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November 8-12
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Society for Immunotherapy of Cancer

November 8-12 • NATIONAL HARBOR, MD

SITC 2017

Targeting Regulatory Molecules in Cancer Therapy: New Insights and Opportunities

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Presenter Disclosure Information

Michael A. Curran

The following relationships exist related to this presentation:

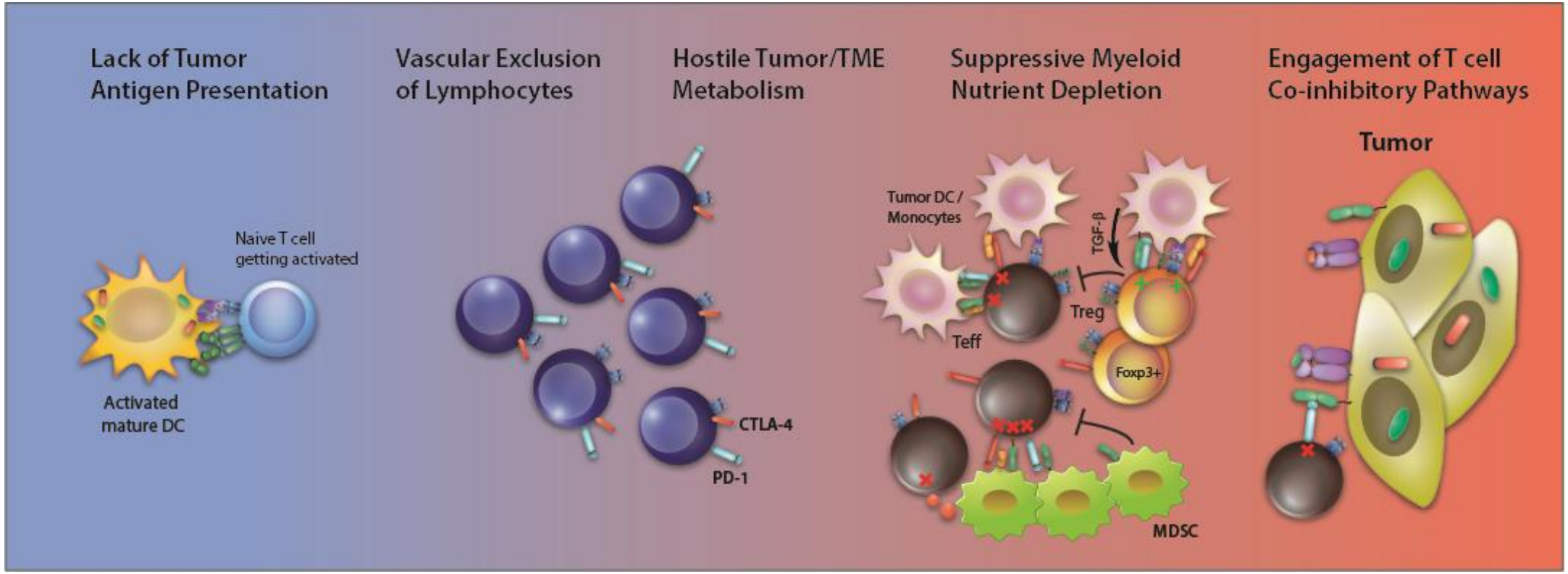
Agenus, Consultant
ImmunOS, Consultant
ImmunoMet, Consultant
Innovio, Consultant
OncoResponse, Consultant
Pieris, Consultant

Ionis, Research Alliance

Goals

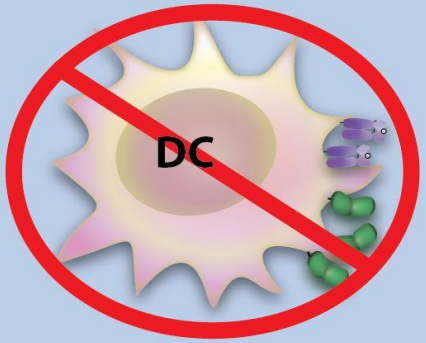
1. Understand the multiple layers of tumor immune suppression across “cold” to “hot” microenvironments.
2. Become familiar with the approved and experimental drugs designed to overcome various aspects of each of these suppressive mechanisms.
3. Develop a paradigm for assembling rational combinations of these agents.

Tumors suppress T cell responses across multiple phases from activation to entry to viability to function.

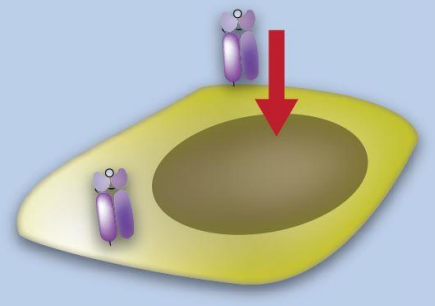


"Cold" tumors often lack in visible antigen or antigen-presenting cells resulting in immune ignorance.

Suppressive Mechanism



Lack of professional antigen-presenting cells in the TME



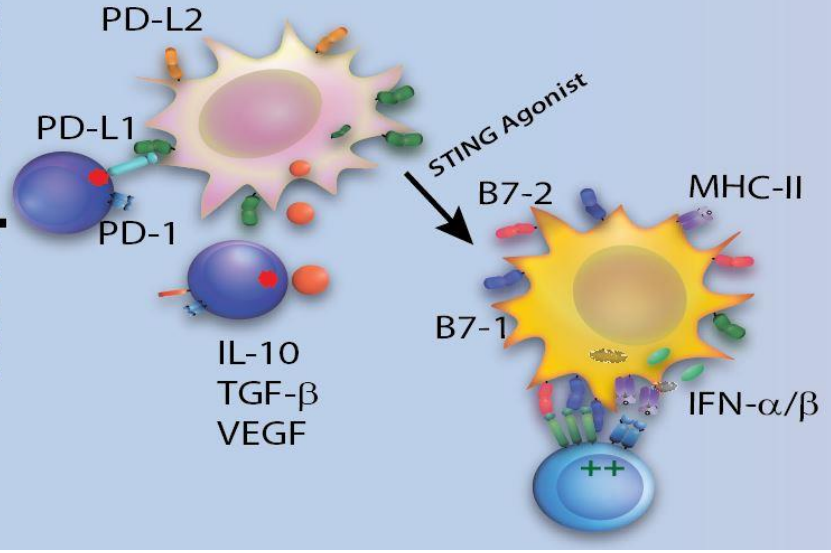
Downregulation of surface MHC and/or antigen presentation. Lack of mutanome antigen.

