Immunosuppressive Cells in the Tumor Microenvironment

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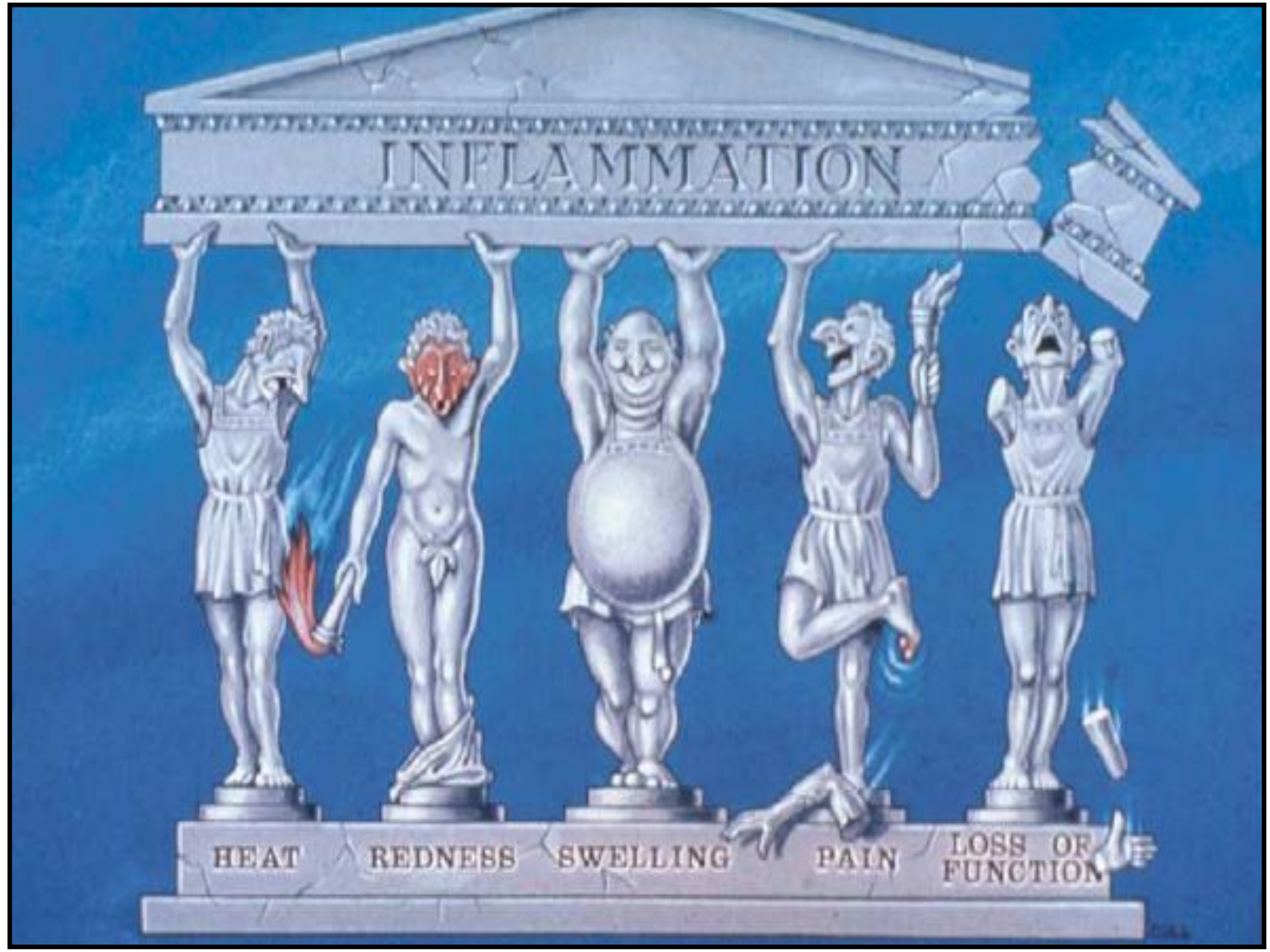
Spontaneous Regression of Tumors or Immunotherapy?

Imhotep (2600 BC- Egypt): Recommends " applying a poultice of herbs over the tumor and making an incision in the site"

StanislawTanchou (1844 –Paris): "treat enlarged lymph glands and tumors by creating pustules on the tumor and other parts of the body"

Others in the 19th century: "infecting tumors with erysipelas (s. pneumo and staph aureus) , "gangrene" (clostridia) or syphilis to establish pustules on the tumores.



Aulus Cornelius Celsus – 1 century AD

Rudolf Virchow - 1863

The "lymphoreticular infiltrate" reflect the site where cancer lesions appear in the inflammed tissues.

William Coley MD
(New York)

"Patients with osteosarcomas or breast tumors infected with erysipelas (*Streptococcus pyogenes*) have a longer survival and in some cases have a decrease in tumor size even in distant tumors" - 1893

1862 - 1936

Coley Toxins: *Streptococcus pyogenes*, *Serratia marcesens* and *Staphylococus epidermidis*: 10% responders

Purified Coley Toxins: *Streptococcus pyogenes* (no effect)

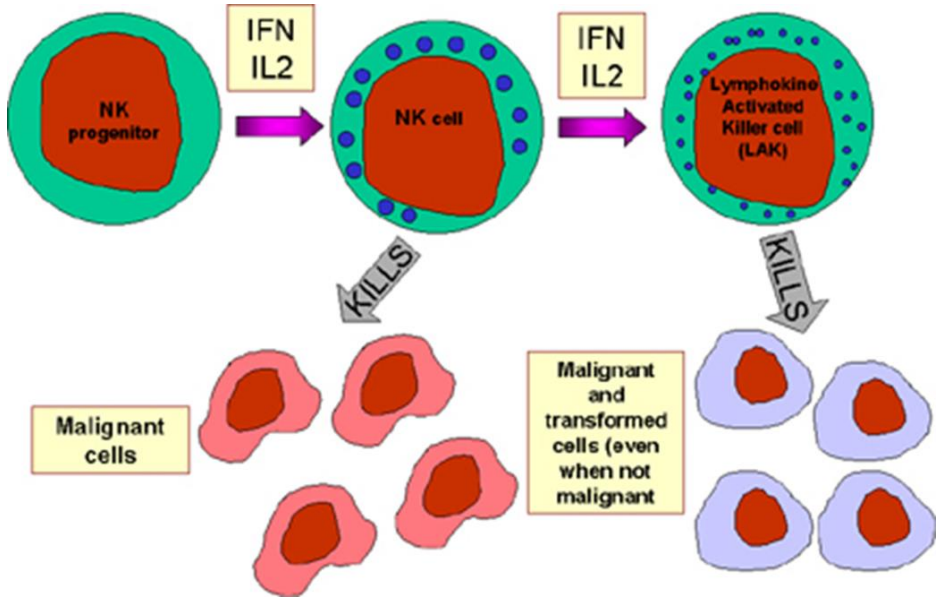
Modern era of Immunotherapy

- 1982 – IL2 gene cloned

  T. Taniguchi

- LAK cells:

  E. Grimm and S. Rosenberg



Great in mice but little effect in patients

Anergy/Tolerance in Cancer

- 1960 – 1970's: Blocking antibodies
- 1980's:
  - Suppressor T cells
  - Absence of tumor associated antigens
  - Loss of MHC class I
  - Changes in the stroma: "tumor ignorance"
  - Production of immunosuppressive cytokines – TGFb
  - Absence of costimulatory molecules – B7 family
- Cheever, Greenberg and Fefer – Low dose cytoxan

- Review J Biol Response Mod. 1984;3(2):113-27.Potential for specific cancer therapy with immune T lymphocytes. M A Cheever, P D Greenberg, A Fefer; PMID: 6233396

Myeloid-Derived Suppressor Cells (MDSC) in Tumors

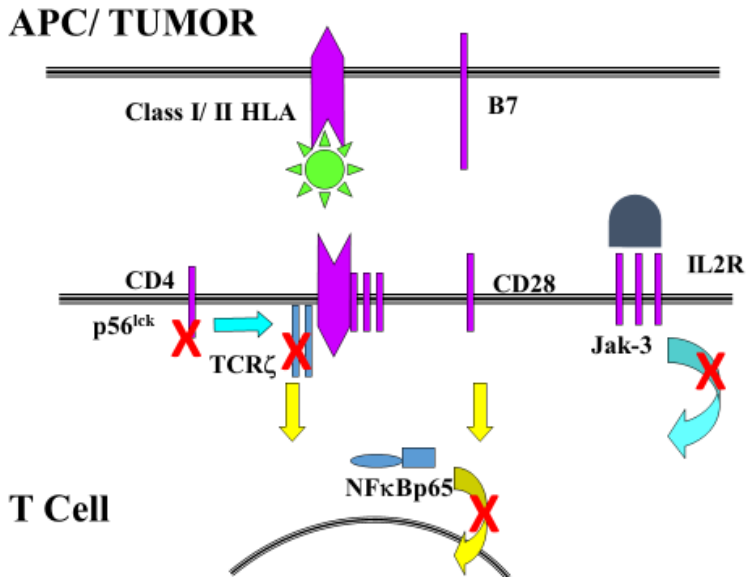
- **Mizoguchi et al** – **Alterations in Signal Transduction Molecules in T Lymphocytes from Tumor-Bearing Mice.** H. MIZOGUCHI, JJ. O'SHEA, DL. LONGO, CM. LOEFFLER, DW. MCVICAR, AC. OCHOA ***SCIENCE*** • 11 Dec 1992 • Vol 258, Issue 5089 • pp. 1795-1798 • DOI: 10.1126/science.1465616

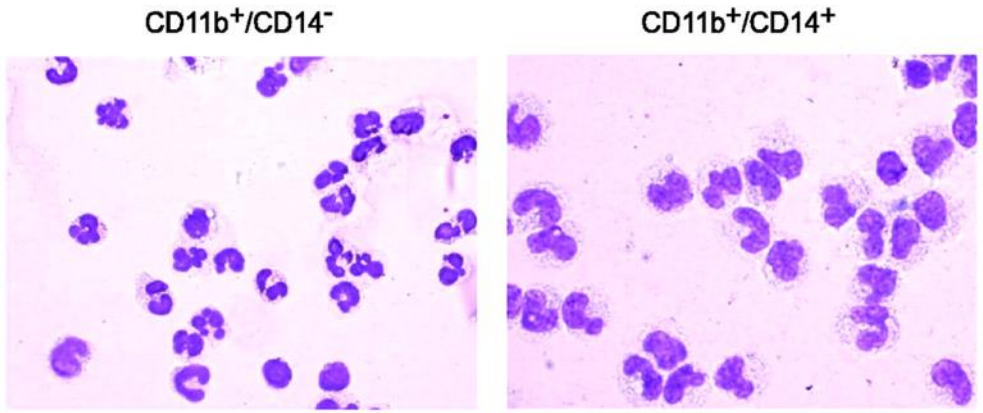
- **Gabrilovich, D**., Chen, H., Girgis, K. *et al.* **Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells.** ***Nat Med*** **2,** 1096–1103 (1996). https://doi.org/10.1038/nm1096-1096

