SITC 2018

NOVEMBER 7-11
WASHINGTON, D.C.
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Society for Immunotherapy of Cancer

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PAK4 inhibition reverses T cell exclusion in cancer and improves PD-1 immunotherapy

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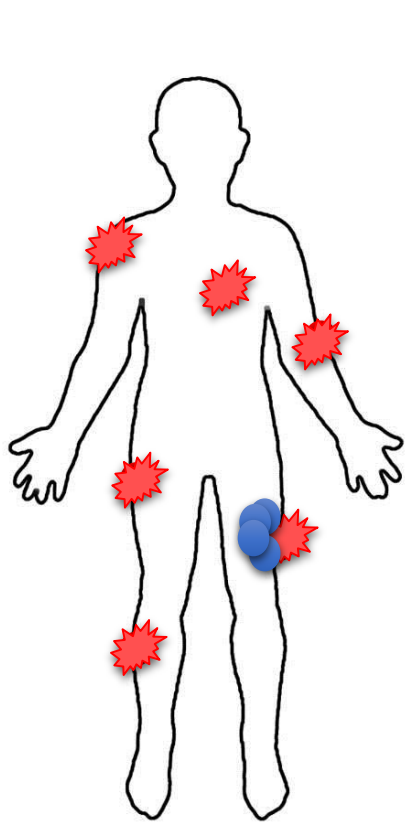
Presenter Disclosure Information

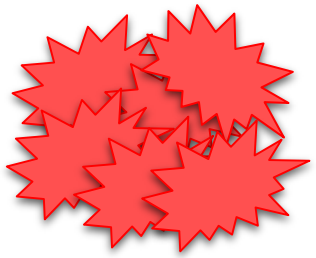
Gabriel Abril-Rodriguez

The following relationships exist related to this presentation:

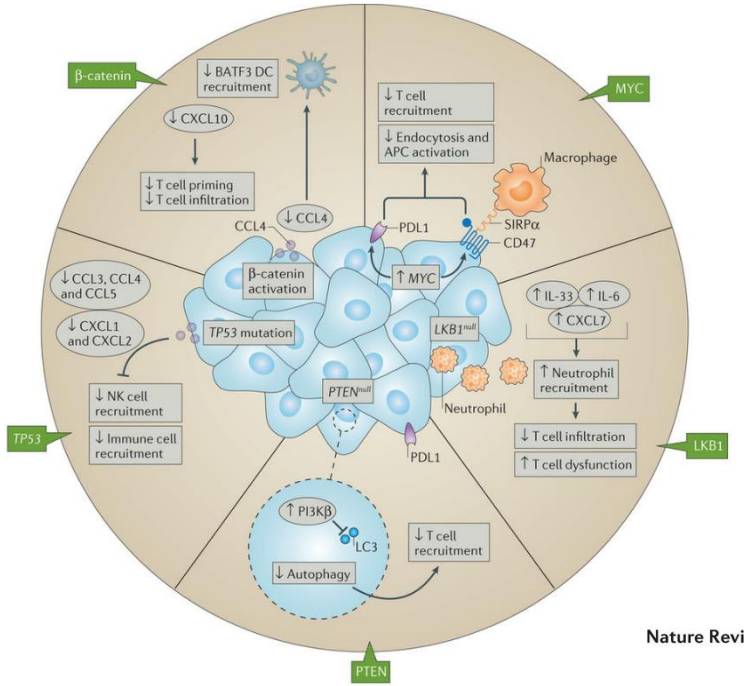
No Relationships to Disclose

Primary resistance to PD-1 blockade through T cell exclusion from tumors





Cancer cell-intrinsic mechanisms of T cell exclusion



Nature Reviews | Cancer

LETTER

doi:10.1038/nature14404

Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity

Stefani Spranger[1], Riyue Bao[2] & Thomas F. Gajewski[1,3]

CANCER DISCOVERY

Genetic mechanisms of immune evasion in colorectal cancer

Catherine S. Grasso, Marios Giannakis, Daniel K. Wells, Tsuyoshi Hamada, Xinmeng Jasmine Mu, Michael Quist, Jonathan A. Nowak, Reiko Nishihara, Zhi Rong Qian, Kentaro Inamura, Teppei Morikawa, Katsuhiko Nosho, Gabriel Abril-Rodriguez, Charles Connolly, Helena Escuin-Ordinas, Milan S. Geybels, William M. Grady, Li Hsu, Siwen Hu-Lieskovan, Jeroen R. Huyghe, Yeon Joo Kim, Paige E. Krystofinski, Mark DM Leiserson, Dennis J. Montoya, Brian B. Nadel, Matteo Pellegrini, Colin C. Pritchard, Cristina Puig-Saus, Elleanor H. Quist, Benjamin J. Raphael, Stephen J. Salipante, Daniel Sanghoon Shin, Eve Shinbrot, Brian Shirts, Sachet Shukla, Janet L. Stanford, Wei Sun, Jennifer Tsoi, Alexander Upfill-Brown, David A. Wheeler, Catherine J. Wu, Ming Yu, Syed H. Zaidi, Jesse M. Zaretsky, Stacey B. Gabriel, Eric S Lander, Levi A. Garraway, Thomas J. Hudson, Charles S. Fuchs, Antoni Ribas, Shuji Ogino, and Ulrike Peters

DOI: 10.1158/2159-8290.CD-17-1327 Check for updates

LETTER

doi:10.1038/nature25492

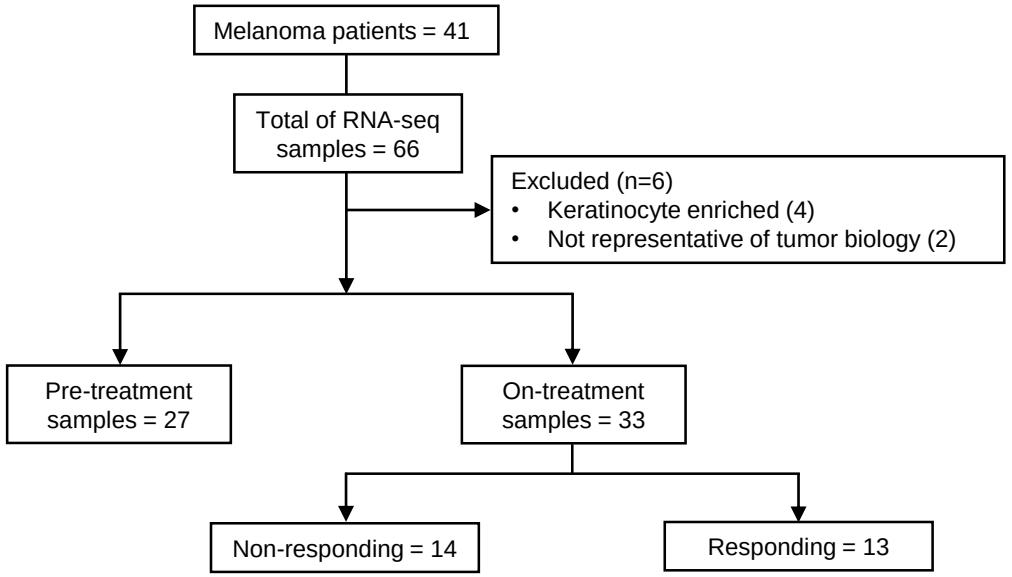
TGFβ drives immune evasion in genetically reconstituted colon cancer metastasis

