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The Suppressive Yin Versus Pro-Inflammatory Yang of the Myeloid Stroma

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Presenter Disclosure Information

Michael A. Curran

The following relationships exist related to this presentation:

ImmunoGenesis, Founder and SAB
ImmunOS, SAB and Consultant

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

ImmunoMet, Sponsored Research Agreement
Ionis, Research Alliance

Plasticity of Myeloid Phenotype and Activation State

Pro-Inflammatory (anti-tumor)

1. **Cell Types**
   1. Dendritic Cells
   2. M1 Macrophages
   3. N1 Neutrophils
   4. Monocytes
2. **Features**
   1. Antigen Presentation
   2. Co-stimulation (B7-1/-2)
   3. Inflammatory cytokine (IFN, IL-12)
   4. T/NK/Inf. Myeloid recruitment
   5. NOS, ROS, Phagocytosis

Immunosuppressive

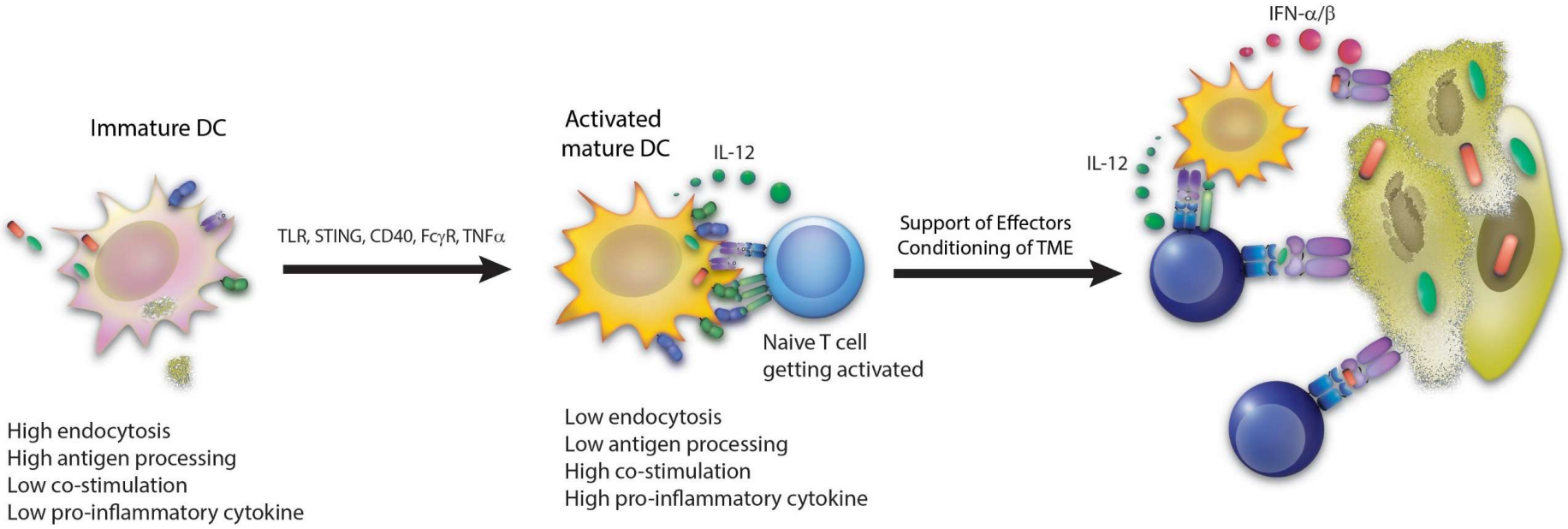
1. **Cell Types**
   1. Granulocytic MDSC
   2. M2 Macrophages
   3. Monocytic MDSC
   4. Mast cells
2. **Features**
   1. Nutrient deprivation (Arginase, IDO)
   2. Co-inhibition (e.g. PD-L1/-L2)
   3. Suppressive cytokine (TGF-β, IL-10)
   4. M2 and Treg recruitment and support
   5. Angiogenesis (VEGF)
   6. Adenosine production (CD73/CD39)

Goals

1. Understand the features of active versus suppressive polarization in key myeloid stromal populations.
2. Identify and define the functions of key myeloid receptors influencing their active versus suppressive fate.
3. Become familiar with interventions under investigation to reverse suppressive myeloid polarization and activate anti-tumor immuno-supportive functions.

Tumor Myeloid Stroma: The Players

Dendritic Cell (DC) Activation Initiates Tumor Immunity

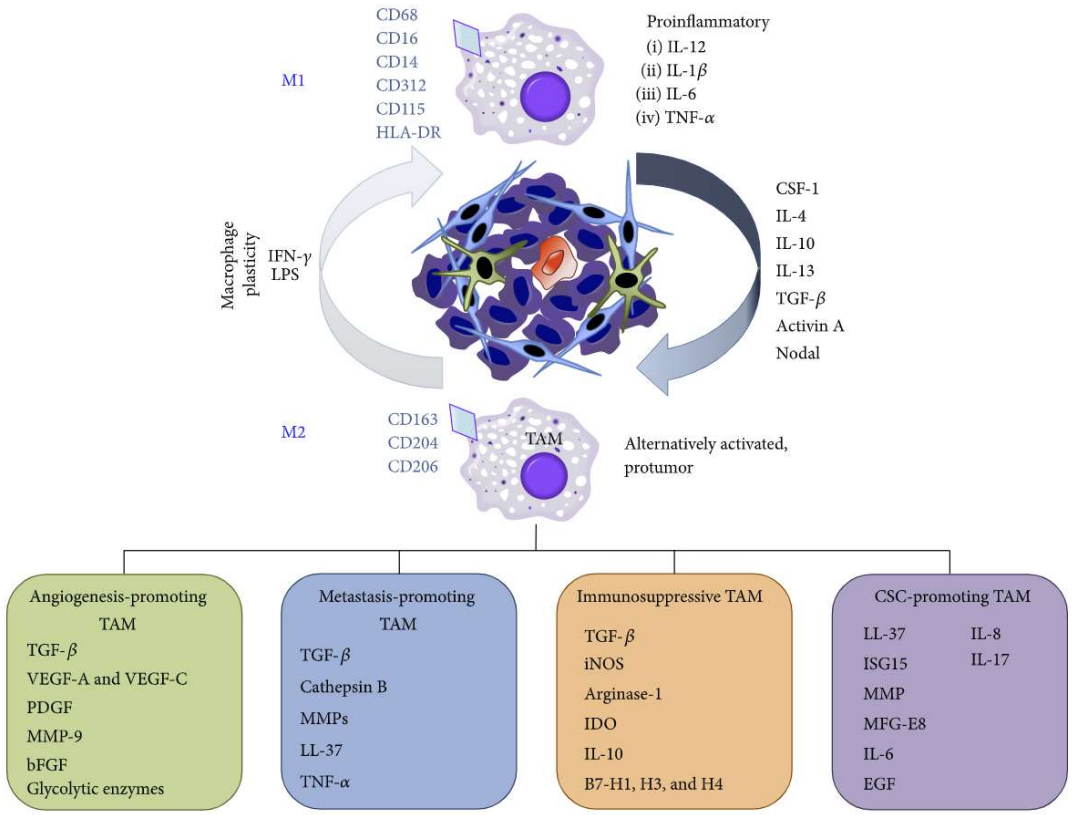


Tumor > Tumor Draining LN

Tumor Draining LN >> Tumor

Tumor >> Tumor Draining LN

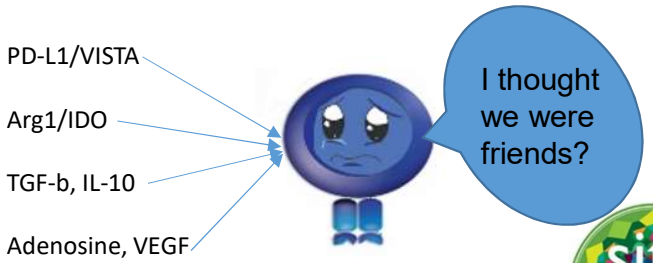
Suppressive Macrophages Maintain Tumor Immune Privilege



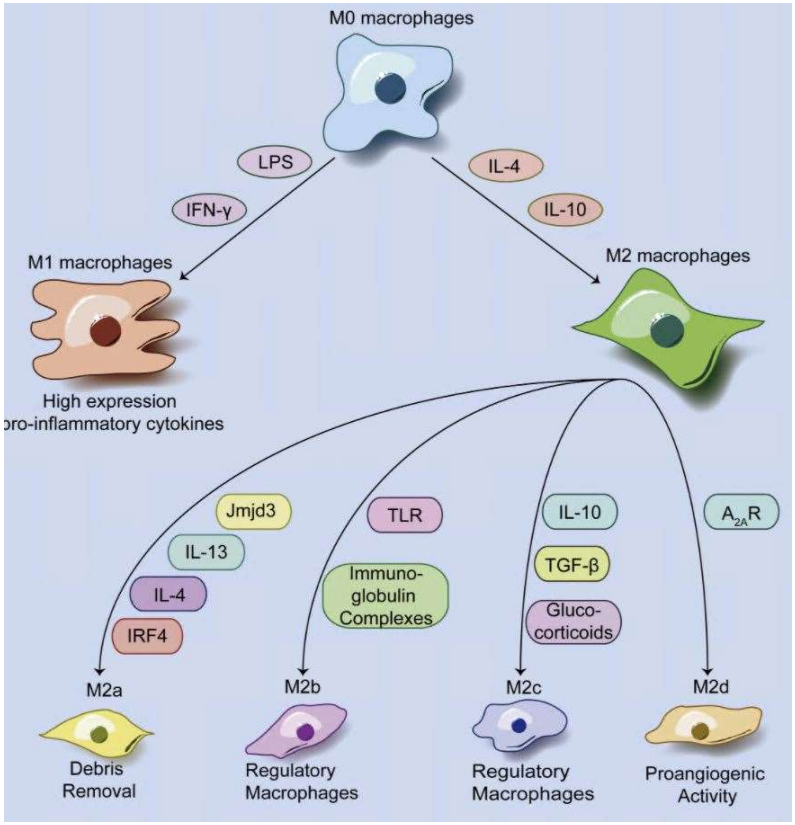
Sainz et. Al., Mediators Inflamm. 2016;2016:9012369.