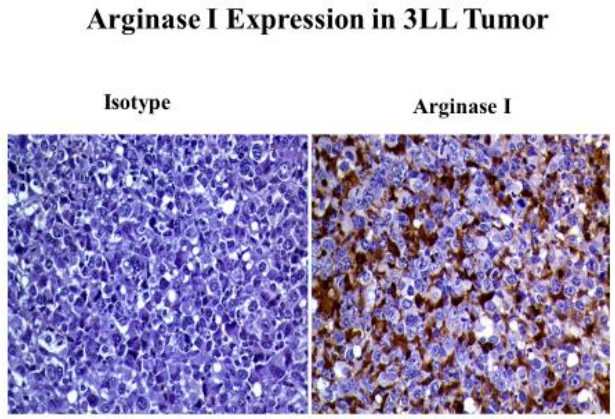
- **V Bronte** 1, P Serafini, E Apolloni, P Zanovello**. Tumor-induced immune dysfunctions caused by myeloid suppressor cells**. PMID: 11759067 DOI: 10.1097/00002371-200111000-00001

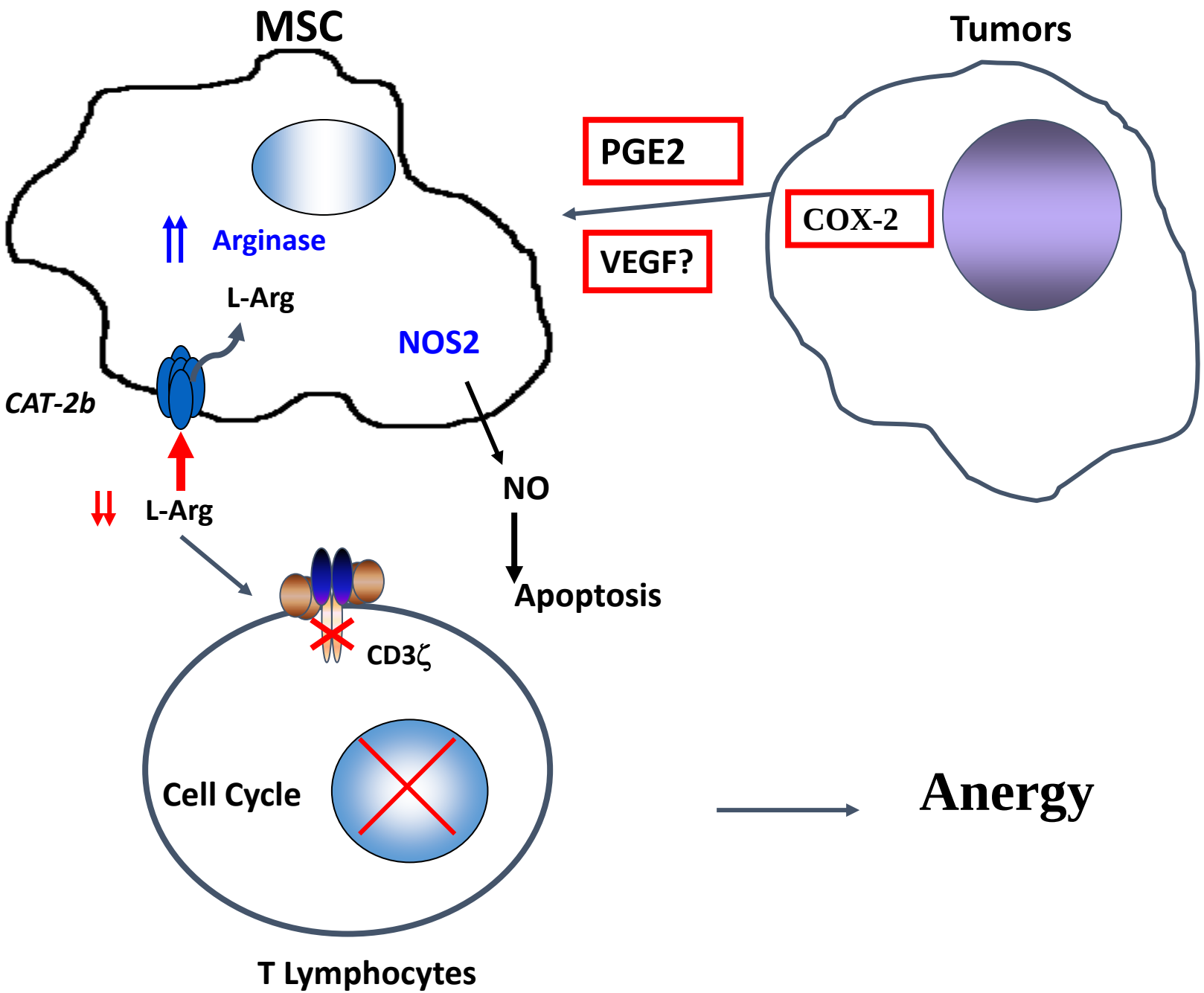
- **PC. Rodriguez**, …….AC. Ochoa. **Arginase I Production in the Tumor Microenvironment by Mature Myeloid Cells Inhibits T-Cell Receptor Expression and Antigen-Specific T-Cell Responses** DOI: 10.1158/0008-5472.CAN-04-0465 Published August 2004

- **V Bronte** 1…. PC Rodriguez …. A. Ochoa , Dmitry I Gabrilovich. **Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards.** PMID: 27381735 PMCID: PMC4935811 DOI: 10.1038/ncomms12150



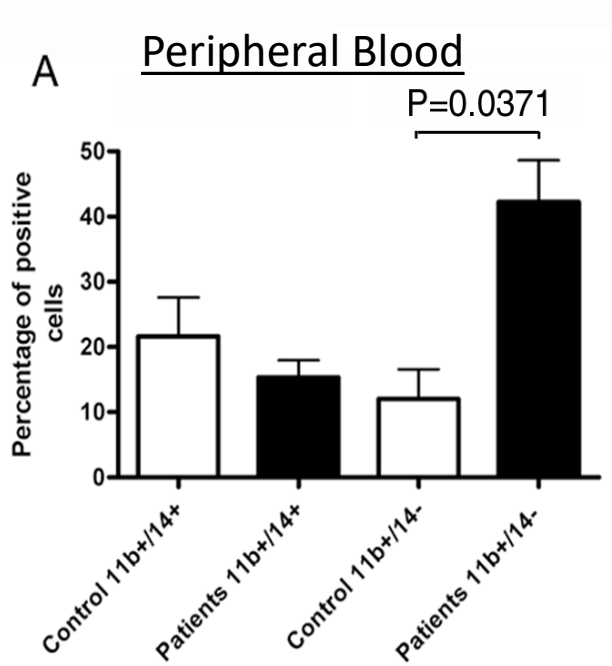




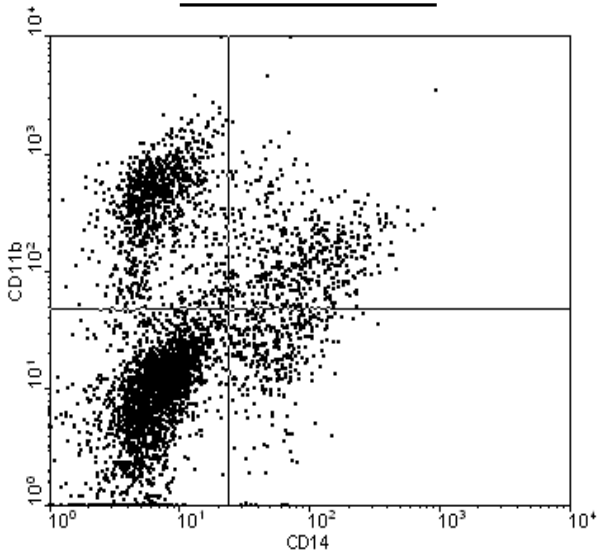

MSC
Tumors
PGE2
COX-2
VEGF?
Arginase
L-Arg
NOS2
CAT-2b
L-Arg
NO
Apoptosis
CD3ζ
Cell Cycle
T Lymphocytes
Anergy

