

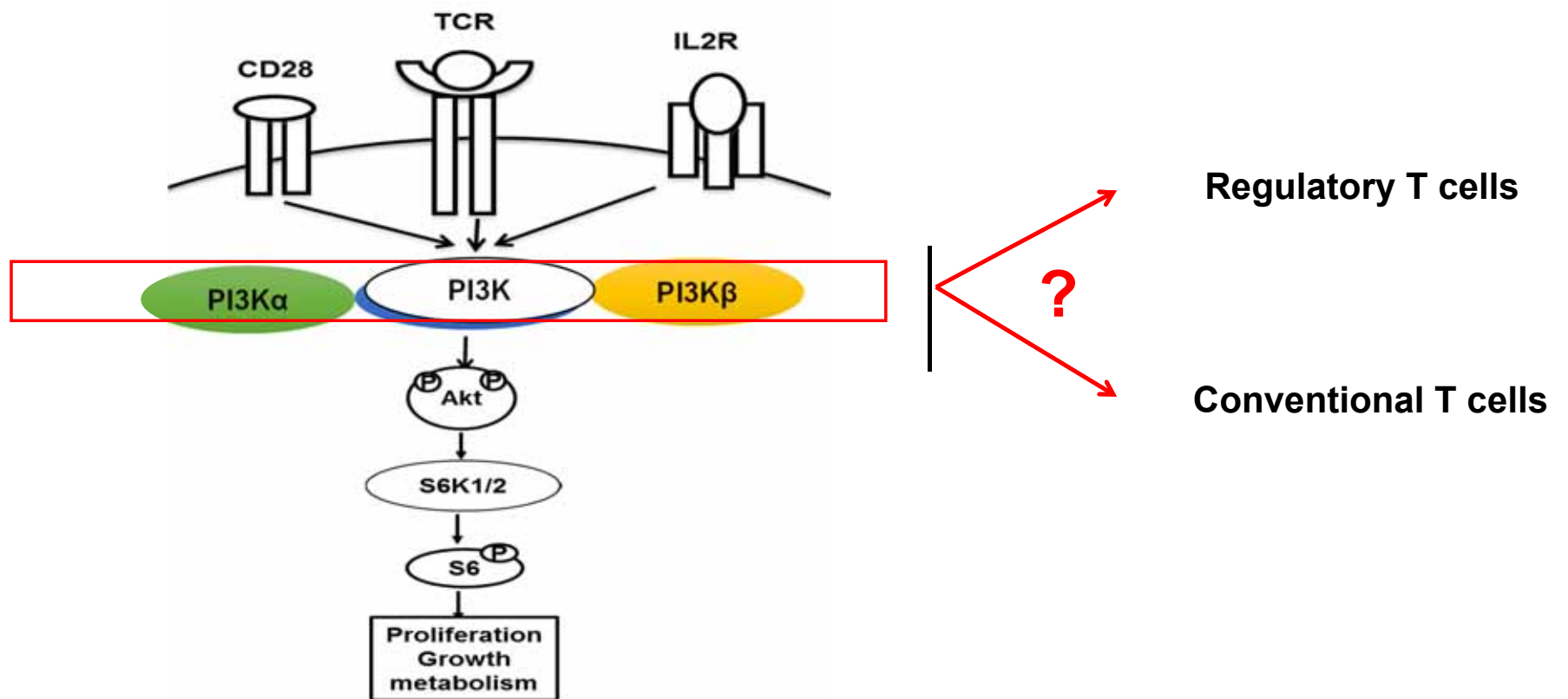
Modulation of T cell response by targeting the PI3K-Akt pathway

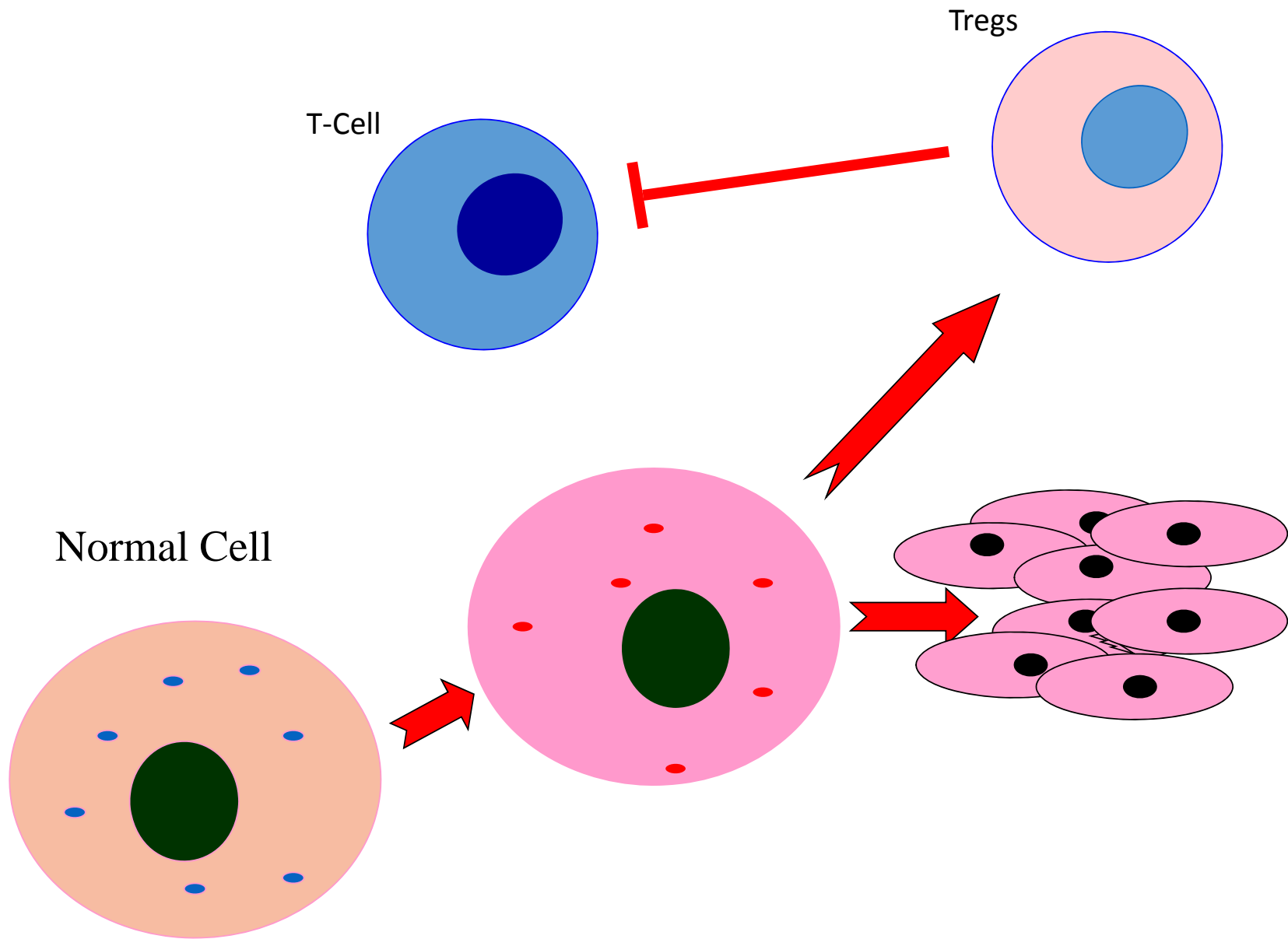
John Janik, M.D.

