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November 8-12
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Society for Immunotherapy of Cancer

November 8-12 • NATIONAL HARBOR, MD

SITC 2017

Fueling immunotherapy through modulation of the metabolic axis

UPMC | HILLMAN CANCER CENTER

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Presenter Disclosure Information

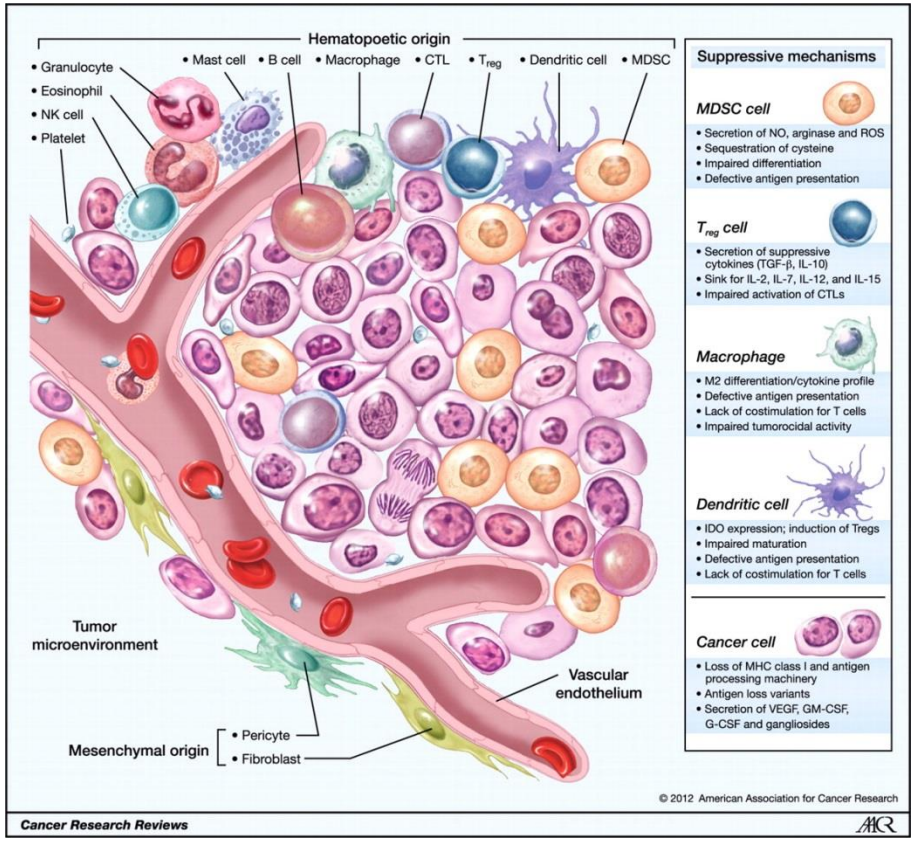
Greg M. Delgoffe

The following relationships exist related to this presentation:

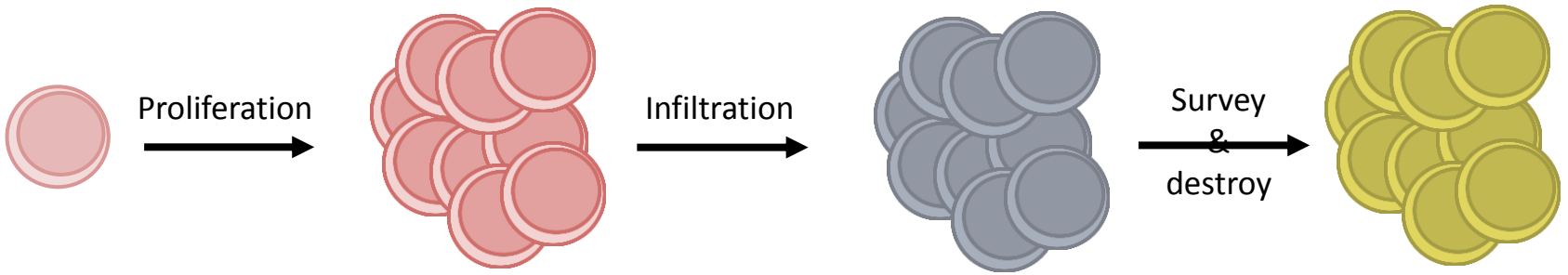
Merck & Co., Received, Consultant

Tumor microenvironment metabolism as a patient-specific resistance mechanism to immunotherapy

- Progressing tumors develop a potently immunosuppressive **tumor microenvironment**, which fosters tumor adaptation and progression
- Characterized by many different differentiation stages of tumor cell, altered fibroblasts, and a constellation of immunosuppressive cell types
  - Myeloid derived suppressor cells
  - Tumor associated macrophages
  - Regulatory T cells
- The tumor microenvironment also generates a **distinct metabolic landscape**
  - Hypoxia
  - Acidosis
  - Hypoglycemia
  - Saturated fats and ketone bodies
  - Depleted essential amino acids



T cell activation is metabolically demanding

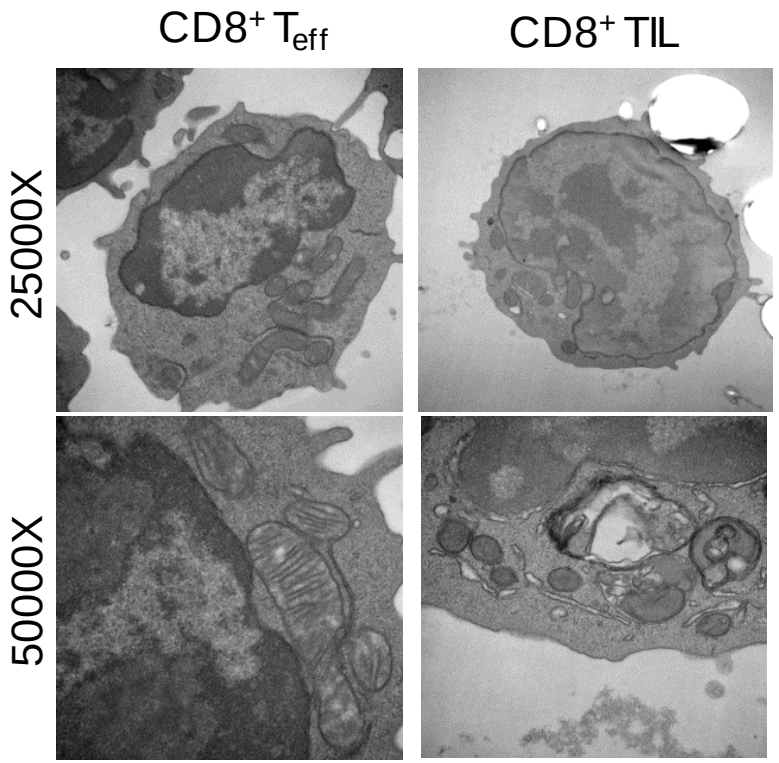


	Naïve T cells	Early effector	Infiltration	Peak effector
FUNCTION	- Functionally quiescent - Persist for a lifetime	- 2-6 h cell cycles - Transcriptional and epigenetic changes	- Migrate into tissues - Secrete inflammatory cytokines	- Scan targets - Lyse target cells - In situ proliferation
FUEL	- Catabolic - Minimal nutrient uptake	- Biosynthetic - Glycolytic	- Mitochondrial changes support actin remodeling	- Glycolysis - ROS production

