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Society for Immunotherapy of Cancer

Extrinsic Mechanisms of Resistance: *A Miserable Microenvironment*

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The University of Texas, MD Anderson Cancer Center

Presenter Disclosure Information

Michael A. Curran

The following relationships exist related to this presentation:

ImmunoGenesis, Founder and President
ImmunOS, Board Member and Consultant

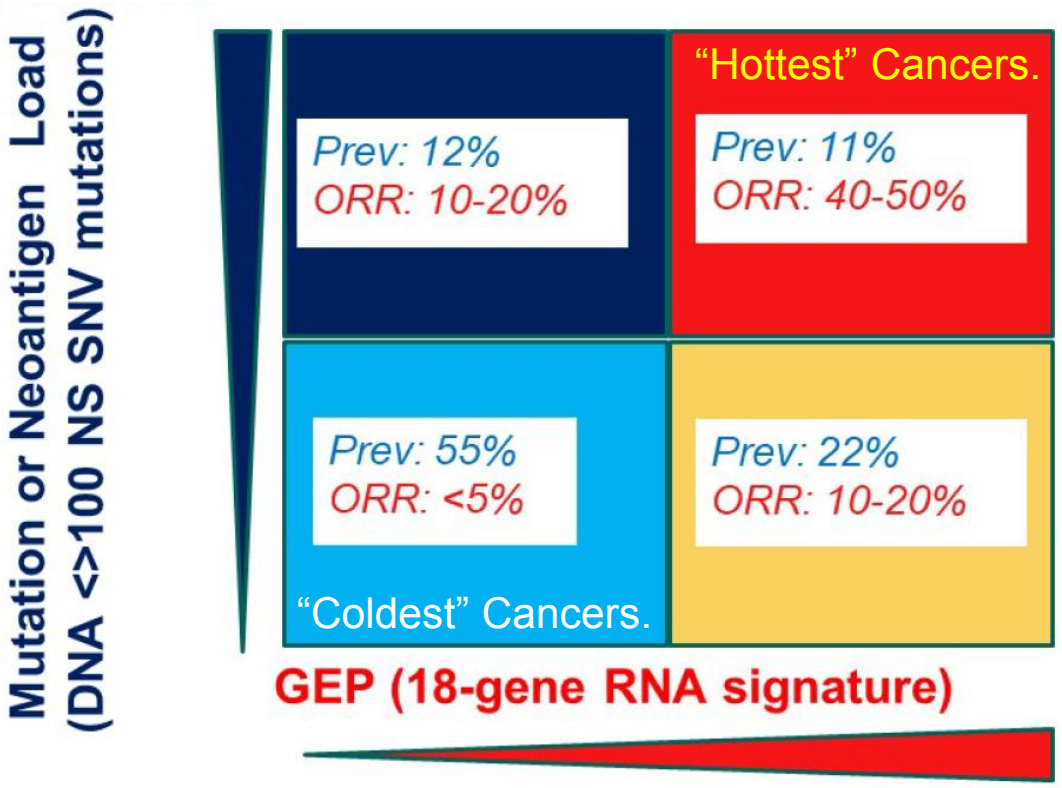
Agenus, Consultant
Alligator, Consultant
Aptevo, Consultant, SAB
ImmunoMet, Consultant
Innovio, Consultant, SAB
Mabimmune, SAB
Nurix, Consultant, SAB
OncoResponse, Consultant, SAB
Pieris, Consultant
Salarius, Consultant, SAB
Xencor, Consultant, SAB

ImmunoMet, Sponsored Research Agreement
Ionis, Research Alliance

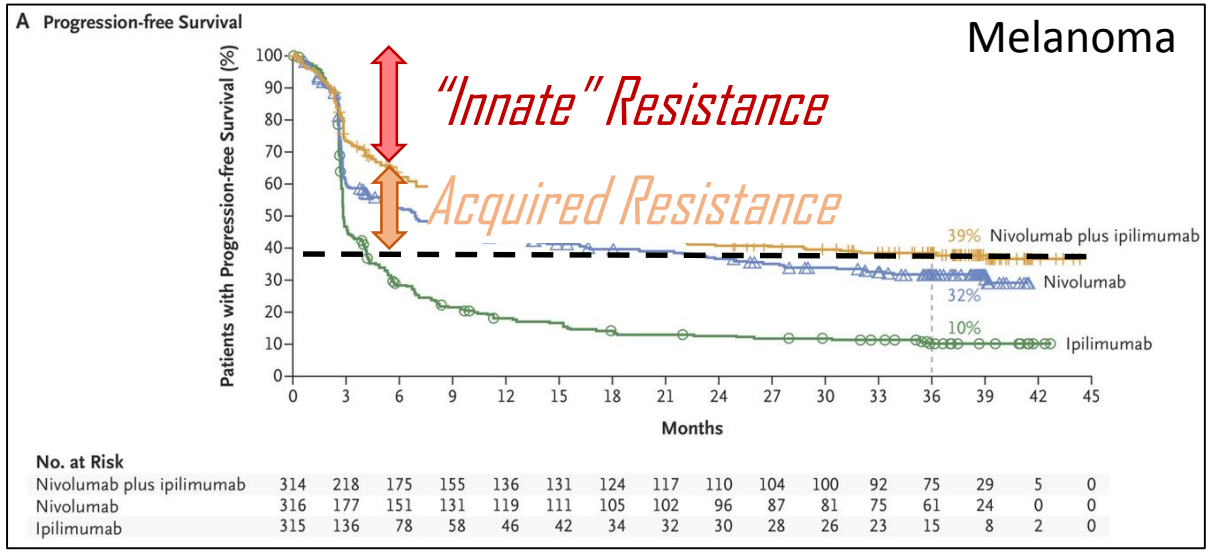
Goals

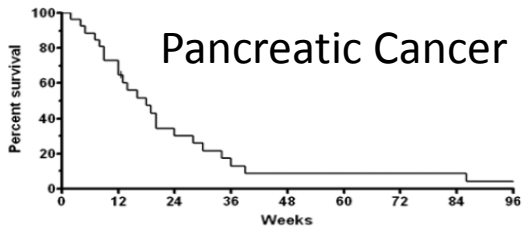
1. Understand how tumors condition their local microenvironment to suppress T cell immunity.
2. Learn the mechanisms by which myeloid stroma, regulatory T cells, and cancer-associated fibroblasts suppress immunity.
3. Become familiar with interventions under investigation to counteract these diverse extrinsic mechanisms of T cell immune suppression.

Most cancers remain resistant to Immunotherapy.

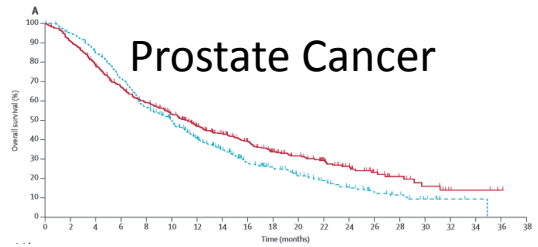


Seiwert, T., and Kaufman D.R. JCO.2018.36.5_suppl.25 *Journal of Clinical Oncology* 36, 2018.



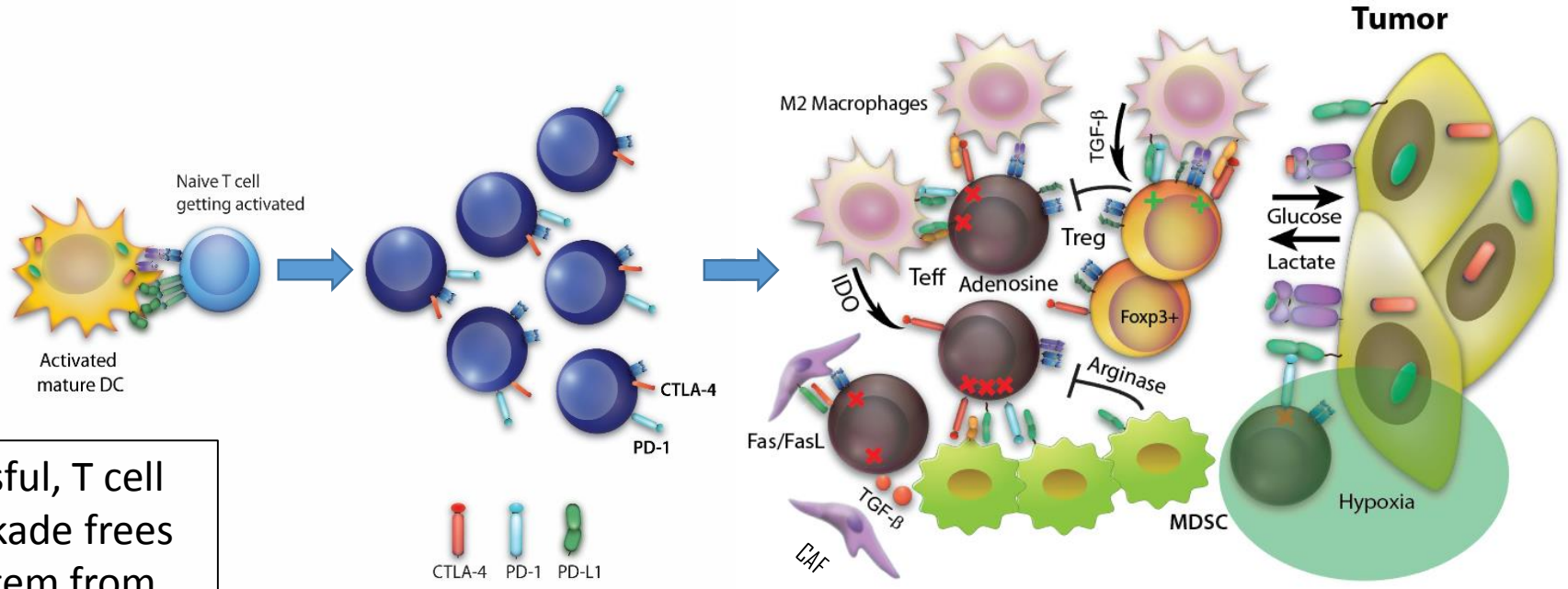


J Immunother • Volume 33, Number 8, October 2010



Lancet Oncol 2014; 15: 700–12

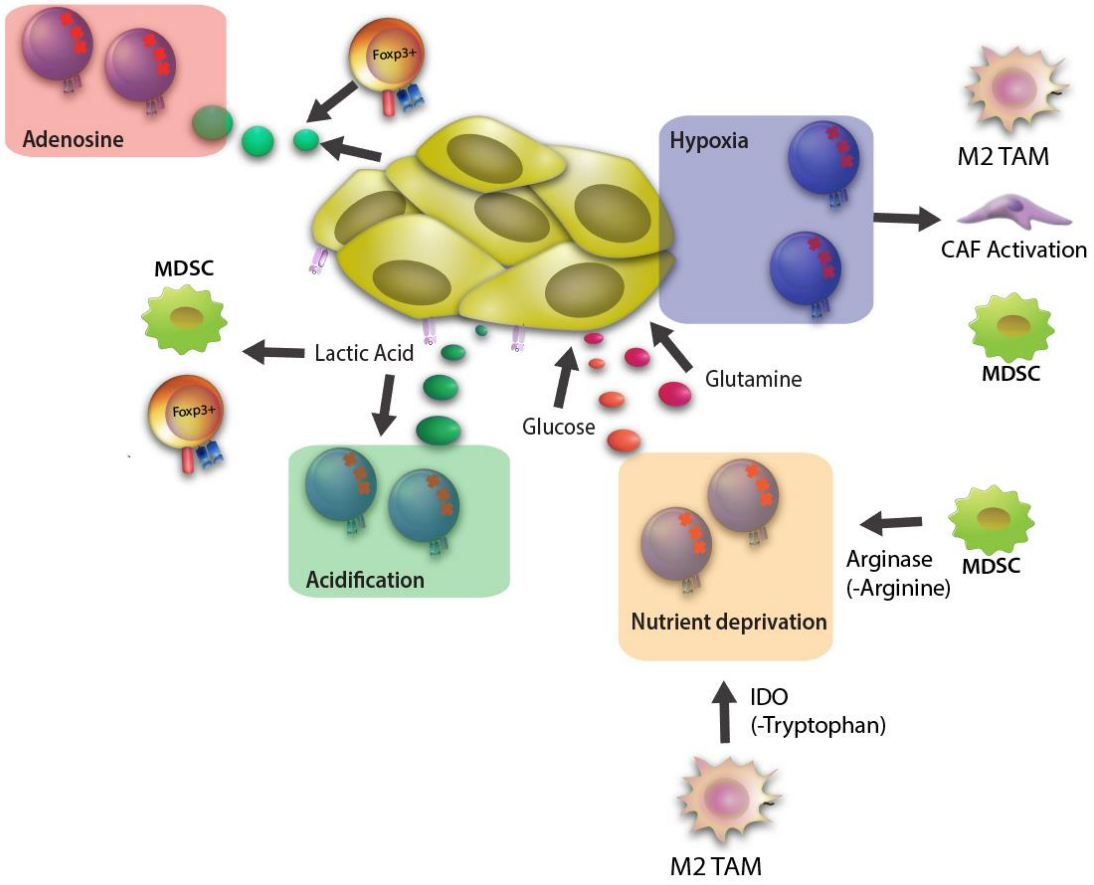
Extrinsic suppression can be dominant over T cell checkpoint blockade