MDSC in Renal Cell Carcinoma

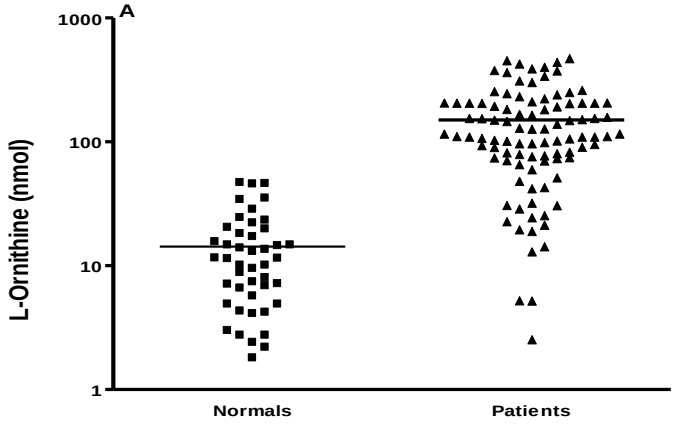
Peripheral Blood



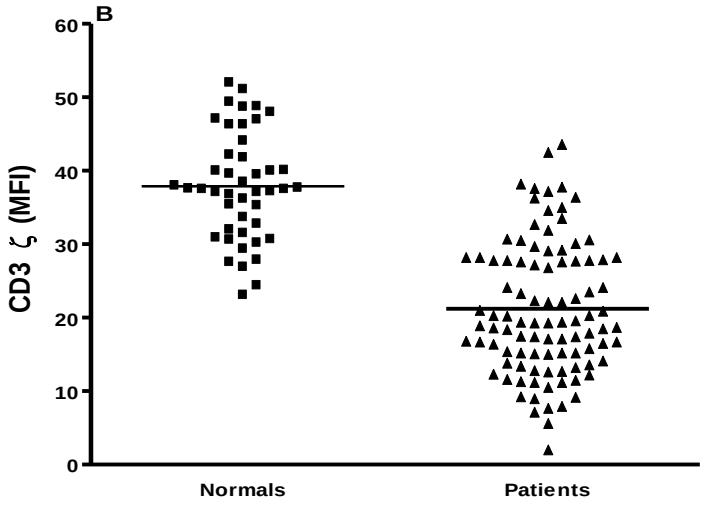
Intratumoral



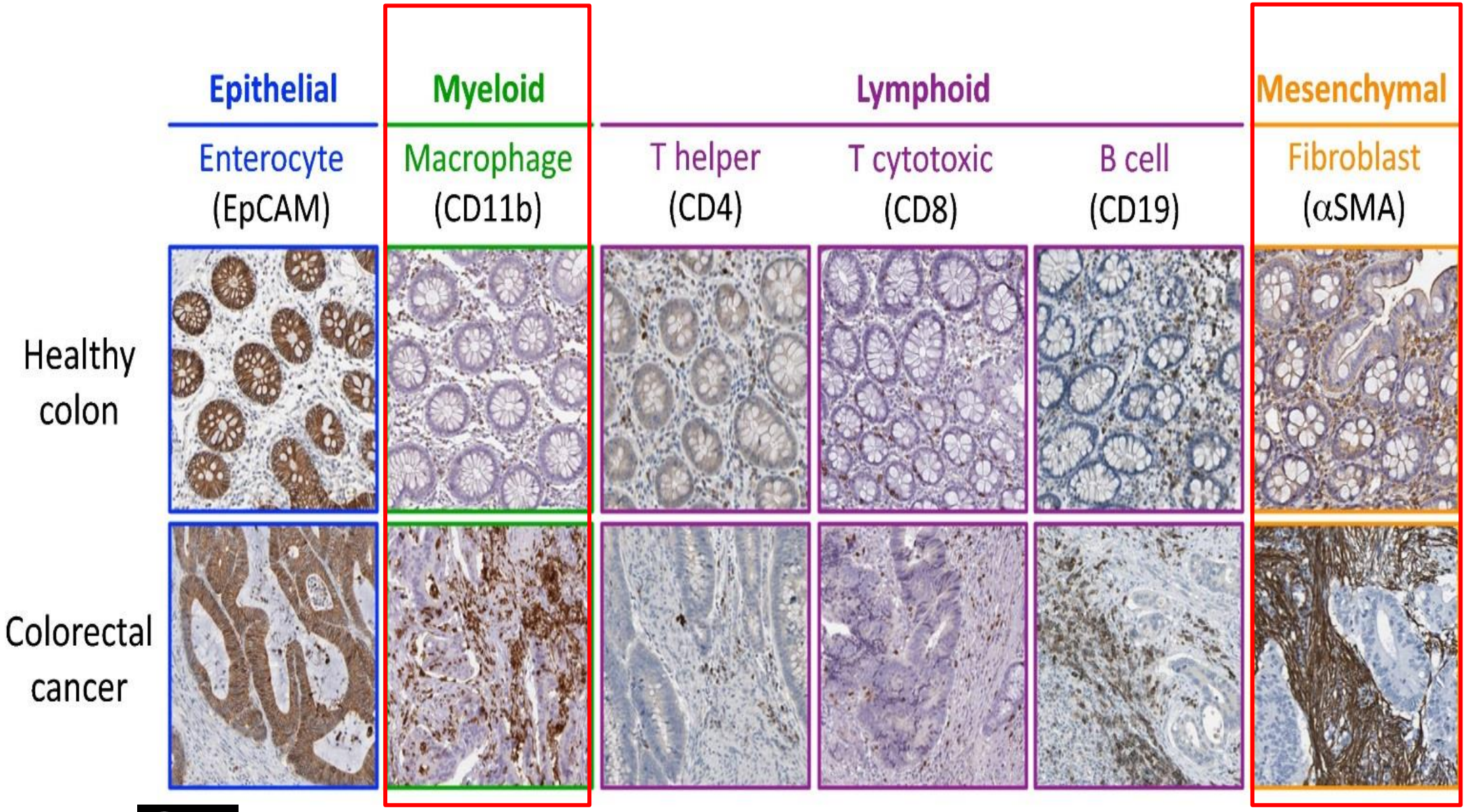
Arginase Activity



Loss of CD3ζ in T cells



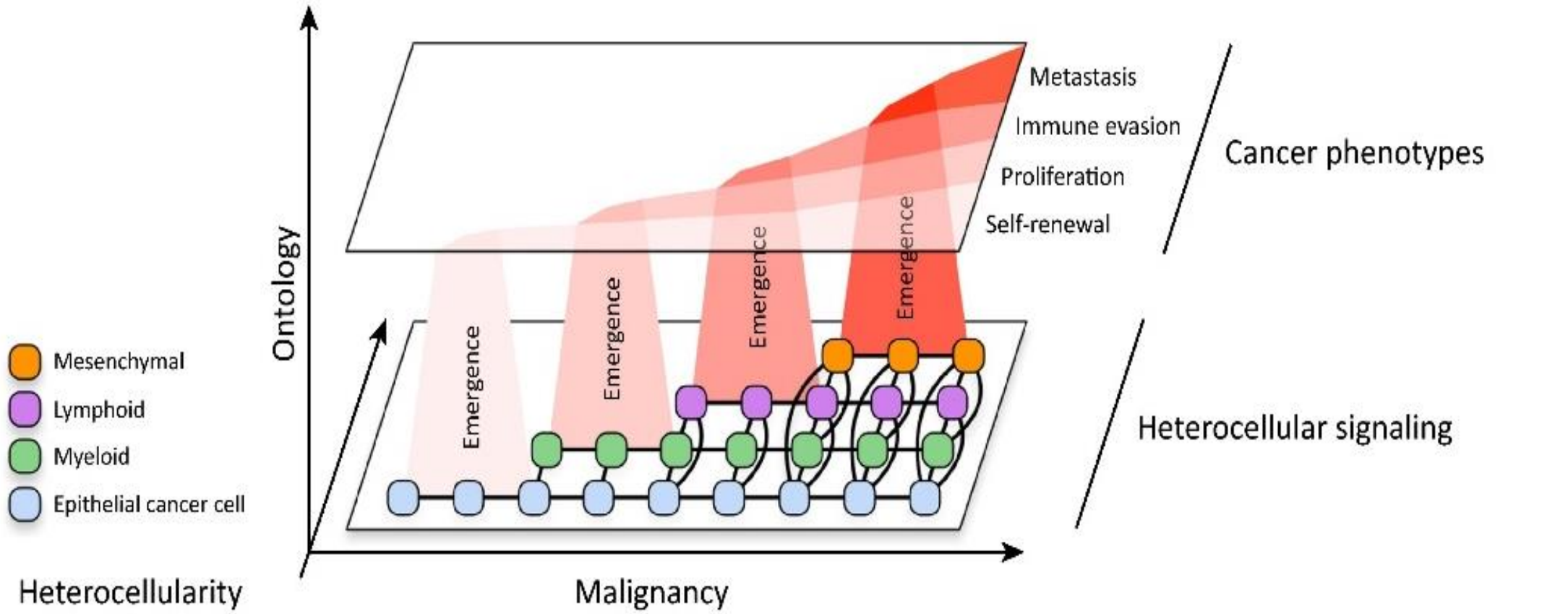
HETEROCELULLAR IMMUNE INFILTRATION OF COLORECTAL CANCER



Cell PRESS

Christopher J. Tape - Trends in Cancer 2017 3, 79-88DOI: (10.1016/j.trecan.2016.12.004)

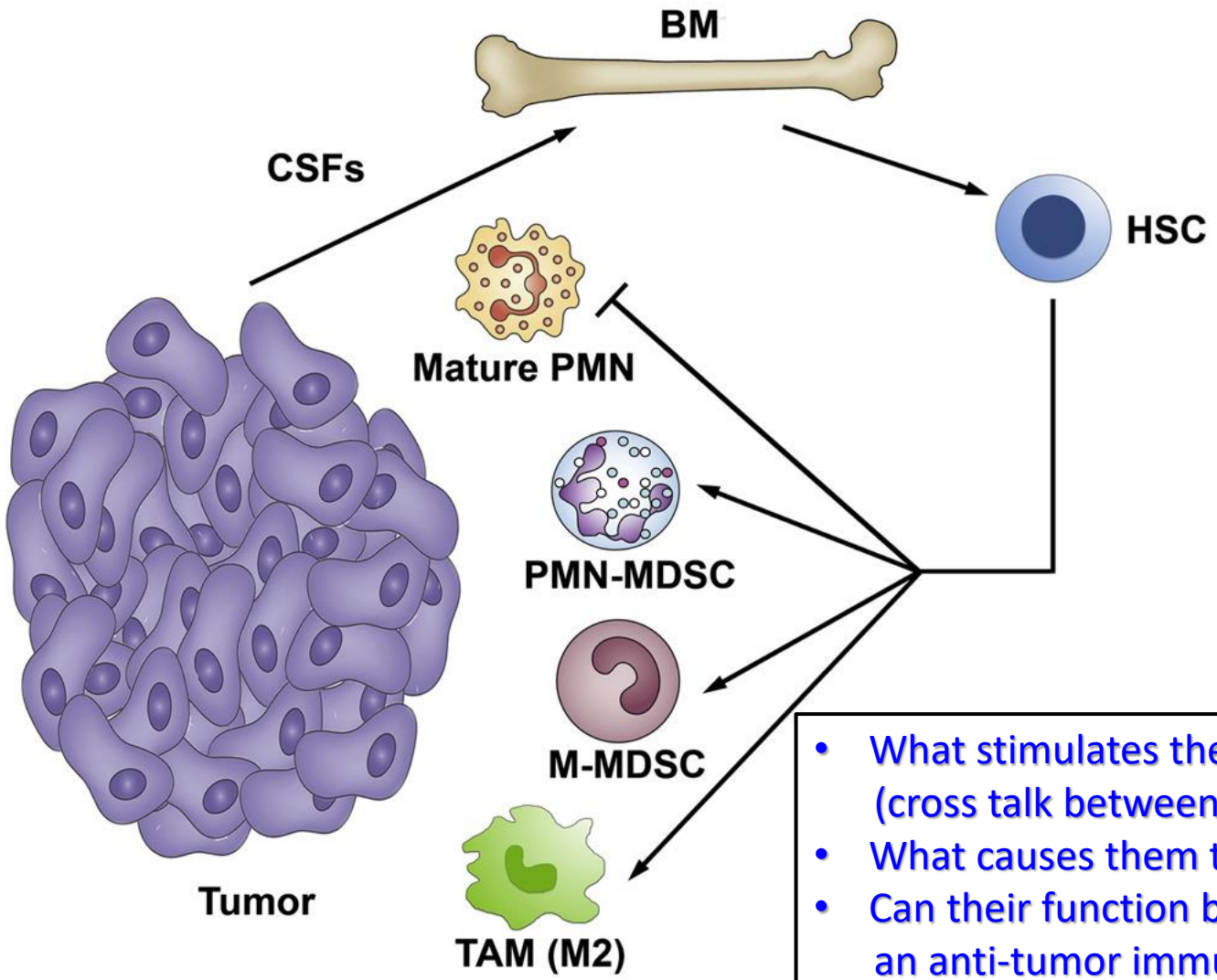
Trends in Cancer



Trends in Cancer

Trends in Cancer 2017 3, 79-88DOI: (10.1016/j.trecan.2016.12.004)

