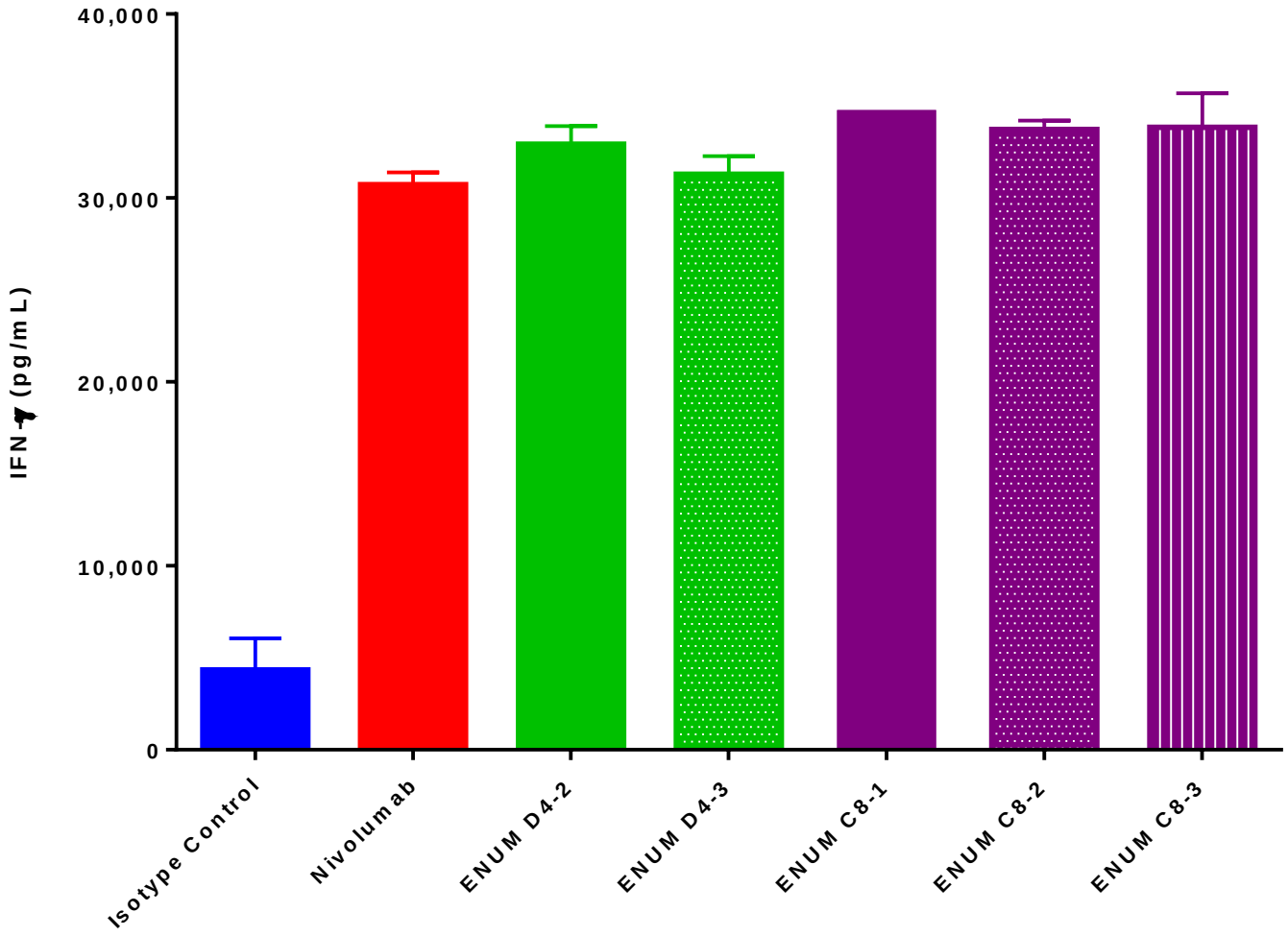
Ex Vivo PD-1 blockade Can Reverse TIL Exhaustion



Experimental Protocol:
300,000 cells purified from Tumor WD3644 were stimulated with anti-CD3+anti-CD28 in the presence of 20 ug/mL isotype control or the indicated anti-PD1 antibody.

Supernatants were analyzed by ELISA after 24 hours of Activation.

