Presenter Disclosure Information

Stock ownership: Bristol Myers Squibb and Lion Biotechnologies

Society for Immunotherapy of Cancer

Increased STAT3 signaling and decreased suppressive function of regulatory T-cells are biomarkers of positive patient outcome to nivolumab therapy

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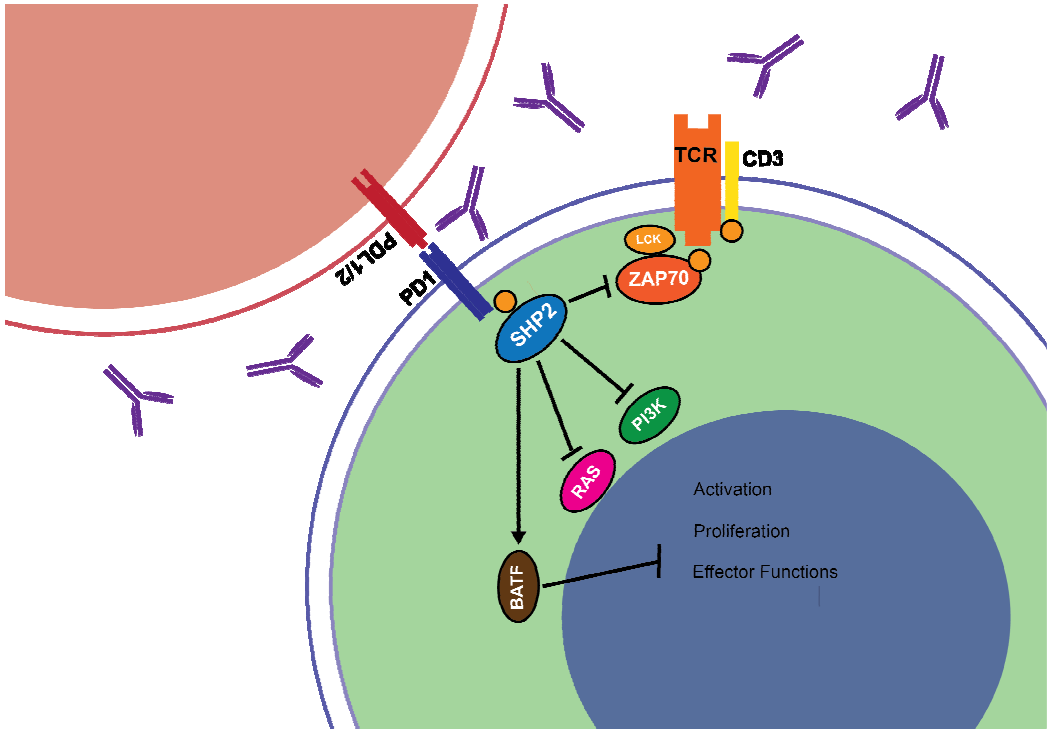
PD-1 Blockade for the Treatment of Melanoma



Clinical Trial MCC15651 (Cohorts 1-3)
Anti-PD-1 Antibody MDX-1106
Resected Stages IIIC/IV Melanoma.

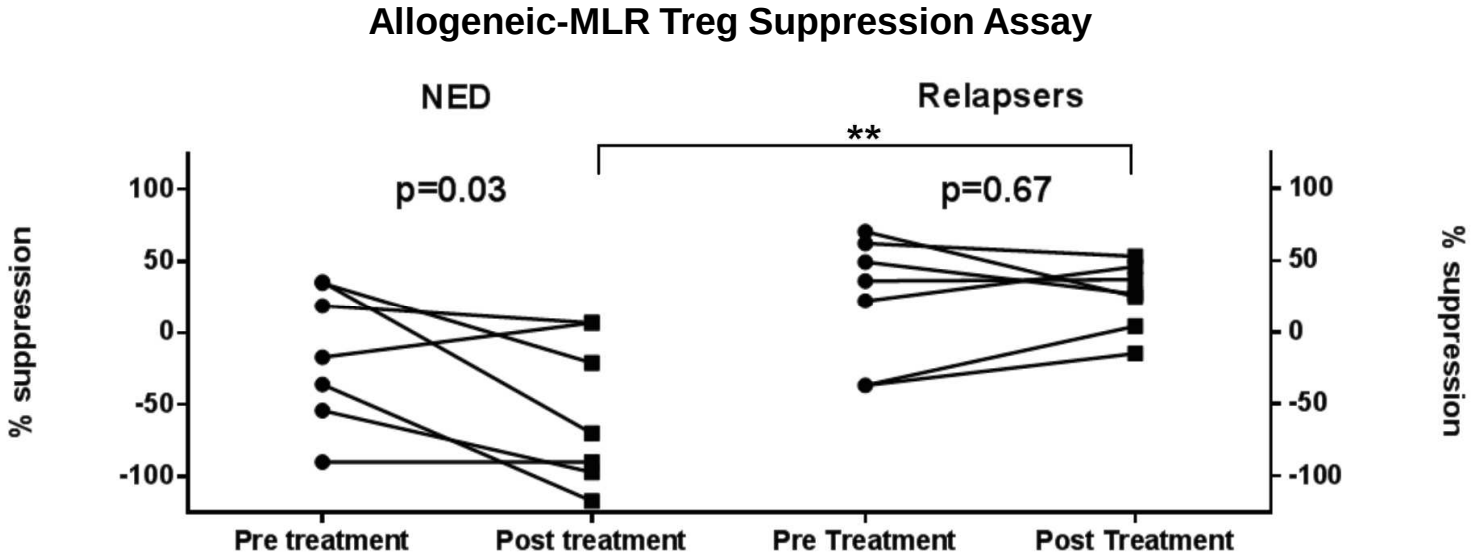
Clinical Trial MCC15400 (Cohorts 1-3)
Anti-PD-1 Antibody MDX-1106
Unresectable Stages III/IV Melanoma.