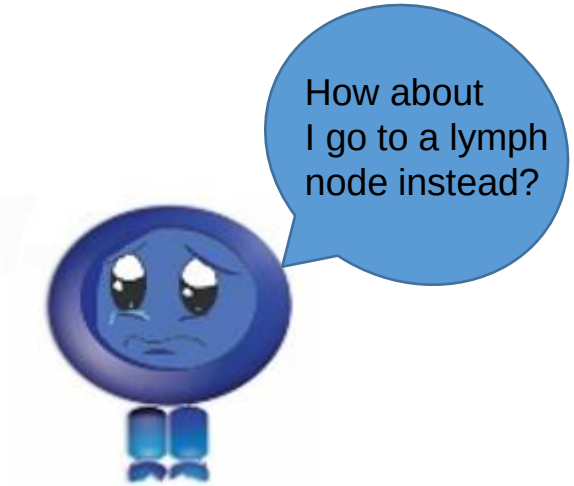


1) When successful, T cell checkpoint blockade frees the immune system from repression in the tumor eliciting durable regression of even widespread cancer.

2) Multiple mechanisms of immune suppression can repress T cells and prevent tumor regression even in the presence of checkpoint blocking antibodies.

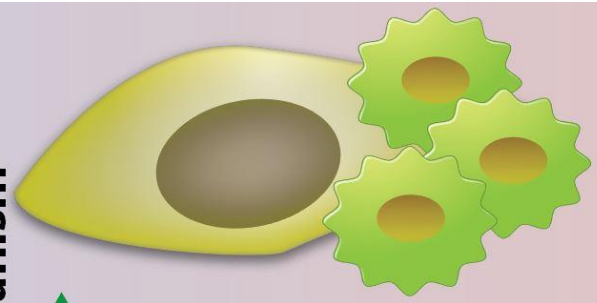
Tumors nucleate a metabolically-hostile micro-environment in which T cells fail to thrive





Resistant tumors become "hyper-metabolic" and outcompete infiltrating T cells for essential nutrients.

Suppressive Mechanism



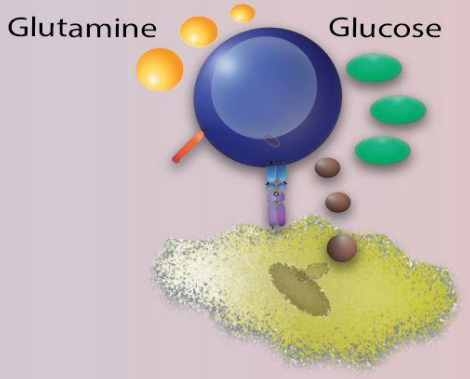
Glycolysis, Gluc and Glut uptake, OxPhos and Oxireductase activity, Hypoxia, ROS, ONOO-

Tumor hypermetabolism (high OxPhos and glycolysis) depletes oxygen and "fuel" from the TME starving T cells of energy and depriving them of effector function.

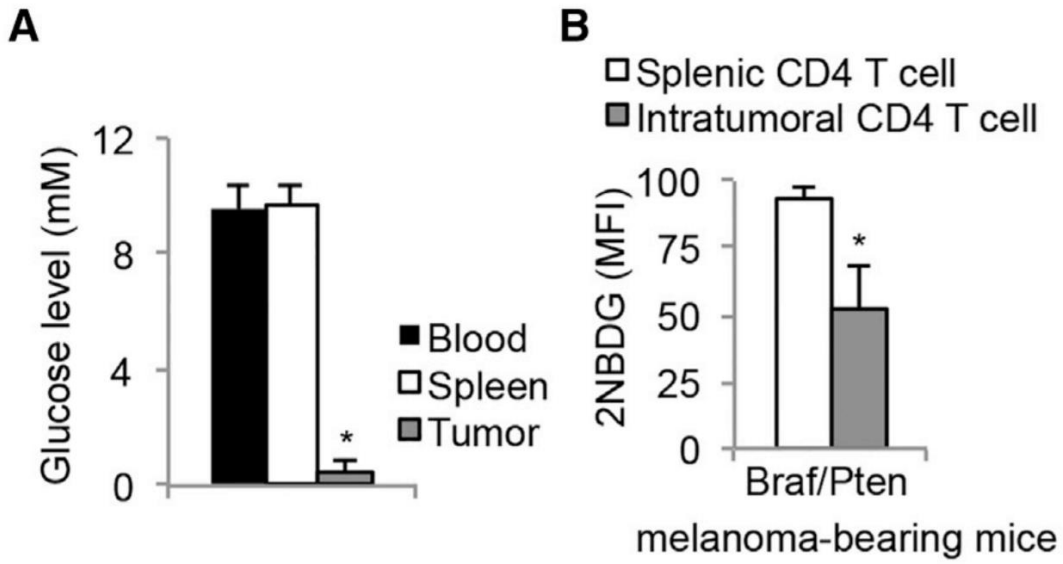
Therapeutic Intervention

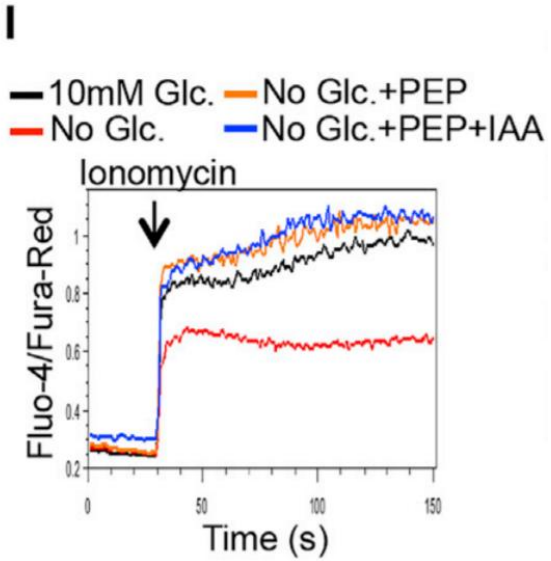
Inhibition of tumor metabolism:

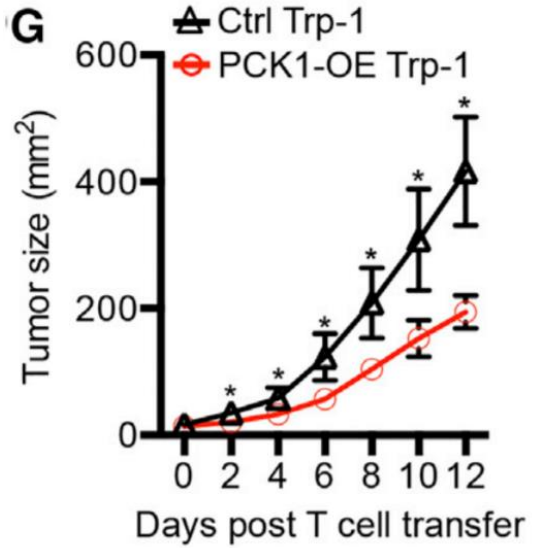
Glutaminase inhibitors
Glycolysis inhibitors
OxPhos inhibitors



Tumors metabolically out-compete T cells for glucose leaving them dysfunctional due an inability to flux calcium..







A) The TME lacks glucose. B) TME CD4 have low Glu uptake. I) PEP is required for CA^{2+} flux. G) T cells engineered to make PEP slow melanoma tumor growth.

Cell. 2015 Sep 10;162(6):1217-28. doi: 10.1016/j.cell.2015.08.012. Epub 2015 Aug 27.

Phosphoenolpyruvate Is a Metabolic Checkpoint of Anti-tumor T Cell Responses.

Ho PC[1], Bihuniak JD[2], Macintyre AN[3], Staron M[4], Liu X[5], Amezquita R[6], Tsui YC[7], Cui G[4], Micevic G[8], Perales JC[9], Kleinstein SH[10], Abel ED[11], Insogna KL[2], Feske S[12], Locasale JW[5], Bosenberg MW[13], Rathmell JC[3], Kaech SM[14].

Tumors foster hypoxia through dysregulated angiogenesis and rapid oxygen consumption.

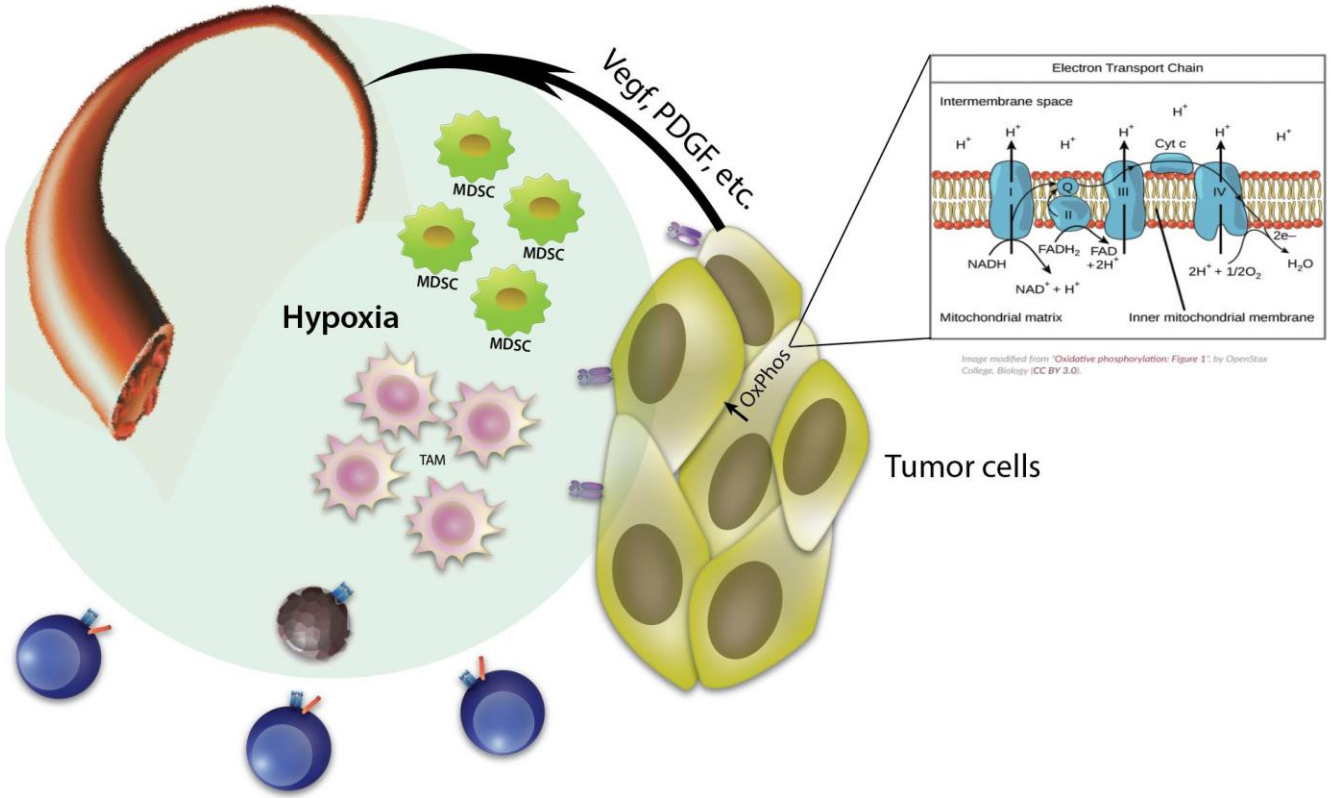
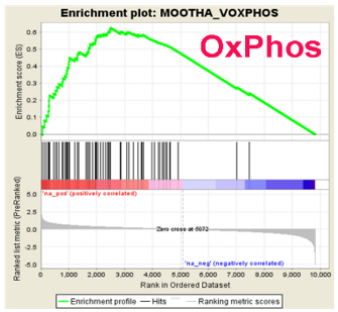
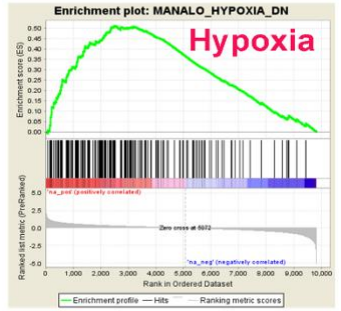


Image modified from "Oxidative phosphorylation: Figure 1", by OpenStax College, Biology (CC BY 3.0).

