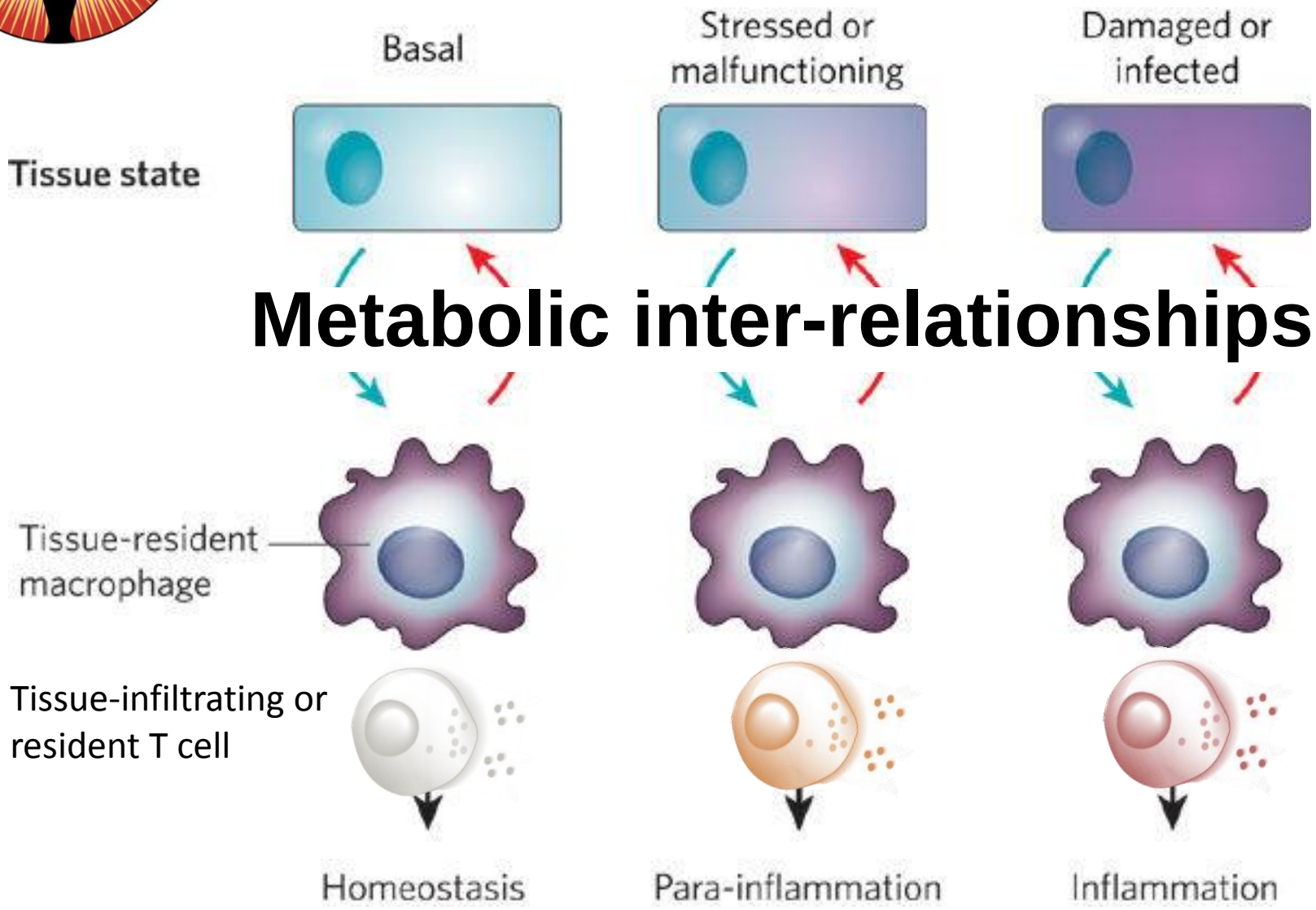
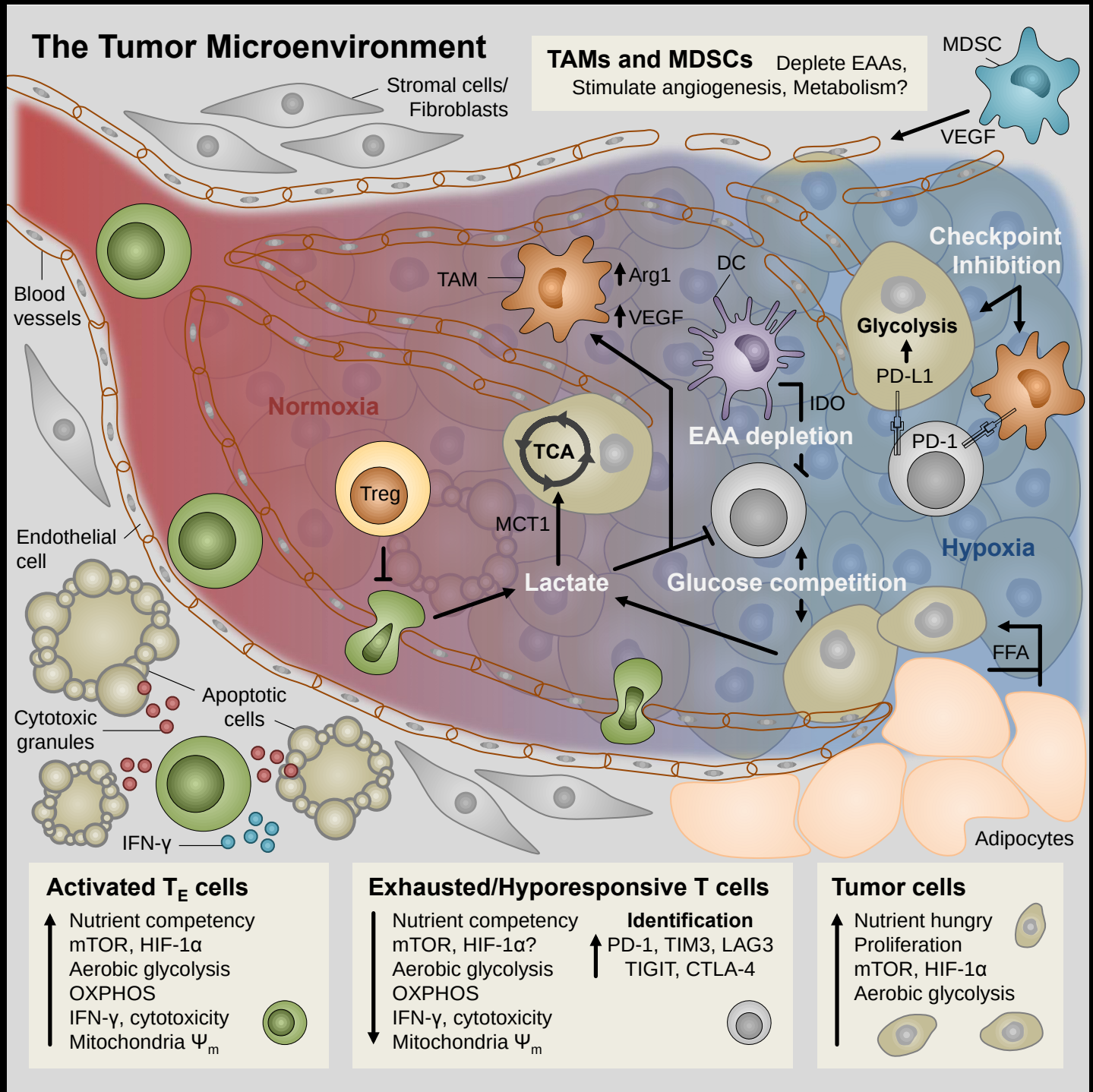
Anti-tumor T cells: You are what you eat

Susan Kaech
Department of Immunobiology, Yale University
Salk Institute

Tissue Homeostasis and Dystasis




The Tumor Microenvironment
TAMs and MDSCs Deplete EAAs, Stimulate angiogenesis, Metabolism?
MDSC
VEGF
Stromal cells/ Fibroblasts
Blood vessels
TAM
Arg1
VEGF
DC
Checkpoint Inhibition
Glycolysis
PD-L1
PD-1
IDO
EAA depletion
Normoxia
TCA
Treg
MCT1
Lactate
Glucose competition
Hypoxia
FFA
Endothelial cell
Apoptotic cells
Cytotoxic granules
IFN-γ
Adipocytes
Activated T_E cells
Nutrient competency
mTOR, HIF-1α
Aerobic glycolysis
OXPHOS
IFN-γ, cytotoxicity
Mitochondria Ψ_m
Exhausted/Hyporesponsive T cells
Nutrient competency
mTOR, HIF-1α?
Aerobic glycolysis
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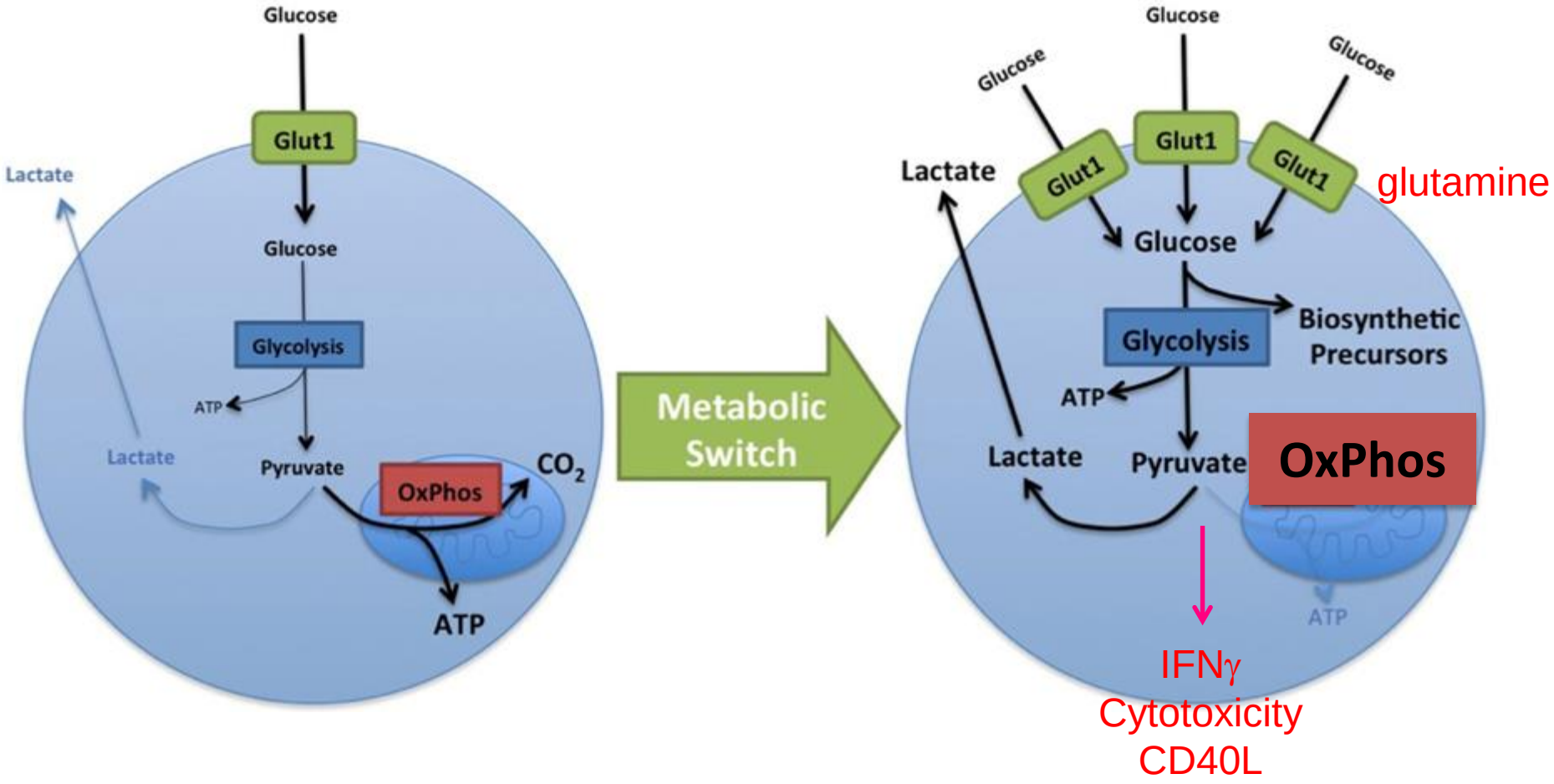
Identification
PD-1, TIM3, LAG3
TIGIT, CTLA-4
Tumor cells
Nutrient hungry
Proliferation
mTOR, HIF-1α
Aerobic glycolysis

Does metabolic adaptation contribute to T cell dysfunction in tumors?

