SITC 2016

NATIONAL HARBOR, MD
NOVEMBER 9-13, 2016

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Society for Immunotherapy of Cancer

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Mitochondrial biogenesis is repressed in tumor-infiltrating CD8+ T cells resulting in metabolic insufficiency and T cell dysfunction

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SITC Presidential Session

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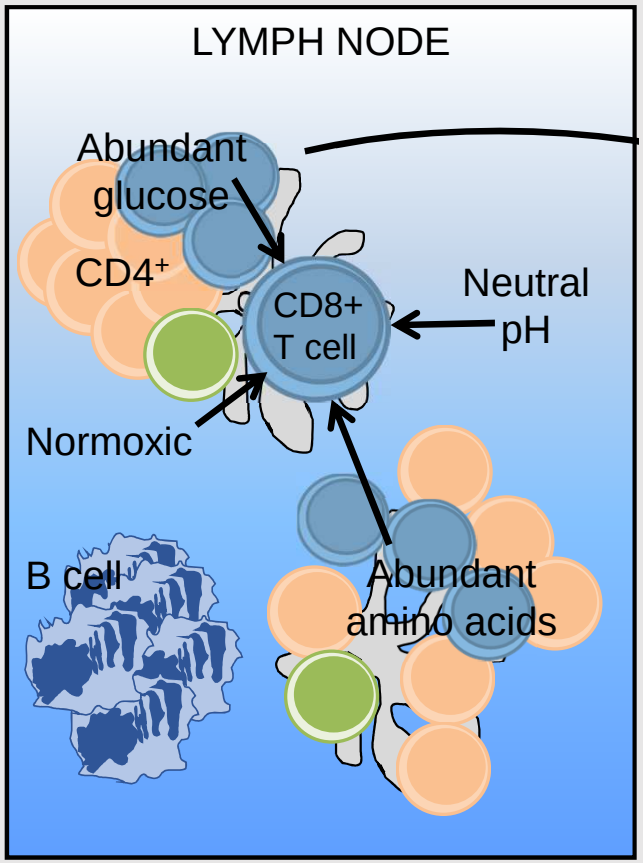
Presenter Disclosure Information

Nicole Scharping

The following relationships exist related to this presentation:

No Relationships to Disclose

The TME is immuno- and metabolically suppressive

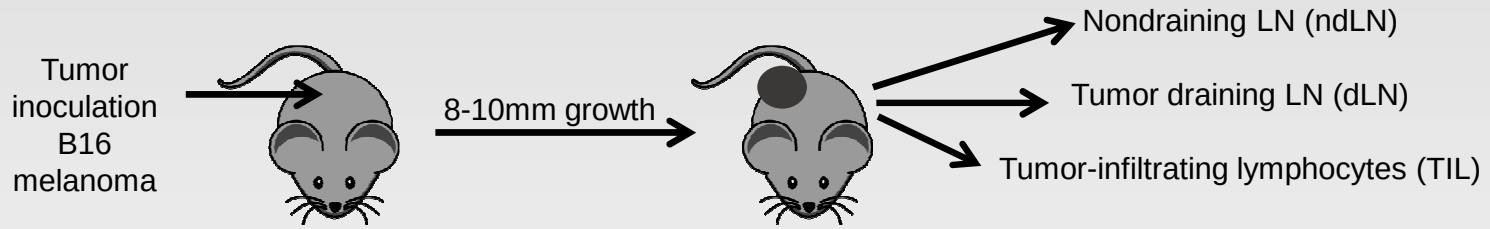


Greg Delgoffe

Hypothesis:

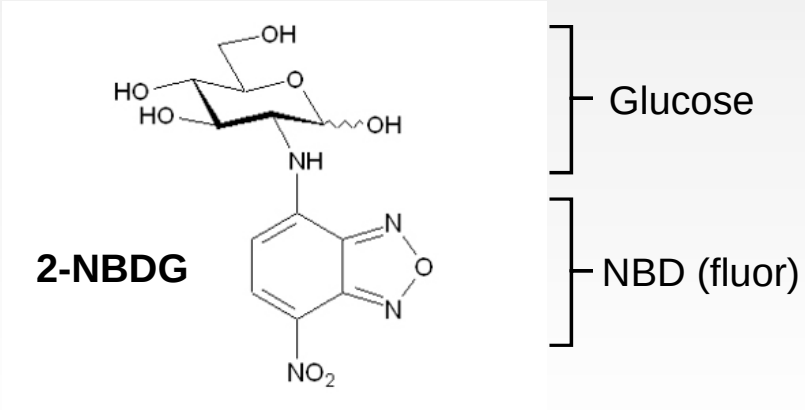
CD8+ TIL dysfunction & resistance to immunotherapy is due in part to metabolic insufficiency

How do we assay the metabolic capacity of T cells?