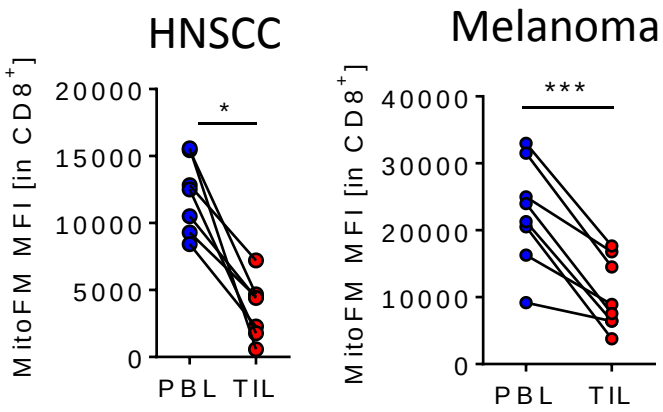
Thus, access to nutrients and the ability to process them represents a mechanism by which T cells can be regulated

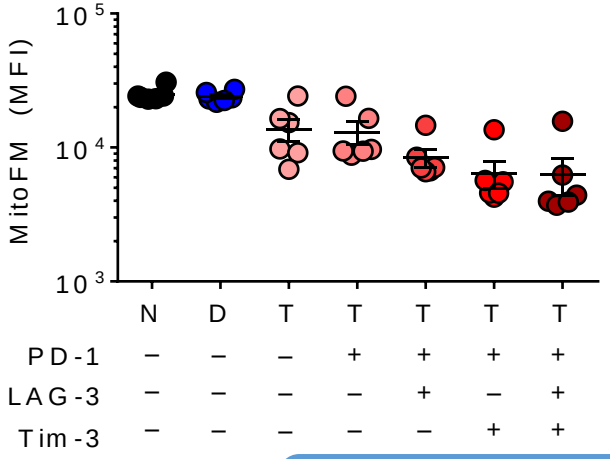
Curr Opin Immunol 2016
and Delgoffe, *Vaccines* 2016
Delgoffe, *Cancer Immunol Res* 2016

What is the metabolic phenotype of tumor infiltrating T cells?



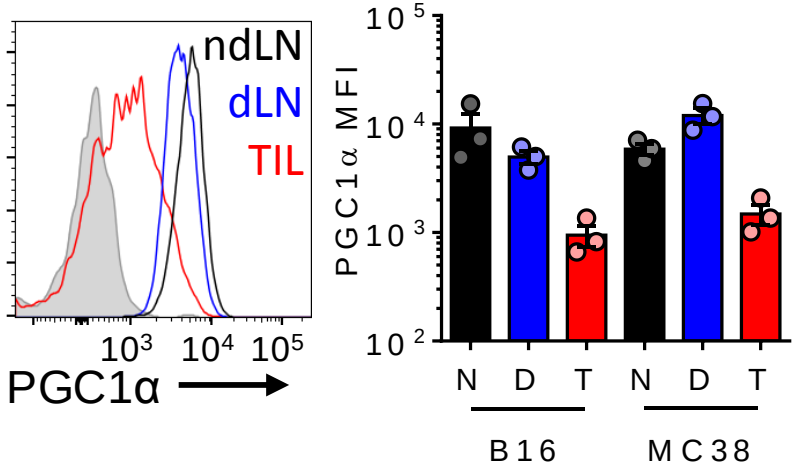
- Tumor infiltrating T cells in murine and human cancer show defects in glucose uptake and dysfunctional mitochondria
- Loss of T cell metabolic sufficiency correlates with upregulation of co-inhibitory molecules, but occurs even in the presence of PD-1 blockade!



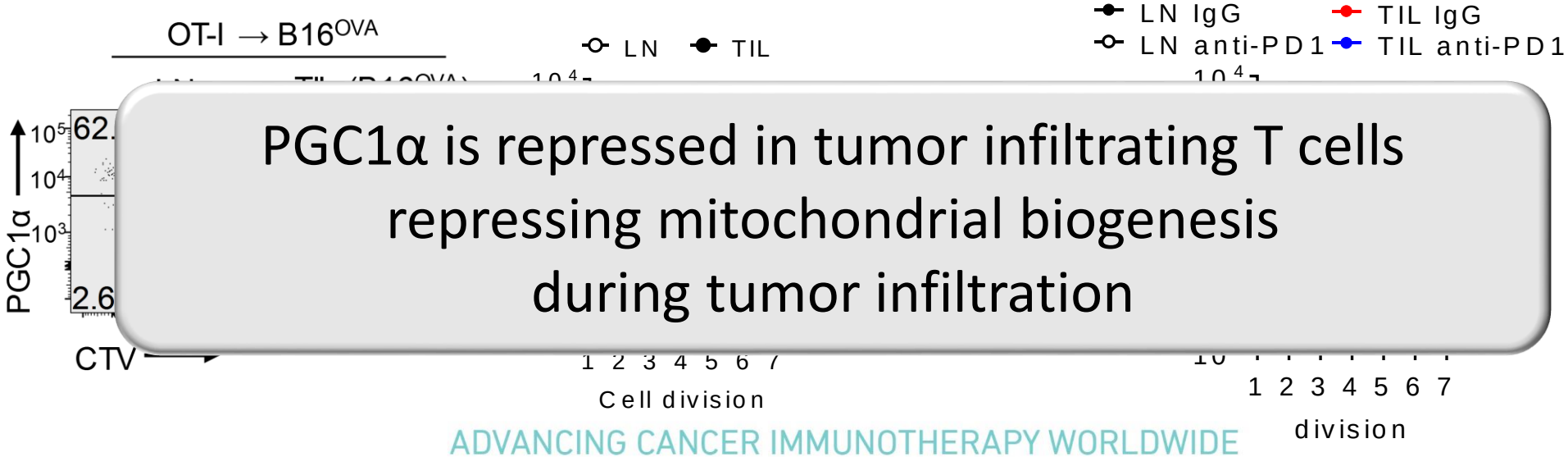


Scharping et al, *Immunity* 2016

What is the molecular mechanism of mitochondrial loss in intratumoral T cells?