Samir Khleif Laboratory

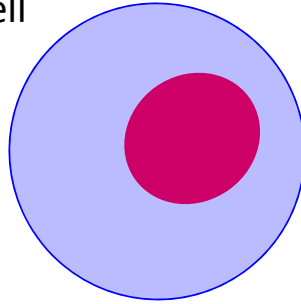
Augusta University

PI3K-Akt Signaling Pathway in T cells



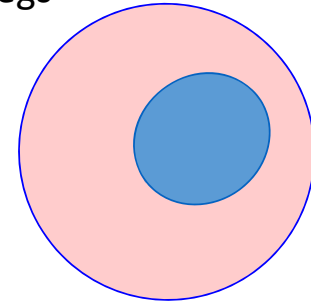


T-Cell



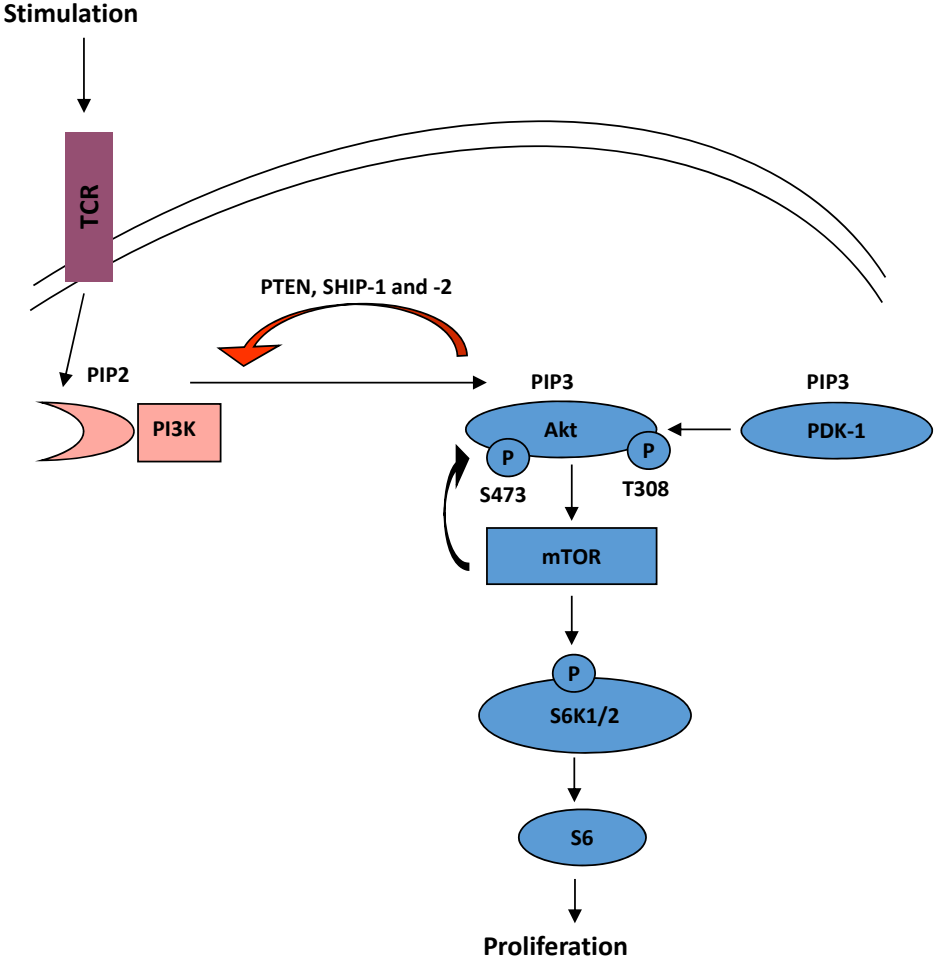
CD4+
Foxp3-

Tregs

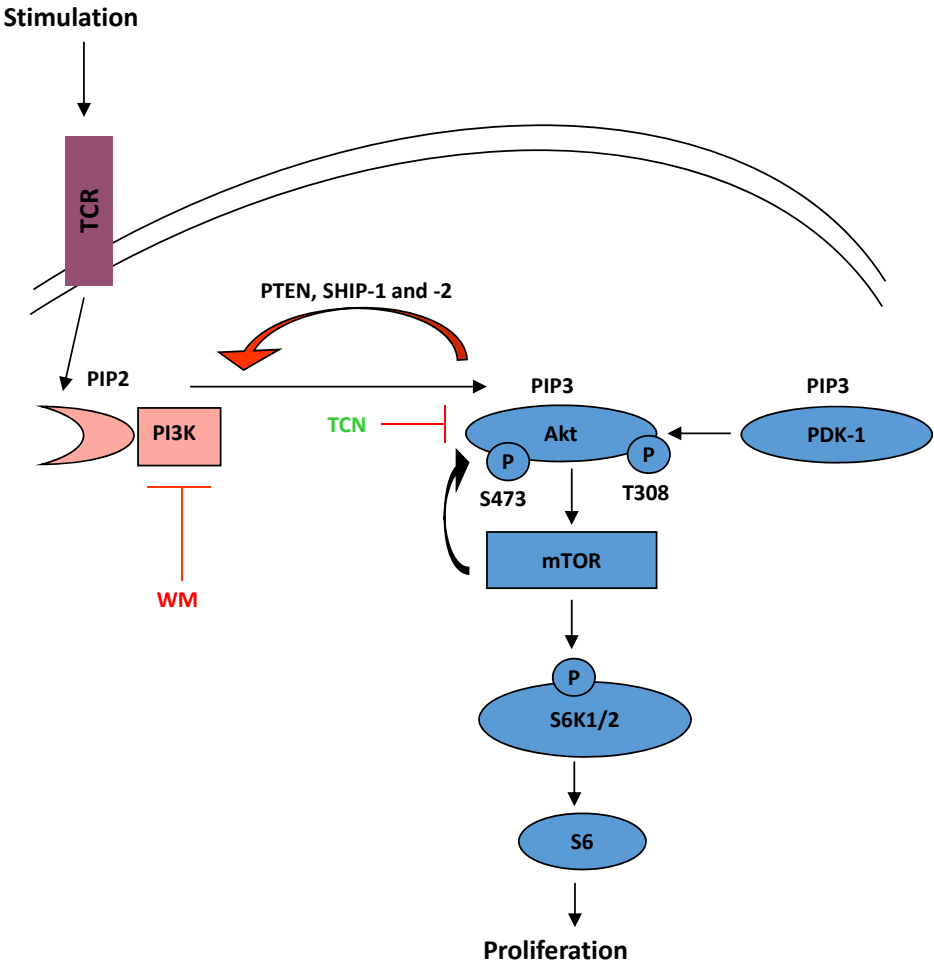


CD4+
Foxp3+

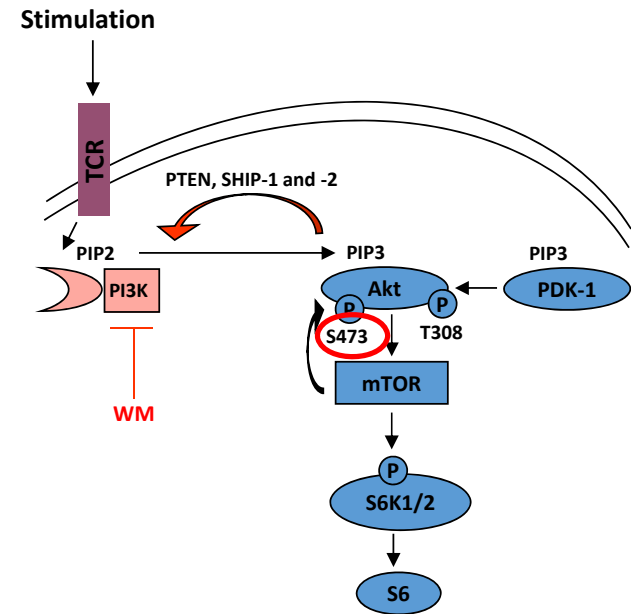
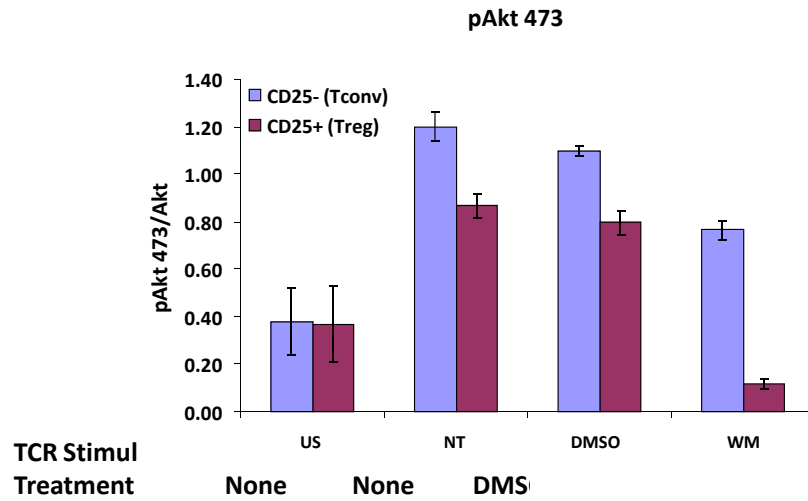
Effects of PI3K-Akt pathway inhibition in Tregs vs. Tconv cells



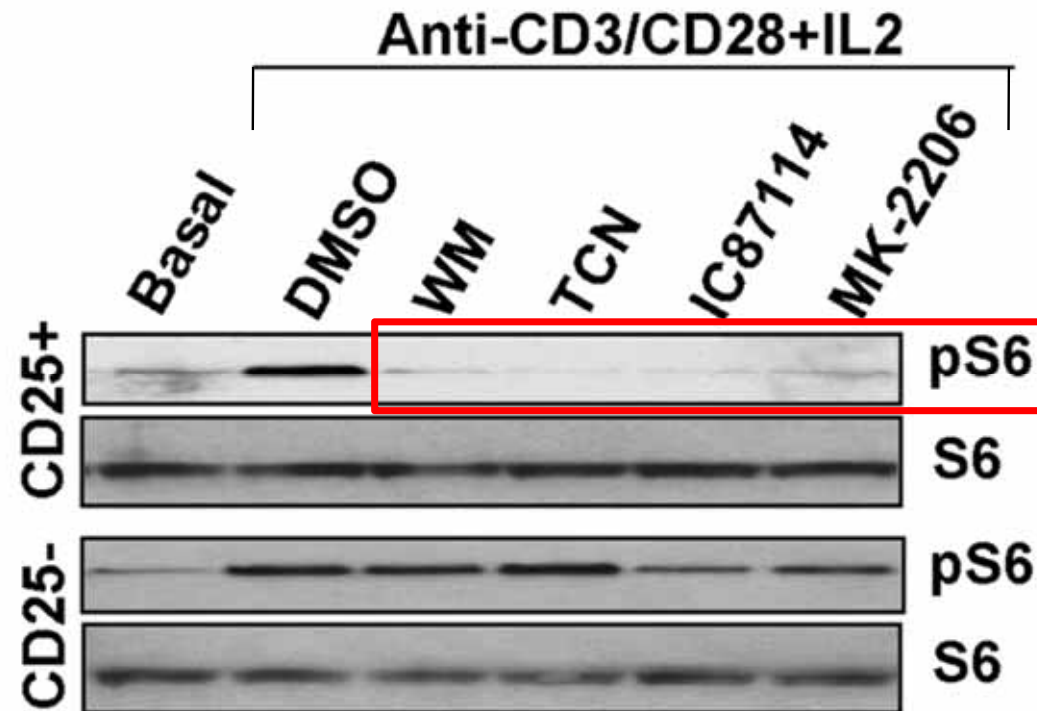
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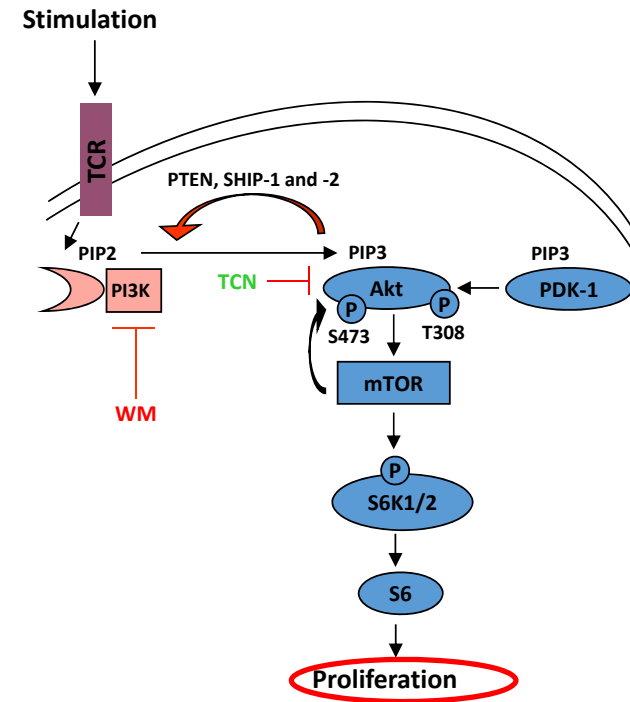
Effects of PI3K-Akt pathway inhibition in Tregs vs. Tconv cells