1. **Activated M1 macrophages**
   1. **Pro-inflammatory cytokines (IL-12, TNFα)**
   2. **T cell co-stimulation (CD80/86)**
   3. **T cell chemokines**

2. **M2 Macrophages suppressive and tumor supportive**
   1. **Suppressive cytokines (TGF-β, IL-10)**
   2. **T cell co-inhibition (PD-L1/2, VISTA)**
   3. **Angiogenesis and DC suppression (VEGF)**
   4. **Support invasion and metastasis (MMPs)**
   5. **Nutrient deprivation (Arg1, IDO)**



Drivers of Macrophage TME Polarization



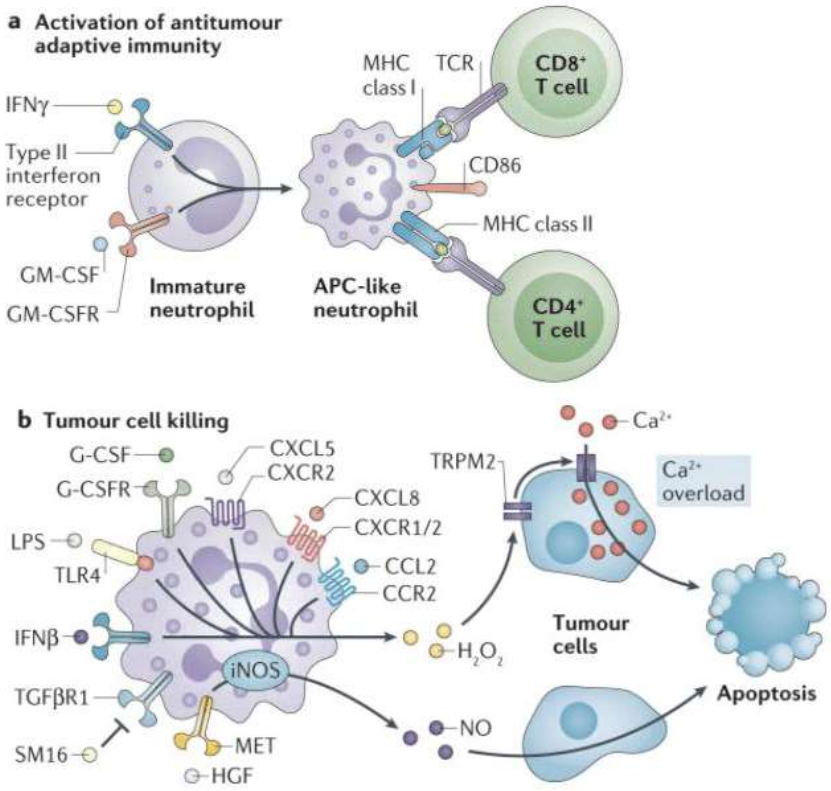
1. **M1 Macrophage determinants**
    1. **Pro-inflammatory cytokines (IL-12, IFNγ)**
    2. **Myeloid costimulatory receptors (CD40, 4-1BB)**
    3. **Pathogen associated molecular patterns (LPS)**

2. **M2 Macrophage determinants**
    1. **Suppressive cytokines (TGF-β, IL-10, IL-13, MCSF)**
    2. **Myeloid co-inhibition (LILRB, Siglec, VISTA)**
    3. **TME metabolism (lactate, hypoxia, adenosine)**
    4. **Certain TLR with immune complexes (TLR2)**
    5. **Certain chemokine receptor signals (CSF1-R)**

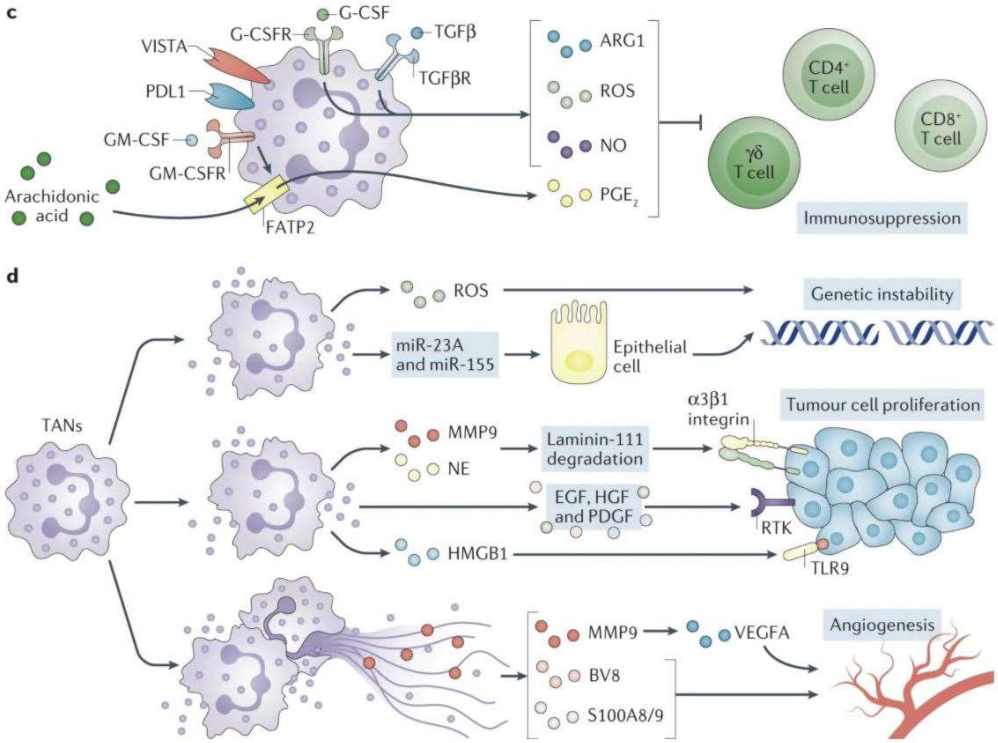
Int Immunopharmacol. 2019 May;70:459-466.