Clinical Trial MCC17365 (Cohort A)
Nivolumab Given Sequentially with Ipilimumab
Unresectable Stages III/IV Melanoma.

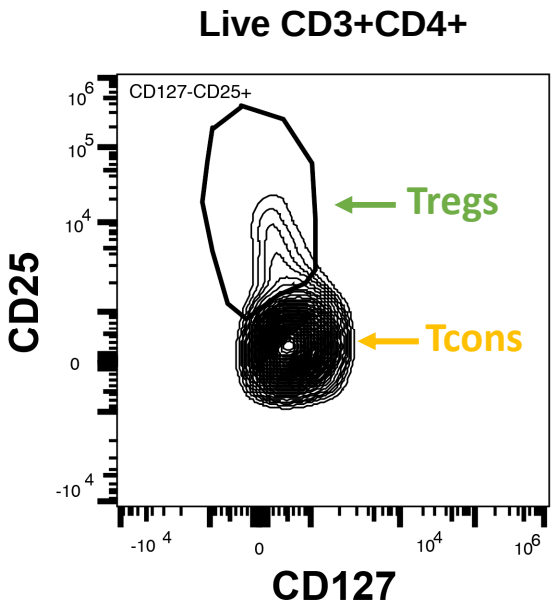
*All samples assessed were ipilimumab naïve.

Lack of Biomarkers

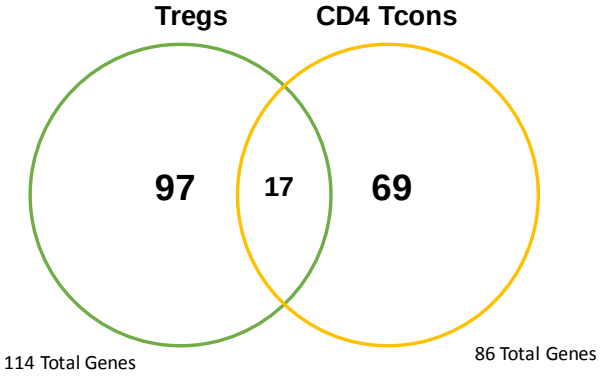
Patients Benefiting from Nivolumab Therapy Have Decreased Treg Suppressive Function



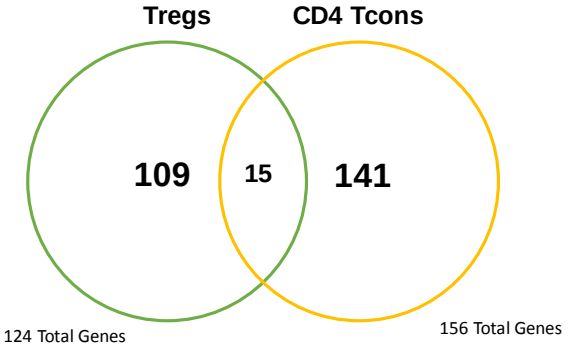
Tregs and Conventional T-cells Have Distinct Gene Profile Changes in Response to Nivolumab



Upregulated Genes (Pre vs. Post)



Downregulated Genes (Pre vs. Post)



