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Tumor-intrinsic pathway activation associated with the non-T cell-inflamed tumor microenvironment

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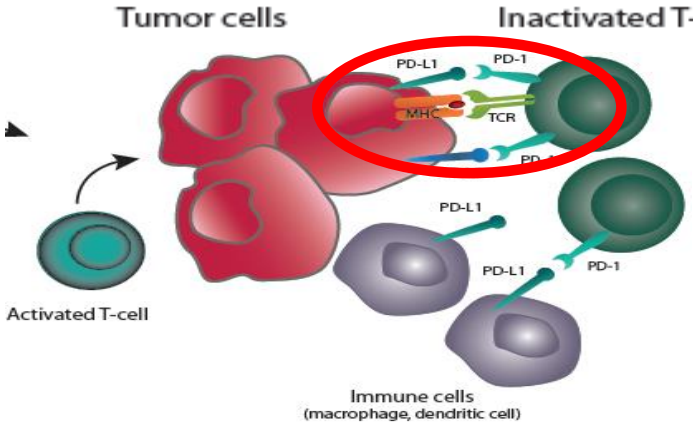
Tumors With Substantial Susceptibility to Anti-PD1 Antibody (partial list…)

FDA approved:

- Melanoma
- Non-Small Cell Lung Cancer
- Renal Cell Carcinoma - Clear Cell
- Urothelial Cancer
- Hodgkin's Lymphoma
- Head and Neck Squamous Carcinoma
- Merkel Cell Carcinoma
- Mis-Match Repair Deficient Colorectal Carcinoma
- Gastroesophageal Cancer
- Hepatocellular Carcinoma

Registrational trial on-going

- Mesothelioma
- Triple-Negative Breast Cancer
- Small Cell Lung Cancer
- Ovarian Cancer
- Glioblastoma

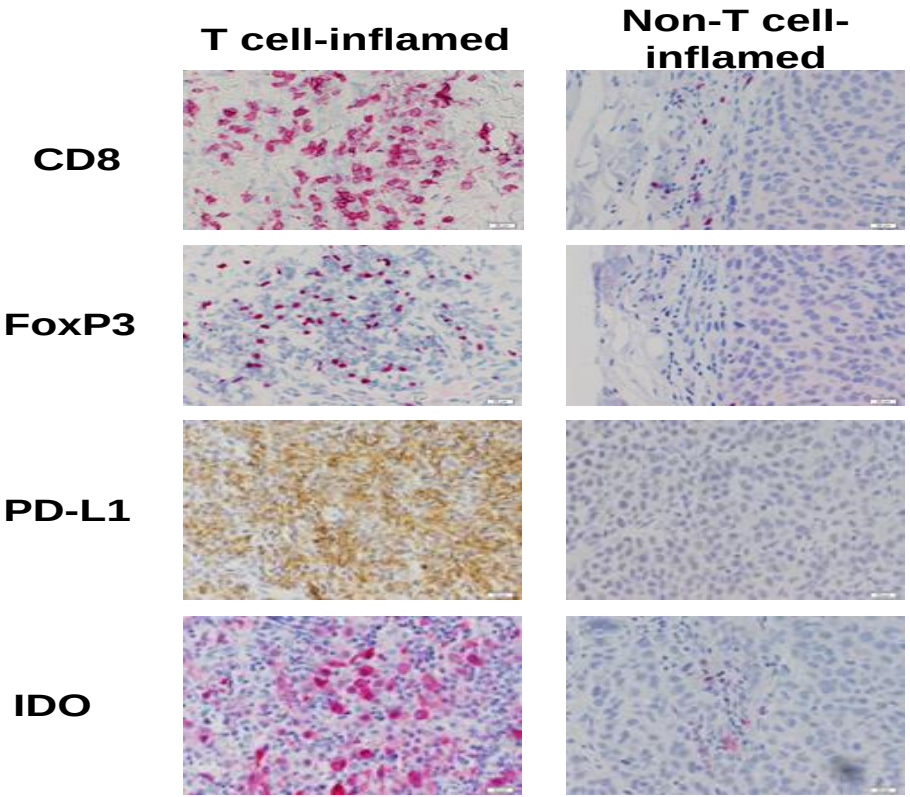


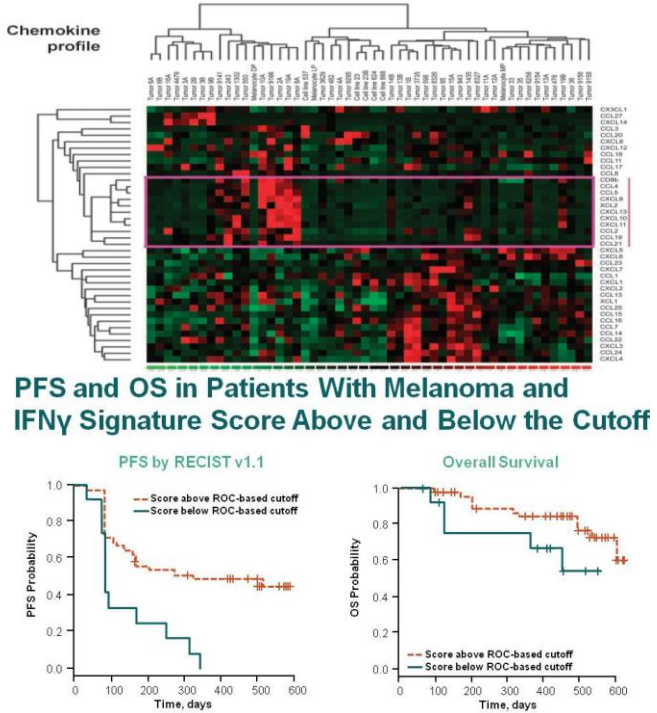
PD1/L1 Abs:

- Nivolumab (BMS)
- Pembrolizumab (Merck)
- Atezolizumab (Genentech)
- Durvalumab (AZ/Medimmune)
- Avelumab (EMD Serono/Pfizer)
- REGN281 (Regeneron)
- PDR001 (Novartis)

Luke *et al*. Oncotarget 2015

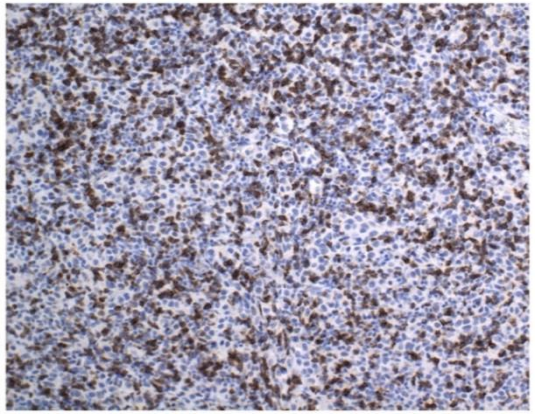
Working Model: Immunobiology of T cell-inflamed & Non-Inflamed Tumor Microenvironment

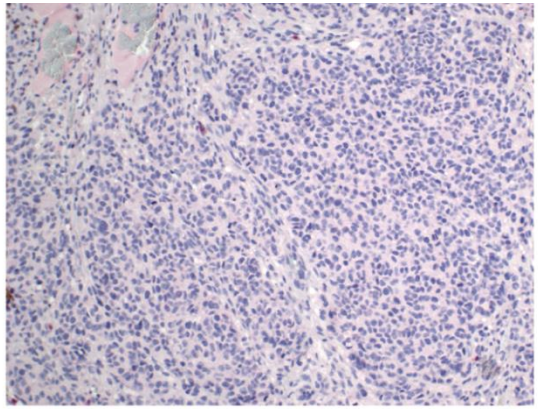




Gajewski et al. Nature Immunol. 2013
Spranger et al., Science Trans. Med. 2013
Harlin et al. Clin Can Res. 2009
Ribas et al. J Clin Oncol 33, 2015 (suppl; abstr 3001)

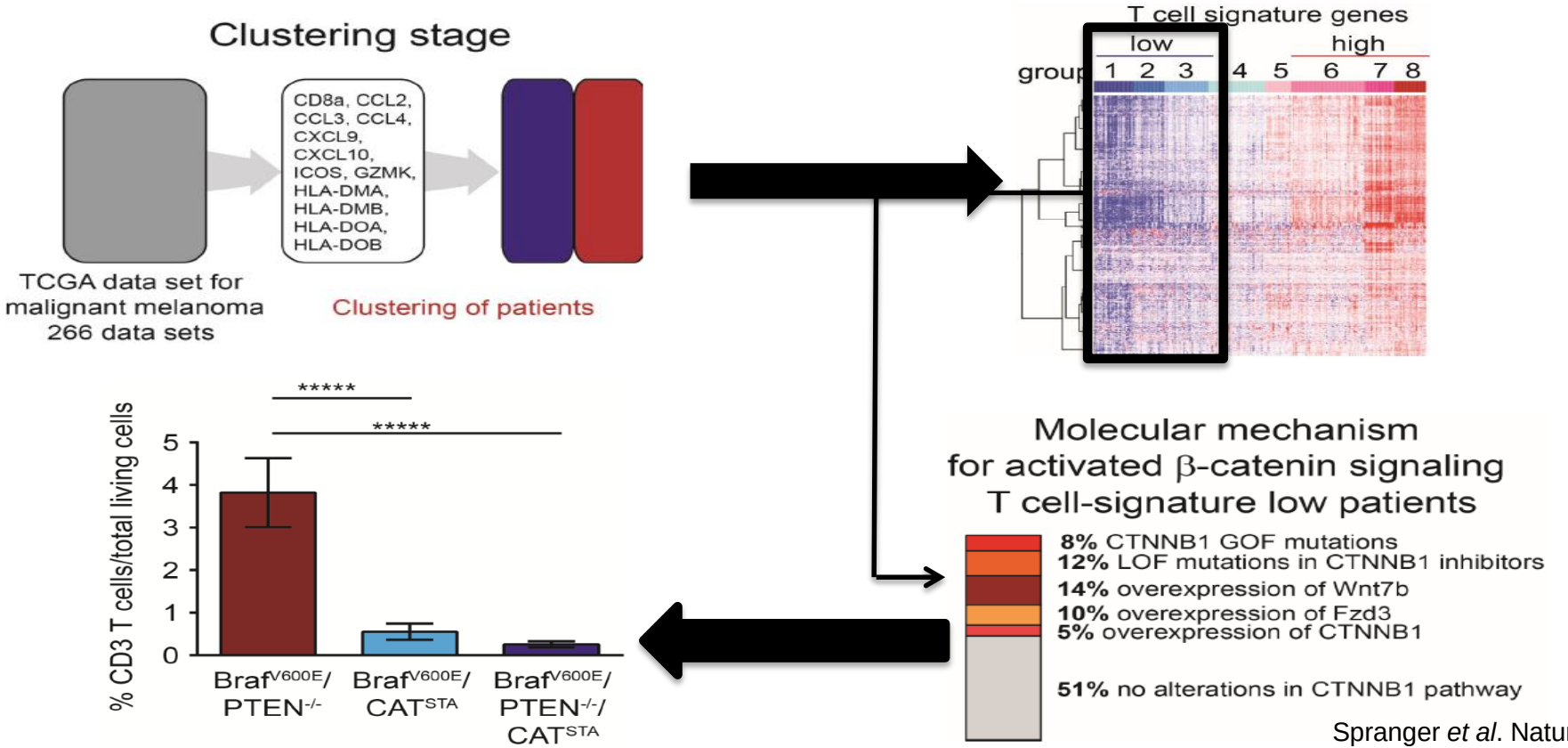
What Are the Molecular Mechanisms That Explain the T Cell-Inflamed vs. Non-Inflamed Tumor Microenvironments?