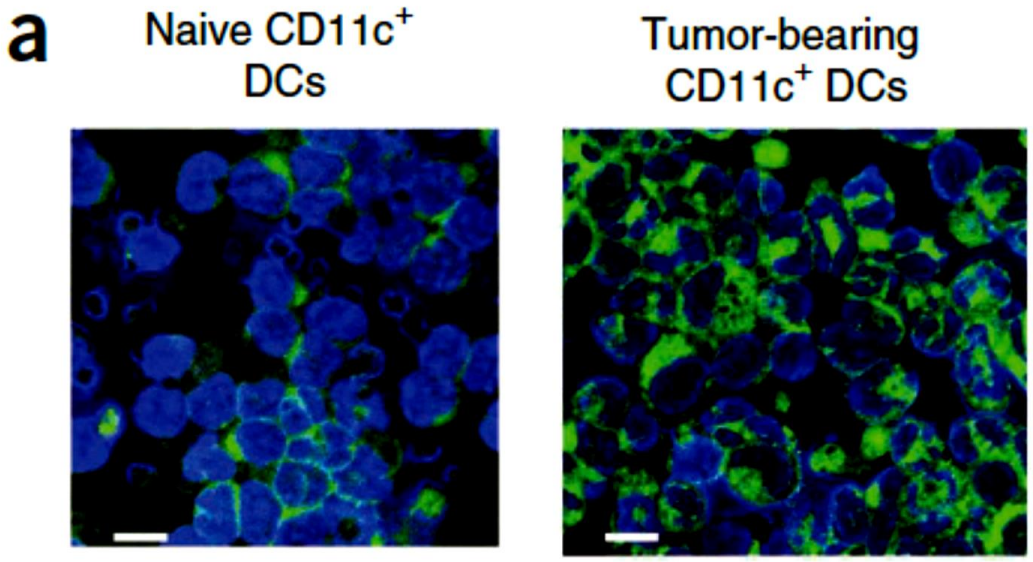
Myeloid- derived Suppressor Cells - (MDSC)



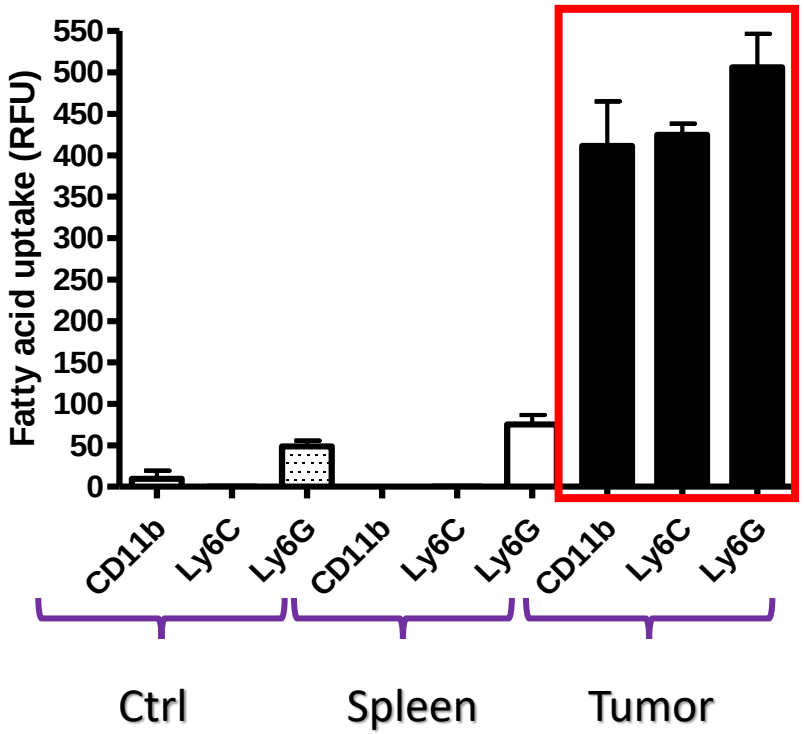
- What stimulates the production of MDSC (cross talk between tumor cells – MDSC)
- What causes them to be immunosuppressive
- Can their function be reversed to increase an anti-tumor immune response.

Strauss et al.
Cancer Cell 2015 28, 253-269DOI: (10.1016/j.ccell.2015.07.006)

MDSC Have Increased Lipid Uptake

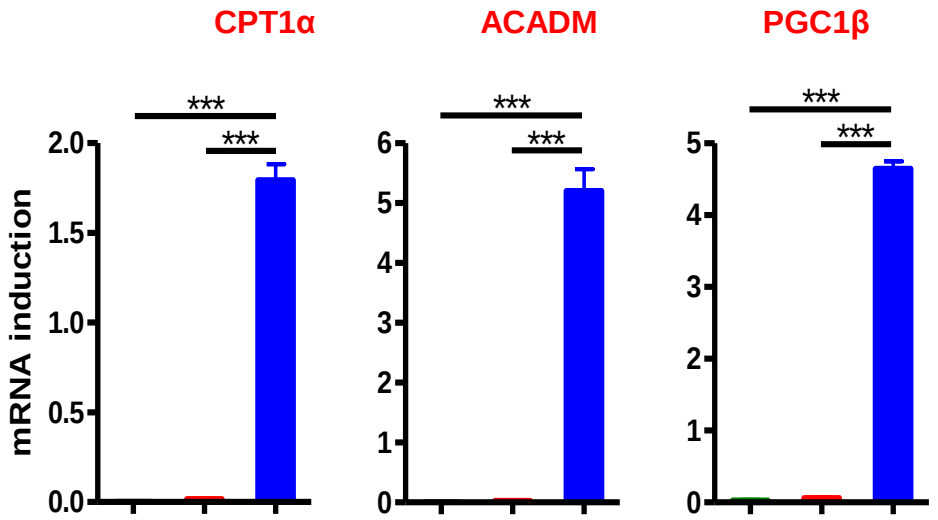


D. Garbrilovich et al, Nature Medicine VOLUME 16 , 2010

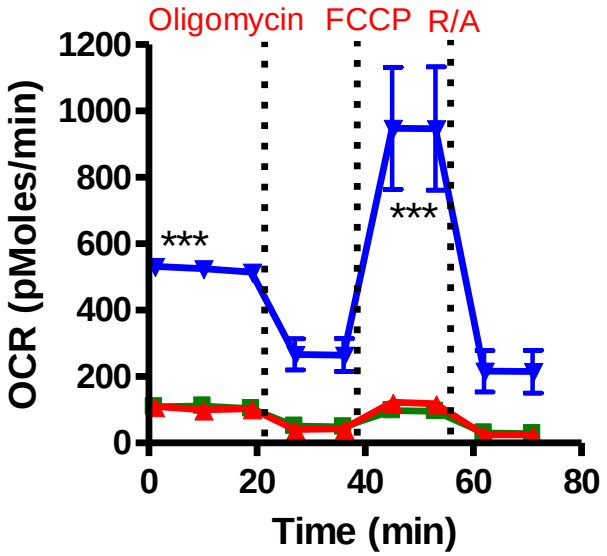


Hossain, A. Al Khami et al . Can Imm Res 2015

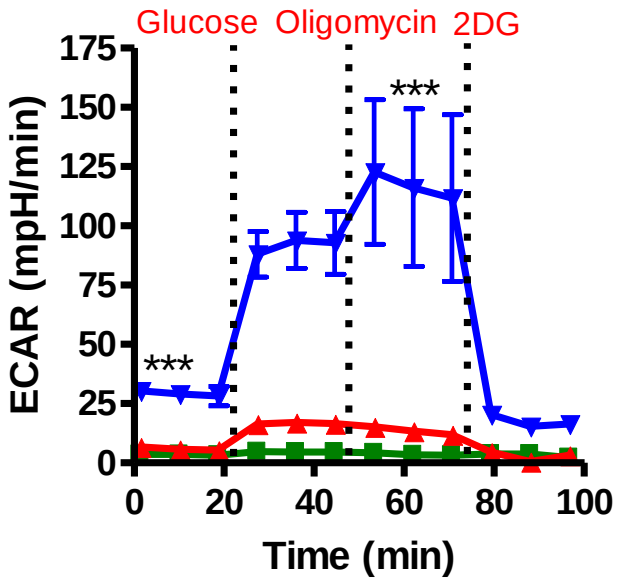
MDSC Have Increased Fatty Acid Oxidation (FAO)