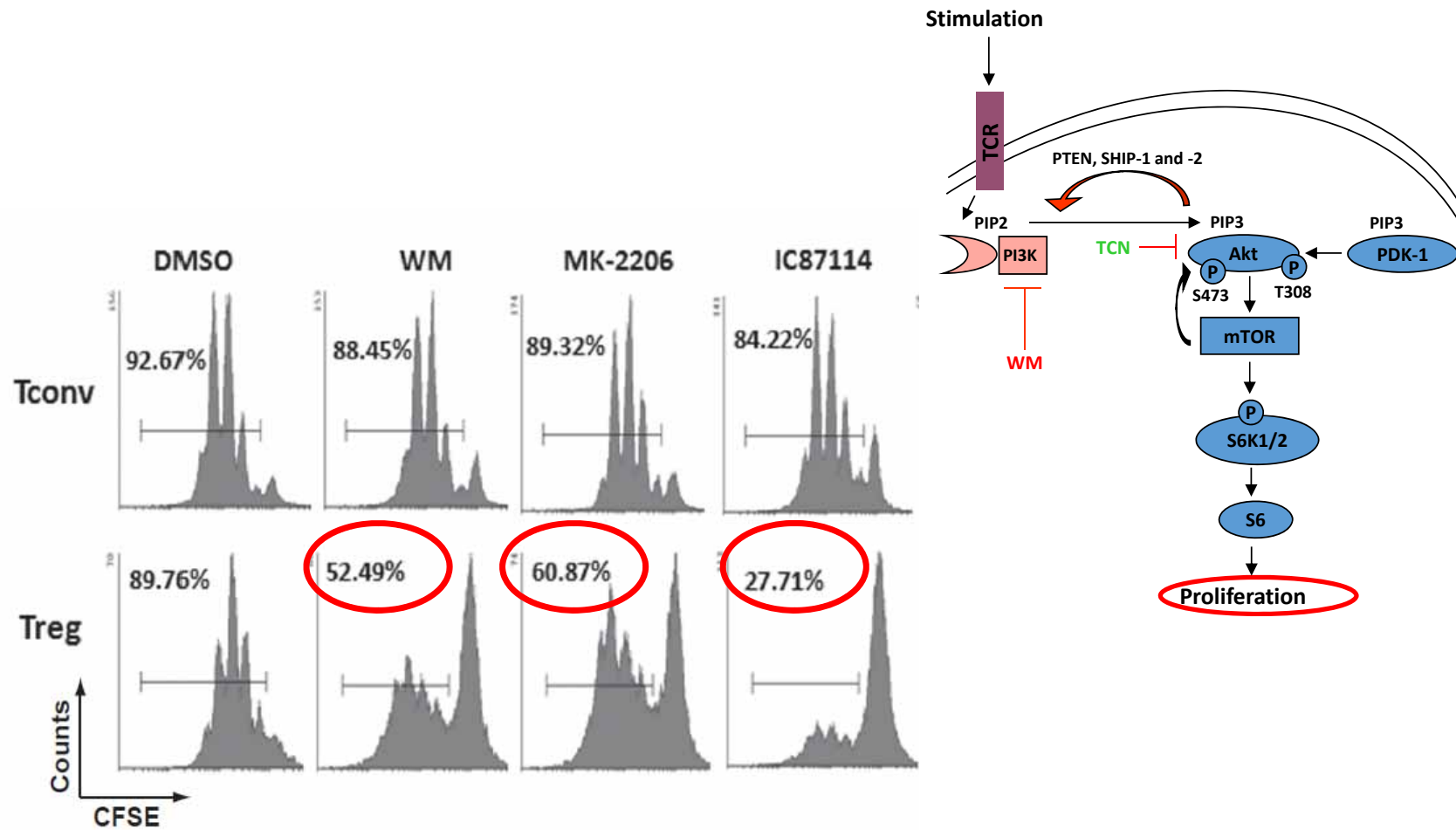
S6 phosphorylation is diminished in mouse Treg in presence PI3K/AKT inhibitors



Effects of PI3K-Akt pathway inhibition on the TCR/IL2 Induced proliferation of Tregs vs. Tconv cells



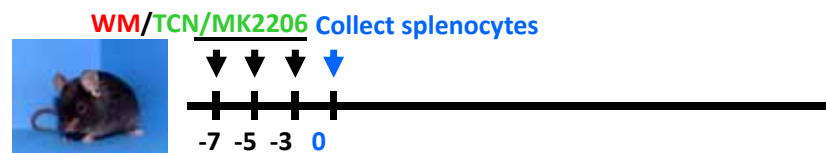
Effects of PI3K-Akt pathway inhibition on the TCR/IL2 Induced proliferation of Tregs vs. Tconv cells



Inhibition of PI3K-Akt pathway in vivo

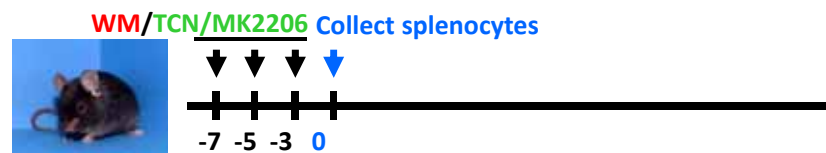
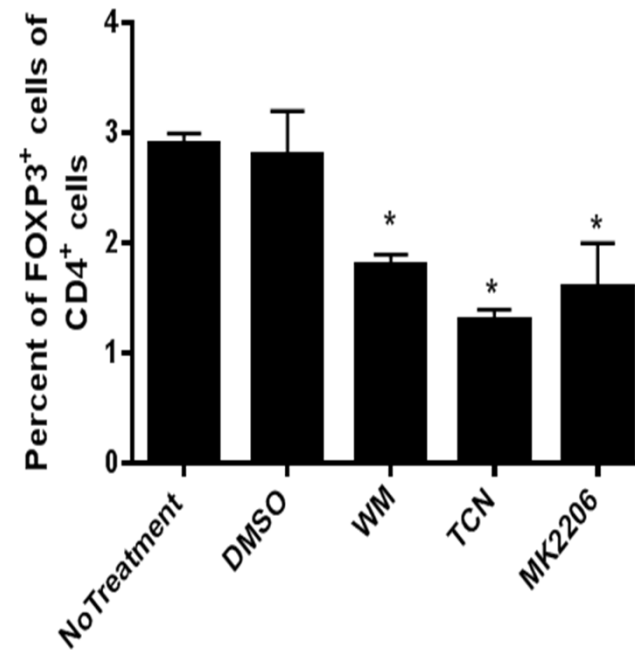


PI3K/ Akt pathway is essential for the *in vivo* maintenance of Treg in naïve tumor free mice