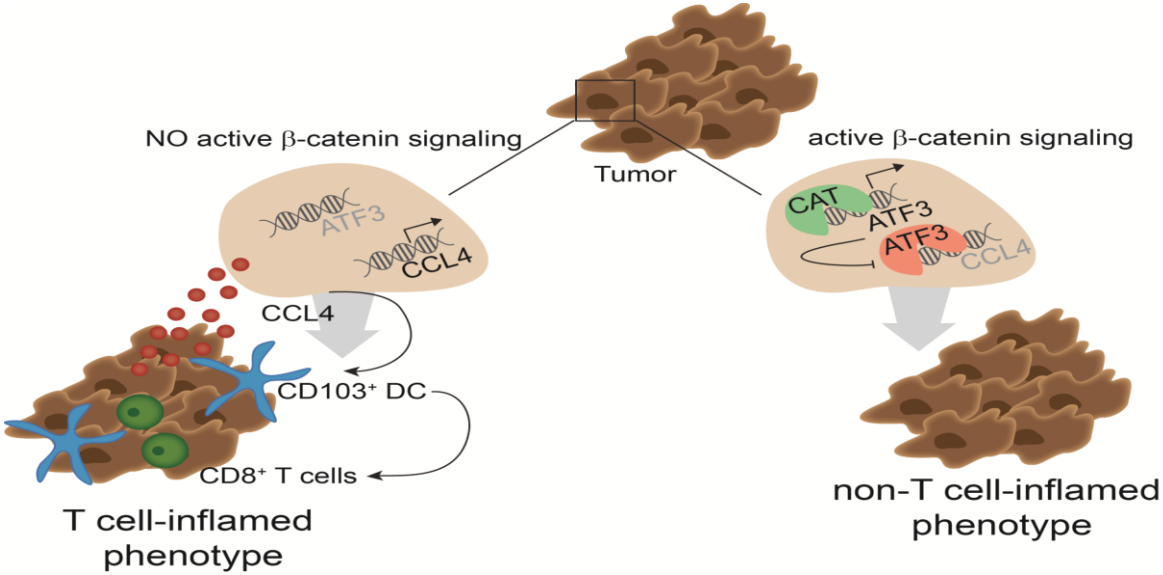
1. Somatic differences at the level of tumor cells
   - Mutational landscape and antigenic repertoire
   - Distinct oncogene pathways activated in different patients
2. Germline genetic differences at the level of the host
   - Polymorphisms in immune regulatory genes
3. Environmental differences
   - Commensal microbiota
   - Immunologic/pathogen exposure history

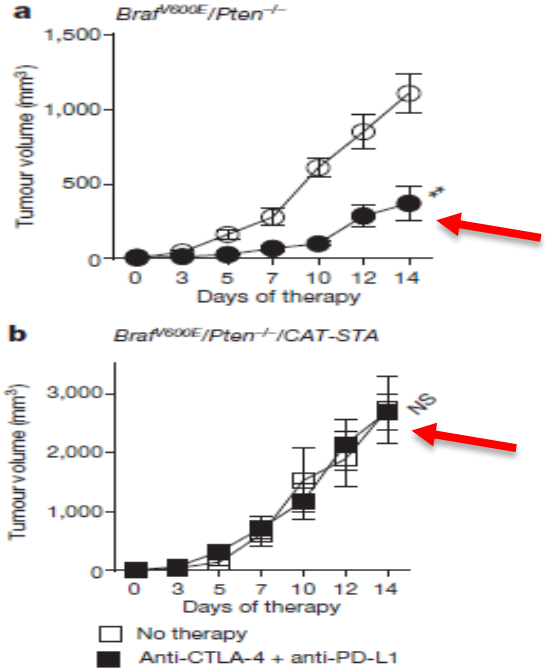
Workflow Identifying WNT/β-catenin Signaling Between T Cell-Inflamed & Non-T Cell-Inflamed Melanoma



Spranger *et al*. Nature 2015

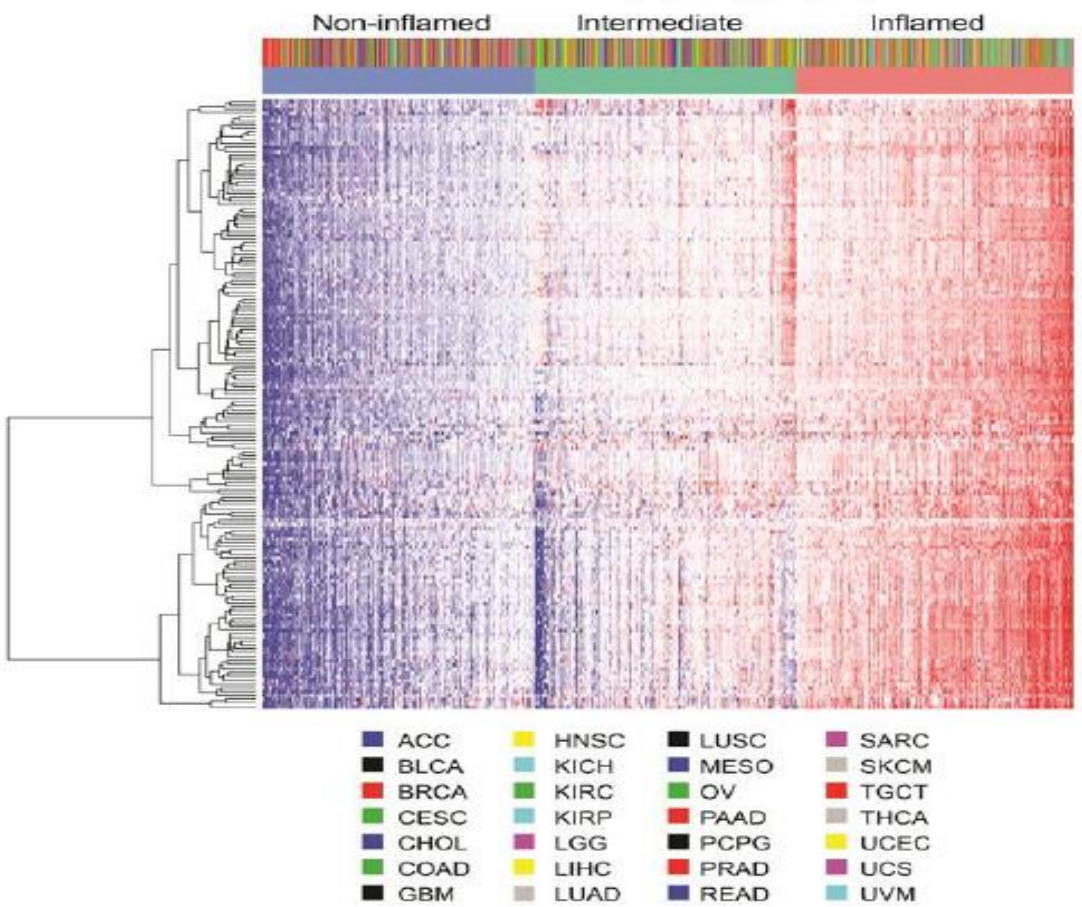
β-catenin Represses CCL4, Leading to Lack of Batf3^{+} DC Recruitment, Failed T cell Priming, and Non-Response to Checkpoint Blockade





Spranger *et al*. Nature 2015

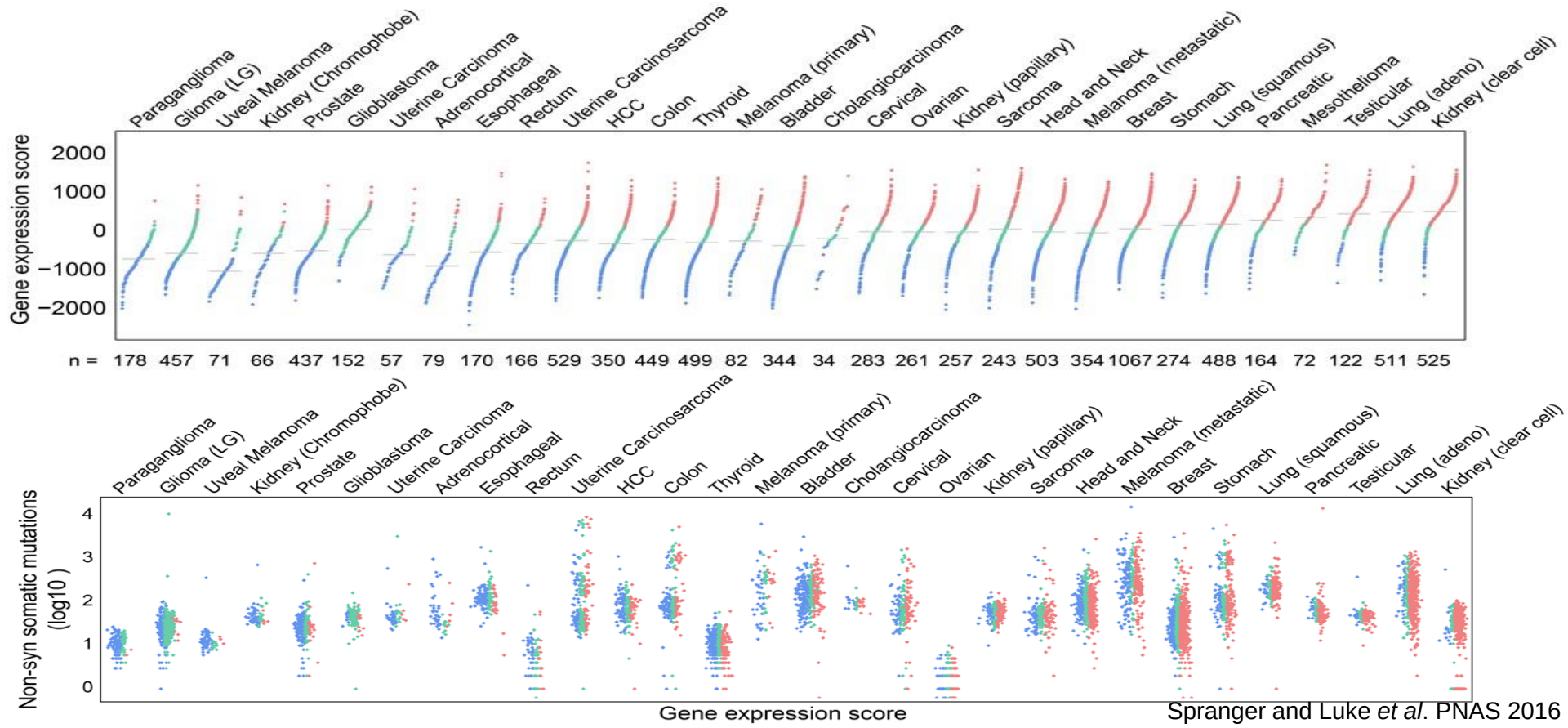
Genetic Landscape of the T Cell-Inflamed Tumor Microenvironment Across TCGA Solid Tumors



