Tumor Immune Microenvironment: A Holistic Approach Workshop

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#SITCworkshop

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Society for Immunotherapy of Cancer

Lactic acid uptake through MCT11 enforces dysfunction in terminally exhausted T cells

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UPMC | HILLMAN CANCER CENTER

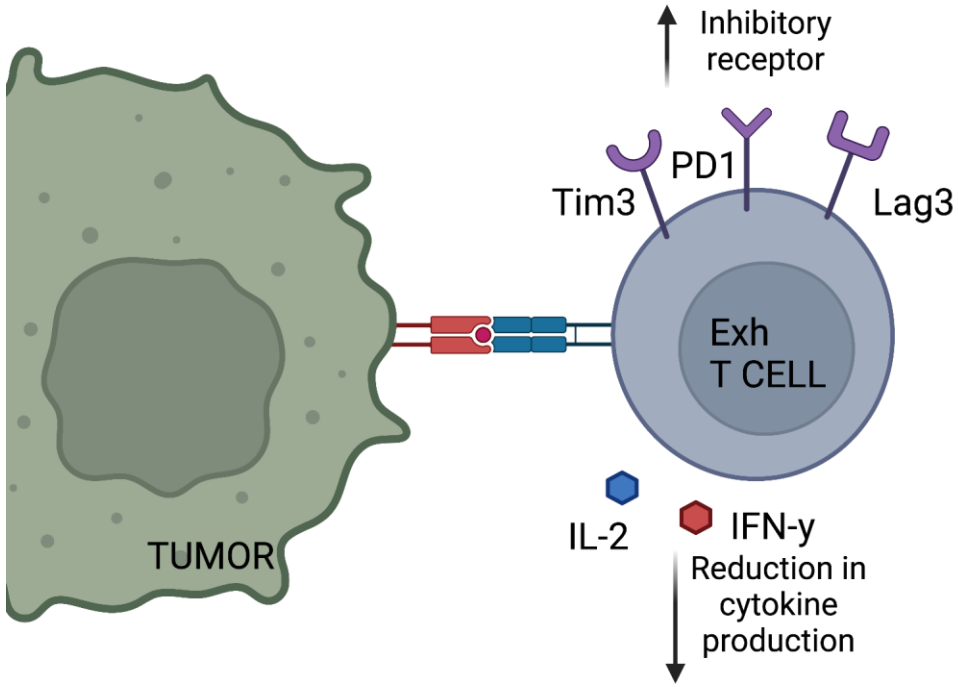
PMI

Disclosures

- Patent for the use of anti-MCT11 licensed by Remplir Bio

Exhausted T cells in the tumor microenvironment (TME) exist in a state of metabolic dysfunction

- CD8+ T cells infiltrating the TME experiencing chronic TCR stimulus become exhausted
  - High expression of PD1, TIM3, CTLA4 and LAG3
  - Reduction in polyfunctionality



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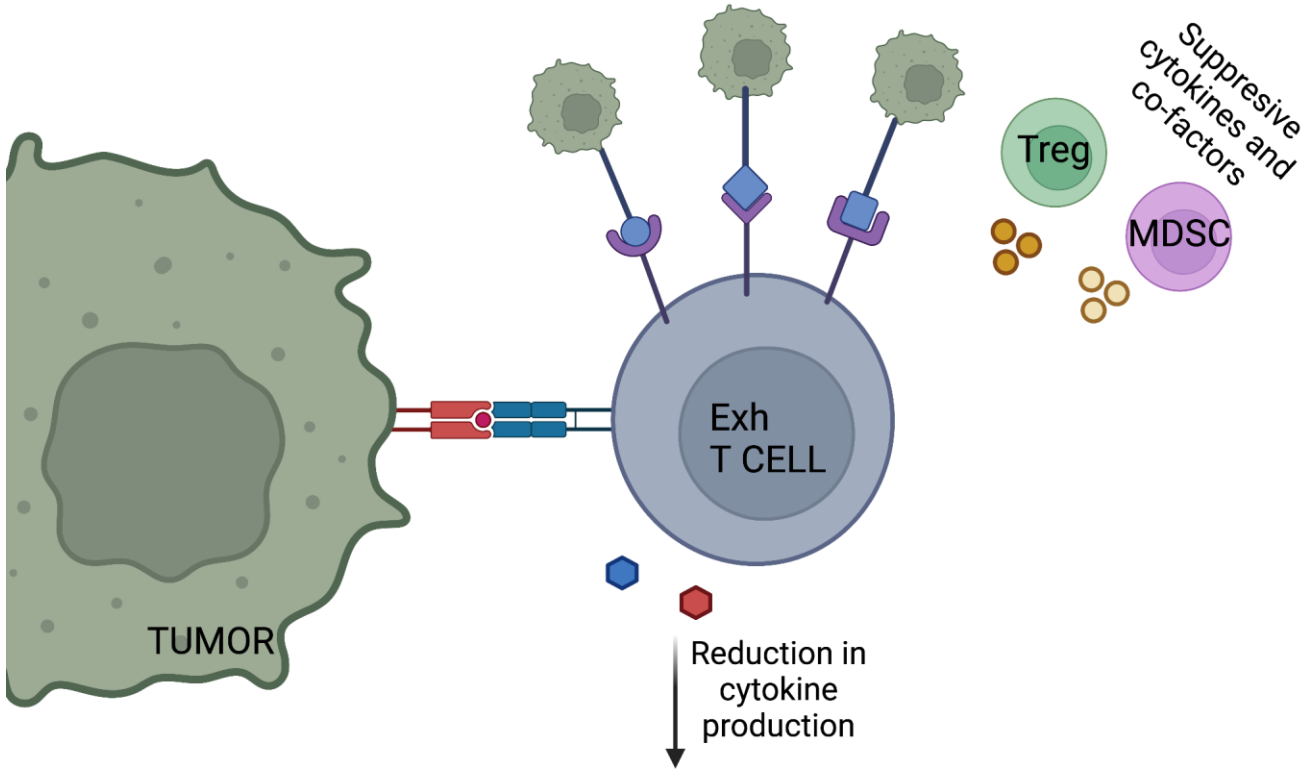