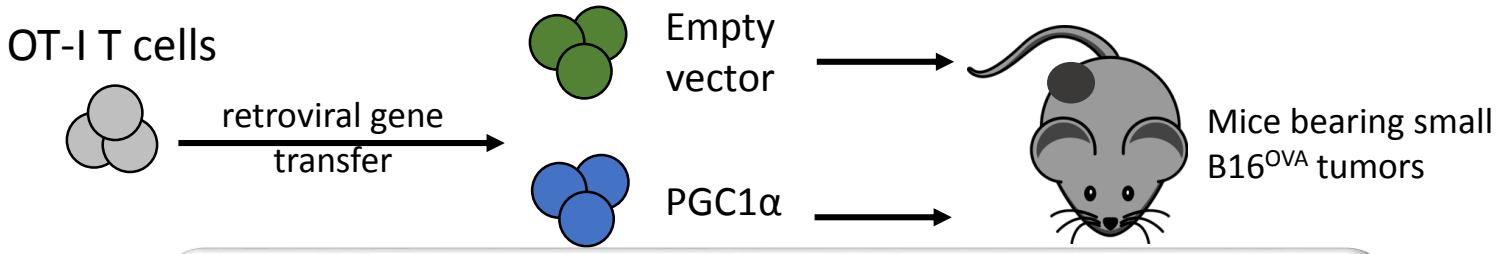


- Mitochondrial biogenesis, the process by which new mitochondria are generated, is programmed in part by the transcriptional co-activator PGC1α
- PGC1α protein is dramatically reduced in TIL CD8⁺ T cells
- PGC1α loss occurs progressively as T cells become activated in tumors
- PGC1α downregulation occurs independently of PD-1 signaling

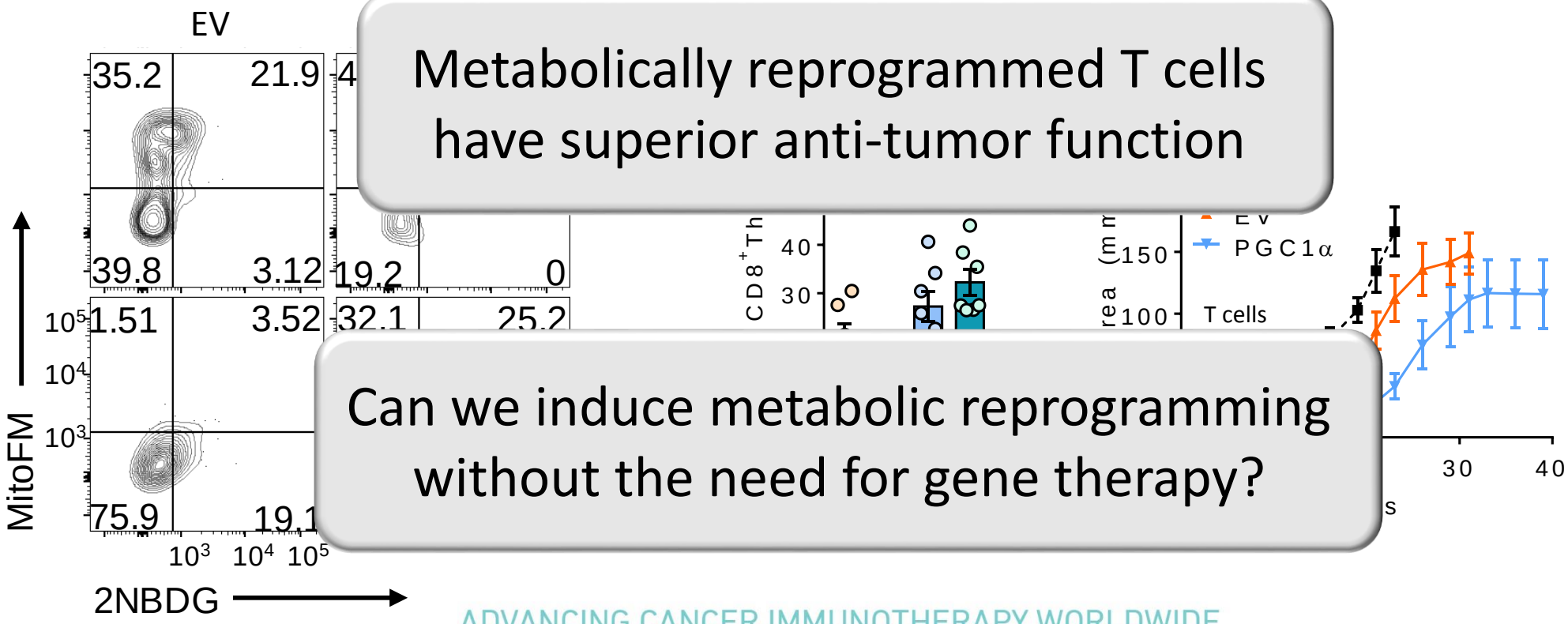


PGC1α is repressed in tumor infiltrating T cells repressing mitochondrial biogenesis during tumor infiltration

Can T cells be reprogrammed metabolically to bolster function in the tumor?



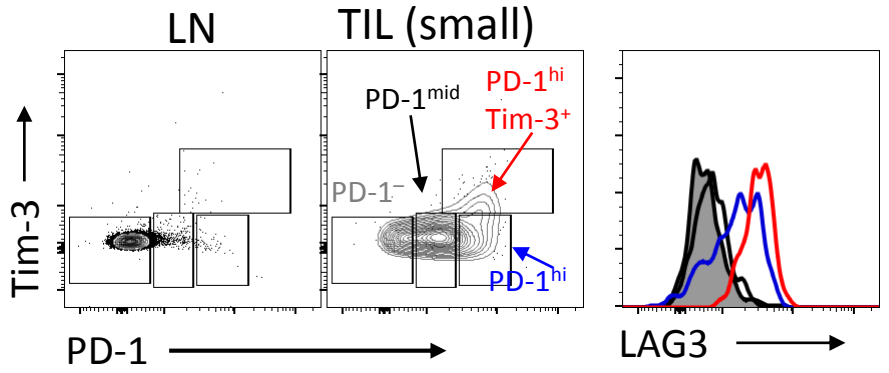
Metabolically reprogrammed T cells have superior anti-tumor function

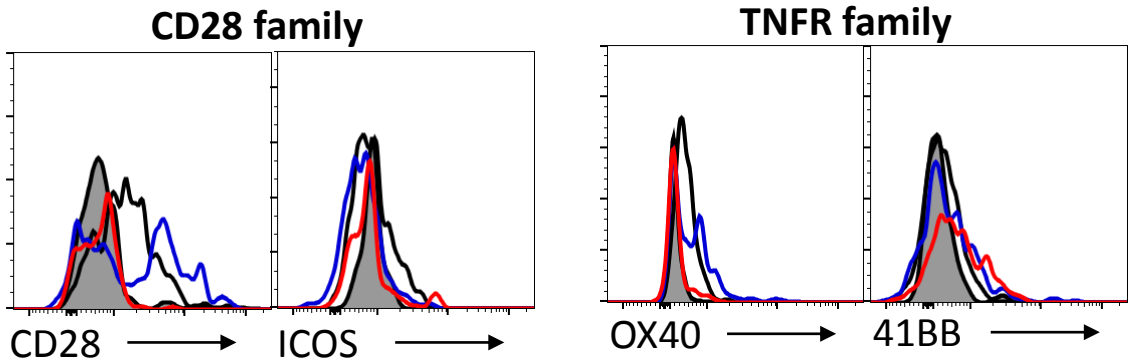


Can we induce metabolic reprogramming without the need for gene therapy?