From N1 Neutrophil to Granulocytic MDSC

N1 : Effector potentiation and direct killing

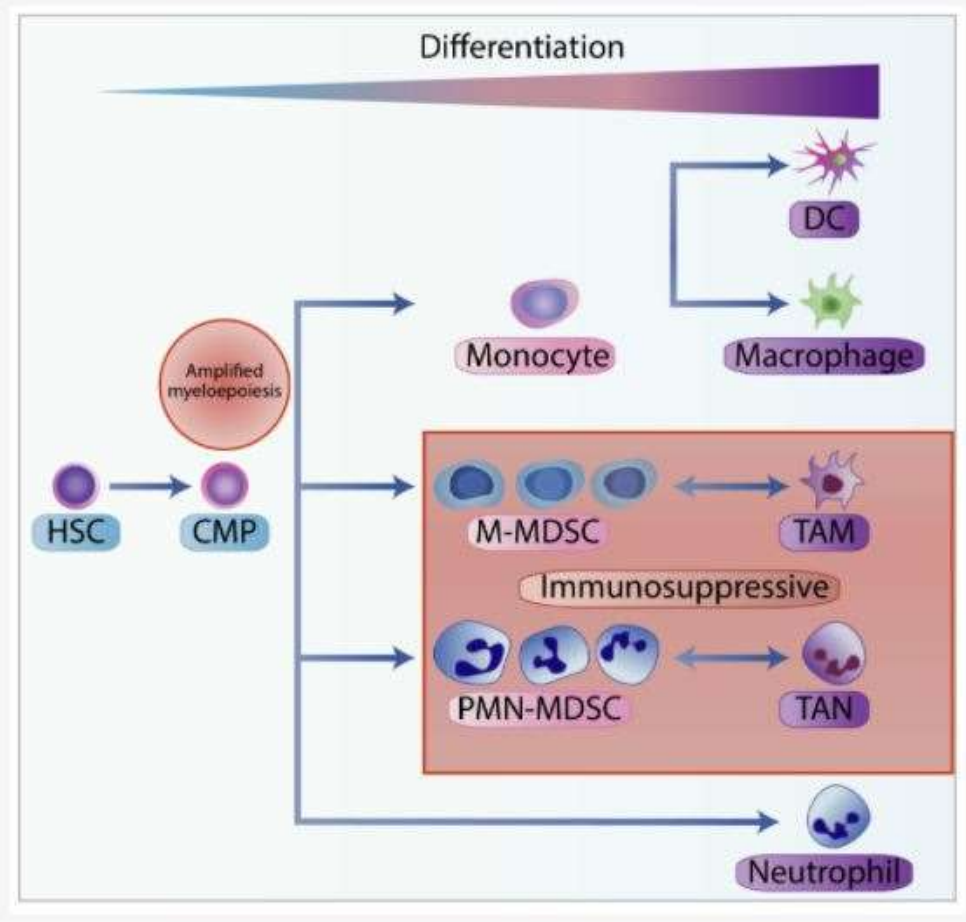


N2 (Gr-MDSC): Arg1, NO, PD-L1/2, angiogenesis

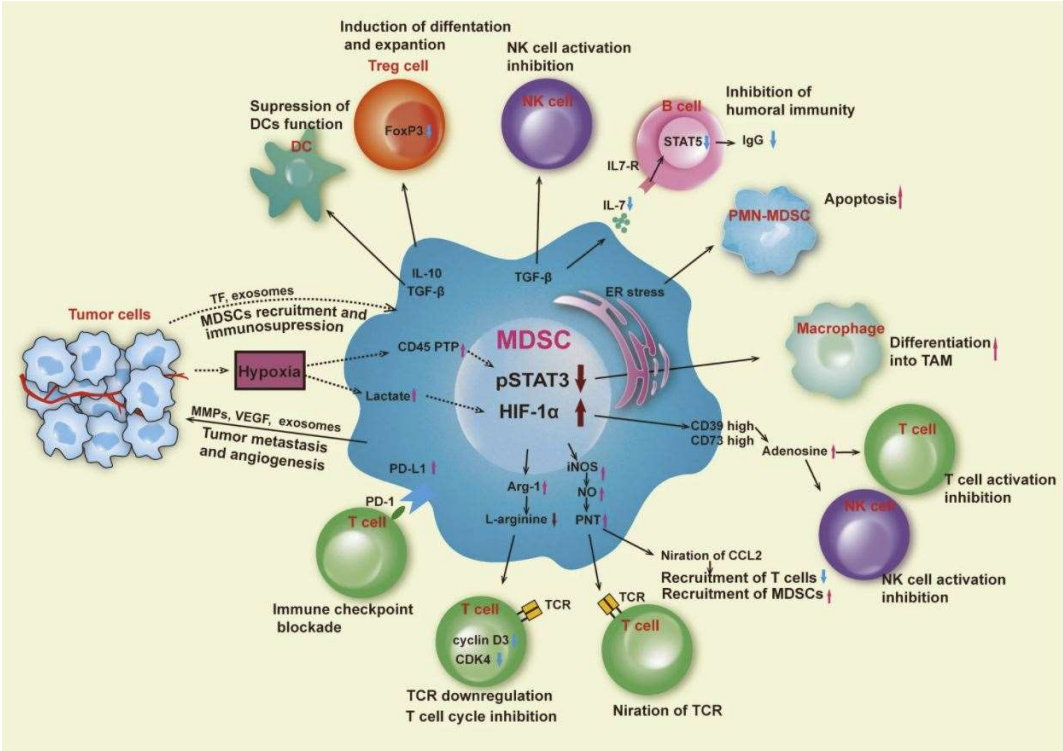


Jaillon et. Al., Nat Rev Cancer. 2020 Sep;20(9):485-503.

Mo-MDSC also Suppress T cells and Promote Angiogenesis



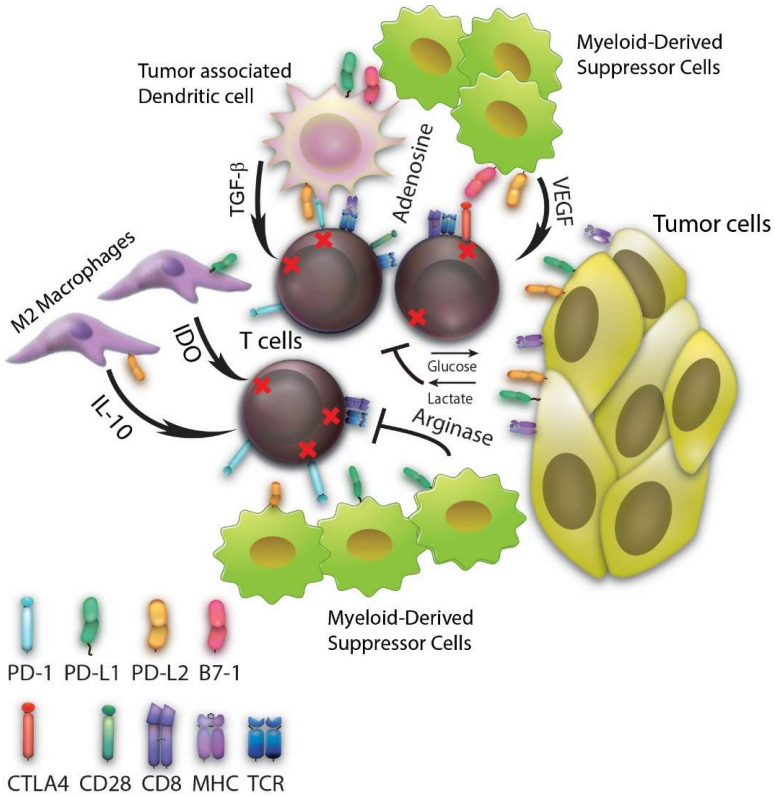
Law et. Al., Cells. 2020 Feb 27;9(3):561.



Yang et. Al., J Hematol Oncol. 2020 Jan 31;13(1):10.

How Can The Underdog Immune Response Win?

Anti-Tumor Immunity Losing



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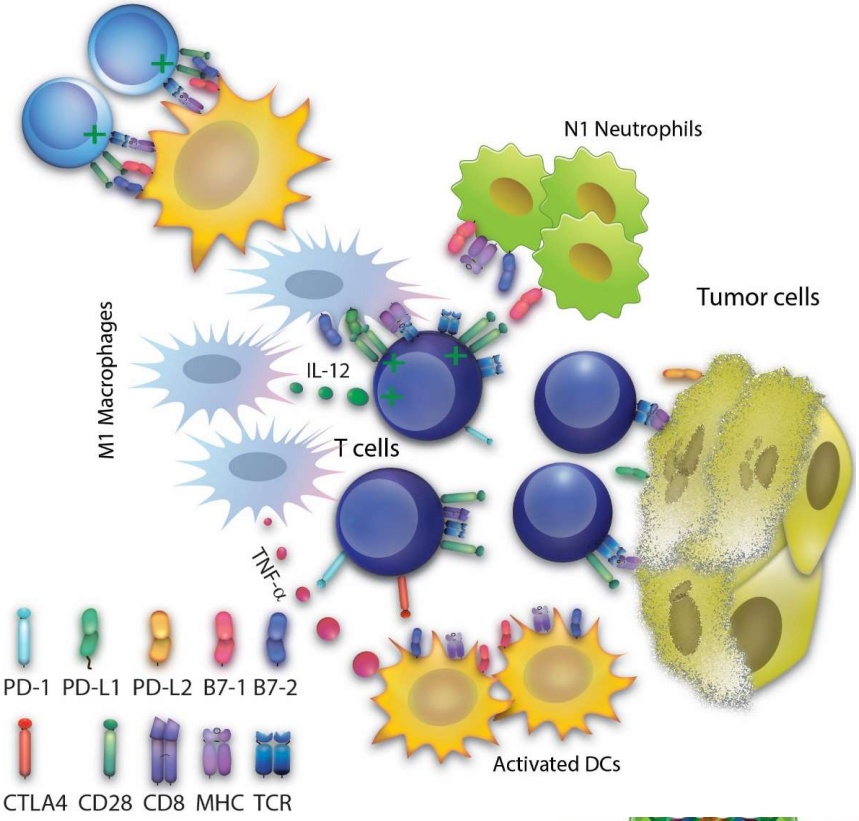
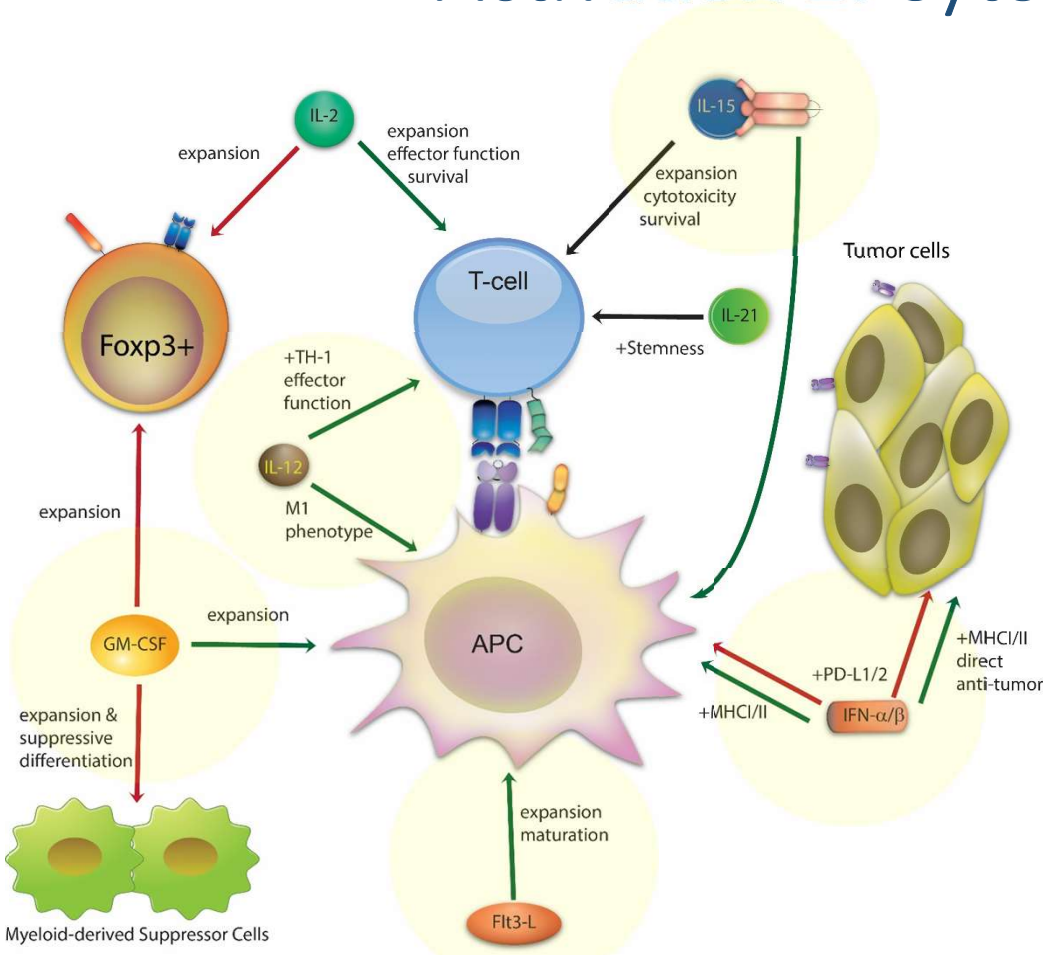
Anti-Tumor Immunity Winning