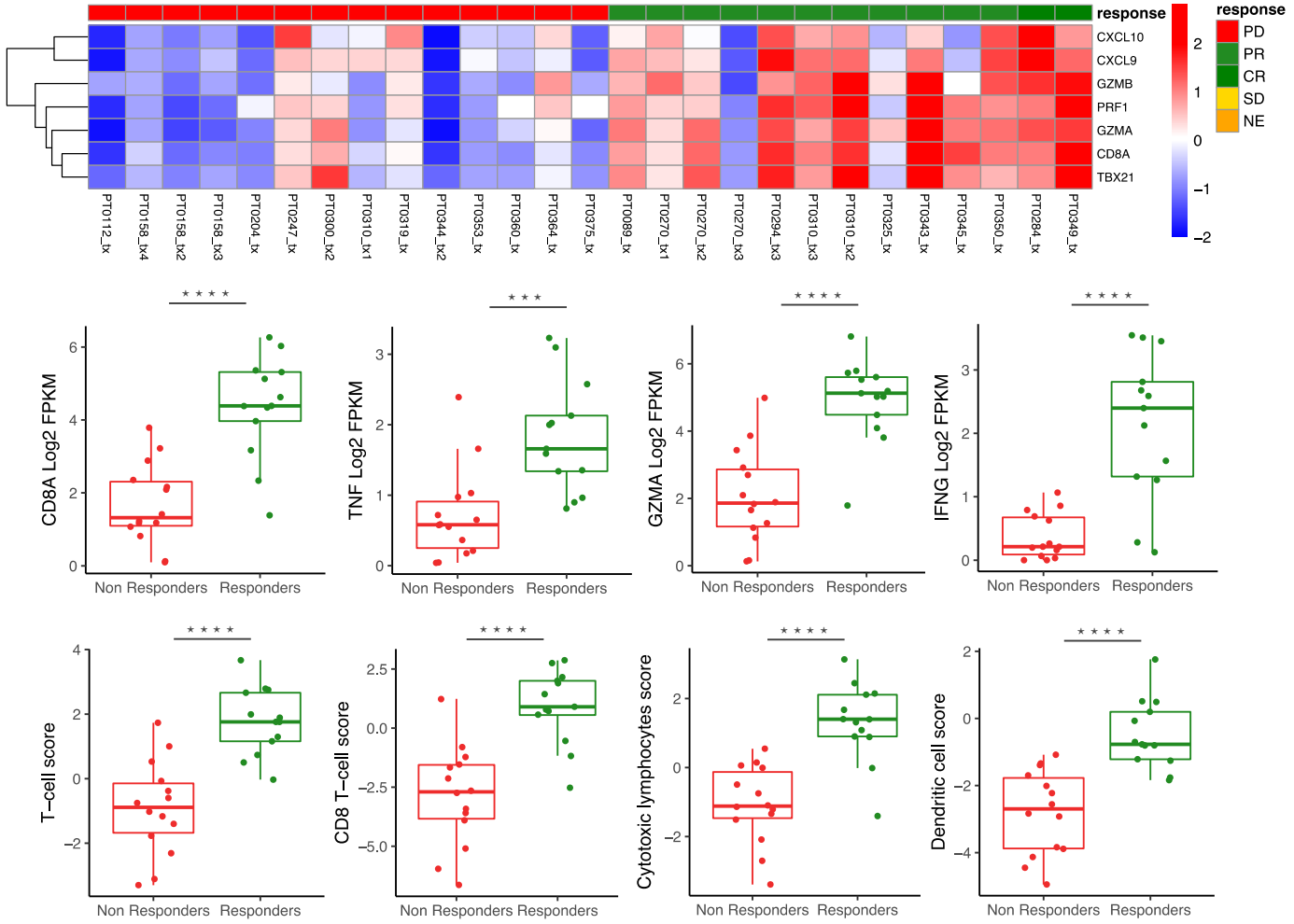
Daniele V. F. Tauriello[1,2], Sergio Palomo-Ponce[1,2], Diana Stork[1], Antonio Berenguer-Llergo[1], Jordi Badia-Ramentol[1], Mar Iglesias[2,3,4,5], Marta Sevillano[1,2], Sales Ibiza[1], Adrià Cañellas[1], Xavier Hernando-Momblona[1,2], Daniel Byrom[1], Joan A. Matarin[1], Alexandre Calon[1†], Elisa I. Rivas[1†], Angel R. Nebreda[1,6], Antoni Riera[1,7], Camille Stephan-Otto Attolini[1] & Eduard Batlle[1,2,6]

Cancer cell

T-cell

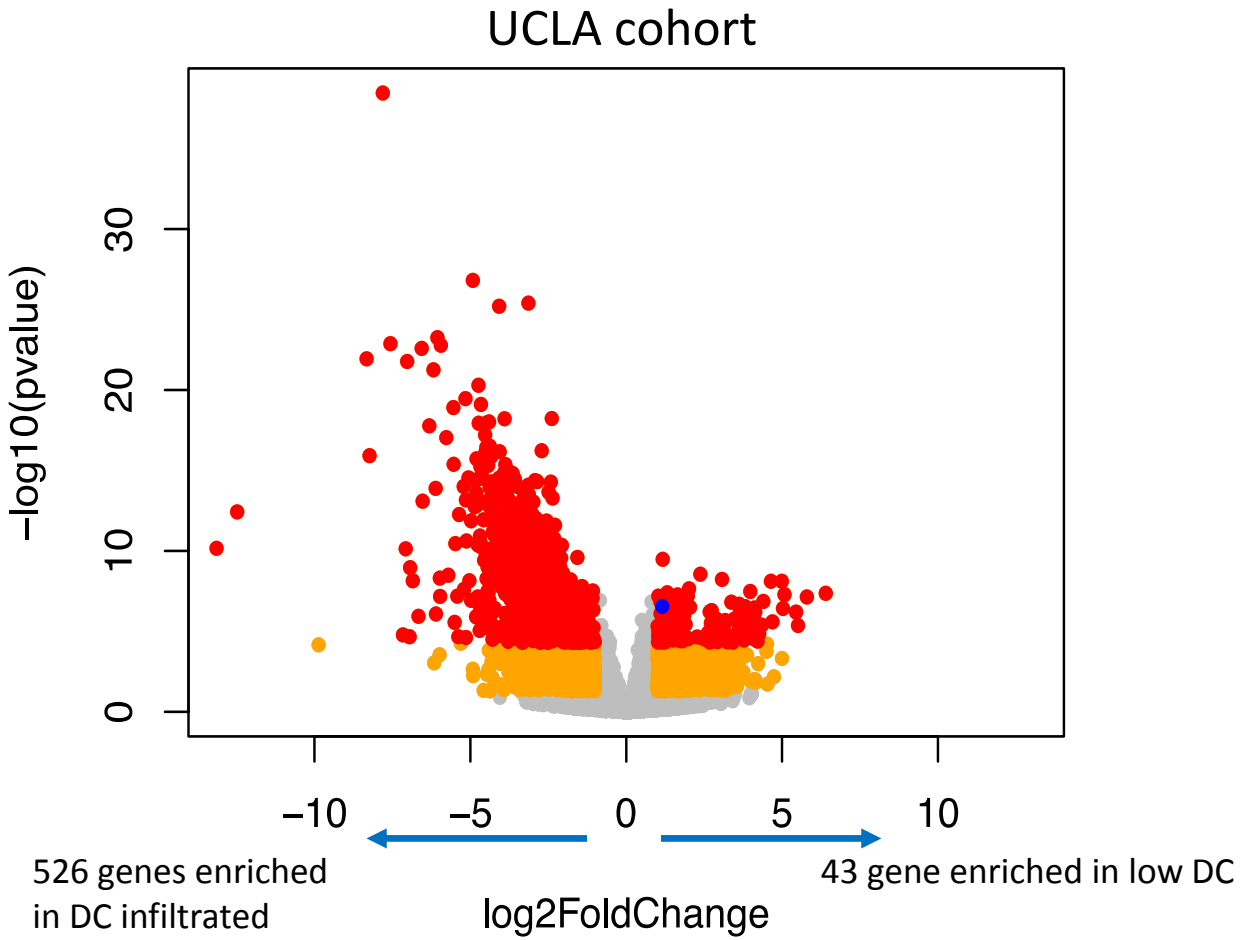
Biopsies of patients responding to PD-1 blockade have increased CD8 cytotoxic T cell signatures