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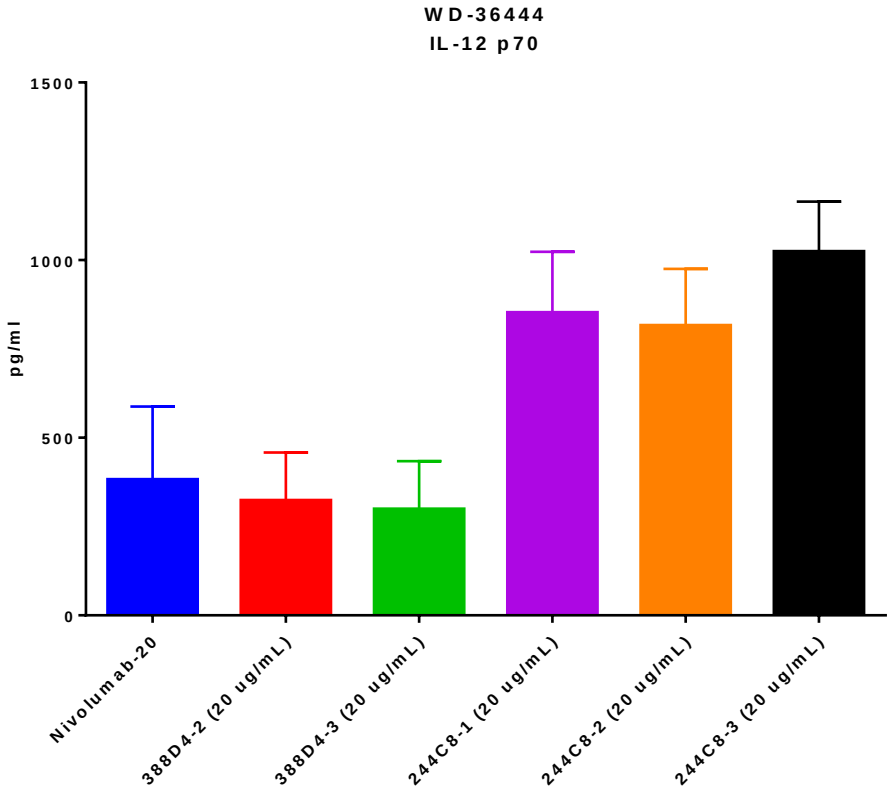
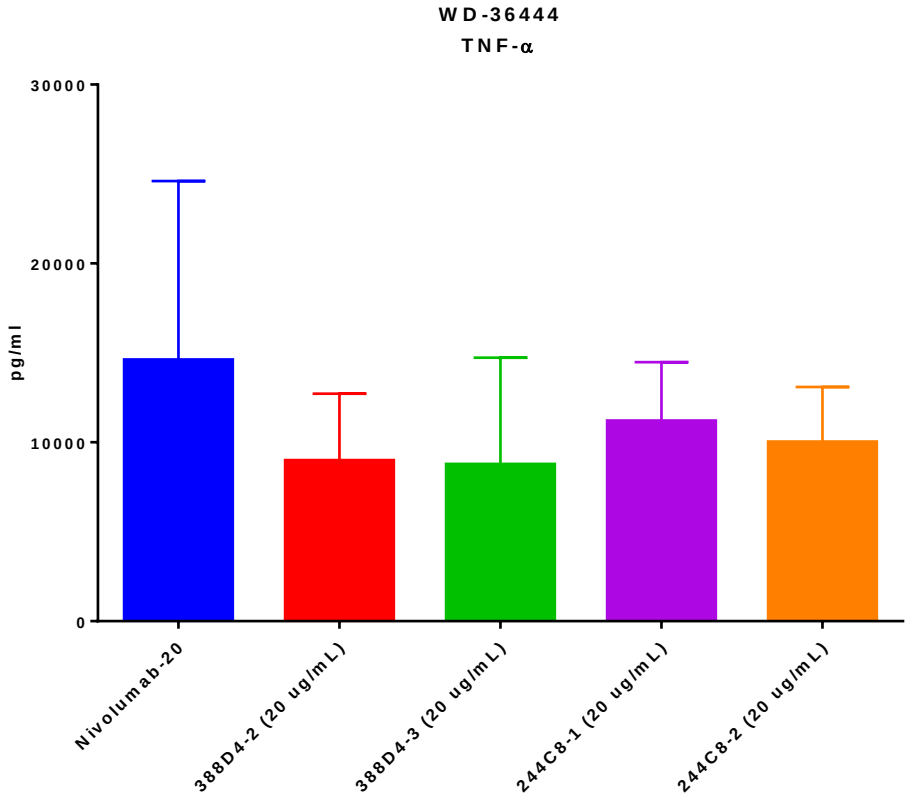
Selective IL-12 Induction with 244C8 in TIM-3^{lo} NSCLC