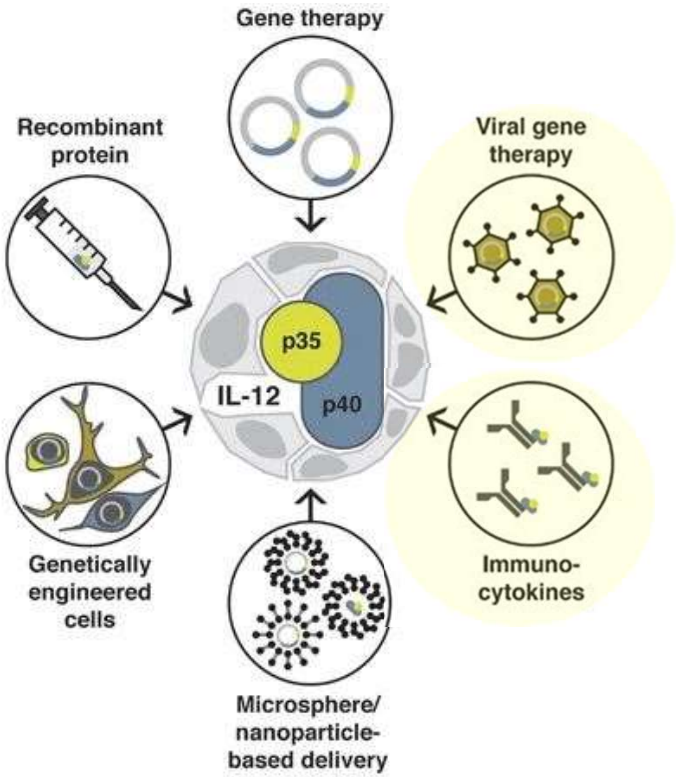
Tumor Myeloid Stroma: Pro-Inflammatory Activation

Activation 1: Cytokine Activation



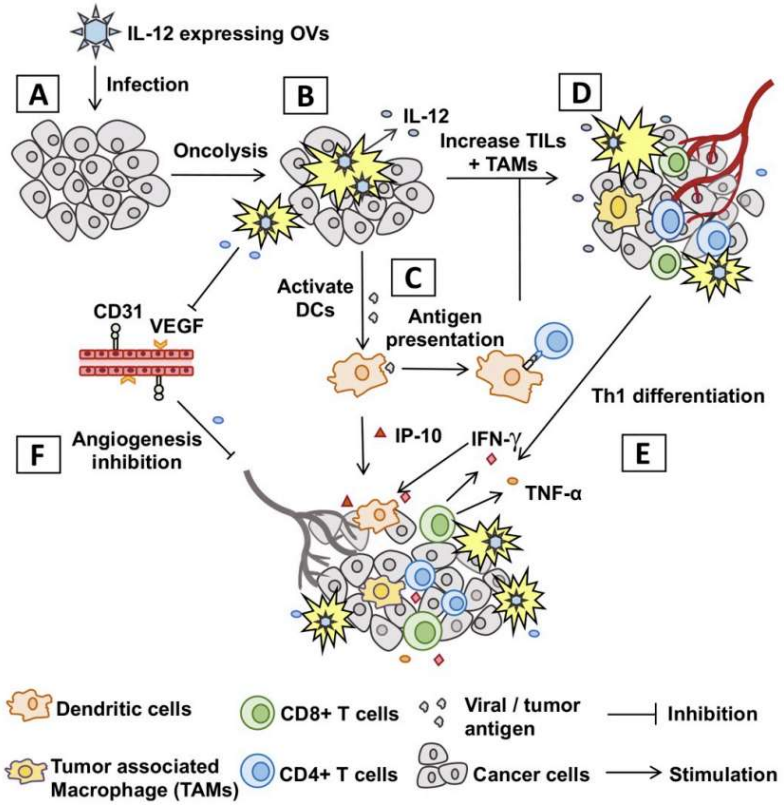
1. IL-12 and Flt3-Ligand (Flt3L) favor M1 / pro-inflammatory myeloid polarization
2. GM-CSF favors development of an immune-suppressive over supportive myeloid stroma
3. Interferons favor pro-inflammatory myeloid differentiation but also trigger acquired resistance mechanisms
4. IL-12 can be uniformly beneficial but also has high toxicity systemically.

Leveraging IL-12 for Myeloid Activation Requires Targeting



1. **Local delivery of IL-12 increases therapeutic window.**
2. **IL-12 favors M1 polarization and DC activation directly and indirectly through IFN-γ**

Local oncolytic virus



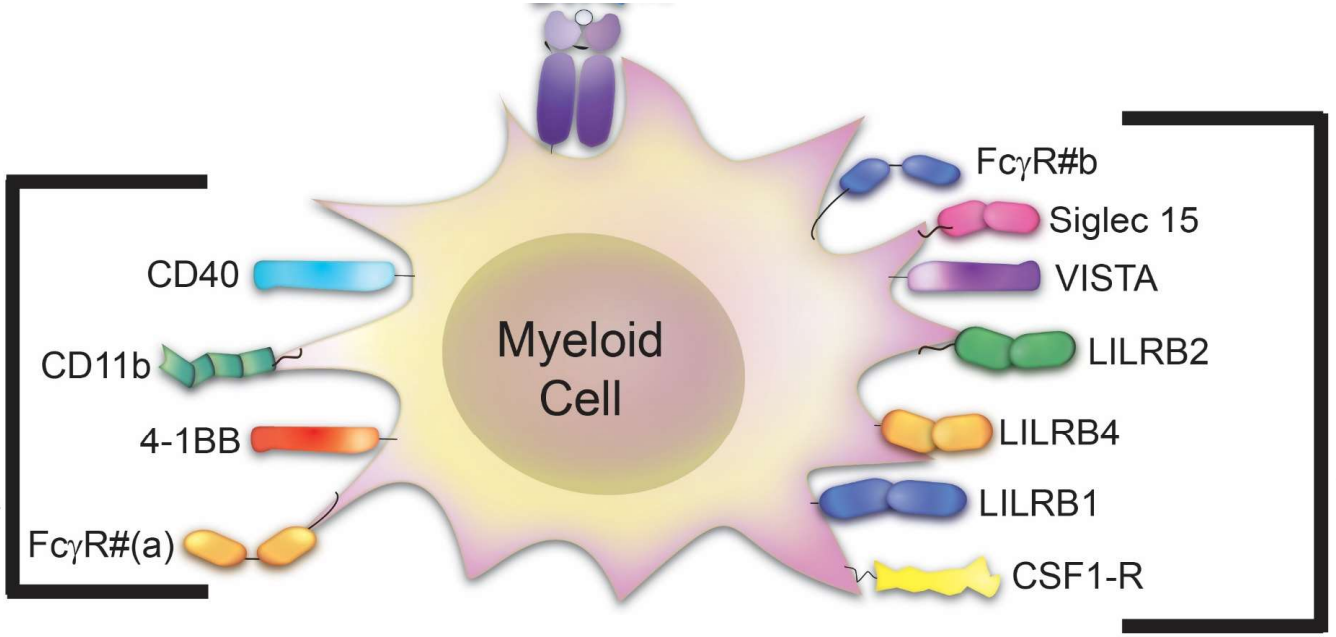
Tugues et. Al., Cell Death Differ. 2015 Feb;22(2):237-46.