Cancer Type	Non-inflamed	Int	Inflamed	Total
30 solid primary tumors	3000 (32.7%)	2873 (32.3%)	3017 (33.9%)	8890

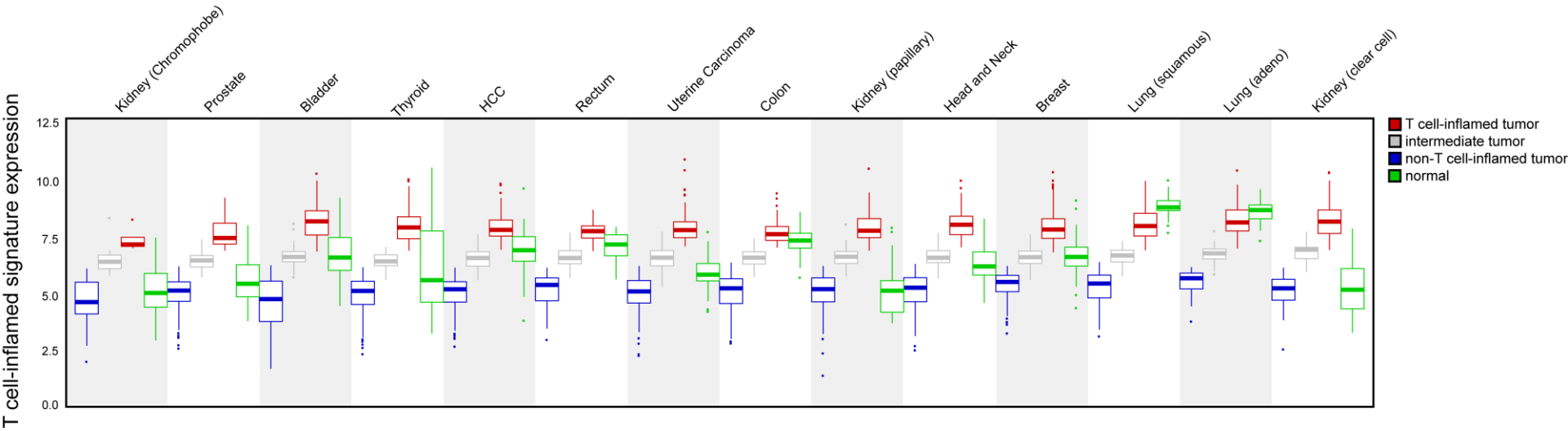
Spranger and Luke *et al*. PNAS 2016

Spectrum of T Cell-Inflamed Tumor Microenvironment by Increasing Frequency Across Tumor Types



Spranger and Luke *et al*. PNAS 2016

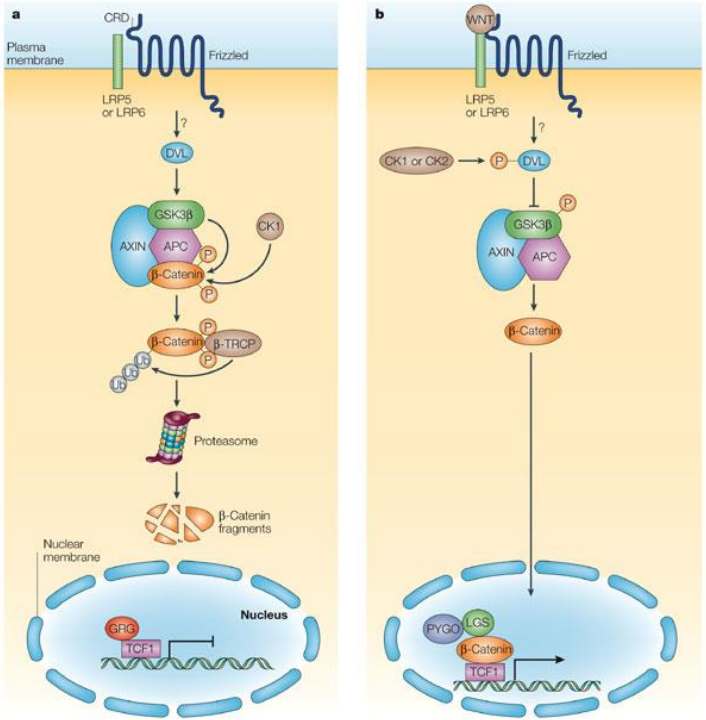
The Lack of T Cell Infiltration is Unique to Non-Inflamed Tumor Microenvironment Relative to Matched Normal



Non-T cell-inflamed tumors show lower gene immune gene expression score relative to normal tissue controls (p=1.10e-111)
T cell-inflamed tumors showed a significantly higher gene expression score relative to normal tissue (p=2.23e-106).

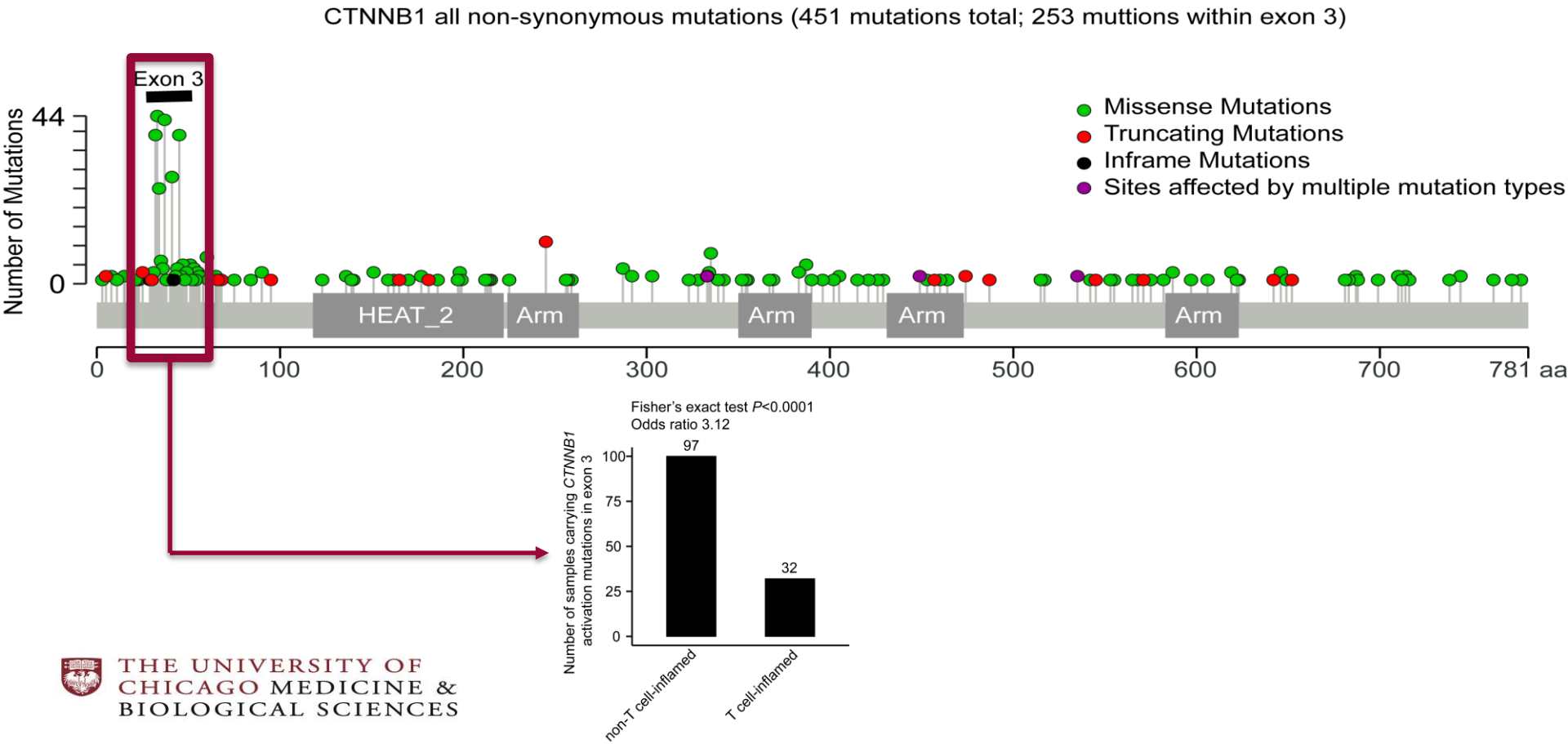
Mechanisms of β-catenin pathway activation interrogated in non-T cell-inflamed tumors

- Mutation
  - Activating mutations *CTNNB1*
  - Inactivating mutations in negative regulators
    - *Axin1*, *Axin2*, *APC1*, *APC2*
- Pathway activation without mutations
  - E.g. overexpression of Wnt ligands, Fzd receptors, β-catenin itself