Costimulatory molecules in the TME

- Previous work has highlighted the importance of costimulation in metabolic reprogramming, but typically in a nontumor setting
- The costimulatory/inhibitory molecules expressed by functional/dysfunctional states of TIL may provide insight into how to properly rejuvenate them
- We assayed which molecules were expressed on T cells in various functional states as defined by PD-1 and Tim-3 in small melanomas
- LAG3, as expected, progressively rose as T cells upregulated PD-1 and began making Tim-3
- CD28 family members were markedly repressed as T cells became more and more phenotypically 'exhausted'
- OX40 was repressed in terminally exhausted T cells
- 41BB, however, was exp
most exhausted T cells i

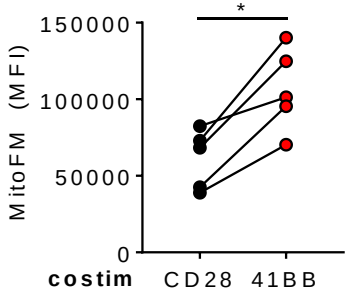


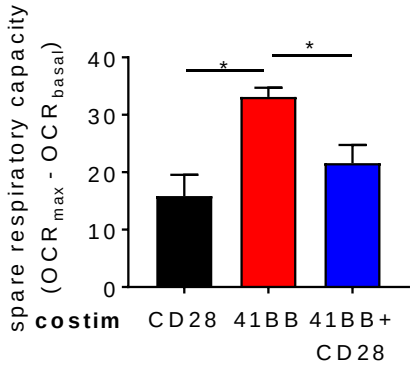


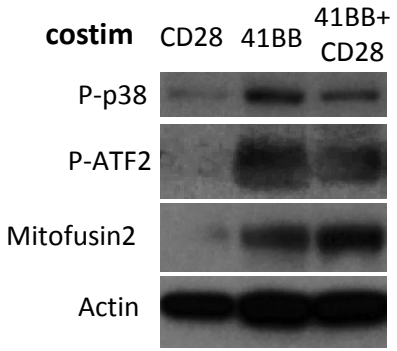
Can 41BB ligation provide metabolic support to the most exhausted TIL?

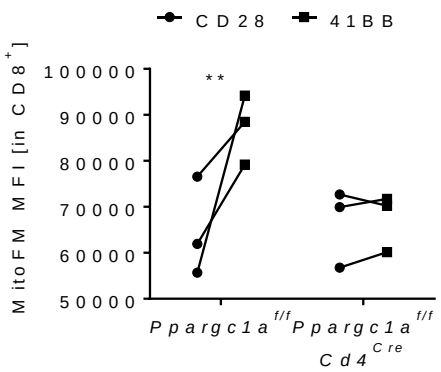
Can 41BB support mitochondrial metabolism?

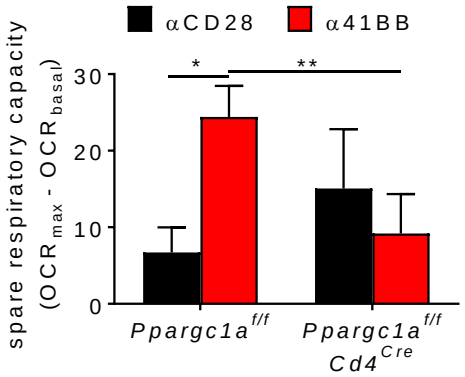
- 41BB costimulation of murine T cells results in cells with increased mitochondrial mass
- Costimulation of 41BB does not induce increased mitochondrial oxidation, but rather improves mitochondrial capacity
- 41BB ligation promotes increases in PGC1α expression and a program of mitochondrial fusion and biogenesis
- PGC1α is required for 41BB-mediated metabolic reprogramming

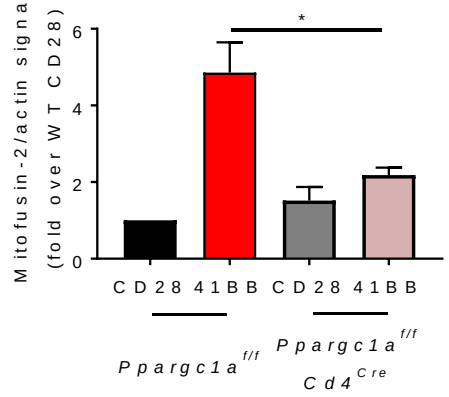








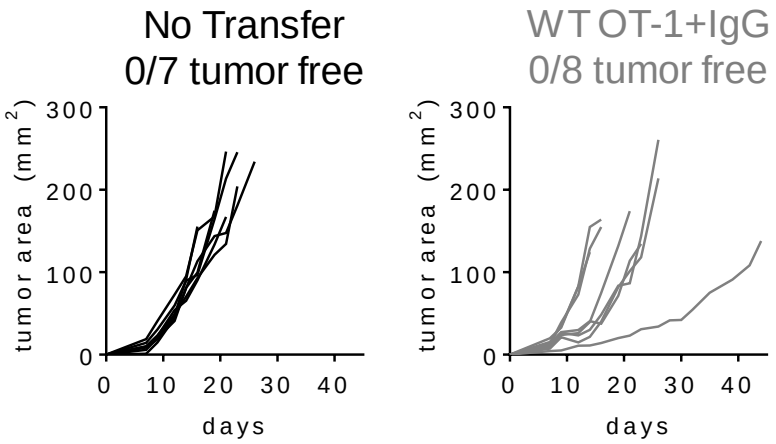




Menk et al, *J Exp Med* (in revision)