Nguyen, H-M. et. Al., Cells. 2020 Feb 10;9(2).

Activation 2: Co-stimulatory Activation

Myeloid Co-Stimulatory Receptors

Agonism activates co-stimulatory function and inflammatory cytokine.

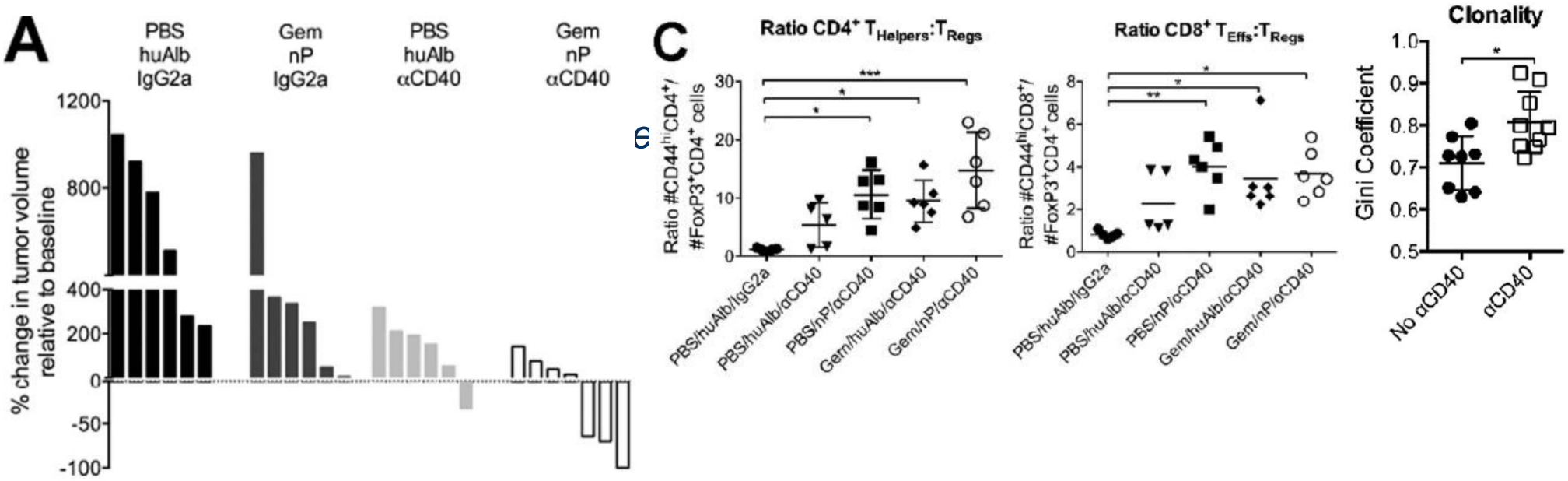


Myeloid Co-Inhibitory Receptors

Activation favors M2 and/or MDSC differentiation and elaboration of immunosuppressive molecules.

CD40 agonist antibodies are the best established agents for therapeutic activation of tumor myeloid stroma.

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

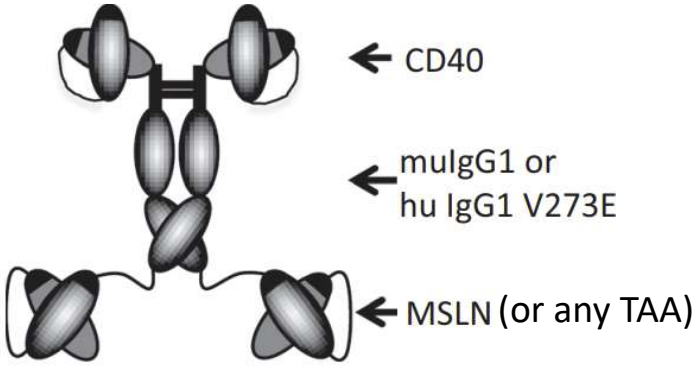


Cell Rep. 2016 Jun 21;15(12):2719-32. doi: 10.1016/j.celrep.2016.05.058. Epub 2016 Jun 9.

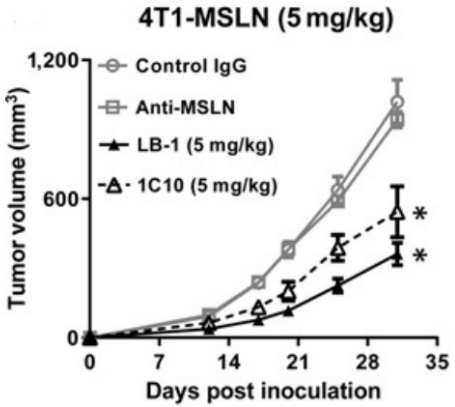
CD40 Stimulation Obviates Innate Sensors and Drives T Cell Immunity in Cancer.

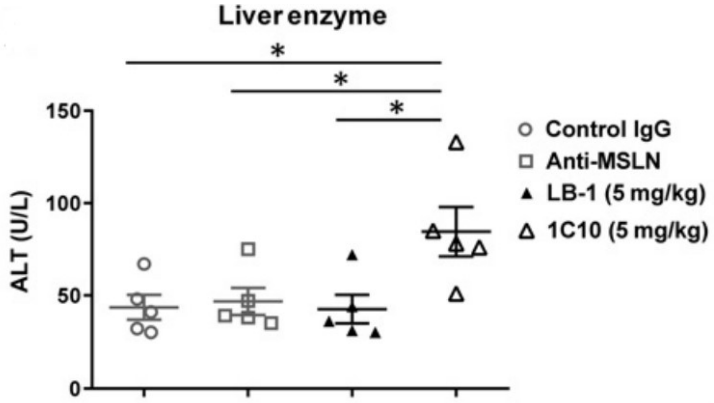
Byrne KT[1], Vonderheide RH[2].

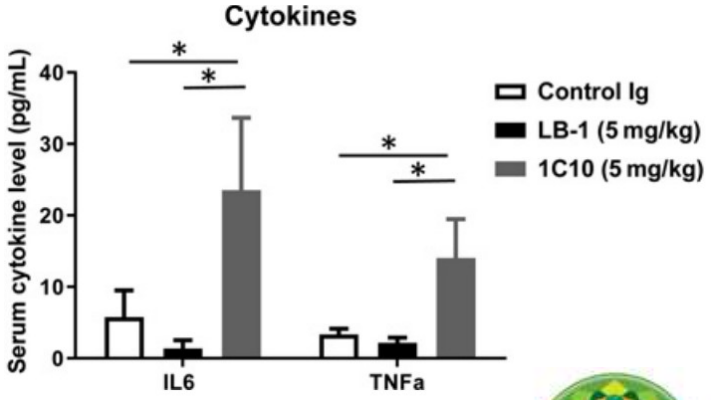
Targeted Activation of CD40 Widens Therapeutic Window



1. **CD40 agonist bispecific antibodies are as or more effective therapeutically versus systemic administration.**
2. **When localized to the TME, CD40 activation has a much larger therapeutic window sparing the liver and avoiding CRS.**

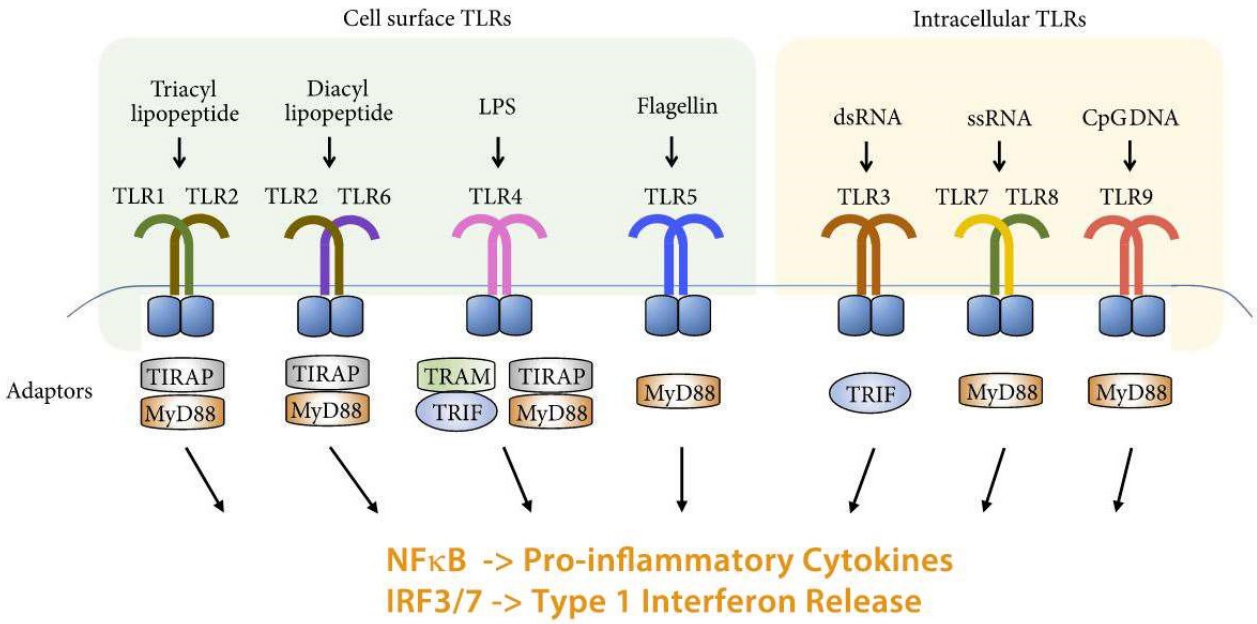






Ye et. Al., Cancer Immunol Res. 2019 Nov;7(11):1864-1875.

