Myeloid suppressive cells in cancer

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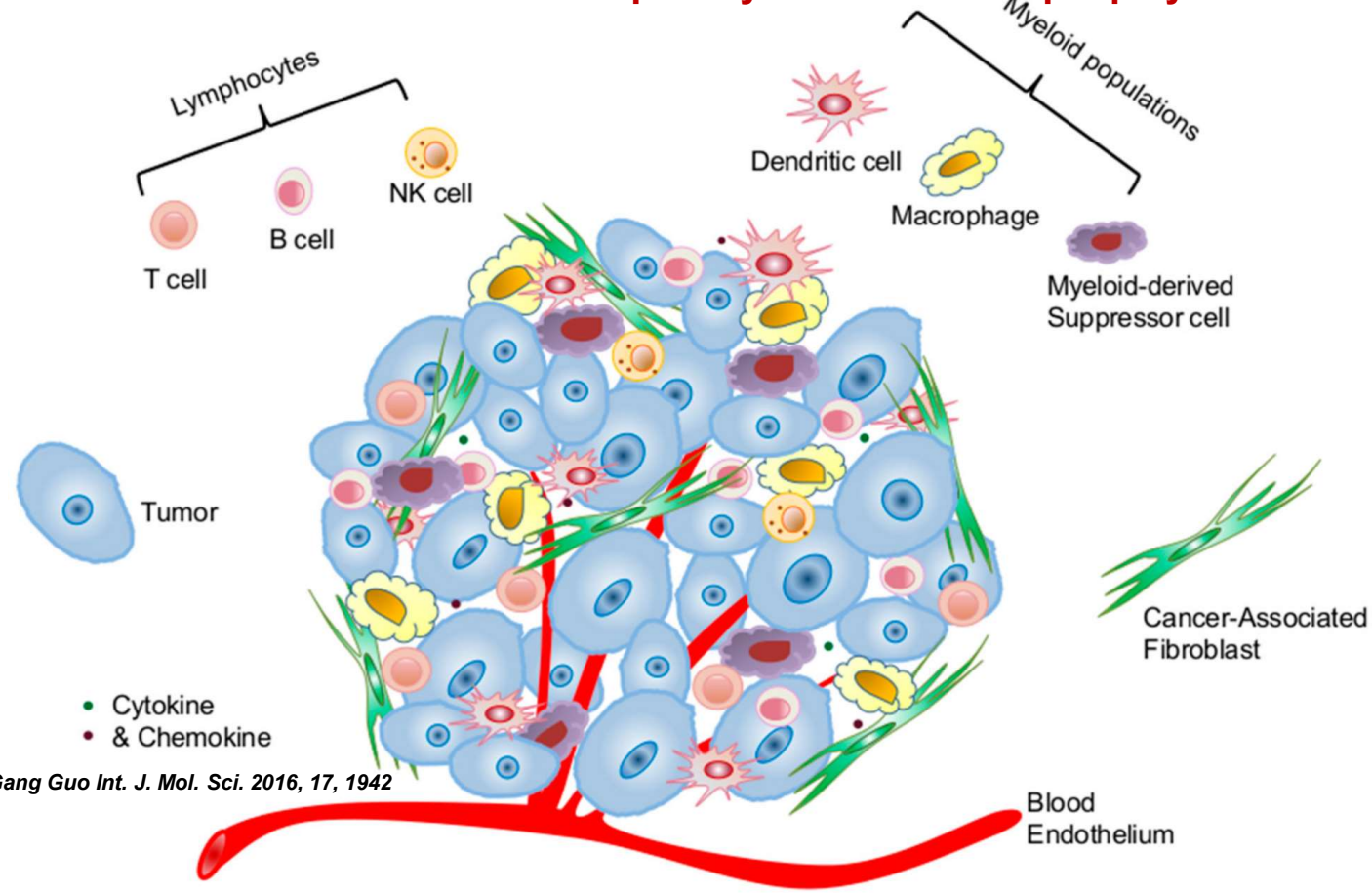
AstraZeneca

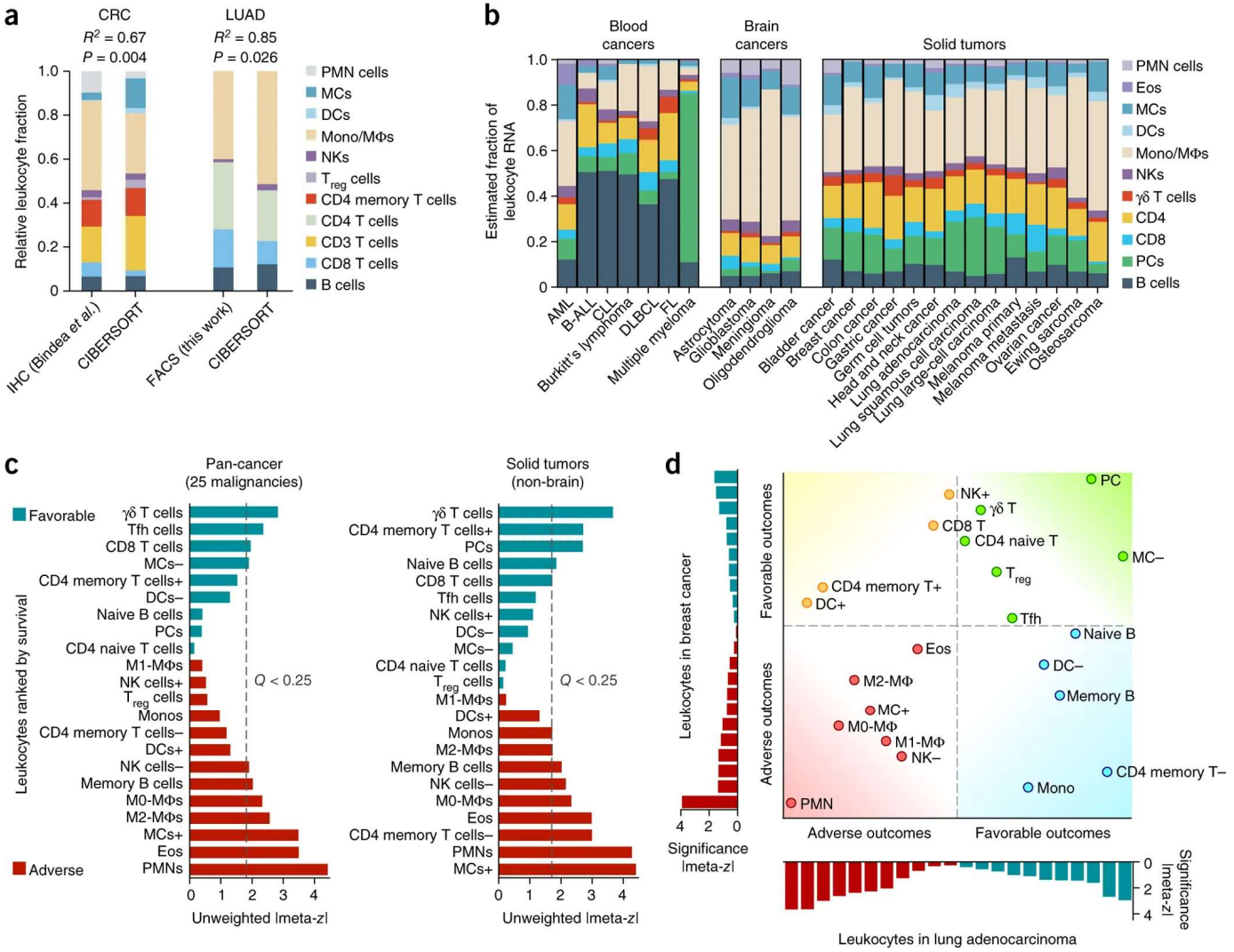
Tumor microenvironment is a complex system with multiple players



Yan Cui and Gang Guo Int. J. Mol. Sci. 2016, 17, 1942

Myeloid cells are most abundant white blood cells in human body
They are present in practically all tissues
There are no "cold" tumors for myeloid cells

Myeloid cells are strongly associated with negative clinical outcome in cancer



Gentles et al. Nat. Med. 2015

Classically activated myeloid cells

Strong activation signal. Short duration

Monocytes and mature neutrophils mobilization from bone marrow

MAIN TRIGGERS
TLR, PAMPR, DAMPR
METABOLISM
OxPHOS
FUNCTION
Activated phagocytosis
Respiratory burst
Pro-inflammatory cytokines
Up-regulation of co-stimulatory molecules