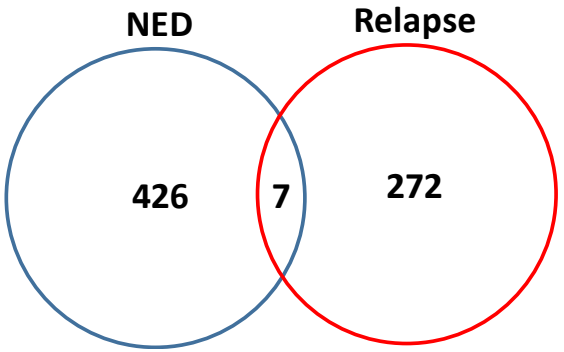
Tregs from Patients with No Evidence of Disease (NED) and Relapsing Patients have Distinct Gene Profile Changes in Response to Nivolumab

Significantly Changed Genes: Same Direction

		Relapse Pre vs. Post	NED Pre vs. Post
PCDHA9	protocadherin alpha 9	-1.06	-1.12
GZMK	granzyme K (granzyme 3; tryptase II)	0.99	1.08
CX3CR1	chemokine (C-X3-C motif) receptor 1	1.01	1.19
CCNB1	cyclin B1	1.24	0.87
PDCD1	programmed cell death 1	1.41	1.31
GZMA	granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)	1.55	0.76
DLGAP5	discs, large (Drosophila) homolog-associated protein 5	1.99	0.96

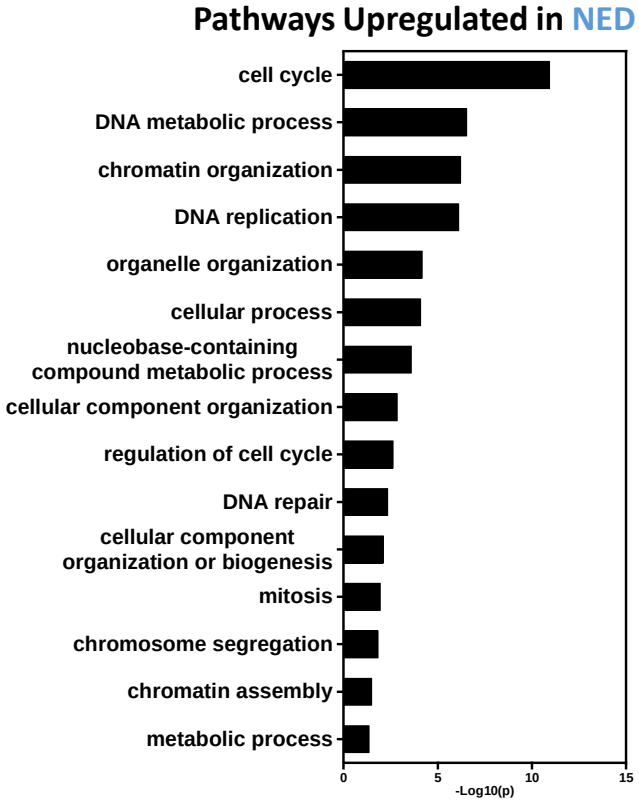
Significantly Changed Genes: Opposite Direction

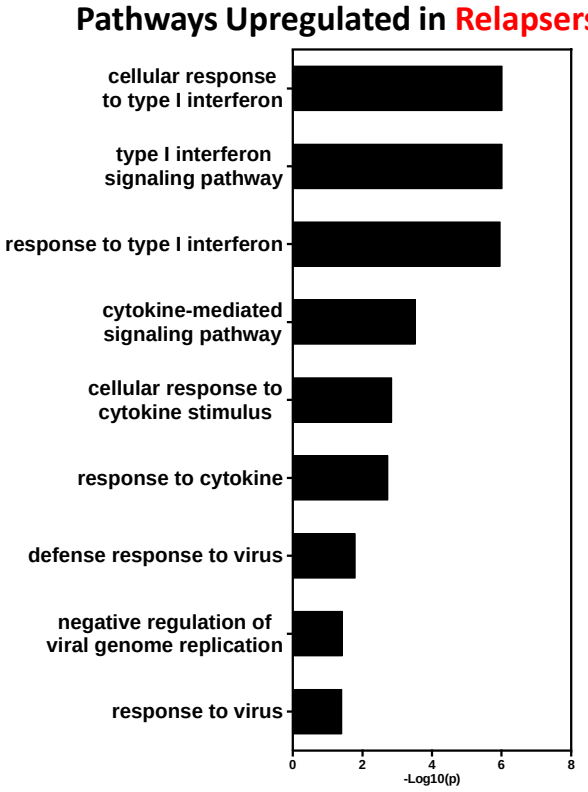
		Relapse Pre vs. Post	NED Pre vs. Post
POLQ	polymerase (DNA directed), theta	-2.36	1.13
SESTD1	SEC14 and spectrin domains 1	-1.41	1.81
NEFL	neurofilament, light polypeptide	-0.83	0.99
SNORA76	small nucleolar RNA, H/ACA box 76C	-0.56	0.68
IFI44L	interferon-induced protein 44-like	1.39	-0.65
WDR61	WD repeat domain 61	3.72	-0.49