Staal and Clevers. Nat Rev Immunol. 2005

Location of literature annotated β-catenin mutations



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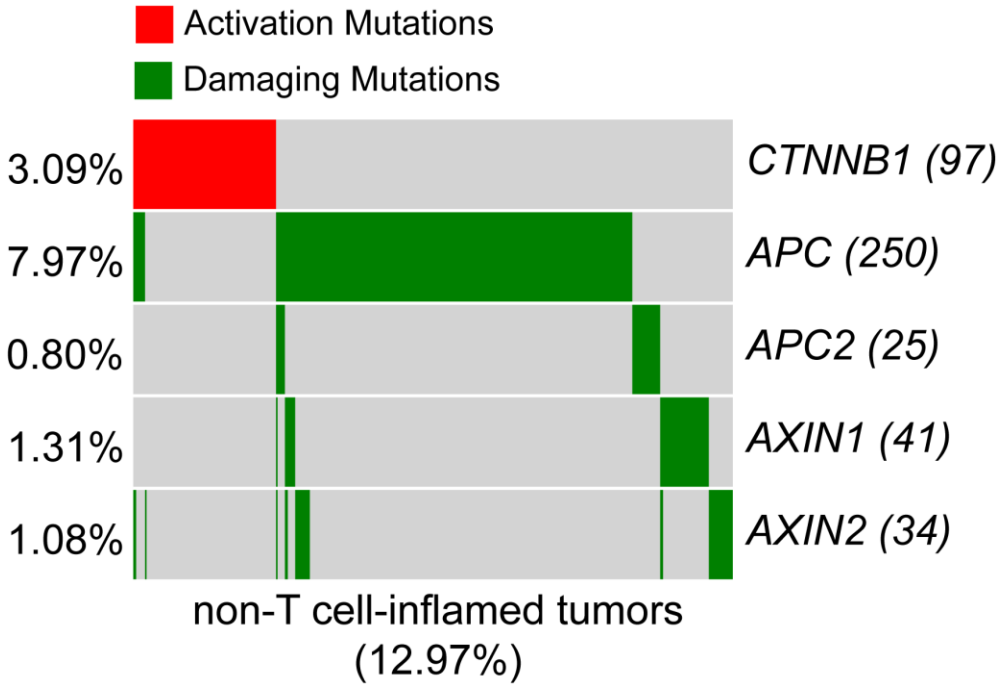
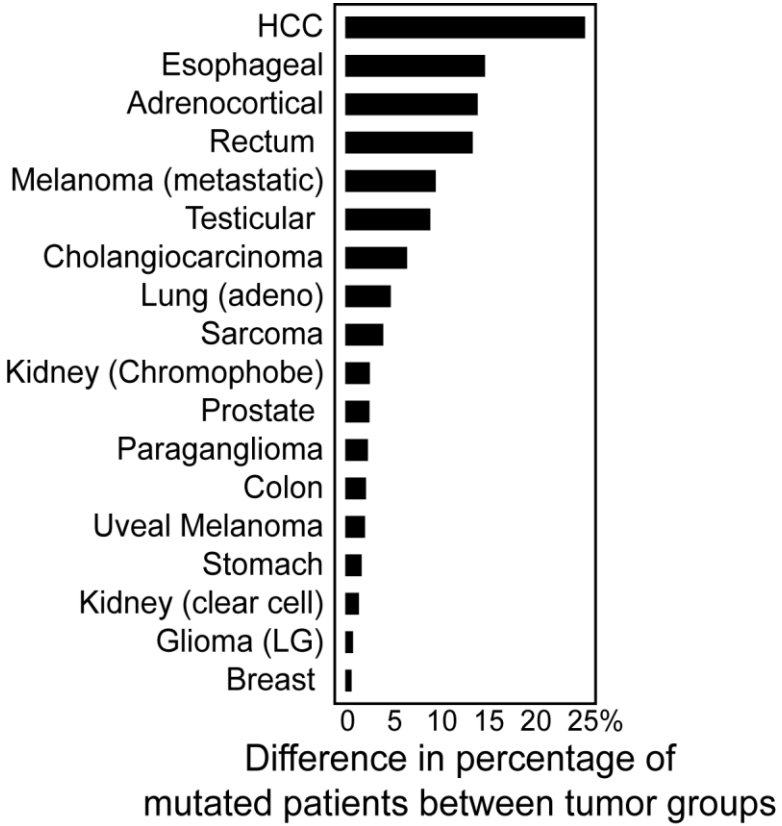
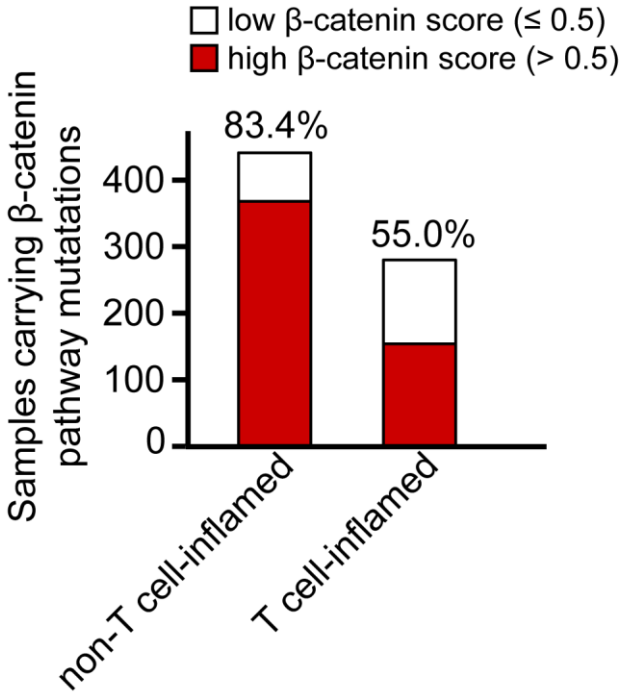
Frequency of β-catenin pathway mutations in non-T cell-inflamed tumors



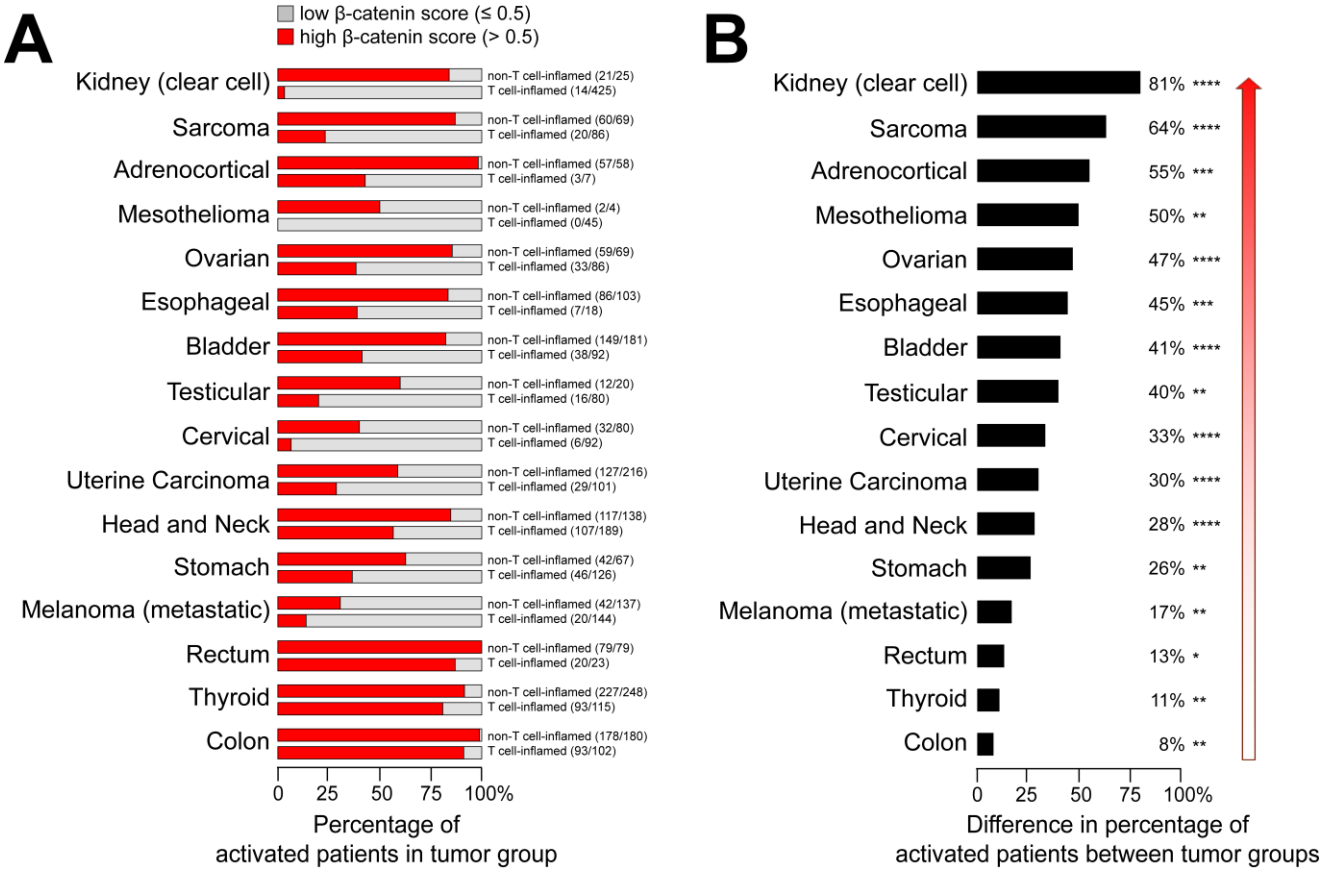
- **Note that this is likely an underestimate as few mutations are well characterized outside of exon 3**

Difference of β-catenin mutated patients between non-T cell-inflamed and inflamed tumor groups per cancer

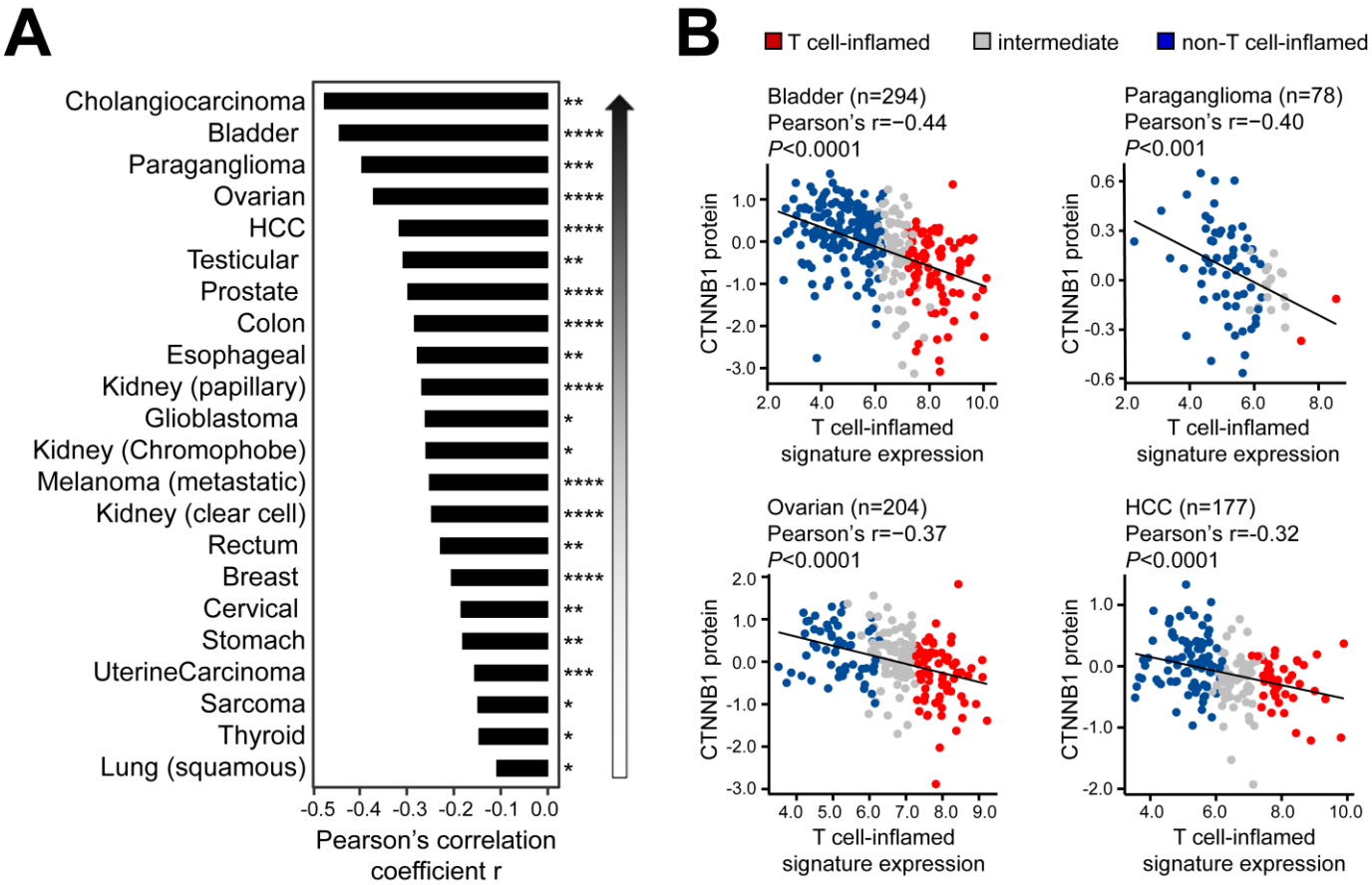




16 tumors show β-catenin activation as greater in non-T cell-inflamed versus T cell-inflamed tumor groups