Metabolic switch to aerobic glycolysis is essential for effector T cell development and function

Naïve/Quiescent T cell

Activated T cell



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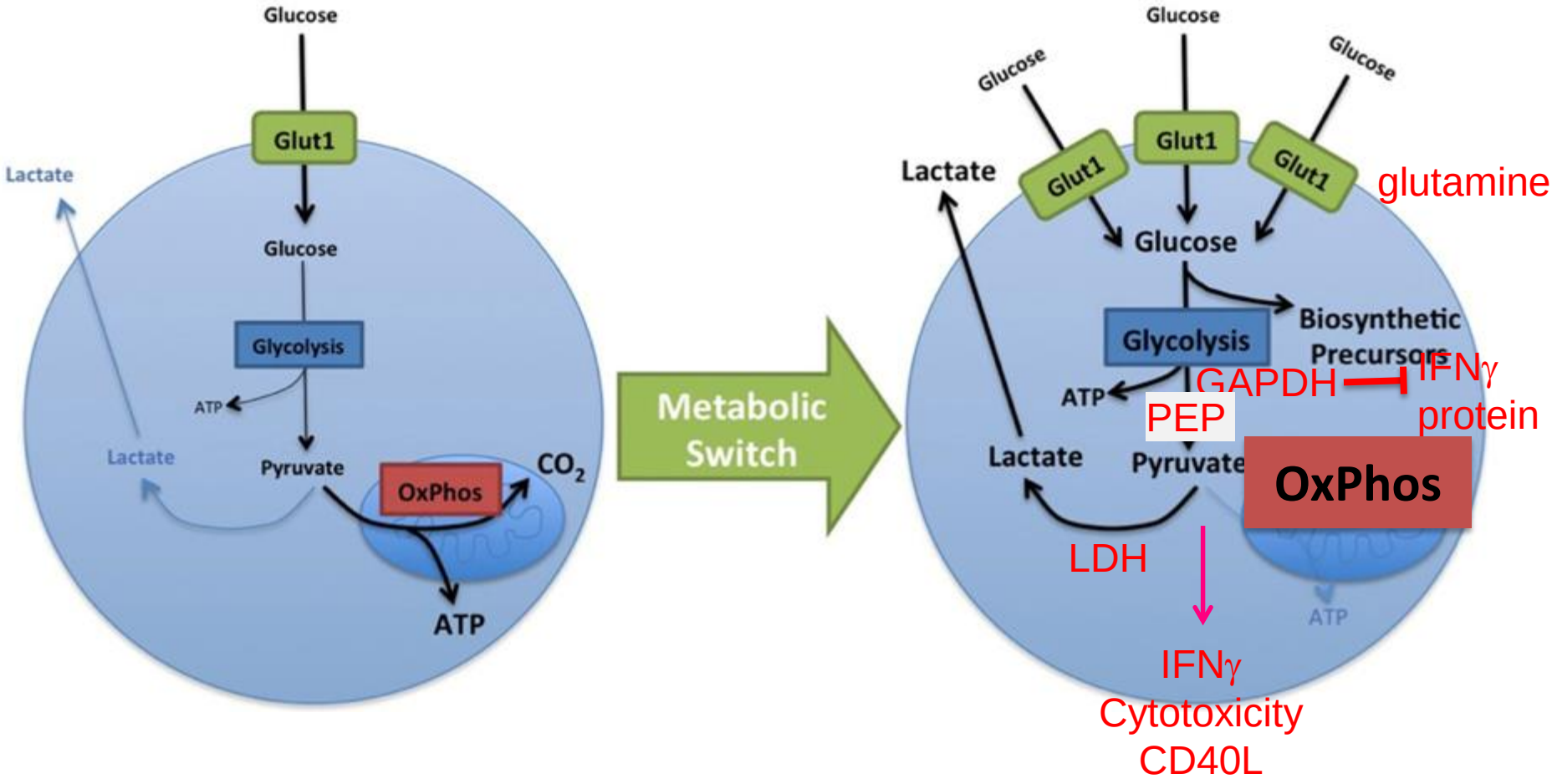

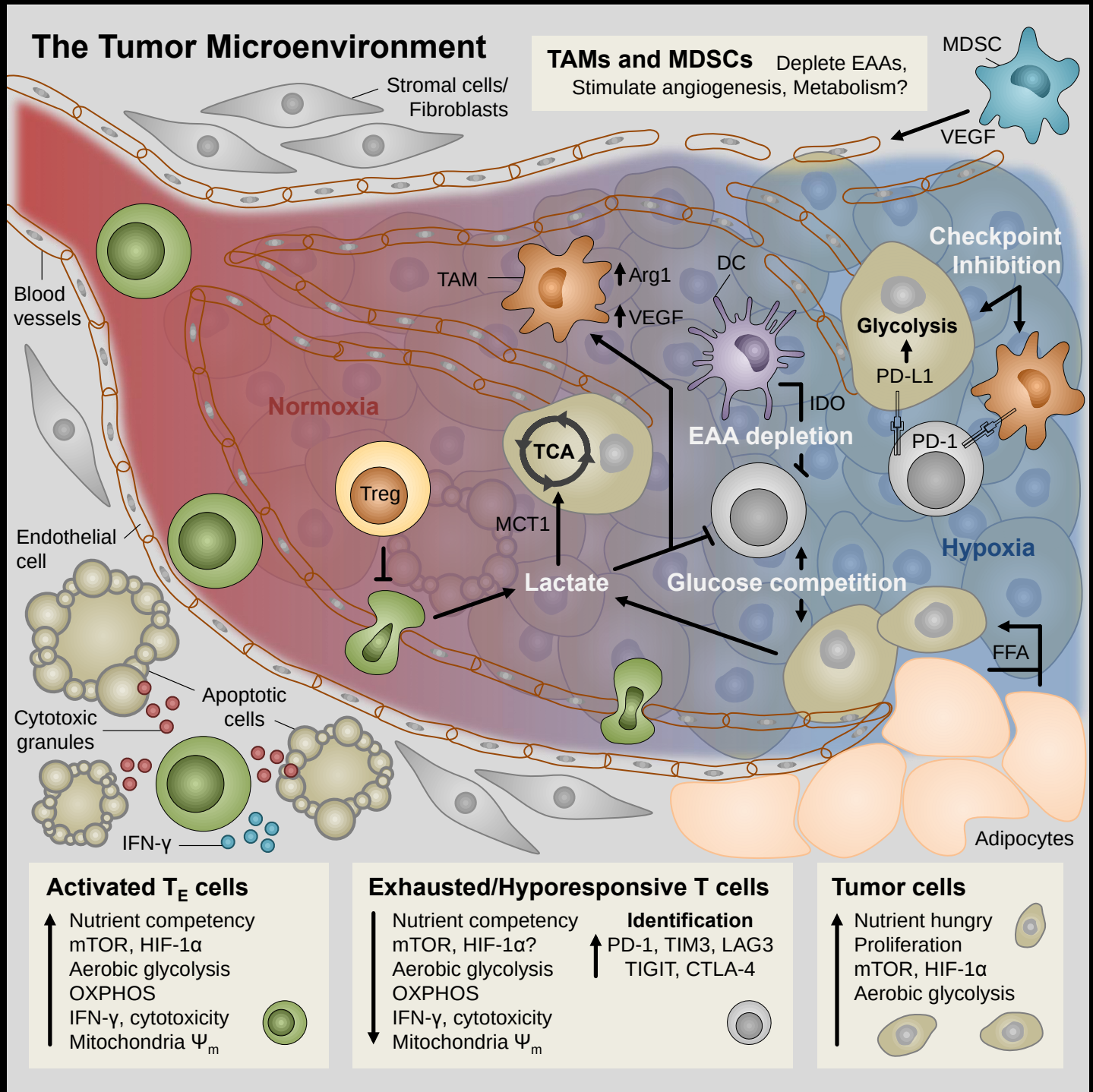
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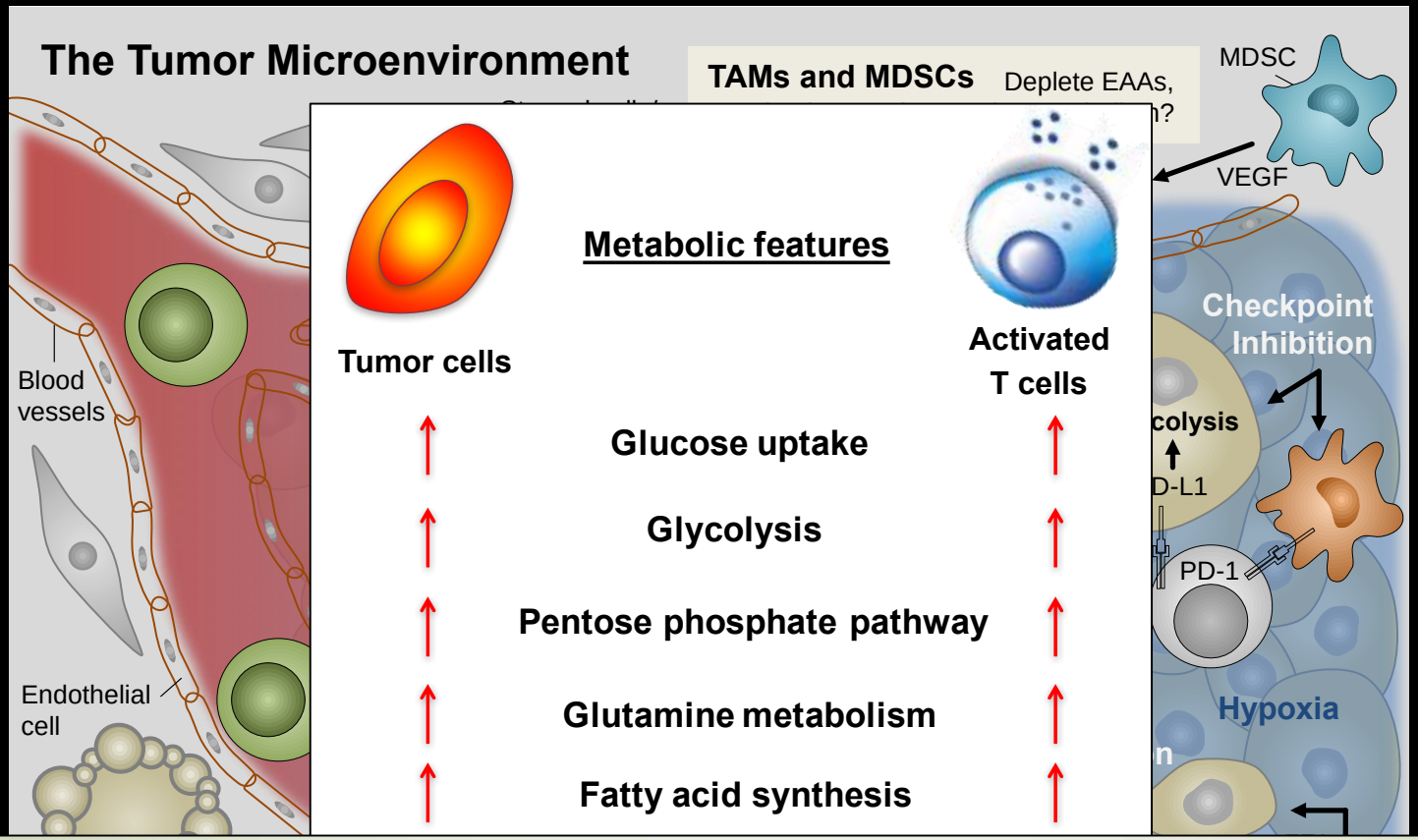
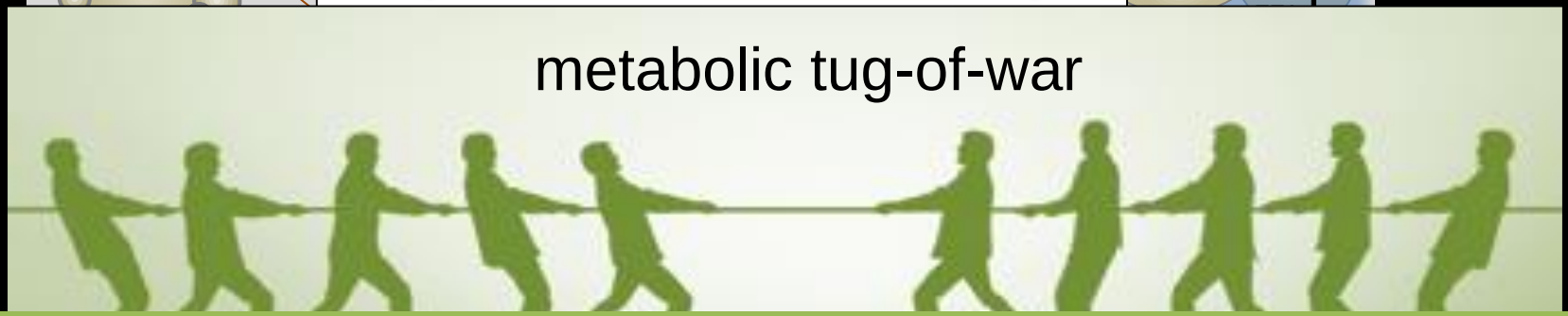
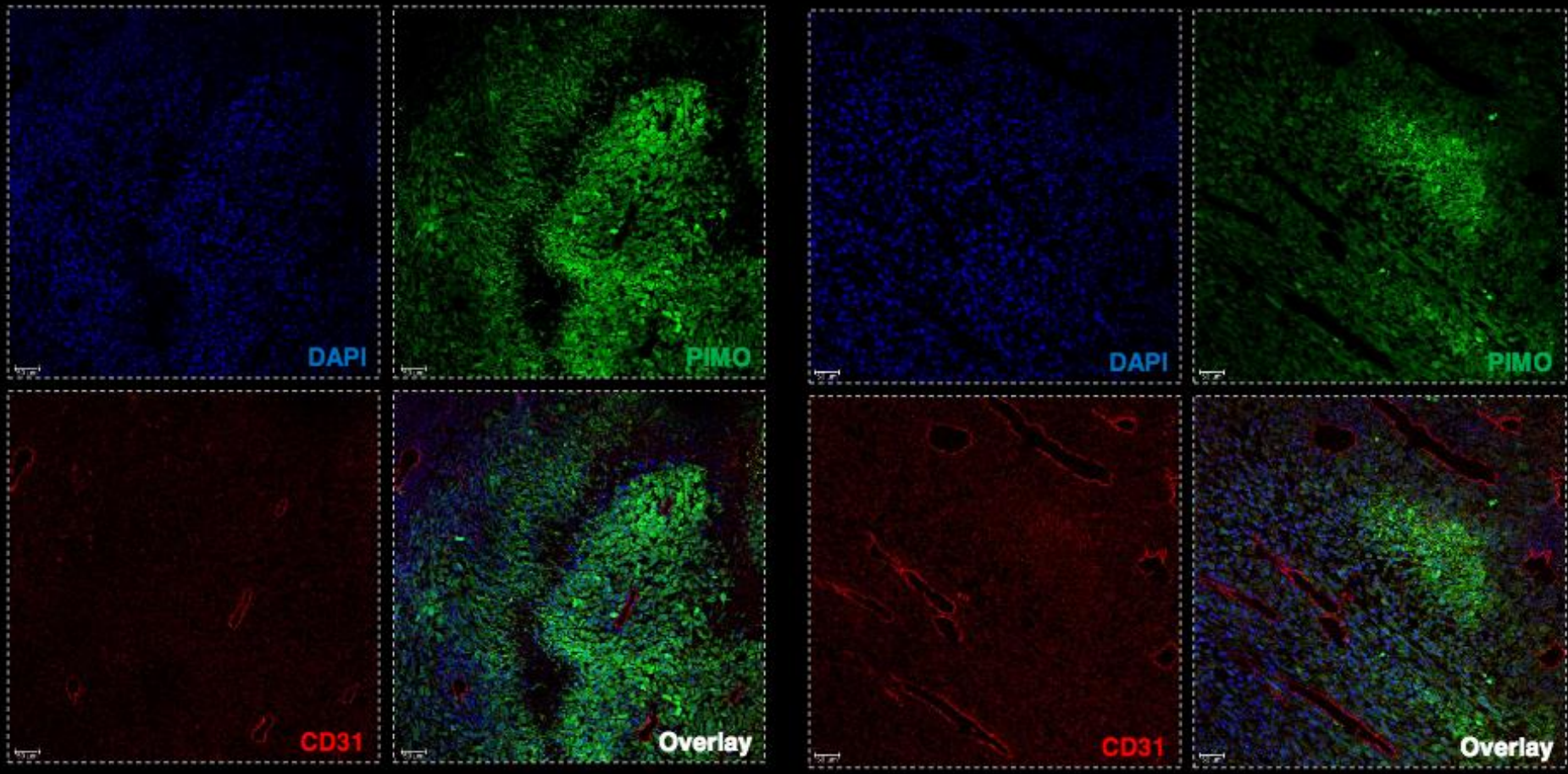