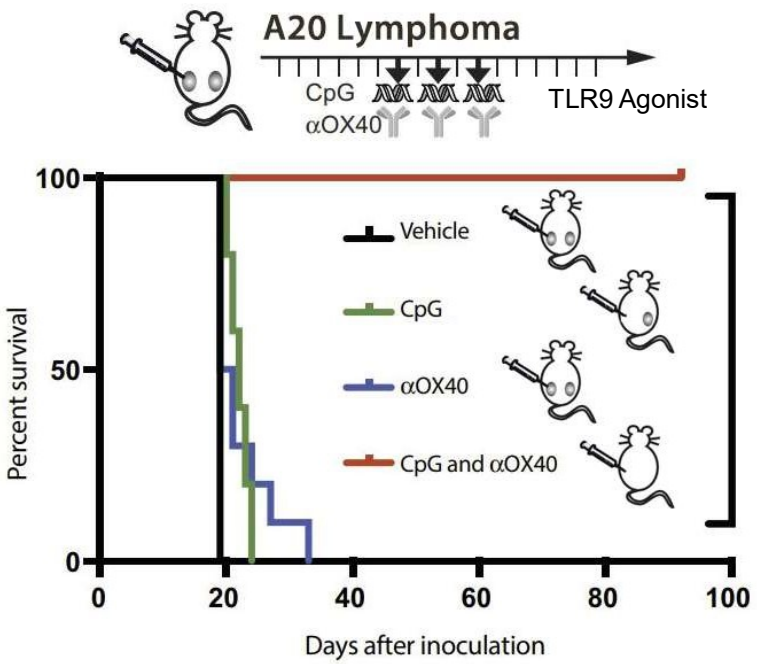
Activation 3: Innate activation – Toll-Like Receptors



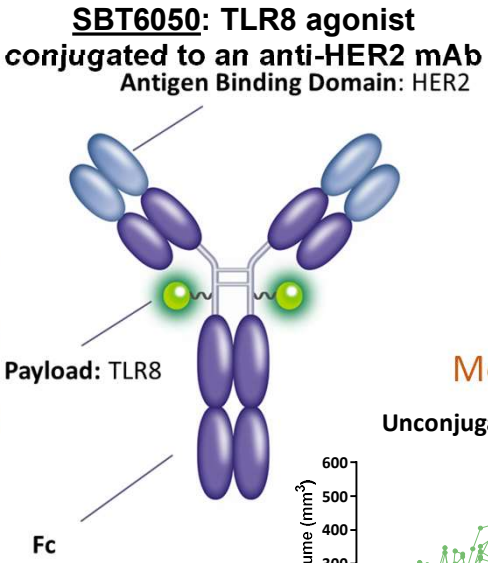
1. **TLR agonists can mimic PAMPs and activate both intrinsic co-stimulation and inflammatory cytokine secretion from myeloid cells**
2. **Some TLR can support immune suppression in some settings (e.g. TLR2,4)**
3. **TLR expression is restricted to certain myeloid and lymphoid subsets and some may be absent in some tumor microenvironments**

Noh et. Al., J Immunol Res. 2020 Jan 4;2020:2045860.

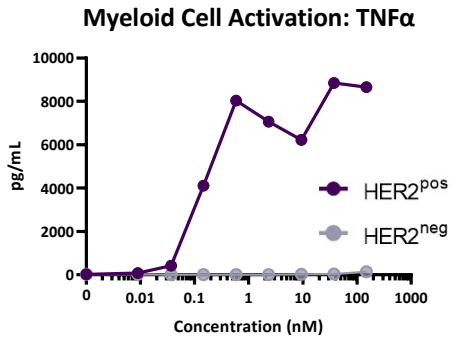
TLR Agonists Activate Myeloid Stroma and Tumor Immunity



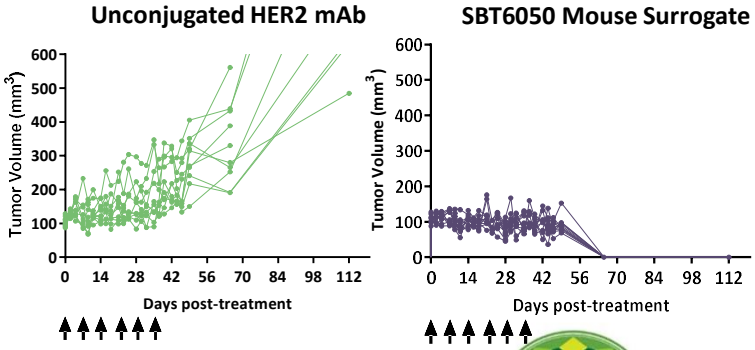
Overcoming local limitations with systemic targeted delivery



Tumor-localized activity



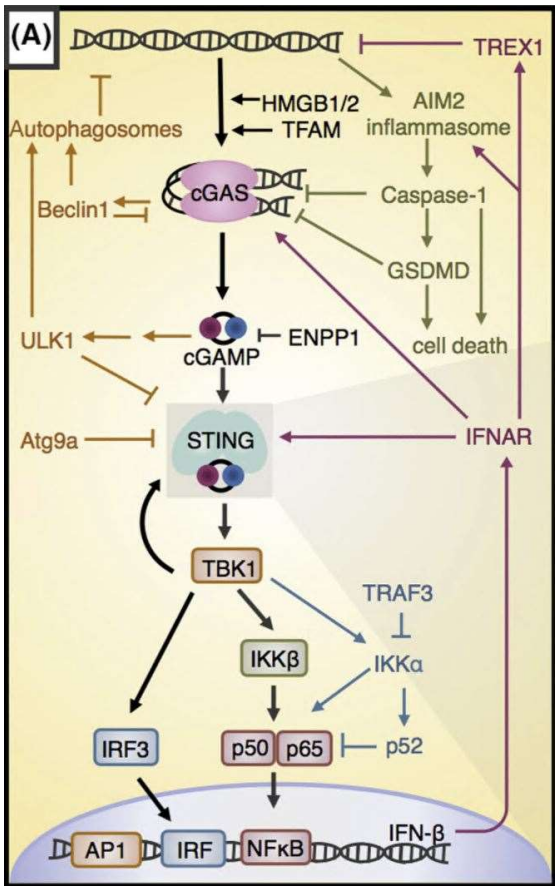
Monotherapy anti-tumor activity



Idit Sagiv-Barfi et al., Sci Transl Med 2018;10:eaan4488

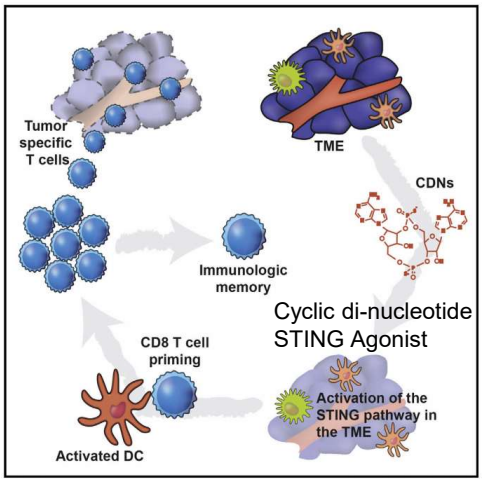
Latchman Y. and Odegard V. SITC 2019

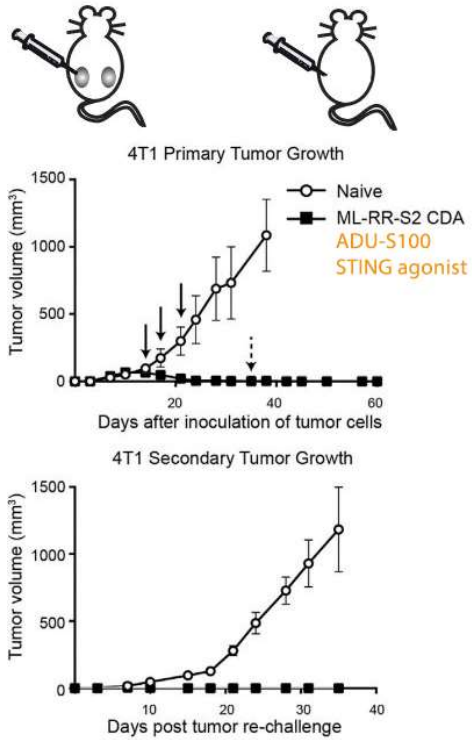
Activation 4: Innate Activation - STING



1. **Unlike TLR, the Stimulator of Interferon Genes (STING) innate sensor is expressed in most cells, although tumors often suppress it.**

2. **In response to cytoplasmic DNA or cyclic dinucleotides, STING triggers NFkB activation and IRF3 driven secretion of IFN-α/β.**