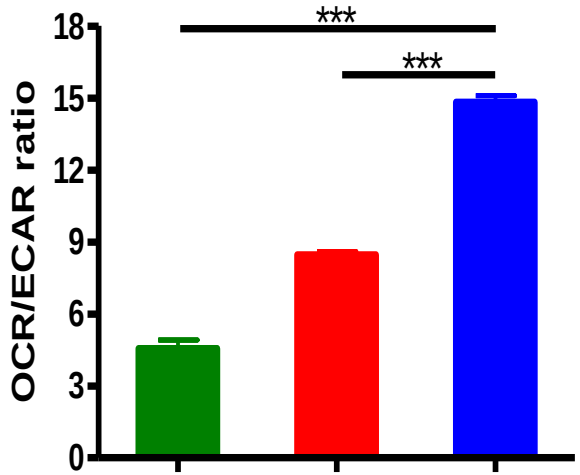


Mitochondrial stress test

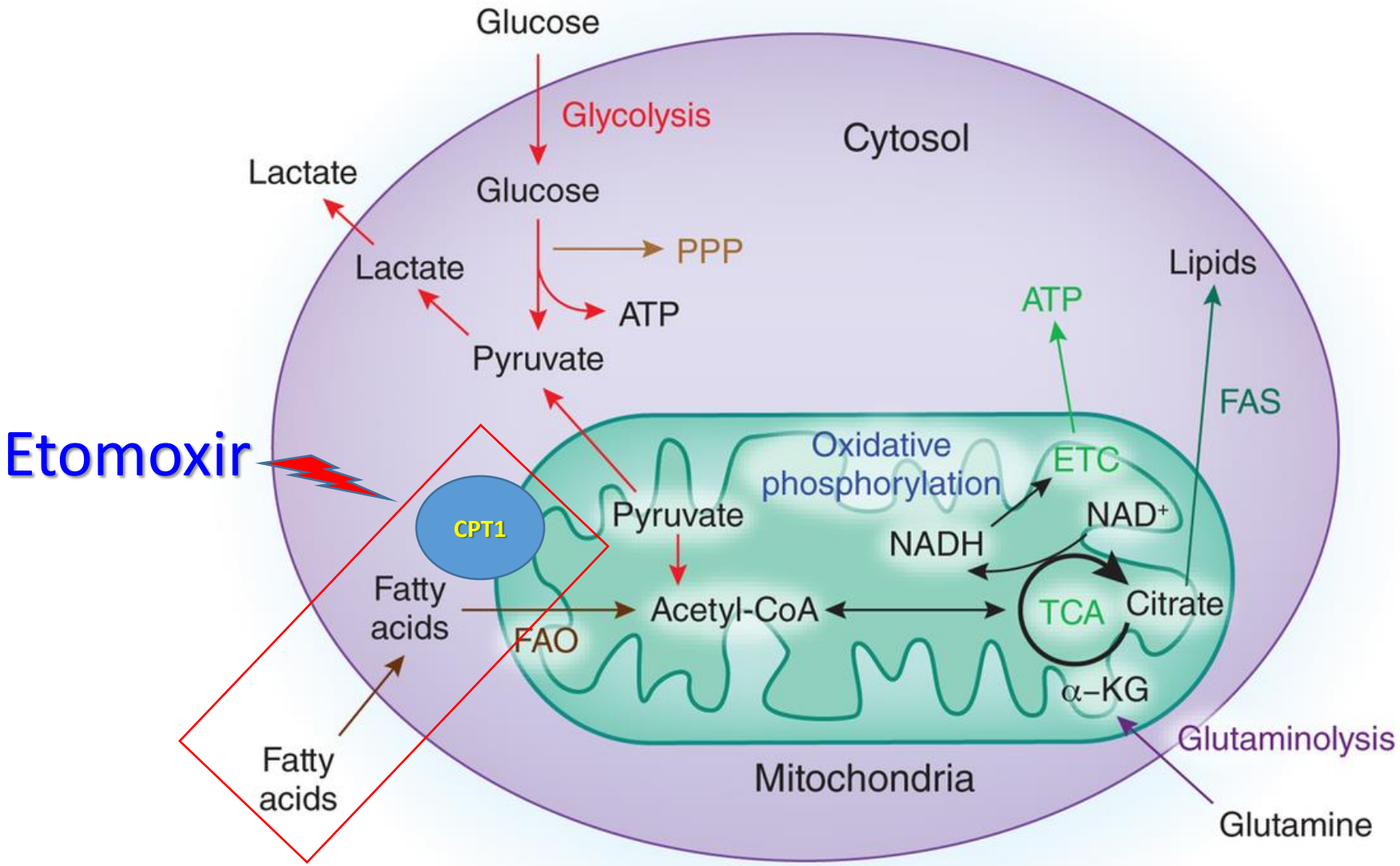


Glycolytic stress test



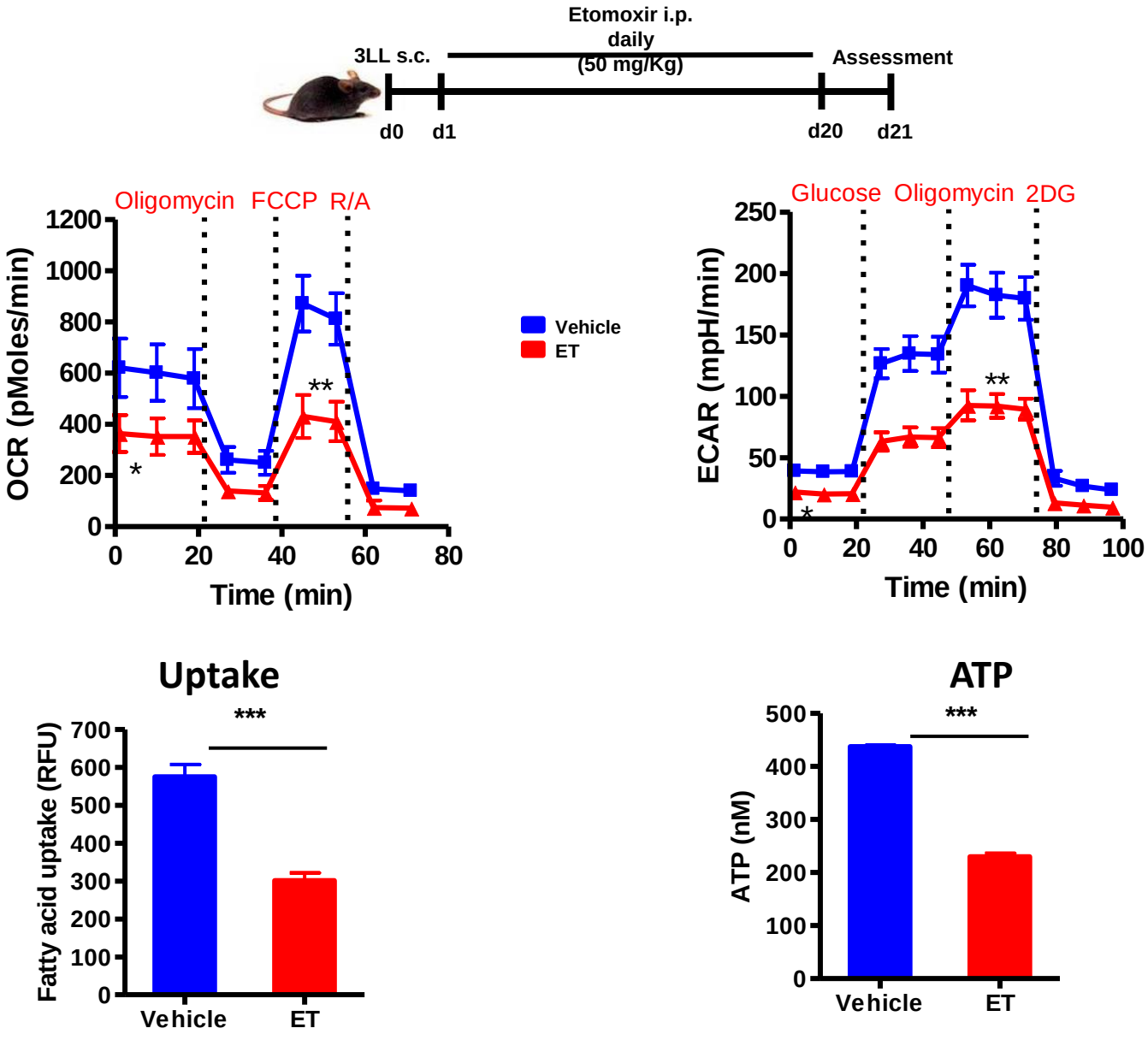


Cancer Immunology Research 2015;3(11):1236-1247. Oncoimmunology 2016;27;5(8):e1200771



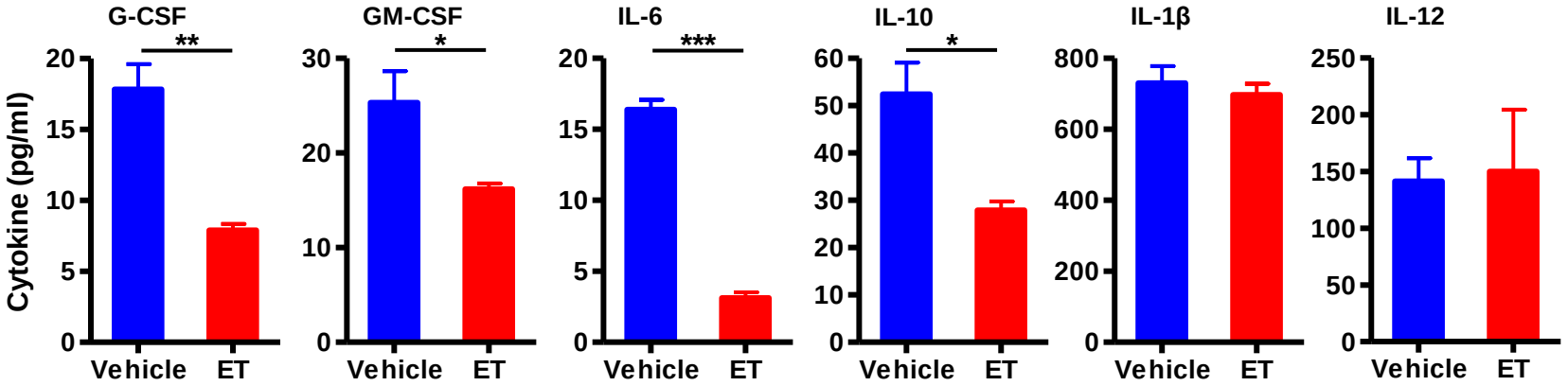
MDSC

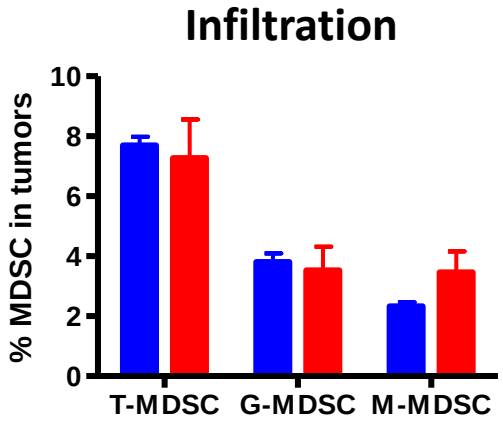
Chang and Pearce – Nat Immun 2016



Cancer Immunology Research 2015;3(11):1236-1247.
Oncoimmunology 2016;27;5(8):e1200771

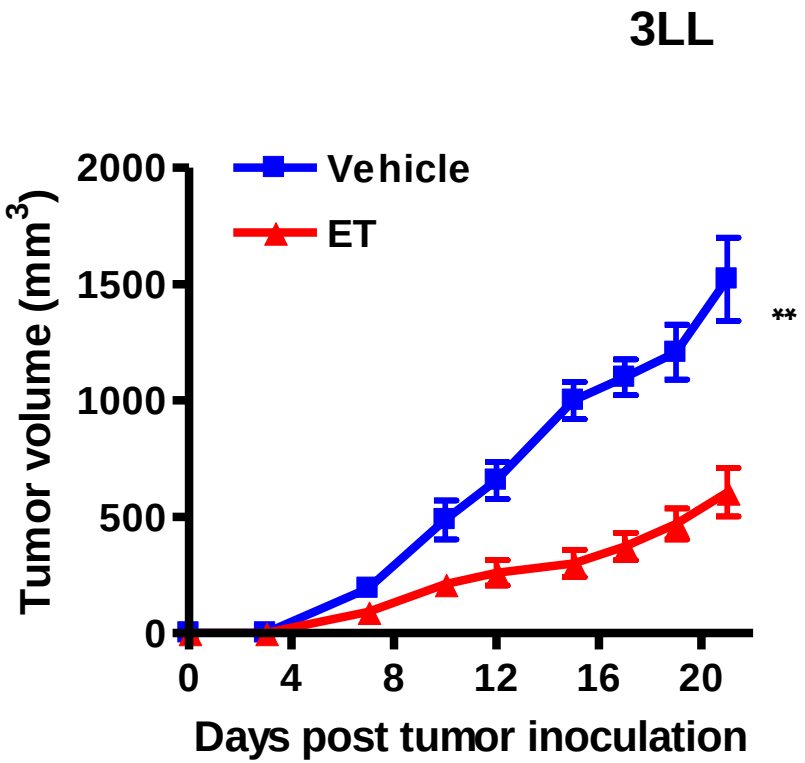
Inhibition of Fatty Acid Oxidation in vivo on MDSC