Elimination of threat (killing pathogens)
Activation of adaptive immunity

Pathologically activated myeloid cells

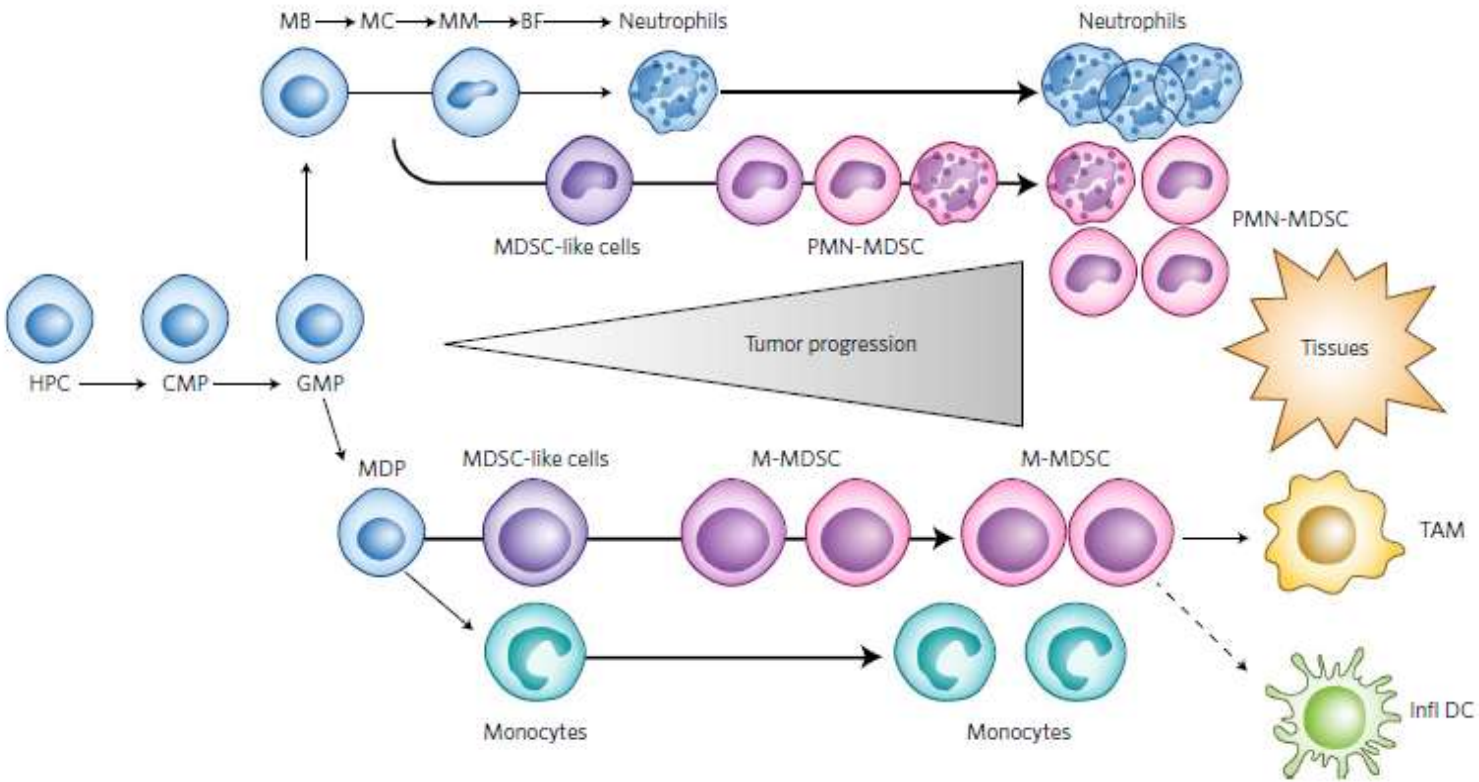
Weak activation signal mostly growth factors and cytokines. Long duration

Mild but prolong production of monocytes and neutrophils

MAIN TRIGGERS
pro-inflammatory cytokines, growth factors, DAMPR
ER stress
METABOLISM
Oxidized lipids
glycolisis
FUNCTION
Constant production of ROS and NO, and peroxynitrite
Anti-inflammatory cytokines
Arginase, PGE2

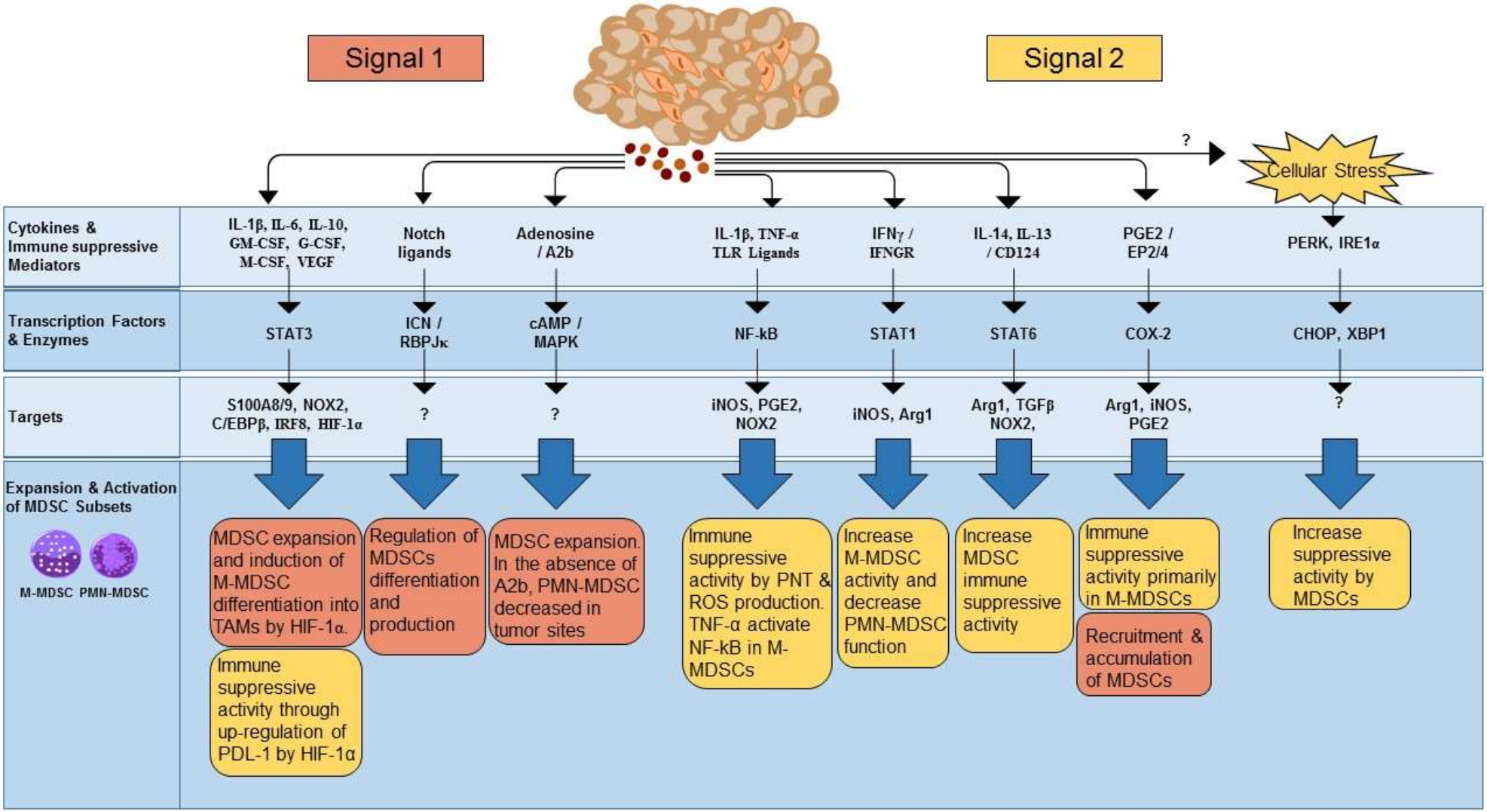
Inhibition of adaptive immunity (immune suppression)
“Pathologic tissue remodeling” leading to metastases

At any given moment classically activated myeloid cells co-exist with pathologically activated cells