All values given in log2 scale

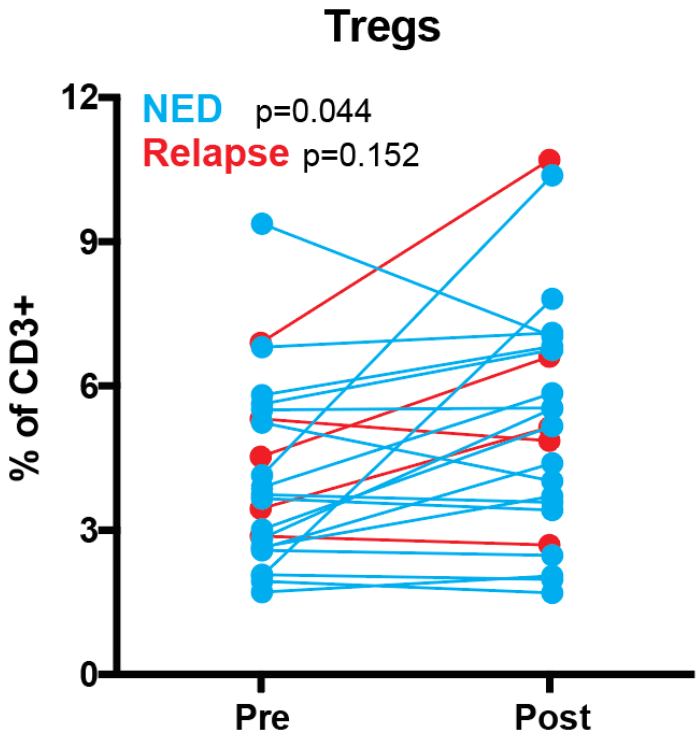
Tregs from Relapsed and NED Patients have Distinct Pathways Upregulated in Response to Nivolumab