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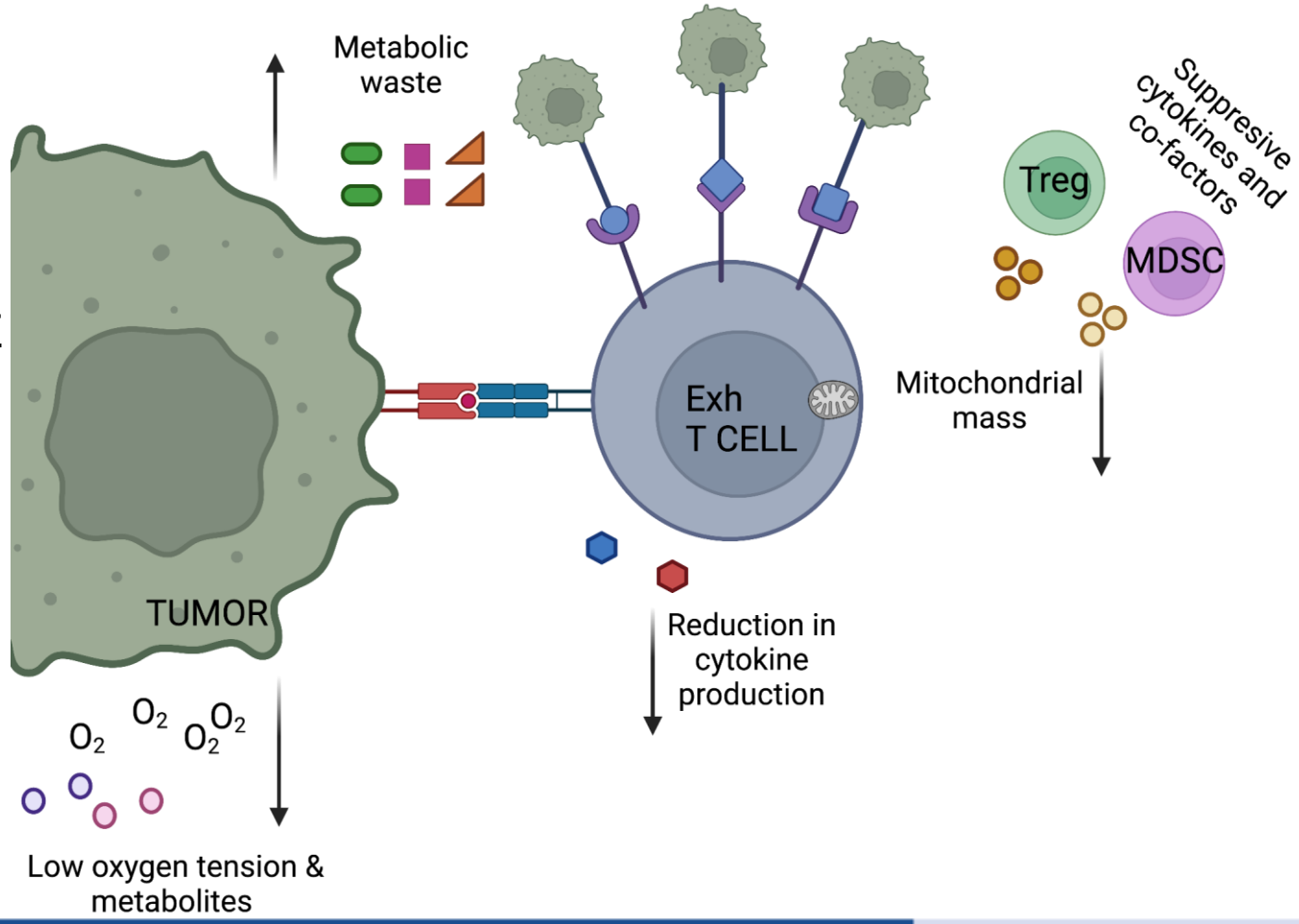
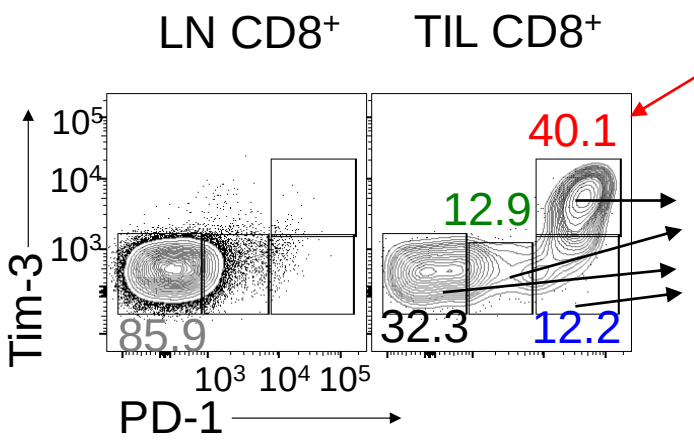
  - High expression of PD1, TIM3, CTLA4 and LAG3
  - Reduction in polyfunctionality
- Exhausted CD8+ T cells' functions in the TME are repressed by suppressive cells and by **nutrient availability and buildup of metabolic wastes**
  - Low glucose & amino acids
  - Hypoxia
  - Increased extracellular lactate & acidosis
  - Reduced mitochondrial biogenesis
- Despite the lack of nutrients/metabolites, exhausted CD8+ T cells persist in the TME