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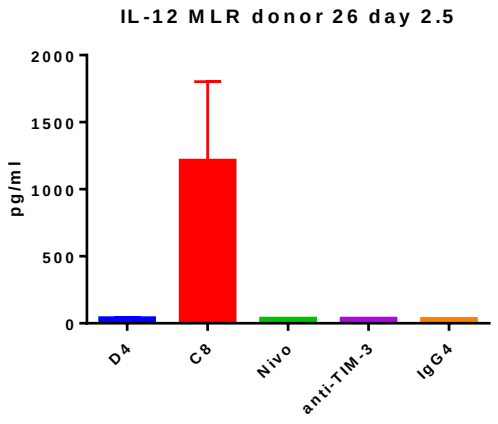
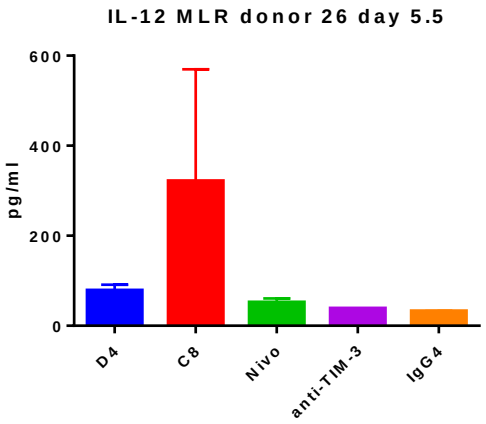
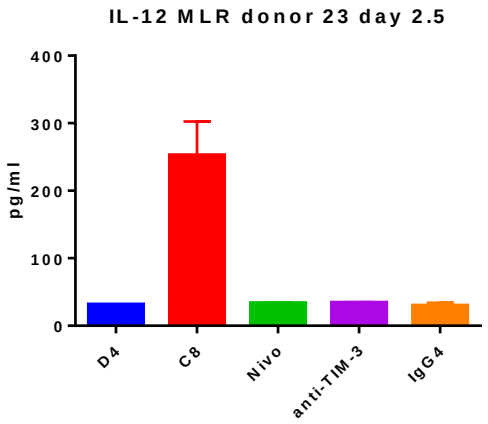
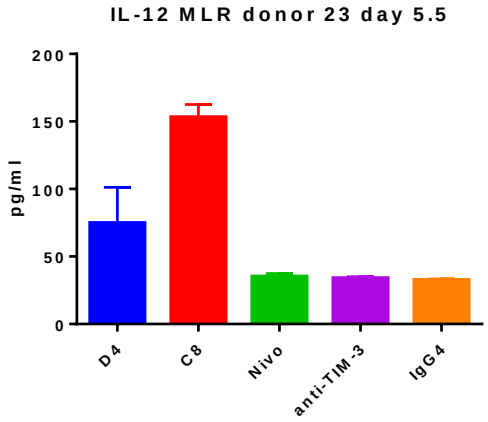
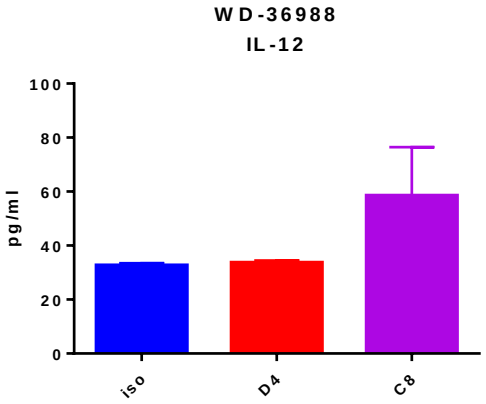
IL-12 Induction is Consistent and Specific to 244C8-based PD-1 Blockade