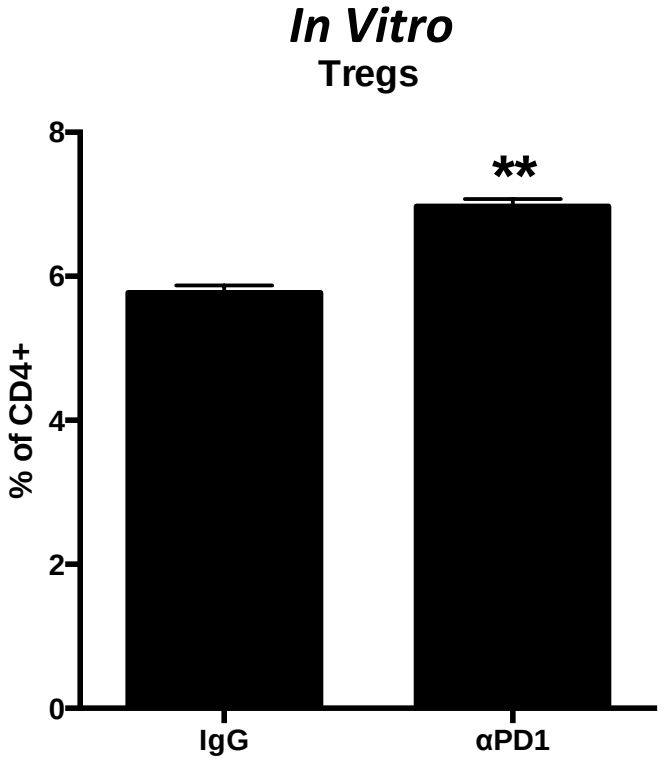




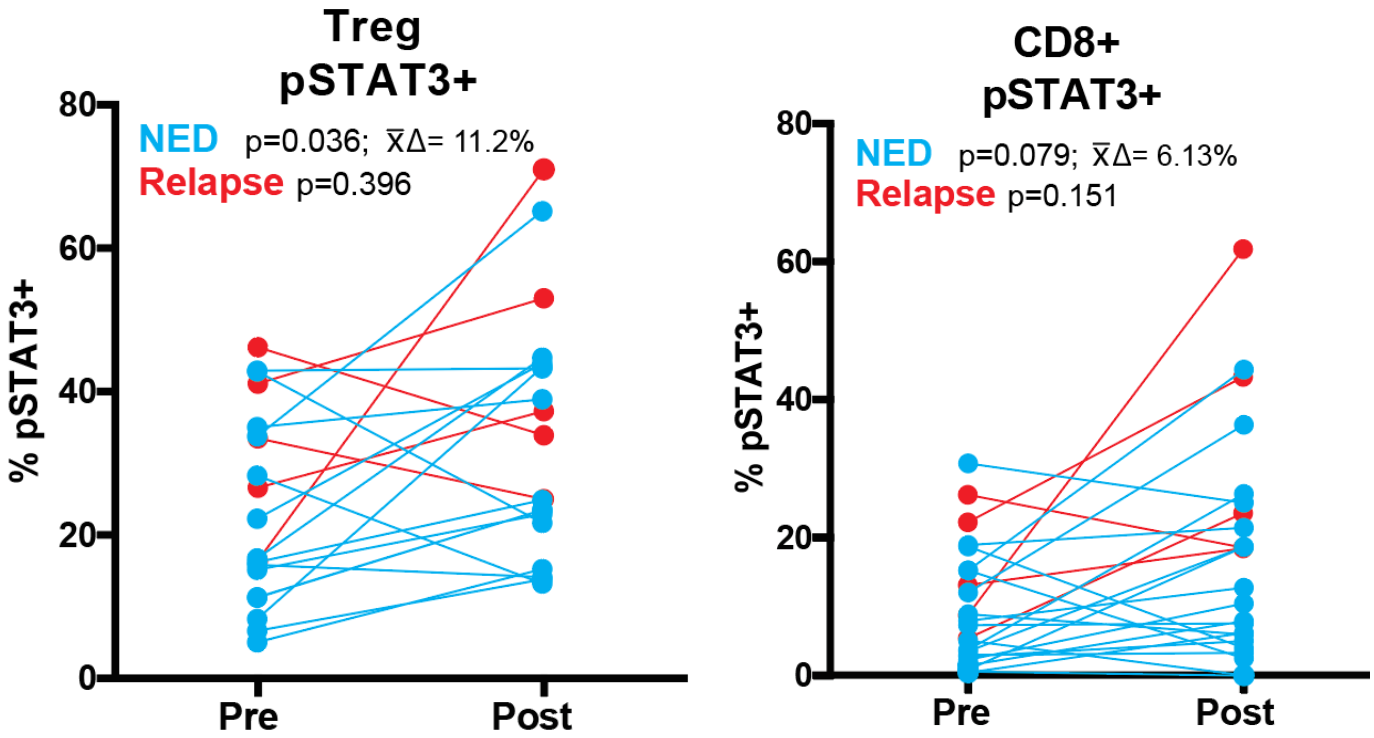
Results from Panther (similar results with GeneGo)