- Increased tumor cell glycolysis enhances immunoevasion.
- Decreased tumor cell Ldha-suppression promotes anti-tumor immunity.

Little T cell infiltration into hypoxic areas in tumors



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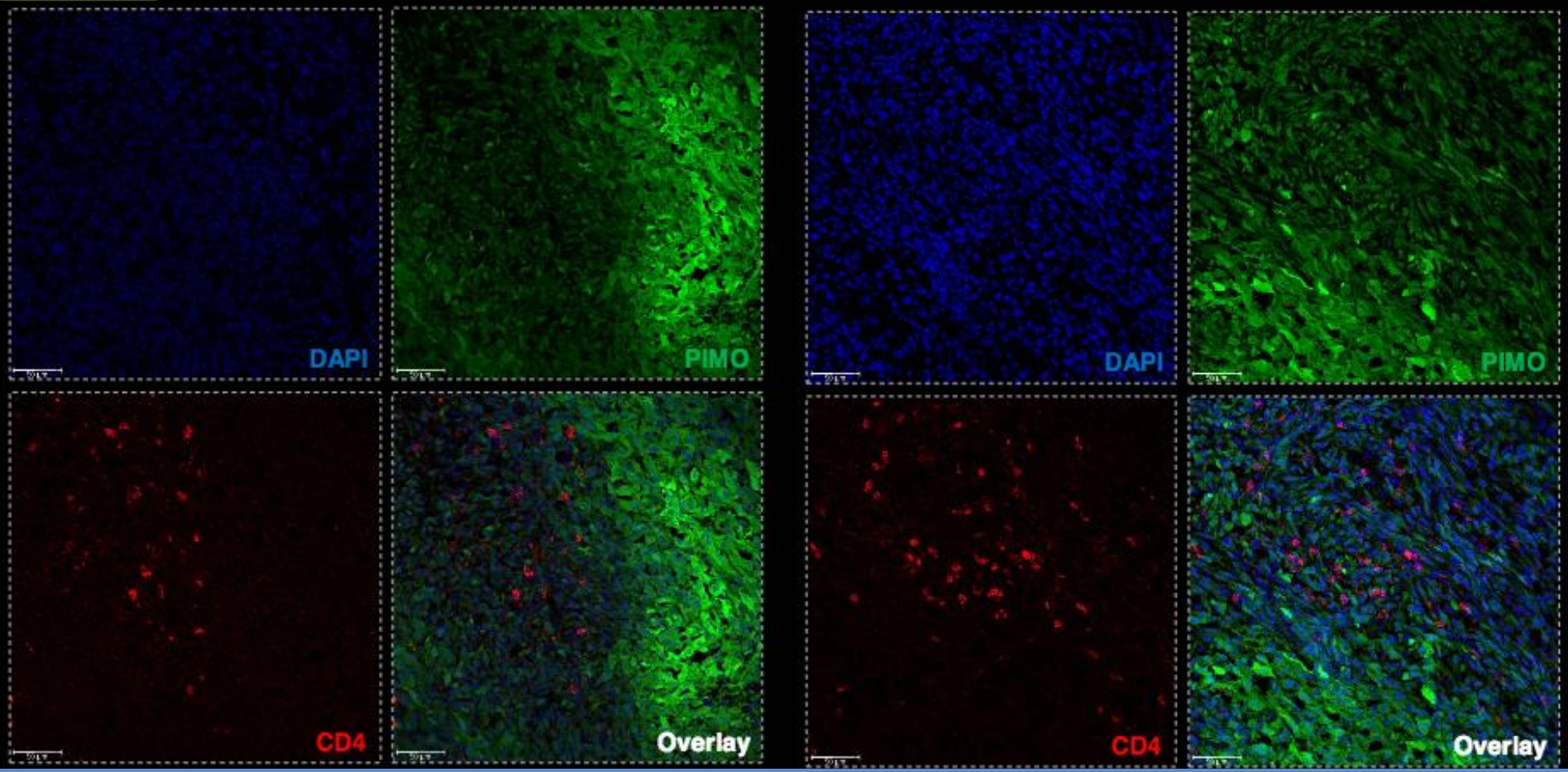
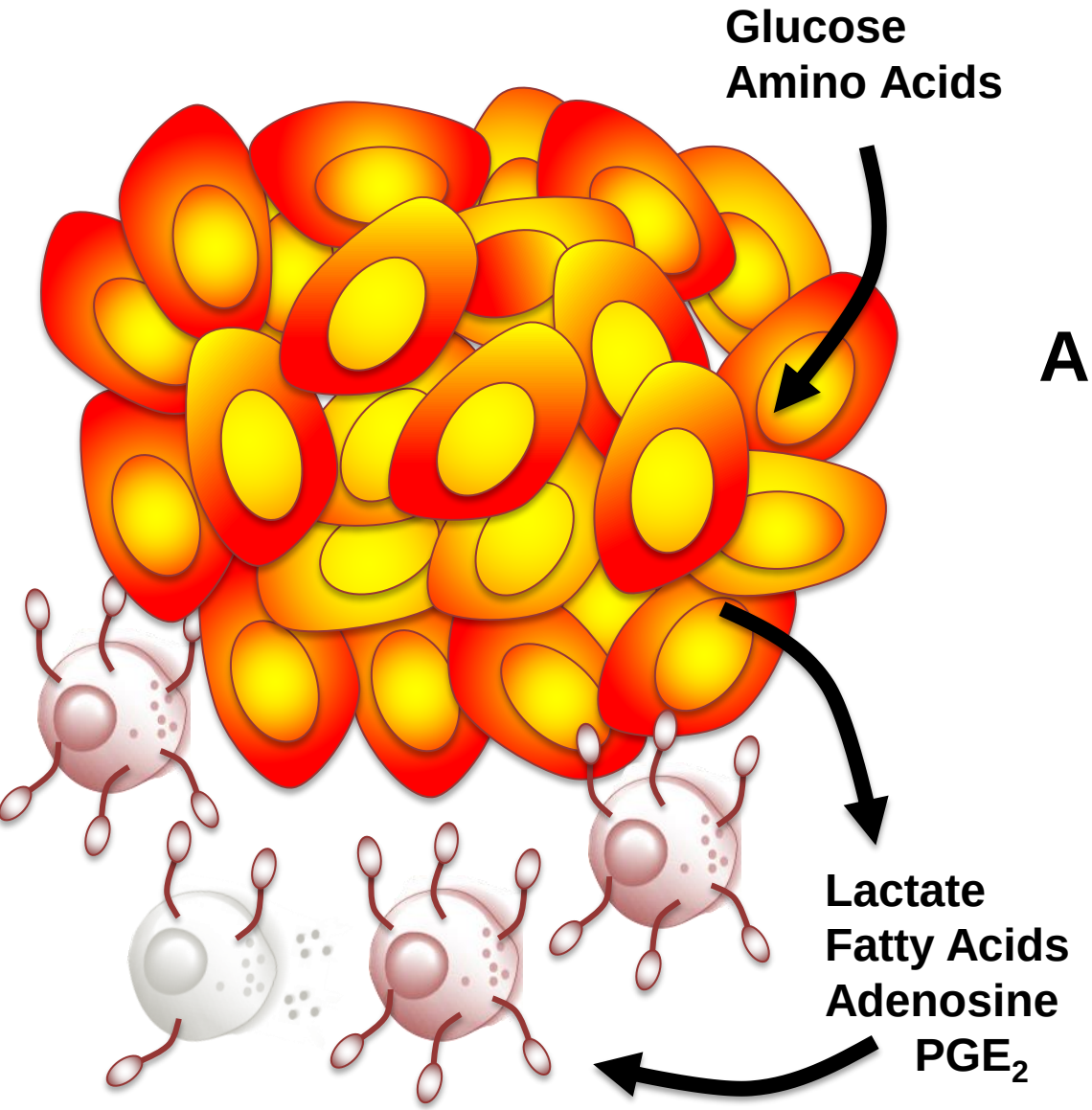