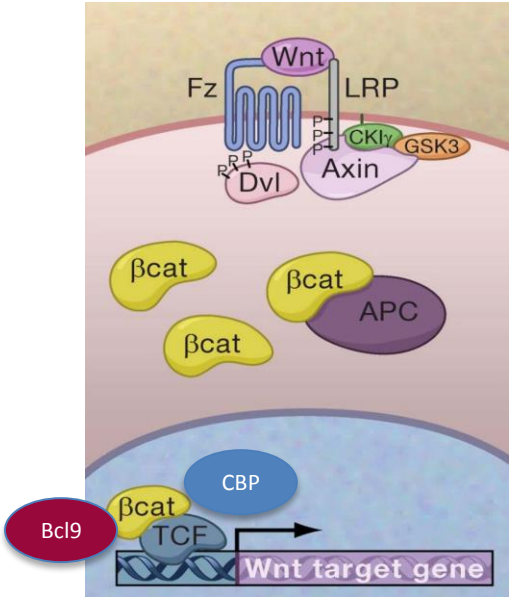


Inverse correlation between β-catenin protein level and T cell-inflamed gene expression



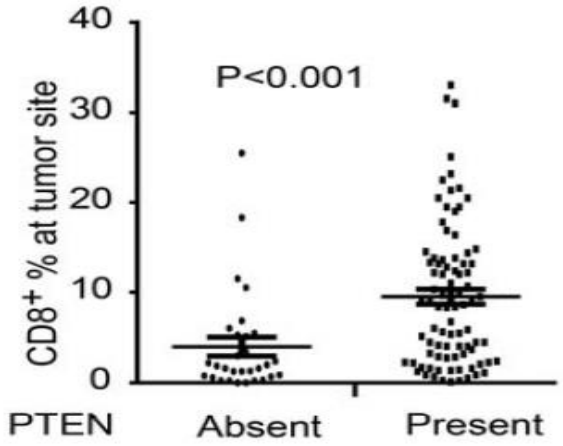
Select list of therapeutics to target β-catenin

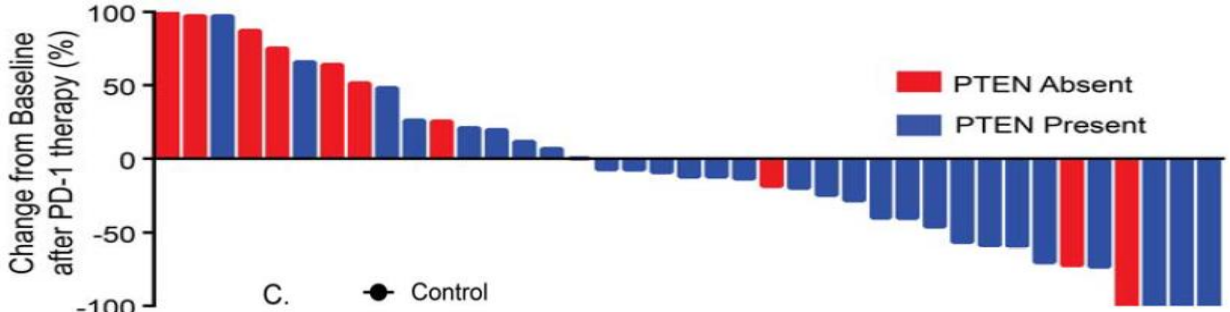
- **Small molecules**
  - E7386 (Eisai - CREB-binding protein/β-catenin transcription activation complex)
  - PRI-724 (Prism Biolabs - CREB-binding protein)
  - BC-2059 (Beta-cat Pharma - Transducin β-like 1)
  - Preclinical Venn Therapuetics
- **Macrocyclic scaffolds**
  - Preclinical (Circle Pharma)
- **Stapled peptides**
  - Preclinical (Fogpharma)
  - Preclinical (WntRx)
- **Antibody drug conjugates**
  - Preclinical to clinic (Several)

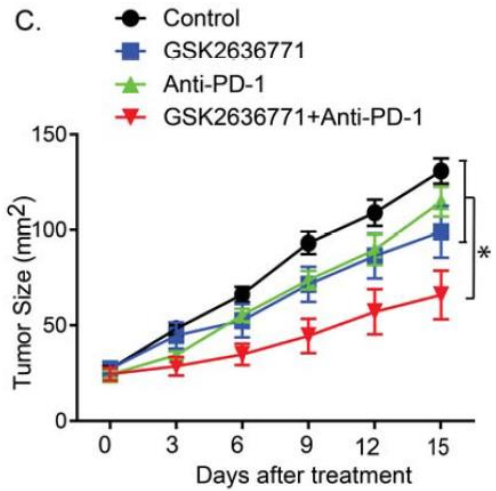


Yamada *et al*. AACR 2017 – abstract 5177
El-Khoueiry *et al*. ASCO 2013 – 2501
Savvidou et al. Mol Cancer Ther. 2017

Beyond β-catenin: PTEN Loss in Melanoma Associates with Non-T Cell-Inflamed Tumor Microenvironment and Resistance to anti-PD-1







Phase I study of PI3K-β inhibitor in combination with anti-PD1 in PTEN deficient tumors on-going

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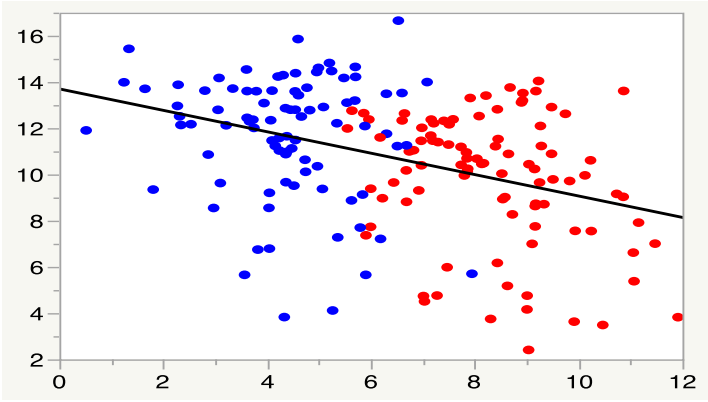
Peng *et al*. Can Discovery 2015

ClinicalTrials.gov Identifier: NCT03131908

Beyond Melanoma:
FGFR3 Expression Present in Non-T Cell-Inflamed Bladder Cancer



• Non-inflamed • Inflamed

Phase I study of FGFR inhibitor in combination with anti-PD1 in FGFR3 expressing tumors in development!

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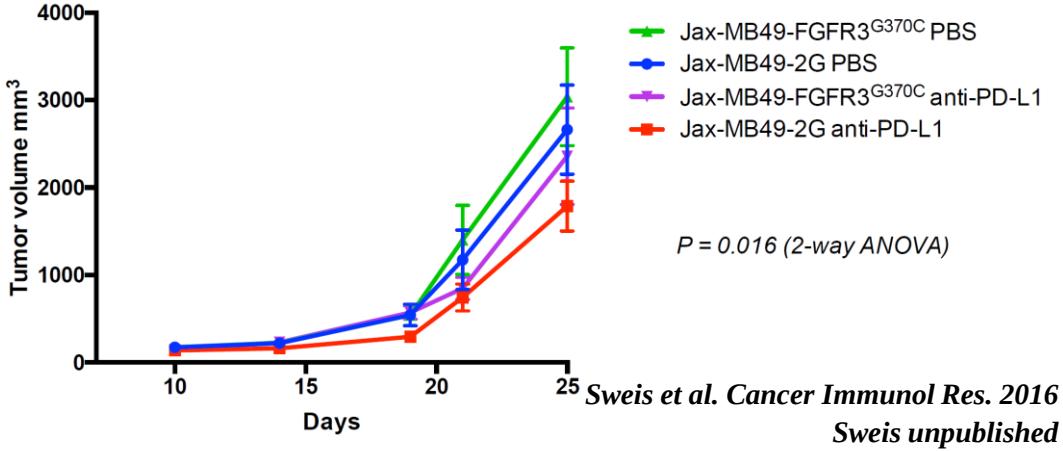
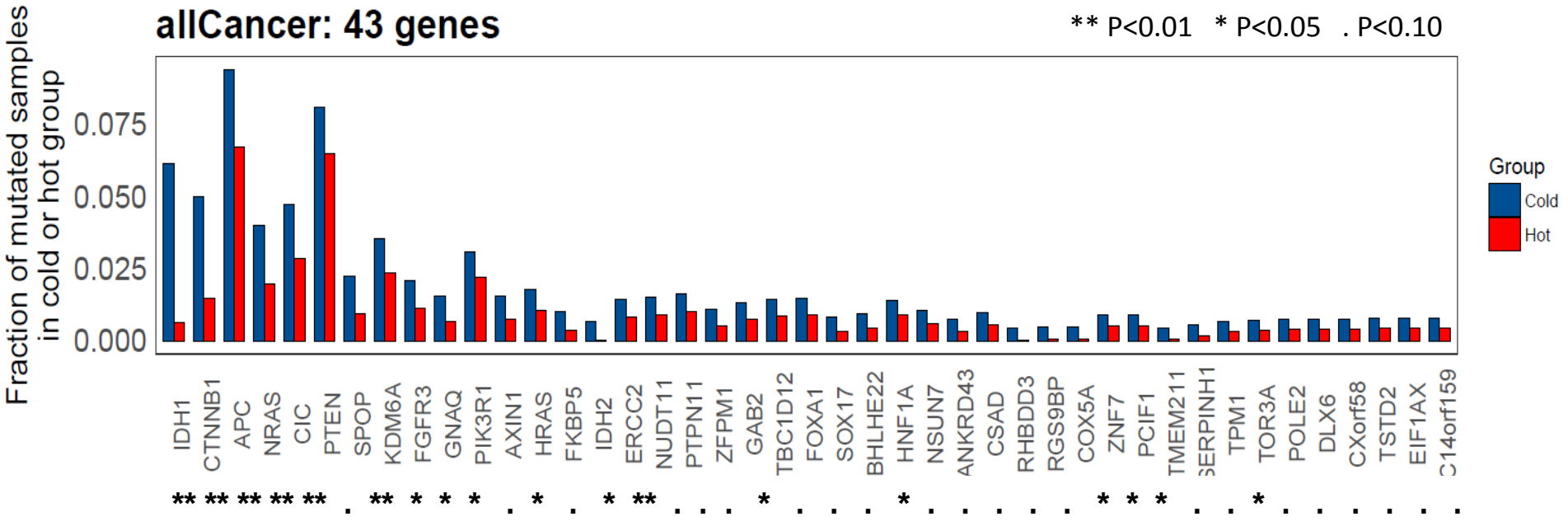
	Non-T cell-inflamed (n= 76)		T cell-inflamed (n =85)	
Gene	**Samples**	**Variants**	**Samples**	**Variants**
FGFR3	11	14	0	0
Gene Fusion	**Non-T cell-inflamed Samples**		**T cell-inflamed Samples**	
FGFR3-TACC3	3		0	