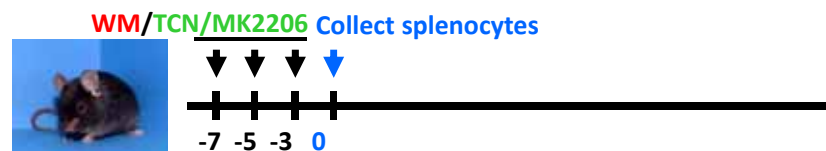
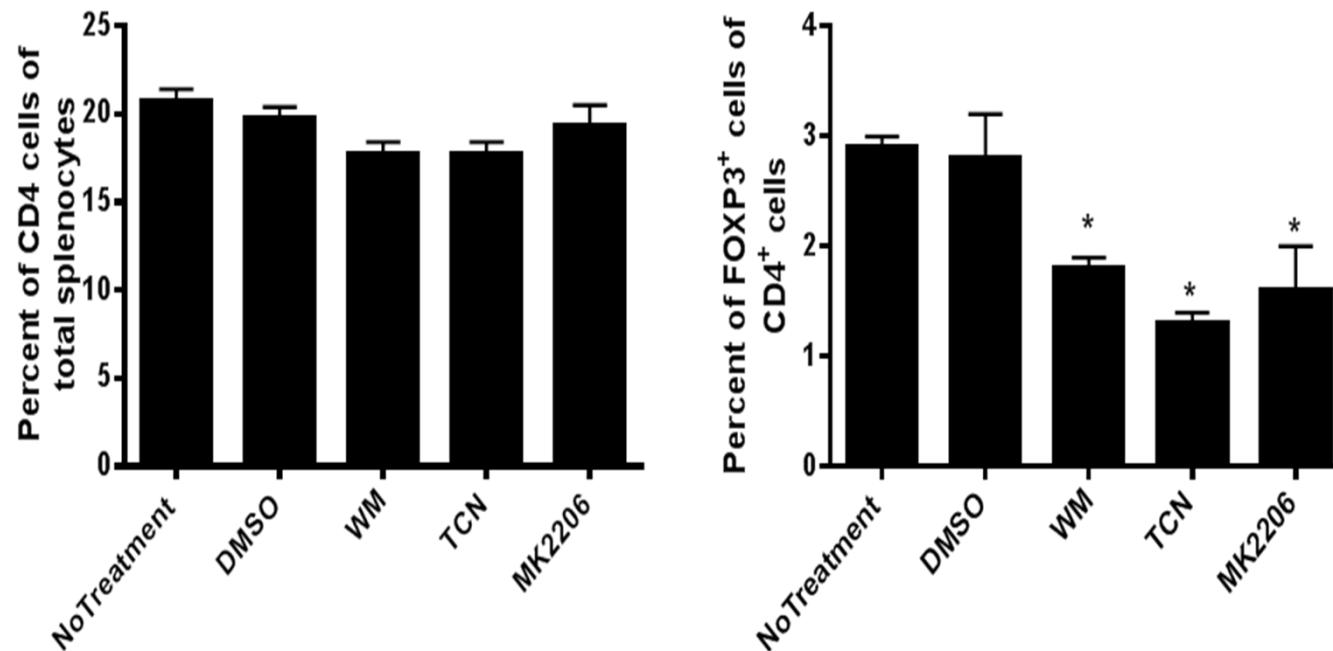
Abu Eid R.et al, CIR, 2014

PI3K/ Akt pathway is essential for the *in vivo* maintenance of Treg in naïve tumor free mice

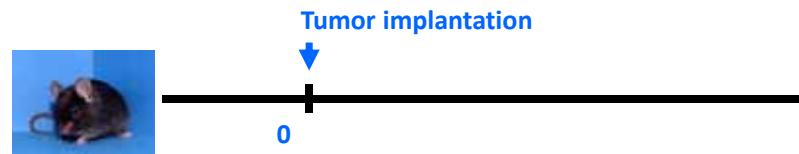
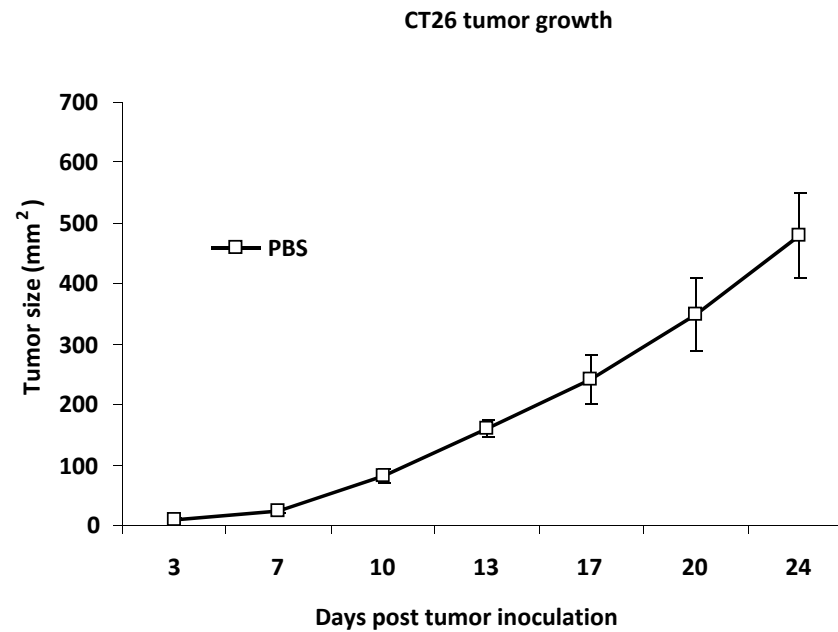


Abu Eid R. et al, CIR, 2014

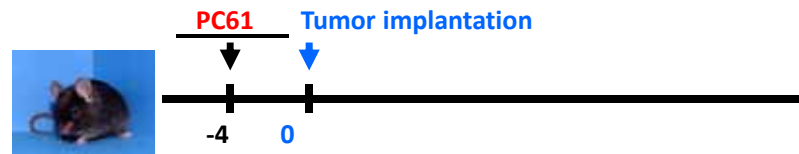
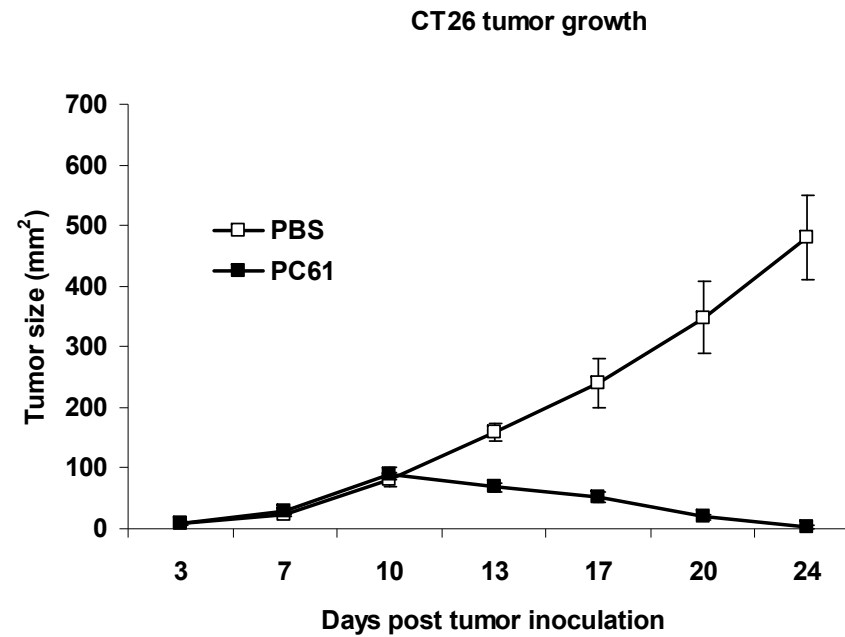
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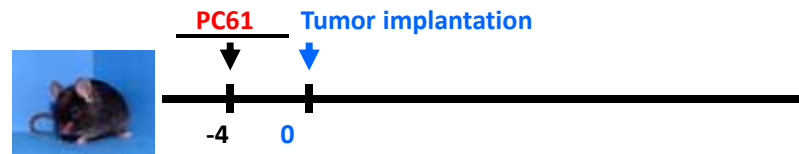
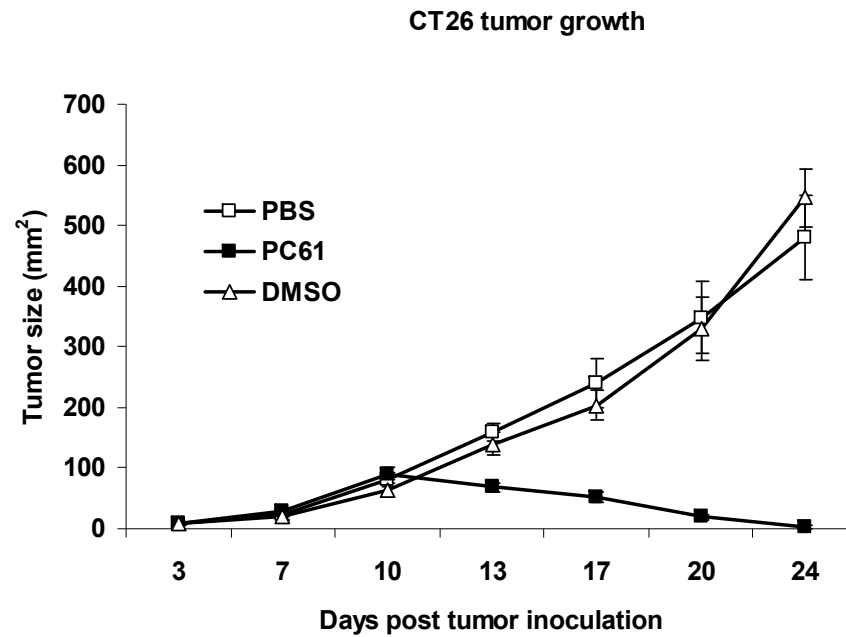
PI3K-Akt pathway inhibition indirectly decrease tumor growth



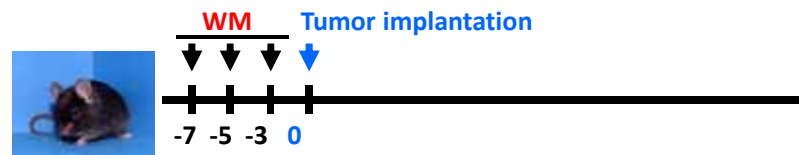
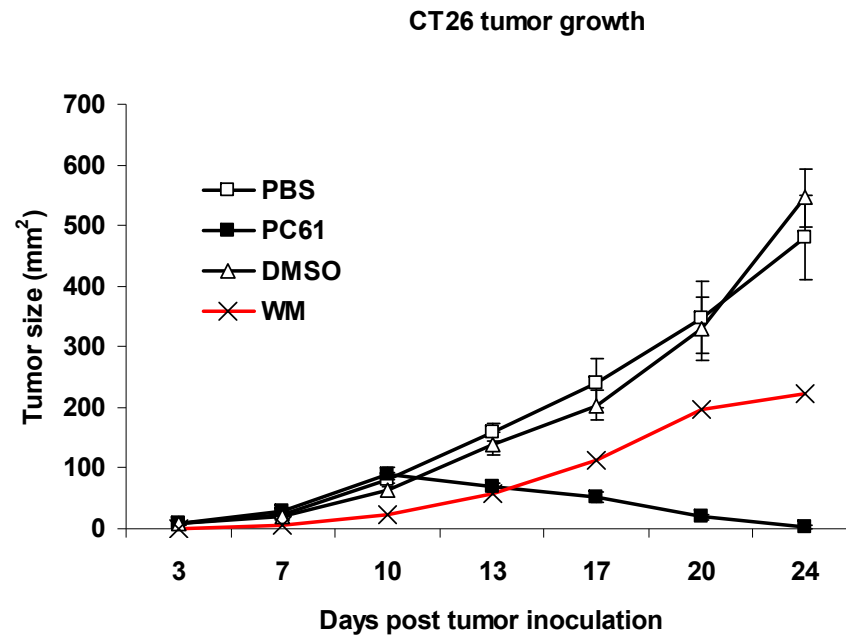
PI3K-Akt pathway inhibition indirectly decrease tumor growth