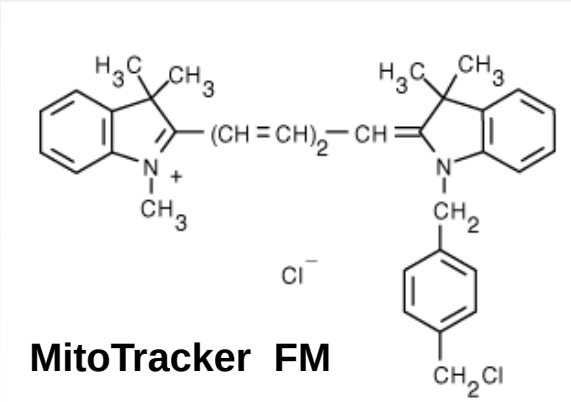
Flow cytometric analysis of TIL metabolic capacity

Pulse cells with 2NBDG



2-NBDG

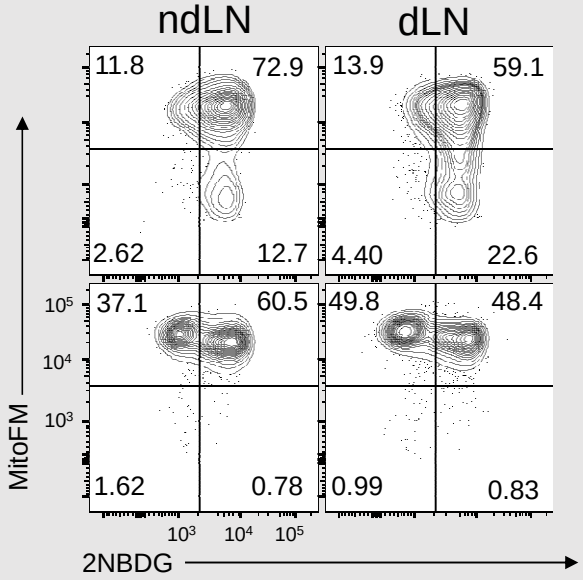
Load cells with MitoTracker FM

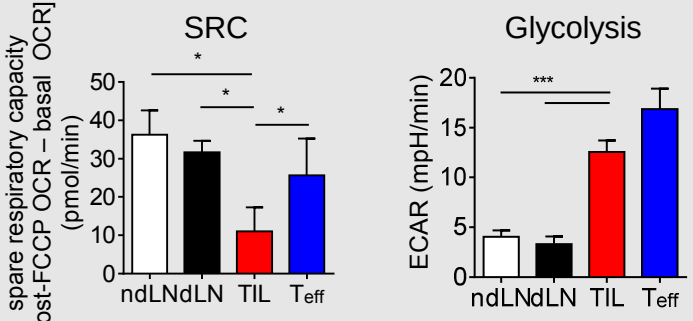


MitoTracker FM

Greg Delgoffe

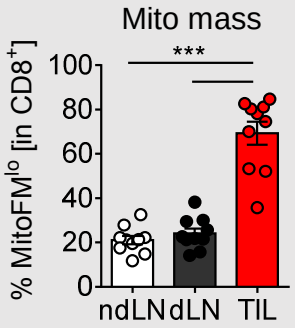
What is the metabolic capacity of T cells?

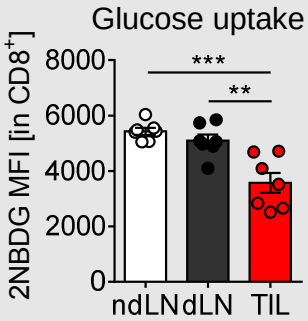


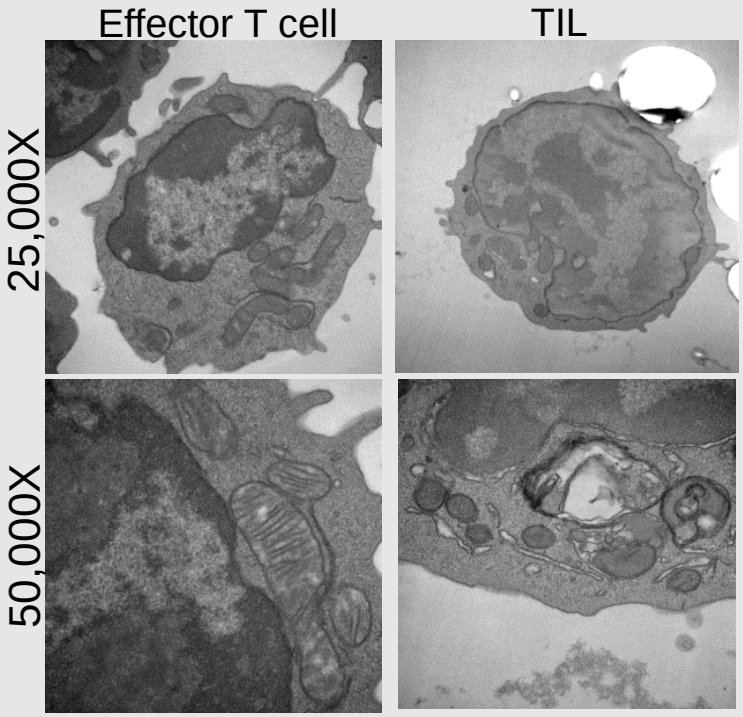


CD8+

CD4+





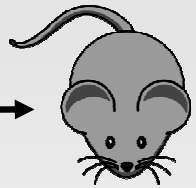


CD8+ TIL exhibit loss of mitochondrial mass and function

Do T cells lose mitochondrial mass as a result of robust activation?