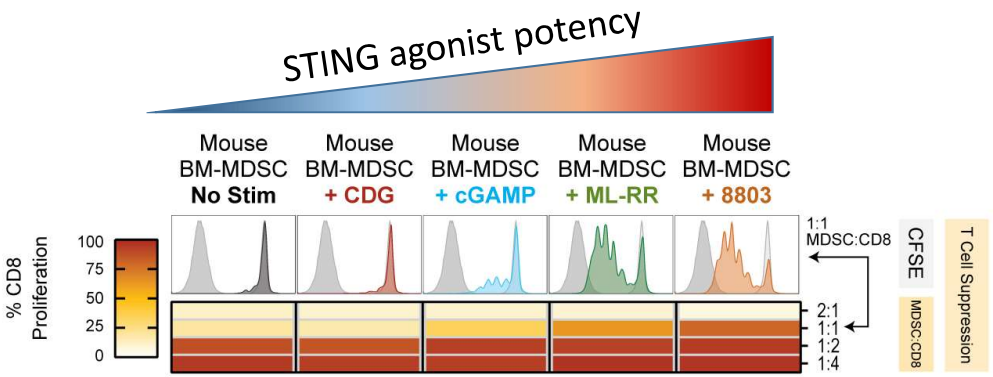




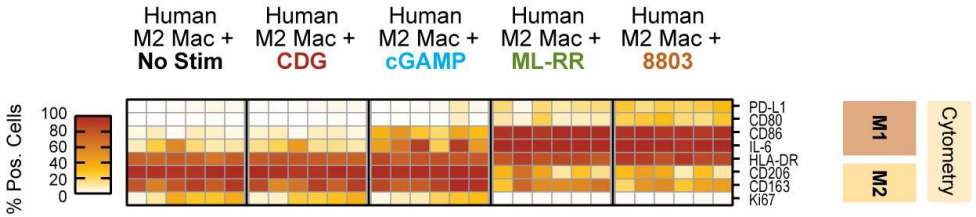
Corrales et. Al., Cell Rep. 2015 May 19;11(7):1018-30.

STING Agonists Reverse Myeloid Suppression

Function Repolarization of Myeloid Stroma

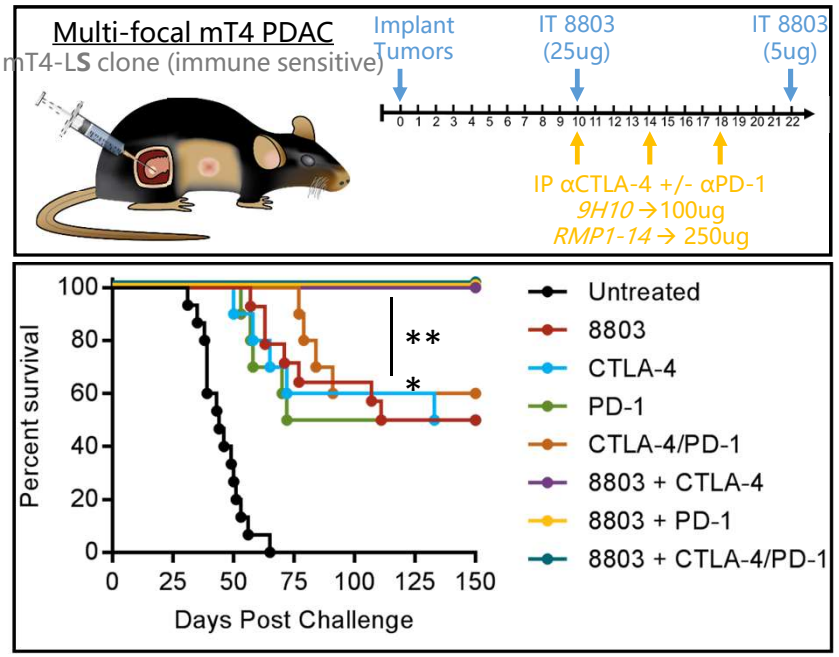


STING activation reverses MDSC suppression of T cells



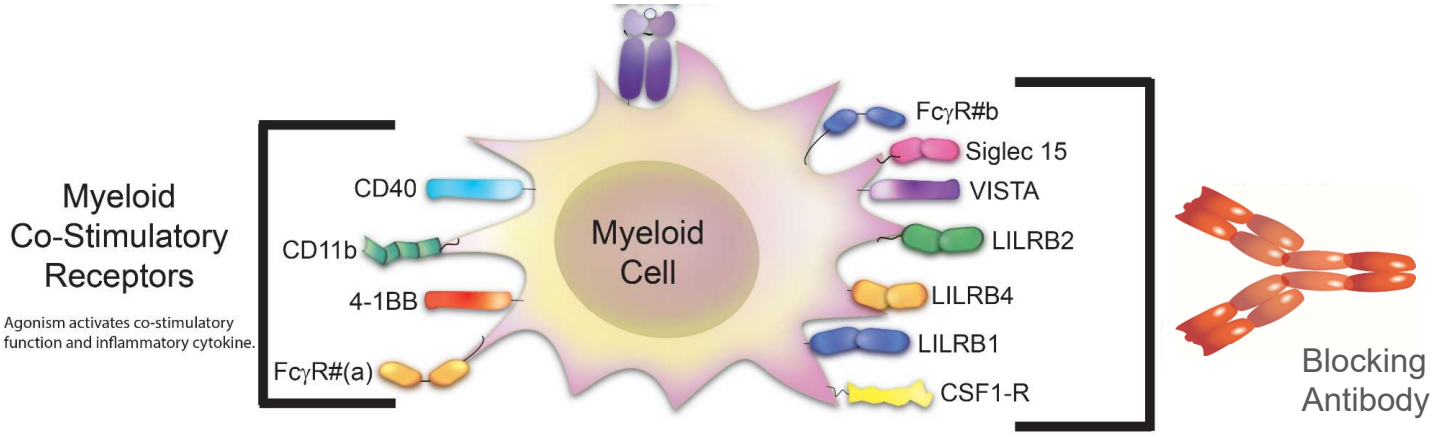
STING activation converts human M2 macrophages to M1

Synergy of Local STING with Checkpoint Blockade



Ager, C.R. and Curran, M.A. *In Revision.*

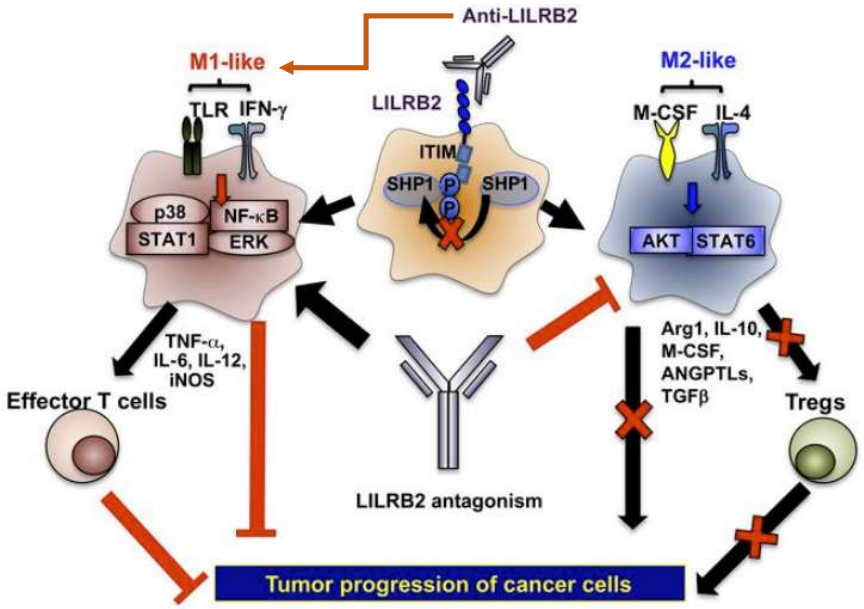
Activation 5: Blockade of "Co-Inhibition"



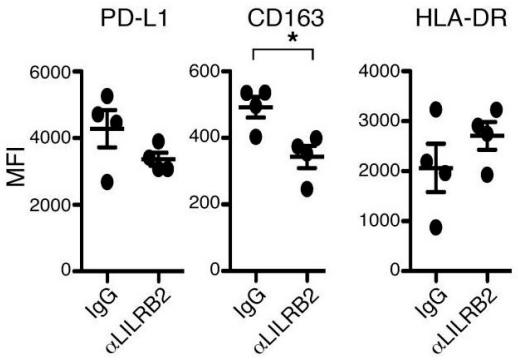
1. **Rather than induce exhaustion, quiescence and apoptosis as in T cells, myeloid "co-inhibitory" receptors are those that drive "alternative" polarization (M2, MDSC, etc).**

2. **Blockade of these suppressive polarization signals, skews differentiation in favor of immune potentiating states (e.g. M1, N1, active monocytes, etc).**

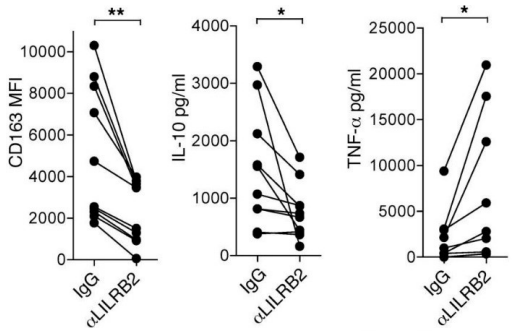
LILRB2 Signals Macrophages to Adopt M2 Features