Therapeutic Intervention

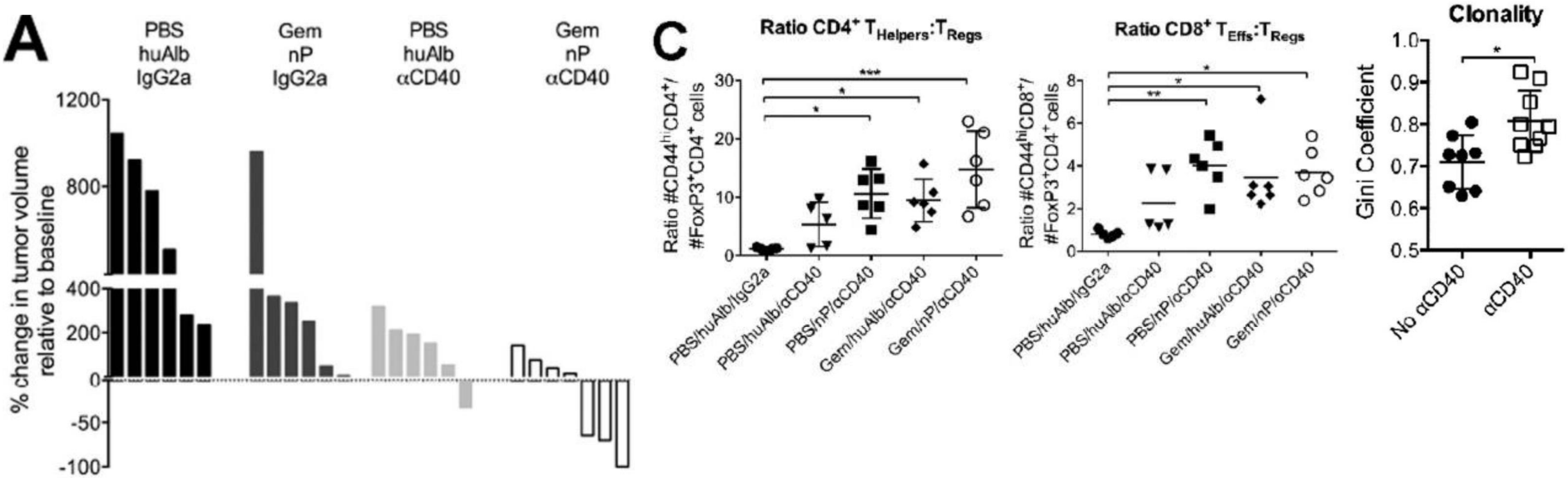
Activation and expansion of antigen-presenting cells:

CD40 agonist antibody
STING agonist
TLR/RIG-I agonist

Tumor Vaccines (mutanome):
Adoptive T cell Therapy (CAR,TIL)



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



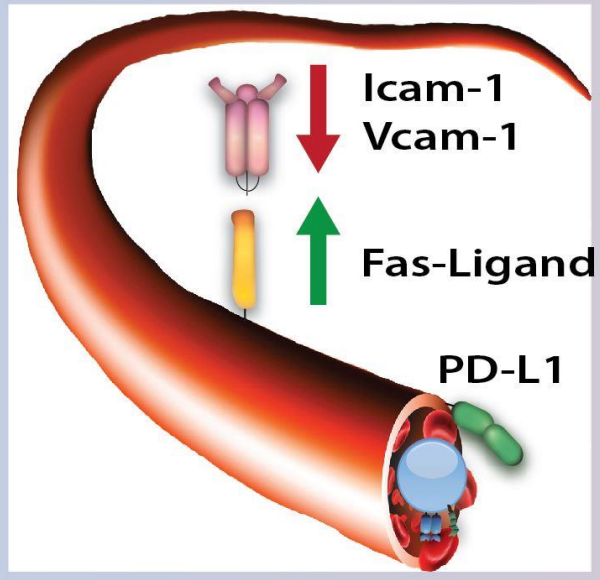
Cell Rep. 2016 Jun 21;15(12):2719-32. doi: 10.1016/j.celrep.2016.05.058. Epub 2016 Jun 9.

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

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

Tumor vasculature often lacks adhesion molecules and chemokines to support T cell arrest and extravasation.

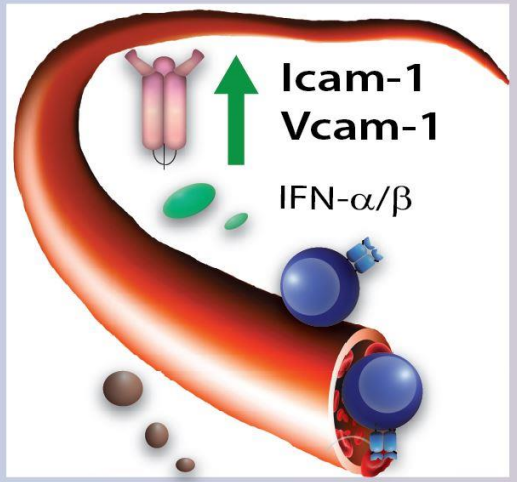
Suppressive Mechanism



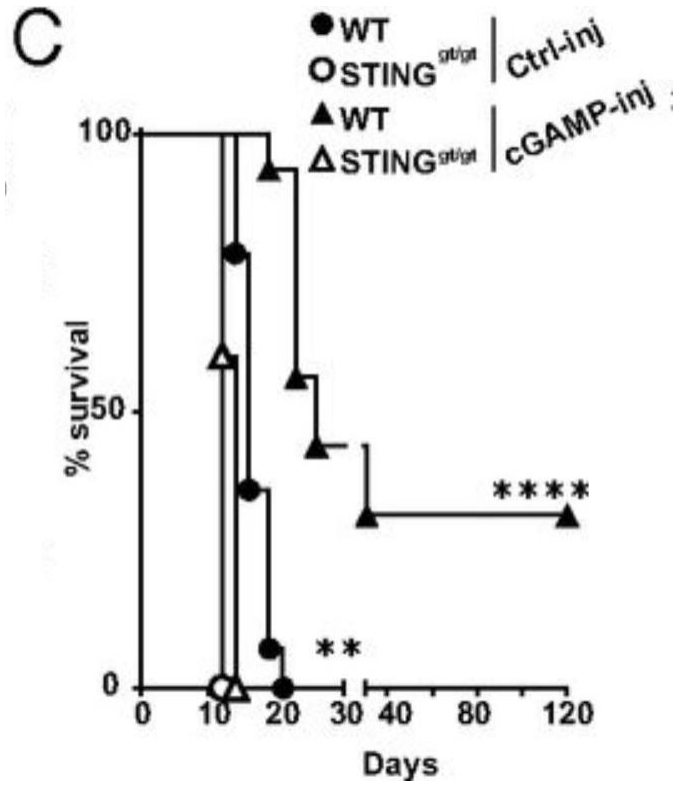
Cold tumor vasculature lacks T cell adhesion molecules and chemokine signals and may be induced to express Fas-ligand.