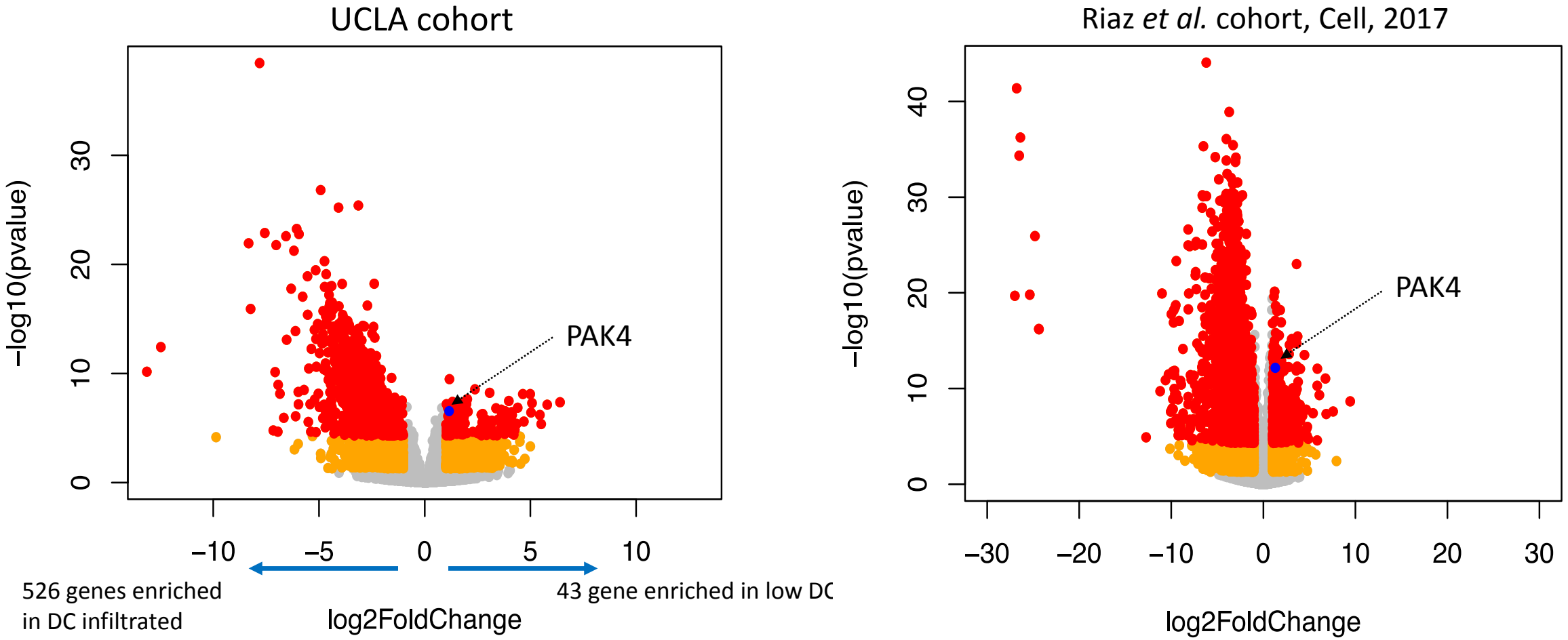


Unpublished

Very few genes are enriched in T and Dendritic cell-low samples

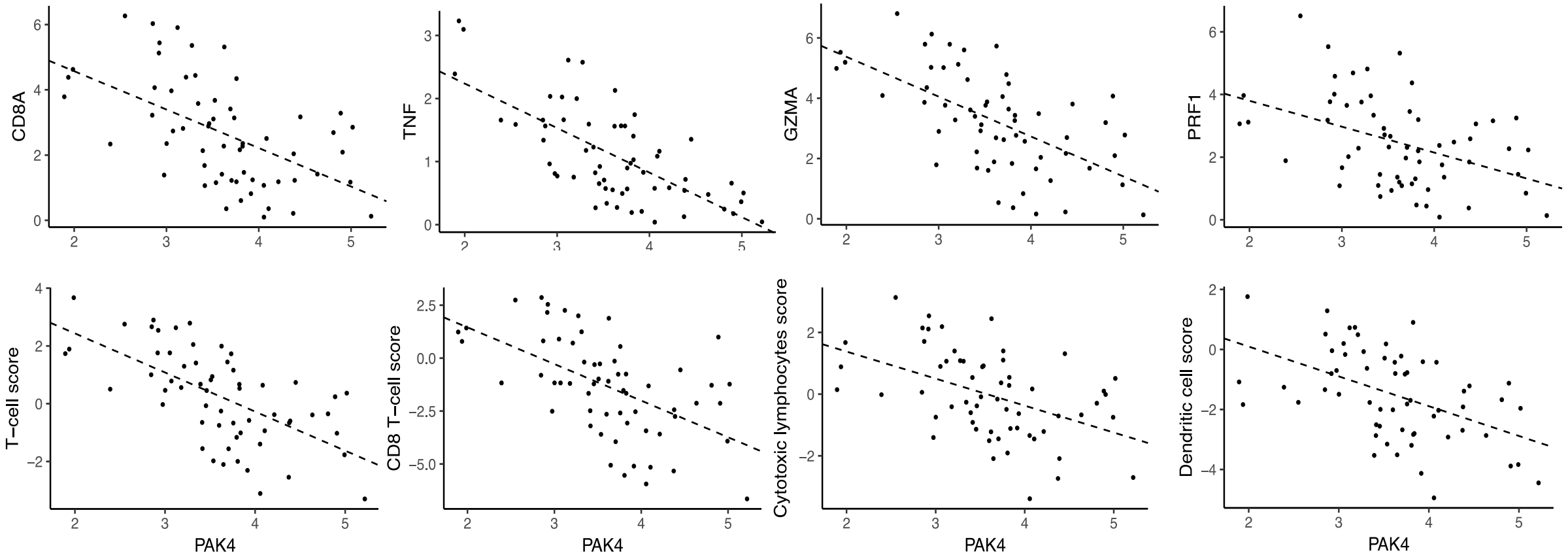


PAK4 expression is enriched in poorly infiltrated tumor samples



Unpublished

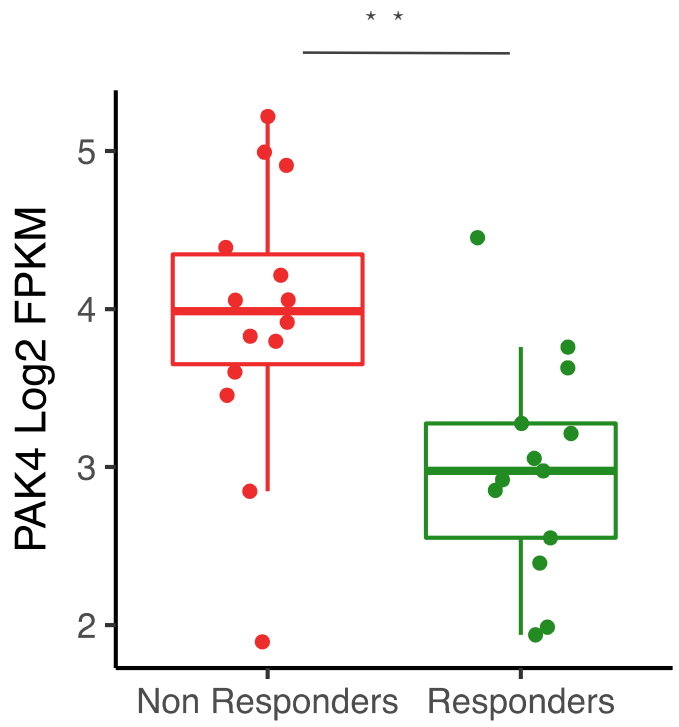
PAK4 strongly anti-correlates with cytotoxic T cell infiltration