Perhaps hypoxia will be a major
'metabolic checkpoint' for T cells in some tumors?
-Increased glycolysis, lactate, pH
-Decreased glucose availability

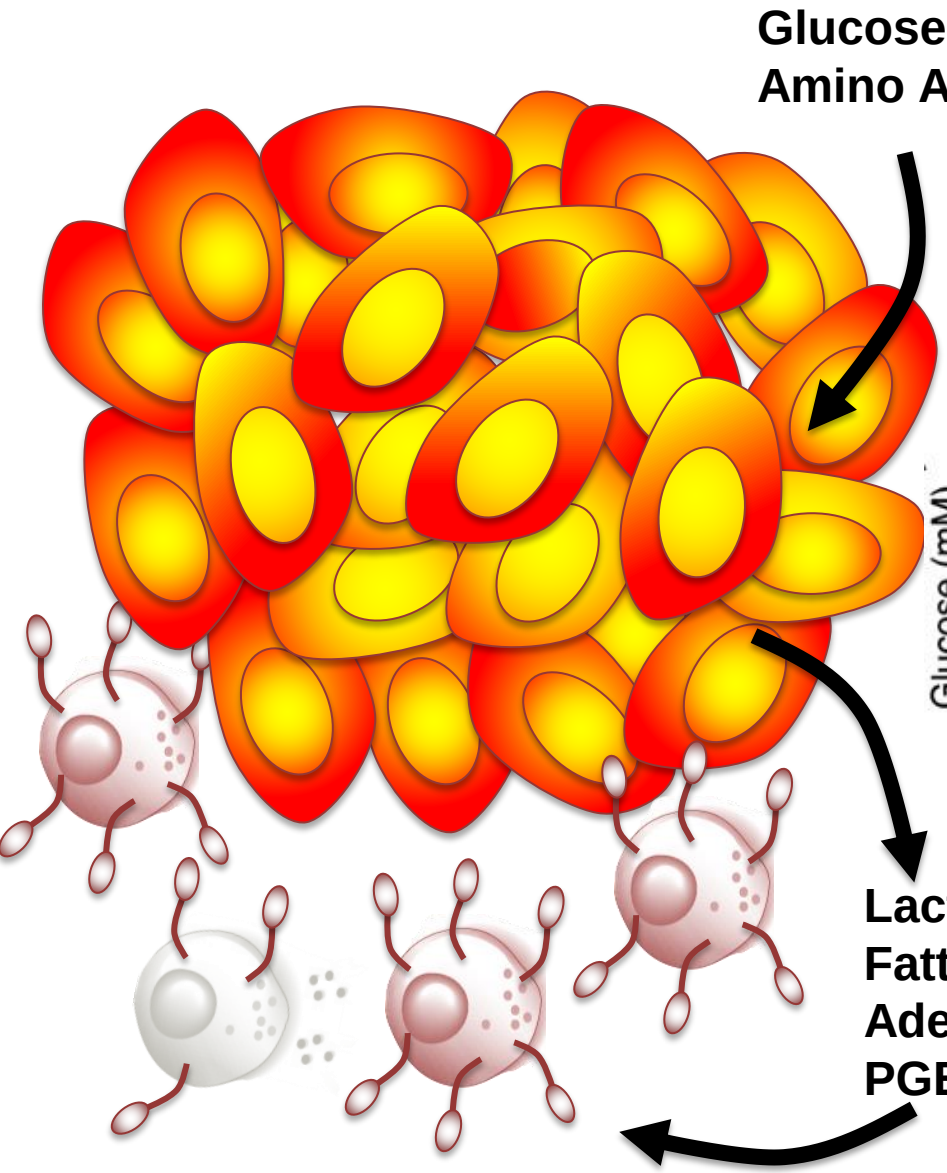
Metabolic tug-of-war in tumors?

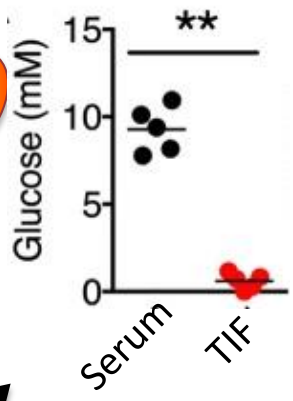


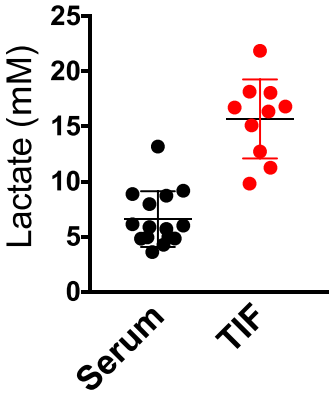
Are there alterations in nutrient availability that affect T cell function in tumors?

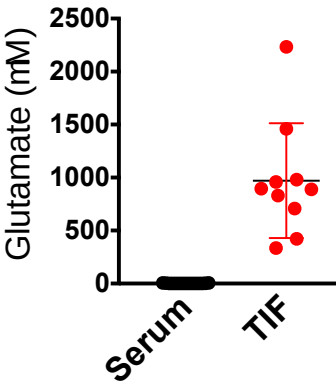
T cell dysfunction/ exhaustion

Metabolic regulation of T cell function in tumors?