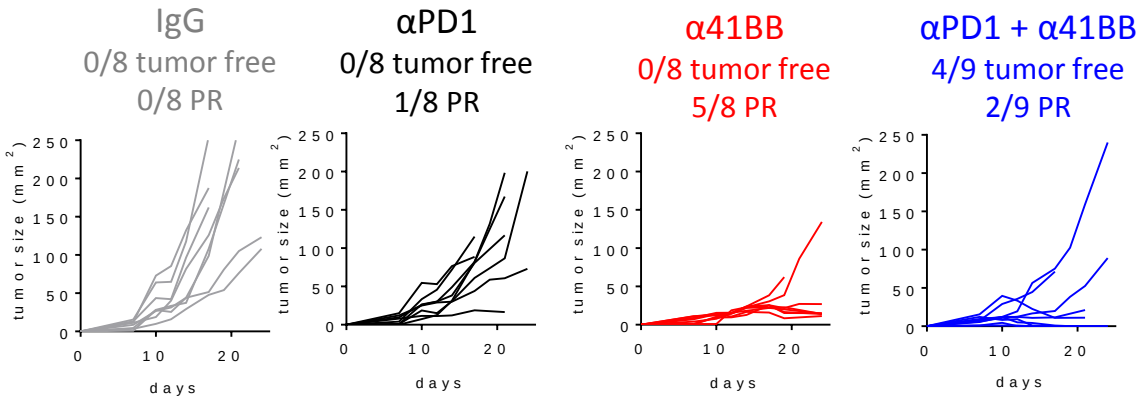
How does metabolic support by 41BB impact immunotherapy?

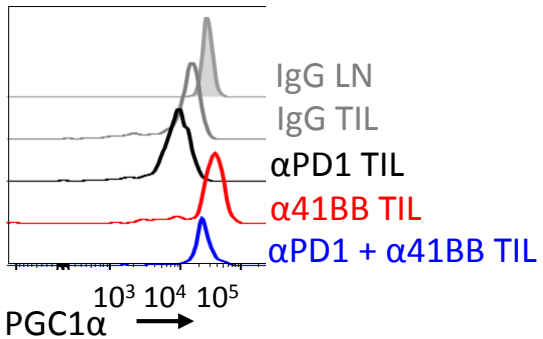
- Adoptive cell therapy using activated OT-I T cells transferred into $B16^{OVA}$ bearing mice results in a very limited response
- ACT into mice receiving 41BB agonists results in potent synergy resulting in a majority of mice experiencing complete regression
- This 41BB effect requires the expression of PGC1α by the therapeutic T cell

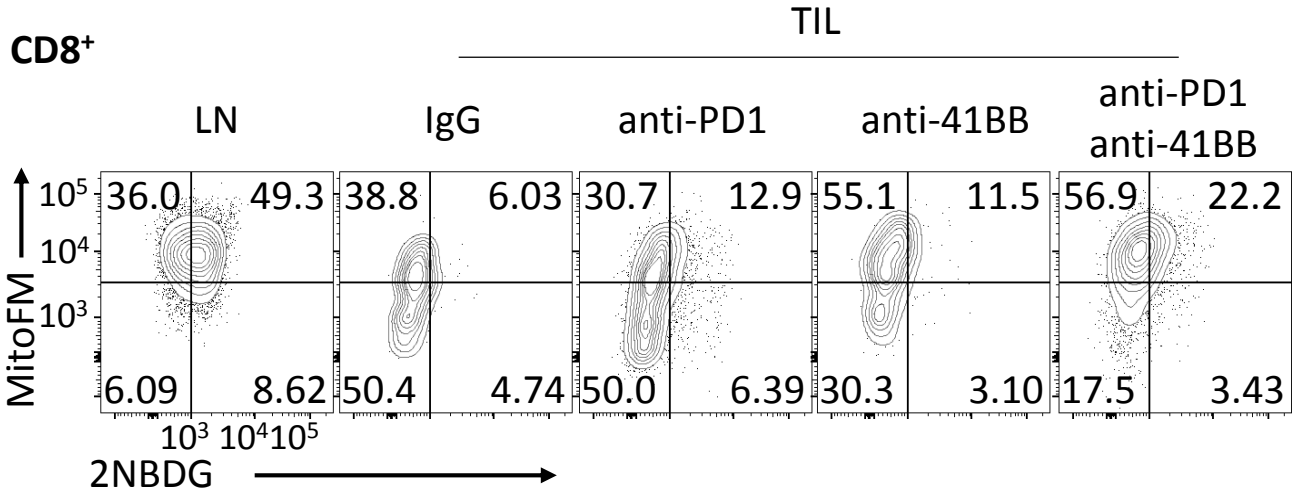


41BB also impacts checkpoint blockade immunotherapy

- As previously reported, 41BB combinatorial therapy promotes tumor clearance
- PGC1α is significantly upregulated in TIL of 41BB treated animals
- 41BB agonism reverses the mitochondrial insufficiency observed in TIL