PD-1 Blockade Increases the Proportion of Tregs

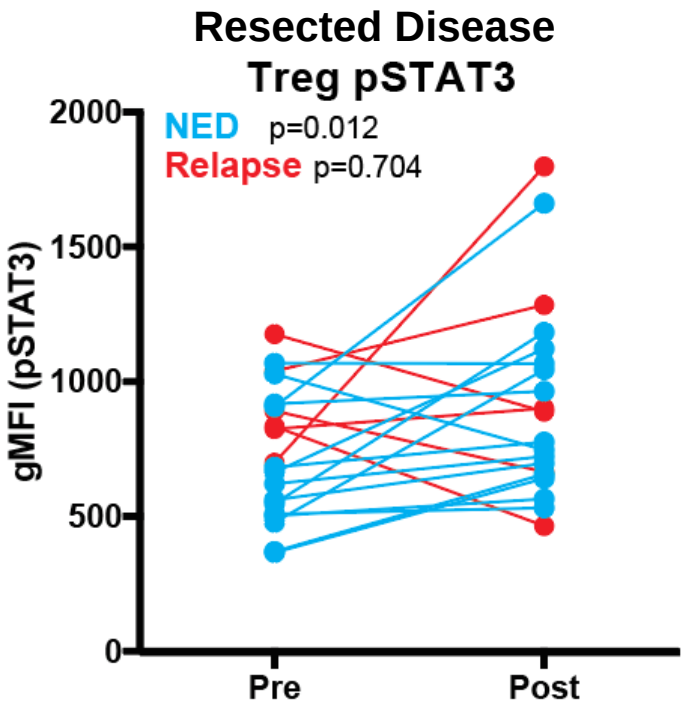


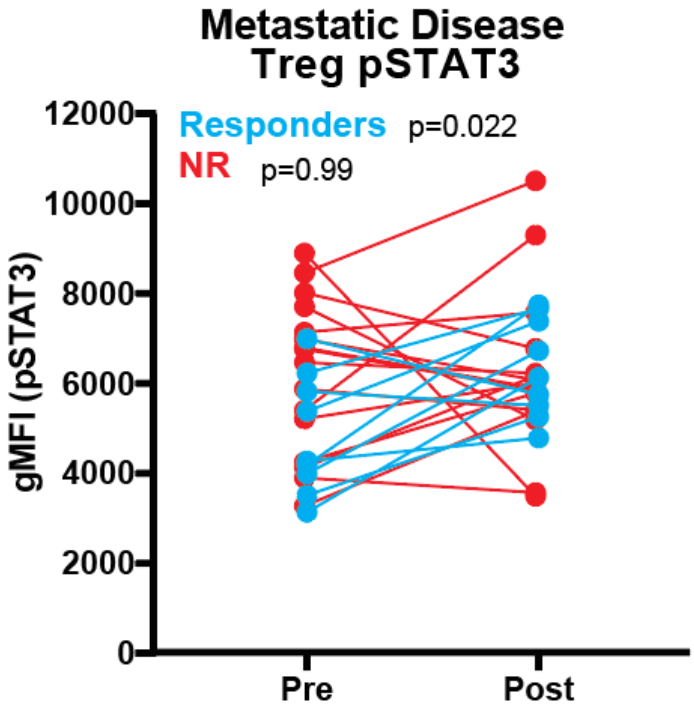


Resected Patients that are NED after Nivolumab Therapy have Increased Phospho-STAT3 Expression in Tregs

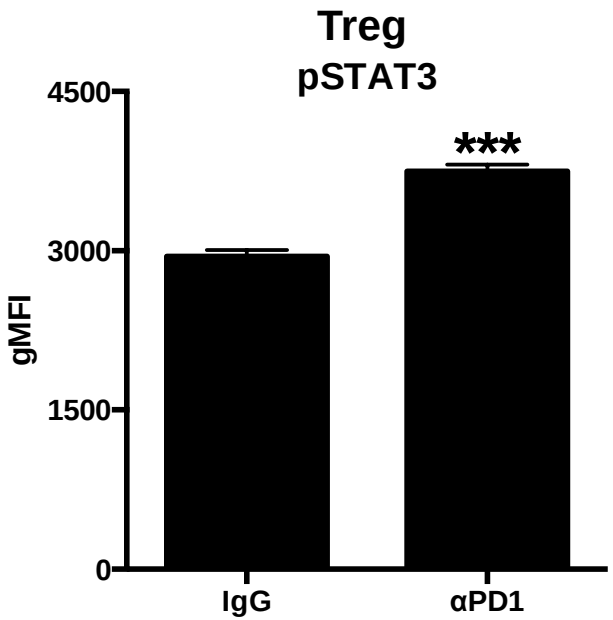


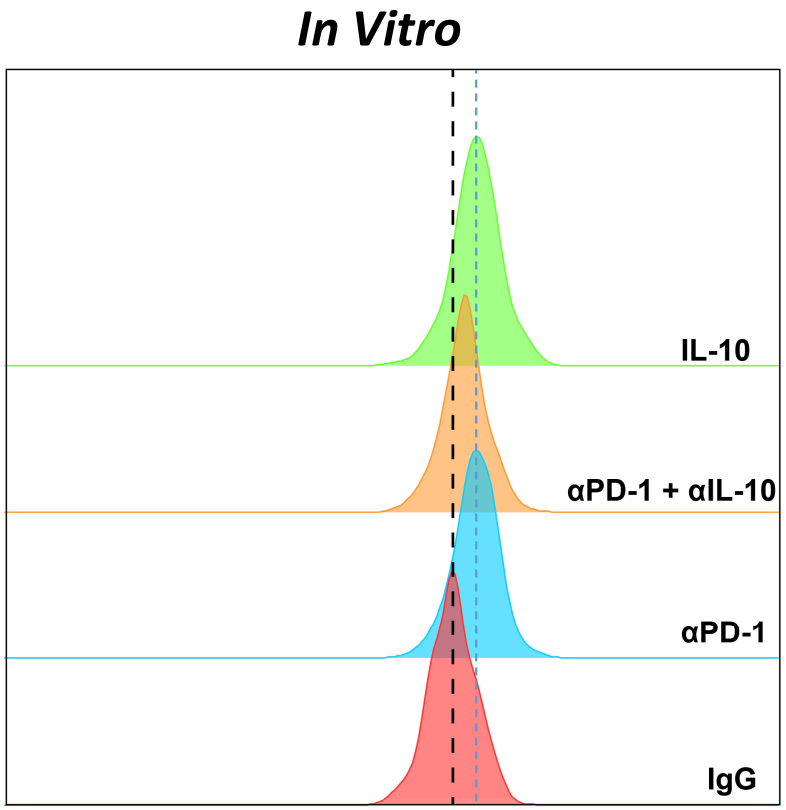
NED Resected Patients and Responding Metastatic Patients Have Induction of pSTAT3 in Tregs Post-Nivolumab