What sustains exhausted T cell metabolism in the TME?

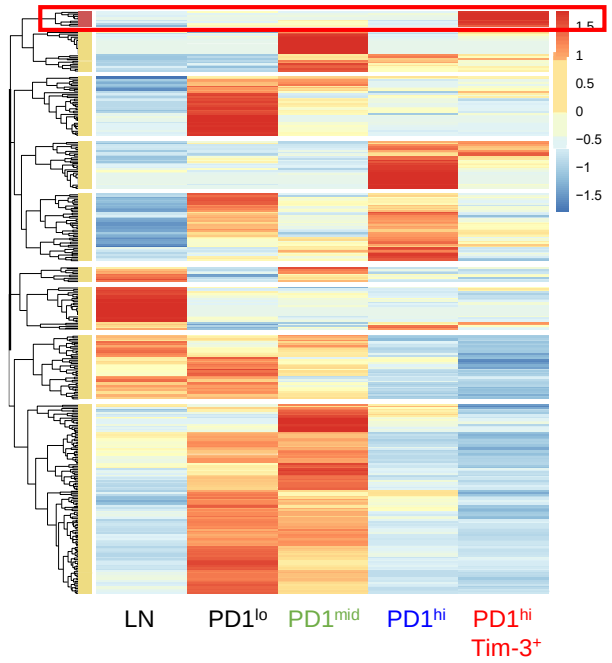
- Nutrient transporters expressed on the cell surface control access to metabolites in different environments
- Members of the solute carrier (SLC) superfamily are involved in transport of a wide variety of metabolites
- Some SLCs are **preferentially expressed** in terminally exhausted T cells