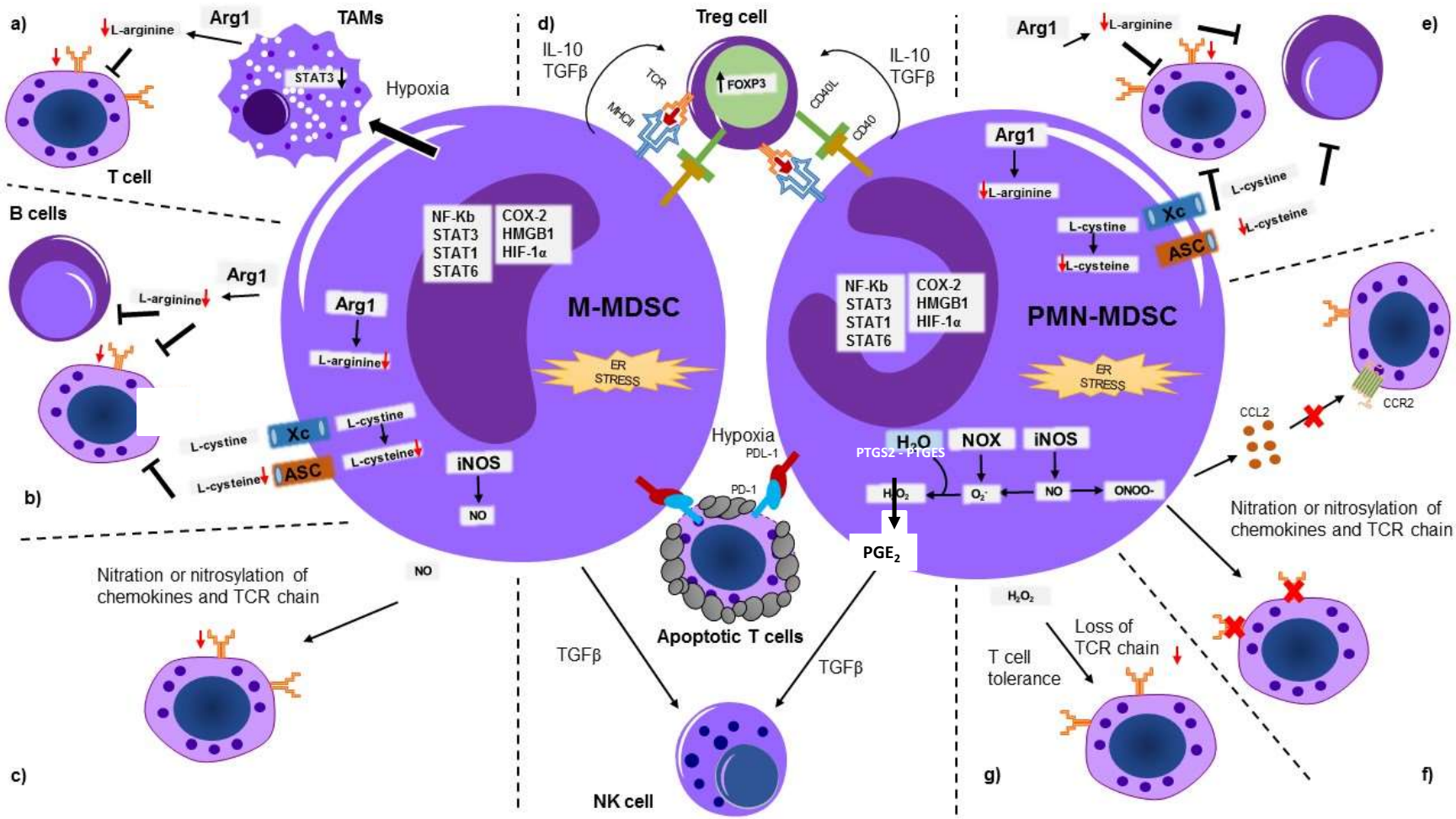


and their balance may define clinical outcome in cancer

Veglia F et al. Nat Immunol. 2018

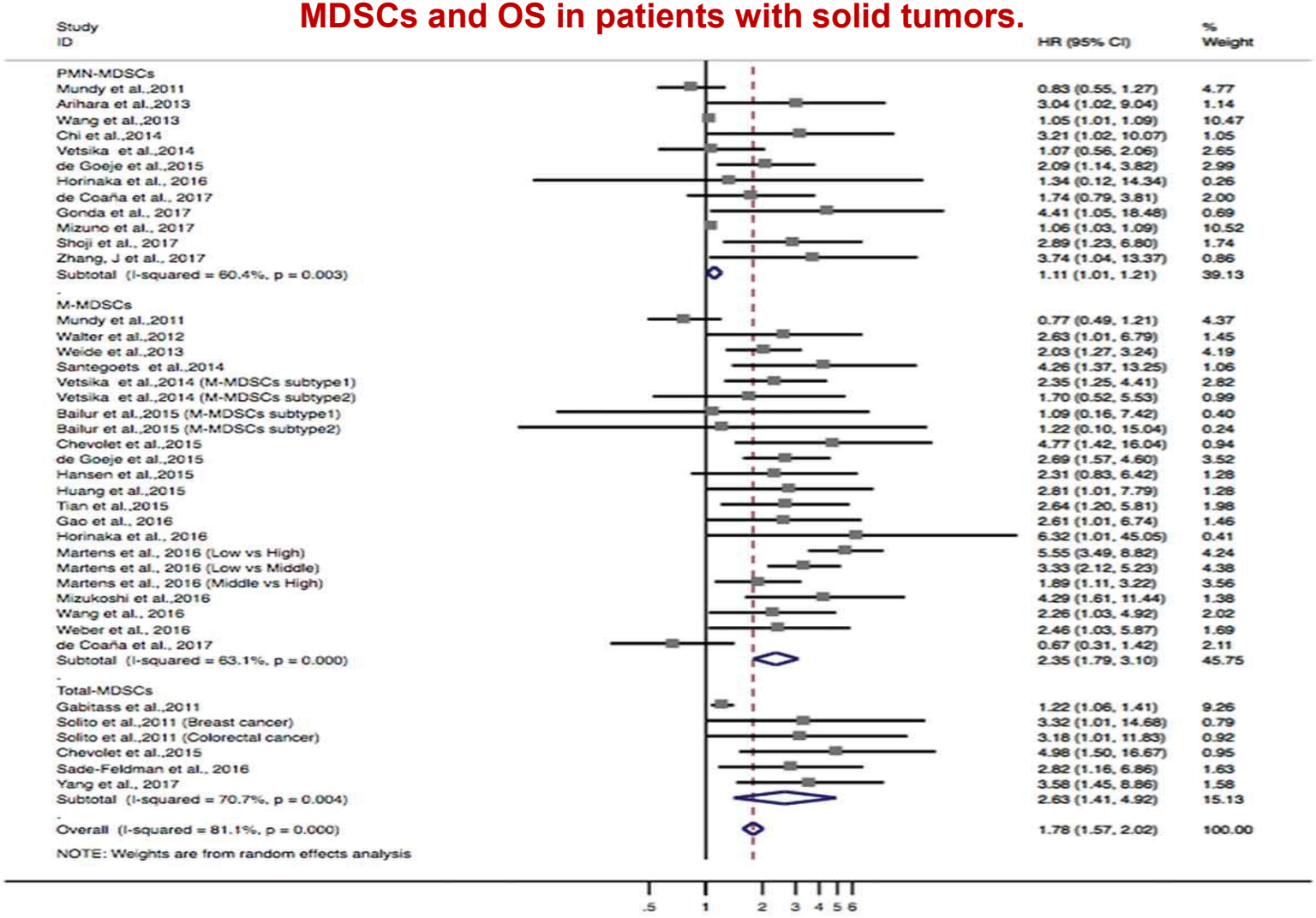

Signal 1
Signal 2
?
Cellular Stress
Cytokines & Immune suppressive Mediators
IL-1β, IL-6, IL-10, GM-CSF, G-CSF, M-CSF, VEGF
Notch ligands
Adenosine / A2b
IL-1β, TNF-α TLR Ligands
IFNγ / IFNGR
IL-14, IL-13 / CD124
PGE2 / EP2/4
PERK, IRE1α
Transcription Factors & Enzymes
STAT3
ICN / RBPJκ
cAMP / MAPK
NF-kB
STAT1
STAT6
COX-2
CHOP, XBP1
Targets
S100A8/9, NOX2, C/EBPβ, IRF8, HIF-1α
?
?
iNOS, PGE2, NOX2
iNOS, Arg1
Arg1, TGFβ NOX2,
Arg1, iNOS, PGE2
?
Expansion & Activation of MDSC Subsets
M-MDSC PMN-MDSC
MDSC expansion and induction of M-MDSC differentiation into TAMs by HIF-1α.
Immune suppressive activity through up-regulation of PDL-1 by HIF-1α
Regulation of MDSCs differentiation and production
MDSC expansion. In the absence of A2b, PMN-MDSC decreased in tumor sites
Immune suppressive activity by PNT & ROS production. TNF-α activate NF-kB in M-MDSCs
Increase M-MDSC activity and decrease PMN-MDSC function
Increase MDSC immune suppressive activity
Immune suppressive activity primarily in M-MDSCs
Recruitment & accumulation of MDSCs
Increase suppressive activity by MDSCs

Multiple suppressive mechanisms in different cells



Alicea-Torres, K. & Gabrilovich, D.I. OncoImmunol. (2018)

Meta-analysis of the association between different types of MDSCs and OS in patients with solid tumors.



Wang et al. Oncoimmunology, 2018, e1494113

Classical approach to targeting

Activate to promote immune responses

STING, CD40, TLR7/8, etc.

Can it work? Yes, but there are major raodblocks

Potent activation may result in tissue damage and autoimmune pathology

Activation of pathologically changed myeloid cells may result in increased pro-tumorigenic activity

Inactivate inhibitory pathways

IDO, adenosine, arginase, etc

Can it work? Yes, but …

Multiple redundant mechanisms limit efficacy

Many clinical disappointments

Target the source of the problems - MDSC

Patients selection. Patients with high proportion of specific pathological myeloid cells.

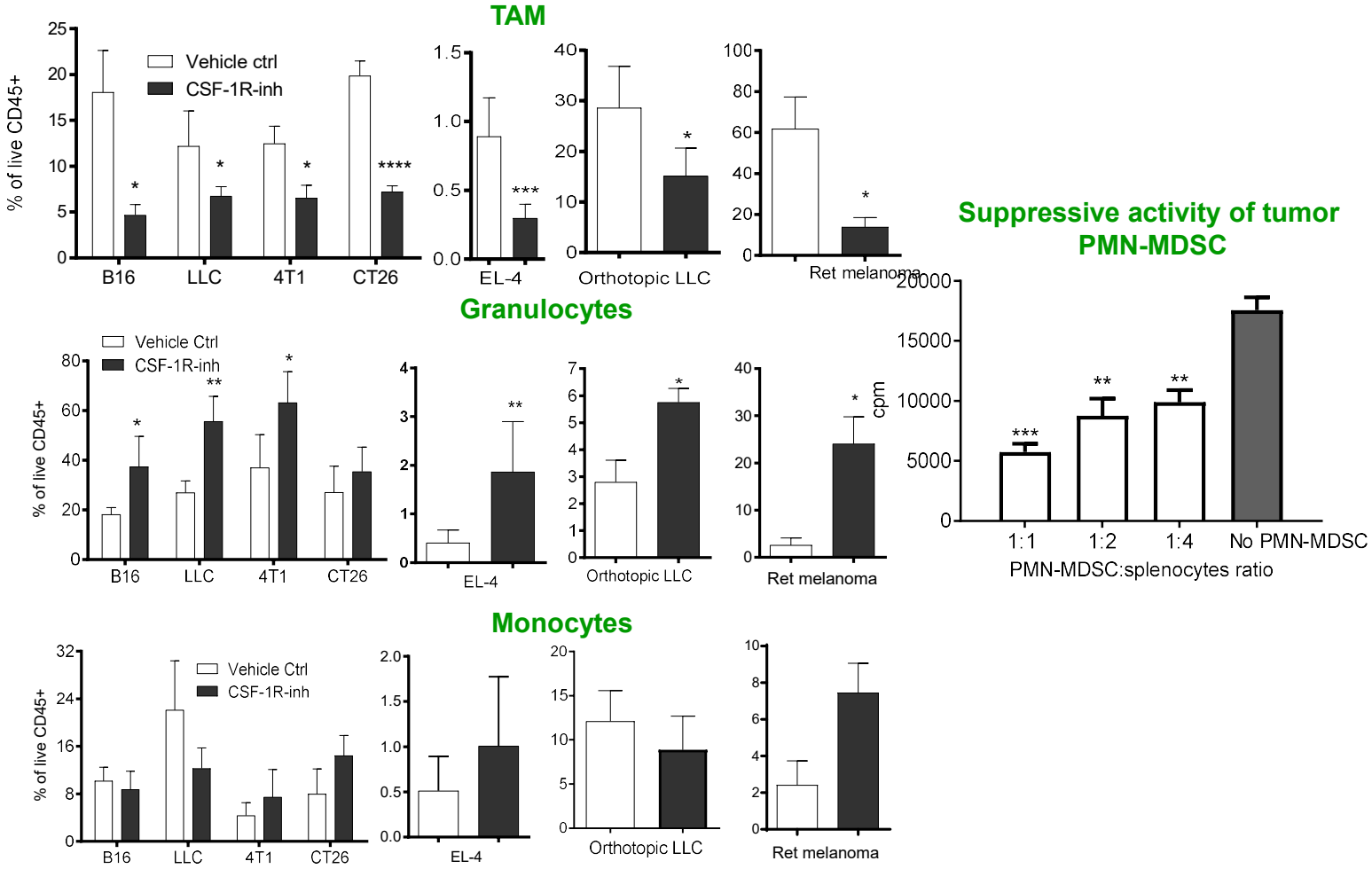
Eliminate only pathologically activated myeloid cells without removing normal cells.