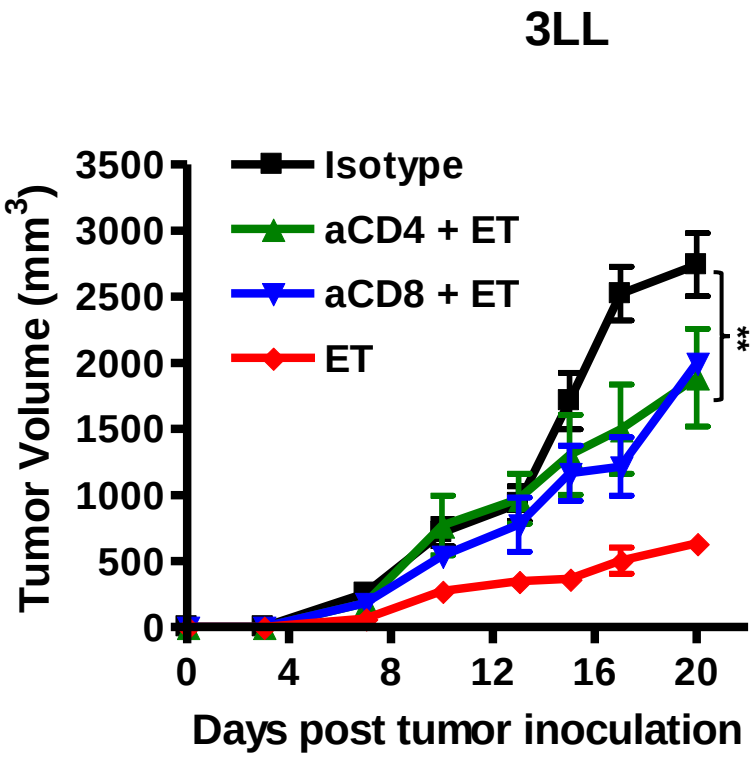




ET = Etomoxir 50mg/kg

Anti-tumor Effect of Cpt1 Inhibition

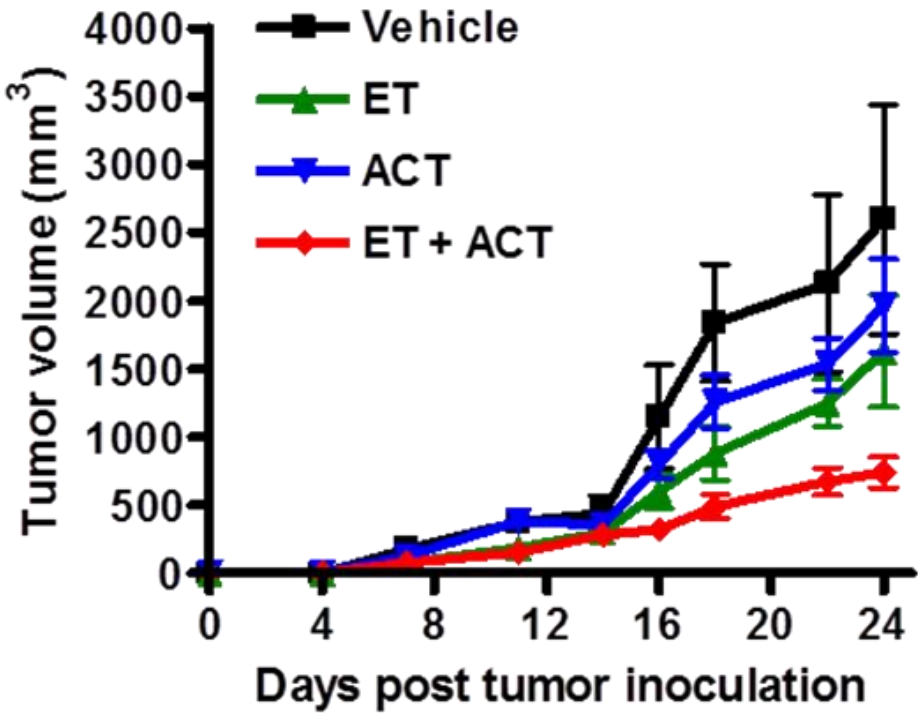




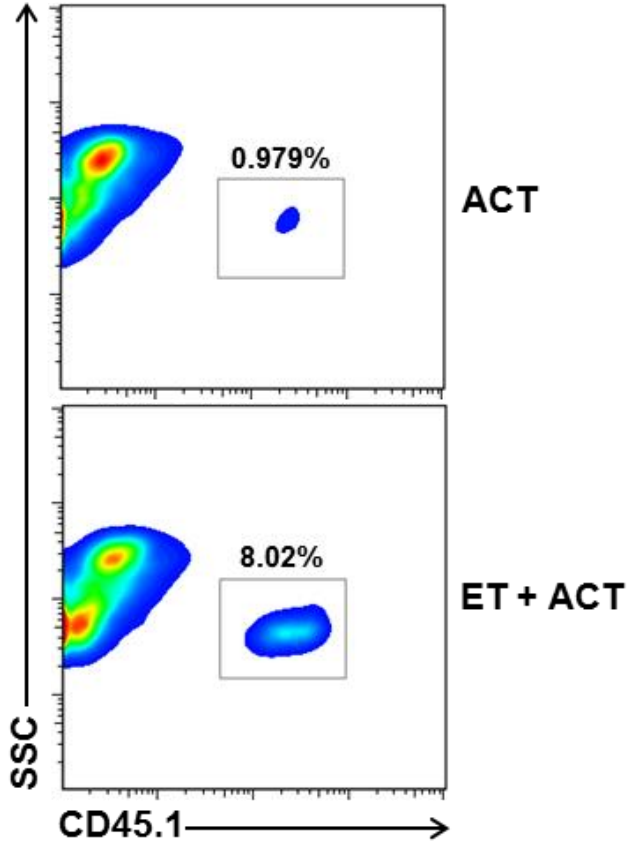
3LL – Lewis Lung Carcinoma
ET: etomoxir 20mg/kg i.p.