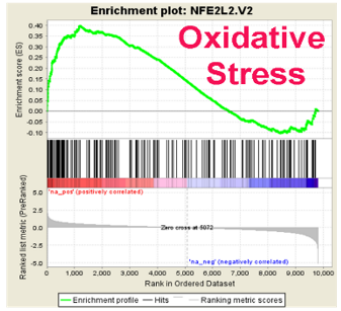
Immune-resistant melanoma elevates OxPhos metabolism but adapts to buffer resulting hypoxic and oxidative stress.



Elevated OxPhos

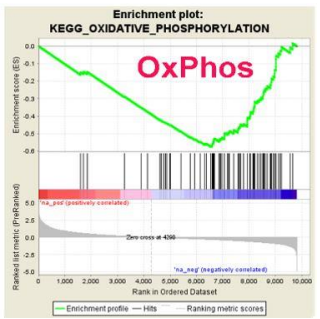


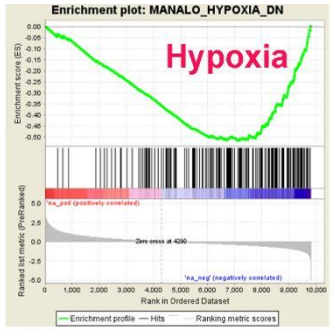
Improved adaptation to hypoxic stress.

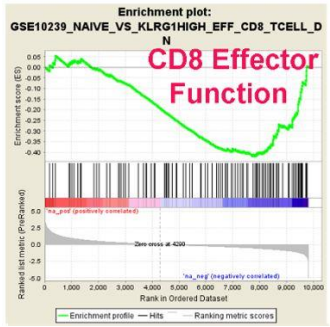


Improved buffering of oxidative stress.

The surrounding stroma, however, suffers metabolic depression and experiences elevated hypoxic stress.

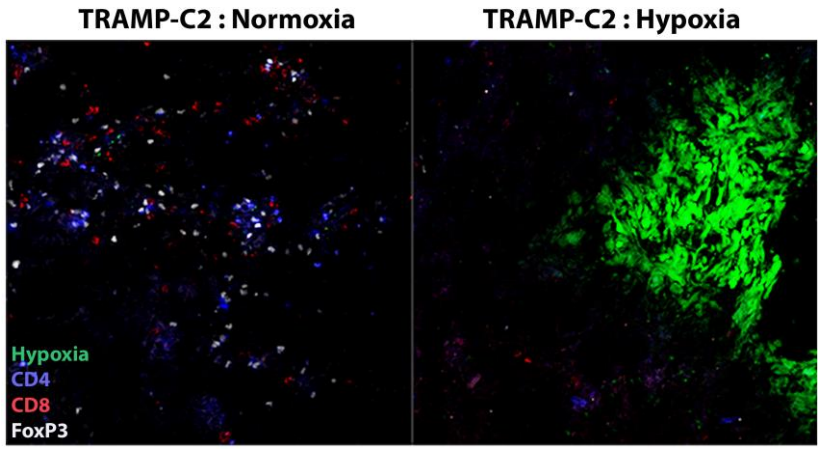




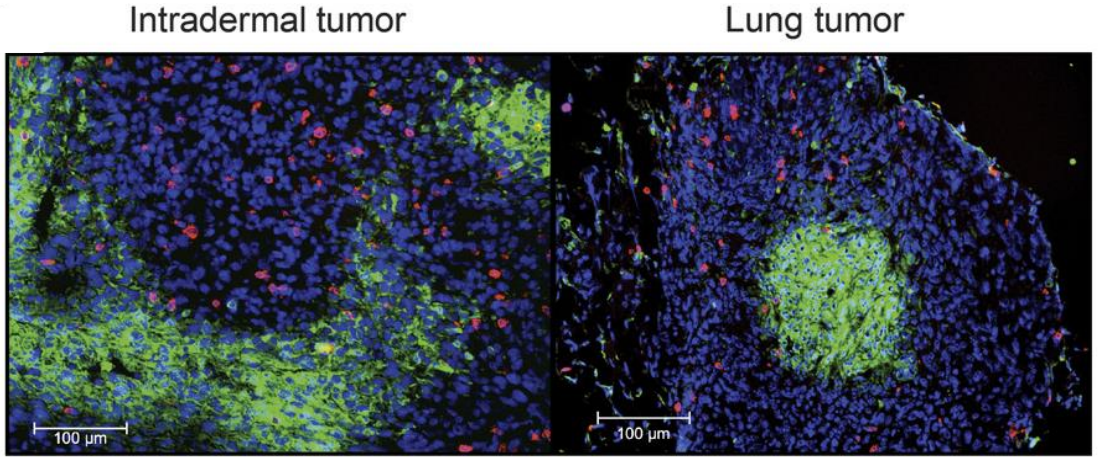


Jaiswal, A.R. and M. A. Curran, *Manuscript in Revision*.

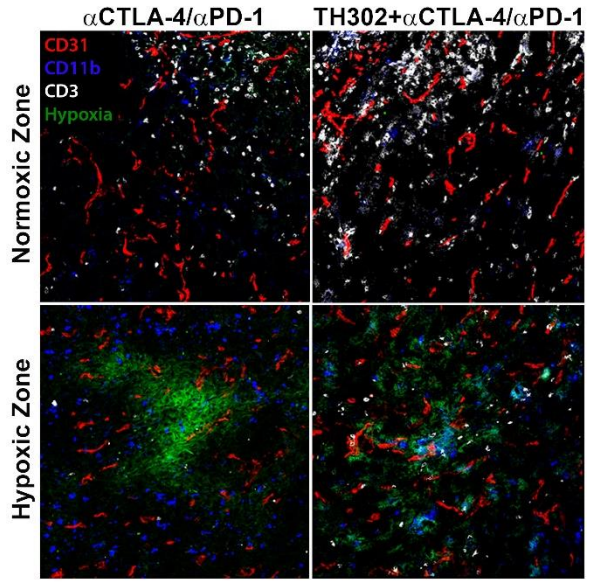
T cell are excluded from hypoxic zones of tumors.



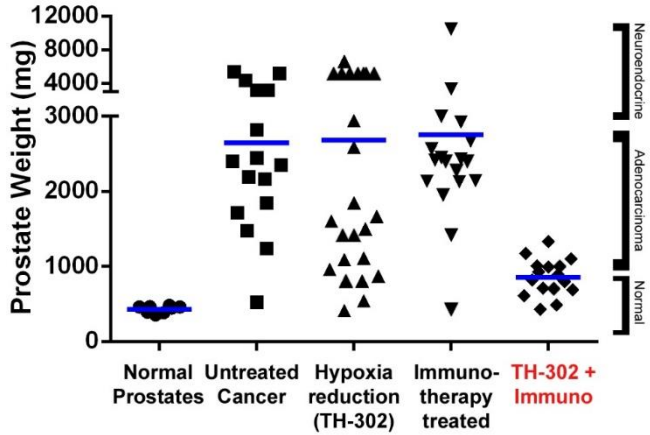
Jayaprakash, P., Ai, M., and Curran, M.A. *J Clin Invest.* 2018



Hatfield, S.M. and Sitkovsky, M.V. *Sci Trans Med.* 2015



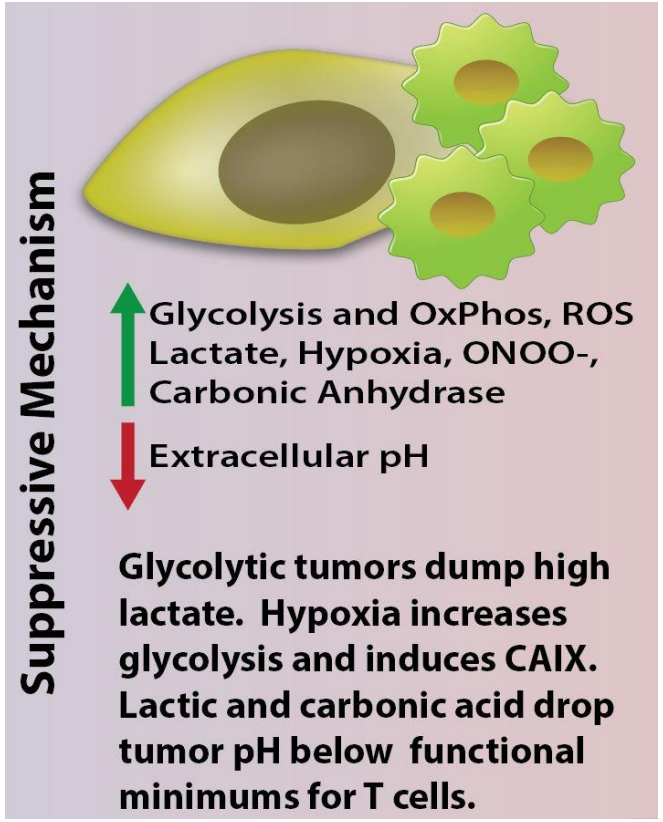
The hypoxia prodrug, TH-302 breaks down hypoxia and allows checkpoint blockade mobilized T cells to infiltrate throughout the prostate tumor.

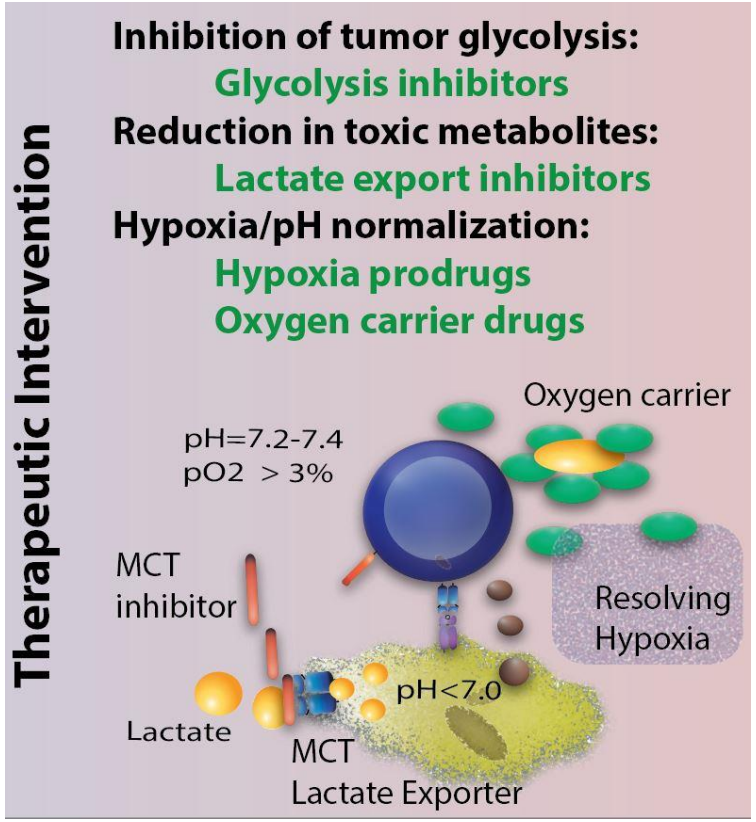


Hypoxia reduction renders checkpoint resistant TRAMP mice sensitive to CTLA-4/PD-1 blockade.