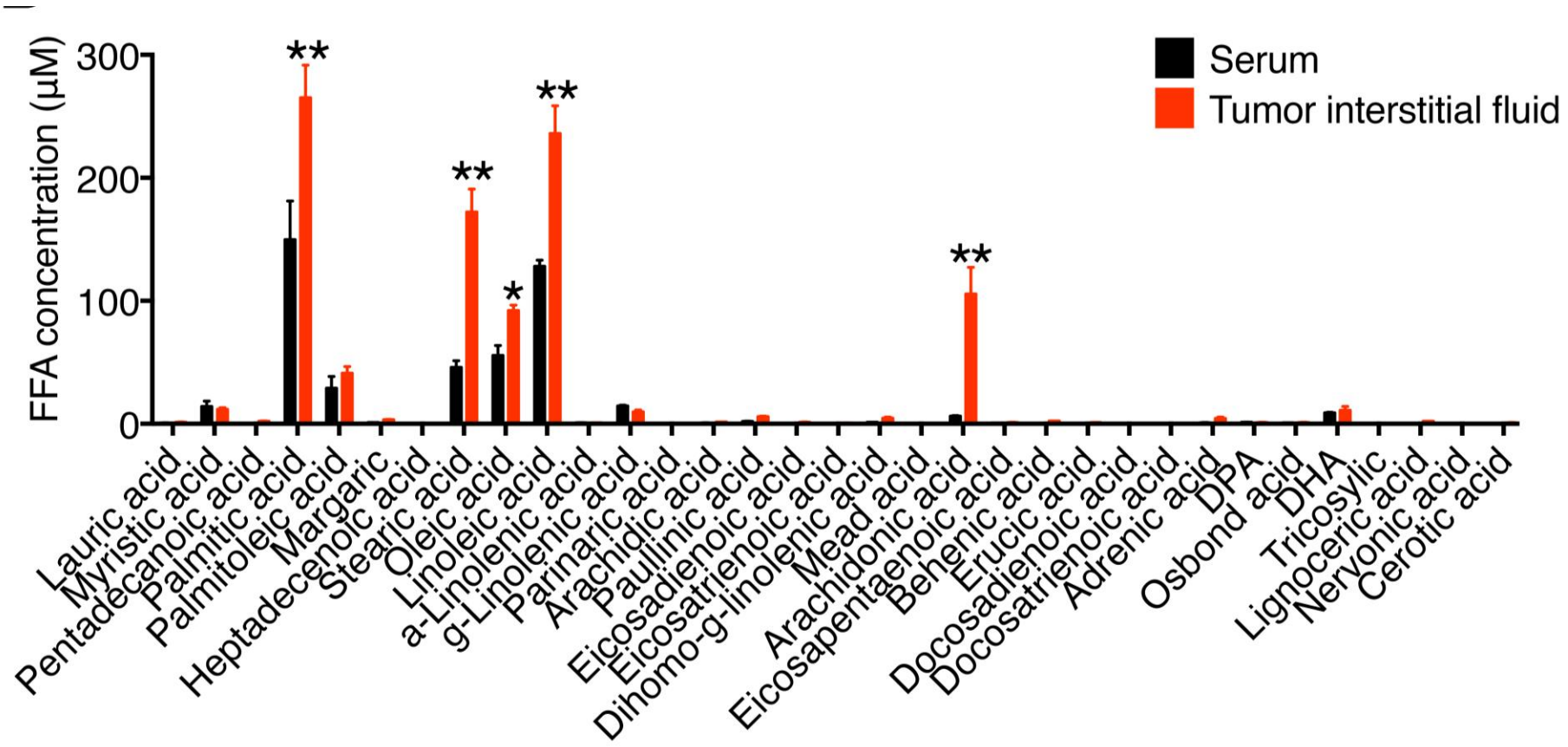




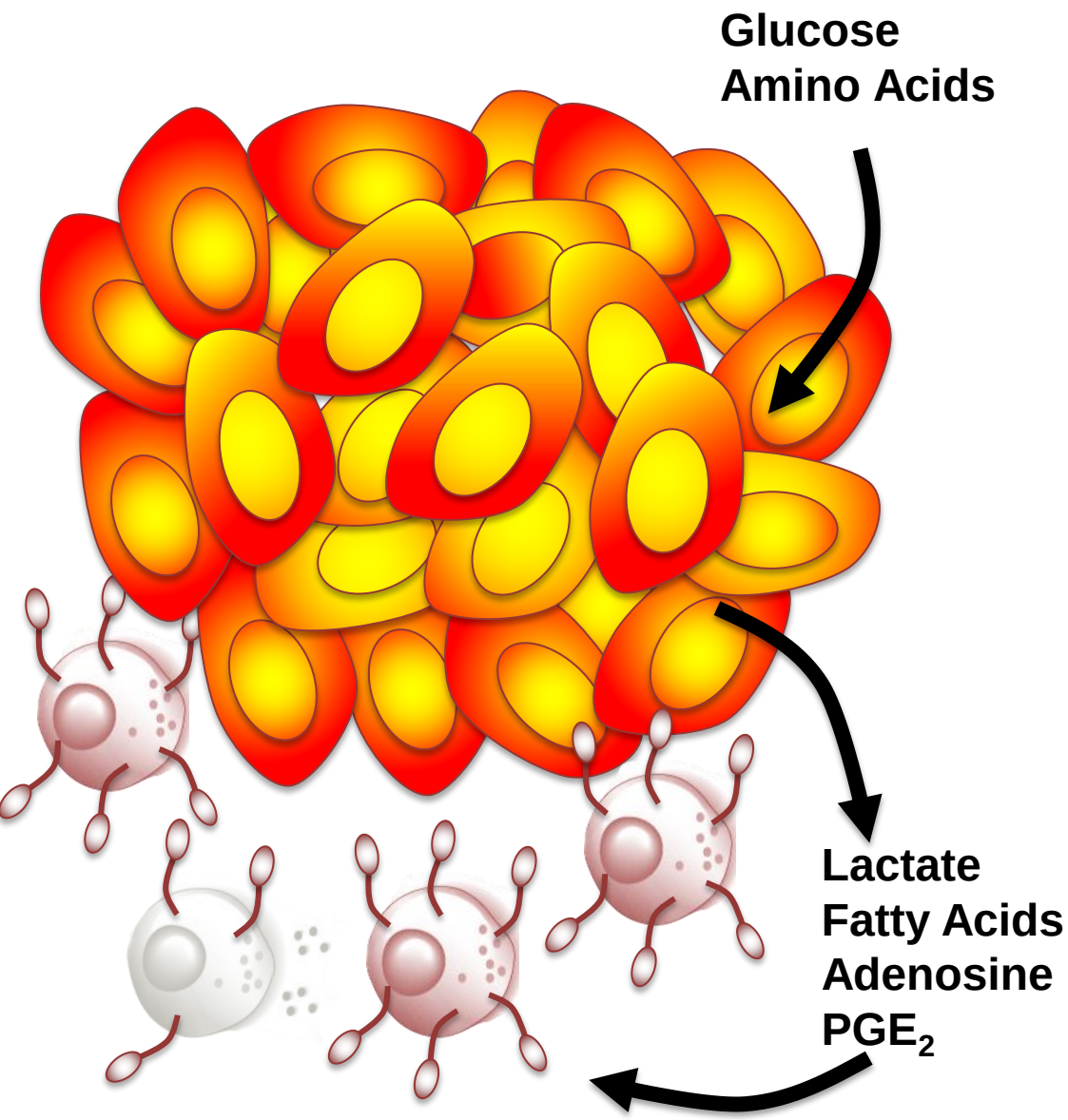


T cell dysfunction/ exhaustion

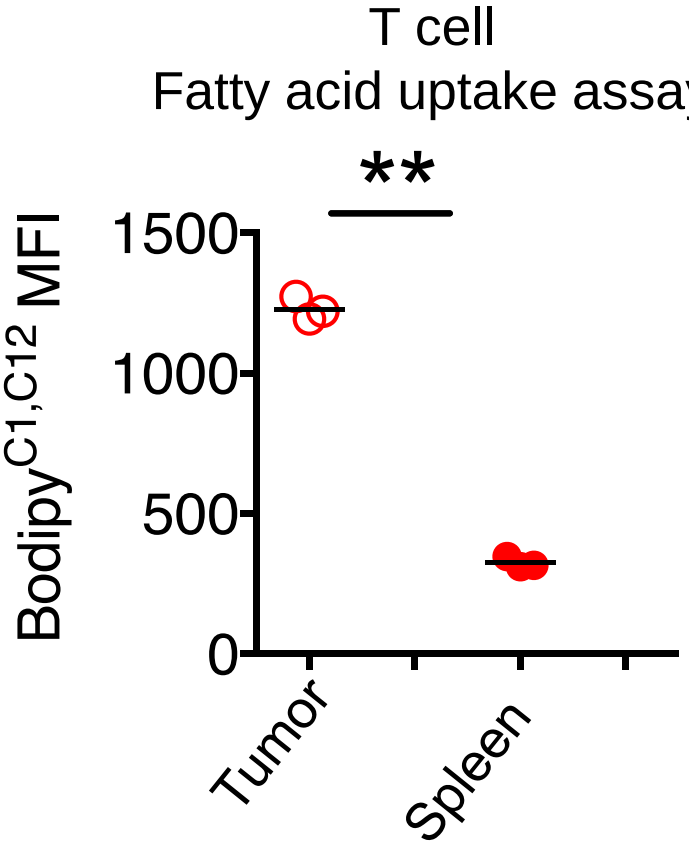
Fatty Acids in tumor interstitial fluid



Metabolic regulation of T cell function in tumors?

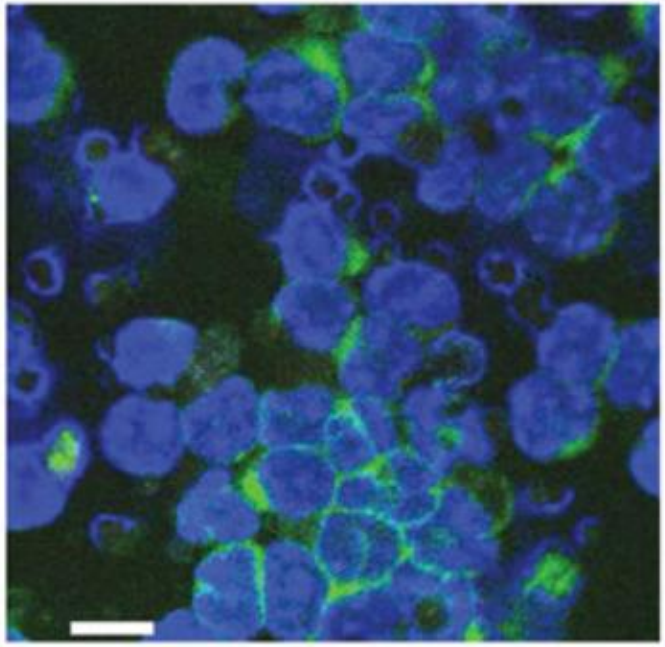


T cell dysfunction/ exhaustion

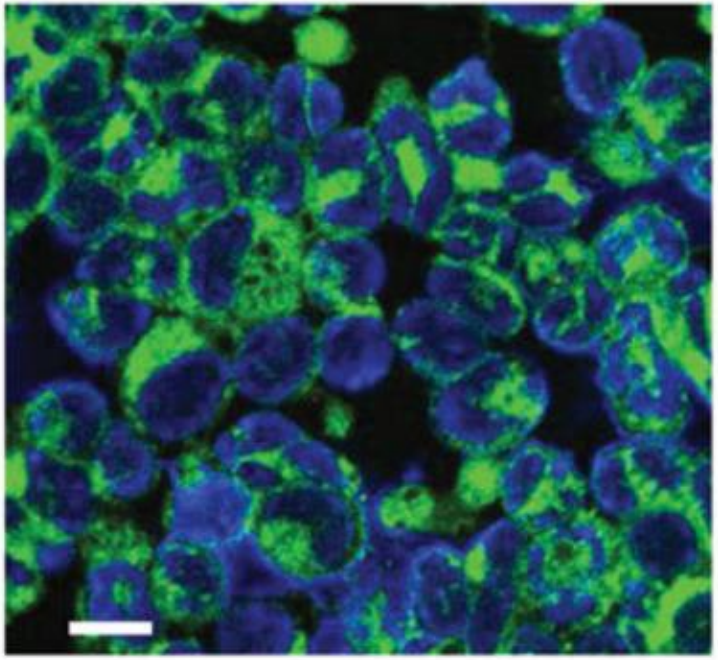


Precedence for Fatty Acid Metabolism's Immune Suppression of Myeloid Cells

Naive $CD11C^+$



Tumor Burdened $CD11C^+$

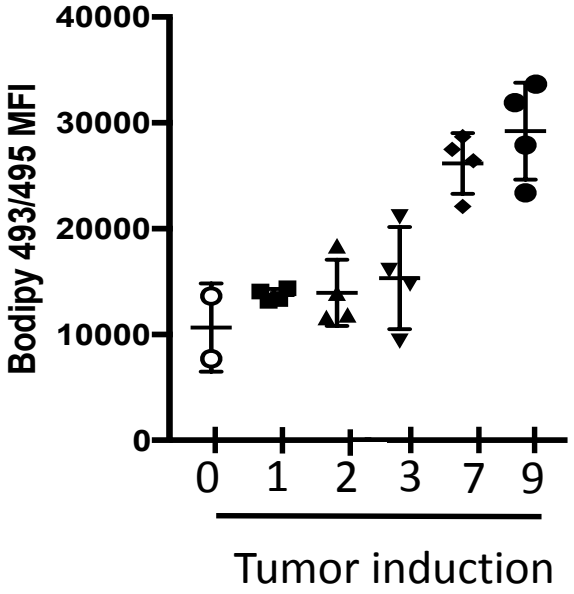


- Increased in lipid uptake of DCs in tumor burdened mice
- Lipid density was associated with inadequate antigen presentation
- Suppressing fatty acid synthesis partially rescued the DCs

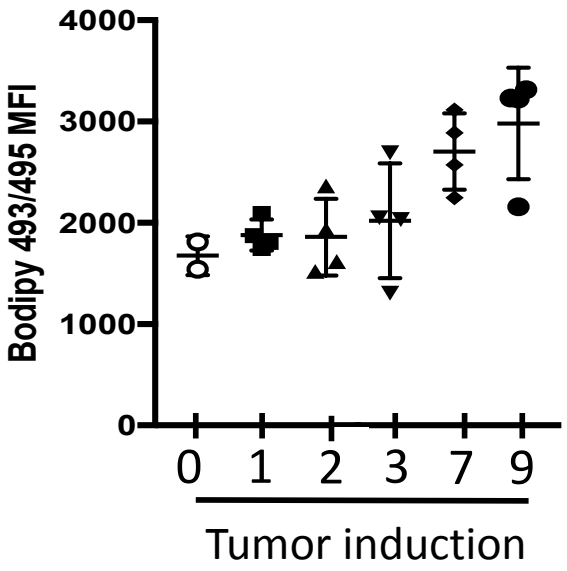
Donna L. Herber et al. Nat. Med 2010

Progressively increased lipid storage in immune cells in murine LUAD ($EGFR^{L858R}$) model