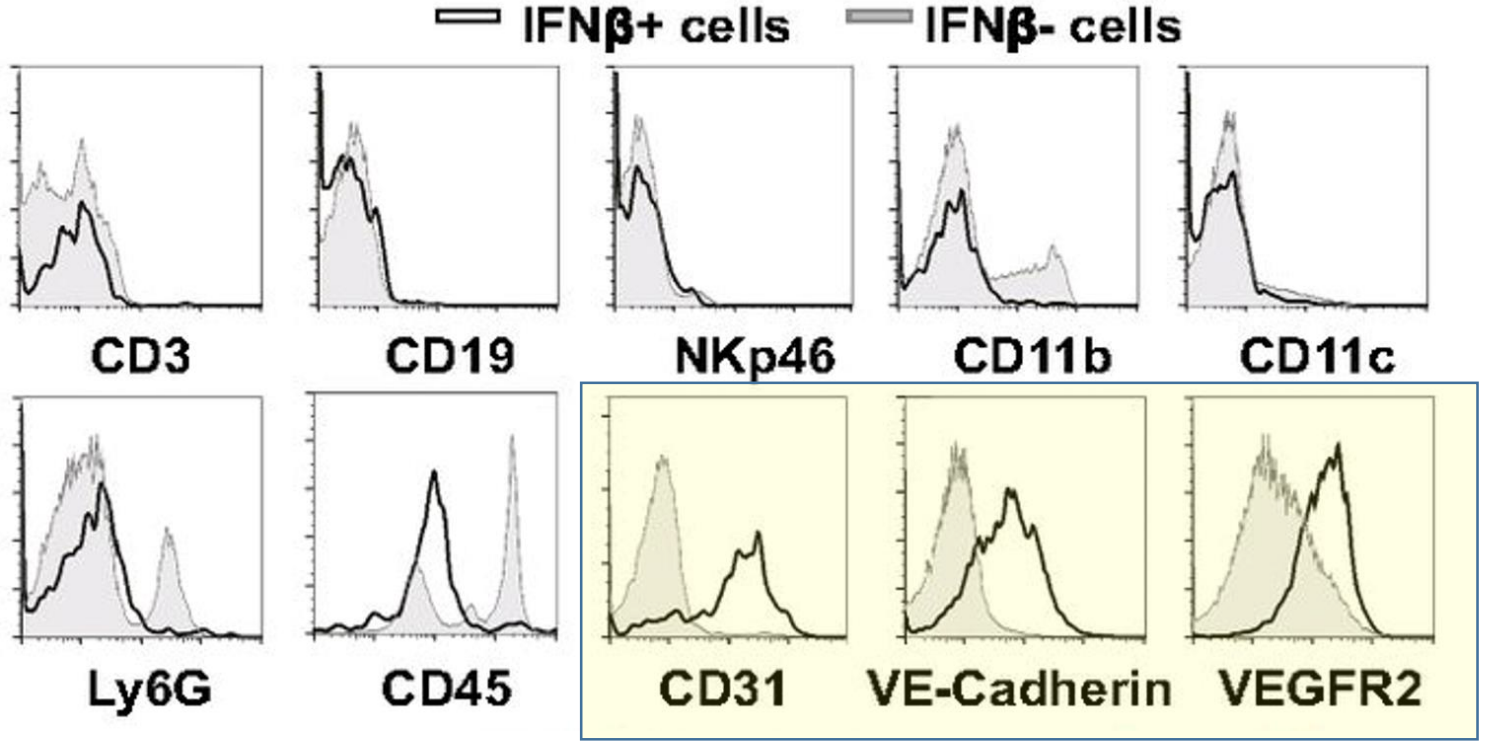
Therapeutic Intervention

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 IFN producers in response to intra-tumoral STING agonist injection.





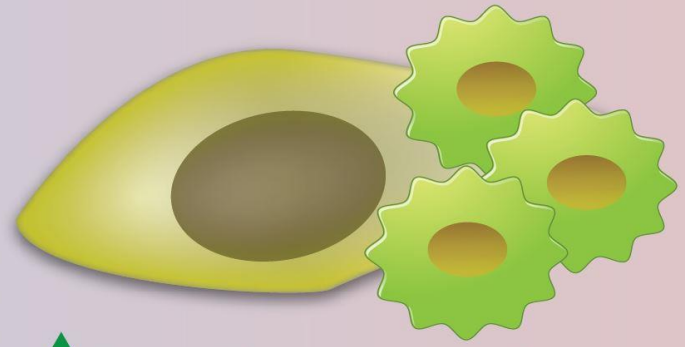
Proc Natl Acad Sci U S A. 2015 Dec 15;112(50):15408-13. doi: 10.1073/pnas.1512832112. Epub 2015 Nov 25.

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].

Tumors outcompete T cells for essential nutrients and create a milieu averse to effector function and persistence.

Suppressive Mechanism



↑ Gluc, Glut consumption, EC Lactate, Hypoxia, ROS, ONOO-

↓ Extracellular pH

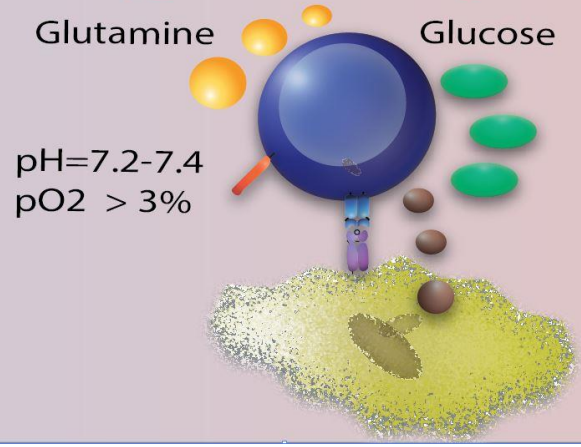
High tumor glycolysis depletes "fuel" from the TME starving T cells of energy. Low pH and high toxic metabolites induce T cell anergy and apoptosis.

Therapeutic Intervention

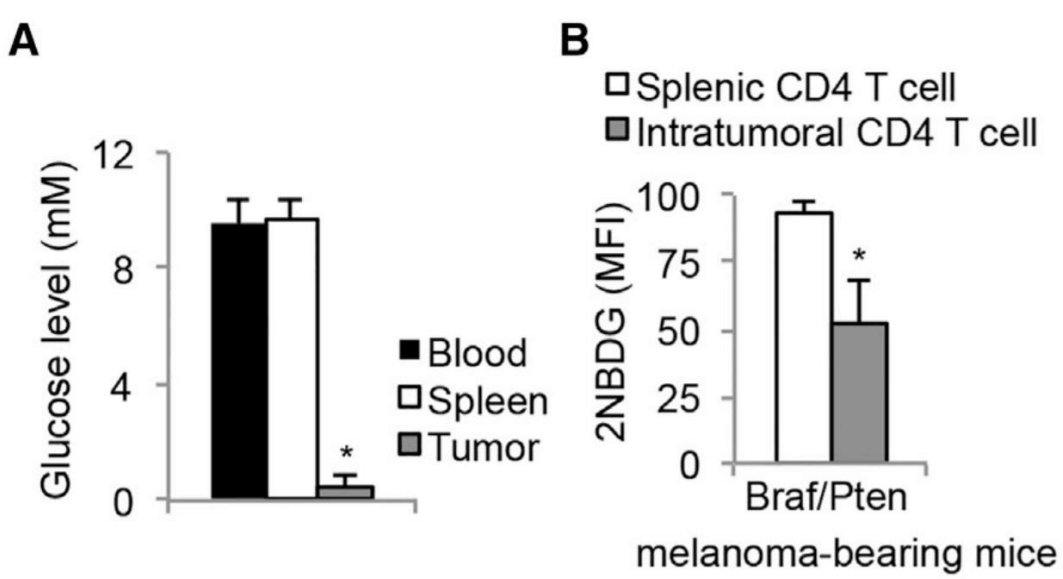
Inhibition of tumor metabolism:
- Glutaminase inhibitors
- Glycolysis inhibitors
- OxPhos inhibitors?