Terminally exhausted
Most dysfunctional

Low-input RNAseq

Solute carrier gene superfamily

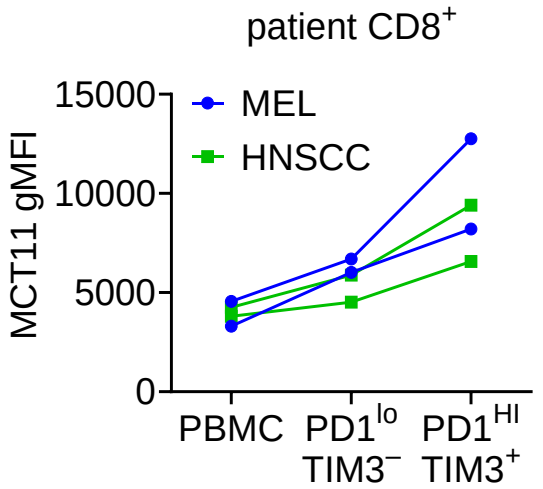


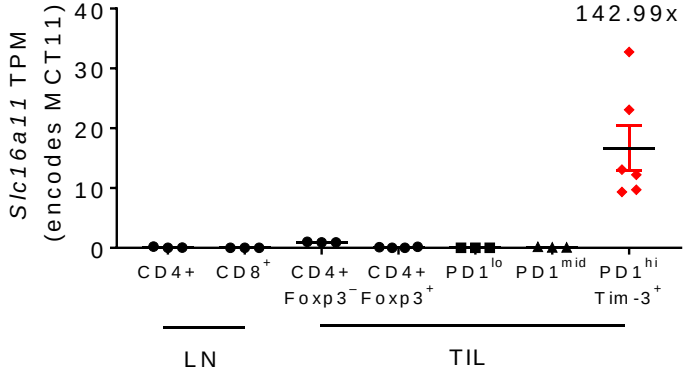
What metabolites are transported by these molecules?

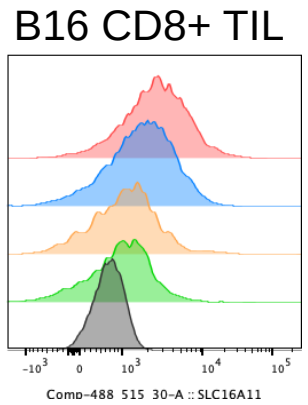
Do these molecules promote or hinder antitumor Immunity?

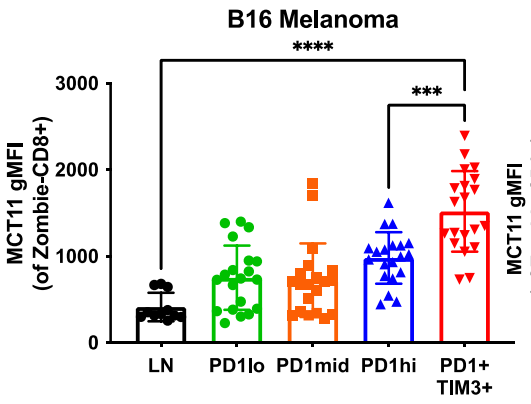
Slc16a11 (MCT11) is highly and uniquely expressed in exhausted CD8+ TIL

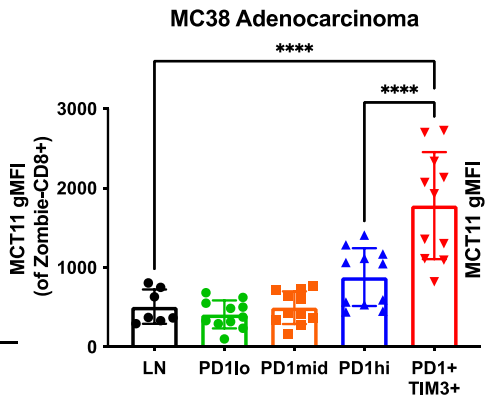
- *Slc16a11* is the third highest – non granzyme – gene differentially expressed in terminally exhausted T cells
- MCT11 is highly expressed on the surface of terminally exhausted T cells across tumor models
- MCT11 is also expressed on human exhausted CD8+ TIL

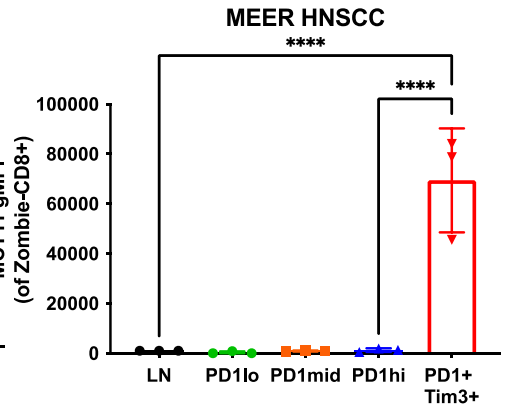












Understanding the function of MCT11

- A member of the *Slc16* family, which are **monocarboxylates transporters (MCTs):** short chain carbons like lactate, pyruvate and ketone bodies
- MCT11 was first described in 2014 – only 4 studies since
- MCT11 is a type 1 proton-coupled monocarboxylate transporter & is chaperoned to cell surface by CD147 (basigin)
- Lactic acid is the most abundant monocarboxylate in the TME