© Can Stock Photo

Target different types of myeloid cells simultaneously

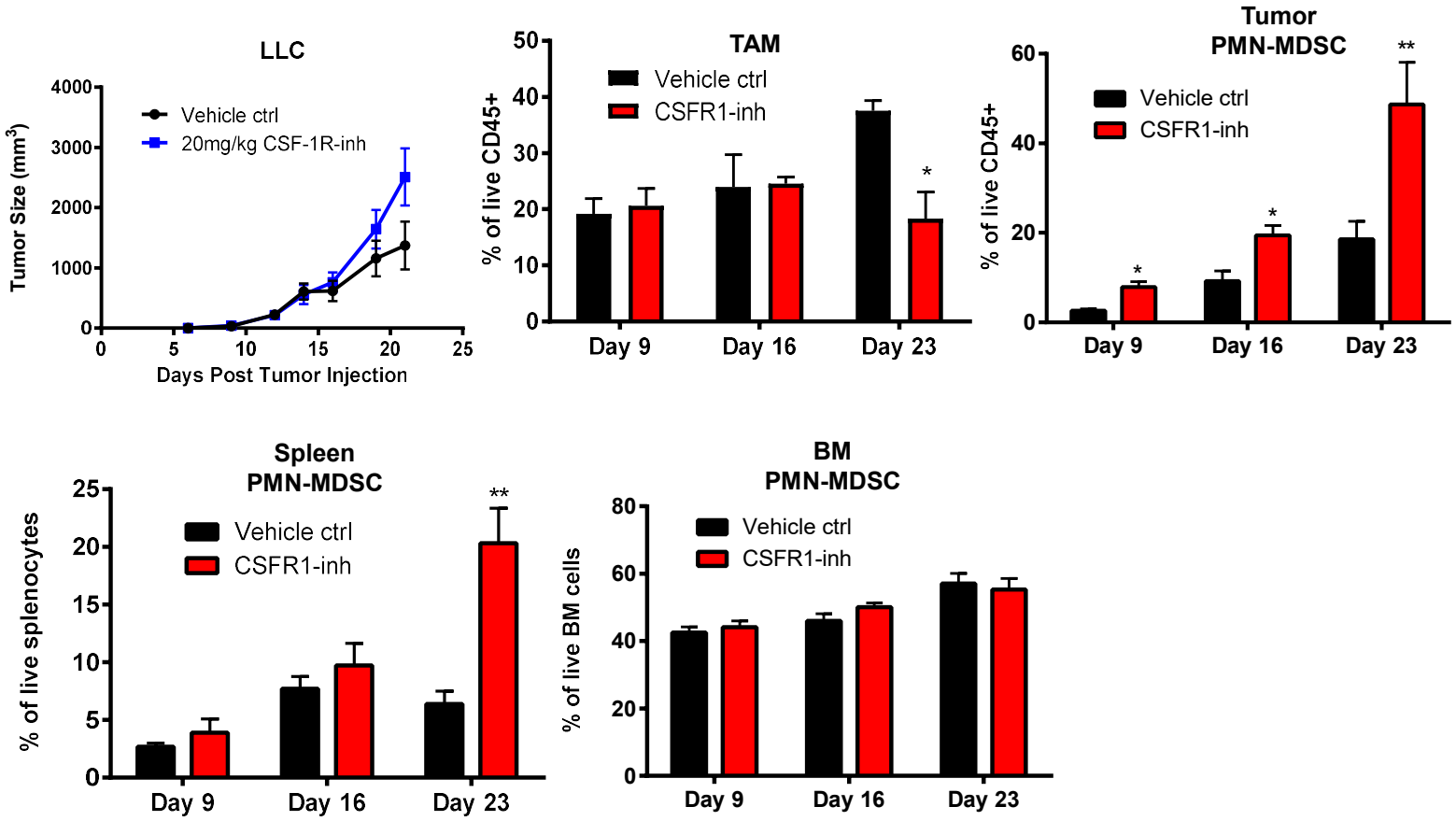
Convert pro-tumor myeloid cells to antitumor

Targeting of macrophages with CSF-1R inhibitor decrease TAM but increase tumor PMN-MDSC



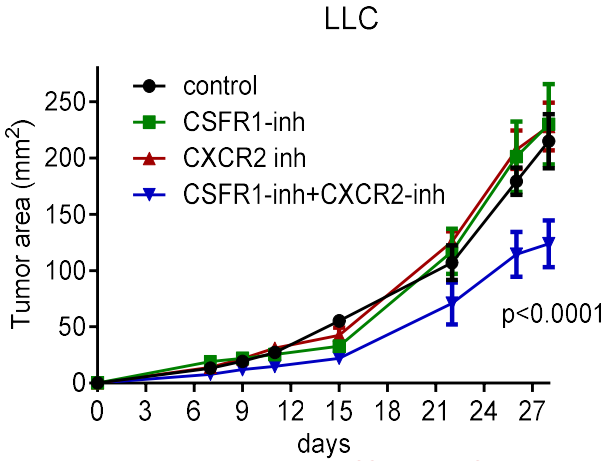
Kumar et al. Cancer Cell 2017;32(5):654-668

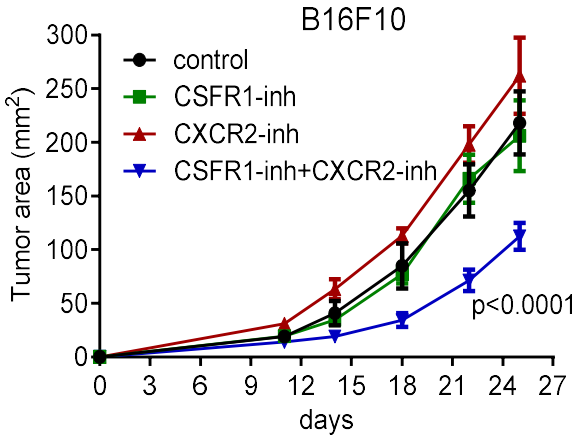
CSF-1R inhibition did not induce expansion of granulocytes but caused early accumulation in tumors



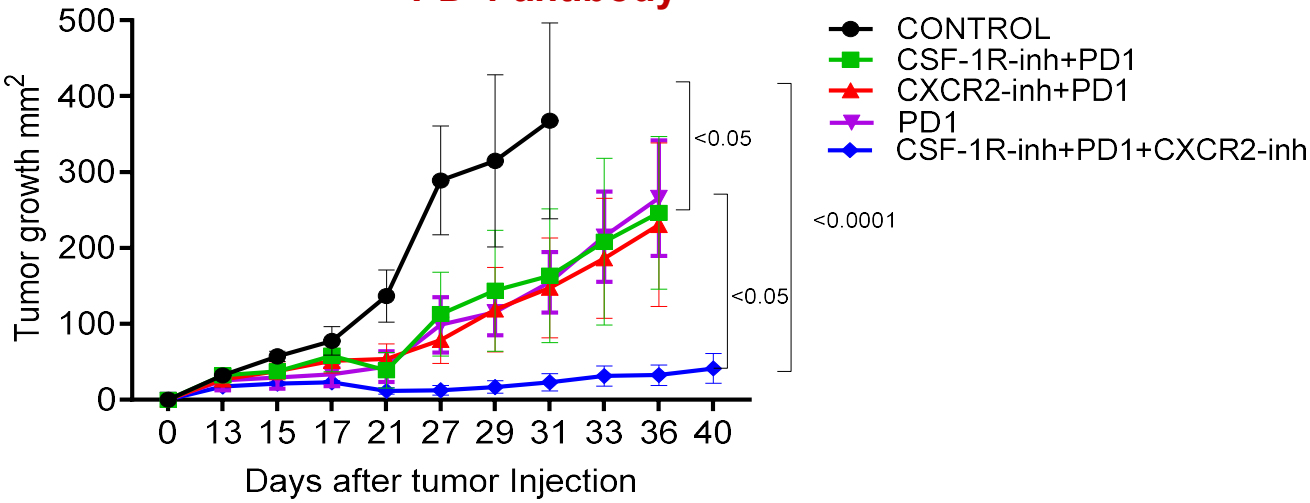
Kumar et al. Cancer Cell 2017 ;32:654-668