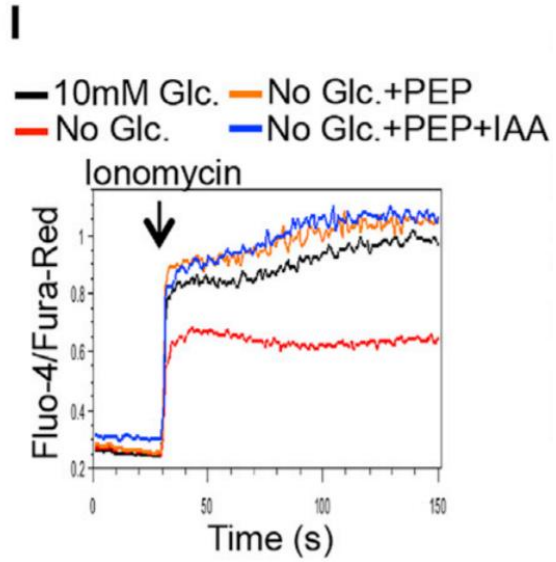
Reduction in toxic metabolites:
- Lactate export inhibitors

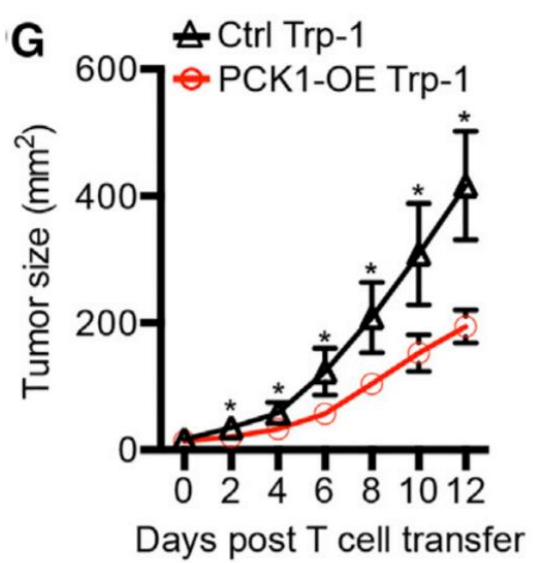
Hypoxia/pH normalization:
- Hypoxia prodrugs
- Oxygen carrier drugs



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.

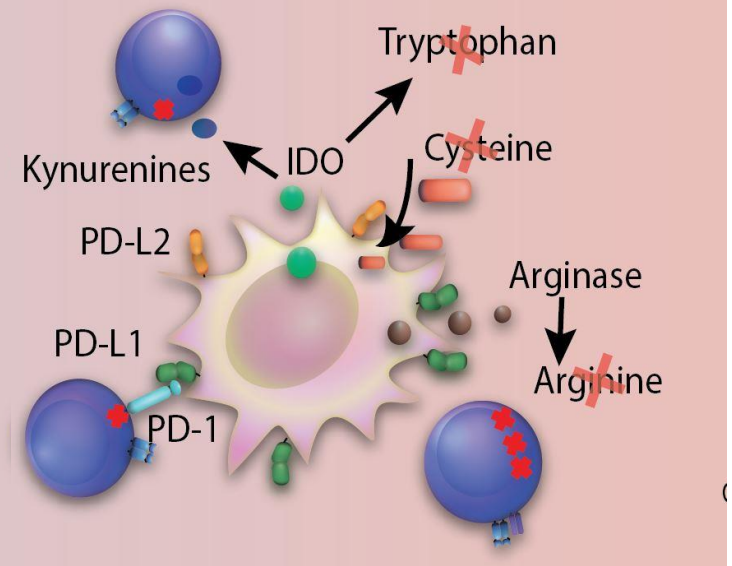
Cell. 2015 Sep 10;162(6):1217-28. doi: 10.1016/j.cell.2015.08.012. Epub 2015 Aug 27.

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].

Suppressive myeloid stroma depletes critical amino acids from the microenvironment.

Suppressive Mechanism



Tumor myeloid stroma (e.g. TAM, MDSC) produce enzymes that deplete Arginine and Tryptophan and actively sequester Cysteine.

Therapeutic Intervention

Direct/indirect Arginase block:

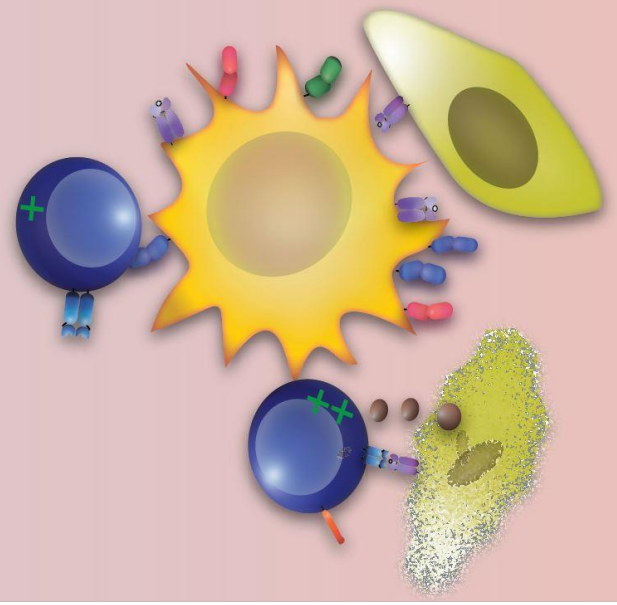
Arginase inhibitors

PDE5 inhibitors

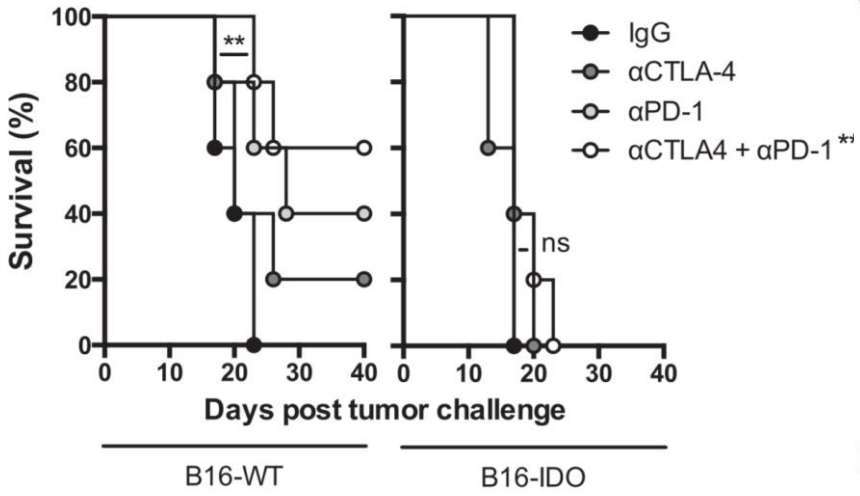
STAT3 inhibitors

Inhibition of IDO activity:

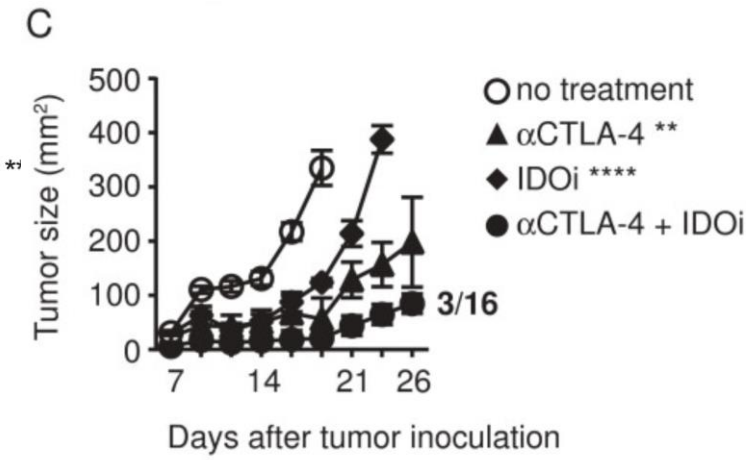
IDO inhibitors

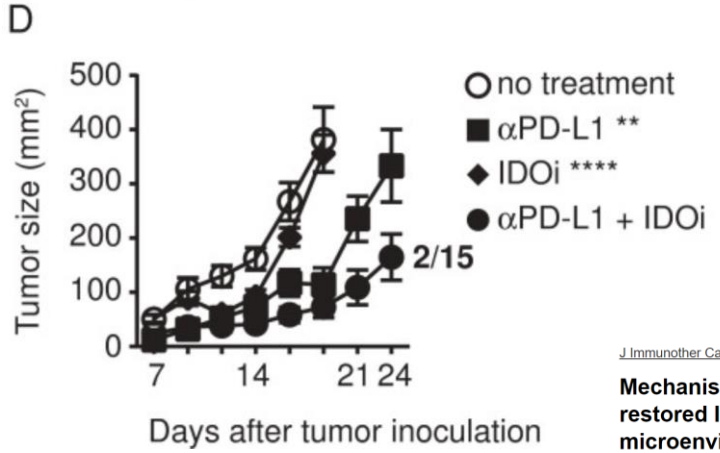


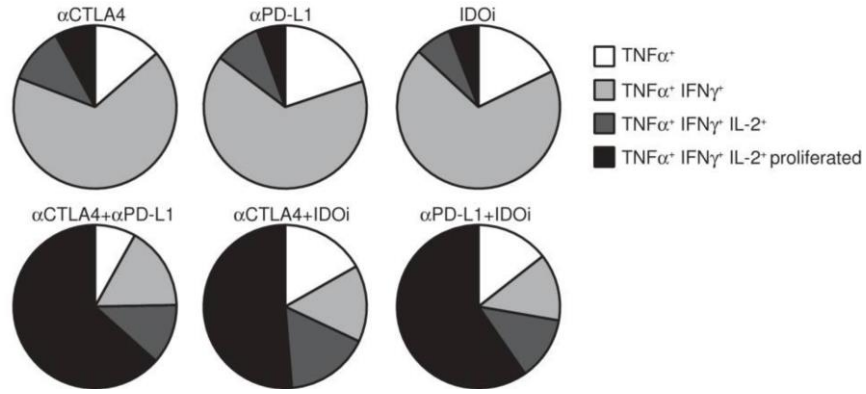
Inhibition of IDO synergizes with checkpoint blockade to reject murine melanoma tumors.



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,*]

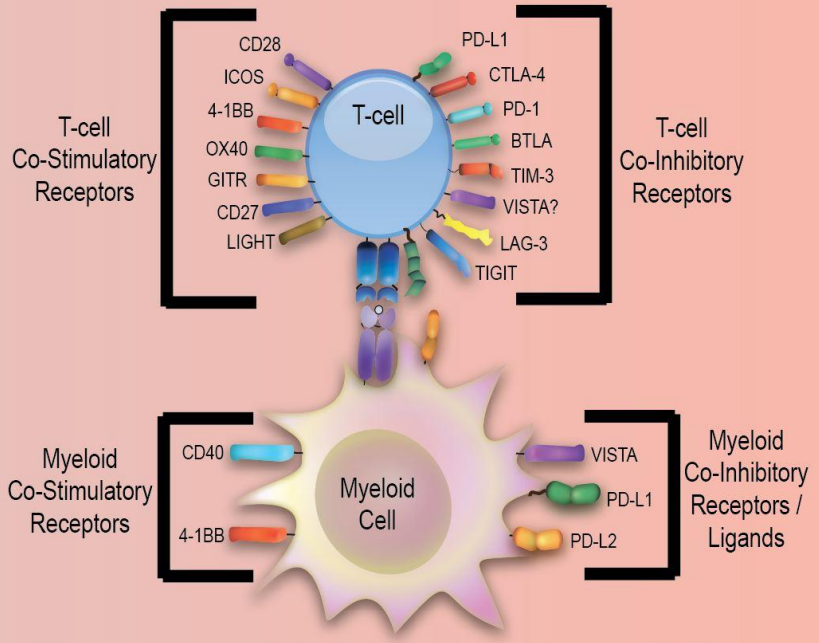
J Immunother Cancer. 2014 Feb 18;2:3. doi: 10.1186/2051-1426-2-3. eCollection 2014.

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].

"Hot" tumors often have high densities of co-inhibitory ligand expression and lack T cell co-stimulation.

Suppressive Mechanism



Tumors and their stroma are rich in ligands for T cell checkpoint receptors and lacking in co-stimulation. Myeloid phenotype can also be modulated by both activating and inbitory receptors.

Therapeutic Intervention

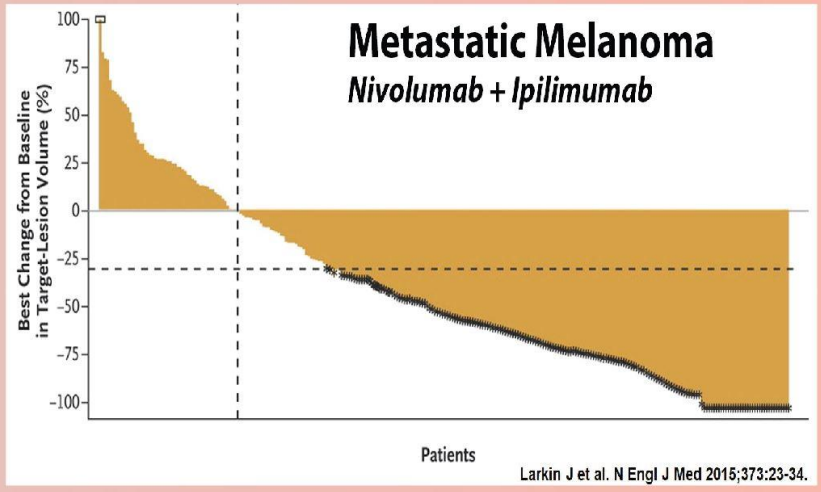
Checkpoint blocking antibodies:

FDA: αPD-1, αPD-L1, αCTLA-4

Trials: αTIM-3, αVISTA, αLAG-3 αTIGIT, αCD73

Co-stimulatory agonist antibodies:

Trials: α4-1BB, αOX-40, αICOS αGITR, αCD27, αCD40

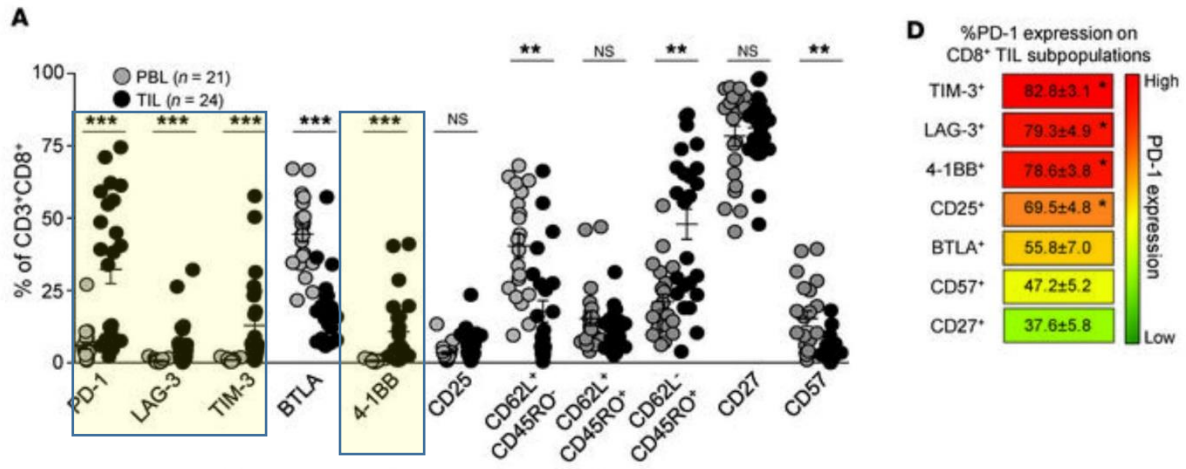


Checkpoint receptor expression by TIL in the TME identifies tumor-specific CD8 T cells which can be functionally re-activated.

J Clin Invest. 2014 May;124(5):2246-59. doi: 10.1172/JCI73639. Epub 2014 Mar 25.

PD-1 identifies the patient-specific CD8⁺ tumor-reactive repertoire infiltrating human tumors.

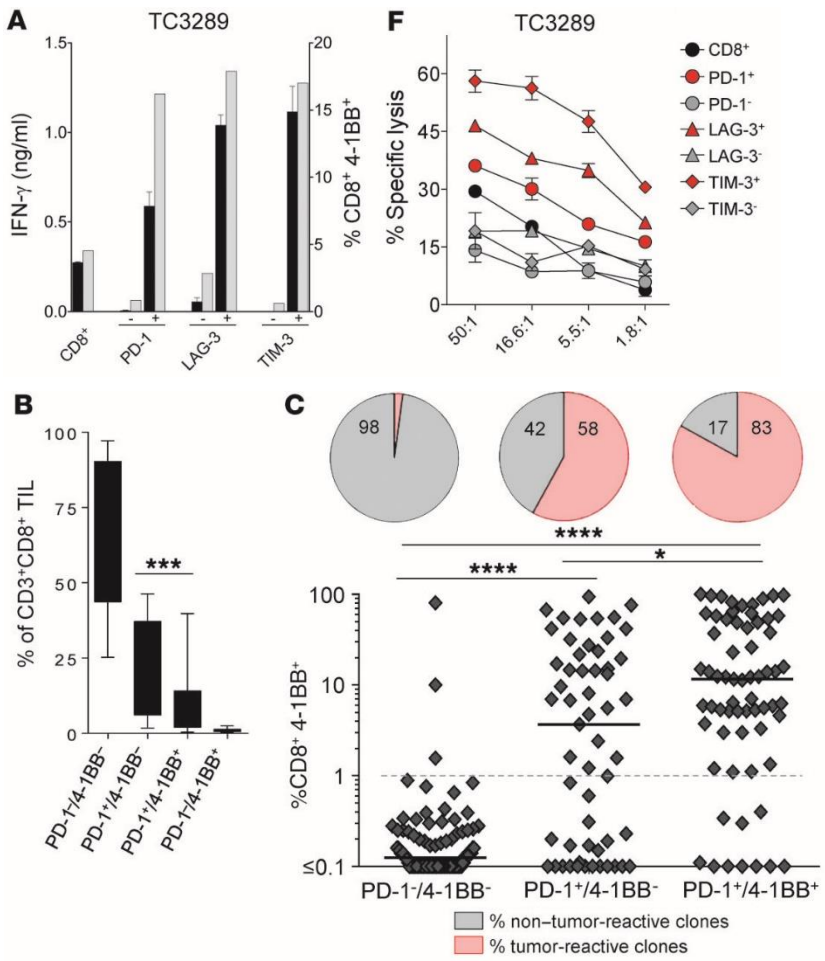
Gros A, Robbins PF, Yao X, Li YF, Turcotte S, Tran E, Wunderlich JR, Mixon A, Farid S, Dudley ME, Hanada K, Almeida JR, Darko S, Douek DC, Yang JC, Rosenberg SA.



Both co-inhibitory receptors (PD-1, LAG3, TIM-3), and co-stimulatory receptors (4-1BB) are enriched in patient TIL versus PBMC. The selective populations co-express PD-1. Receptors with more selective TIL expression will often be better targets for immunotherapy.

Despite checkpoint receptor expression, these populations contain the most active tumor-specific CD8 T cells.

The PD-1+ population of TIL contains the most numerous tumor-specific T cells, but the PD-1+/4-1BB+ population contains the highest frequency.

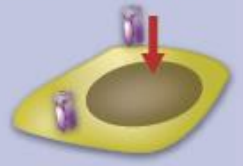


Combination therapies will be essential…

Suppressive Mechanism

Lack of Tumor Antigen Presentation

Lack of professional antigen-presenting cells in the TME



Downregulation of surface MHC and/or antigen presentation. Lack of mutanome antigen.

Vascular Exclusion of Lymphocytes

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

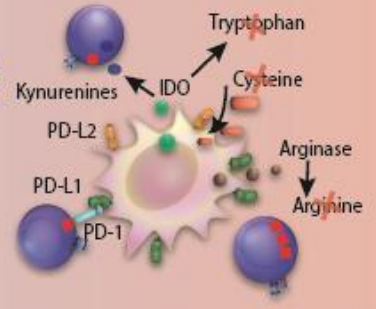
Hostile Tumor/TME Metabolism

Gluc, Glut consumption, EC Lactate, Hypoxia, ROS, ONOO-

Extracellular pH

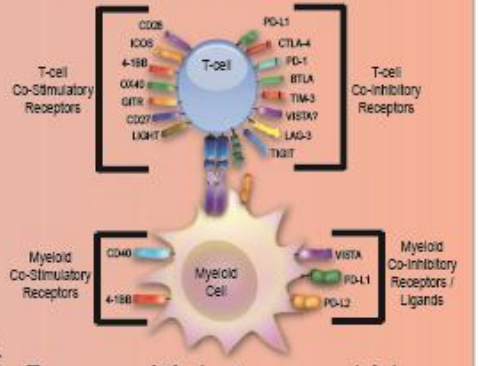
High tumor glycolysis depletes "fuel" from the TME starving T cells of energy. Low pH and high toxic metabolites induce T cell anergy and apoptosis.