Robust activation → memory

OT-I x Thy1.1 T cells

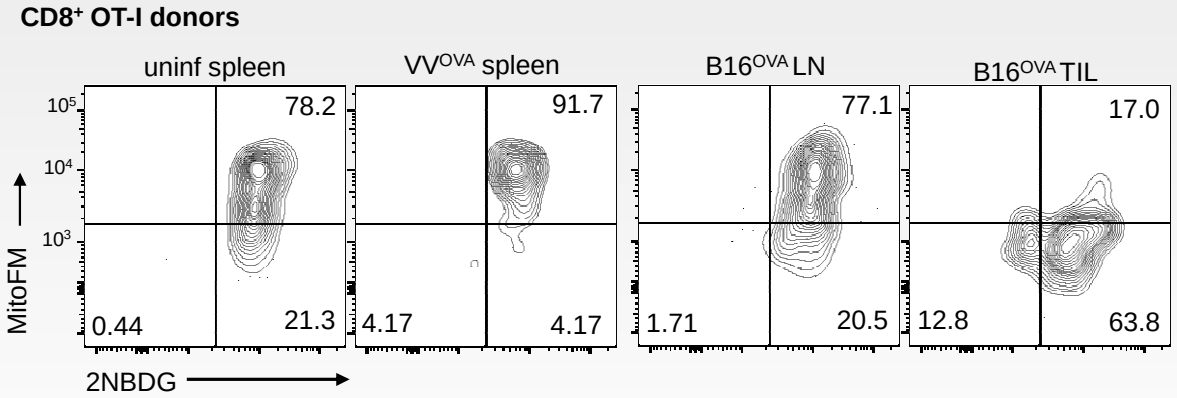


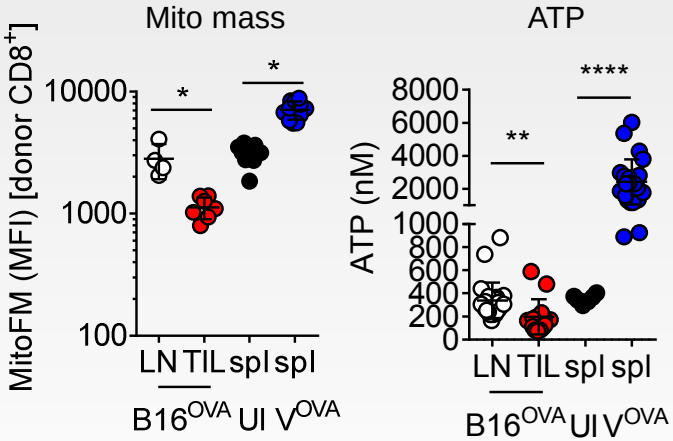
Vaccinia^{OVA} infected
Thy1.2 B6 mouse

Robust activation → dysfunction

OT-I x Thy1.1 T cells

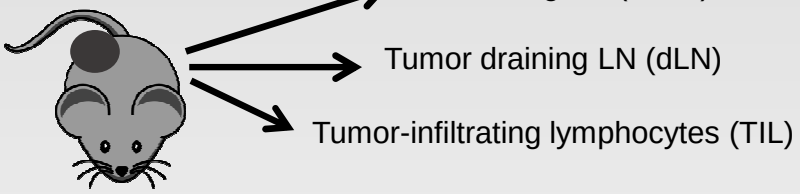
B16^{OVA}-bearing
Thy1.2 B6 mouse

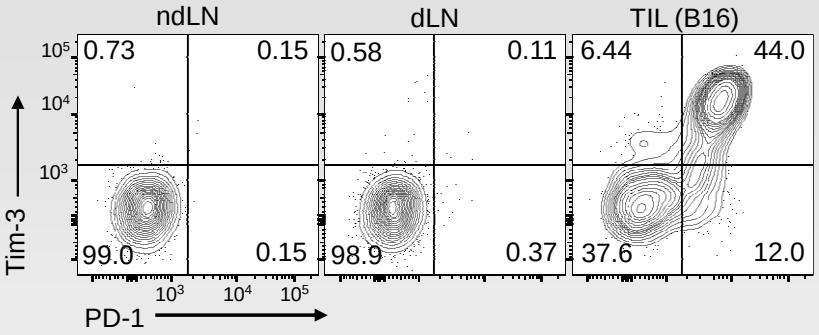




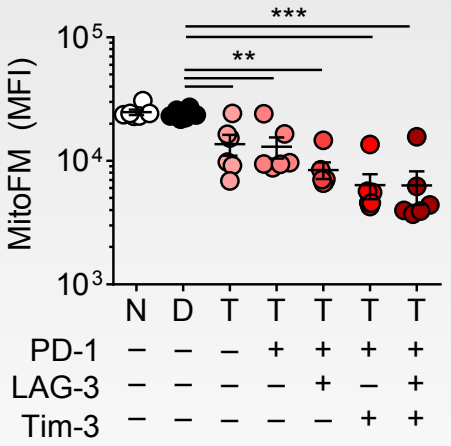
Loss of mitochondrial mass and function is not a phenotype of robust activation *in vivo*