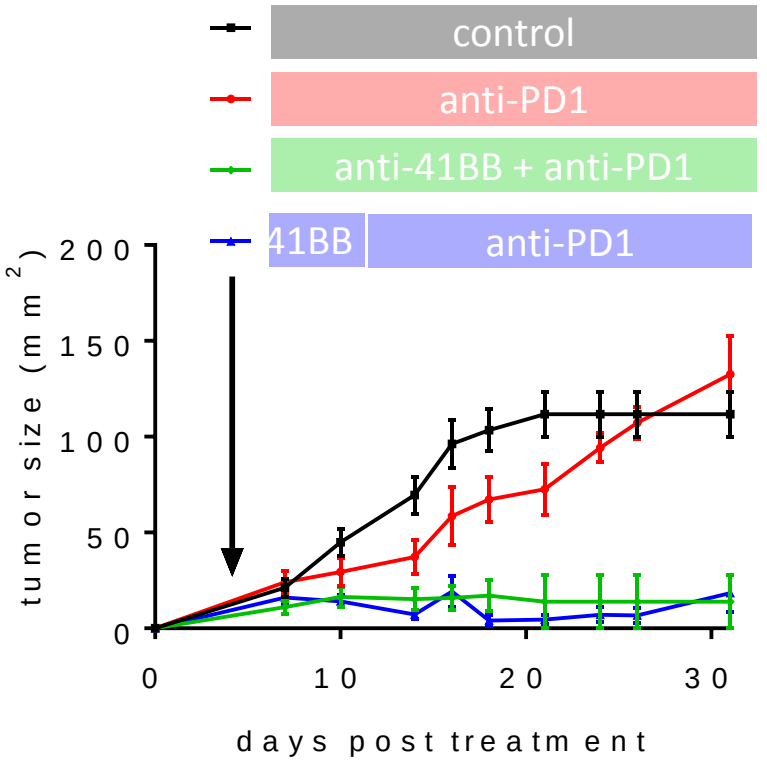






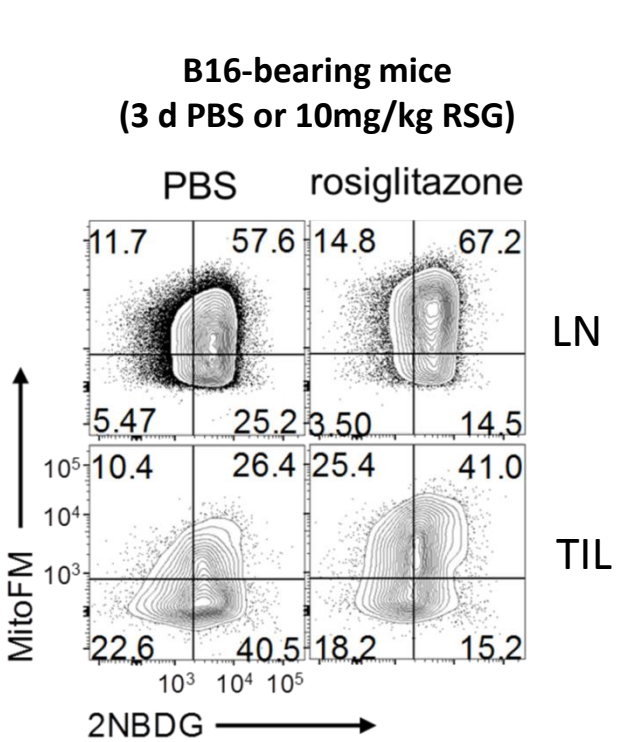
Does metabolic support need to be continuous?

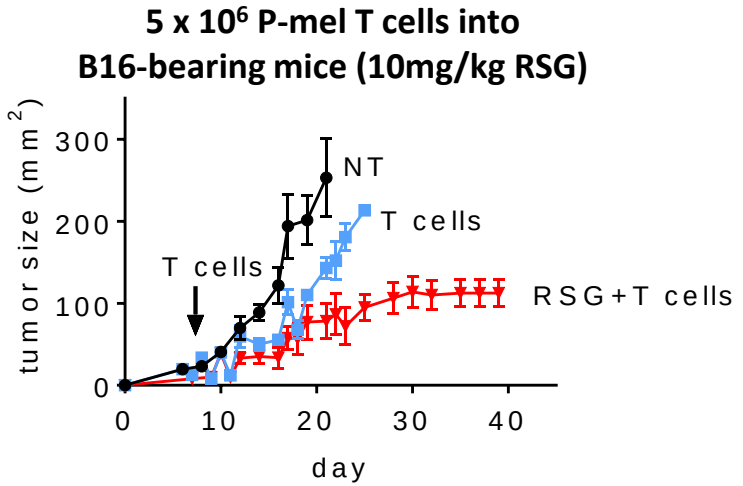
- 41BB has been studied clinically as an immunotherapeutic target, but with significant toxicities
- Our data suggested though that the metabolic support afforded by 41BB ligation occurred quickly and persisted after cessation of treatment
- We asked in our mouse model whether a short-course of 41BB treatment could provide similar therapeutic benefits
- Treatment of mice with 41BB for just three days sensitized mice to PD-1 immunotherapy, with results indistinguishable from the continuous co-treatment

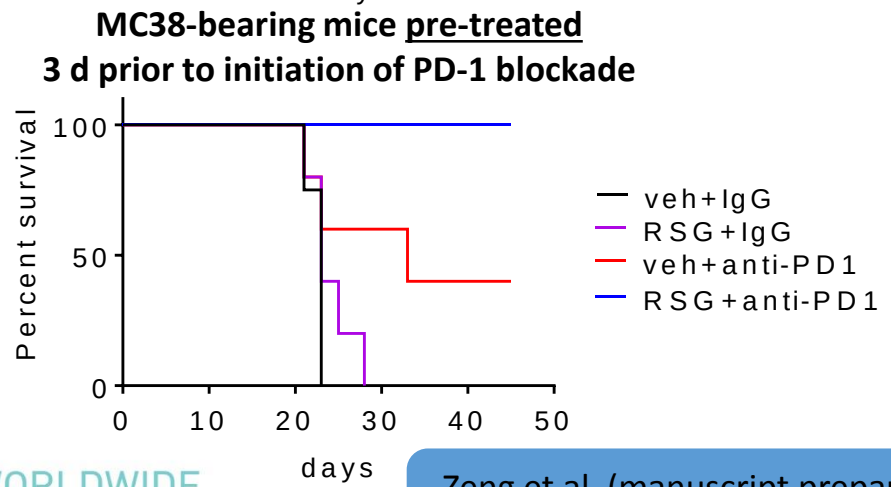


Does metabolic support need to be so heroic?

- Rosiglitazone, a synthetic PPAR agonist, can stimulate mitochondrial biogenesis in tumor infiltrating and peripheral T cells
- Glitazones can improve adoptive T cell therapy
- Even three days of pre-treatment with RSG can prime T cells for response to checkpoint blockade



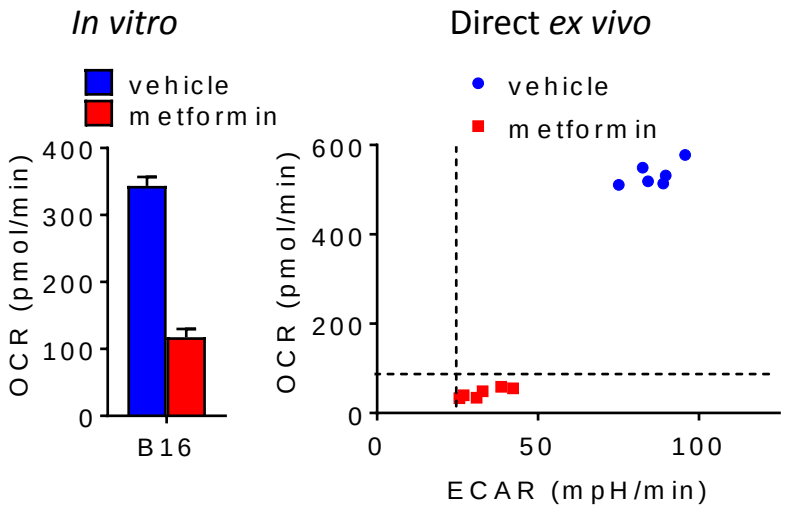




Zeng et al, (manuscript prepared)

The elephant in the room… the tumor cell

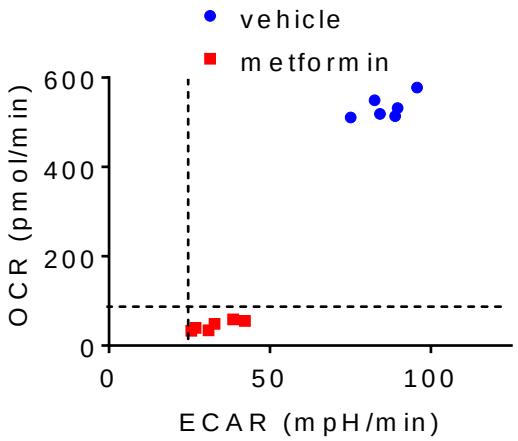
- Our data so far has focused on providing a T cell with a metabolic advantage
- However, it is competition with the **tumor cell** that drives the need for this energetic support
- Analysis of tumor cell metabolism and response to immunotherapy suggested it was the oxidative axis that was especially detrimental to T cell function
- We identified the widely prescribed type II diabetes drug **metformin** as a tumor microenvironment remodeler
- Metformin acts in part as a (weak) complex I inhibitor, inhibiting mitochondrial oxygen consumption
- Epidemiological studies have revealed that individuals taking metformin have a reduced risk of cancer and do better on various therapies
- Preclinical data suggest that the anti-tumor metformin effect requires T cells