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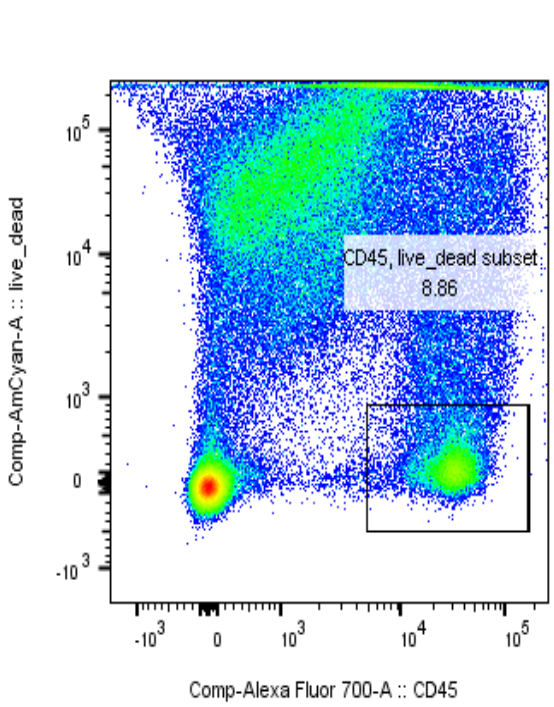
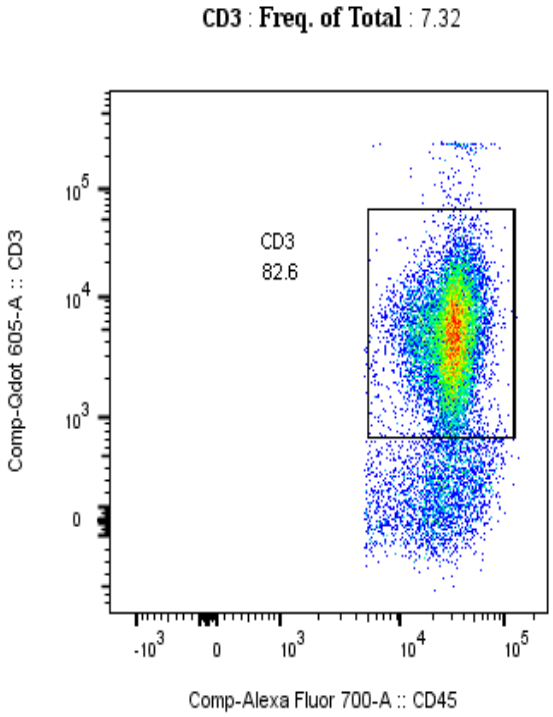