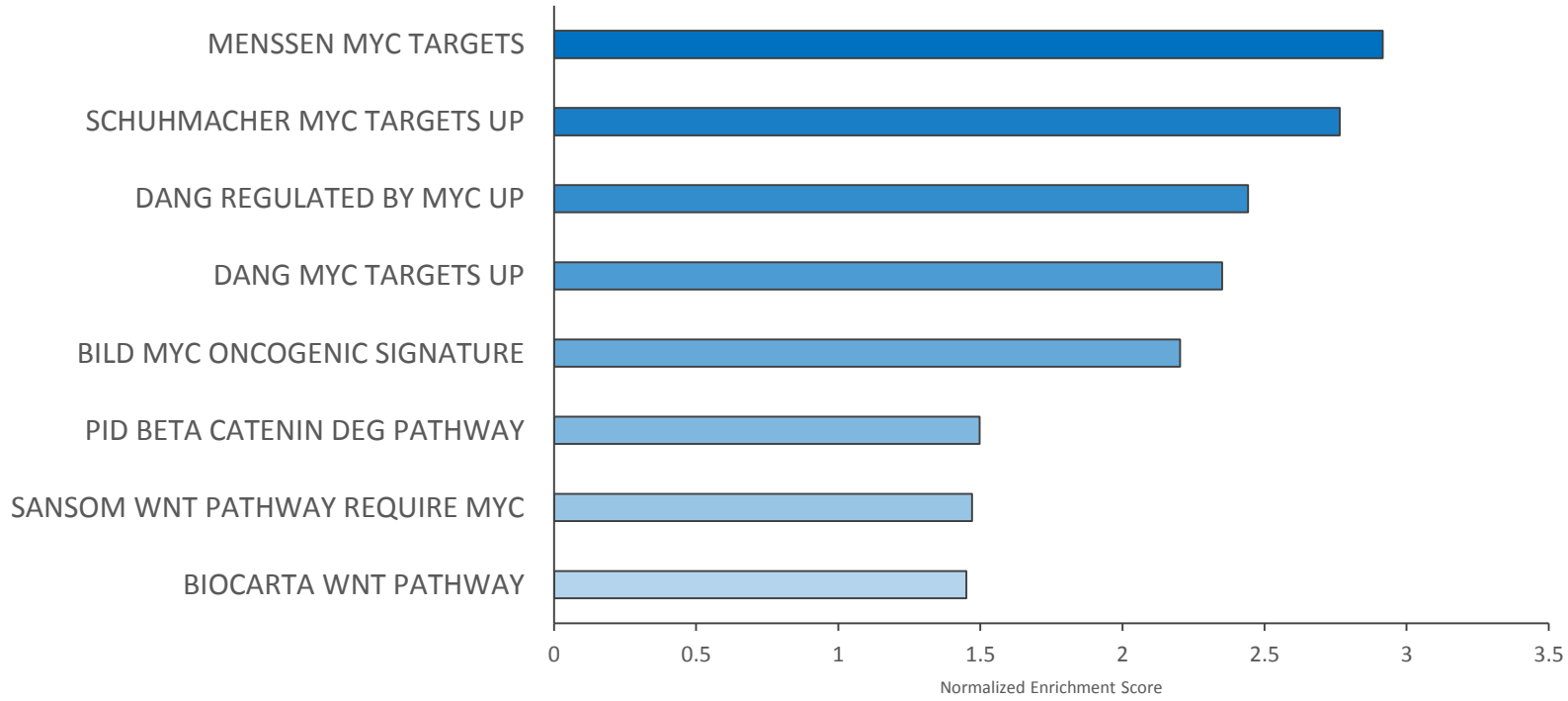


PAK4: P21 activated kinase 4, a group II PAK family of serine/threonine kinases

Unpublished

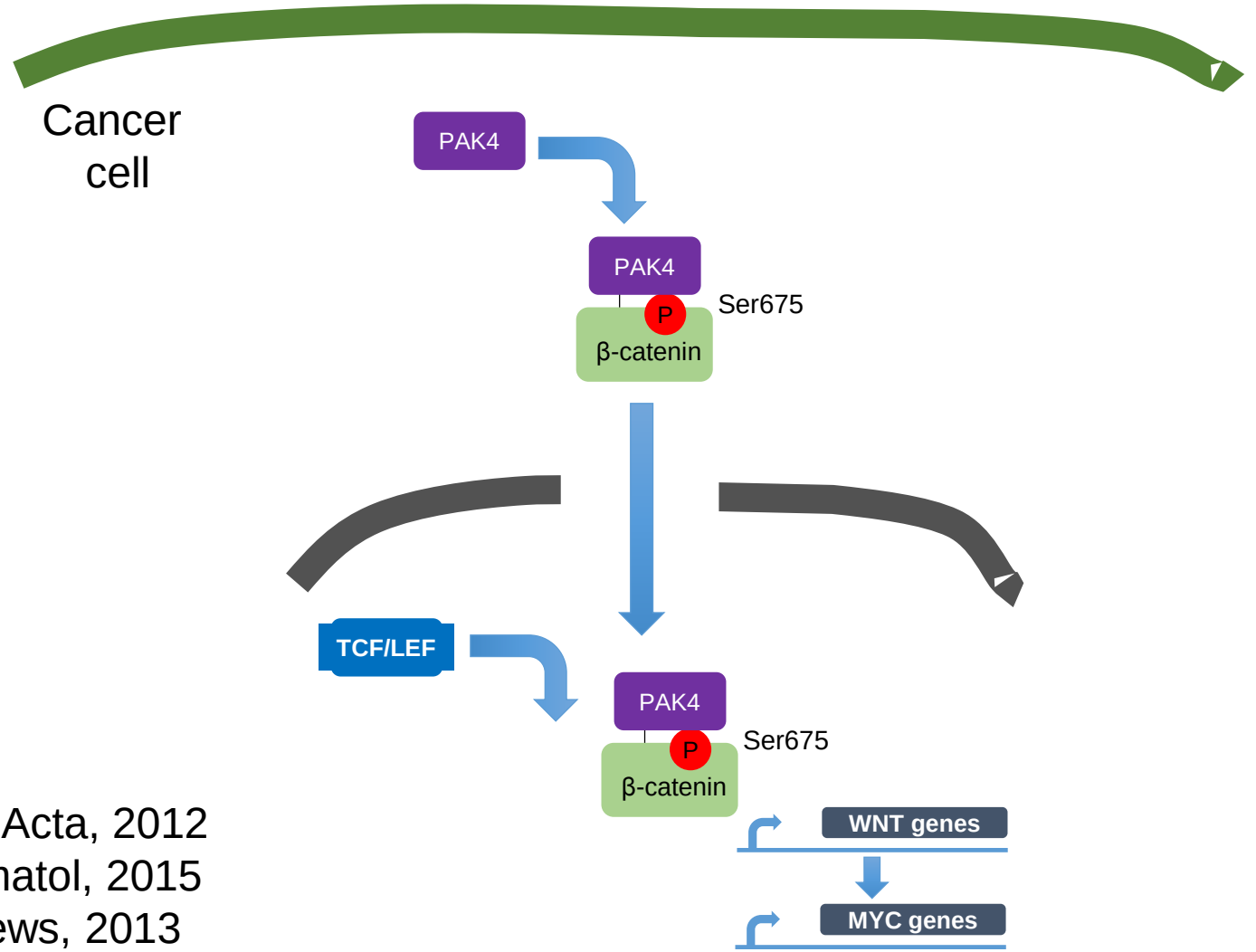
PAK4 is enriched in patients without a response to PD-1 blockade therapy (along with WNT and MYC signatures)