*Cpt1 Inhibition plus Antigen Specific ACT**

OVA-3LL

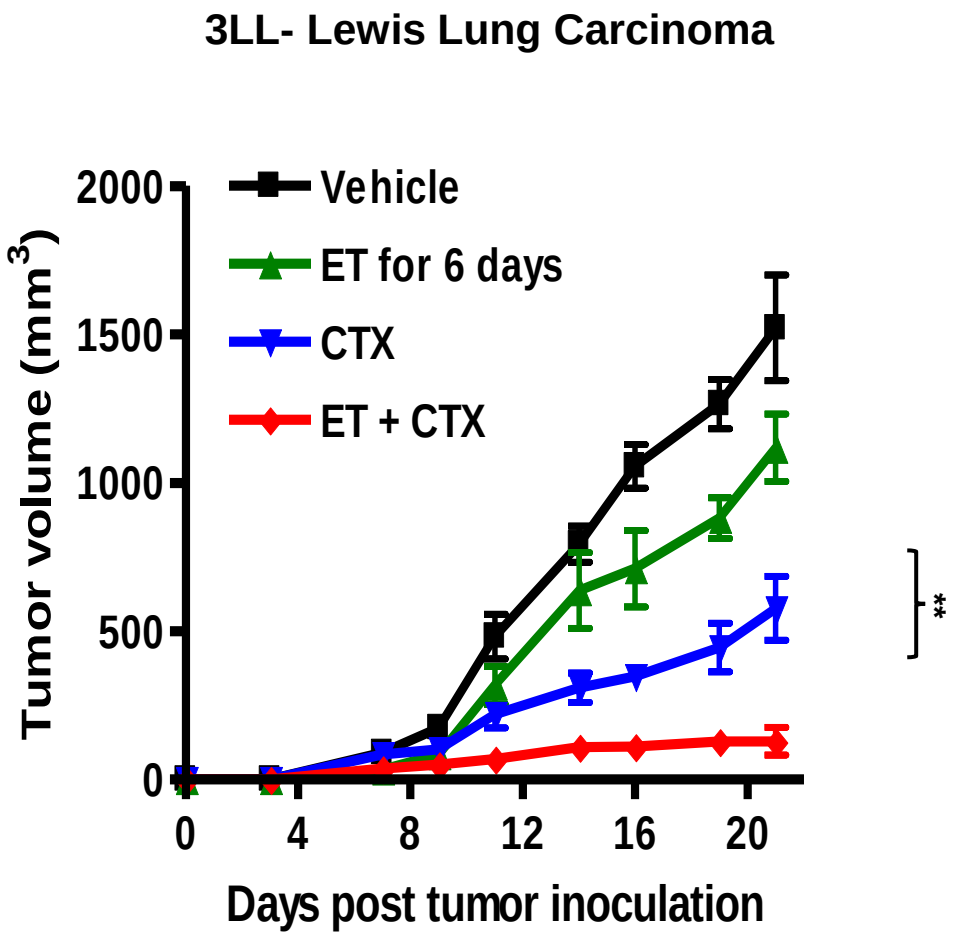


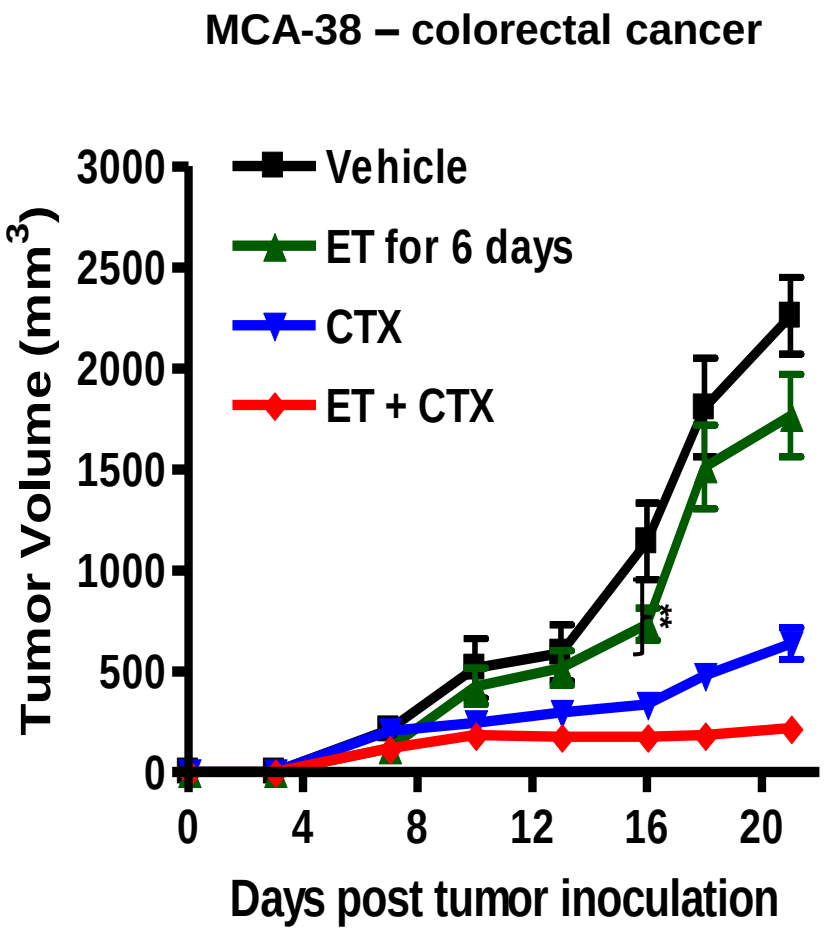
Infiltrating OT-1 T Cells



*OT-1 – CD8T cells

Combined Effect of Cpt1 inhibition plus Chemotherapy

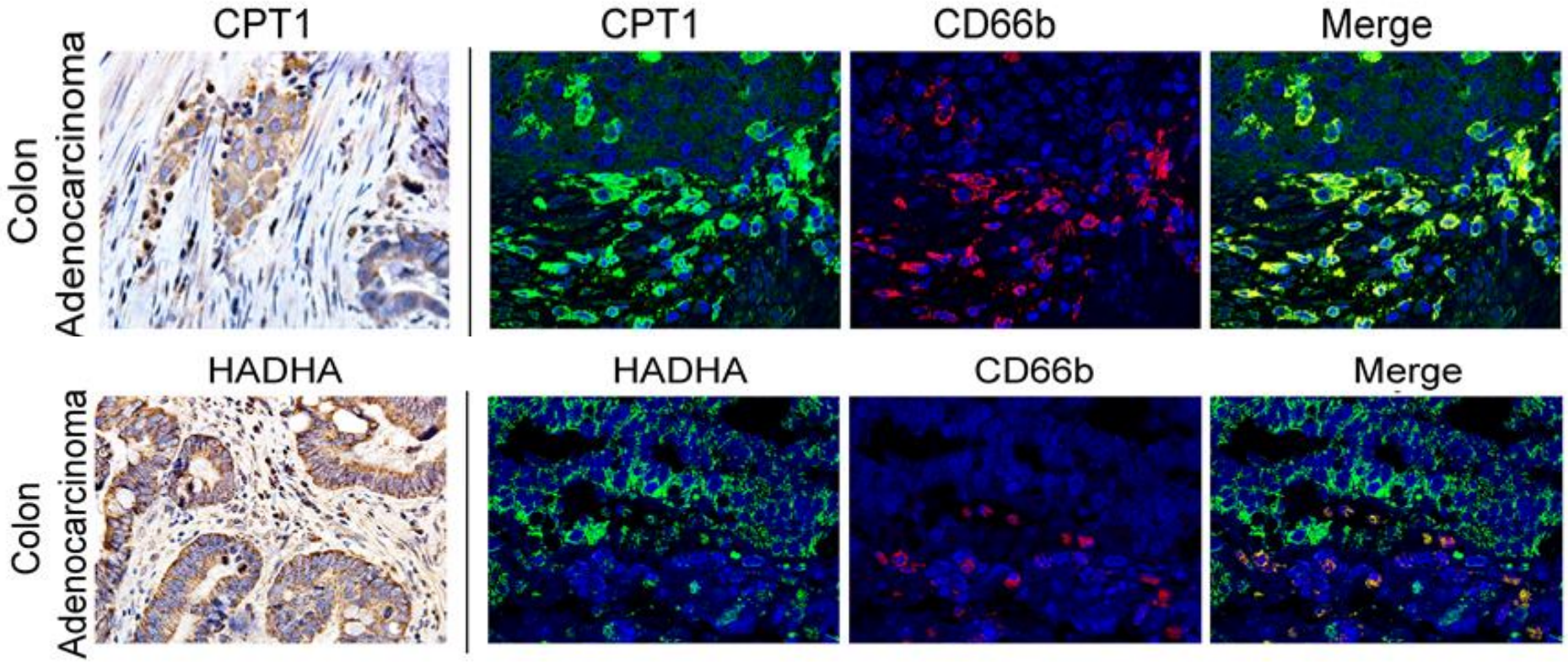


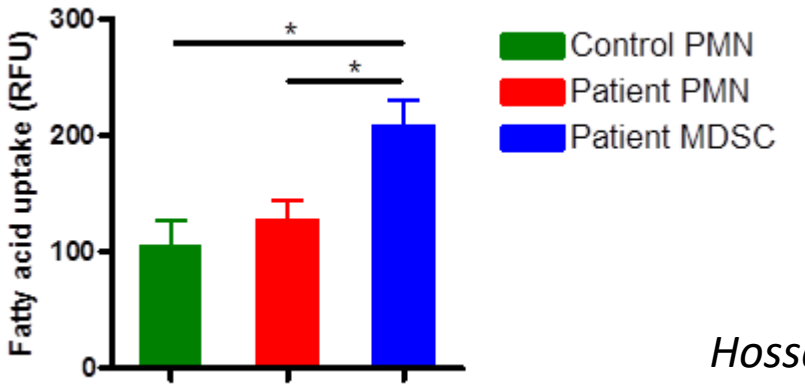


ET - 5 days

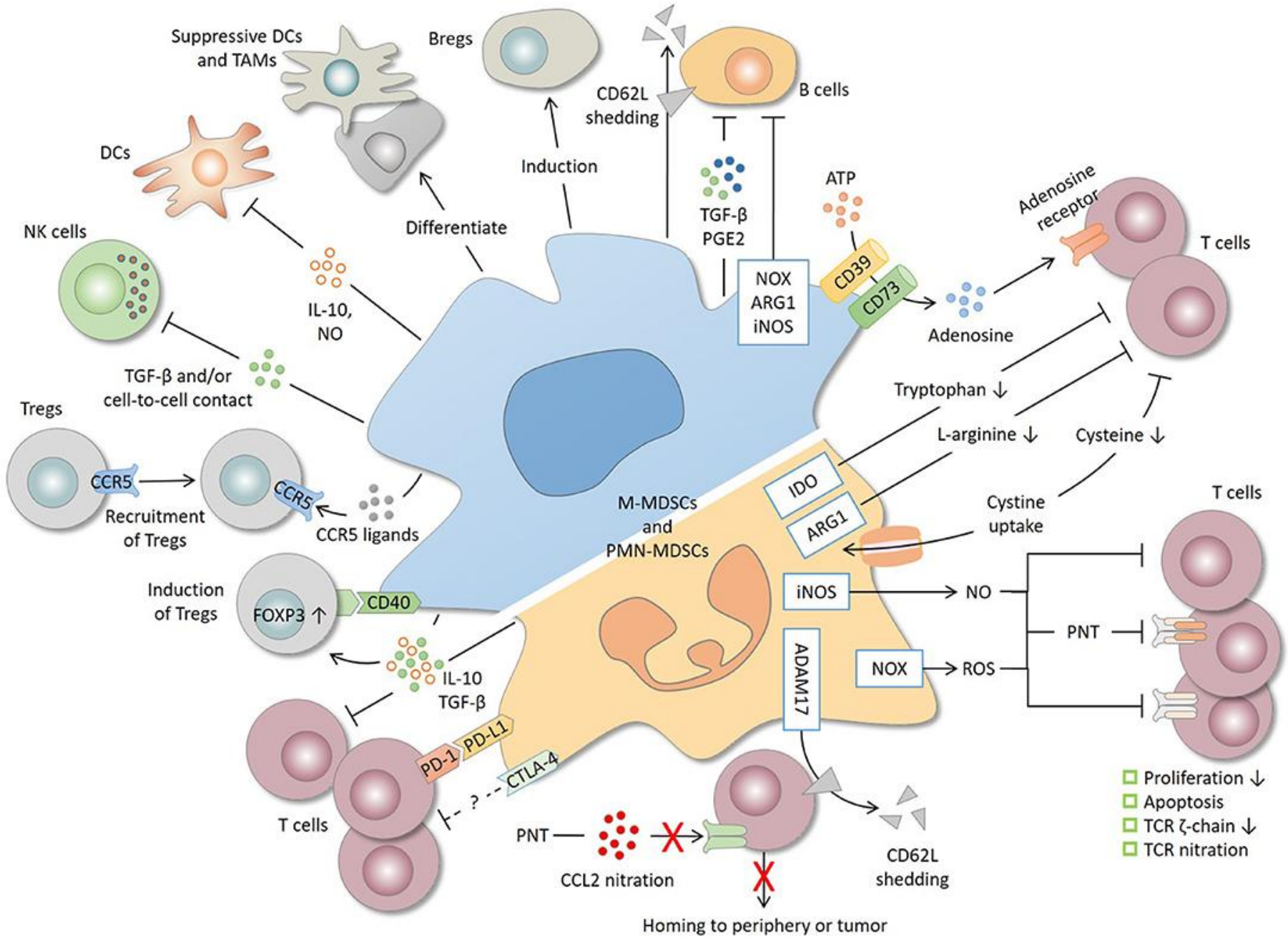
Cyclophosphamide – 100mg/kg x 1

FAO Enzyme Expression in Human MDSC





Hossain F, et al. <u>*Cancer Immunol Res*</u>*. 2015*


Suppressive DCs and TAMs
Bregs
CD62L shedding
B cells
DCs
Induction
ATP
TGF-β PGE2
Adenosine receptor
T cells
NK cells
Differentiate
NOX ARG1 iNOS
CD39
CD73
IL-10, NO
Adenosine
TGF-β and/or cell-to-cell contact
Tryptophan ↓
L-arginine ↓
Cysteine ↓
Tregs
CCR5
Recruitment of Tregs
CCR5
CCR5 ligands
M-MDSCs and PMN-MDSCs
IDO
ARG1
Cystine uptake
T cells
Induction of Tregs
FOXP3 ↑
CD40
iNOS
NO
PNT
IL-10 TGF-β
NOX
ROS
ADAM17
PD-1
PD-L1
CTLA-4
? - -
T cells
PNT
CCL2 nitration
CD62L shedding
Homing to periphery or tumor
Proliferation ↓
Apoptosis
TCR ζ-chain ↓
TCR nitration

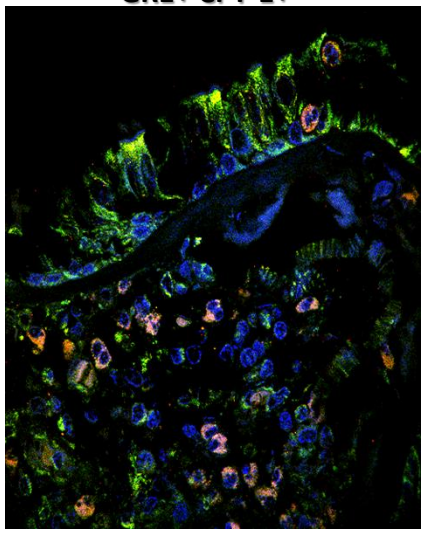
Hallmarks of Cancer

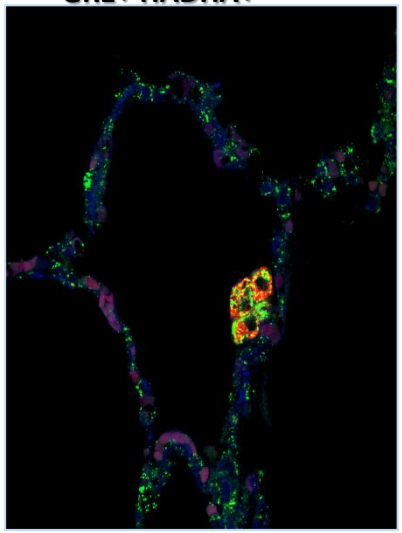
Cell 144, 2011 - D. Hanahan and R. Weinberg

- Sustaining proliferation
- Evading growth suppressors
- Resisting cell death
- Enabling replicative immortality
- Inducing angiogenesis
- Activating invasion/metastasis
- Evading immune destruction
- Reprogramming energy metabolism