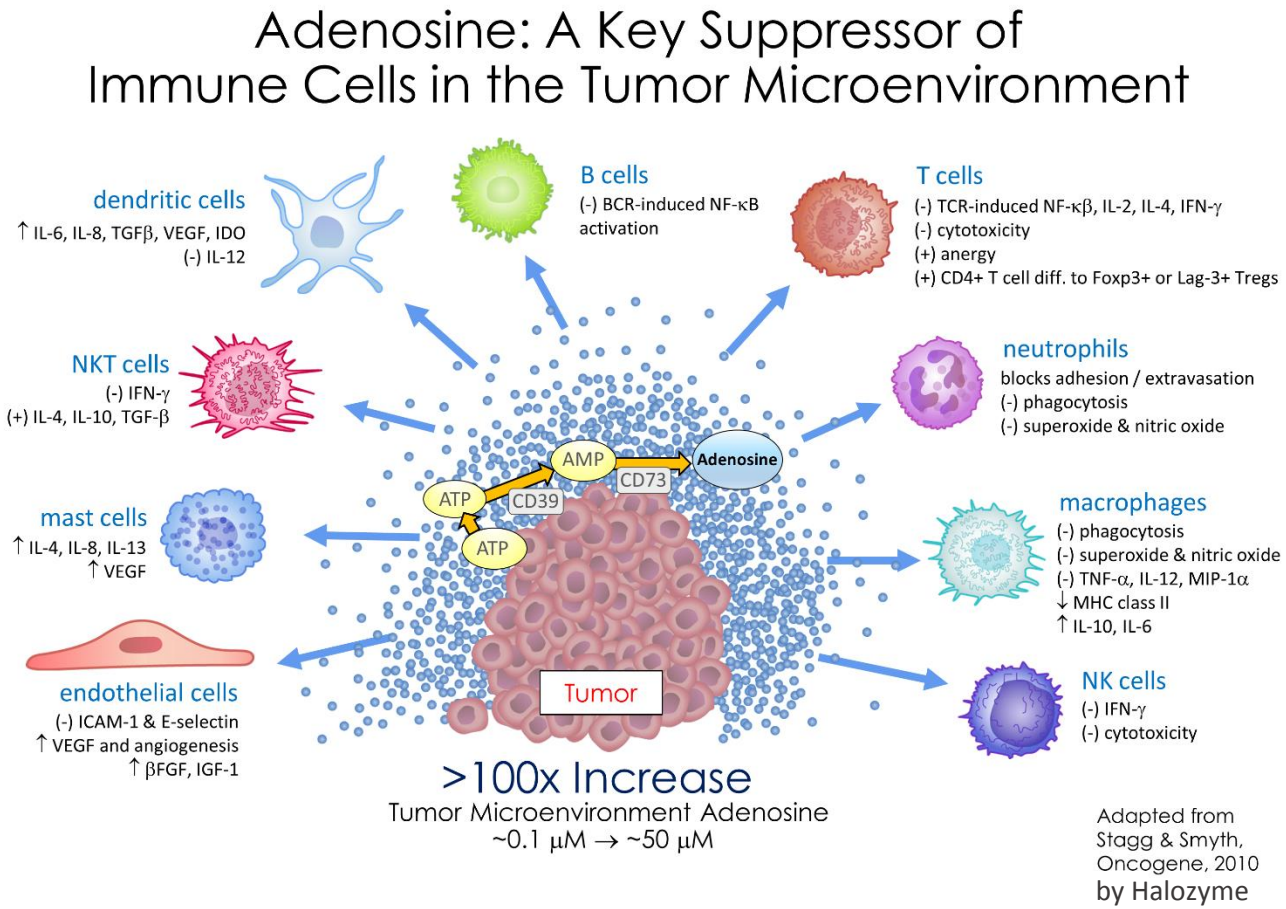
Jayaprakash, P., Ai, M., and Curran, M.A. *J Clin Invest.* 2018

Tumor glycolysis and hypoxia act to promote acidification and lactate accumulation in the TME.





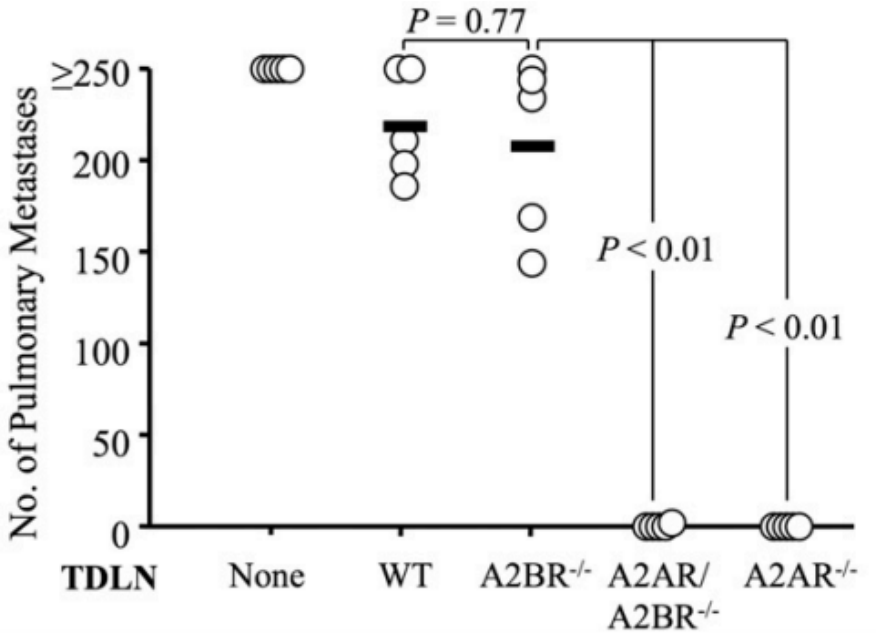
Hypoxia and recruitment of suppressive stroma result in accumulation of extracellular adenosine.



Hypoxia → HIF-1α → { CD39, CD73, Adenosine, A_{2B} AR

Adenosine inhibition improves response to T cell checkpoint blockade

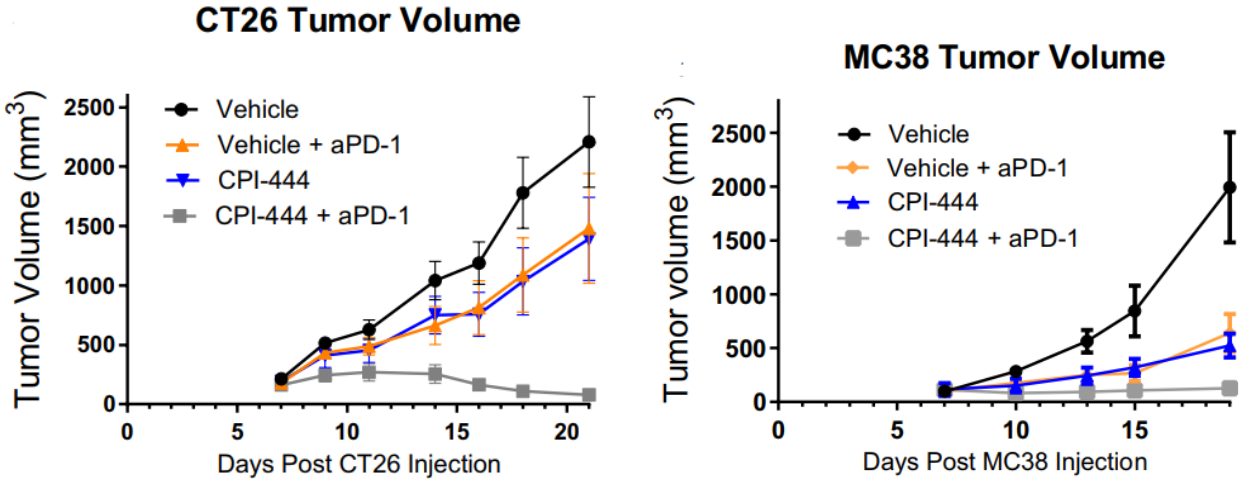
Mice lacking the adenosine A_{2A}-AR resist pulmonary engraftment of MCA205 sarcoma



A2A Adenosine Receptor Gene Deletion or Synthetic A2A Antagonist Liberate Tumor-Reactive CD8+ T Cells from Tumor-Induced Immunosuppression.

Kjaergaard J, Hatfield S, Jones G, Ohta A, Sitkovsky M.
J Immunol. 2018 Jul 15;201(2):782-791. doi: 10.4049/jimmunol.1700850. Epub 2018 May 25.

Inhibition of the A_{2A}-AR with small molecule inhibitors cooperates with T cell checkpoint blockade to reject multiple murine cancers.



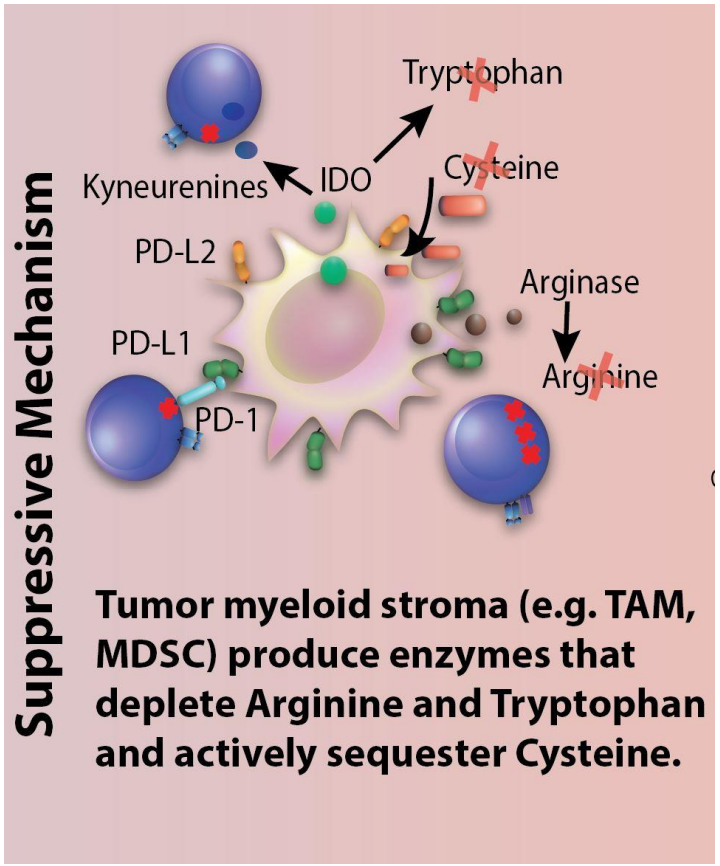
NB: CPI-444 is an oral small molecule inhibitor of A2aR

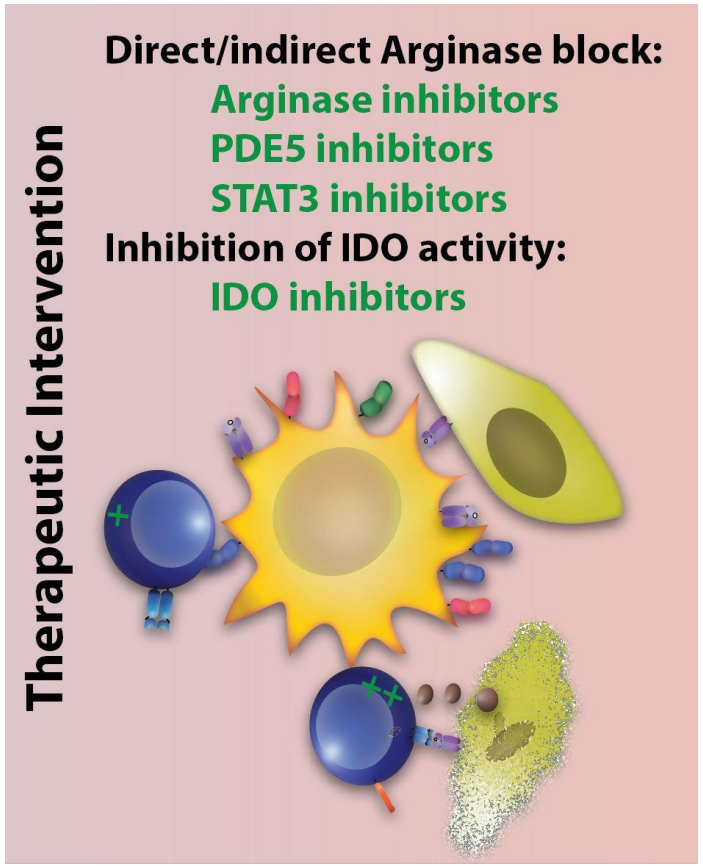
Cancer Immunol Immunother. 2018 Jun 19. doi: 10.1007/s00262-018-2186-0. [Epub ahead of print]

Inhibition of the adenosine A2a receptor modulates expression of T cell coinhibitory receptors and improves effector function for enhanced checkpoint blockade and ACT in murine cancer models.