Sweis et al. Cancer Immunol Res. 2016
Sweis unpublished

Genes enriched for somatic mutations in non-inflamed compared to inflamed tumors



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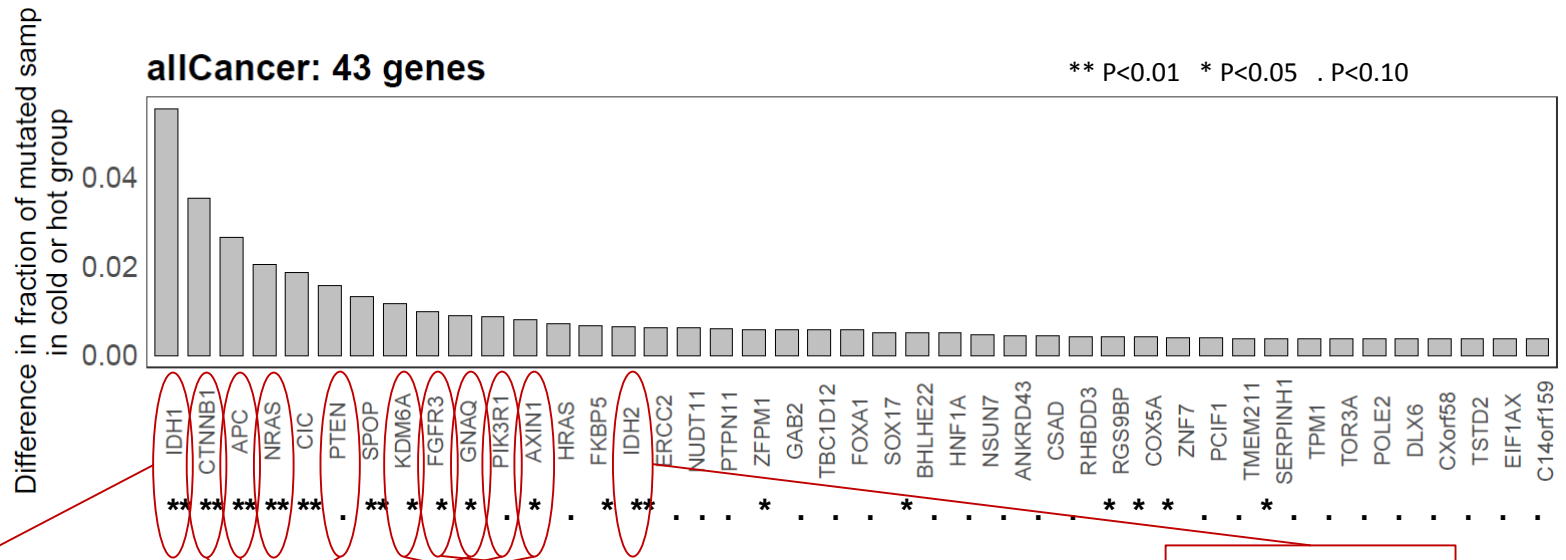
Top Ranked Genes Are Known to Drive Immune Exclusion or Involved in Immune System Regulation



Dominantly in LGG (Glioma (LG))

β-catenin and PTEN signaling

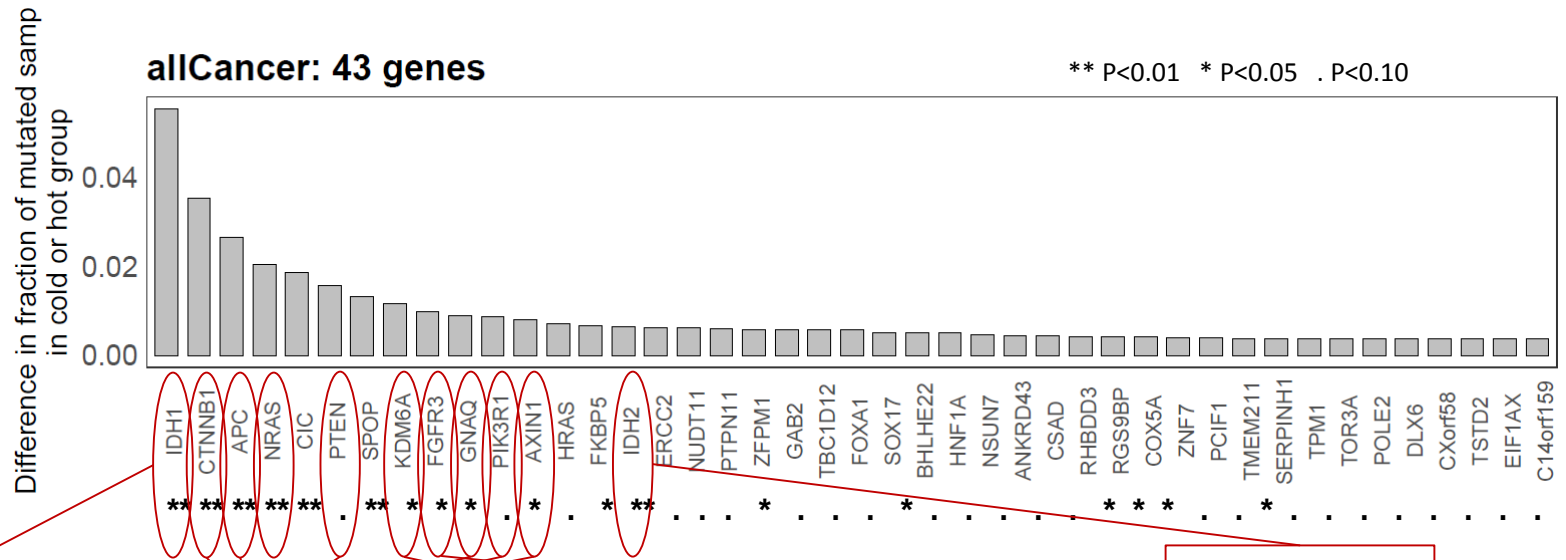
GNAQ malfunction leads to enhanced ARF6, further activating β-catenin signaling

Germline KDM6A mutations lead to Kabuki syndrome with immune dysfunction

Dominantly in BLCA (bladder)

Dominantly in LGG (much less than IDH1)

Top Ranked Genes Are Known to Drive Immune Exclusion or Involved in Immune System Regulation



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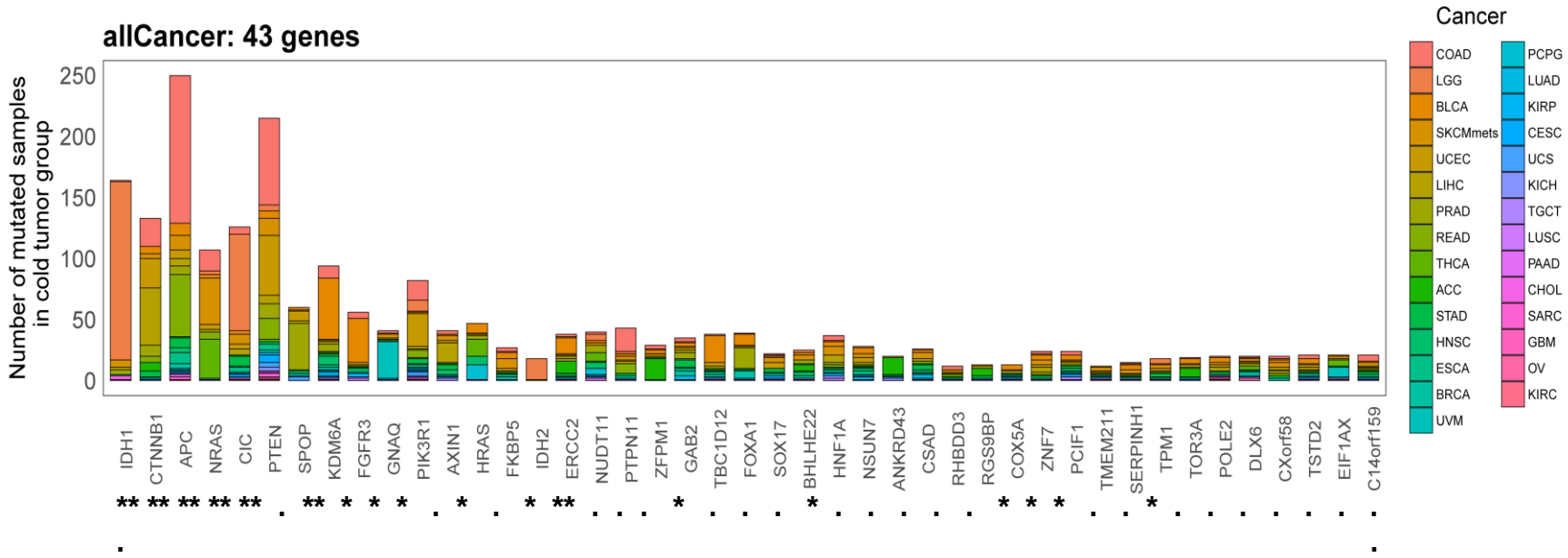
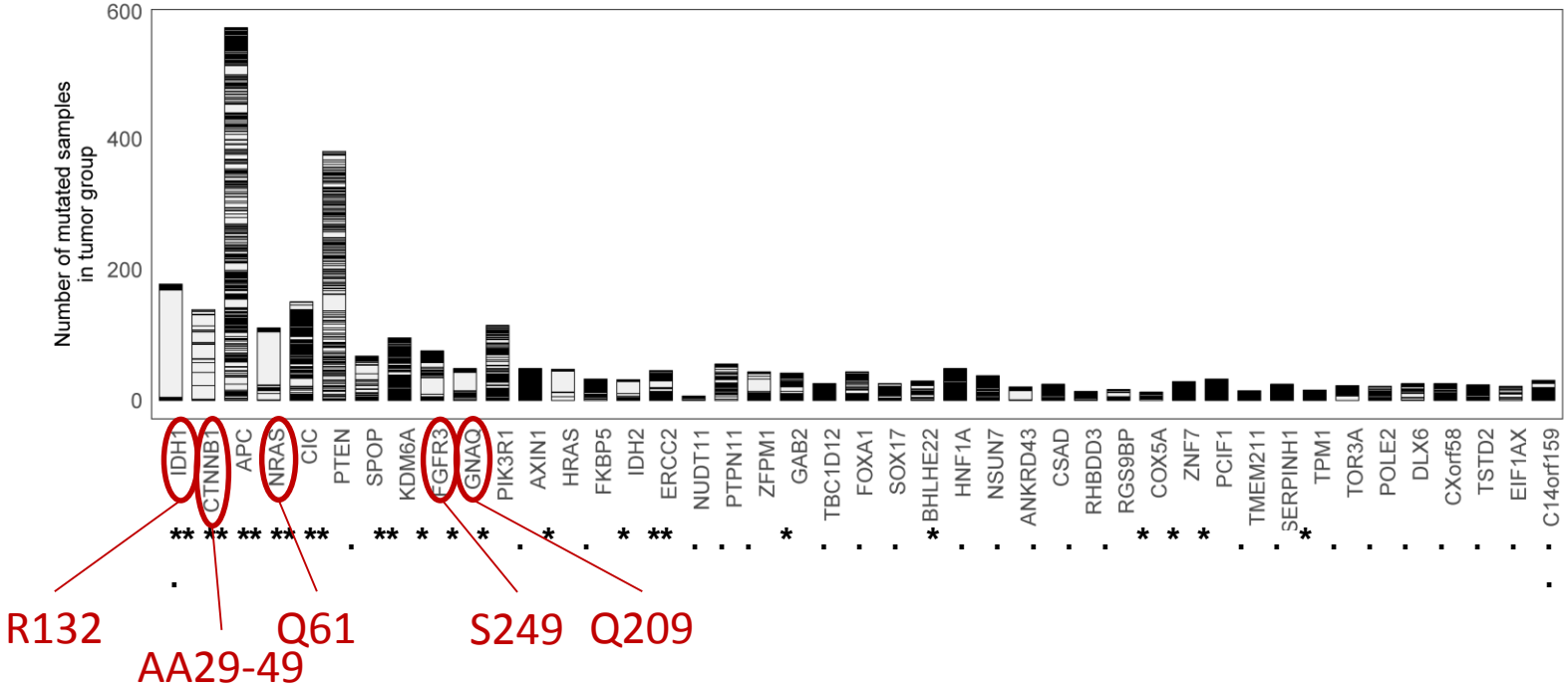
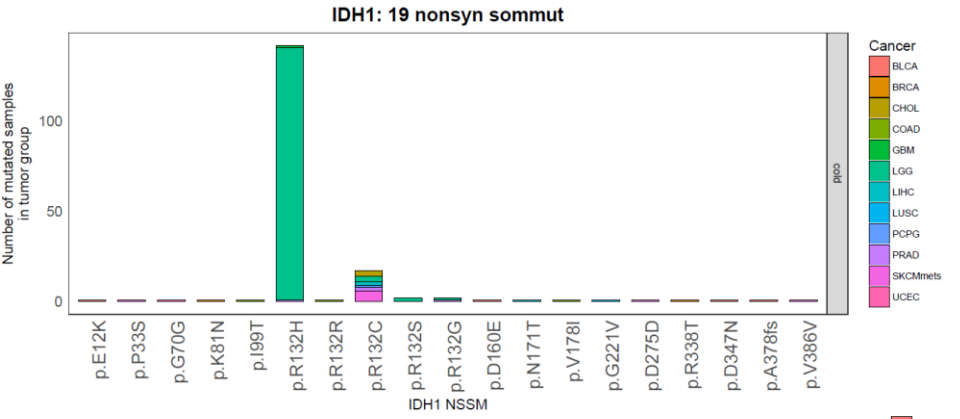
Top Genes Associated With Non-T Cell-Inflamed Microenvironment by Tumor Type