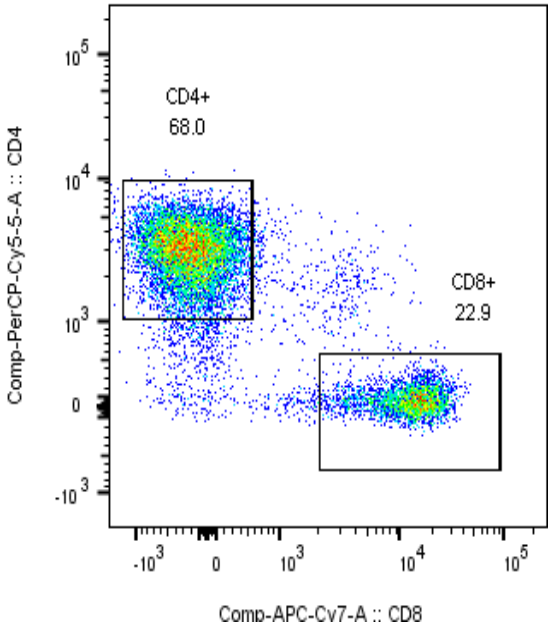
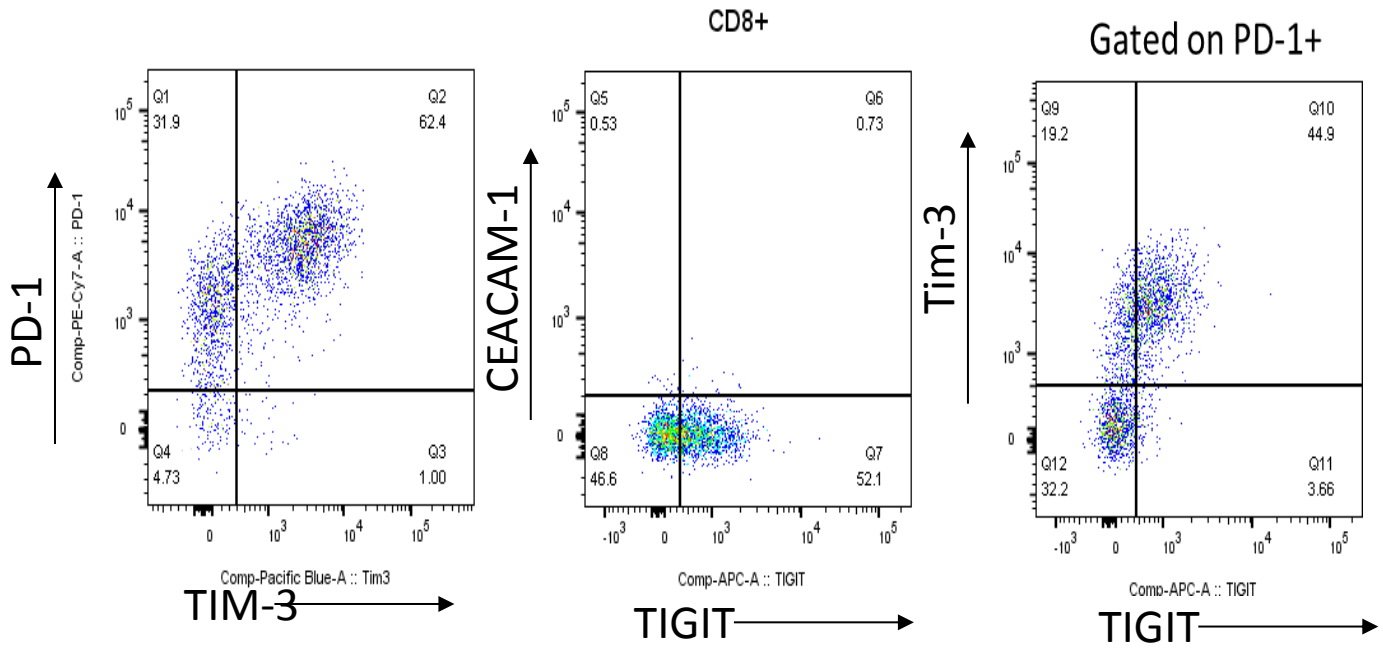
NSCLC WD36988 Contains 7% T Cells