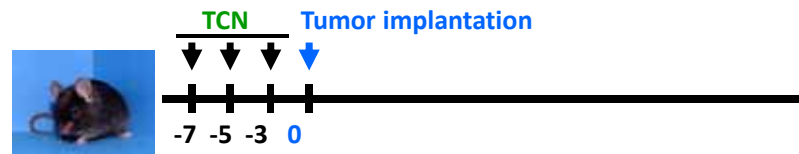
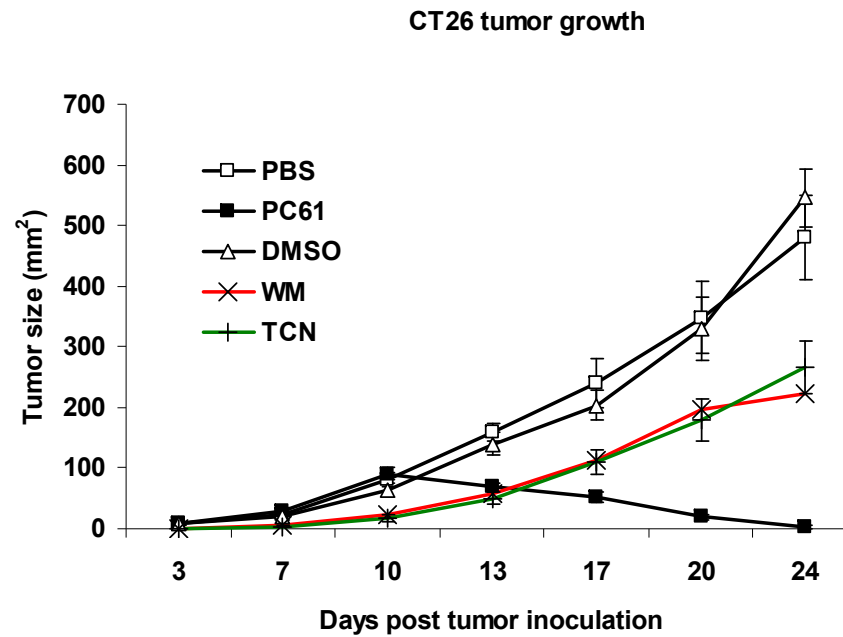
PI3K-Akt pathway inhibition indirectly decrease tumor growth



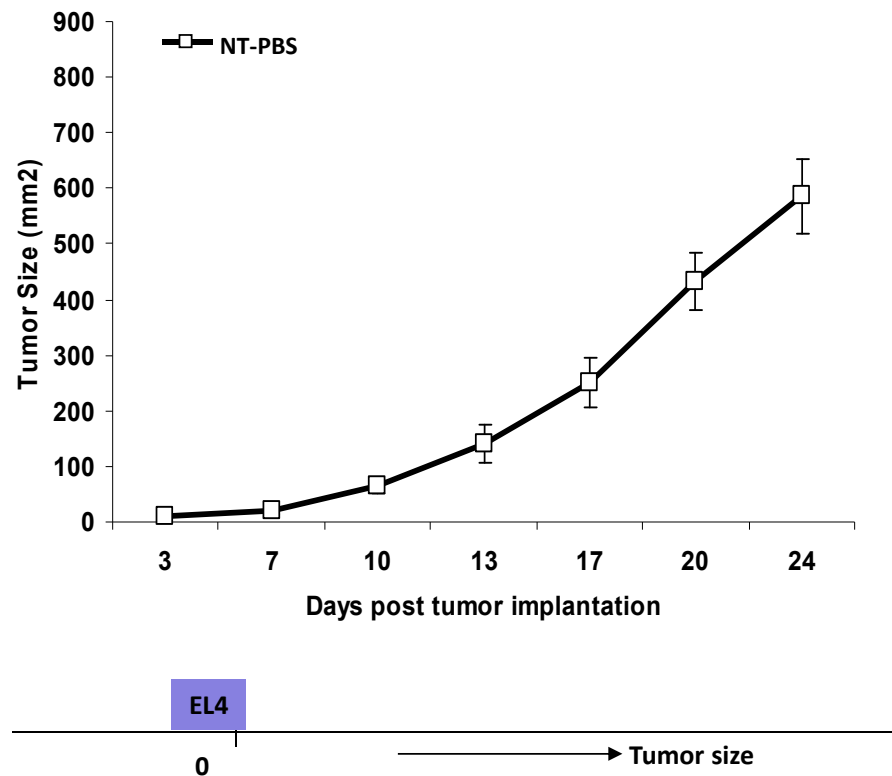
PI3K-Akt pathway inhibition indirectly decrease tumor growth



PI3K-Akt pathway inhibition indirectly decrease tumor growth

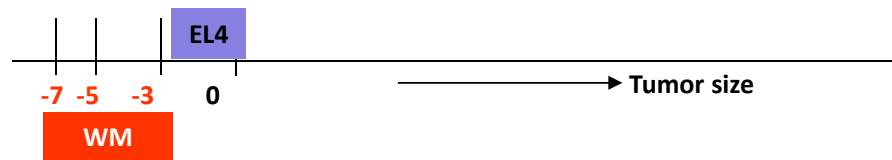
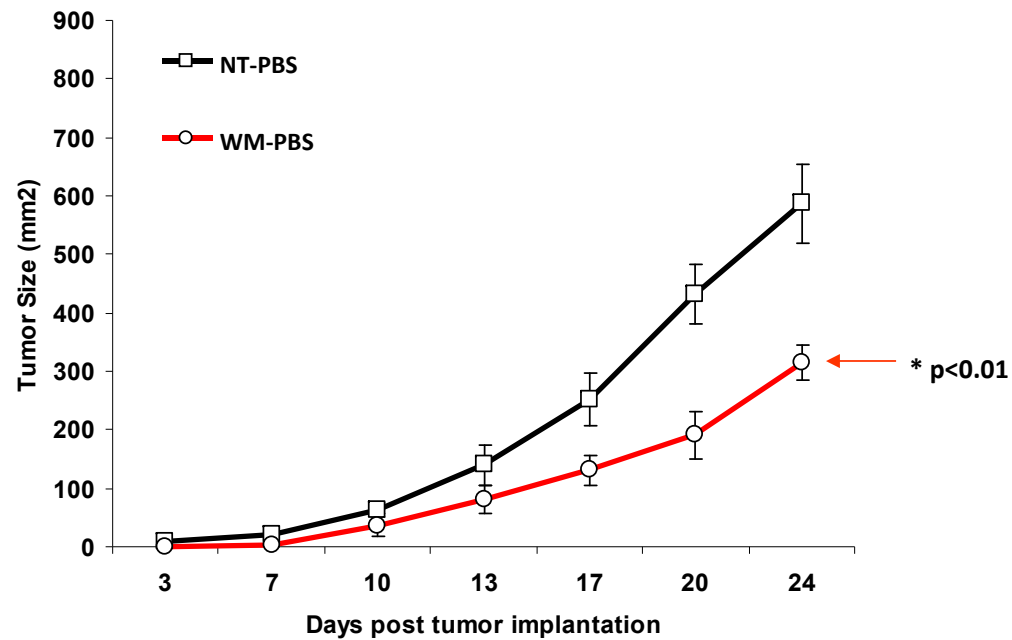