MDSC in Other Diseases

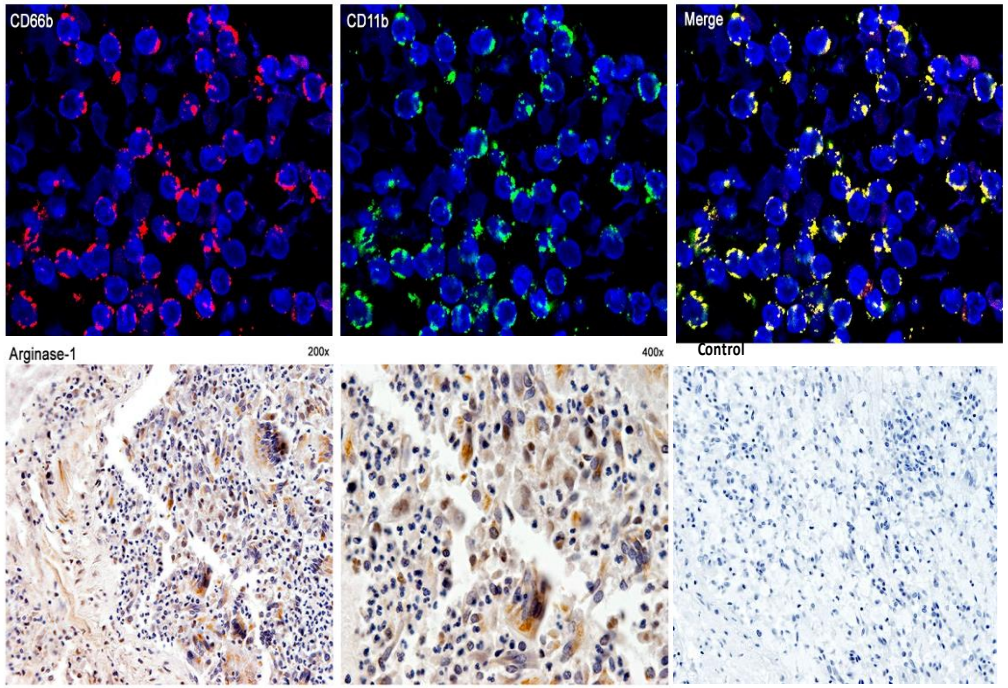
Asthma





Fueling the mechanisms of asthma: Increased fatty acid oxidation in inflammatory immune cells may represent a novel therapeutic target. A. A. Al-KhamiM. M. D. Sanchez-Pino,P. C. Rodriguez,A. C. Ochoa29 April 2017 https://doi.org/10.1111/cea.12947

COVID-19

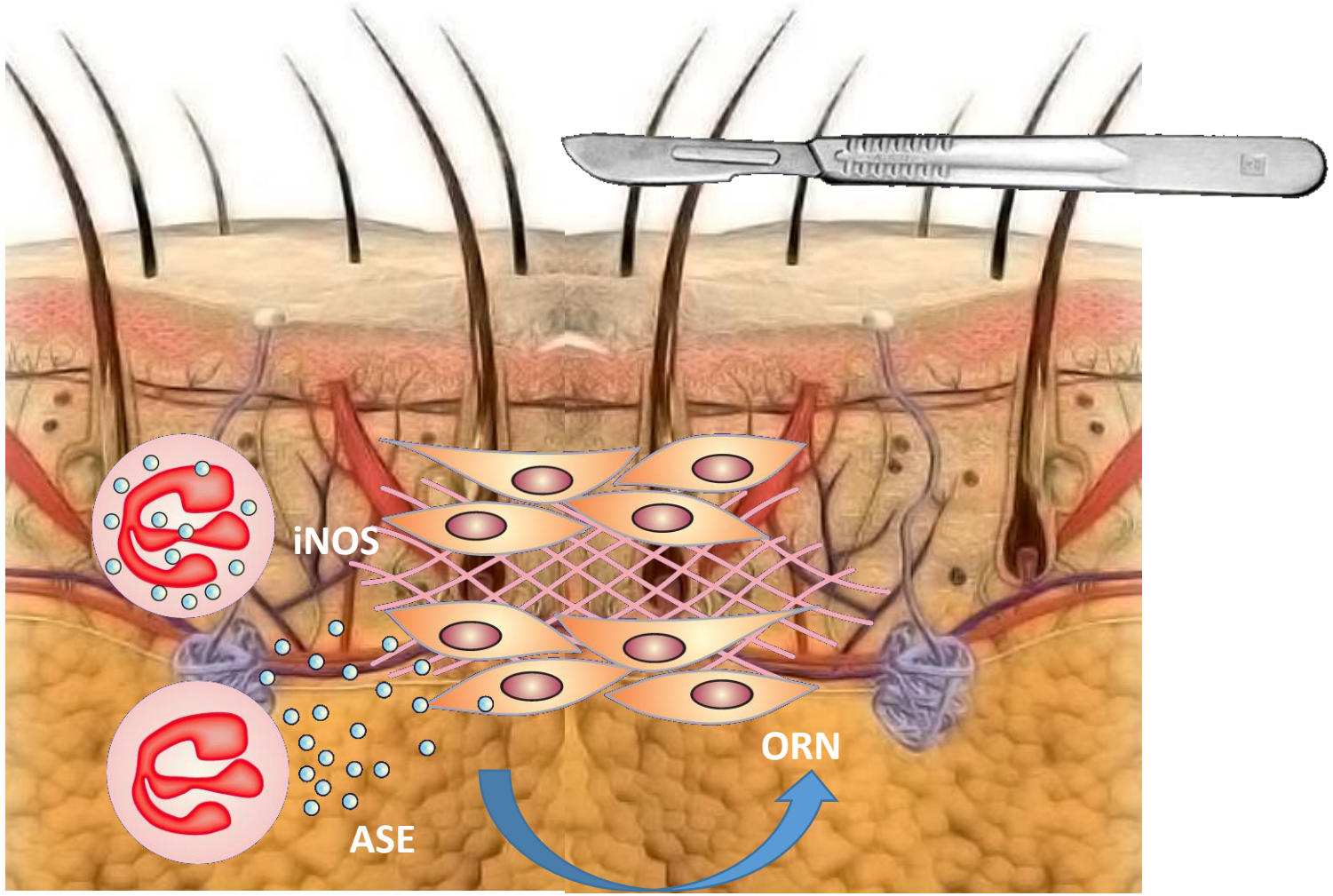


Severe COVID-19 Is Characterized by an Impaired Type I Interferon Response and Elevated Levels of Arginase Producing Granulocytic Myeloid Derived Suppressor Cells. Matthew J Dean…. Augusto C OchoaPMID: 34341659 PMCID: PMC8324422 DOI: 10.3389/fimmu.2021.695972

Immune Response in Severe and Non-Severe Coronavirus Disease 2019 (COVID-19) Infection: A Mechanistic Landscape. Kavitha Mukund….. Shankar Subramaniam. Front. Immunol., 13 October 2021 | https://doi.org/10.3389/fimmu.2021.738073

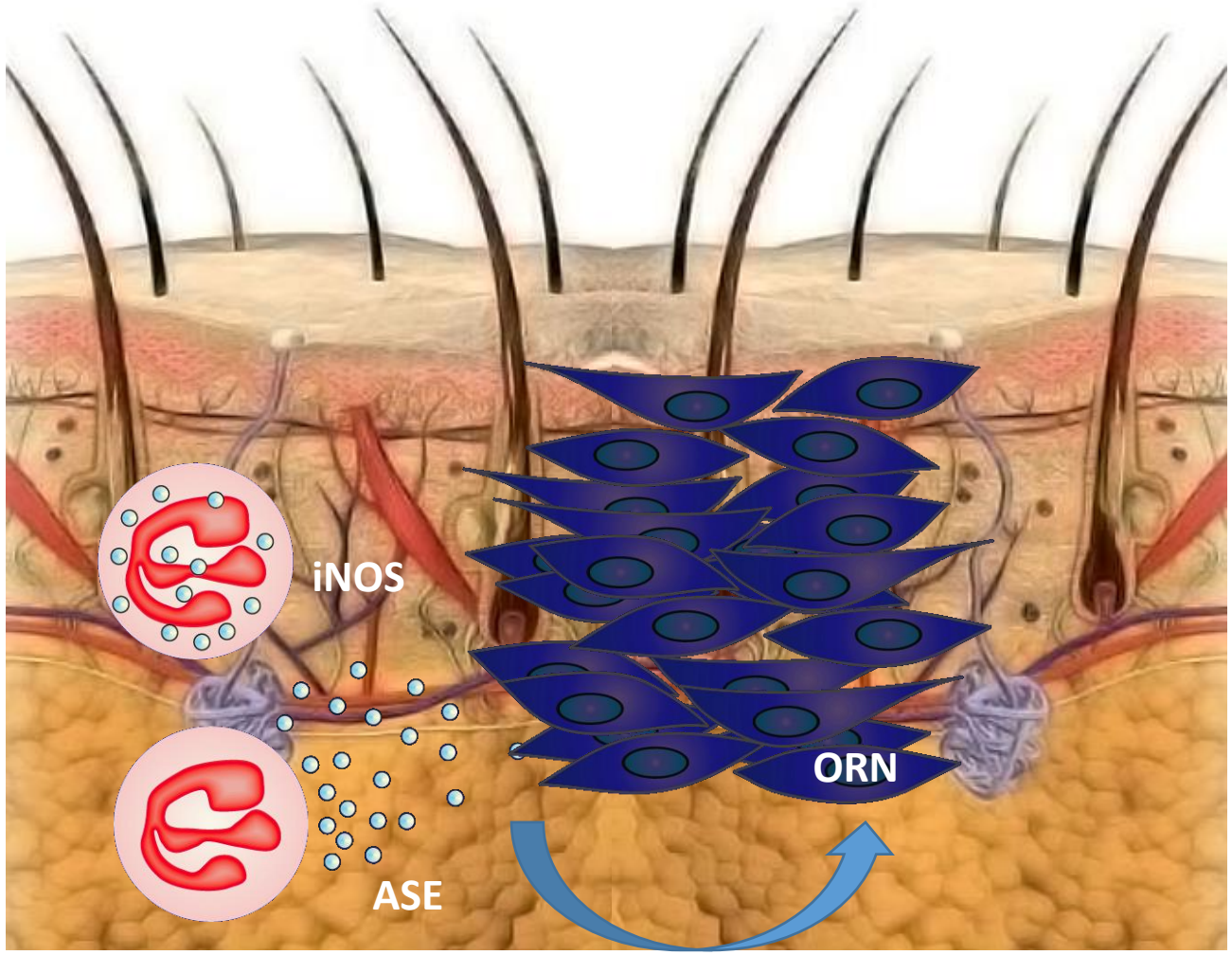
Others:

Trauma
Tuberculosis
Leprosy
Autoimmunity



J. Albina and C Mills, J. Immunol 1989

“Cancer, the wound that never heals” Harold F. Dvorak



Sept. 2018 – Scripps, La Jolla

Questions

Welcome Trust Project

- What is the type of myeloid infiltration during early and late stages of breast cancer in general or TNBC in particular?
- Is myeloid infiltration different in women from different racial backgrounds, different between obese and non-obese or in women with metabolic syndrome (T2D)?
- What molecular signals trigger the infiltration by myeloid cells and what makes them shift to becoming MDSC? How early in carcinogenesis do MDSC appear in the tumor?
- Does the presence of MDSC negatively impact the response to treatment?
- Can we increase the efficacy of immune prevention or immunotherapy in breast cancer?