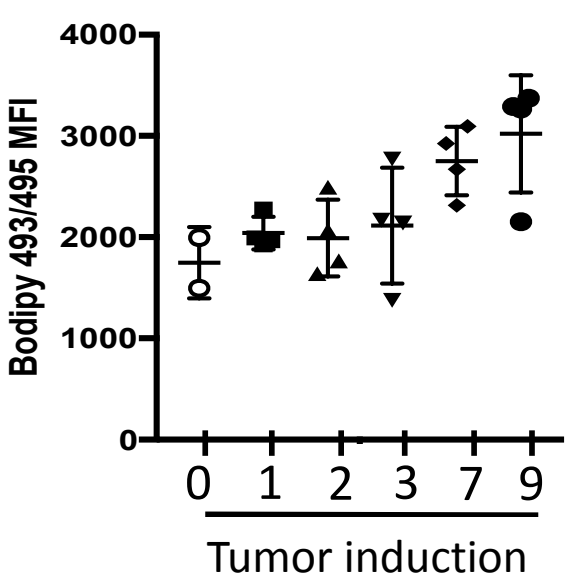
Macrophages



CD4 T cells

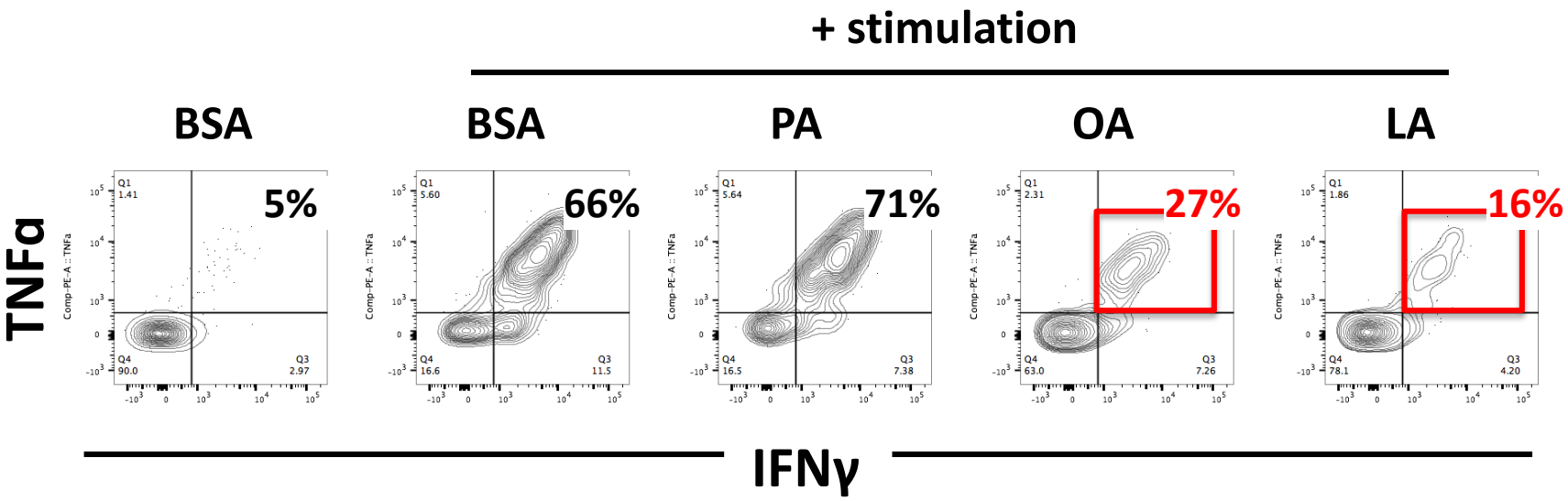


CD8 T cells

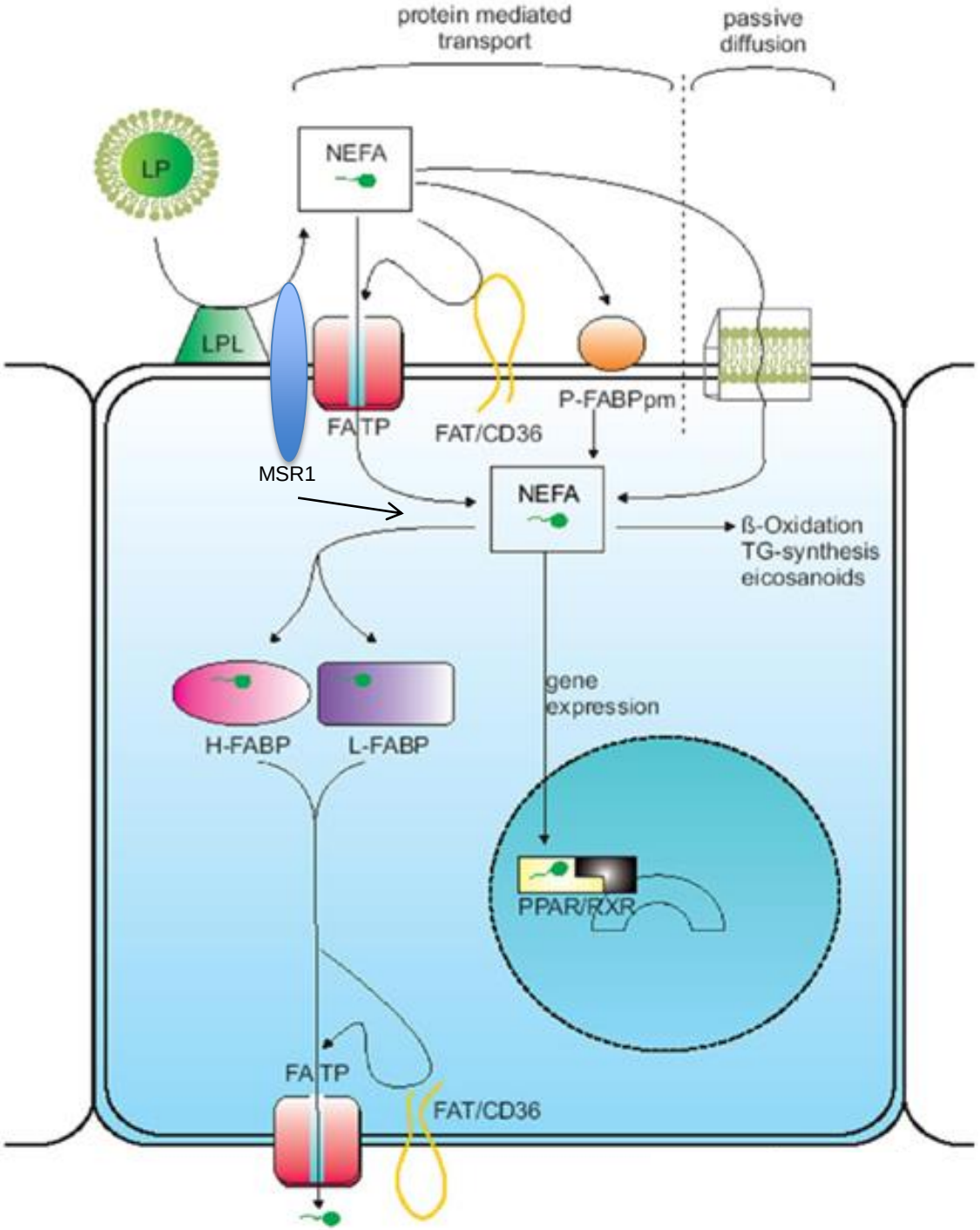


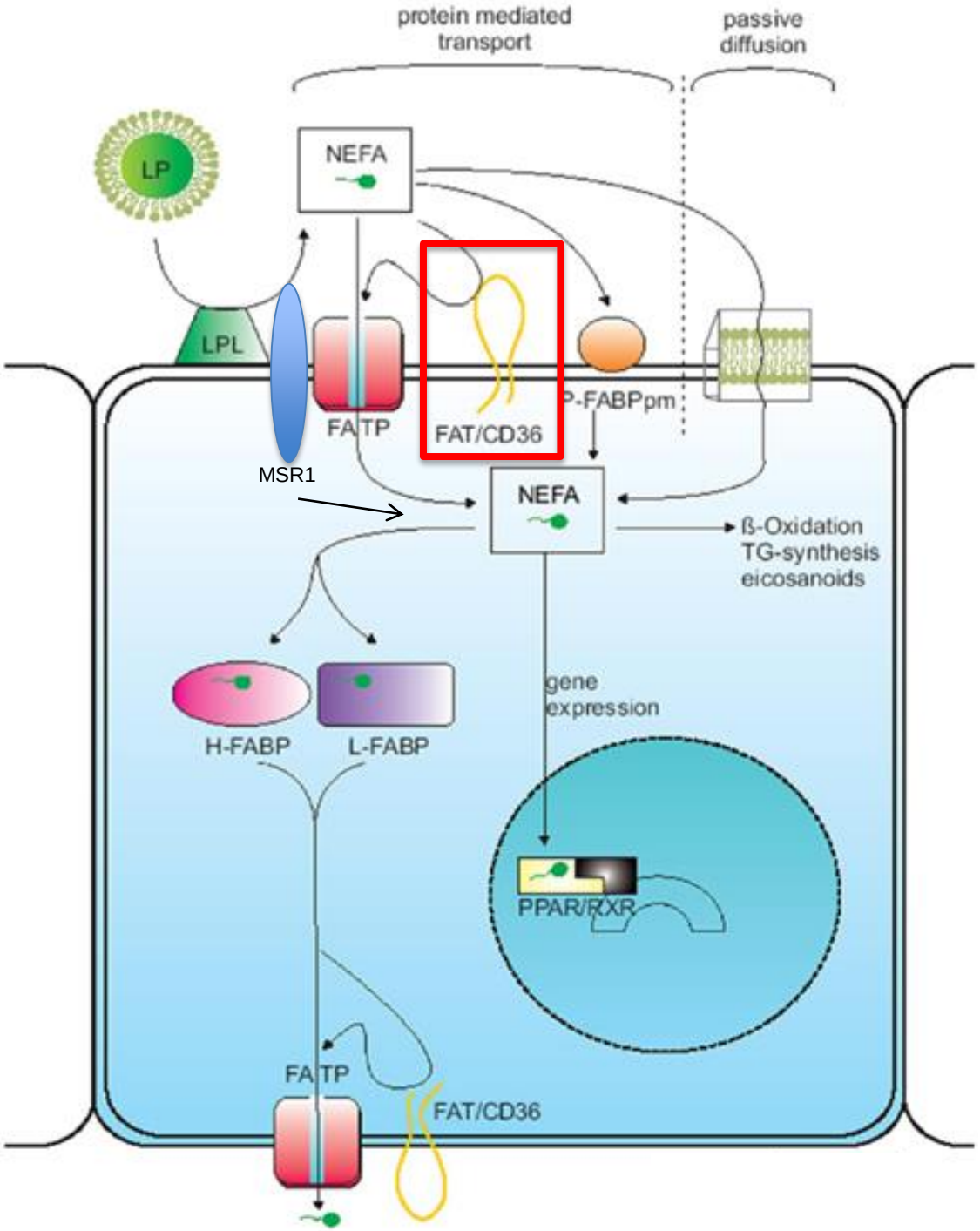
A. Kuhlmann, C. Robles-Oteiz & Katie Politi

Certain FAs suppress T cell effector function



- Palmitic acid (PA 16:0);
- Oleic acid (OA 18:1);
- Linoleic acid (LA 18:2);


protein mediated transport
passive diffusion
LP
NEFA
LPL
MSR1
FATP
FAT/CD36
P-FABPpm
NEFA
ß-Oxidation
TG-synthesis
eicosanoids
gene expression
H-FABP
L-FABP
PPAR/RXR
FATP
FAT/CD36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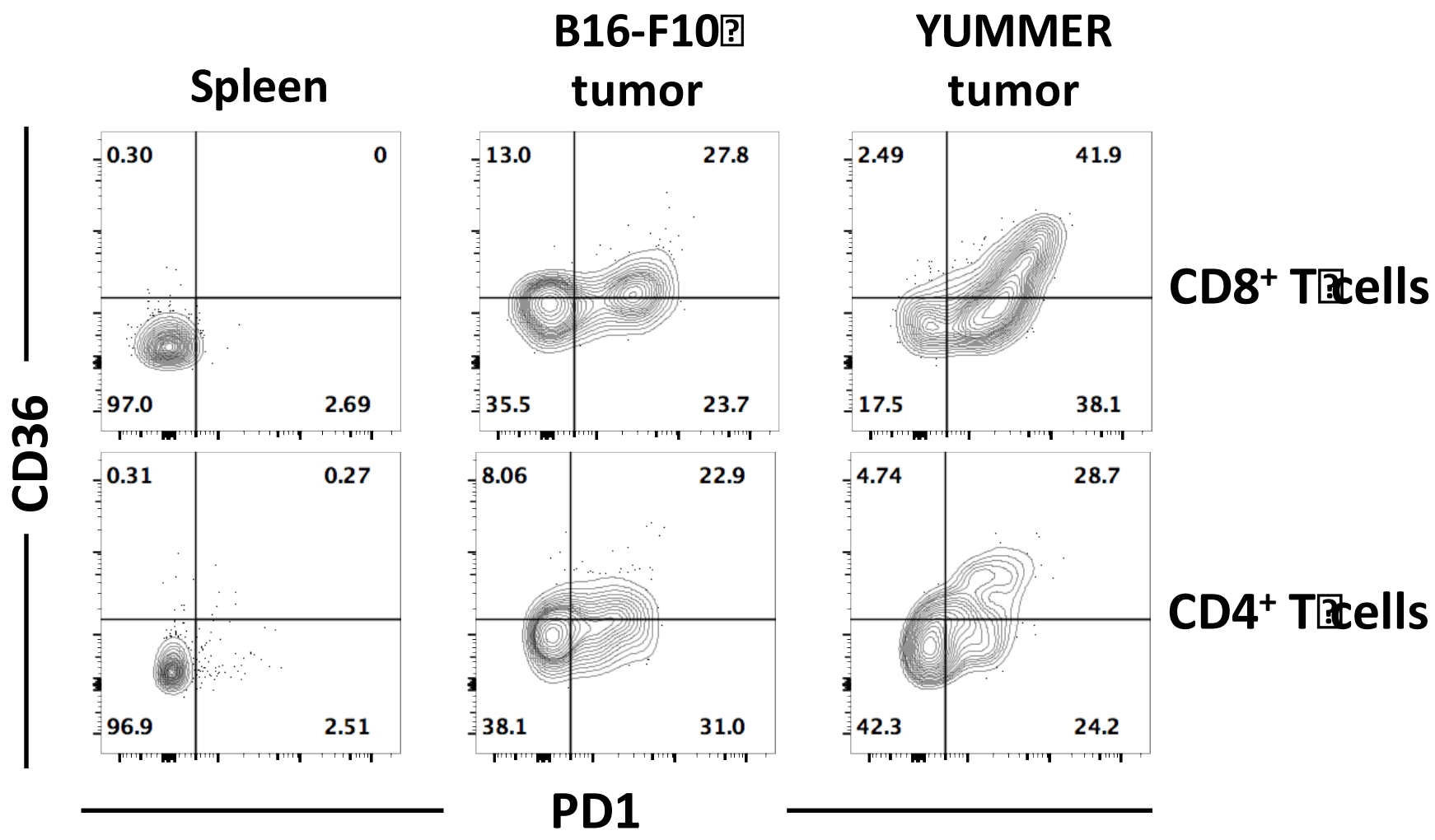
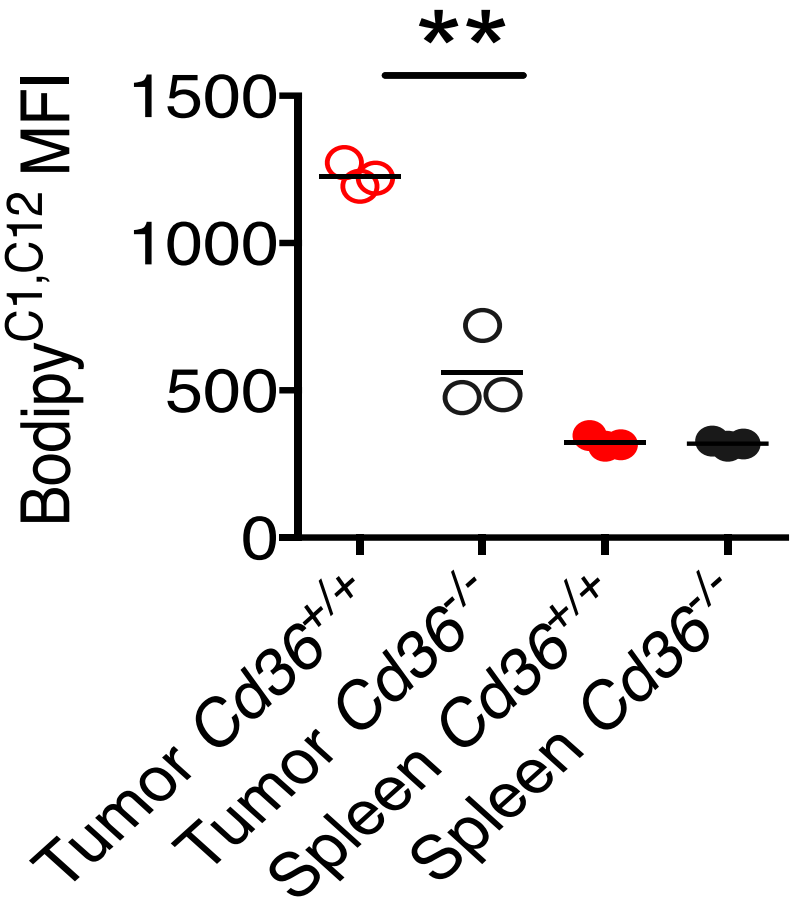
CD36 expression is increased in TILs