Therapeutic effect of combination of CSF-1R and CXCR2 inhibitors





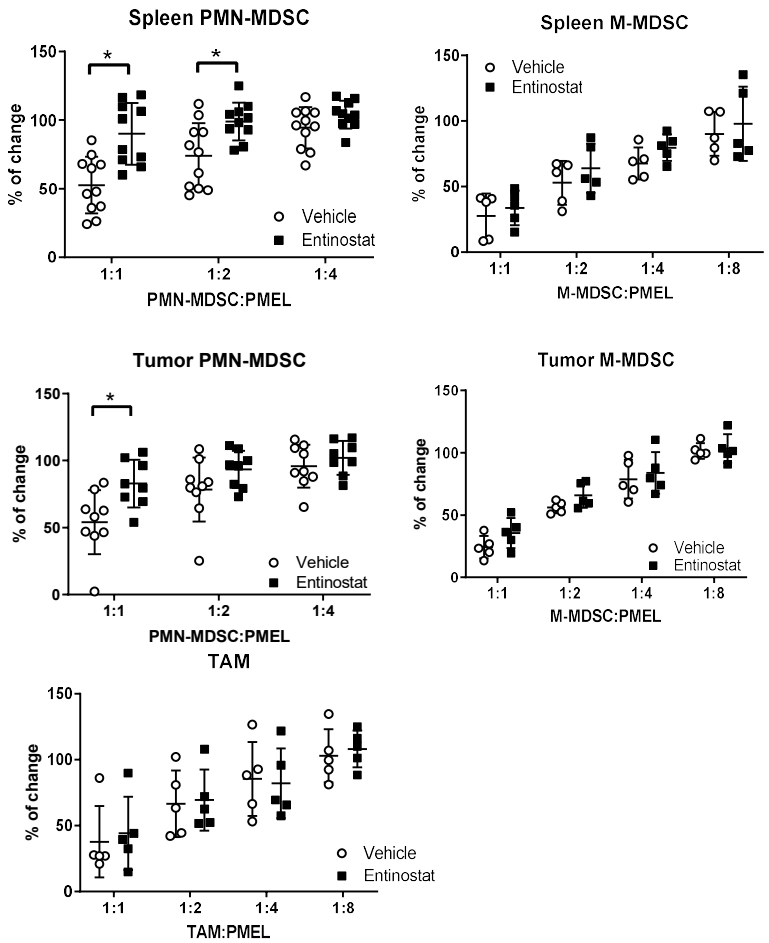
Therapeutic effect of combination of CSF-1R, CXCR2 inhibitors and PD-1 antibody



Kumar et al. Cancer Cell 2017 ;32:654-668

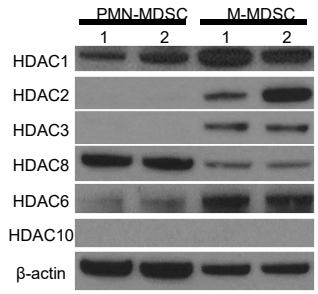
Selective targeting of different populations of myeloid-derived suppressor cells by histone deacetylase inhibitors

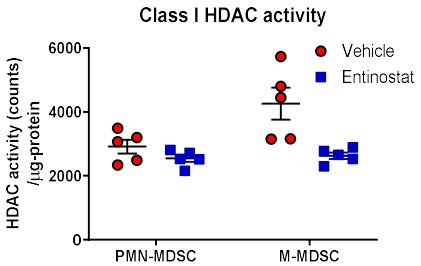
In mice, class I HDACs inhibitor entinostat had good combination activity with CTLA4 (less potent with PD1), but very small antitumor effect as single agent. Results of clinical trials were not encouraging.

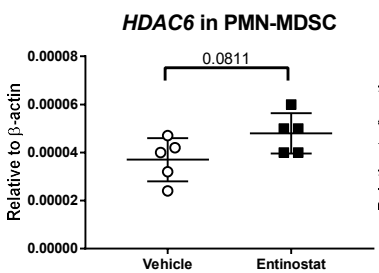


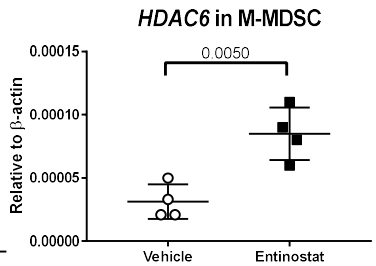
Entinostat abrogated suppressive activity of PMN-MDSC but not M-MDSC or TAM.

Different expression of HDAC6



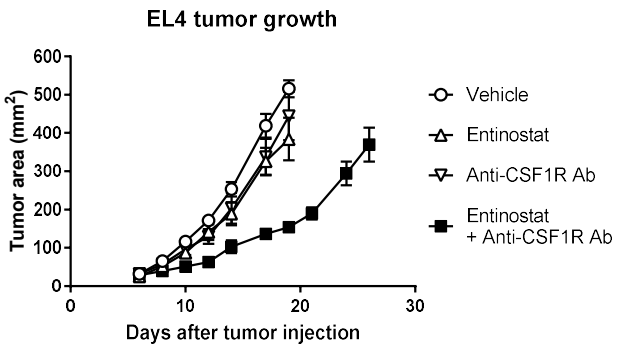




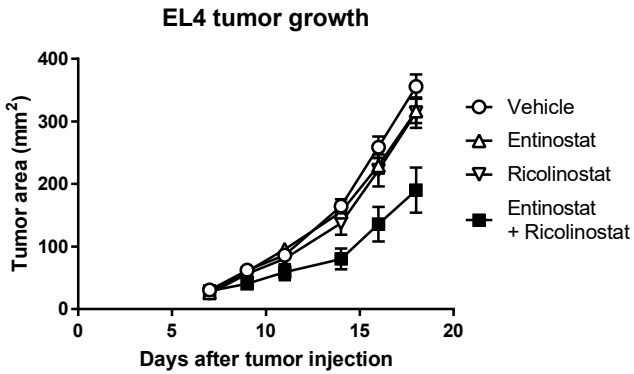


Hashimoto et al. Cancer Immunol. Imunother. 2020

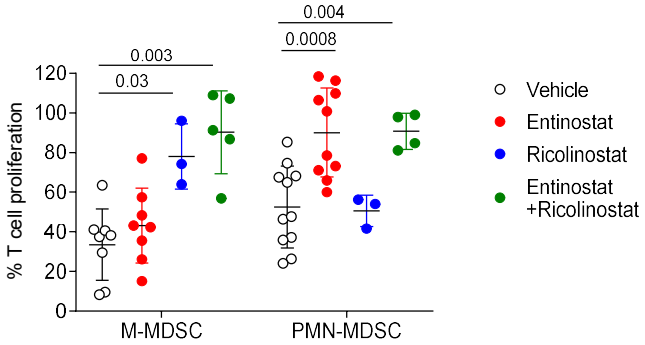
Combination of entinostat (PMN-MDSC targeting) with CSF1R (TAM targeting)

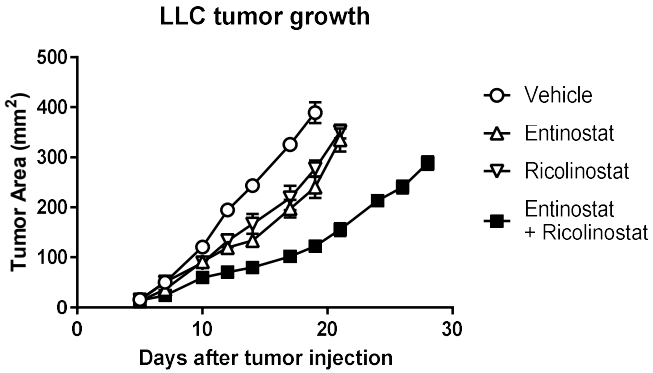


Combination of entinostat (class I HDAC) with ricolinostat (HDAC6)



Abrogation of suppressive activity of both groups of MDSC by combination of entinostat and ricolinostat