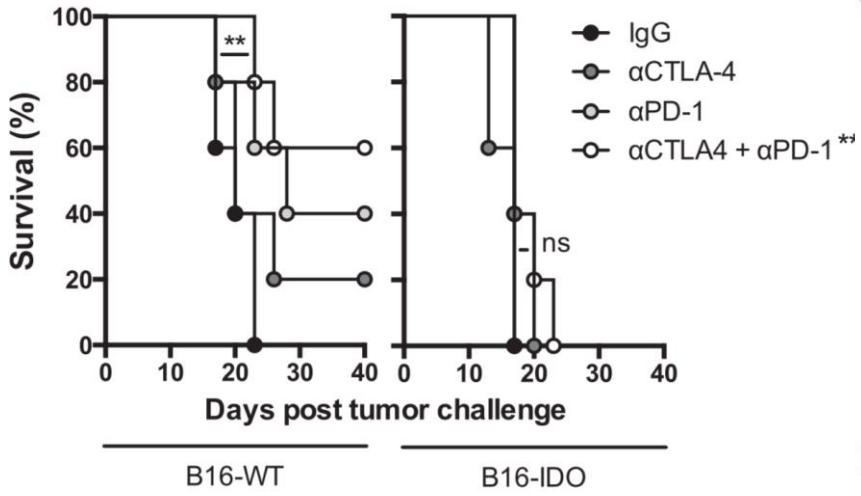
Leone RD[1], Sun IM[1], Oh MH[1], Sun IH[1], Wen J[1], Englert J[1,2], Powell JD[3].

Macrophages and MDSC potently suppress T cells through depletion of essential amino acids.

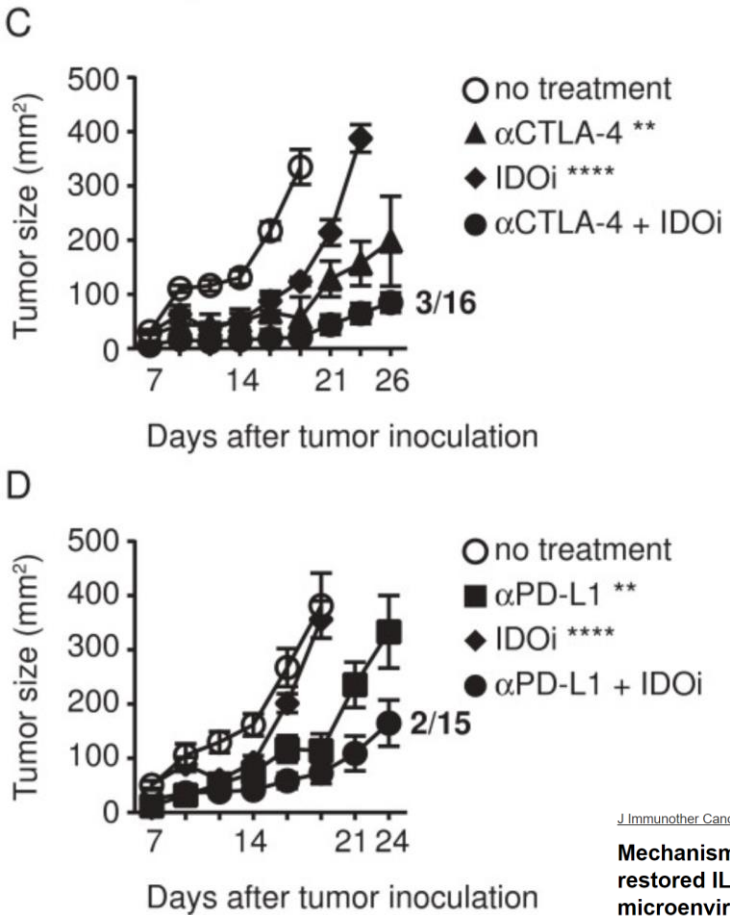


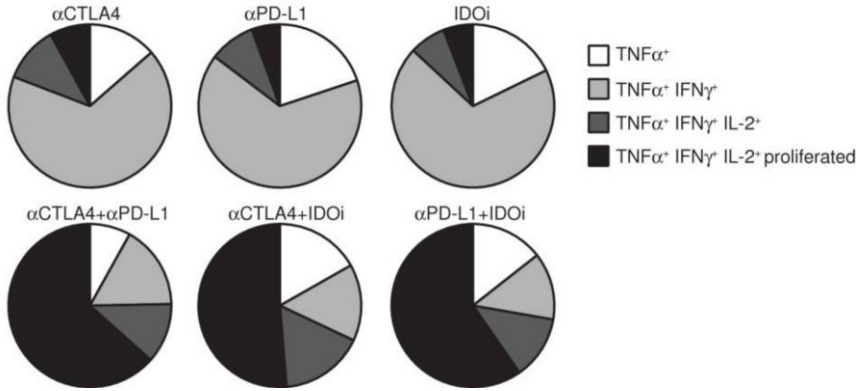


Inhibition of IDO synergizes with checkpoint blockade to reject murine melanoma tumors.



Expression of IDO confers checkpoint blockade resistance to otherwise sensitive tumors.





IDO inhibition enhances the therapeutic response to checkpoint blockade by restoring proliferation and effector function to TIL.

Tumor-expressed IDO recruits and activates MDSCs in a Treg-dependent manner

Rikke B. Holmgaard,[1] Dmitriy Zamarin,[1,2] Yanyun Li,[1] Billel Gasmi,[1] David H. Munn,[3] James P. Allison,[4] Taha Merghoub,[1,*] and Jedd D. Wolchok[1,2,5,*]

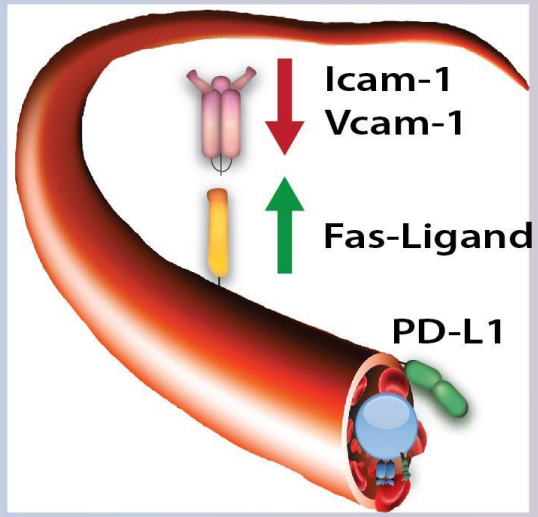
J Immunother Cancer. 2014 Feb 18;2:3. doi: 10.1186/2051-1426-2-3. eCollection 2014.

Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment.

Spranger S[1], Koblish HK[2], Horton B[1], Scherle PA[2], Newton R[2], Gajewski TF[3].

Tumors and their stroma condition vasculature to deny T cells access to the TME.

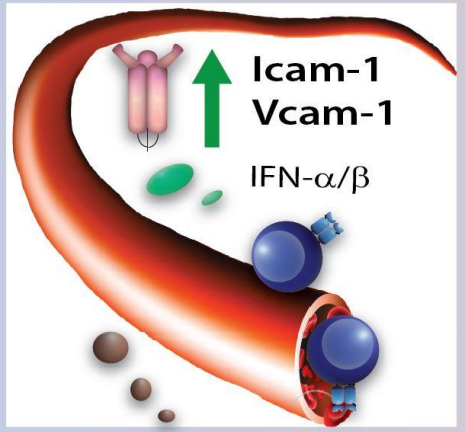
Suppressive Mechanism



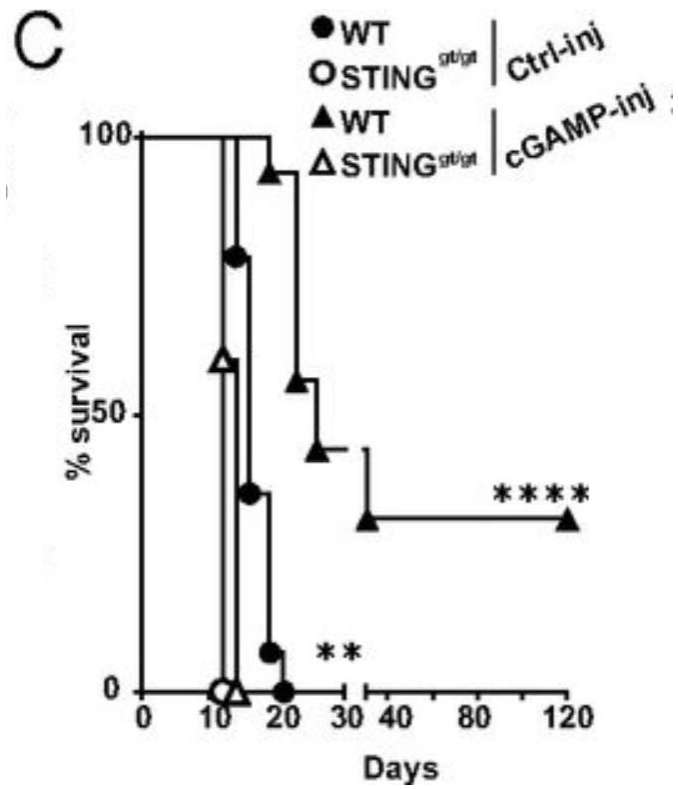
Cold tumor vasculature lacks T cell adhesion molecules and chemokine signals and may be induced to express Fas-ligand.

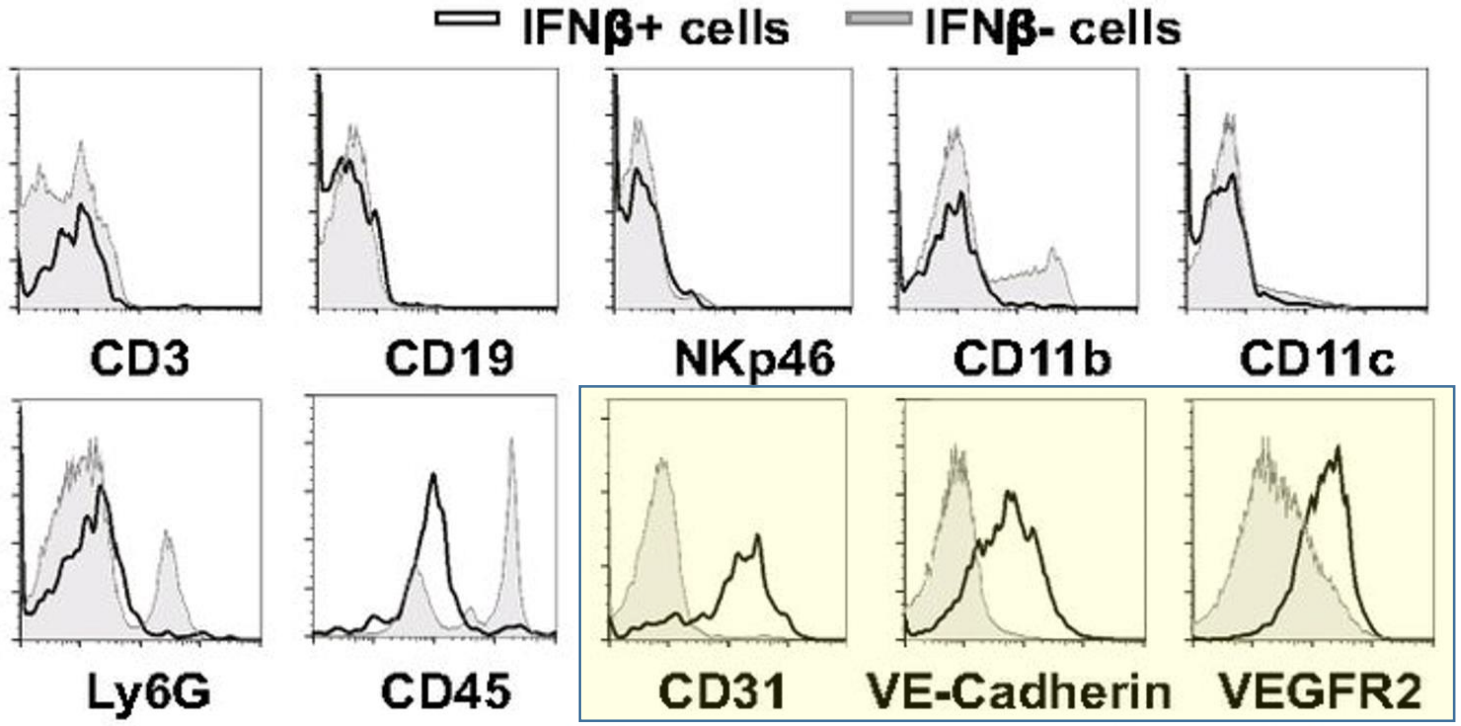
Therapeutic Intervention

Re-activation of tumor vessels and IFN-induced chemokines:
STING agonist
Blockade of vessel checkpoints:
PD-L1 antibody blockade
Angiogenic normalization:
VEGF/PDGF inhibition



Endothelial cells are among the highest Interferon producers in response to intra-tumoral STING agonist injection.