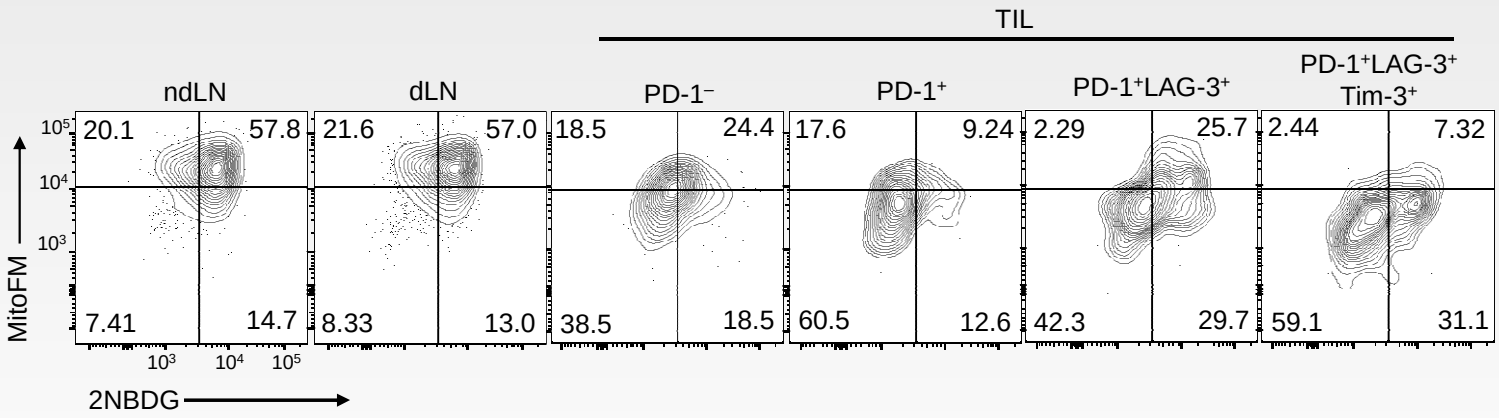
Do ‘exhausted’ TIL exhibit mitochondrial dysfunction?