Suppressive Myeloid Nutrient Depletion



Tumor myeloid stroma (e.g. TAM, MDSC) produce enzymes that deplete Arginine and Tryptophan and actively sequester Cysteine.

Engagement of T cell Co-inhibitory Pathways

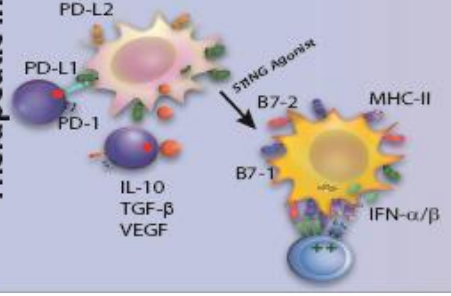


Tumors and their stroma are rich in ligands for T cell checkpoint receptors and lacking in co-stimulation. Myeloid phenotype can also be modulated by both activating and inbitory receptors.

Therapeutic Intervention

Activation and expansion of antigen-presenting cells:
- CD40 agonist antibody
- STING agonist
- TLR/RIG-I agonist

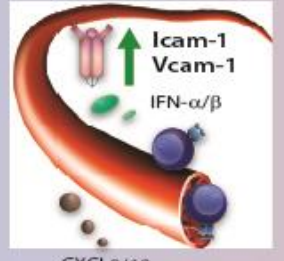
Tumor Vaccines (mutanome):
Adoptive T cell Therapy (CAR,TIL)



Re-activation of tumor vessels and IFN-induced chemokines:
- STING agonist

Blockade of vessel checkpoints:
- PD-L1 antibody blockade

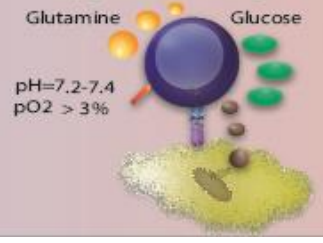
Angiogenic normalization:
- VEGF/PDGF inhibition



Inhibition of tumor metabolism:
- Glutaminase inhibitors
- Glycolysis inhibitors
- OxPhos inhibitors?

Reduction in toxic metabolites:
- Lactate export inhibitors

Hypoxia/pH normalization:
- Hypoxia prodrugs
- Oxygen carrier drugs

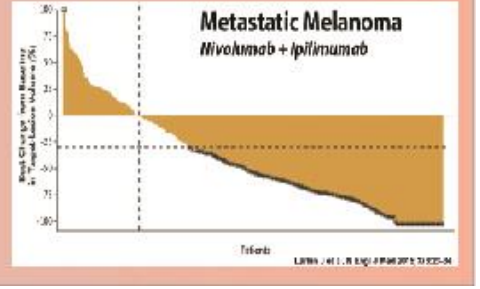


Direct/indirect Arginase block:
- Arginase inhibitors
- PDE5 inhibitors
- STAT3 inhibitors

Inhibition of IDO activity:
- IDO inhibitors

Checkpoint blocking antibodies:
- FDA: αPD-1, αPD-L1, αCTLA-4
- Trials: αTIM-3, αVISTA, αLAG-3 αTIGIT, αCD73

Co-stimulatory agonist antibodies:
- Trials: α4-1BB, αOX-40, αICOS αGITR, αCD27, αCD40



You can’t always get what you want, but maybe now we can get what we need from IO combinations.

Immune-Related Adverse Events can be minimized with tumor-targeted IO antibodies.

1. Current CTLA-4, 4-1BB, CD40 and possibly PD-1 antibodies are under-dosed and sub-optimally engineered relative to their murine counterparts to achieve tolerability

2. Emerging technologies which reduce off-target immune-related adverse events by selectively targeting checkpoint receptors in the tumor microenvironment will enable higher potency monotherapy dosing and high order combinations of multiple drugs.

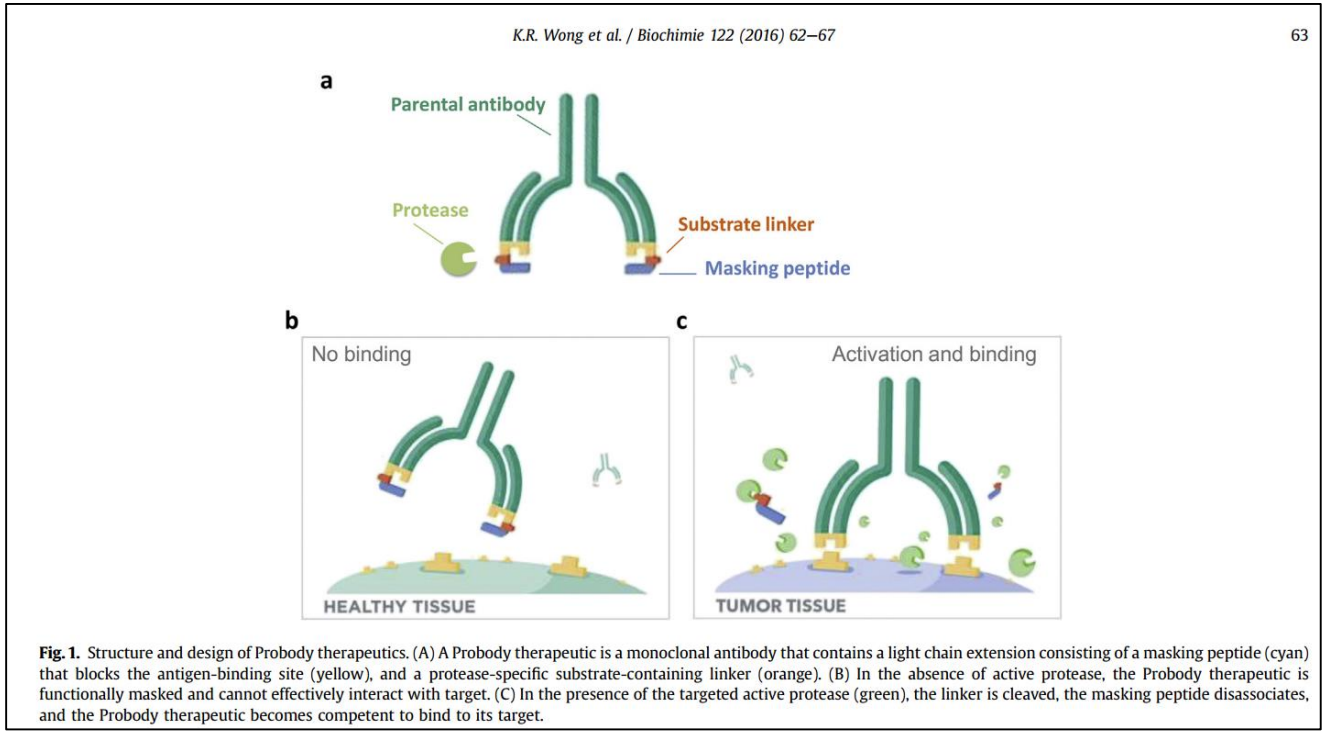
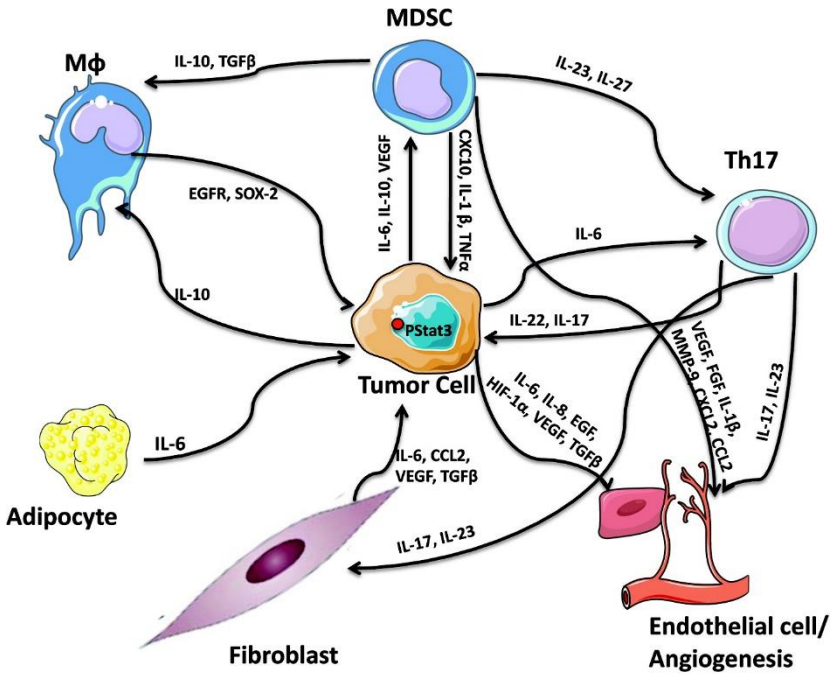