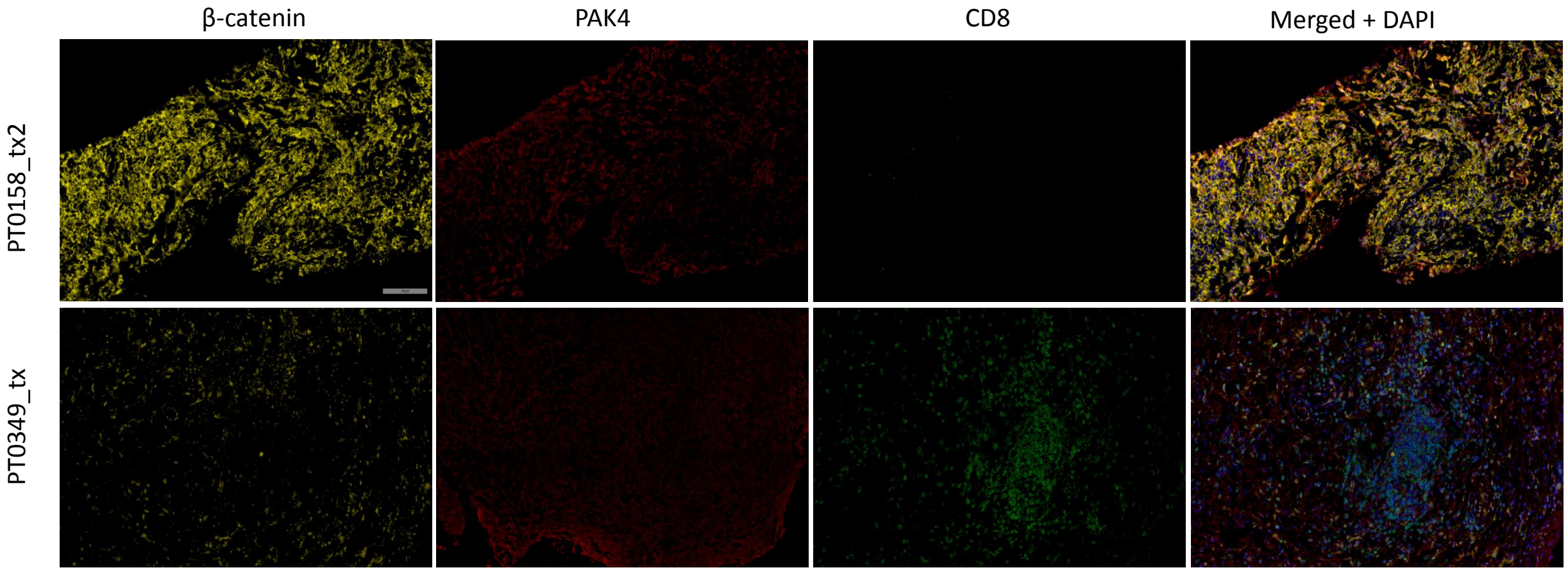
Unpublished

Role of PAK4 in activating β-catenin and MYC gene programs



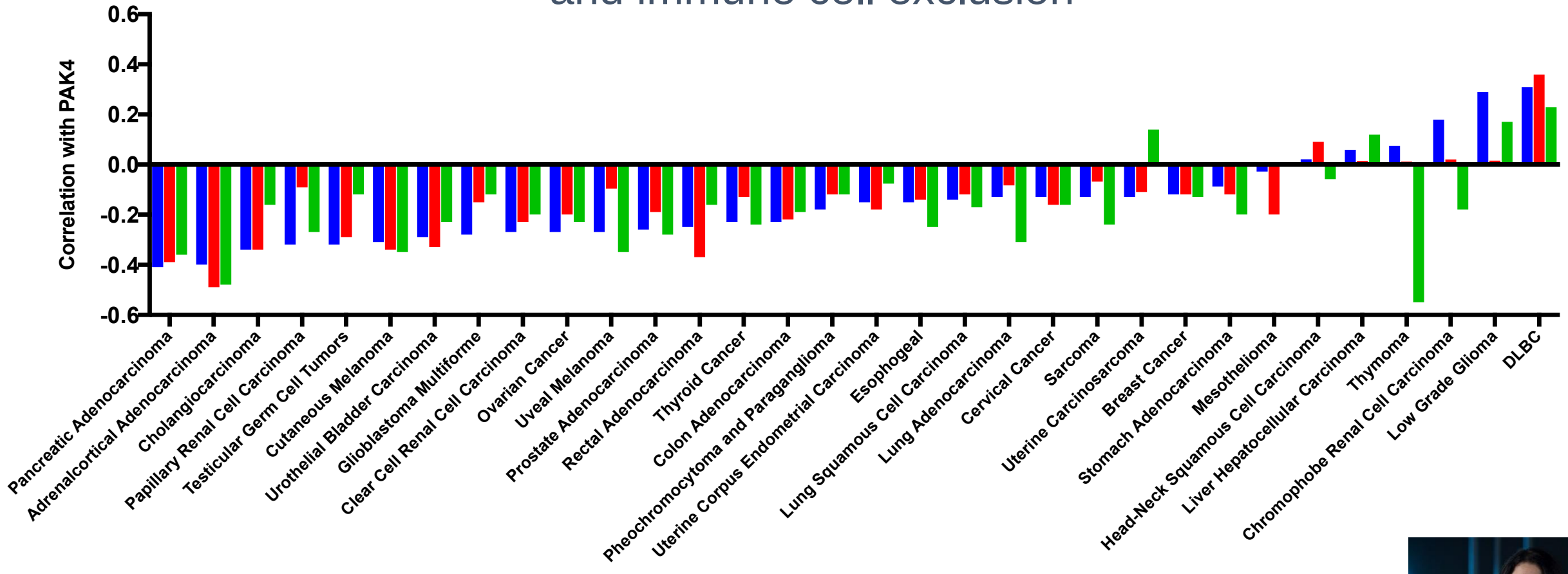
Li Y, *et al*. Biochim Biophys Acta, 2012
Yun CY, *et al*. J Invest Dermatol, 2015
Radu M, *et al*. Nature Reviews, 2013