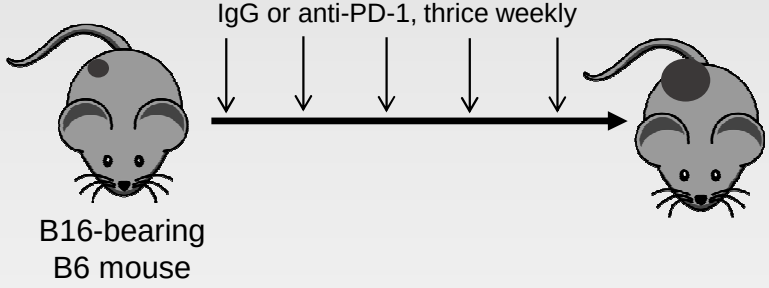
Mito mass by coinhibitory expression

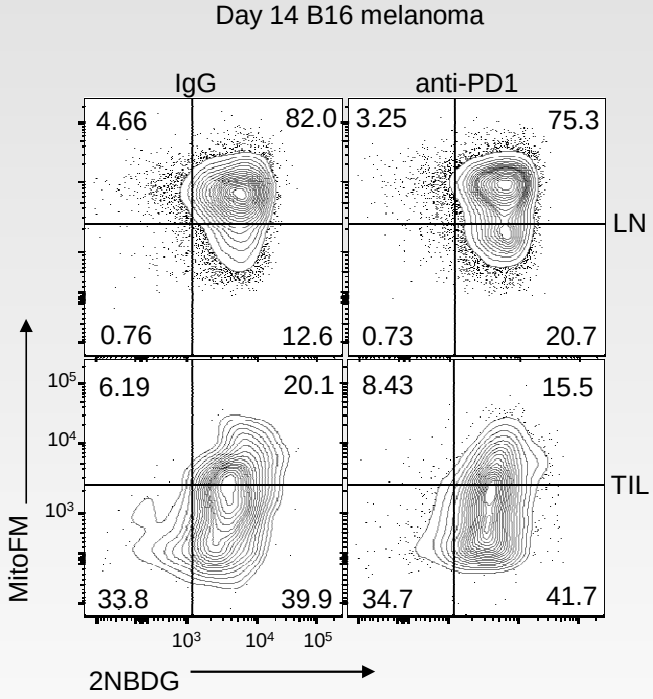


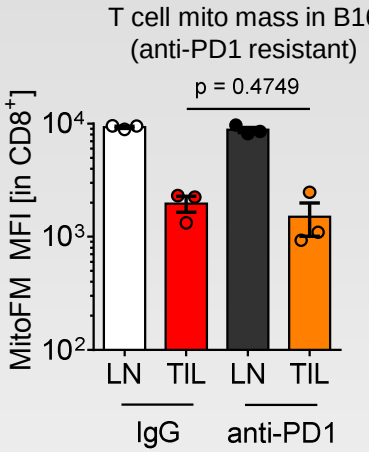


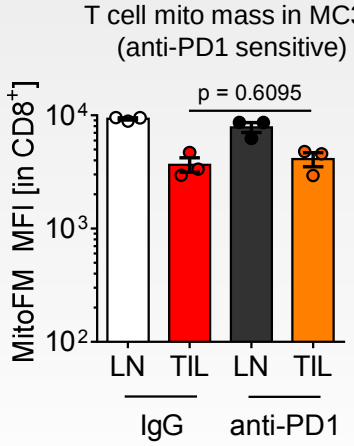
Mitochondrial dysfunction in TIL correlates with coinhibitory molecule expression

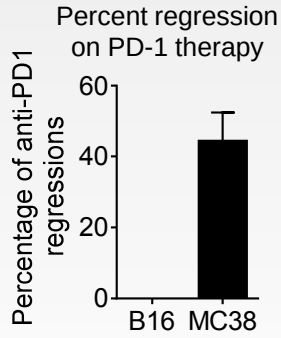
Does PD-1 checkpoint blockade rescue metabolic dysfunction in TIL?







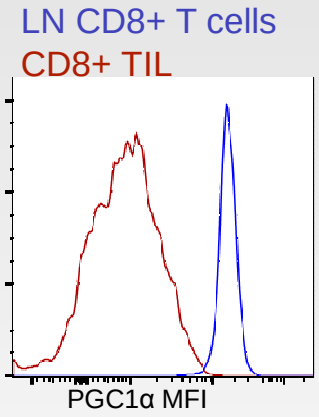


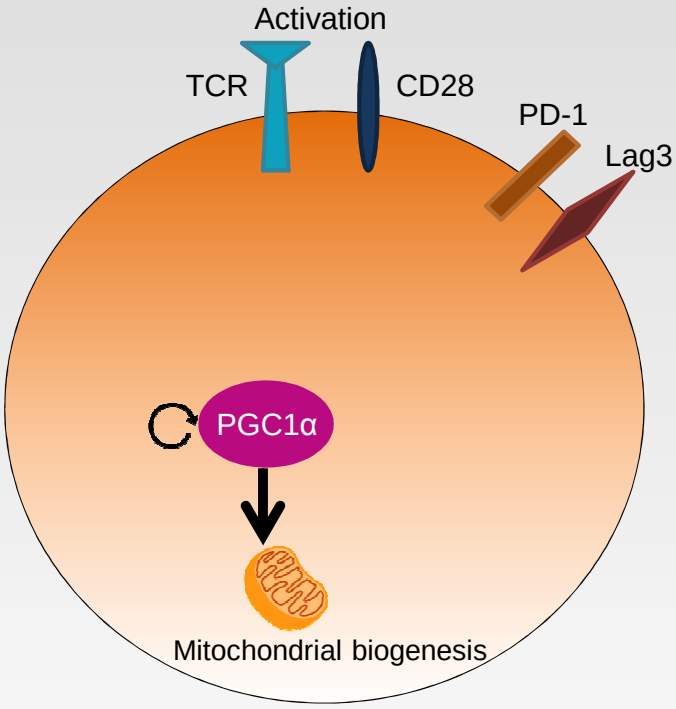


PD-1 blockade does not rescue metabolic dysfunction in TIL

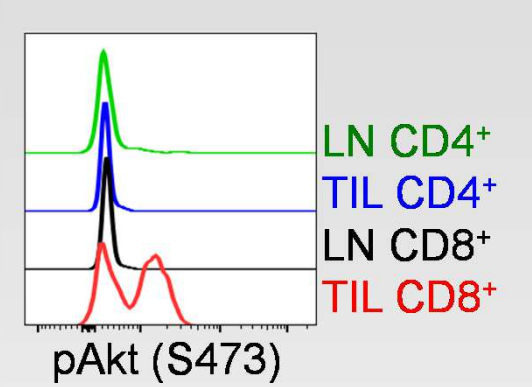
What is the mechanism for TIL mitochondrial dysfunction?

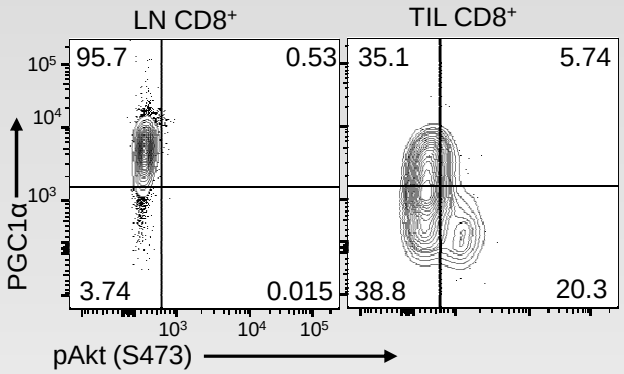
- First checked if TIL have deregulated mitophagy
- Investigated mitochondrial biogenesis
- Focus on PGC1α – transcriptional coactivator, dynamically regulates mitochondrial biogenesis