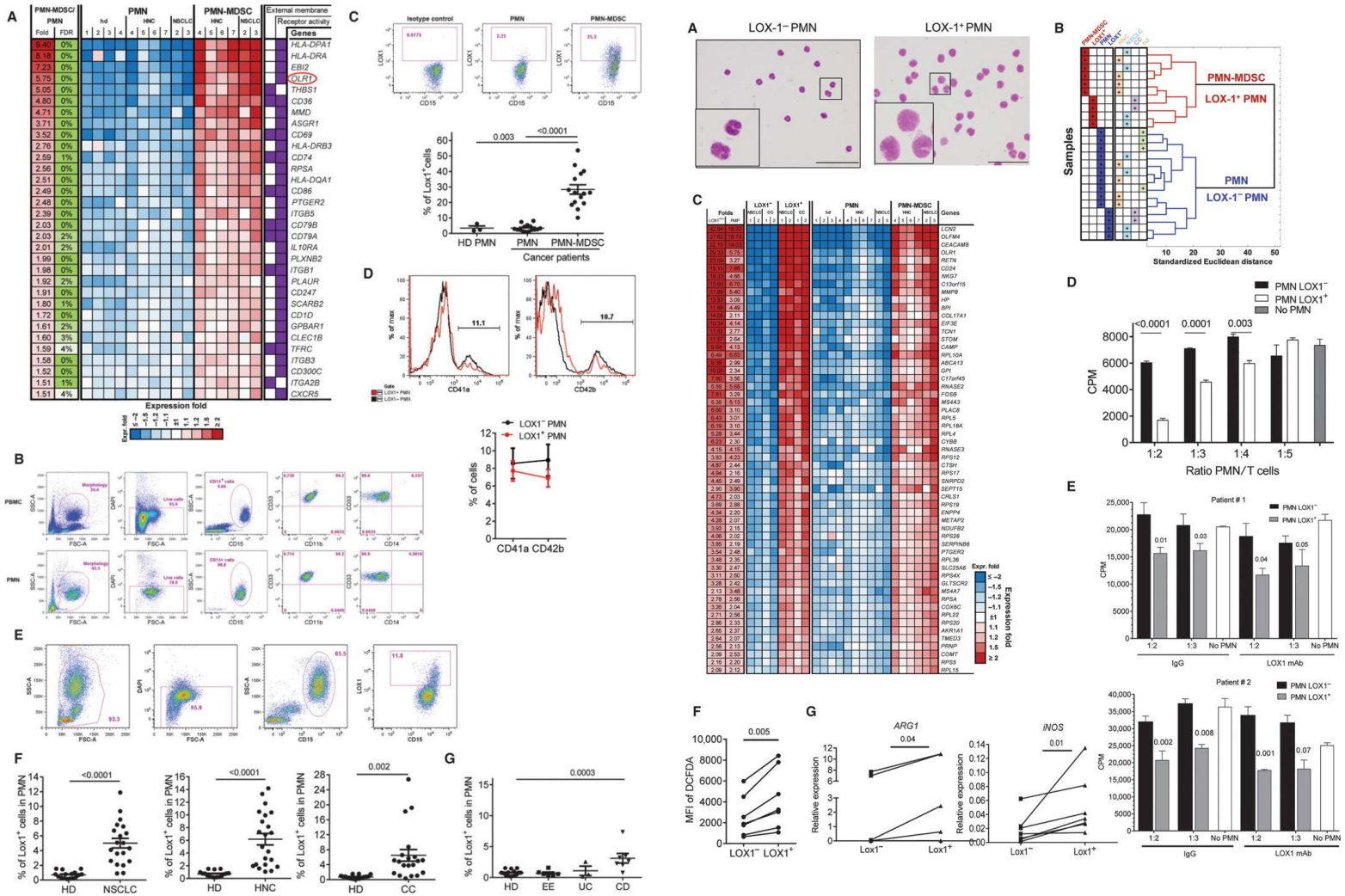




Hashimoto et al. Cancer Immunol. Imunother. 2020

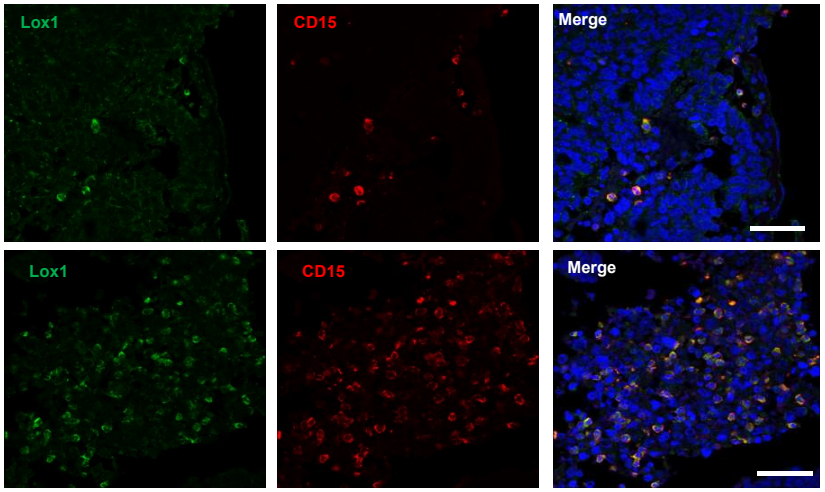
Simultaneous targeting of granulocytic and mononuclear cells provide antitumor effect in mice without CPI and may be beneficial in clinic

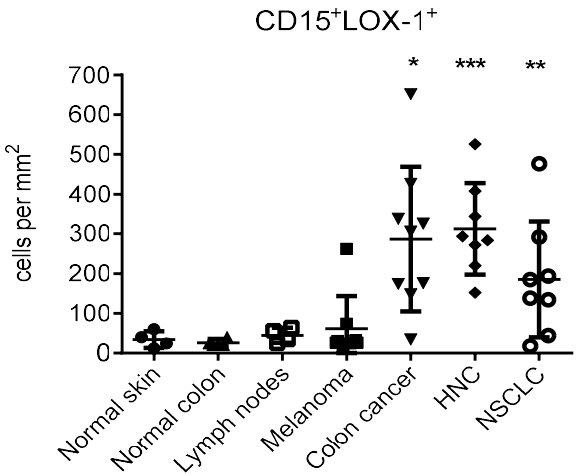
LOX-1 as a marker of PMN-MDSC that distinguish them from PMN

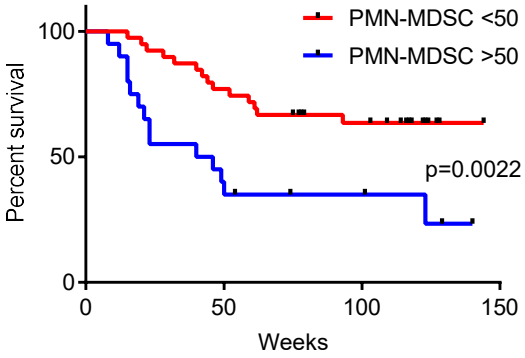


Condamine et al. Sci. Immunol. 2016;1:aaf8943

LOX-1+ PMN-MDSC in tumors predict clinical outcome

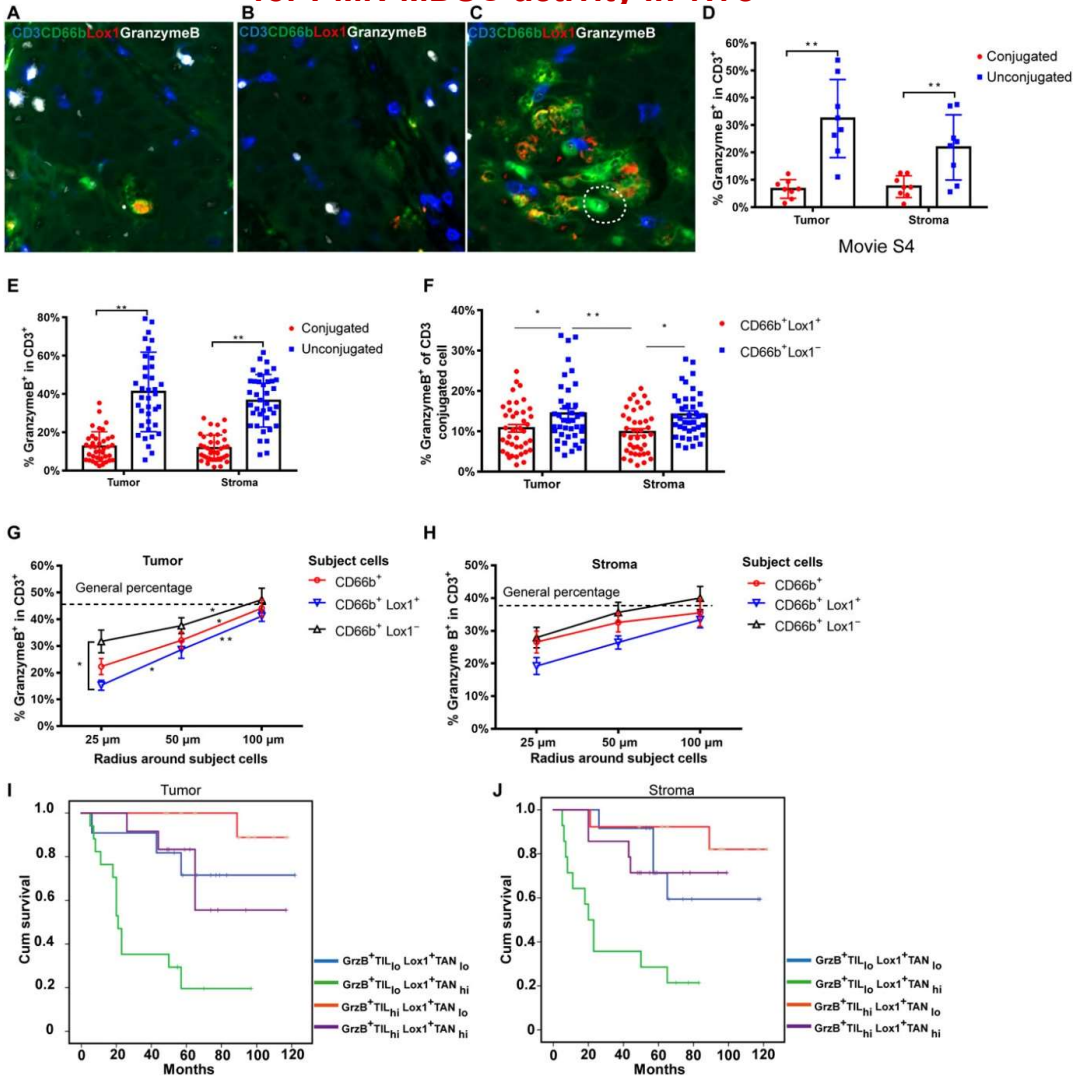






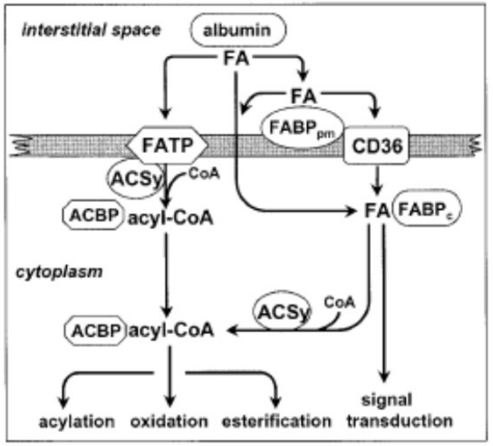
Kumar et al. Cancer Cell 2017;32(5):654-668

Conjugation and functional modulation of TIL by LOX-1+ PMN-MDSC provides evidence for PMN-MDSC activity *in vivo*