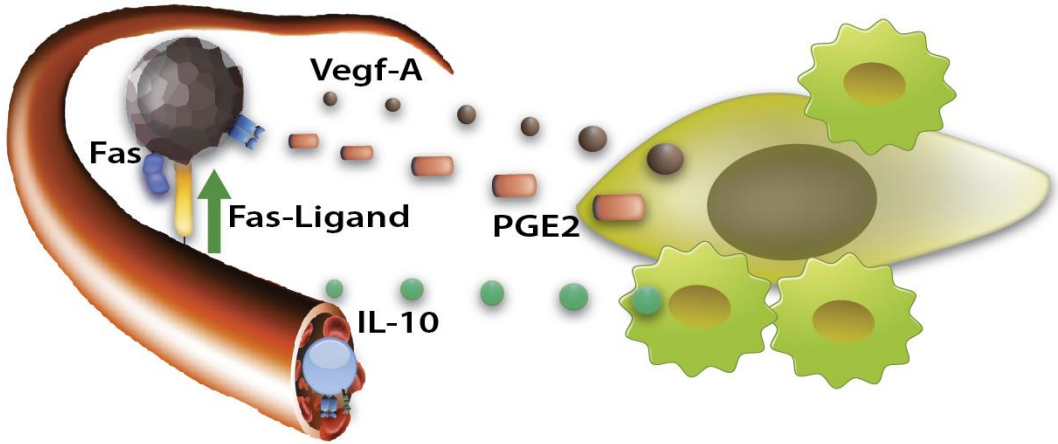
Proc Natl Acad Sci U S A. 2015 Dec 15;112(50):15408-13. doi: 10.1073/pnas.1512832112. Epub 2015 Nov 25.

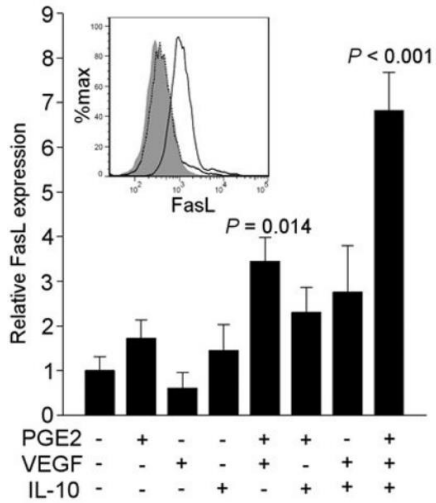
STING activation of tumor endothelial cells initiates spontaneous and therapeutic antitumor immunity.

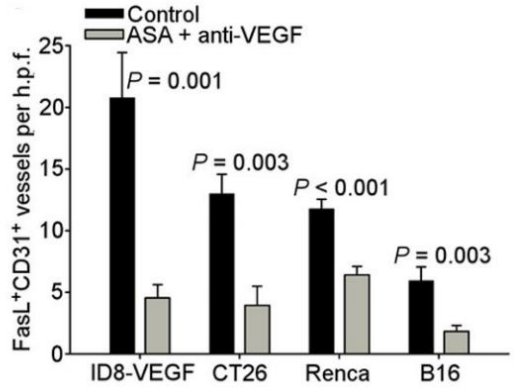
Demaria O[1], De Gassart A[2], Coso S[3], Gestermann N[1], Di Domizio J[1], Flatz L[4], Gaide O[1], Michielin O[3], Hwu P[5], Petrova TV[6], Martinon F[2], Modlin RL[7], Speiser DE[8], Gilliet M[9].

Dying to enter the TME: VEGF-A, IL-10, and PGE2 act together to induce Fas-Ligand on tumor vessels.

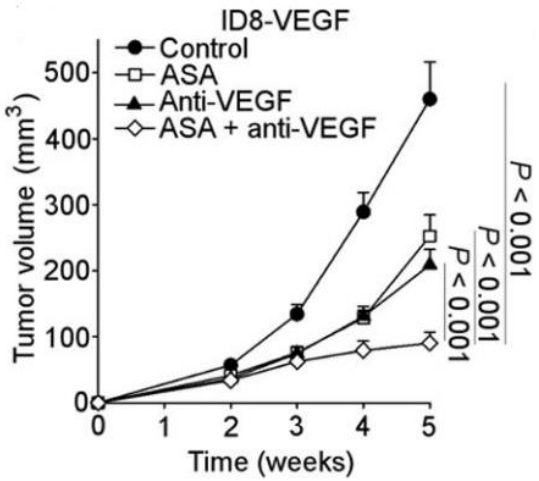
Tumors, especially hypoxic ones, produce VEGF-A, Prostaglandin E2 (PGE2) and IL-10 that induces Fas-Ligand on vessels triggering apoptosis in T cells.







Blocking PGE2 and VEGF decreases vessel Fas-Ligand



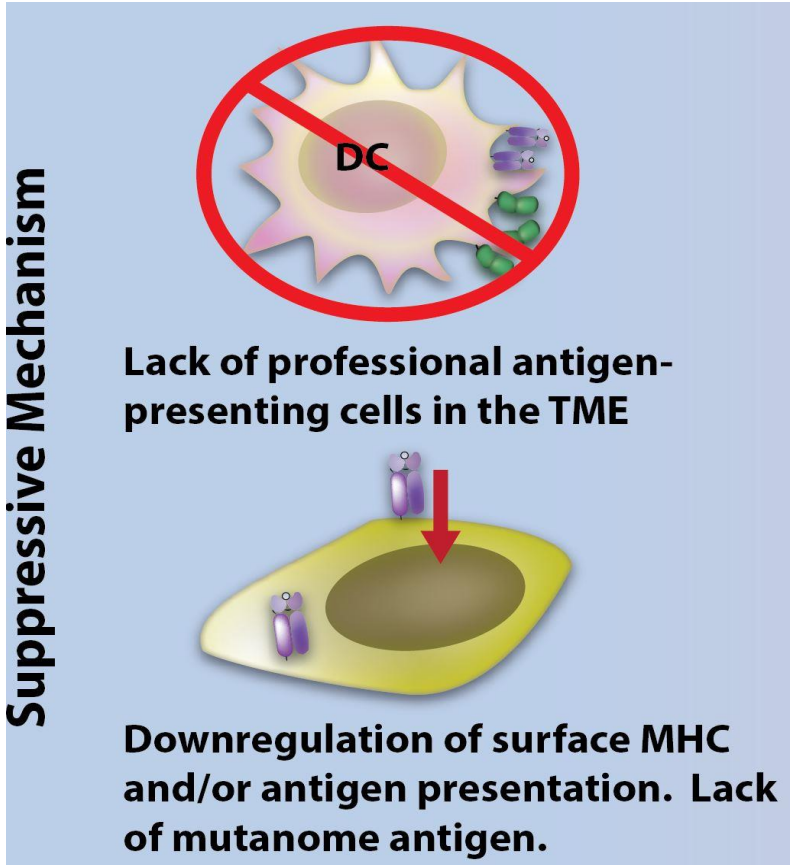
Reducing Fas-L expression by tumor vessels slows tumor growth.

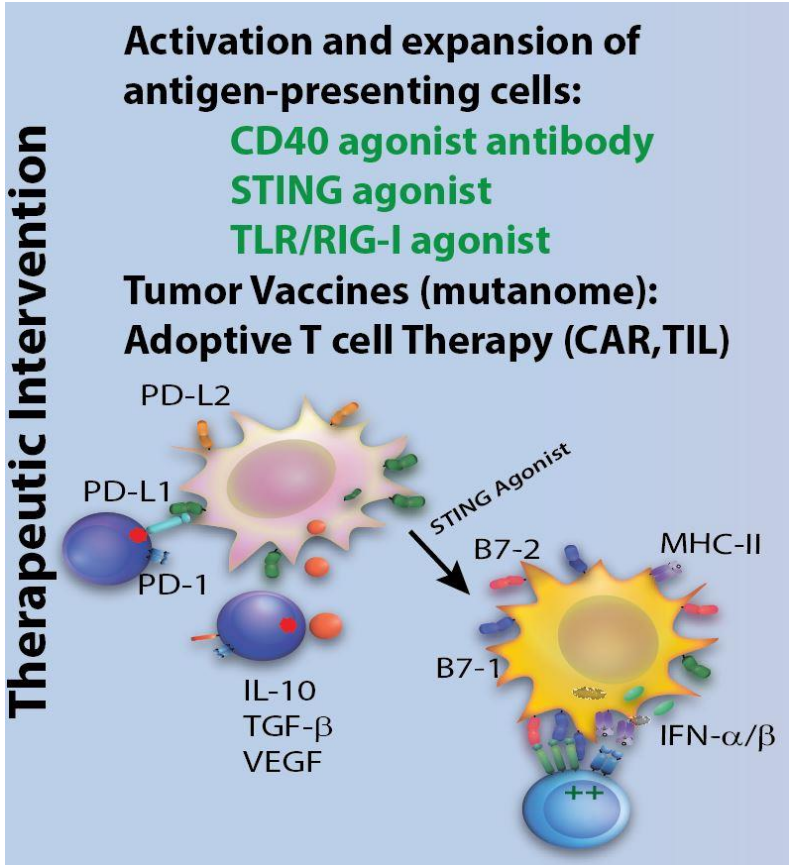
Nat Med. 2014 Jun;20(6):607-15. doi: 10.1038/nm.3541. Epub 2014 May 4.

Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors.

Motz GT[1], Santoro SP[1], Wang LP[2], Garrabrant T[1], Lastra RR[2], Hagemann IS[2], Lal P[2], Feldman MD[2], Benencia F[1], Coukos G[3].

Tumors minimize their immune footprint and deprive T cells of local support through dendritic cell exclusion.





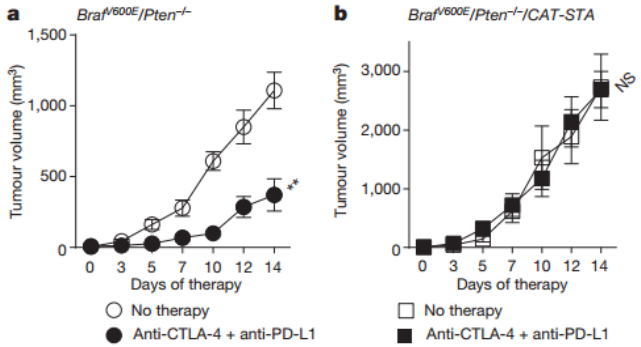
Restoration of antigen presenting cells can reverse immune ignorance in "cold" tumors.