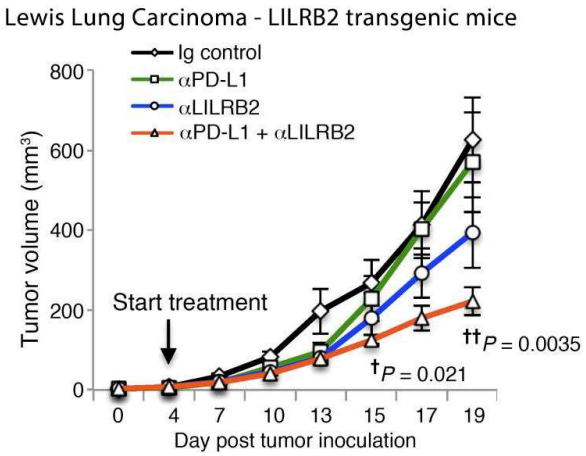
Donor Myeloid Cells : M2 -> M1



A549 Macrophages: M2 -> M1

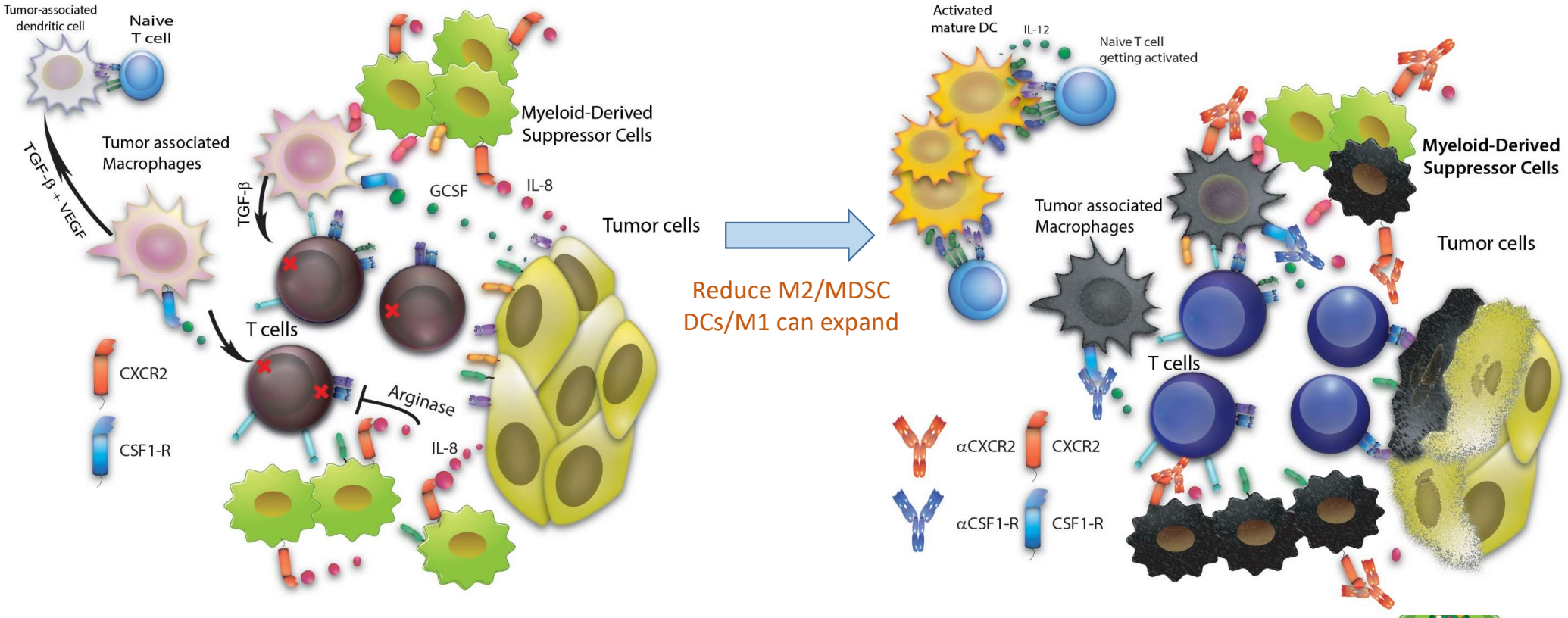


Slowing of LLC Tumor Growth

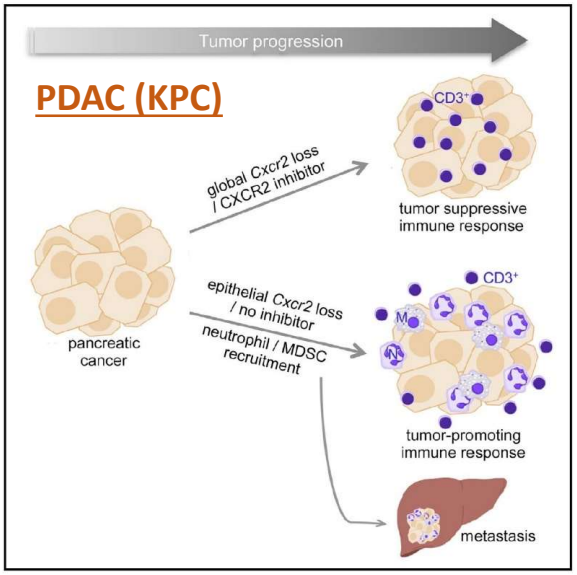


Chen et. Al., J Clin Invest. 2018 Dec 3; 128(12): 5647–5662.

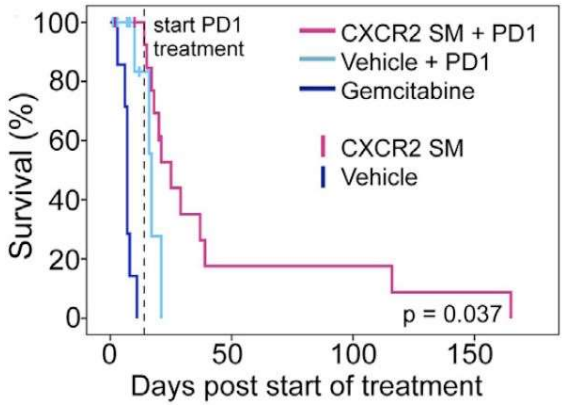
Addition By Subtraction: Remove Suppressive Myeloid Cells

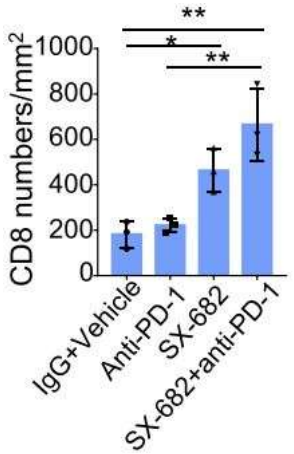


Blockade of CXCR2 Reduces MDSC and Reactivates CD8



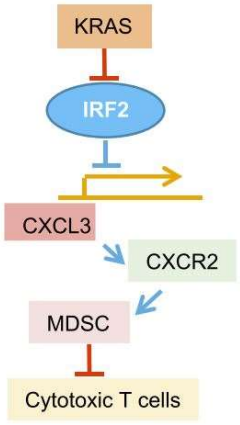
CXCR2 block = ↓MDSC & ↑T-cells

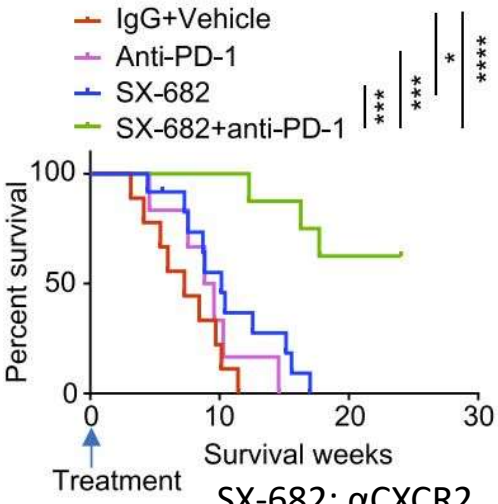




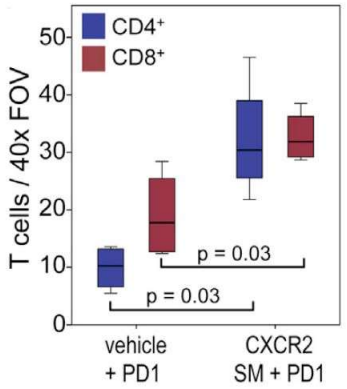
Greater T cell numbers suggests that MDSC depletion increases helps re-activate myeloid stroma to support new T cell infiltration

CRC (iKAP)





SX-682: αCXCR2



Lessons and Take-Home Messages

1. Tumor and stromal derived factors drive myeloid polarization toward suppressive M2 macrophage, Gr-MDSC, and Mo-MDSC phenotypes
2. Pro-inflammatory re-polarization of the myeloid stroma is possible through activation of co-stimulatory receptors or innate sensors
3. Differentiation of myeloid emigrants can be biased away from immune suppressive phenotypes through blockade of “co-inhibitory” receptors