Fig. 1. Structure and design of Probody therapeutics. (A) A Probody therapeutic is a monoclonal antibody that contains a light chain extension consisting of a masking peptide (cyan) that blocks the antigen-binding site (yellow), and a protease-specific substrate-containing linker (orange). (B) In the absence of active protease, the Probody therapeutic is functionally masked and cannot effectively interact with target. (C) In the presence of the targeted active protease (green), the linker is cleaved, the masking peptide disassociates, and the Probody therapeutic becomes competent to bind to its target.

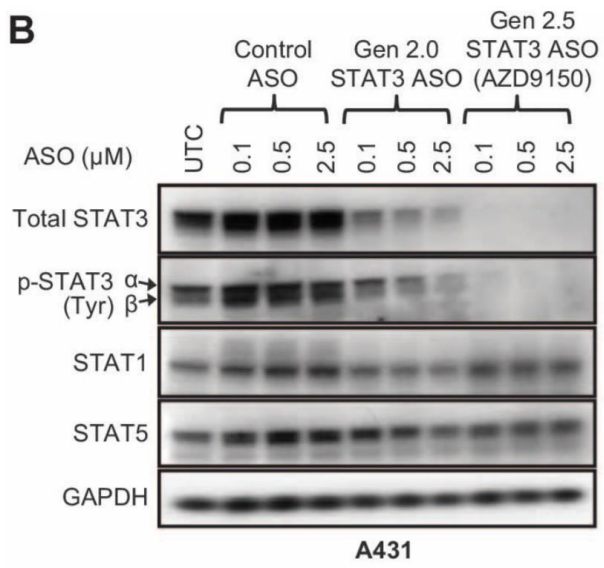
Small molecules which alleviate immune suppression can support T cell checkpoint modulating antibodies.

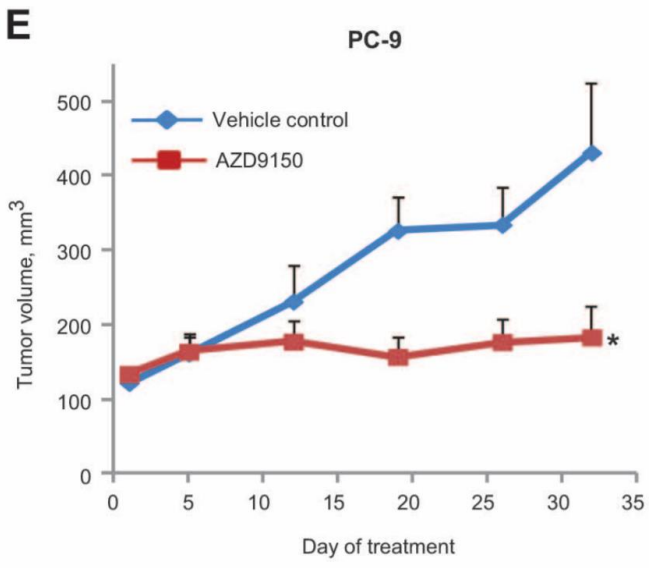
- Stromal immune suppression (e.g. IDO, A2a, Arginase, PGE2, TGF-β).
- Suppressive stromal cell function or viability (e.g. FAK).
- Targeted inhibition of oncogenic drivers (e.g. MEK).
- Inhibitors of suppressive signaling in T cells.
- Inhibitors of suppressive signaling in antigen-presenting cells.
- Tumor selective epigenetic inhibitors (e.g. Ezh2)
- Selective inhibitors of tumor metabolism (e.g. glutaminase, hypoxia)

Anti-sense oligonucleotides (ASO) can be used to target immune suppressive TME signaling pathways.



STAT3 supports tumor growth and immune suppression throughout the TME but has been difficult to target specifically with drugs.





STAT3 ASO specifically deplete both total and active STAT3, leaving STAT1 and STAT5, which are essential for tumor immunity, in tact. STAT3 ASO (AZD9150) has single agent efficacy against a variety of xenografts and in a Phase I study treating relapsed-refractory DLBCL.

JAKSTAT. 2013 Apr 1;2(2):e23828. doi: 10.4161/jkst.23828.

Targeting the tumor microenvironment: JAK-STAT3 signaling.

Bournazou E[1], Bromberg J.

Sci Transl Med. 2015 Nov 18;7(314):314ra185. doi: 10.1126/scitranslmed.aac5272.

AZD9150, a next-generation antisense oligonucleotide inhibitor of STAT3 with early evidence of clinical activity in lymphoma and lung cancer.

Hong D[1], Kurzrock R[2], Kim Y[3], Woessner R[4], Younes A[5], Nemunaitis J[6], Fowler N[1], Zhou T[3], Schmidt J[3], Jo M[3], Lee SJ[3], Yamashita M[3], Hughes SG[3], Fayad L[1], Piha-Paul S[1], Nadella MV[7], Mohseni M[4], Lawson D[4], Reimer C[4], Blakey DC[8], Xiao X[3], Hsu J[3], Revenko A[3], Monia BP[3], MacLeod AR[9].

Lessons and Take Home Messages

1. Underlying mechanisms of immune evasion are often different between “cold” and “hot” tumors and require distinct interventions.
2. Understanding the nature of these limitations in a given cancer allows rational composition of optimal combinations.
3. The “Three Component” paradigm can also help combination therapy design.
4. Tumor-targeted IO antibodies, IO potentiating small molecules, and anti-sense oligonucleotide therapeutics will facilitate combinations.

Shameless Plug

Saturday, 3:00pm

Metabolic Adaptations Establish Immunotherapy Resistance in Melanoma

Ashvin R. Jaiswal

Poster #26