LETTER

doi:10.1038/nature14404

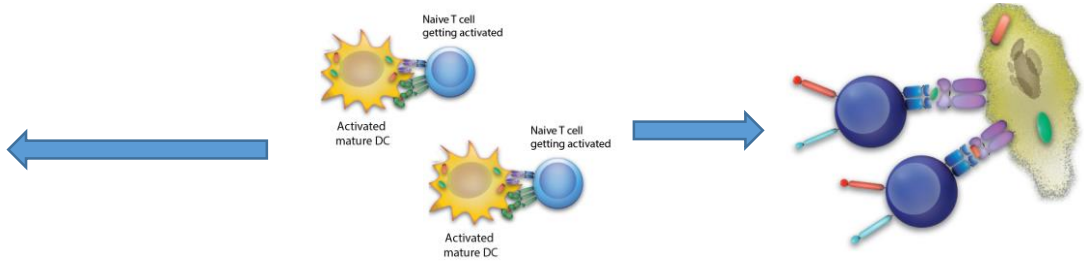
Melanoma–intrinsic β–catenin signalling prevents anti–tumour immunity

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

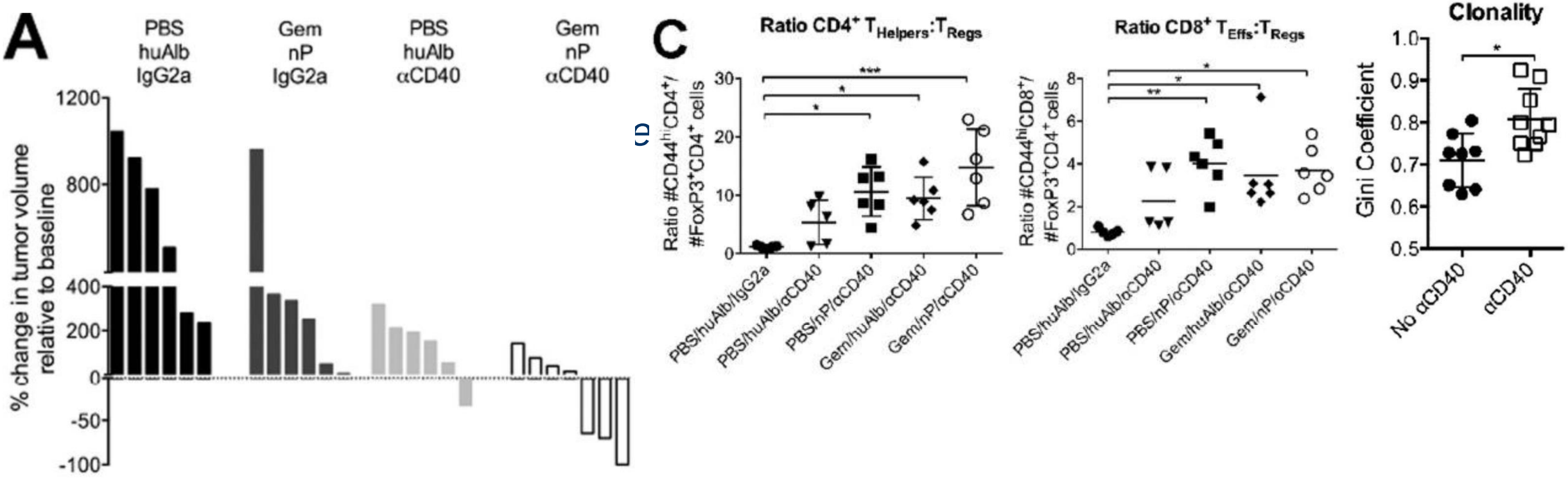


+β-Catenin = ~~CCL4~~ = no  = no tumor antigen presented to T cells = Immune ignorance

Re-introducing DCs and restoring immune infiltration converts "cold" melanoma back to "hot".



CD40 activation can re-activate myeloid antigen presentation in "cold" PDAC mobilizing a more diverse T cell response.

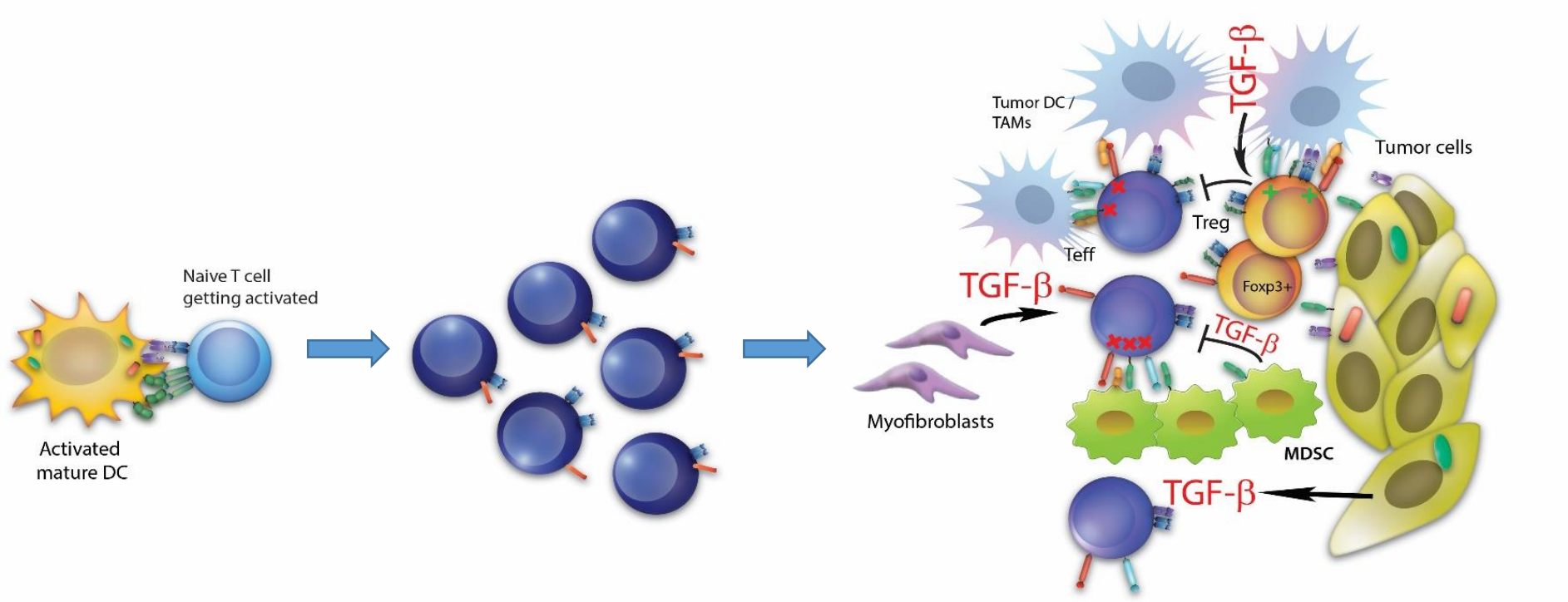


Cell Rep. 2016 Jun 21;15(12):2719-32. doi: 10.1016/j.celrep.2016.05.058. Epub 2016 Jun 9.

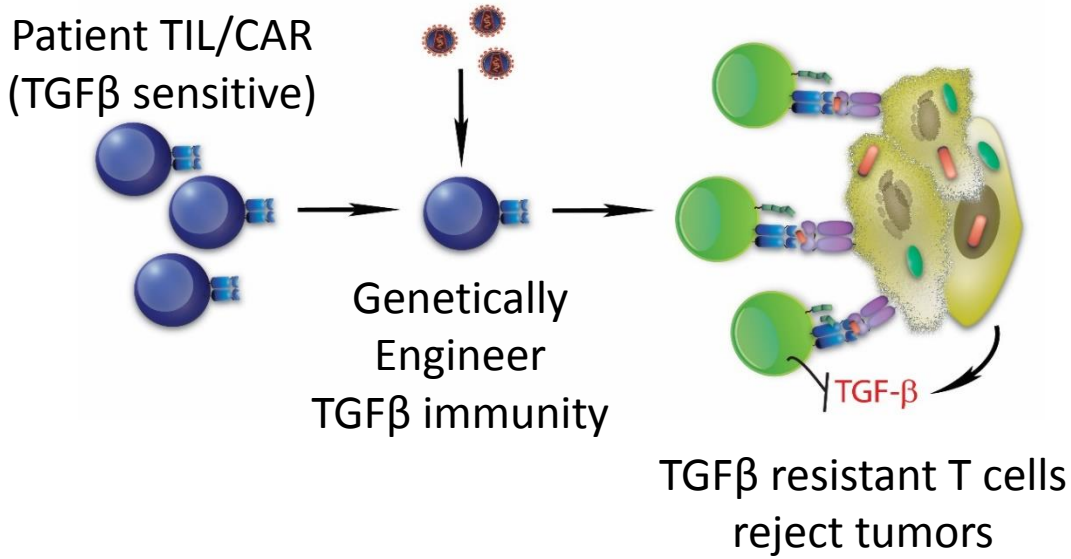
CD40 Stimulation Obviates Innate Sensors and Drives T Cell Immunity in Cancer.

Byrne KT[1], Vonderheide RH[2].

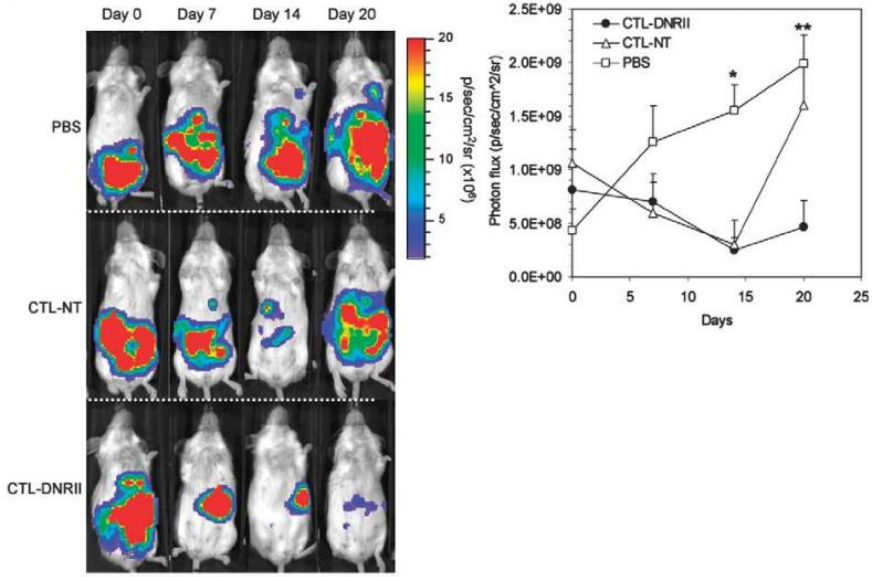
Transforming growth factor β (TGF-β) dampens immunity throughout the microenvironment.



Adoptively-transferred T cells can be engineered to resist TGF-β induced immune suppression.



Only EBV-specific T cells rendered Immune to TGF-β can control tumor.

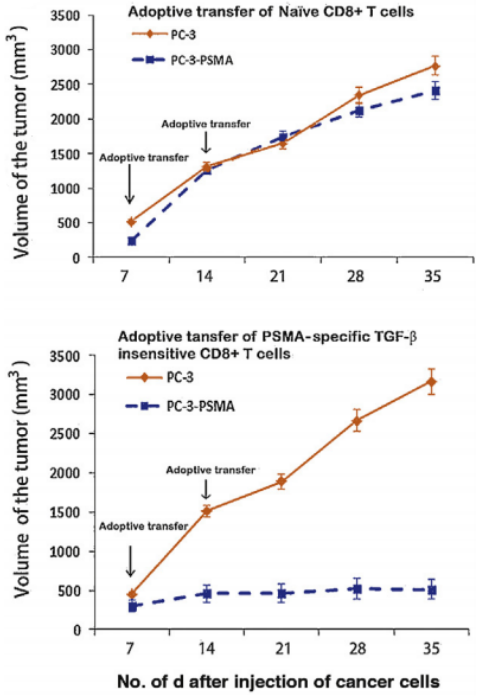


J Immunother. 2008 Jun;31(5):500-5. doi: 10.1097/CJI.0b013e318177092b.