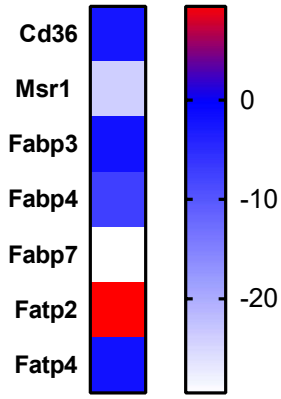


Yu Si et al. Sci. Immunol. 2019;4:eaaw9159

Interference with lipid metabolism can repolarize PMN-MDSC

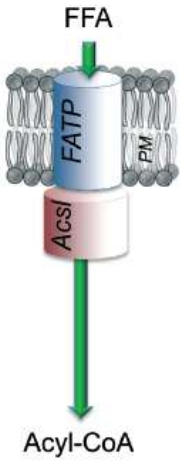


Azzay HME at al. Clinical chemistry, 2006



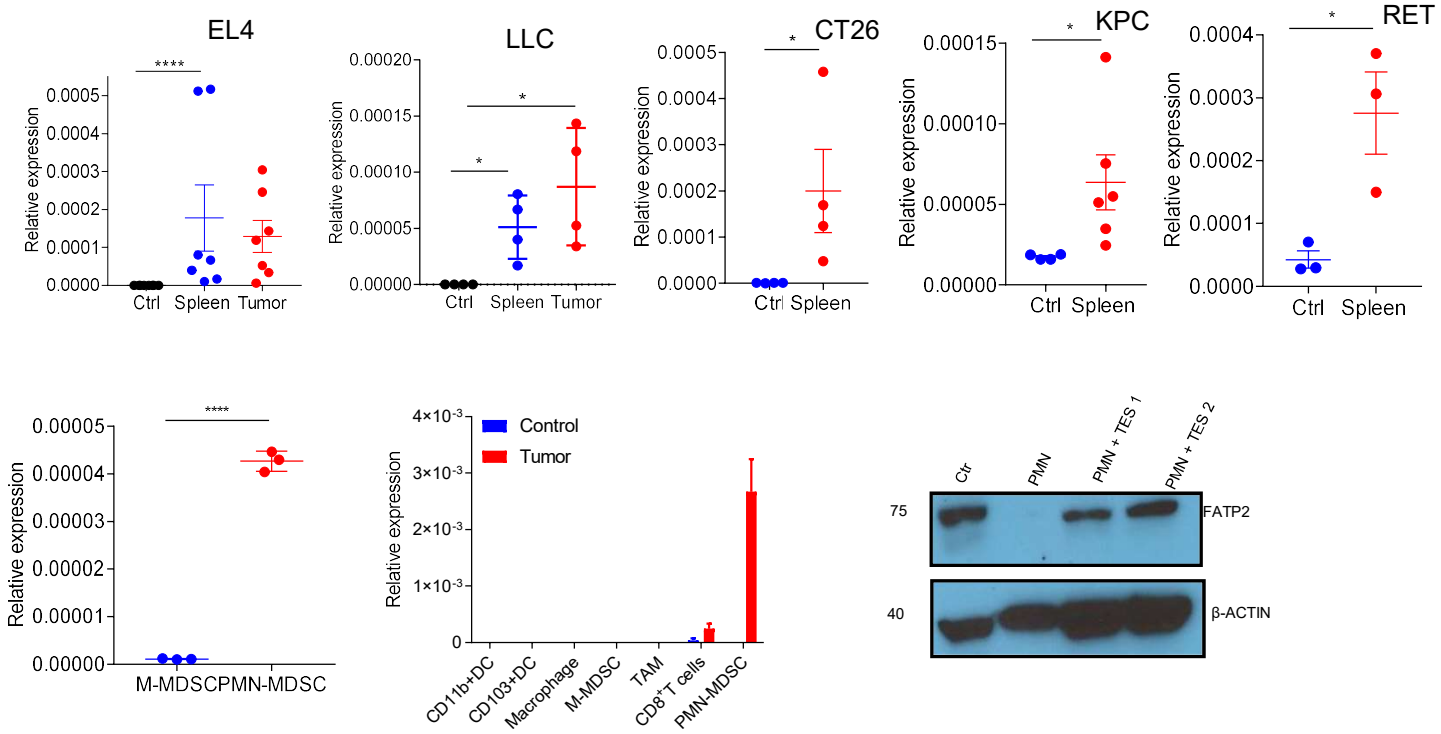
FATPs: fatty acid transporter
FABPs: fatty acid binding protein
CD36: fatty acid translocase
MSR1 (CD204): macrophage scavenger receptor 1

Fatty acid transporter 2 (FATP2)



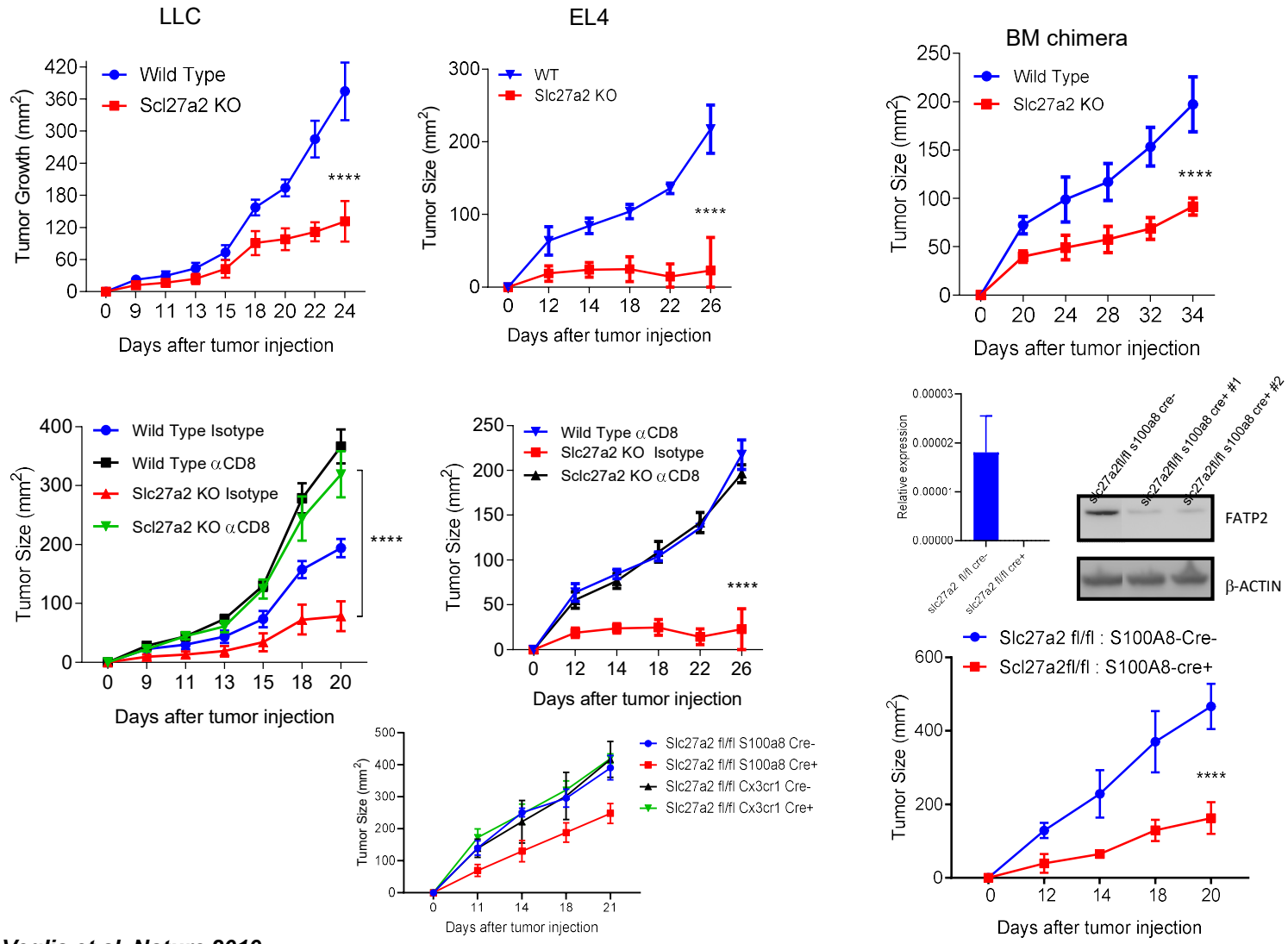
- Member of family composed of six members
- Very long fatty acid transport protein with acyl-CoA synthetase activity
- Key role in lipid biosynthesis and fatty acid degradation
- Specific inhibitors are available
- Good drug target:
  - Limited tissue expression
  - Deletion does not affect development, growth, and normal functions
  - Inhibition does not impact cell viability
- Suggested as biomarker for obesity

FATP2 is selectively increased in PMN-MDSC



F. Veglia et al. Nature 2019

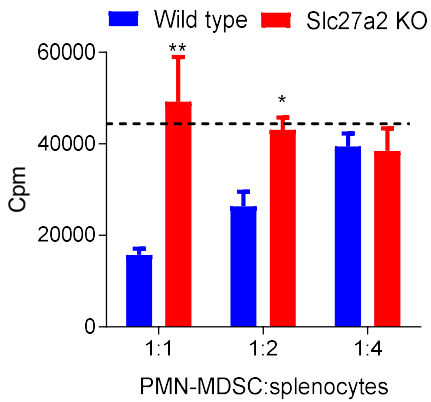
FATP2 deletion has strong antitumor effect