PI3K-Akt pathway inhibition of tumor growth is Treg-dependent

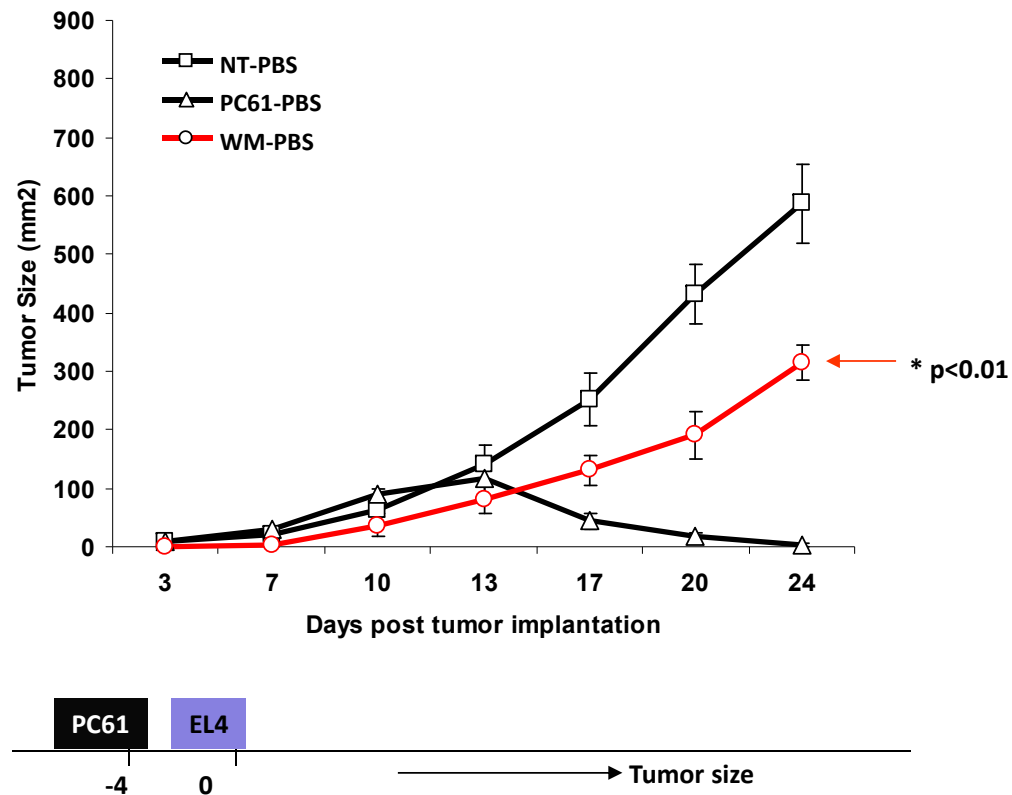


Abu Eid R.et al, CIR, 2014

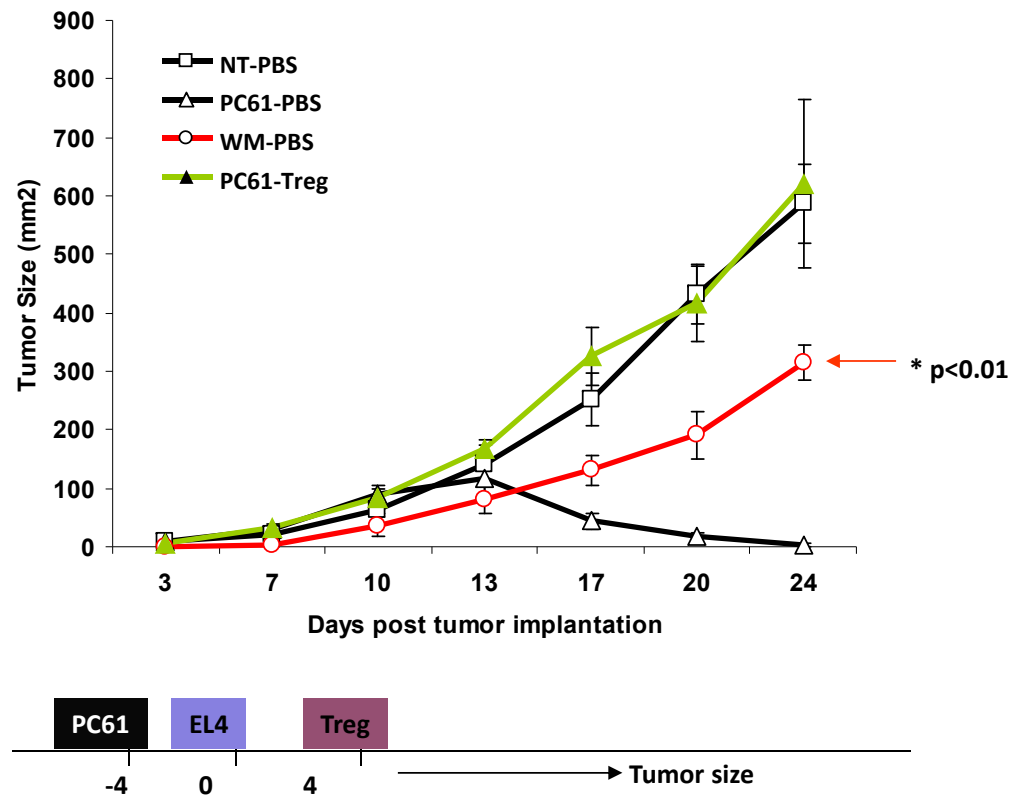
PI3K-Akt pathway inhibition of tumor growth is Treg-dependent



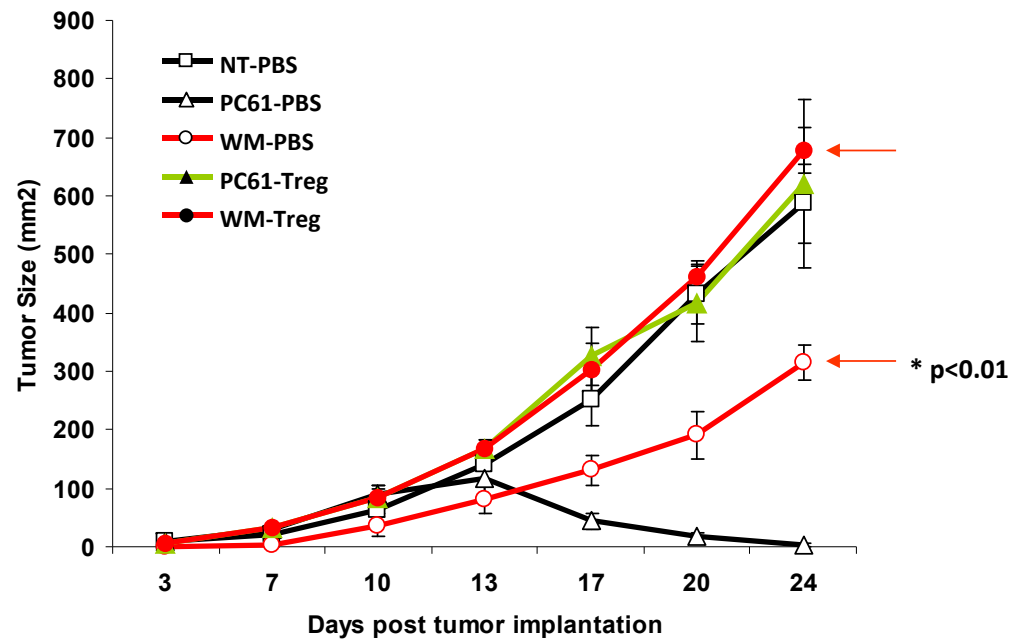
PI3K-Akt pathway inhibition of tumor growth is Treg-dependent



PI3K-Akt pathway inhibition of tumor growth is Treg-dependent

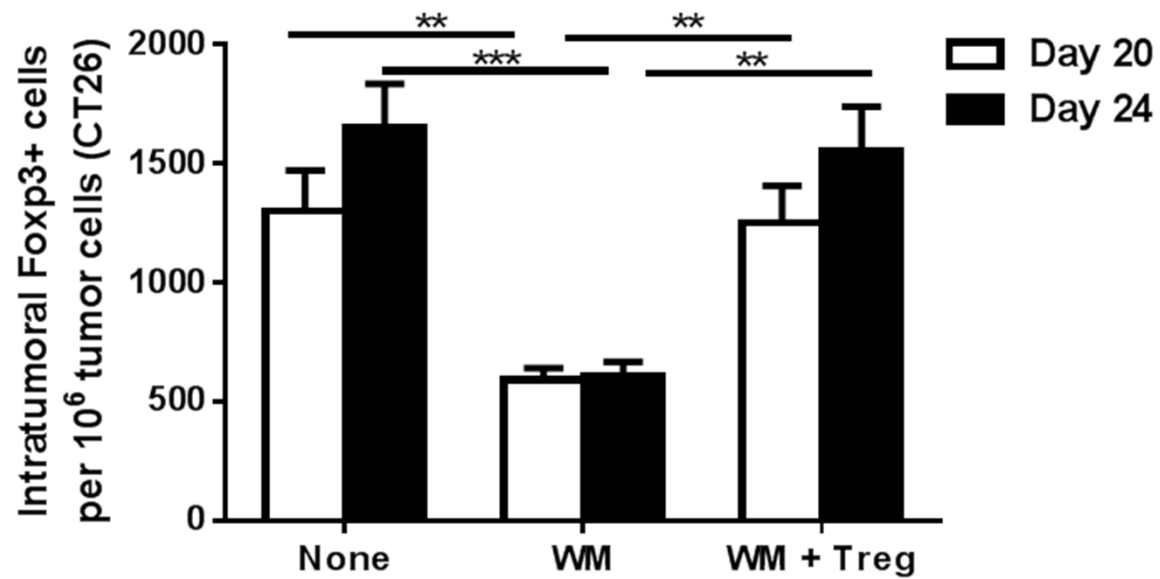


PI3K-Akt pathway inhibition of tumor growth is Treg-dependent

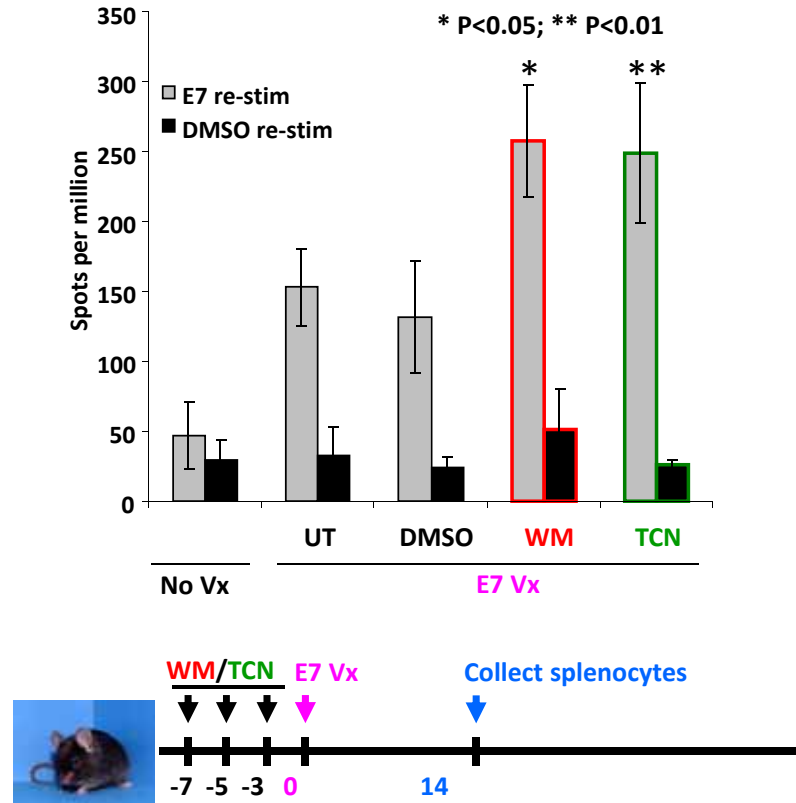


Any effects on vaccine efficacy in vivo?