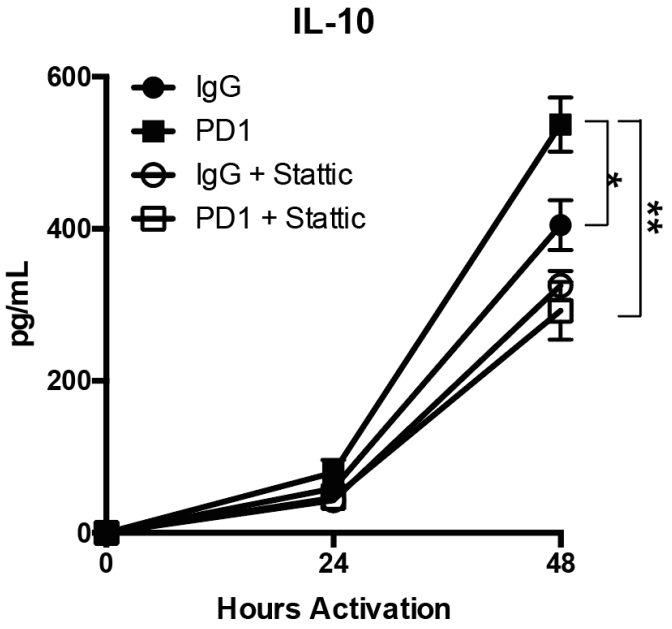


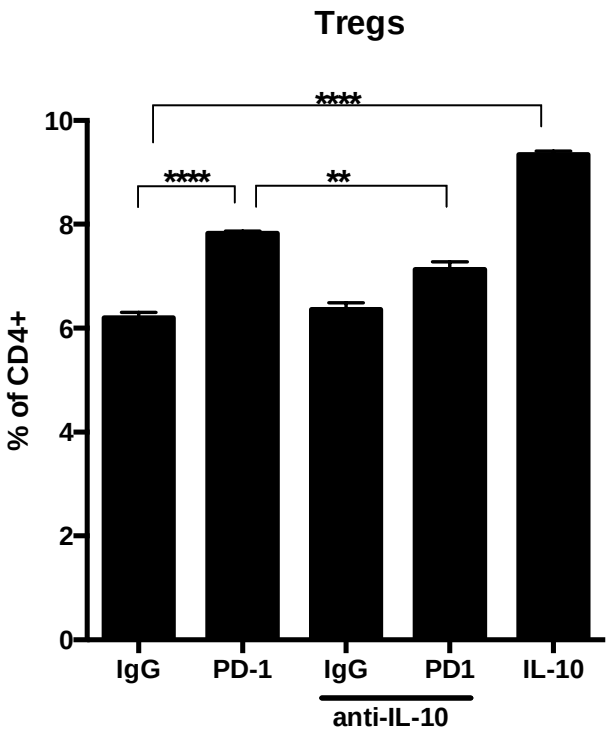
PD-1 Blockade Induces pSTAT3 in Tregs *In Vitro*