- Thus, we hypothesized that metformin might act by inhibiting tumor oxygen consumption, generating a less hypoxic environment for T cells

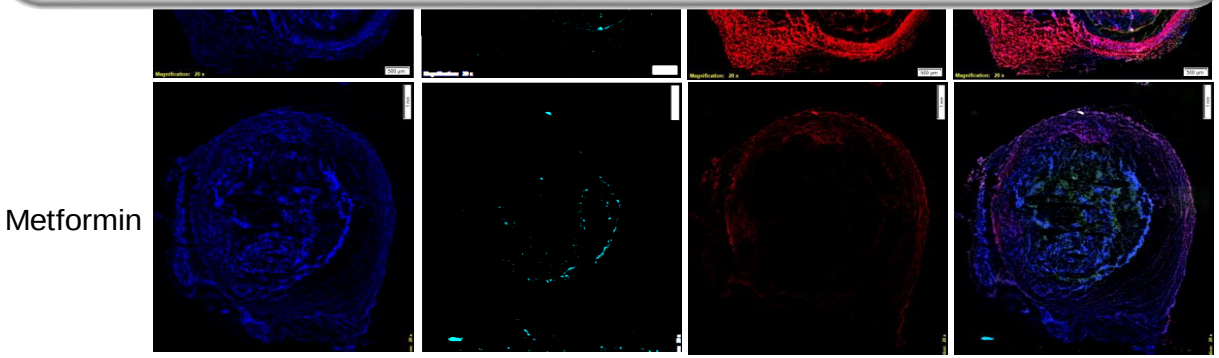
Does metformin inhibit tumor cell oxygen consumption?

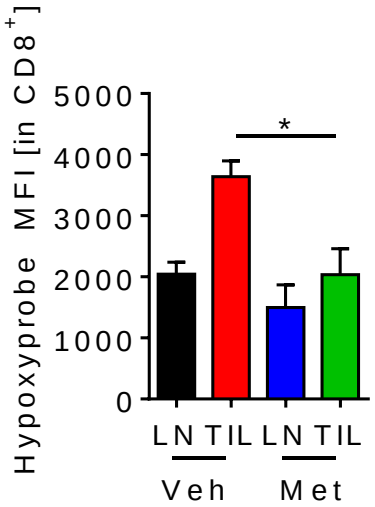
- Metformin treatment of tumor bearing mice remodels TME metabolism
- Loss of oxidative metabolism in tumor cells reduces tumor hypoxia
- Metformin treatment reduces tumor hypoxia experienced by T cells *in vivo*



B16-bearing mice treated 4 days with metformin

Metformin-mediated inhibition of tumor cell metabolism reduces tumor microenvironment hypoxia

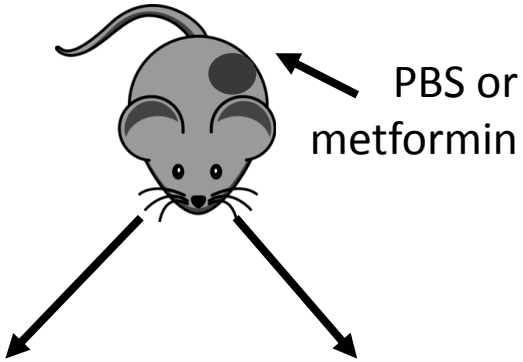




B16 melanoma

Scharping, Menk et al, *Cancer Immunol Res* 2017

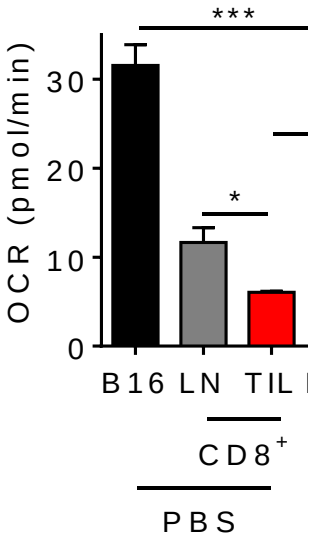
How does metformin affect T cell metabolism?