PAK4 expression co-localizes with β-catenin



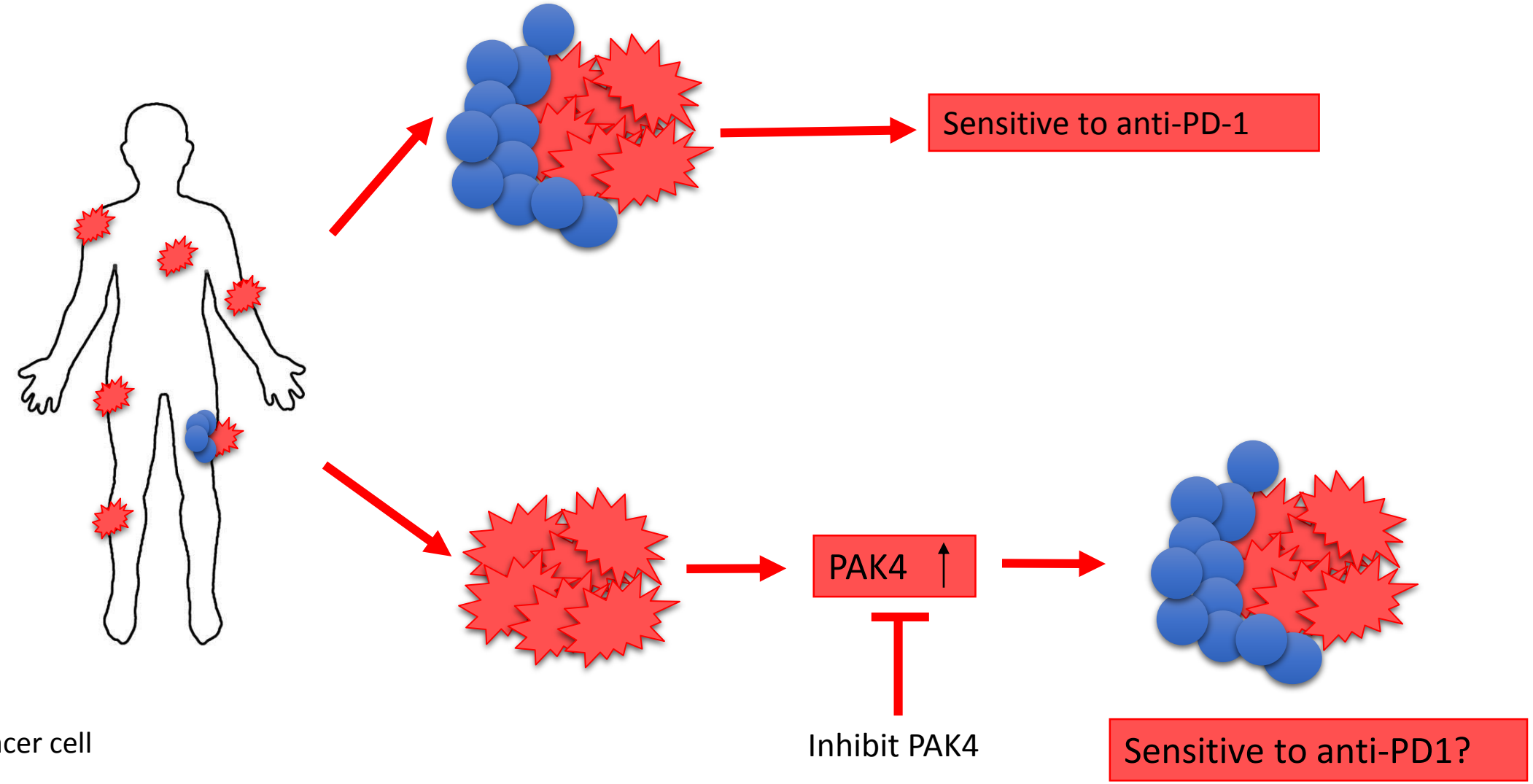
Unpublished

Pan-cancer analysis (TCGA) of PAK4 expression and immune cell exclusion

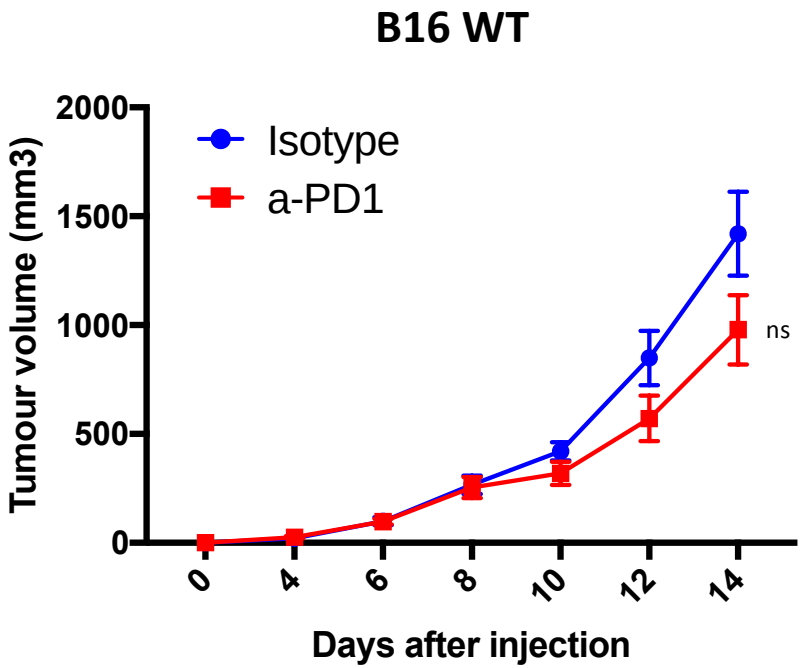


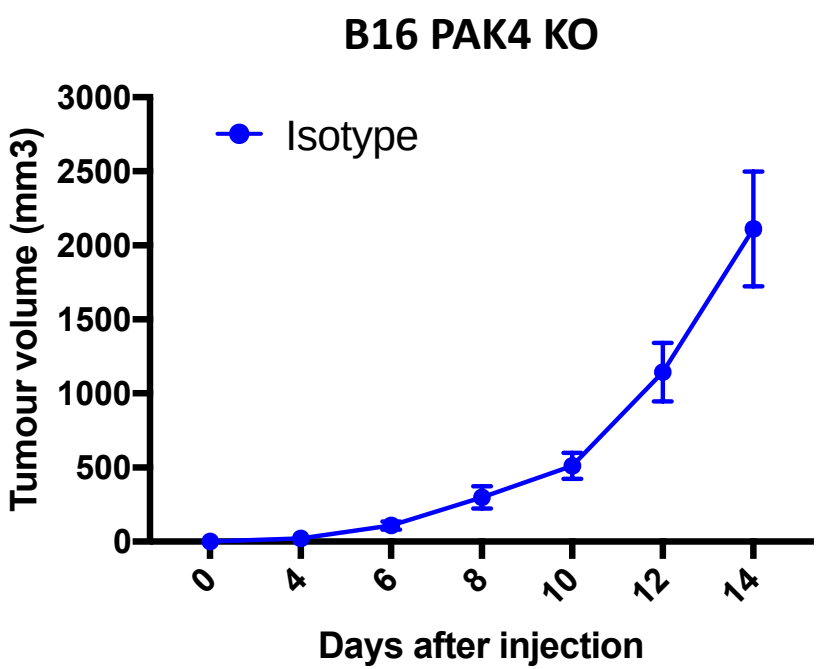
Catie Grasso, PhD, unpublished

Could PAK4 inhibition overcome resistance to PD-1 blockade



Genetic knockout of PAK4 reverses resistance to anti-PD-1 in B16 melanoma

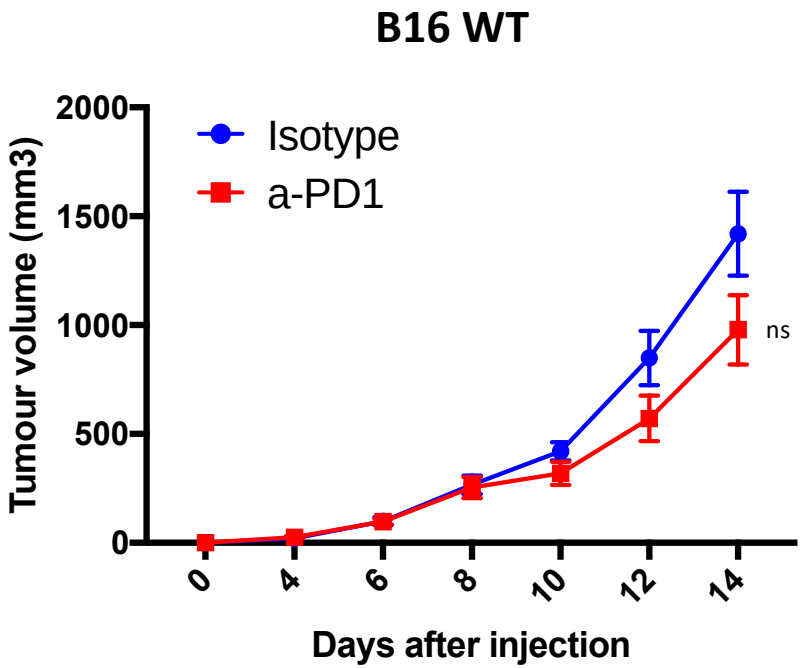




B16 is a cell line primarily resistant to PD-1 blockade therapy

Davis Torrejon, MD, unpublished

Genetic knockout of PAK4 reverses resistance to anti-PD-1 in B16 melanoma



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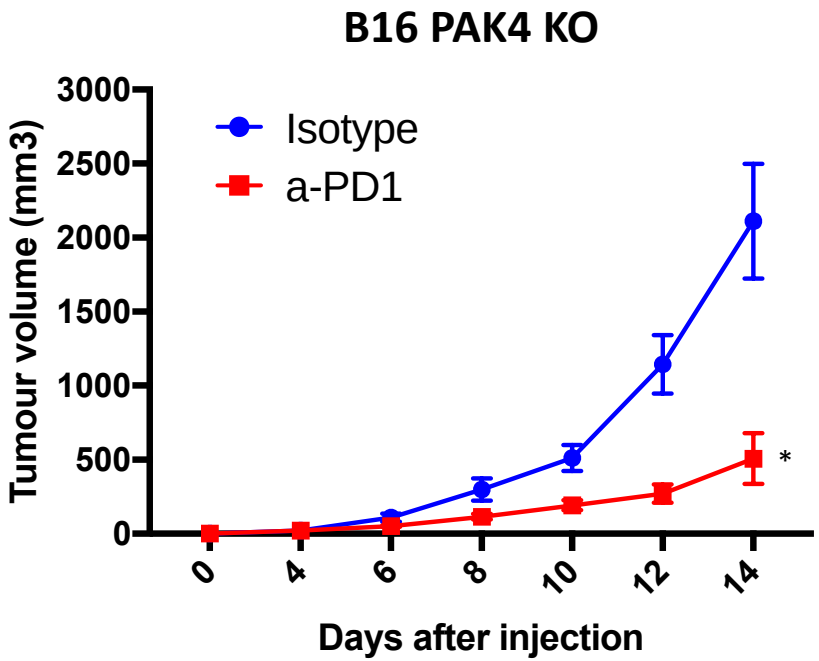
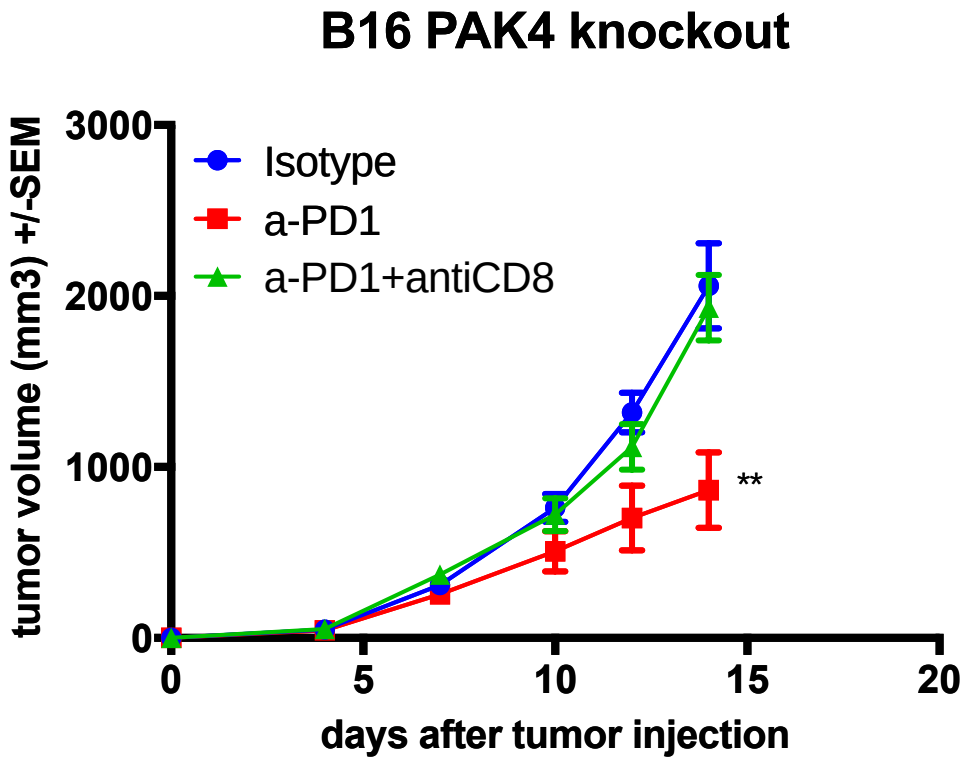


Genetic depletion of PAK4 re-sensitizes B16 to anti-PD-1 therapy

Davis Torrejon, MD, unpublished

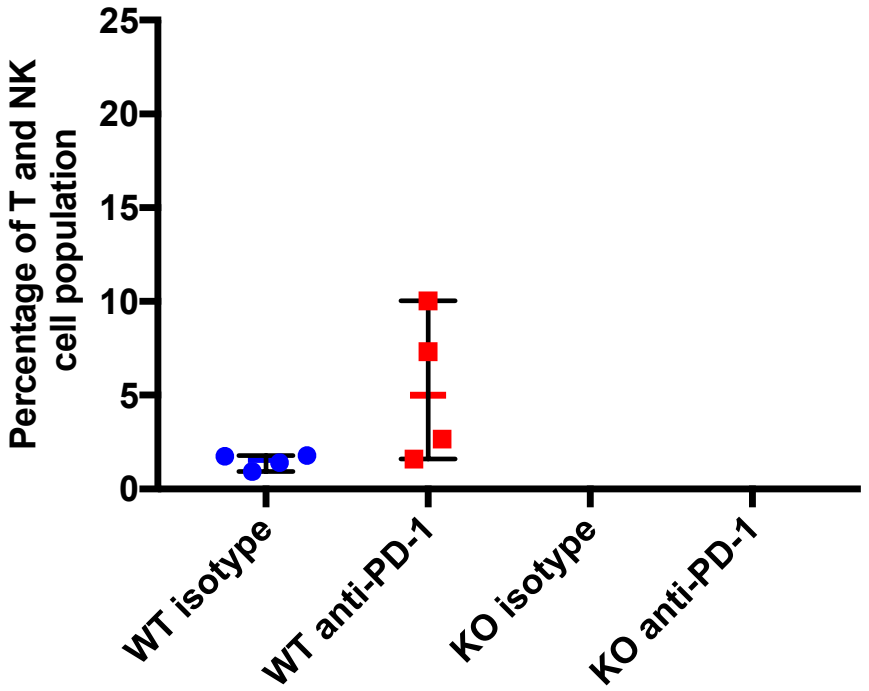
Response to PD-1 blockade in B16 with PAK4 KO is lost with the depletion of CD8+ T cells