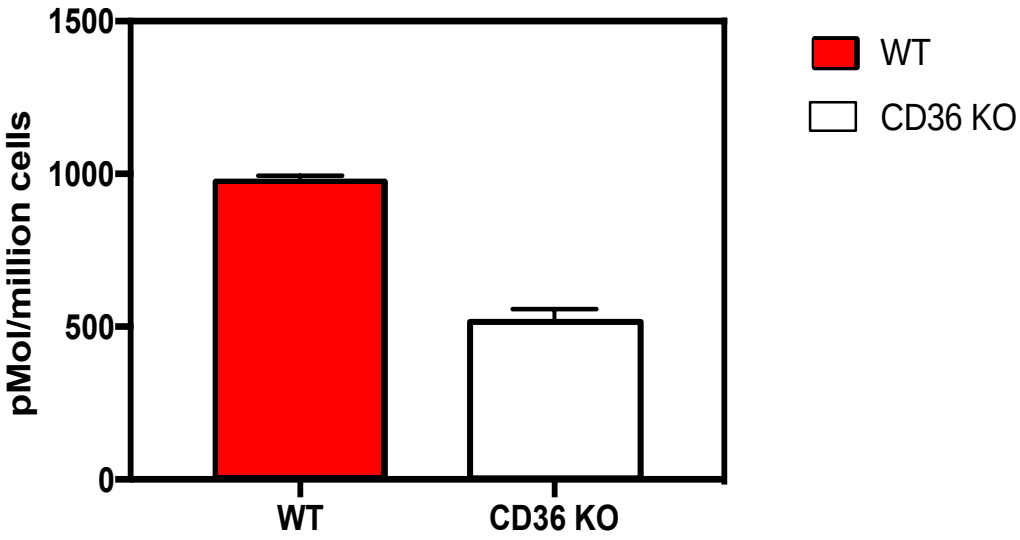


CD36 promotes tumor growth and PD-1 expression

T cell
Fatty acid uptake assay



Intracellular
Fatty acid levels in T cells



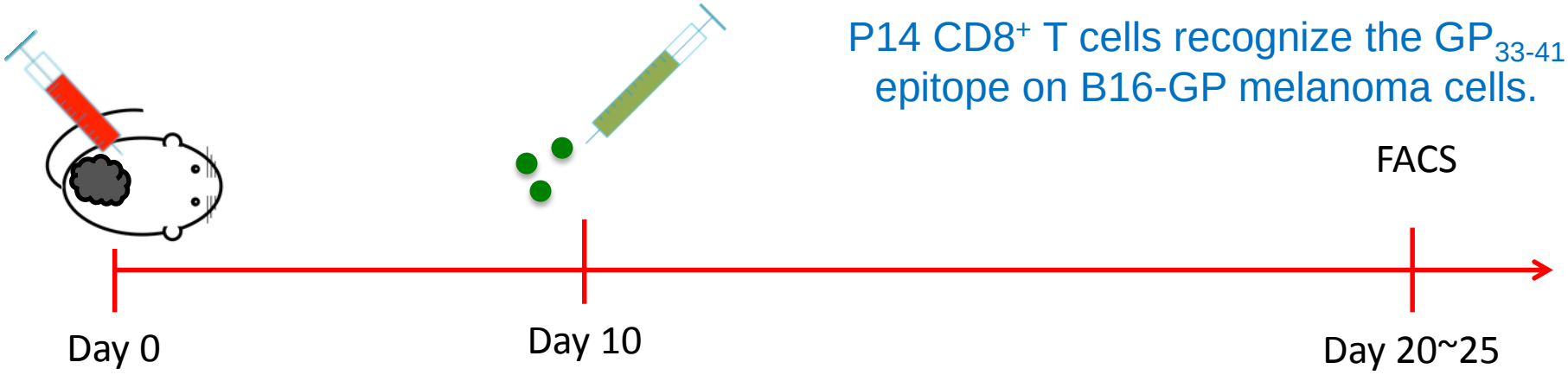
CD36 promotes tumor growth and PD-1 expression

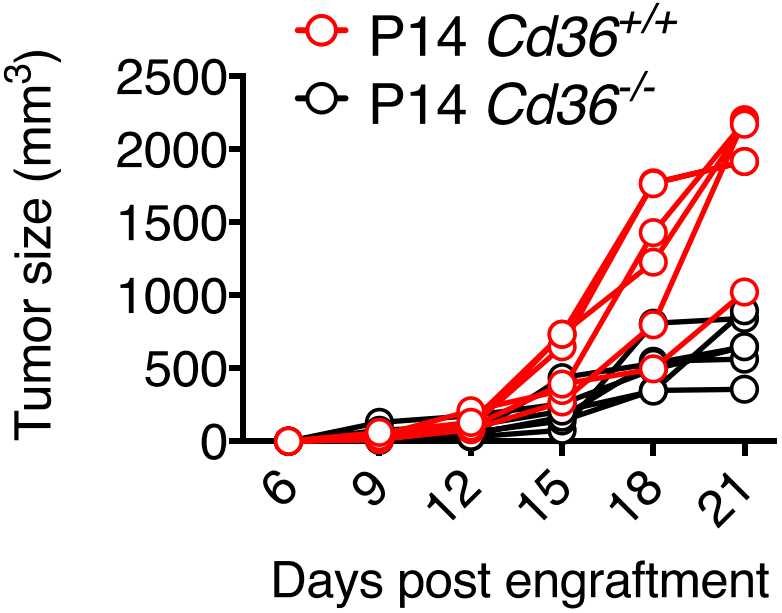
B16-GP$_{33-41}$

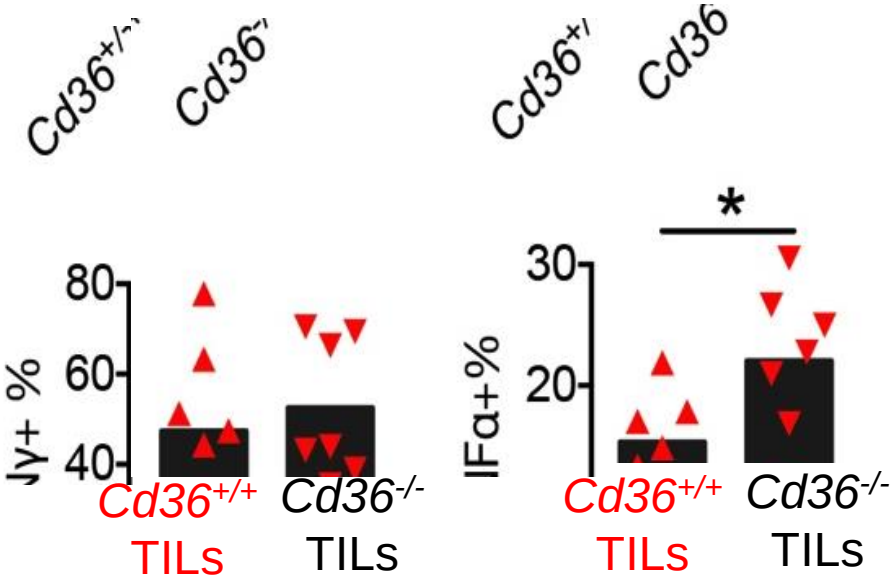
Cd36$^{+/+}$ P14 CD8^{+}

Cd36$^{-/-}$ P14 CD8^{+}

P14 CD8^{+} T cells recognize the GP$_{33-41}$ epitope on B16-GP melanoma cells.