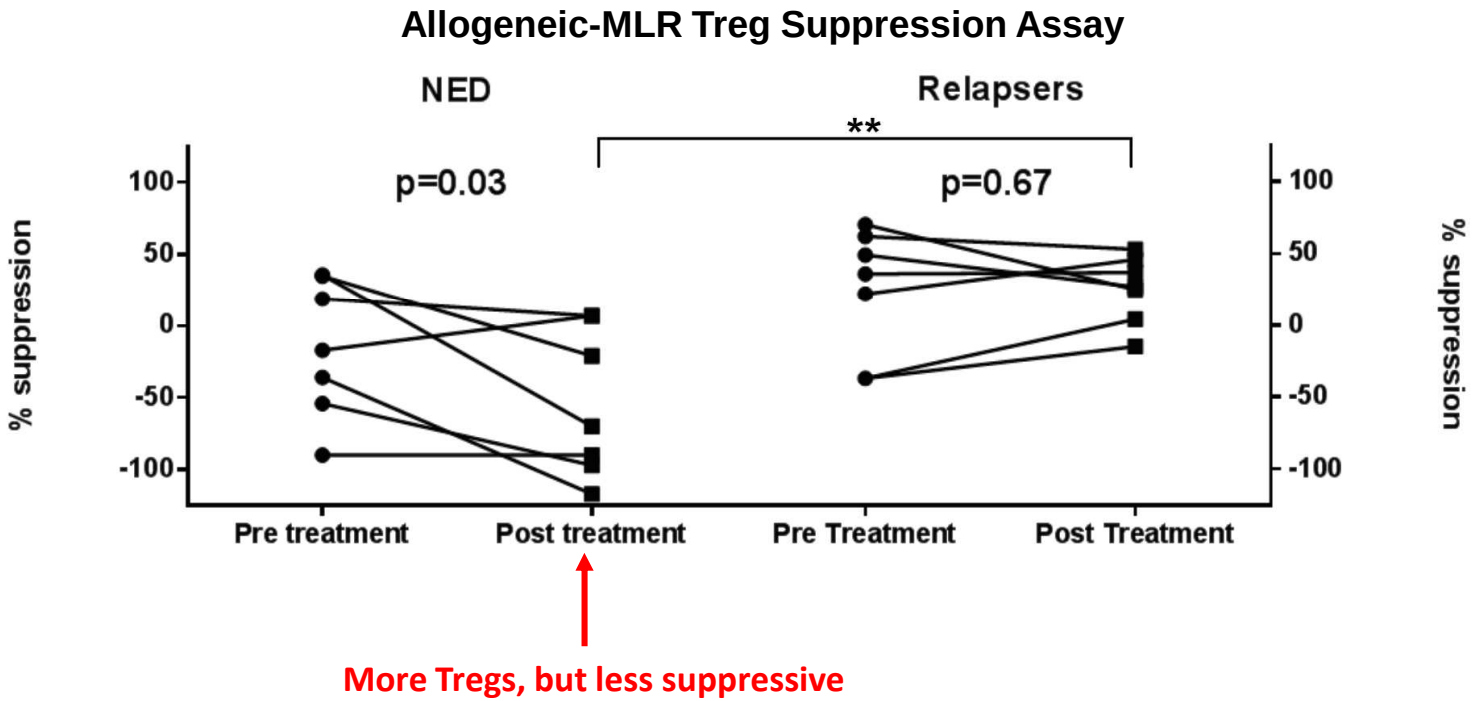


PD-1 Blockade Increases IL-10 Expression by T-cells





NED Resected and Responding Metastatic Patients Show a Decrease in Treg Suppressive Function after Nivolumab Treatment



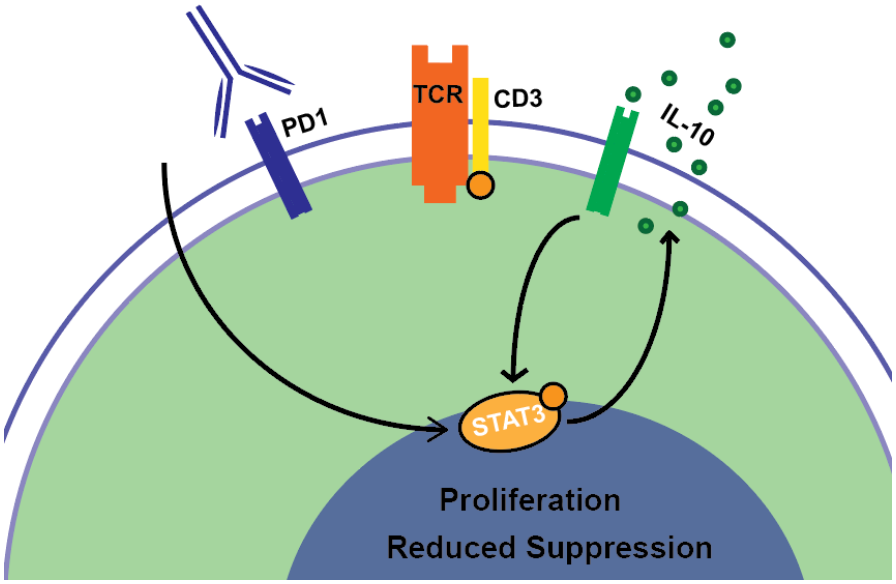
Summary

- Tregs have distinct changes to nivolumab compared to Tcons and based on patient outcome.

- Clinical benefit to nivolumab therapy is associated with:
  - Decreased suppressive Tregs
  - Increased pSTAT3 expression in Tregs
  - Increased percentages of circulating Tregs
  - Gene profile associated with proliferation pathways

- Lack of clinical benefit is associated with:
  - Treg gene profile associated with type I interferon signaling
  - Treg gene profile associated with STAT1/2 signaling

- PD-1 blockade leads to a pSTAT3 dependent increase in IL-10 production, which contributes to increased percentages of Tregs.



Acknowledgements

Jeffrey Weber
Andressa L. Sodré

Anders Berglund
Rupal Ramakrishnan

Funding:
NIH/NCI SPORE Grant 1P50CA168536-01A1
Sullivan Fund at Moffitt Cancer Center