Replicate experiment with CD8 depletion using clone YTS 169.4

Unpublished

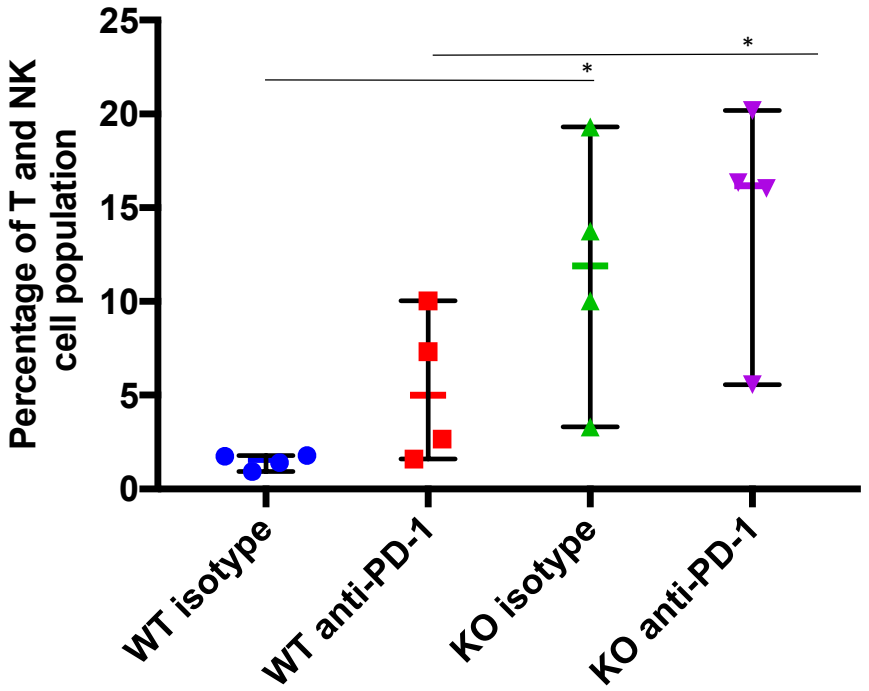
PAK4 deletion results in increased T and NK cell infiltration in B16 melanoma



Median percentage of T and NK positive clusters from CD45^{+} cells determined by Mass Cytometry

Unpublished

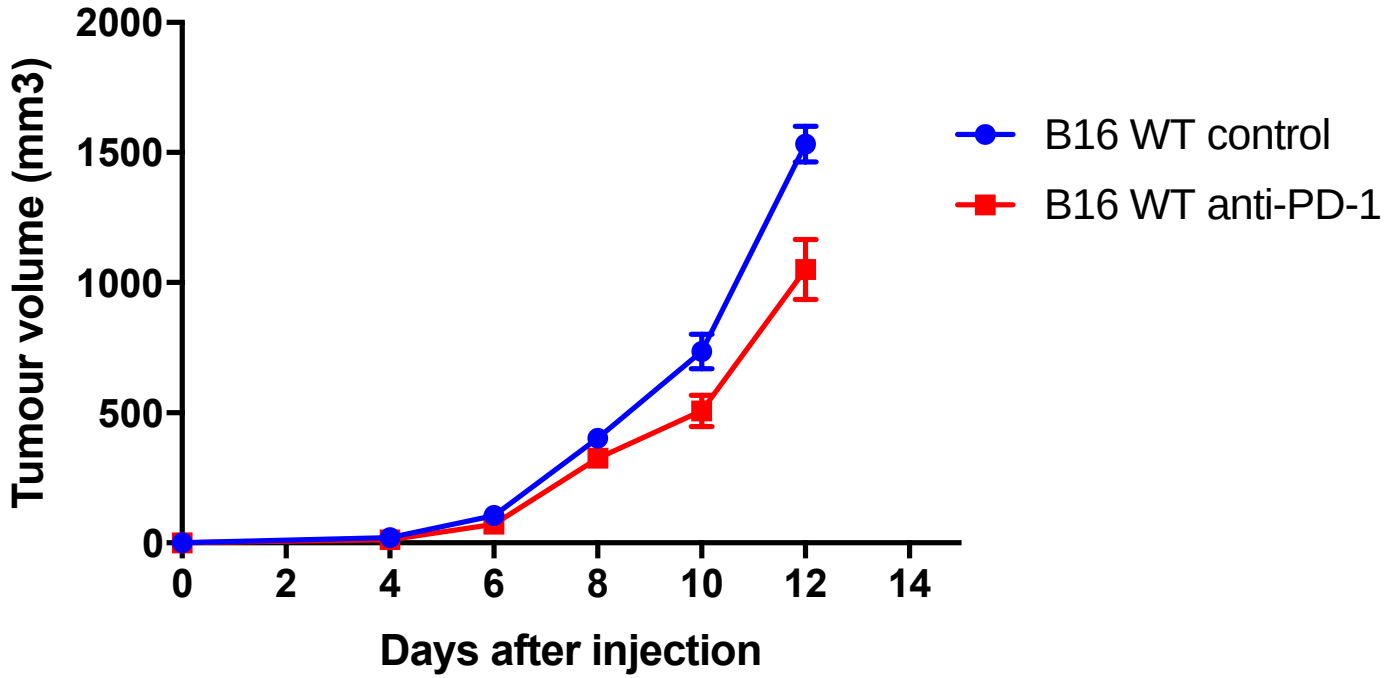
PAK4 deletion results in increased T and NK cell infiltration in B16 melanoma



Median percentage of T and NK positive clusters from CD45^{+} cells determined by Mass Cytometry

Unpublished

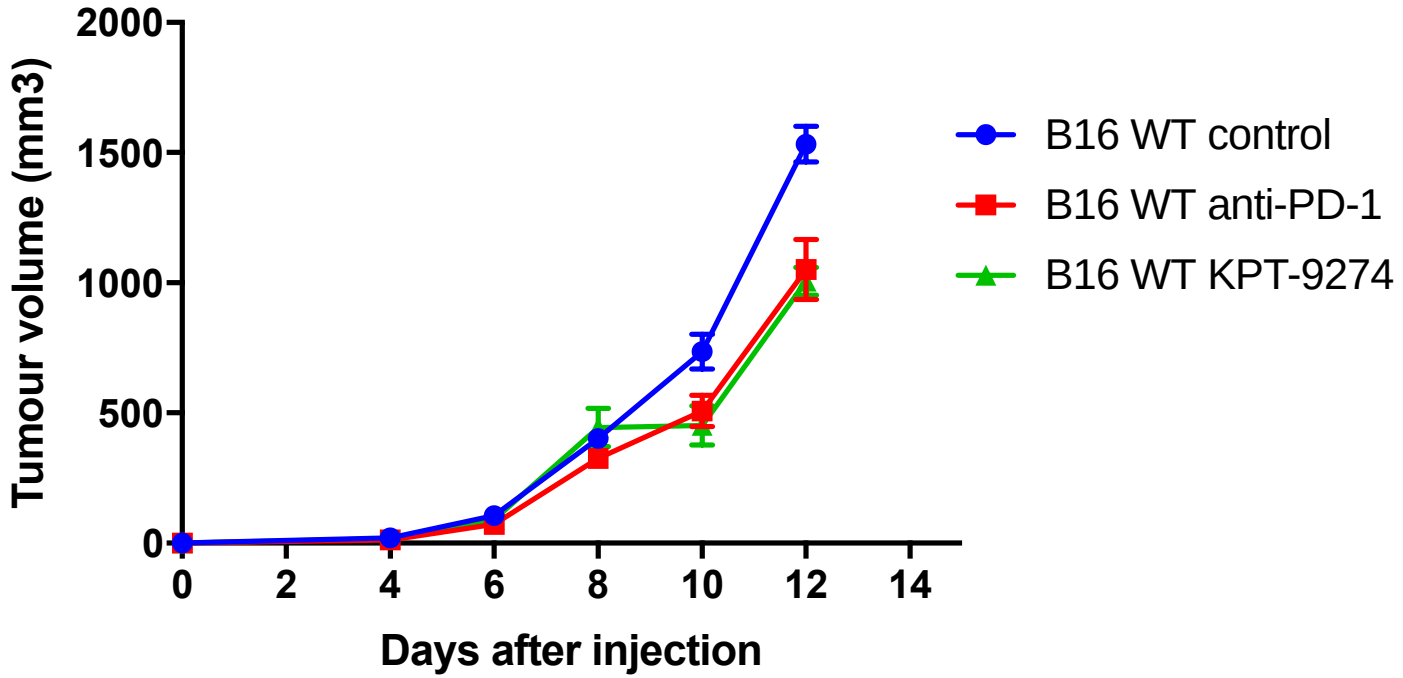
Dual PAK4 and NAMPT inhibitor, KPT-9274, synergizes with anti-PD-1 in B16 melanoma