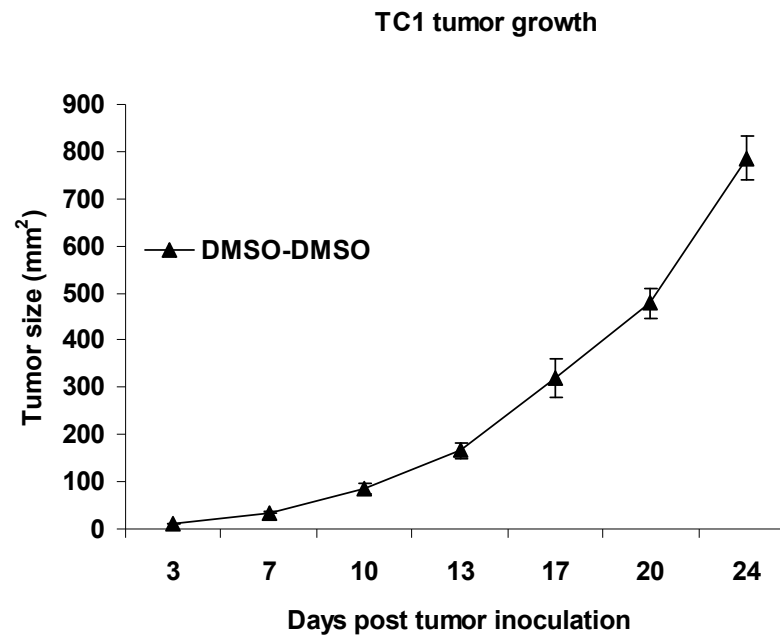
PI3K-Akt pathway inhibition of tumor growth is Treg-dependent