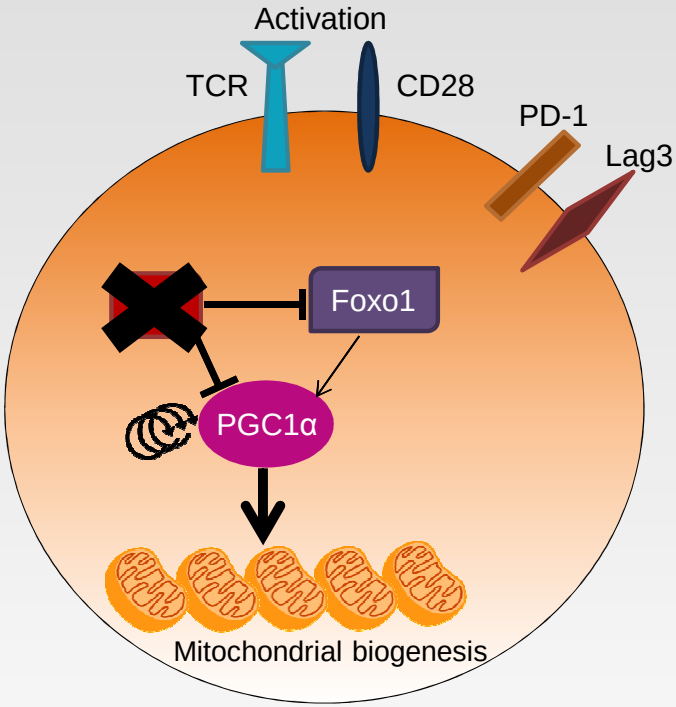


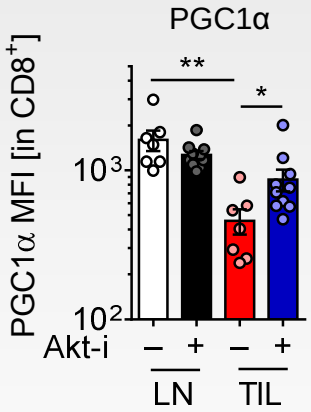


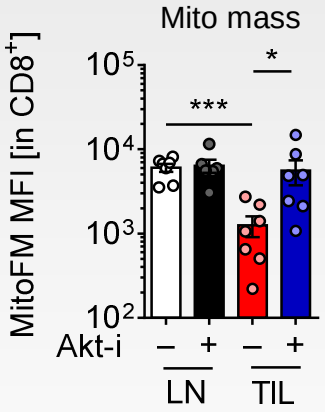
What is suppressing PGC1α?