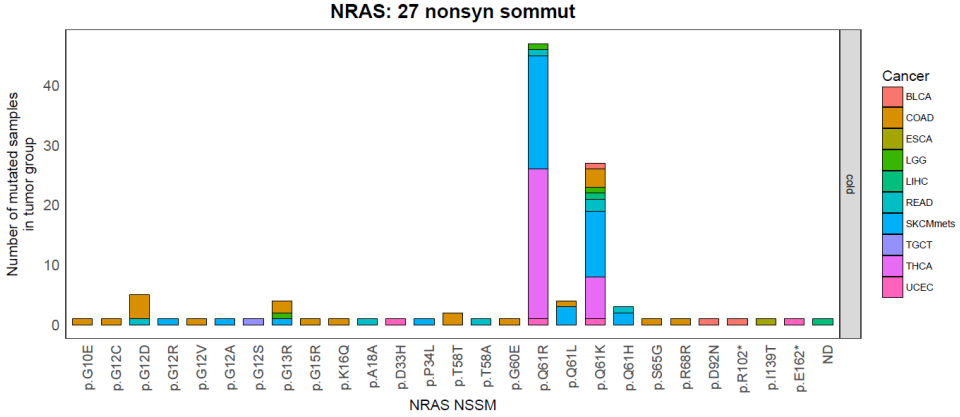


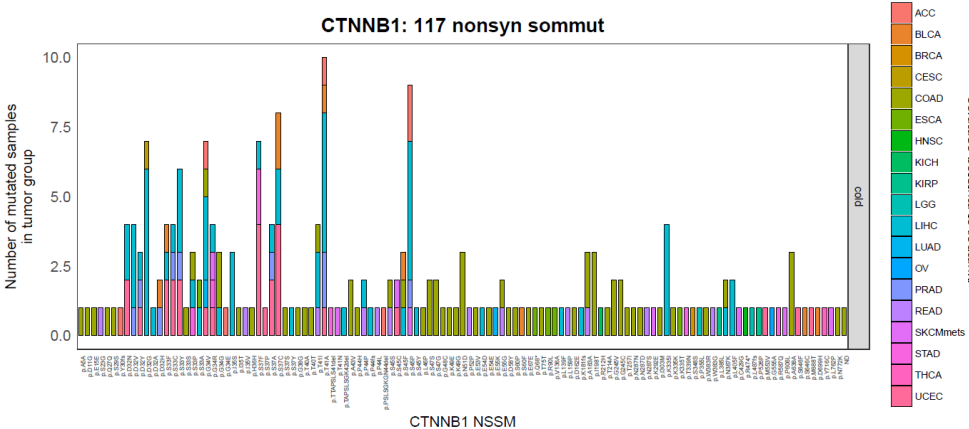
Amino Acid Changes Associated With Non-T Cell-Inflamed Microenvironment

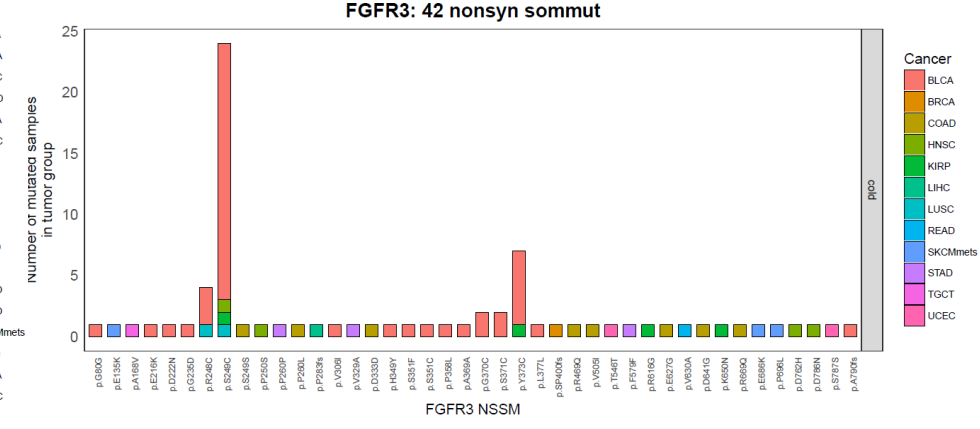


Amino Acid Level Changes Associated With Non-T Cell-Inflamed Microenvironment

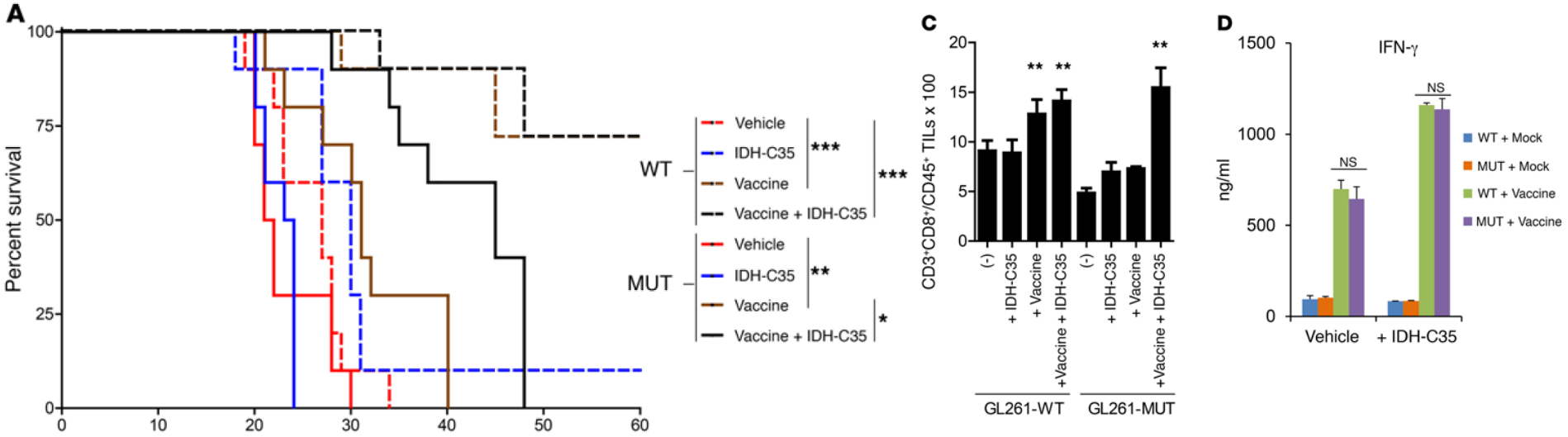








Treatment with IDH-C35 improves the efficacy of peptide vaccines in mice bearing GL261-MUT tumors



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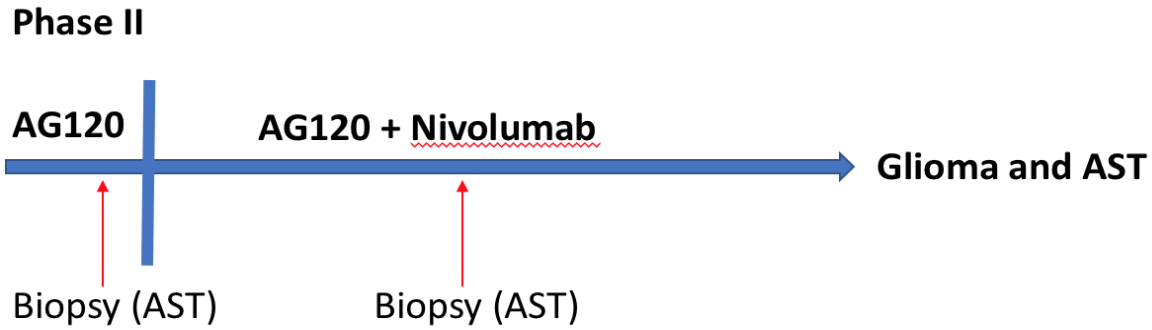
Kohanbash *et al*. JCI 2017