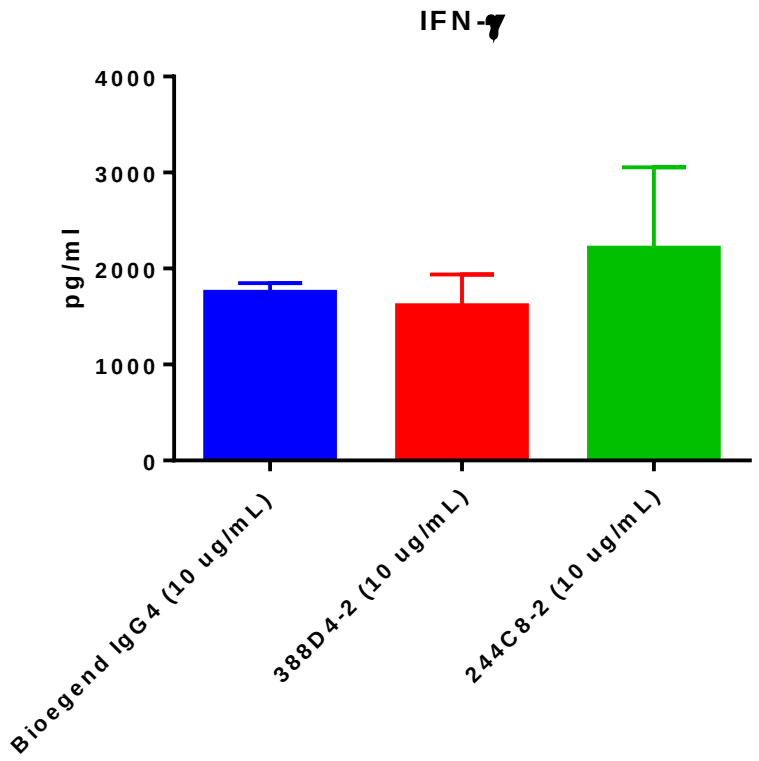
CD8+ TILs Express PD-1,Tim-3,TIGIT

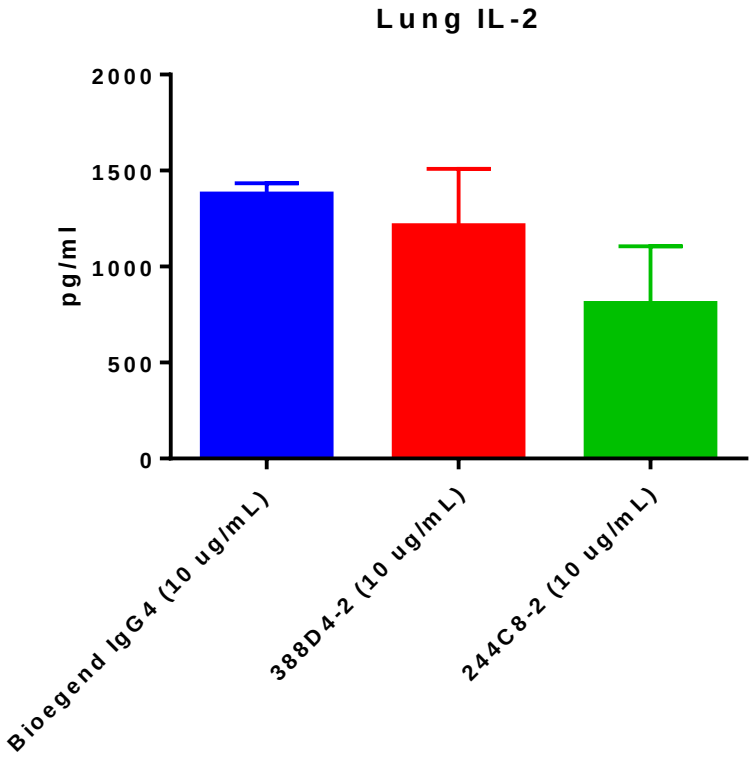


93% of CD8+ express PD-1
62% of CD8+ express TIM-3
No CD8+ express CEACAM-1
52 % of CD8+ express TIGIT

70 % of PD-1+ TIM3+ cells are also TIGIT+

Ex Vivo PD-1 Blockade can still increase IFNγ production in TIM-3^{hi}/TIGIT^{hi} T cells