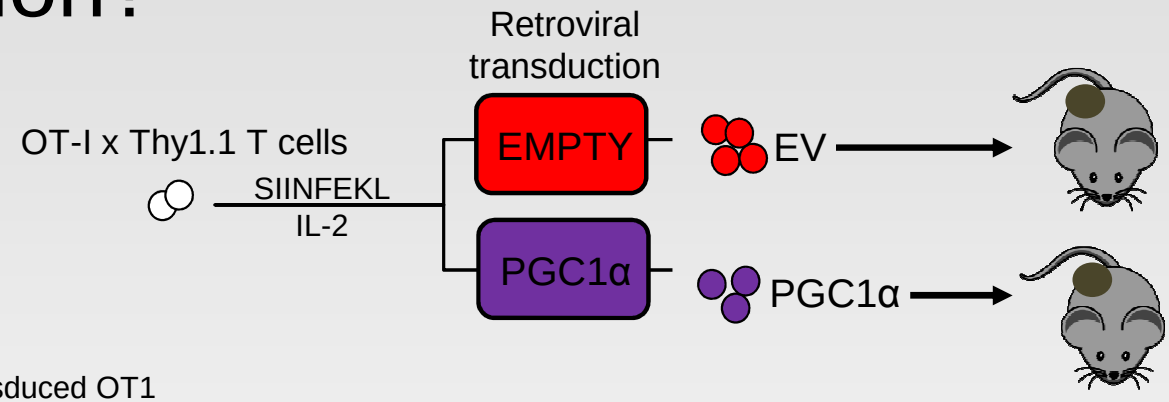


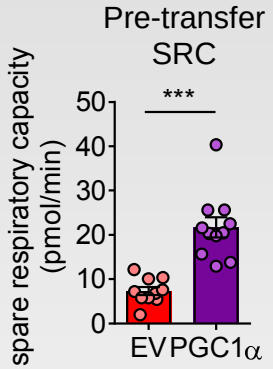


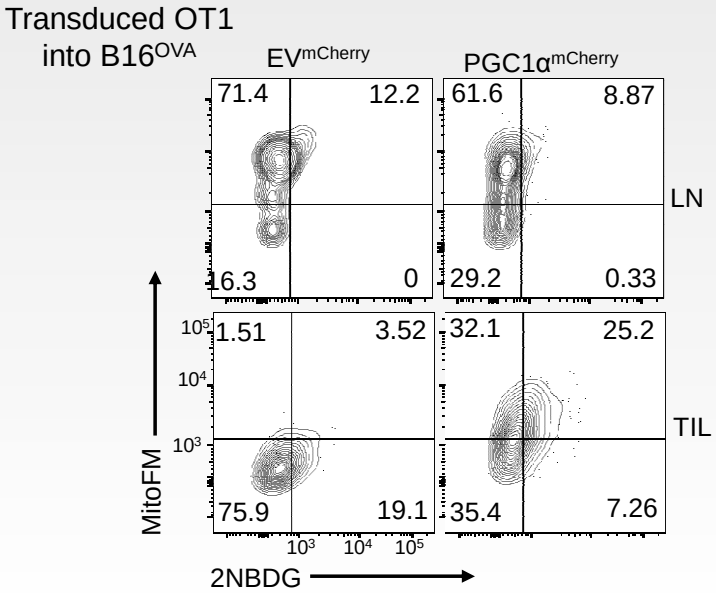


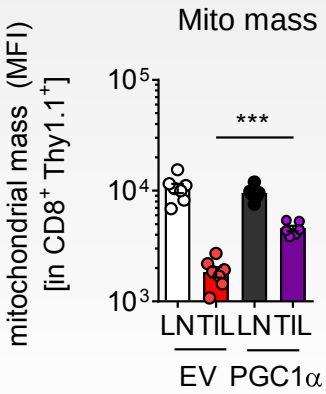
Mitochondrial biogenesis is repressed by Akt-mediated repression of PGC1α

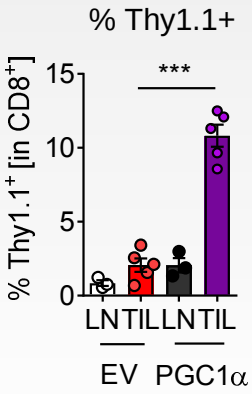
Can enforcing mitochondrial biogenesis improve TIL function?



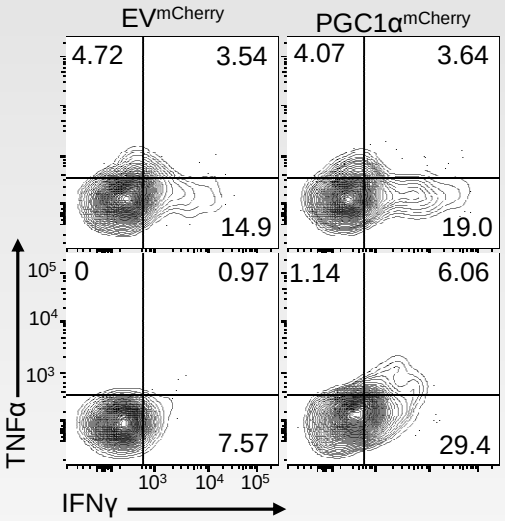


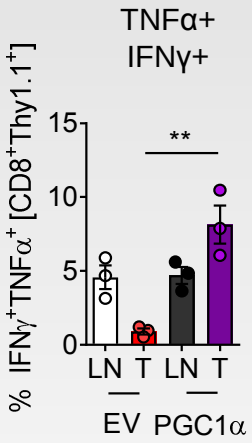


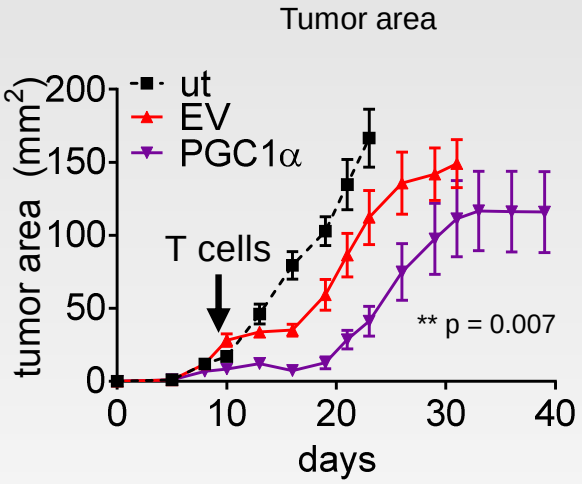


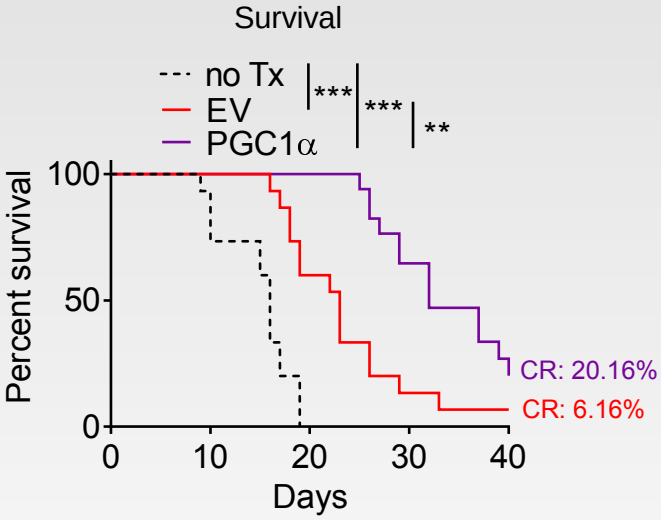


Can enforcing mitochondrial biogenesis improve TIL function?