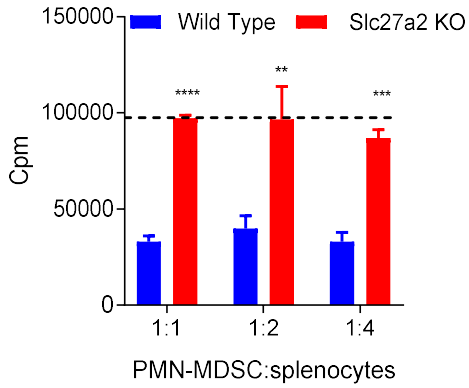


F. Veglia et al. Nature 2019

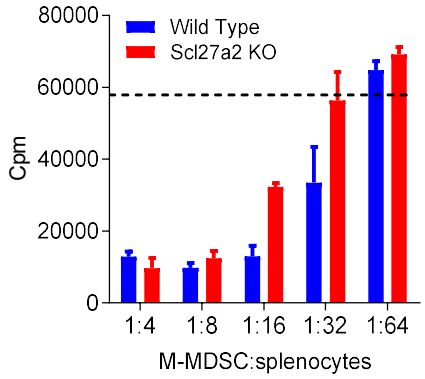
FATP2 deletion cancelled immune suppressive activity of PMN-MDSC, but not M-MDSC and macrophages

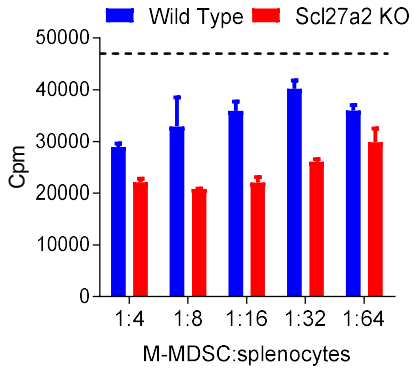
PMN-MDSC



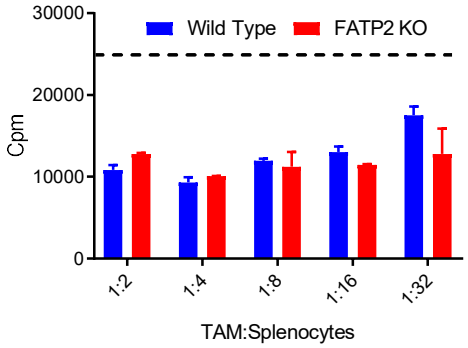


M-MDSC



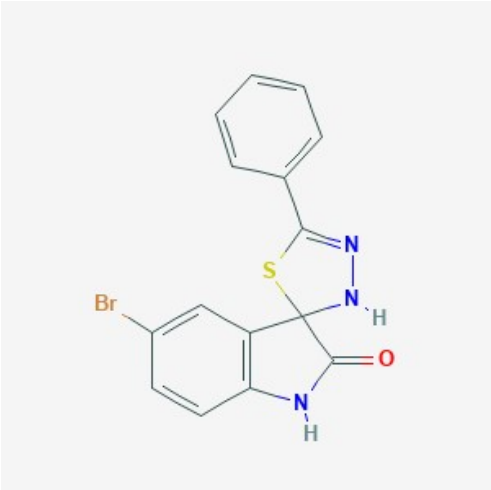


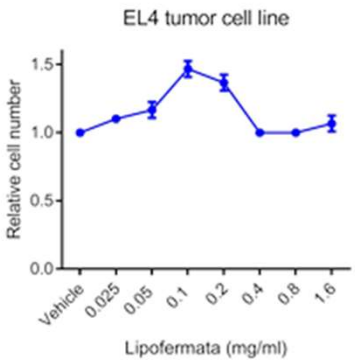
TAM

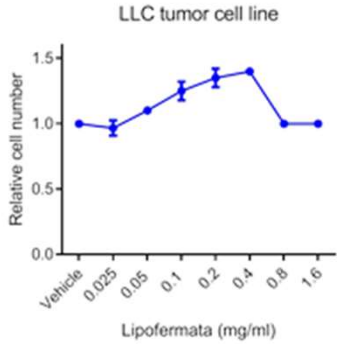


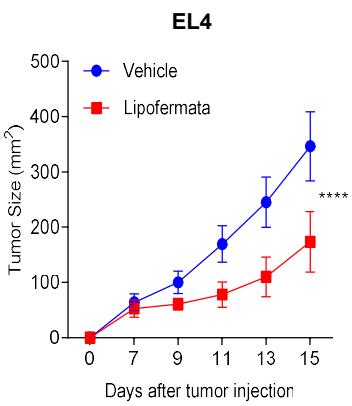
F. Veglia et al. Nature 2019

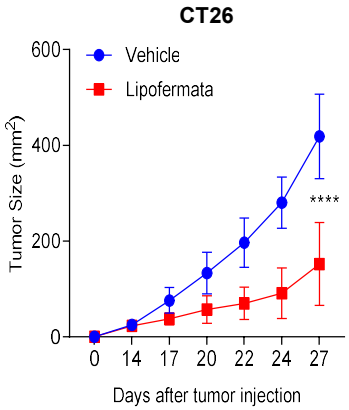
Pharmacological targeting of FATP2

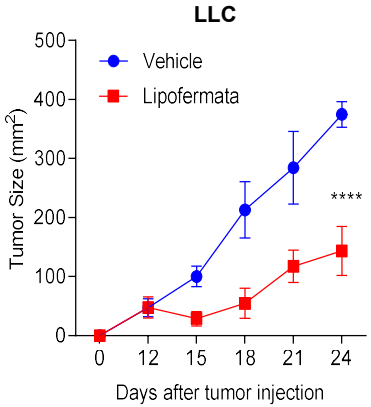


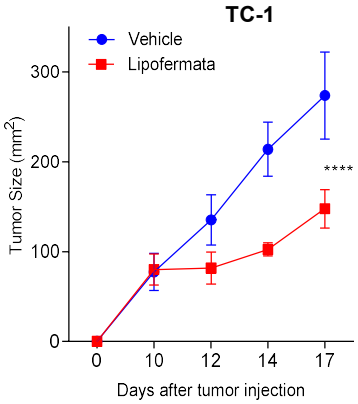


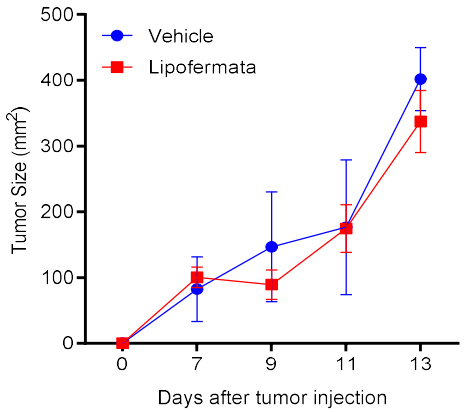


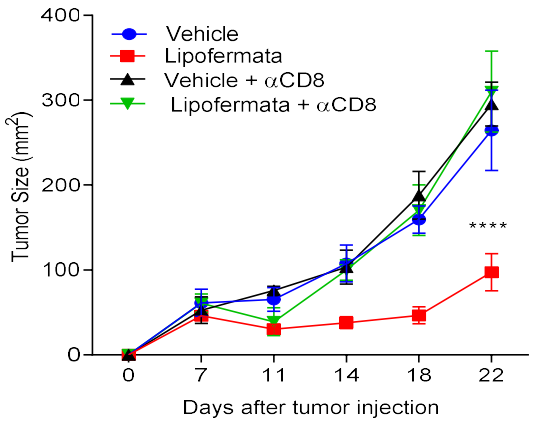


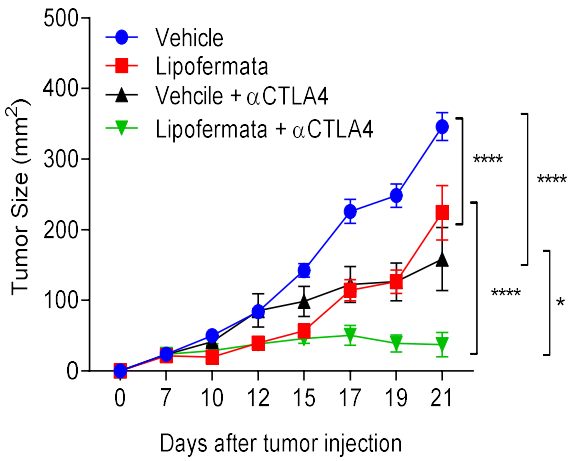


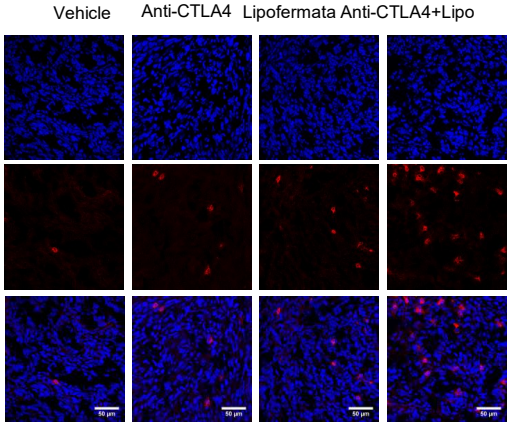


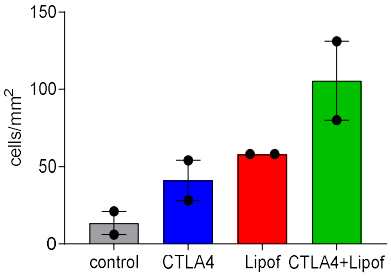












F. Veglia et al. Nature 2019

Conclusions

- **Distinction between classical and pathological myeloid cells is important in the design of targeting strategies;**
- **Pathologically activated myeloid cells can be distinguished in cancer patients and this needs to be leveraged in search for new targets;**
- **Targeting of both major arms of myeloid cells (mononuclear and granulocytic) is important;**
- **Repolarization of pathological myeloid cells may be the future**