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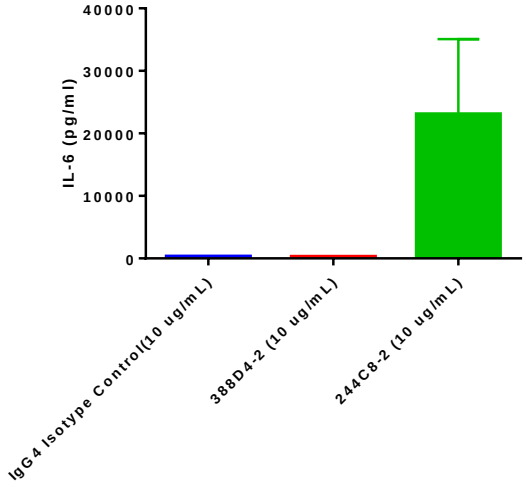
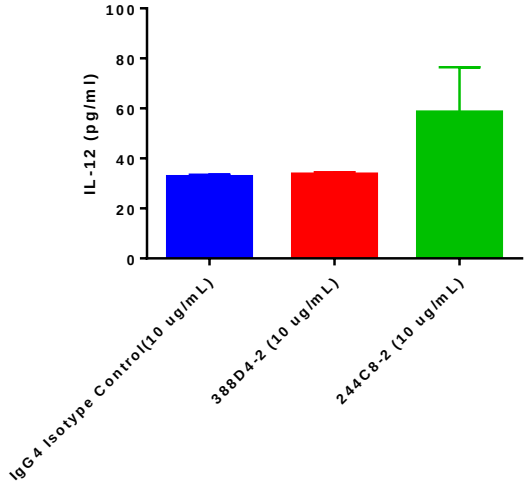
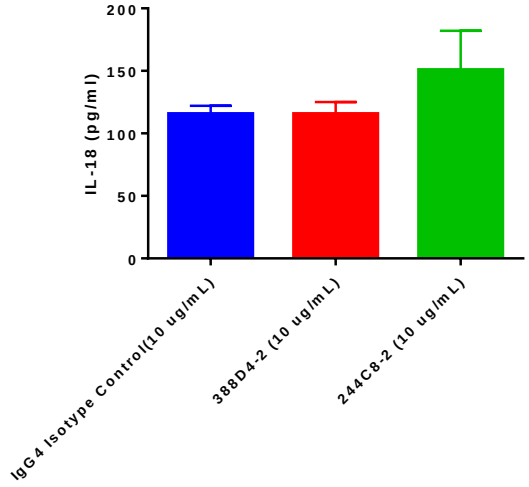
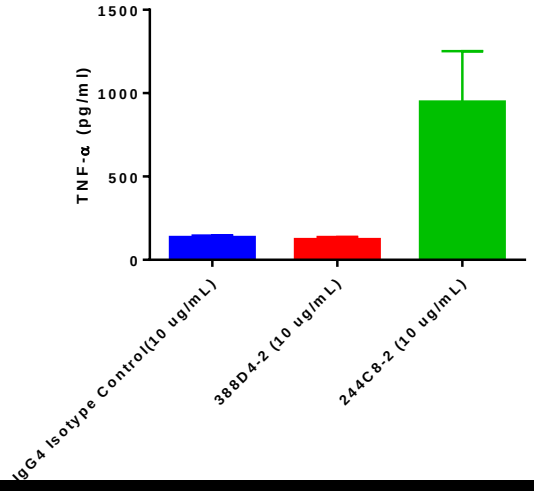
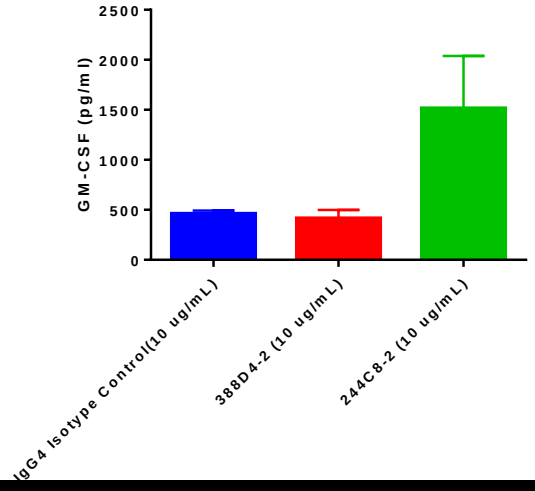
244C8 Specific PD-1 Blockade Generates a Different Molecular Signature than 388D4 in an NSCLC tumor with TIM-3^{hi}/TIGIT^{hi} T cells

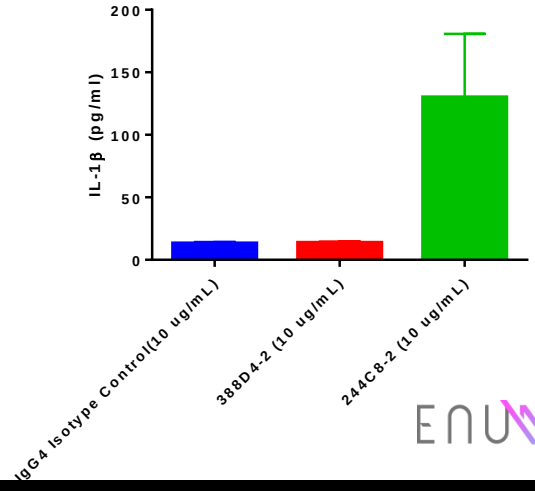












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Summary

- NSCLC tumors generally have PD-1^{hi} T cell infiltrates, however the level of additional checkpoint markers varies considerably
- PD-1 biology appears to be linked to TIM-3 receptor expression and both markers appear to be important in T cell exhaustion in NSCLC tumors
- PD-1 blockade can be biologically distinct between anti-PD-1 antibodies
  - Enumeral 244C8 is an anti-PD-1 antibody that may promote release of non T cell (myeloid) derived anti-tumor cytokines

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