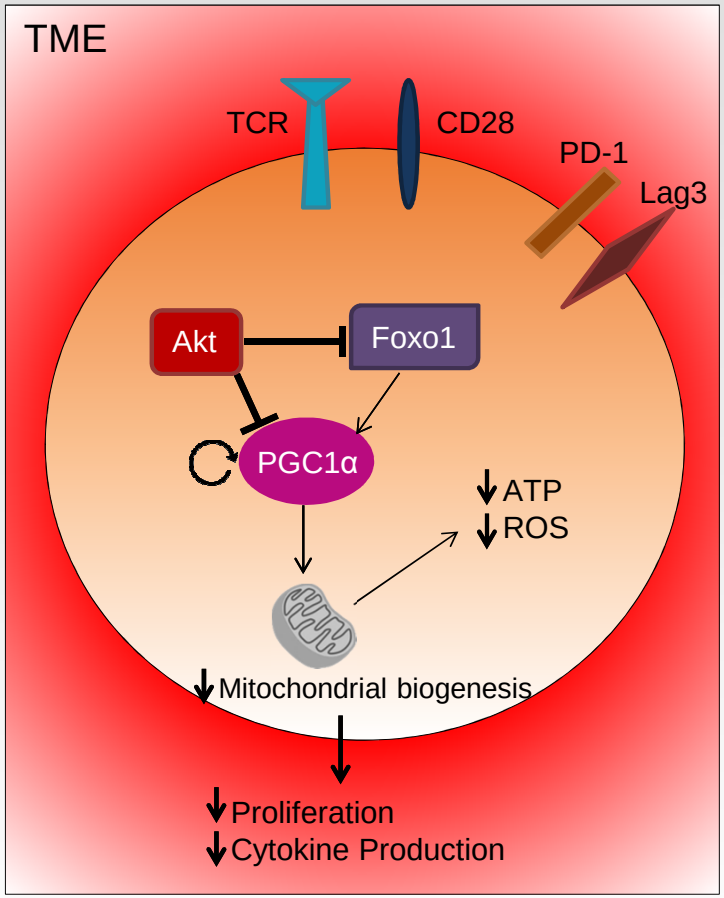




Enforcing mitochondrial biogenesis improves CD8+ TIL function

Summary & Conclusions

- CD8+ TIL exhibit metabolic insufficiency due to repressed mitochondrial biogenesis
- This results in decreased effector function, which can be rescued with enforced PGC1α expression
- PD-1 checkpoint blockade may not be enough to overcome the metabolic disadvantage in the TME
  - Targeting both immune suppression and metabolic insufficiency may be needed for improved TIL effector function
  - The metabolic status of CD8+ TIL could be used as a biomarker for immunotherapeutic efficacy
  - Genetic or pharmacologic metabolic reprograming of CD8+ TIL could improve T cell monotherapy or in combination with PD-1 therapy



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  - Ryan Whetstone
  - Xue (Lucy) Zeng
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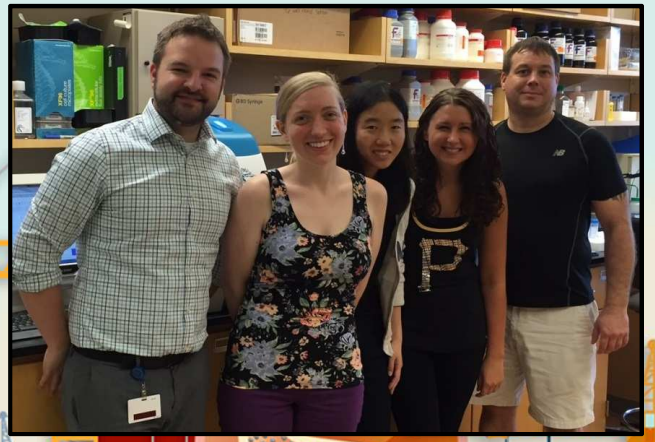

- For more T cell metabolism and cancer from the Delgoffe lab:
- **Nicole Scharping - Poster 280:** Mitochondrial biogenesis is repressed in tumor-infiltrating CD8+ T cells resulting in metabolic insufficiency and T cell dysfunction
- **Ashley Menk - Poster 278**: Metformin treatment synergizes with PD-1 blockade therapy by reducing tumor hypoxia
- **Ryan Whetstone - Poster 281**: Treg cells utilize lactic acid to fuel immune suppression in the tumor microenvironment
- **Xue (Lucy) Zeng - Poster 54**: Pharmacologic rejuvenation of exhausted T cells to improve adoptive TIL therapy