Pharmacologic inhibition of PAK4 re-sensitizes B16 to anti-PD-1 therapy

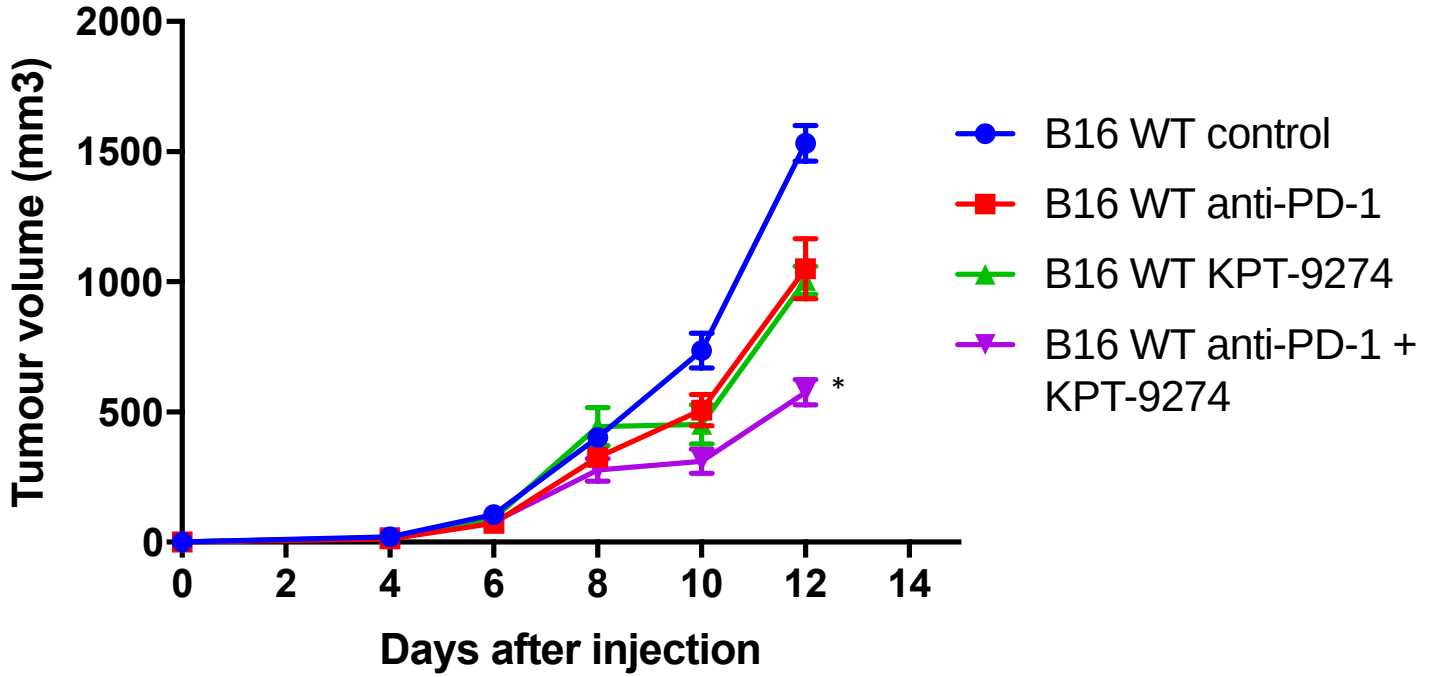
Unpublished

Dual PAK4 and NAMPT inhibitor, KPT-9274, synergizes with anti-PD-1 in B16 melanoma



Pharmacologic inhibition of PAK4 re-sensitizes B16 to anti-PD-1 therapy

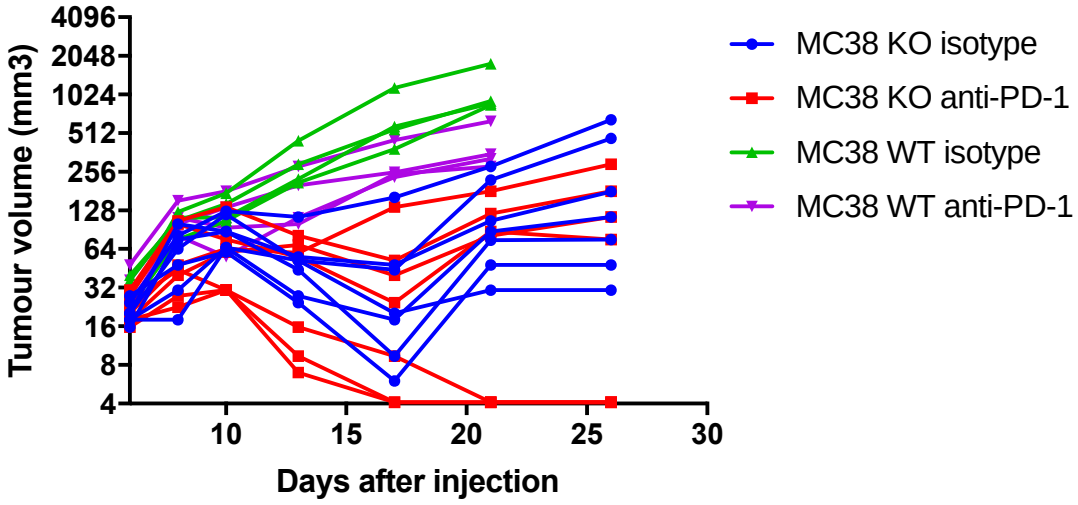
Dual PAK4 and NAMPT inhibitor, KPT-9274, synergizes with anti-PD-1 in B16 melanoma



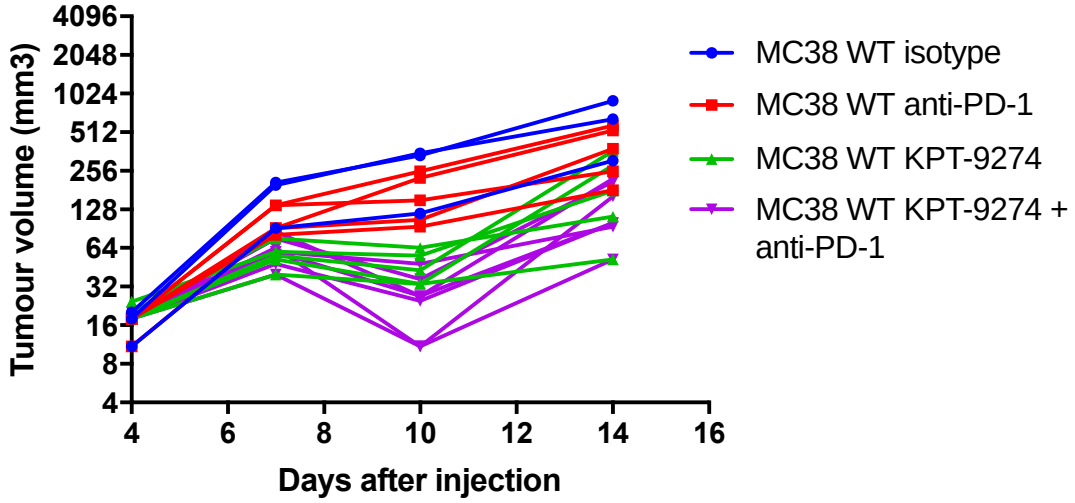
Pharmacologic inhibition of PAK4 re-sensitizes B16 to anti-PD-1 therapy

Unpublished

PAK4 inhibition results in anti-tumor activity in the immunogenic colon adenocarcinoma MC38 model



Genetic deletion of PAK4 results in anti-tumor responses regardless anti-PD-1 treatment but only achieves complete regressions with PD-1 blockade



Pharmacologic inhibition of PAK4 recapitulates the results observed in the MC38 PAK4 KO model

Unpublished

Take home message:

- Tumor biopsies with lack of response to PD-1 blockade immunotherapy are poorly immune cell infiltrated and are enriched for the expression of PAK4 and oncogenic pathways involved in immune evasion.

- PAK4 inhibition increases the amount of tumor-infiltrating T cells and overcomes PD-1 resistance in a CD8+ dependent manner.

- In addition to melanoma, these observations could be expanded to other tumor types that are notoriously resistant to PD-1 blockade.

Acknowledgments

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