Antitumor activity of EBV-specific T lymphocytes transduced with a dominant negative TGF-beta receptor.

Foster AE[1], Dotti G, Lu A, Khalil M, Brenner MK, Heslop HE, Rooney CM, Bollard CM.

Also for PSMA-specific TCR-transduced TIL



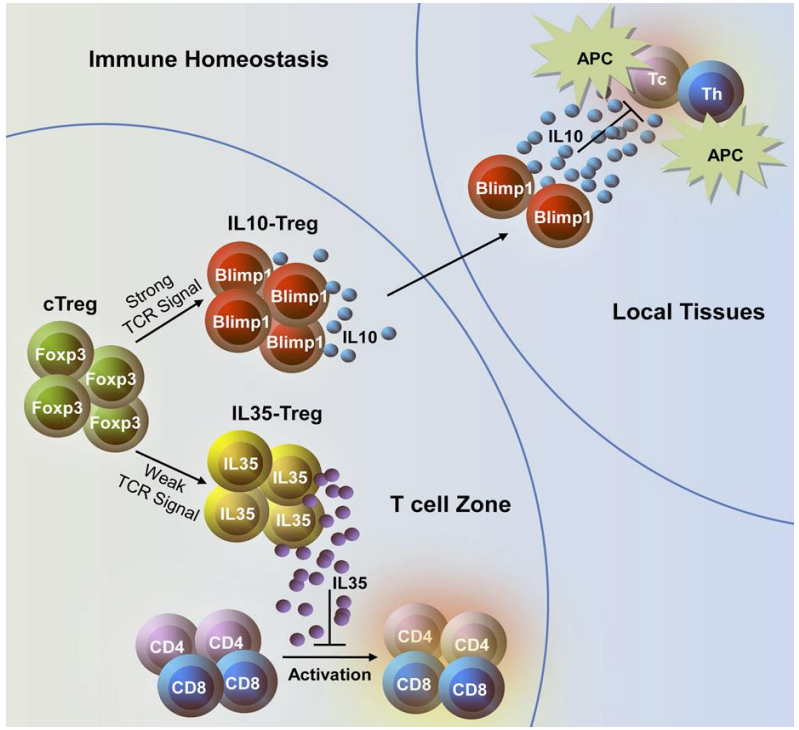
Eur Urol. 2018 May;73(5):648-652. doi: 10.1016/j.eururo.2017.12.008. Epub 2017 Dec 21.

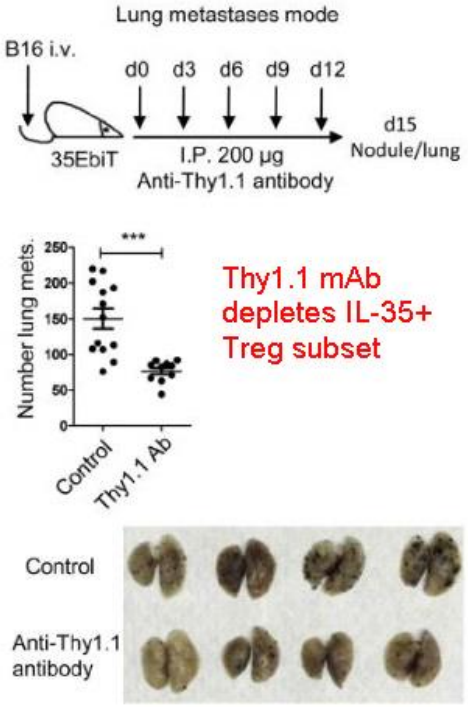
Efficacy Against Human Prostate Cancer by Prostate-specific Membrane Antigen-specific, Transforming Growth Factor-β Insensitive Genetically Targeted CD8+ T-cells Derived from Patients with Metastatic Castrate-resistant Disease.

Zhang Q[1], Helfand BT[2], Carneiro BA[3], Qin W[4], Yang XJ[5], Lee C[6], Zhang W[7], Giles FJ[3], Cristofanilli M[8], Kuzel TM[9].

Regulatory T cells (Treg) elaborate additional immuno-regulatory cytokines.

In addition to TGF-β, Treg produce either IL-10 or IL-35 which further suppress Teff.



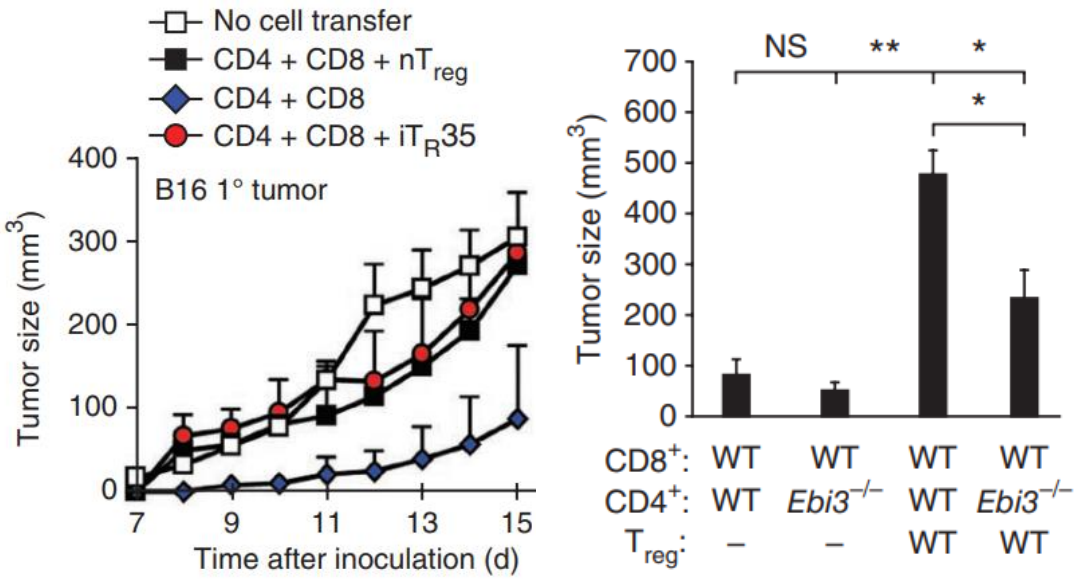


Cell Rep. 2017 Nov 14;21(7):1853-1869. doi: 10.1016/j.celrep.2017.10.090.

Reciprocal Expression of IL-35 and IL-10 Defines Two Distinct Effector Treg Subsets that Are Required for Maintenance of Immune Tolerance.

Wei X[1], Zhang J[2], Gu Q[1], Huang M[1], Zhang W[2], Guo J[2], Zhou X[3].

IL-35 producing Treg significantly suppress anti-tumor T cell responses.



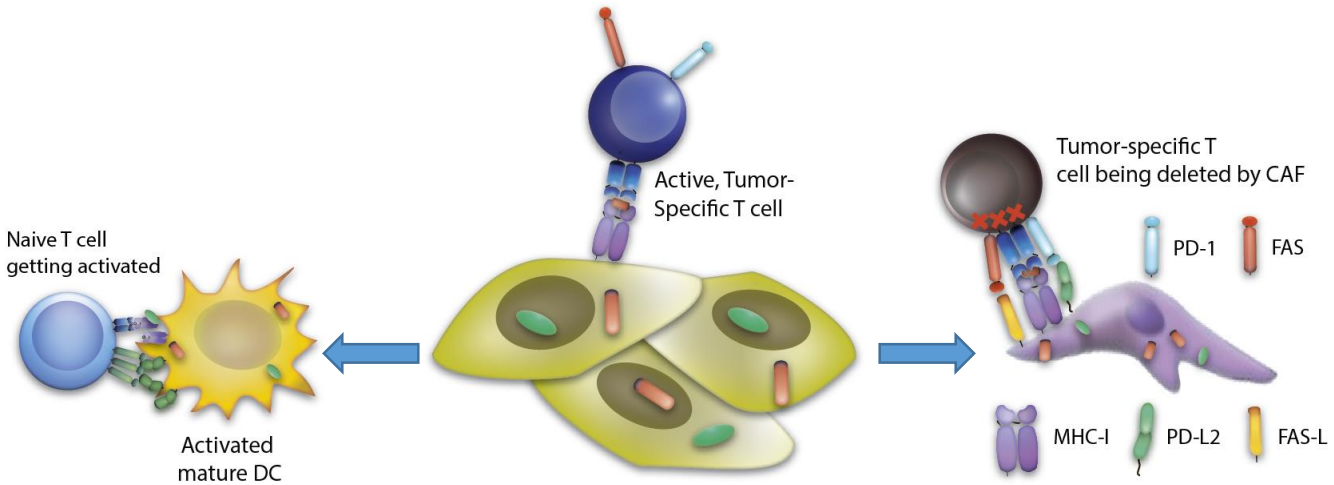
Nat Immunol. 2010 Dec;11(12):1093-101. doi: 10.1038/ni.1952. Epub 2010 Oct 17.

IL-35-mediated induction of a potent regulatory T cell population.

Collison LW[1], Chaturvedi V, Henderson AL, Giacomin PR, Guy C, Bankoti J, Finkelstein D, Forbes K, Workman CJ, Brown SA, Rehg JE, Jones ML, Ni HT, Artis D, Turk MJ, Vignali DA.

Cancer-associated fibroblasts (CAF) can kill tumor-specific CD8 T cells.

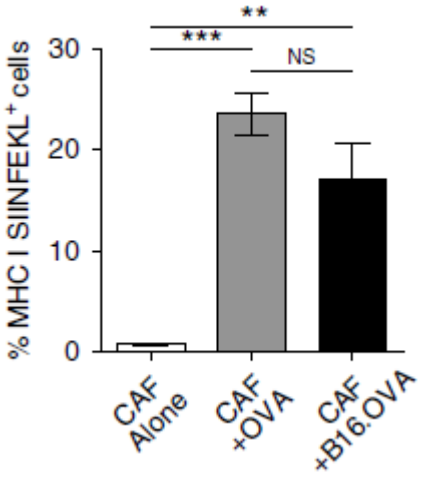
CAF can cross-present antigen and delete tumor-specific T cells

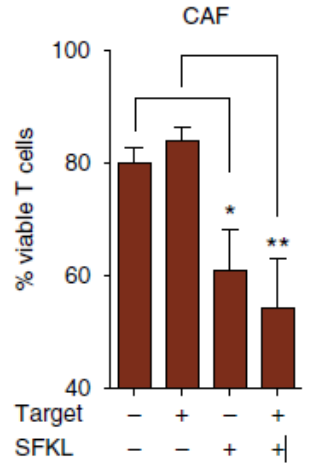


Nat Commun. 2018 Mar 5;9(1):948. doi: 10.1038/s41467-018-03347-0.

Cancer-associated fibroblasts induce antigen-specific deletion of CD8 + T Cells to protect tumour cells.

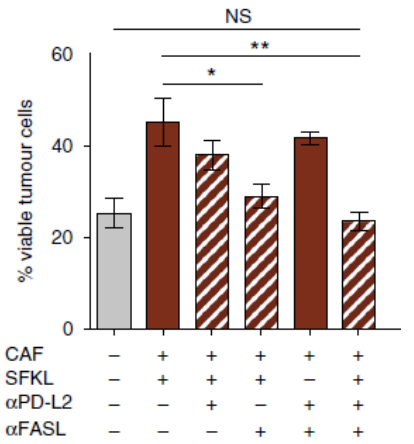
Lakins MA[1], Ghorani E[1], Munir H[1], Martins CP[1], Shields JD[2].





Deletion of T cells requires target antigen and CAF but not the presence of the tumor

Exogenous or Tumor-derived Ovalbumin is processed by CAF and the SIINFEKL peptide presented in surface MHCI



Both PD-L2 and FAS-ligand expressed by CAF help delete T cells and protect tumor.

Lessons and Take Home Messages

1. The majority of tumors remain resistant to T cell checkpoint blockade.
2. Tumor cells, myeloid stroma, regulatory T cells, and cancer-associated fibroblasts can all suppress anti-tumor immunity.
3. Extrinsic T cell suppression can be reversed, but knowing the relevant mechanisms operating in a given cancer will be critical to selecting the most effective therapeutic combination.