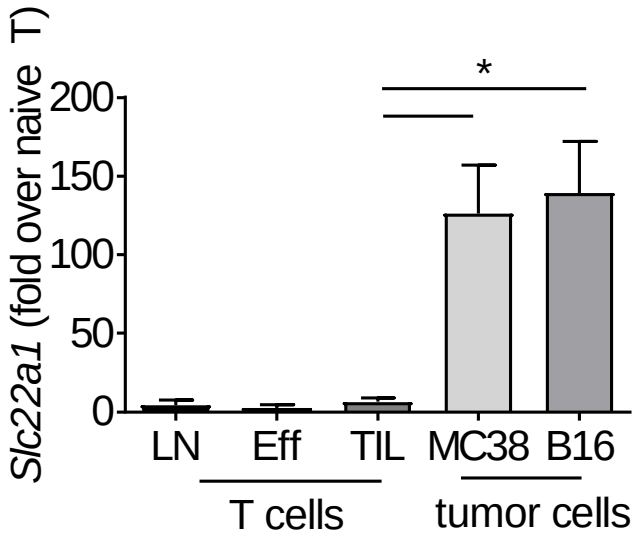


CD45⁻
Tumor cells

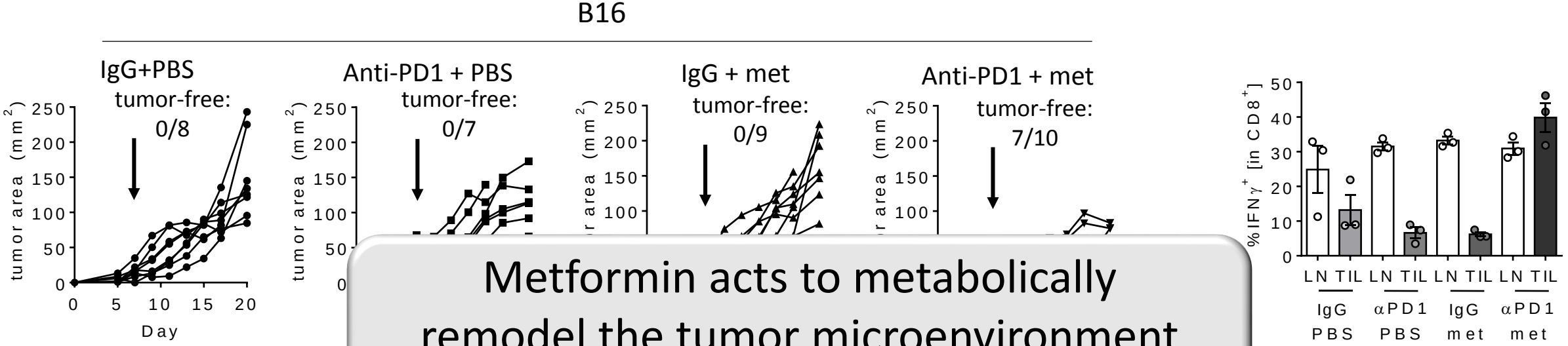
CD45⁺ CD8⁺
LN and TIL

- Tumor cell metabolism dwarfs that of TIL metabolism, consistent with many previous reports
- Metformin treatment inhibits tumor cell OCR, resulting in increased TIL OCR direct *ex vivo*
- Tumor cells express much higher levels of the metformin transporter OCT1 (encoded by *Slc22a1*), suggesting the effect of metformin on TIL T cells is *indirect*





Does metformin treatment synergize with immunostimulatory therapies?



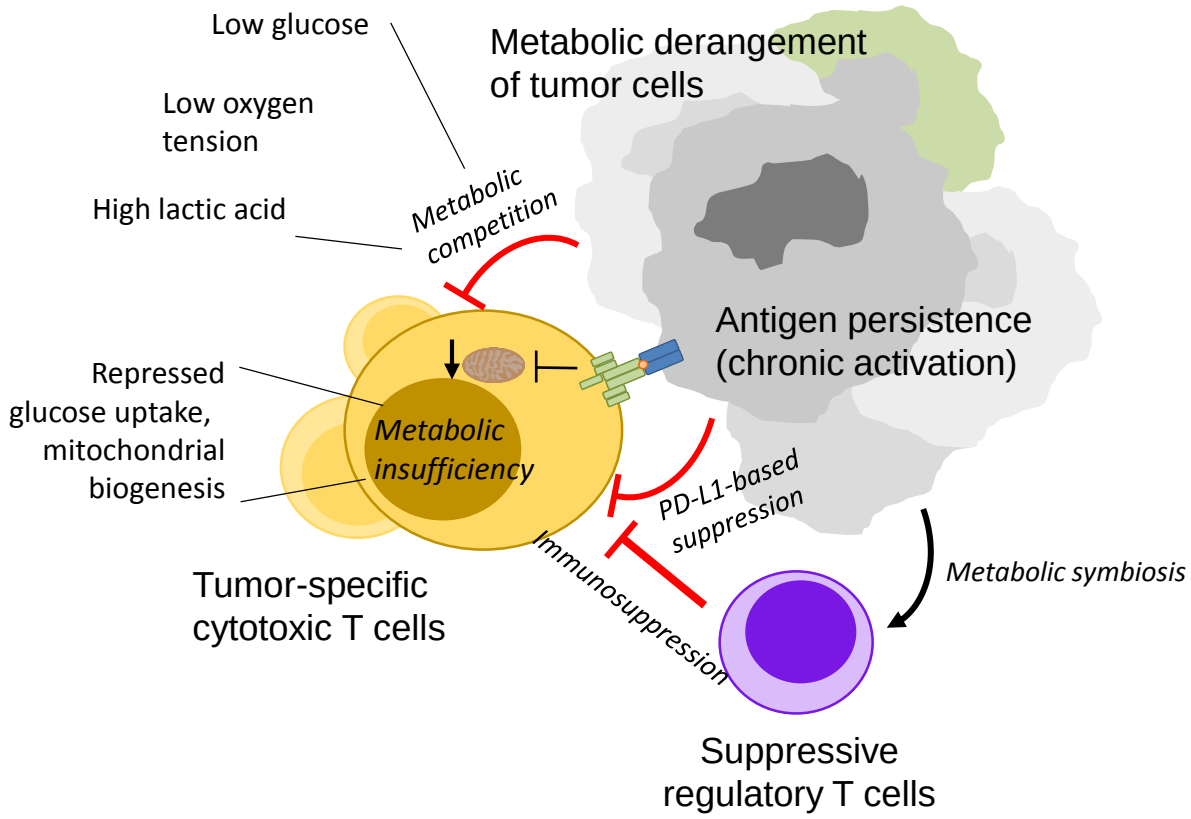
Metformin acts to metabolically remodel the tumor microenvironment to be more permissive to immunotherapy

These exciting preclinical data have led to **funded/in development clinical trials combining metformin and PD-1 blockade in several human cancers**

- Metastatic melanoma
- Locally advanced/recurrent-metastatic head and neck cancer
- Other PD-1 refractory indications

Metabolic barriers to antitumor immunity

- T cells must be reactivated immunologically and bolstered metabolically to fully support their effector function in the tumor microenvironment
- Genetic engineering, costimulatory immunotherapy, or pharmacologic rejuvenation may help counteract these pathways and create superior therapeutic T cells
- Metabolic intervention need not be continuous, although sequencing is likely important
- Targeting oxidative or glycolytic tumor cell metabolism can remodel the microenvironment to be permissive to immunotherapy (and may have differential effects on effector versus regulatory populations)



Acknowledgments

- **Delgoffe Lab**
  - **Nicole Scharping**
  - **Ashley Menk**
  - ***Lucy Zeng***
  - **Dayana Rivadeneira**
  - **McLane Watson**
  - Paolo Vignali
  - *Becca Moreci*
- Robert Ferris
- Yana Najjar
- Dario A. A. Vignali
- Mark Shlomchik
- Abigail Overacre-Delgoffe
- Jonathan Powell

Interested in a postdoc in the Delgoffe lab? Contact me!

Delgoffe-lab.com - @DelgoffeLab

Immunometabolism in **full effect** here at SITC

P156 - Nicole (metabolic underpinnings of T cell exhaustion)
P152 - Ashley (41BB-mediated reprogramming)
P484 - Dayana (oncolytic virus reprogramming)

Coming up soon in this session… Mac (T_{reg} cell metabolism)

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE

- Center for Biologic Imaging
- UPMC Flow Cytometry/Animal Facilities
- Tumor Microenvironment Center
- Department of Immunology
- **Patients and their families**

- Funding sources:
  - Sidney Kimmel Foundation for Cancer Research
  - Stand Up 2 Cancer Innovative Research Grant
  - Melanoma and Skin Cancer SPORE
  - Head and Neck Cancer SPORE
  - Alliance for Cancer Gene Therapy
  - NIH Director's New Innovator Award (DP2AI136598)