PI3K-Akt inhibition enhances vaccine efficacy

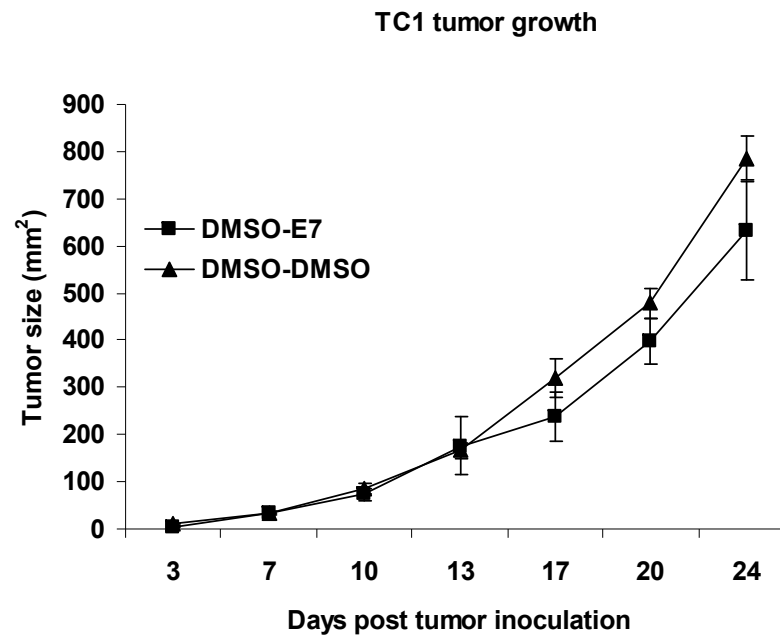


Inhibition of PI3K-Akt synergistically enhances anti-tumor immune responses

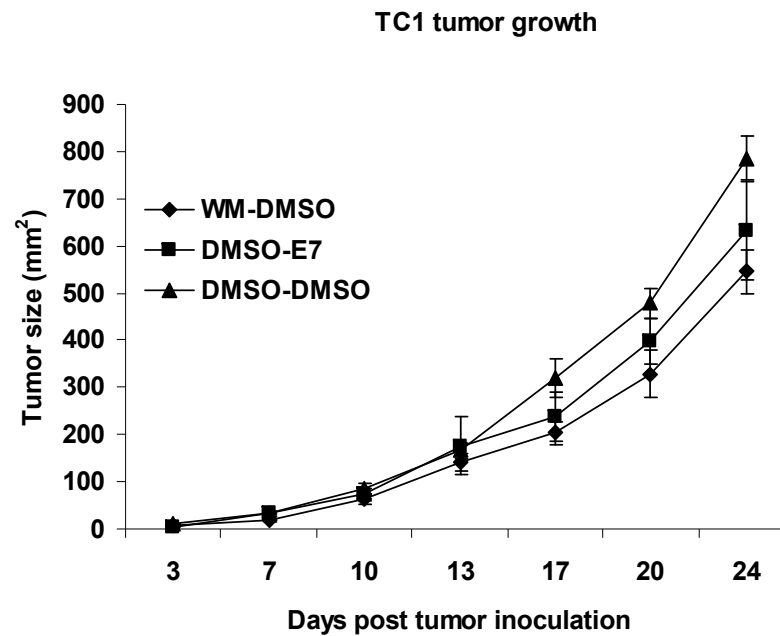


Abu Eid R.et al, CIR, 2014

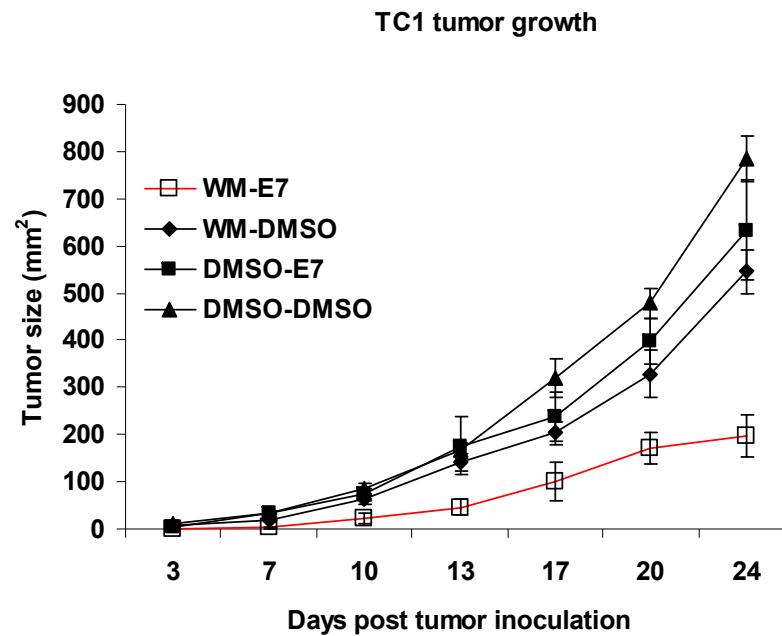
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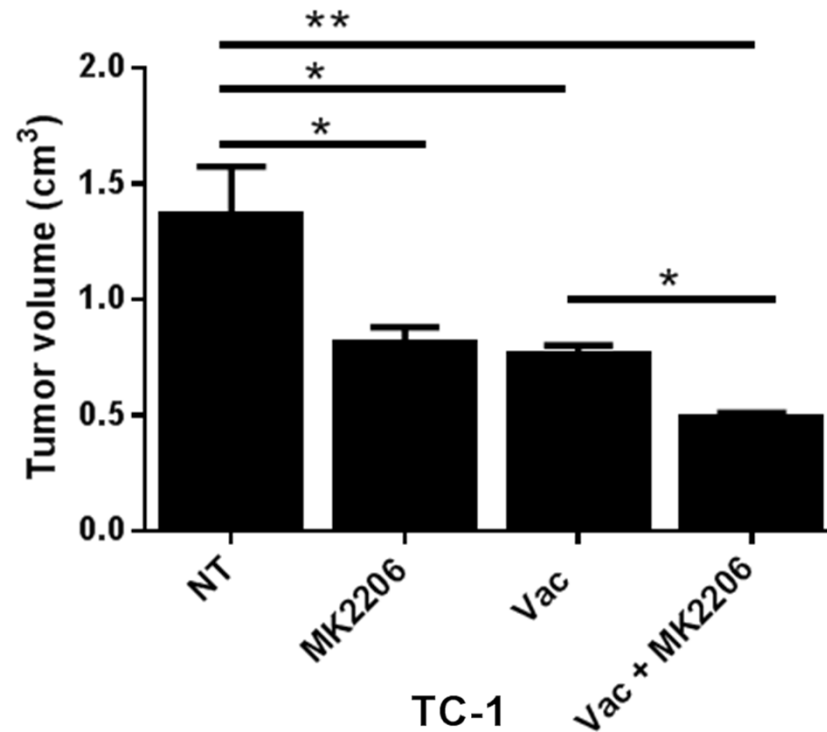
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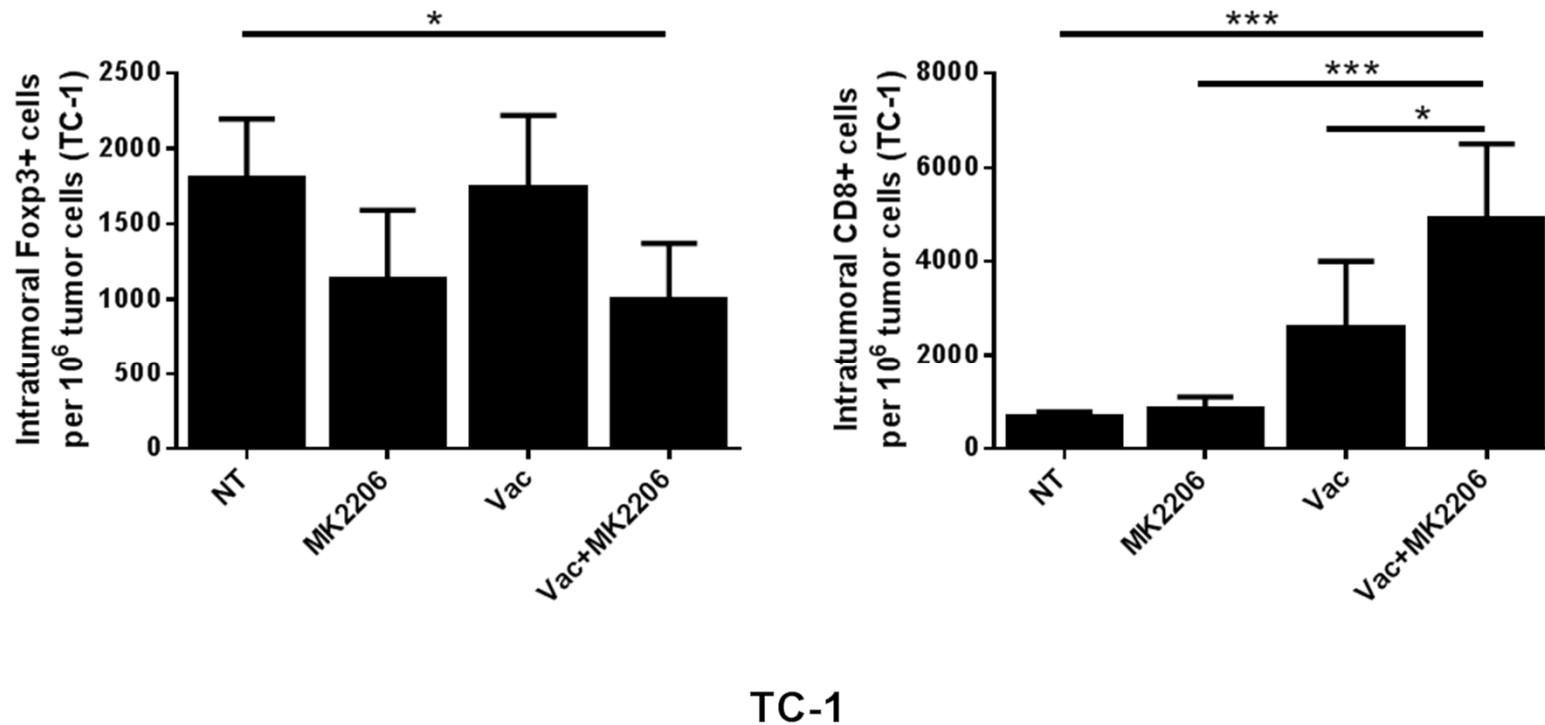
Inhibition of PI3K-Akt synergistically enhances anti-tumor immune responses



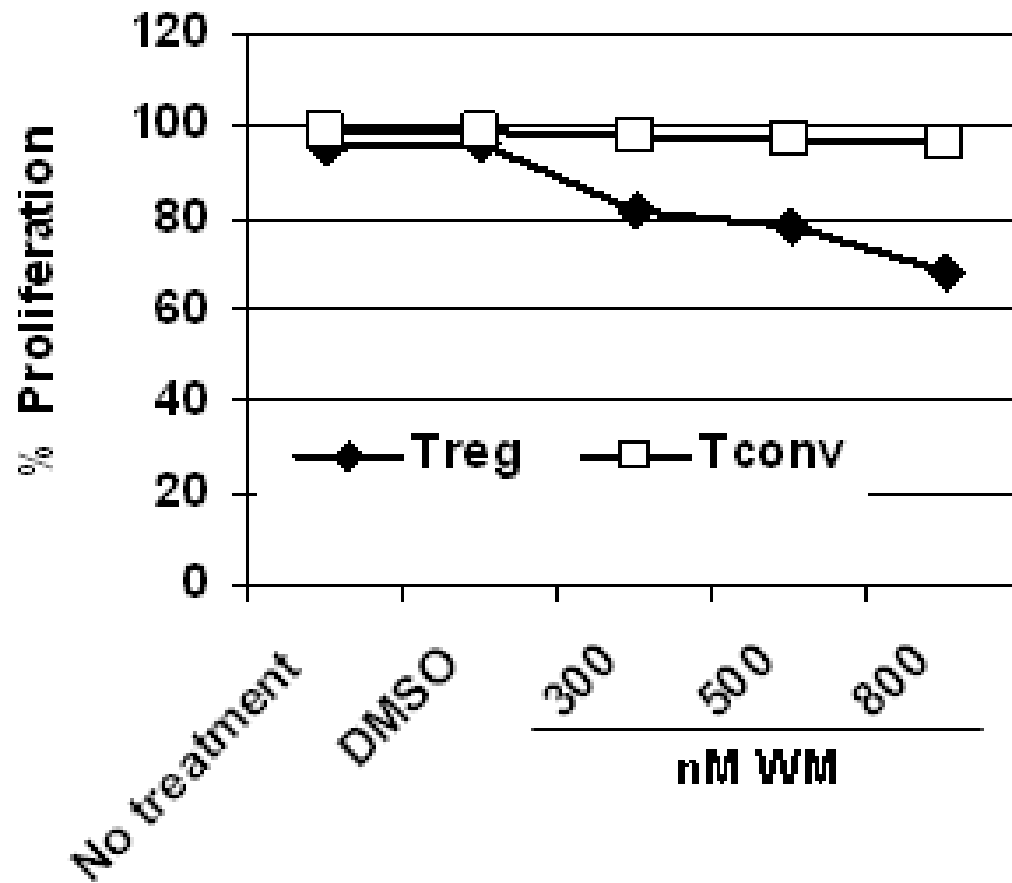
Akt inhibition by MK-2206 enhances the anti-tumor therapeutic effect of tumor-specific vaccine..



Akt inhibition by MK-2206 enhances the anti-tumor immune response of tumor-specific vaccine



WM differentially affects proliferation of human Tregs and Tconv cells

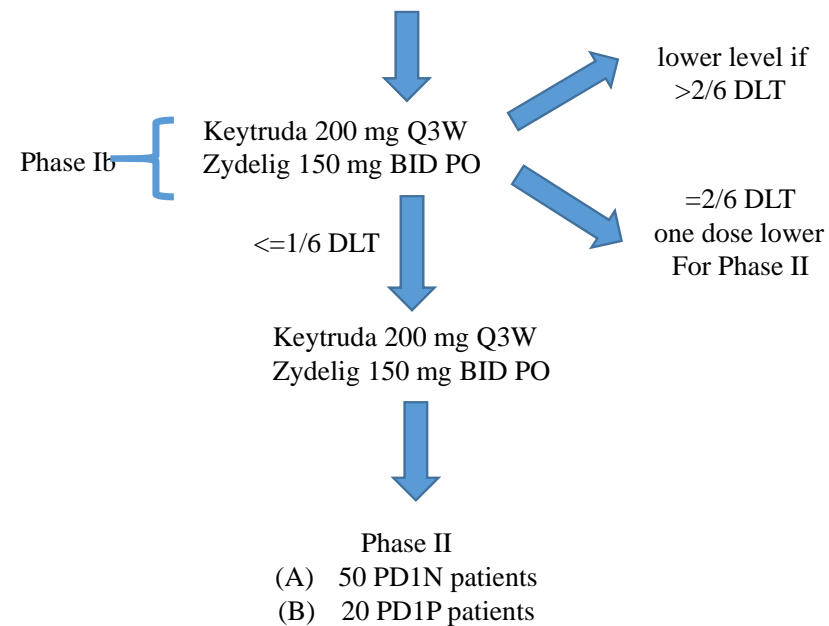


A phase Ib /II trial of pembrolizumab and idelalisib in patients with non-small cell lung cancer (NSCLC)

Metastatic NSCLC

- Progressed on platinum doublets
- OR, Not able to tolerate chemo or unwilling to undergo chemotherapy
- OR EGFR, ALK, ROS1 mutations with disease progression on small molecule inhibitors
- may have also failed prior PD-1/PD-L1 blockade

A phase Ib /II trial of pembrolizumab and idelalisib in patients with non-small cell lung cancer (NSCLC)



Clinical Trials

- Vaccine in combination with AKT inhibitors
- AKT inhibitor in combination with anti-PD1

Acknowledgments

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- Stephanie Zdaniv
- Michiko Shimoda
- Raed Samara
- Osama Rahma

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- Jay Berzofsky, NCI
- Nadia Tarasova, NCI
- Jeff Schlom, NCI
- Micheal Schickler, CureTech
- Ramy Ibrahim, AZ
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- Linda Liu, Medimmune
- Sol Langerman Medimmune