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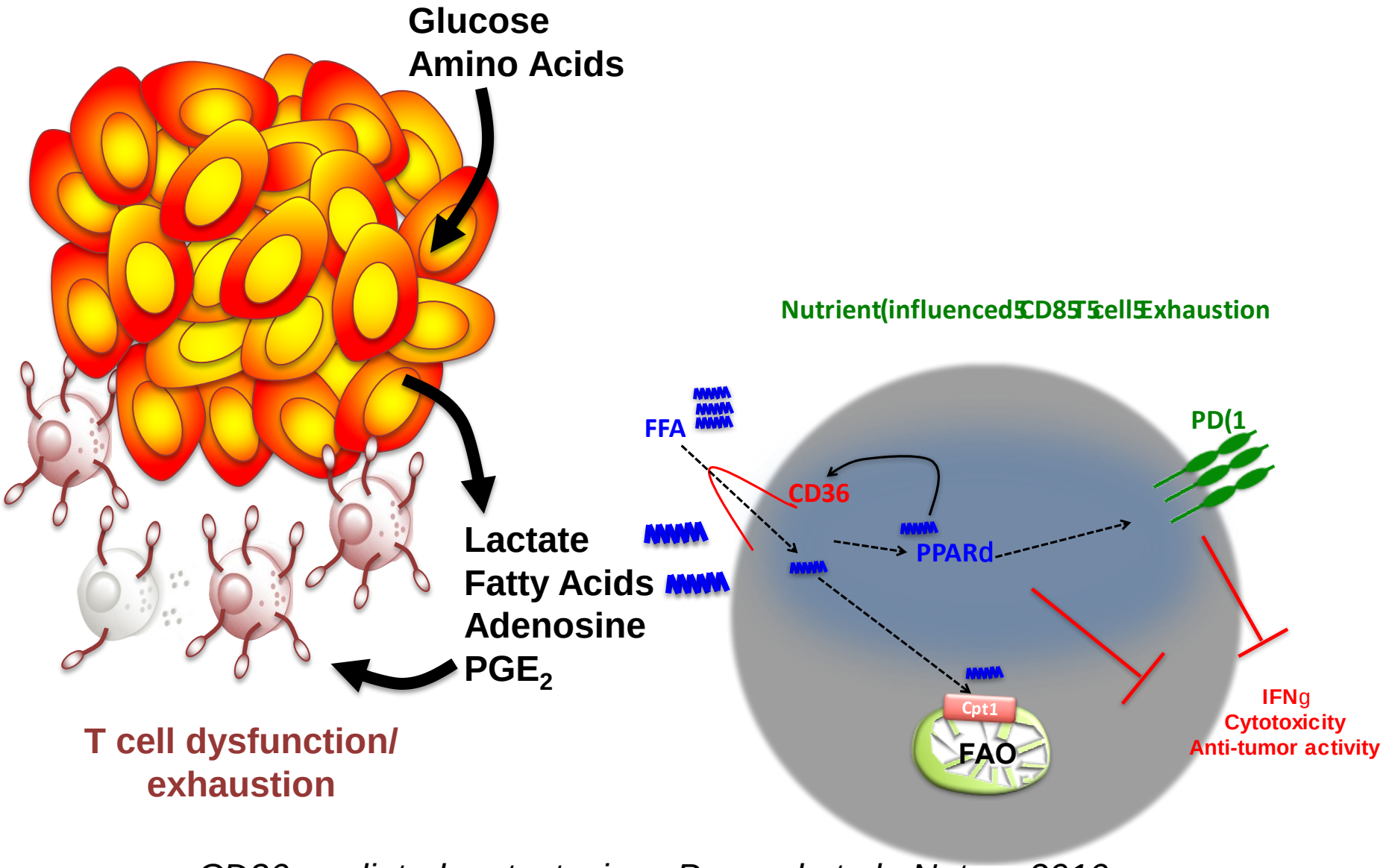
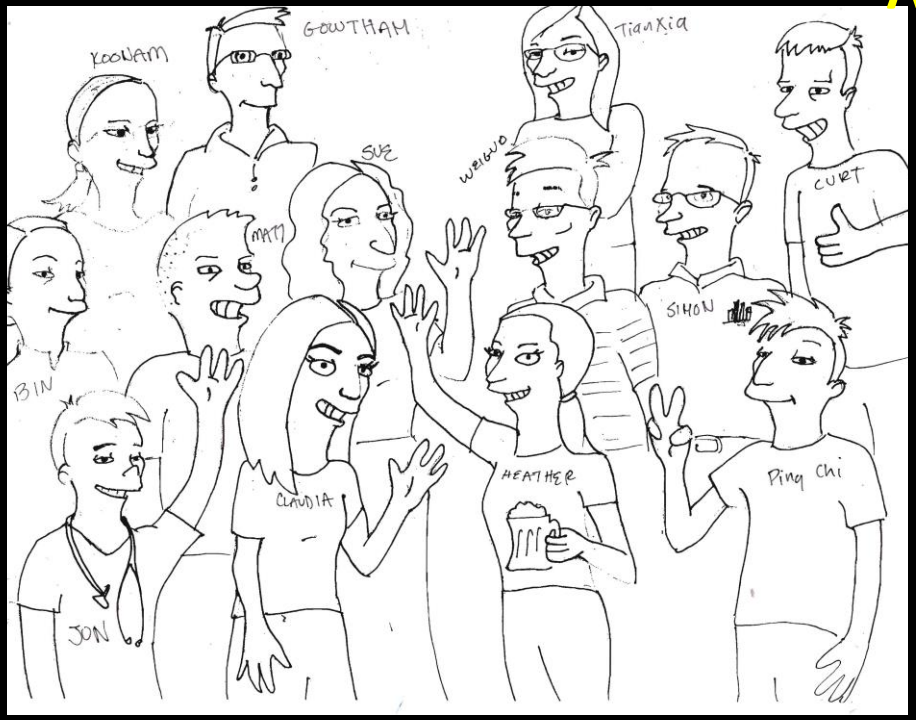


CD36 mediated metastasis *Pascual et al., Nature 2016*

The Kaech Bunch

Robert Amezquita
Magda Coman
Guoliang Cui
Bill Damsky
Victor Du
Ping-Chih Ho
Simon Gray
Tianxia Guan
Xiaodong Jiang
Ali Kuhlman
Jun Siong Low
Bin Lu
Koonam Park
Curtis Perry
Camila Robles-Oteiza
Fabio Santori
Ryan Sowell
Durga Thakral
Shihao Xu
Hao Xu



Marcus Bosenberg

Kathryn Miller- Jense
Andres Muñoz-Rojas

Katie Politi
Roy Herbst

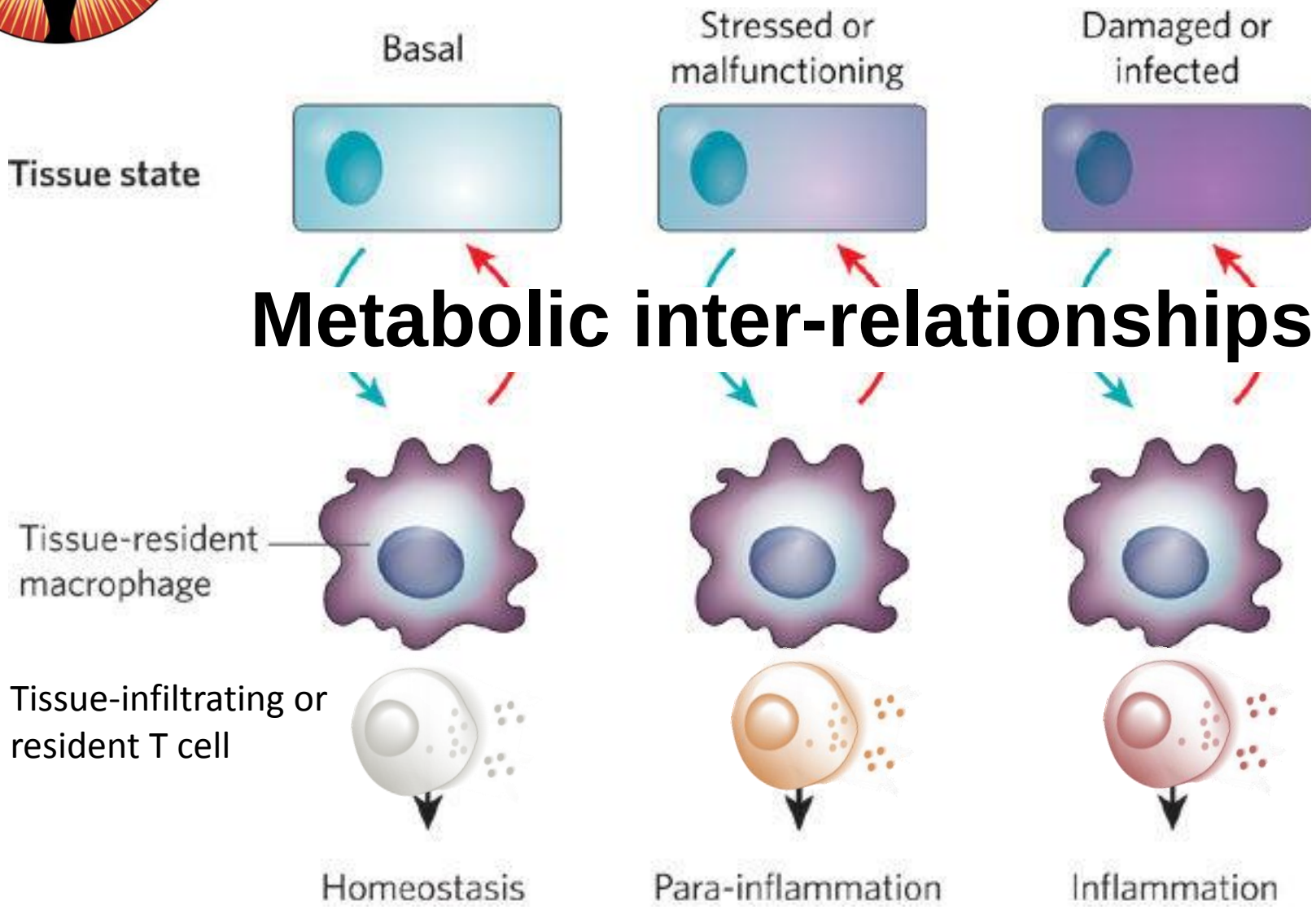
Jeff Townsend
Stephen Gaffey
Ping-Min Chen

Jeff Rathmell
Stefan Feske

Agios
Gillian Kingsbury
Victor Chowdury

NIH, Cancer Research Institute,
Yale SPOREs in Lung and Skin Cancer
Yale Cancer Center,
Melanoma Research Alliance

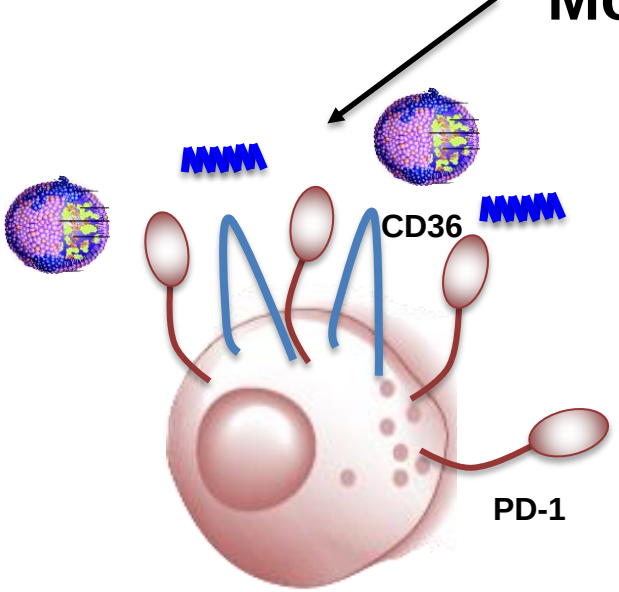
Tissue Homeostasis and Dystasis

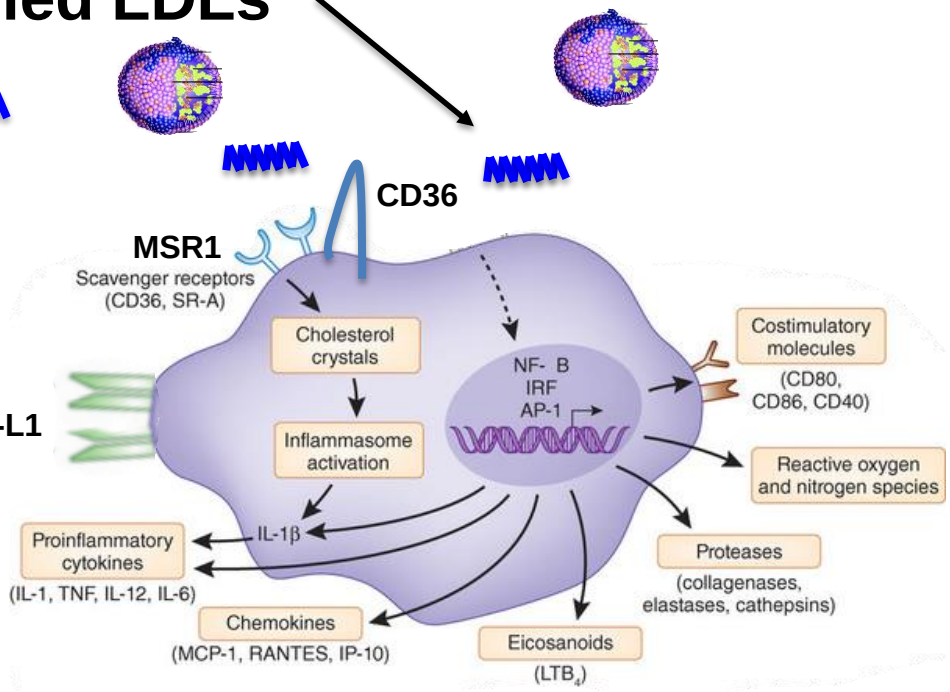


FFA and LDLs act on both T cells and Macrophages to create pro-tumorigenic states

Fatty Acids

Modified LDLs





T cells

- ↑ PD-1^{Hi}
- ↑ CD36^{Hi}
- ↑ T cell dysfunction

Macrophages

- ↑ PD-L1^{Hi}
- ↑ MSR-1^{Hi} CD36^{Hi}
- ↑ Tumor promotion