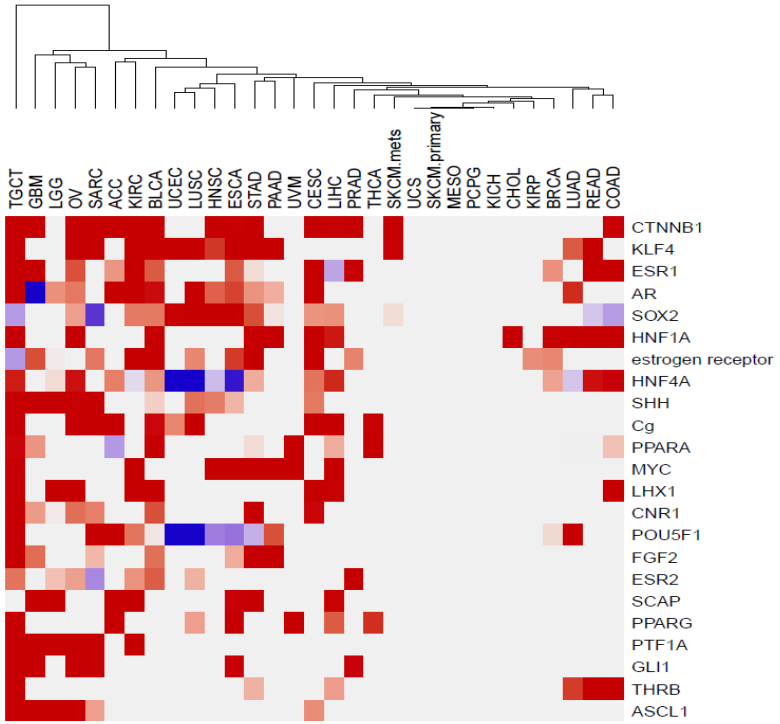
Phase I/II study of IDH1 inhibitor AG-120 and nivolumab in IDH1 mutant advanced solid tumors

Agios IST-2017-10170 in collaboration with BMS

Phase I		
Drug	AG-120	Nivolumab
Dose Level 1	500 mg daily	480 mg IV q4
Dose Level -1	400 mg daily	480 mg IV q4

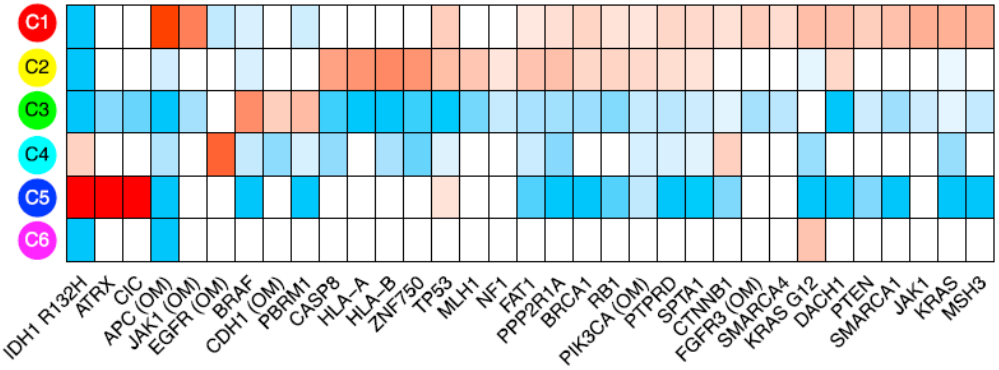


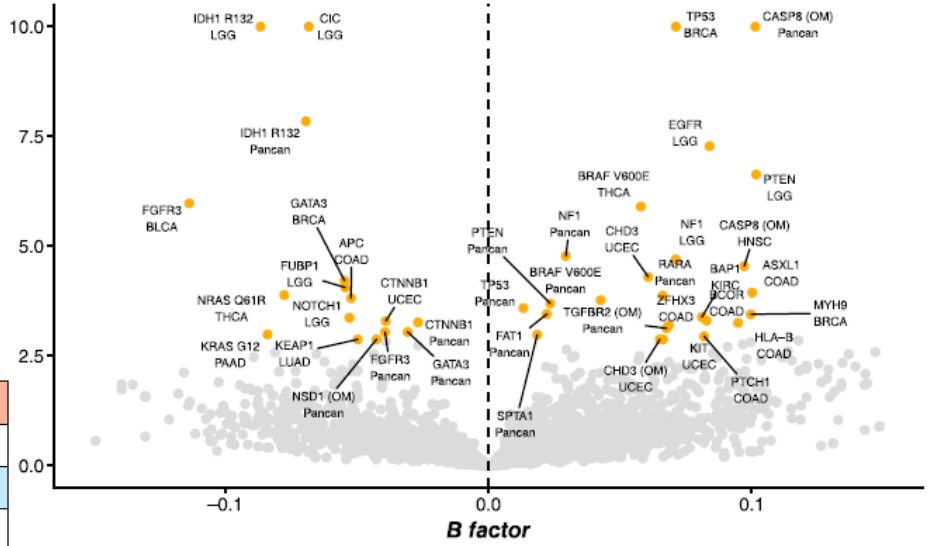
Activated signaling pathways correlated with non-T cell-inflamed tumor microenvironment



Immune subtypes correlate with genome state

	Macrophage: lymphocyte	Th1:Th2	Proliferation	Intratumoral heterogeneity	Other
Wound healing	Balanced	Low	High	High	
IFN-γ dominant	Lowest	Lowest	High	Highest	Highest M1 and highest CD8 T cells
Inflammatory	Balanced	High	Low	Lowest	Highest Th17
Lymphocyte depleted	High	Minimal Th	Moderate	Moderate	
Immunologically quiet	Highest	Minimal Th	Low	Low	Highest M2
TGF-β dominant	High	Balanced	Moderate	Moderate	Highest TGF-β signature





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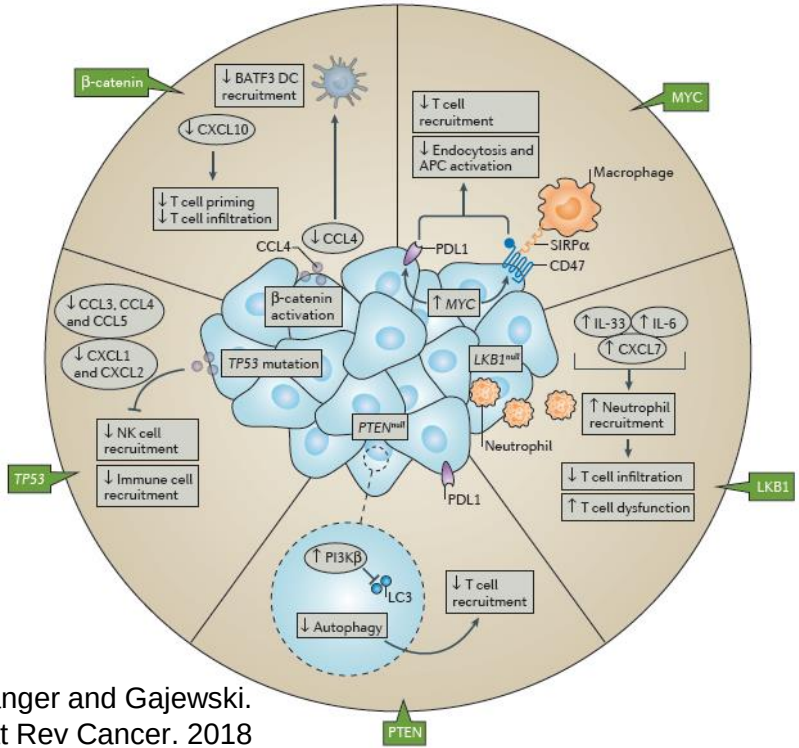
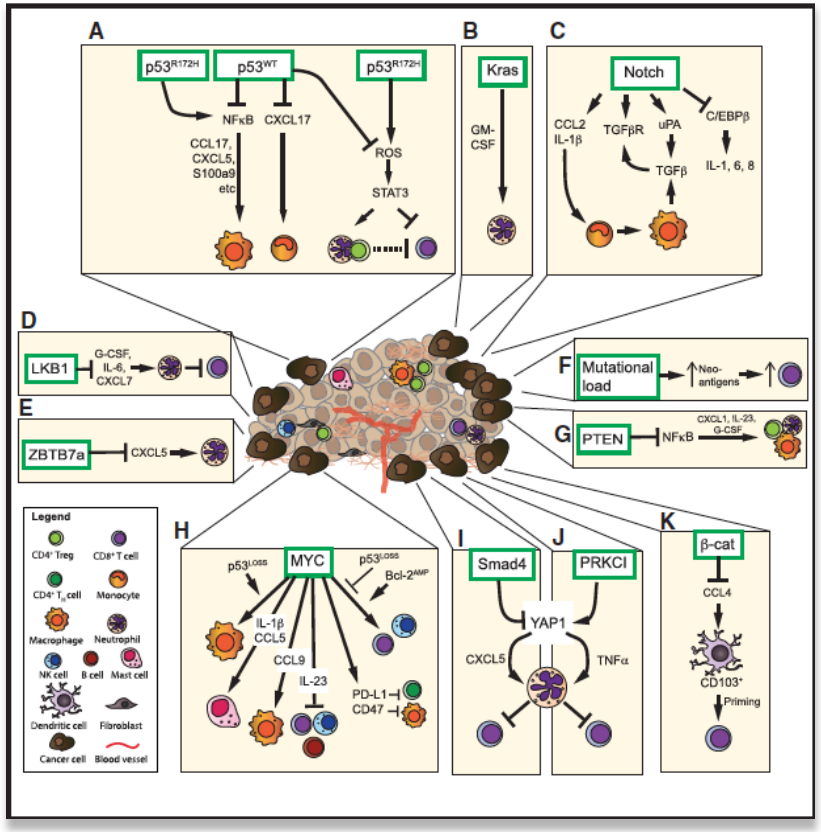
Thorrson *et al*. Immunity 2018

Impact of oncogenic signaling on immune inhibitory pathways and cell populations



Spranger and Gajewski.
Nat Rev Cancer. 2018



Wellenstein and de Visser KE. Immunity. 2018

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Conclusions

- **T cell-inflamed tumor microenvironment may serve as a model for predicting molecular pathways associated with immune inclusion vs exclusion phenotype**
- **Several tumor-intrinsic signaling pathways associated and have been mechanistically shown to drive the non-T cell-inflamed phenotype**
  - Somatic alterations in other pathways may additionally be of relevance: IDH, β-catenin, PTEN, RAS, FGFR3 etc.
- **Clinically validated biomarkers of transcriptional activation needed but may present rational IO combintaion targets**

Acknowledgements

- Department of Defense Career Development Award (W81XWH-17-1-0265)
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- Team Science Award from the Melanoma Research Alliance and Prostate Cancer Foundation
- Scientific Research Agreements with Bristol-Myers Squibb, Array, CheckMate and Palleon
- Arthur J Schreiner Family Melanoma Research Fund, J. Edward Mahoney Foundation Research Fund, Brush Family Immunotherapy Fund

and support from Center for Research Informatics of The University of Chicago Biological Science Division and The Institute for Translational Medicine/CTSA (NIH UL1 RR024999)

@jasonlukemd @UCCancerCenter **ASCO Sun June 3rd – Buddy Guy's Legends BE THERE!!!**