Type 2 Diabetes Variants Disrupt Function of SLC16A11 through Two Distinct Mechanisms

Victor Rusu,[1,2,18,19] Eitan Hoch,[2,3,18] Josep M. Mercader,[2,4,5] Danielle E. Tenen,[6,7] Melissa Gymrek,[2,8,20] Christina R. Hartigan,[6] Michael DeRan,[6] Marcin von Grotthuss,[2] Pierre Fontanillas,[2,21] Alexandra Spooner,[2] Gaelen Guzman,[6] Amy A. Deik,[6] Kerry A. Pierce,[6] Courtney Dennis,[6] Clary B. Clish,[3,6] Steven A. Carr,[6] Bridget K. Wagner,[6] Monica Schenone,[6] Maggie C.Y. Ng,[9] Brian H. Chen,[10] MEDIA Consortium, SIGMA T2D Consortium, Federico Centeno-Cruz,[11] Carlos Zerrweck,[12] Lorena Orozco,[11] David M. Altshuler,[2,13,14,15,16,22] Stuart L. Schreiber,[6] Jose C. Florez,[2,3,4,15,*] Suzanne B.R. Jacobs,[2,3,4] and Eric S. Lander[6,16,17,23,*]

	TMD 8
MCT11	VVAVAAMG**D**AGA**R**LVCGWLADQGW
MCT1	LLSILAFV**D**MVA**R**PSMGLVANTKP

MCT11 shares charged residues on inner pore with MCT1
MCT1 – **Known lactic acid transporter**

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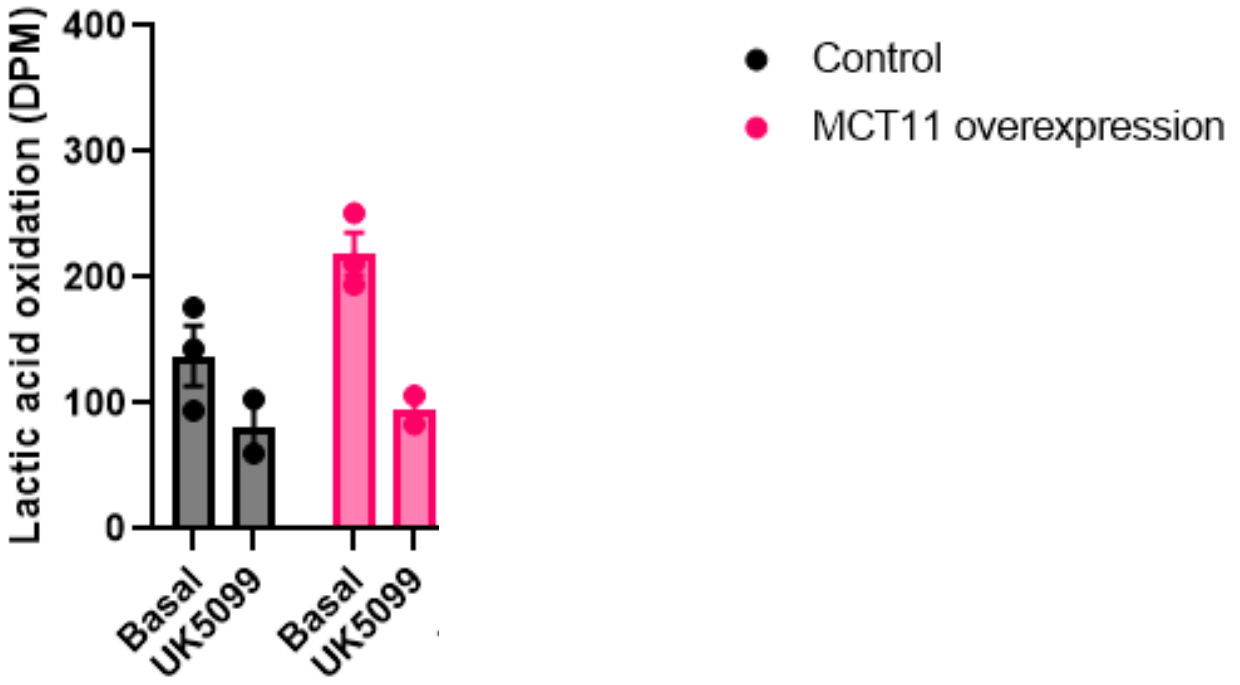
- **Do exhausted T cells from the TME take up lactic acid?**



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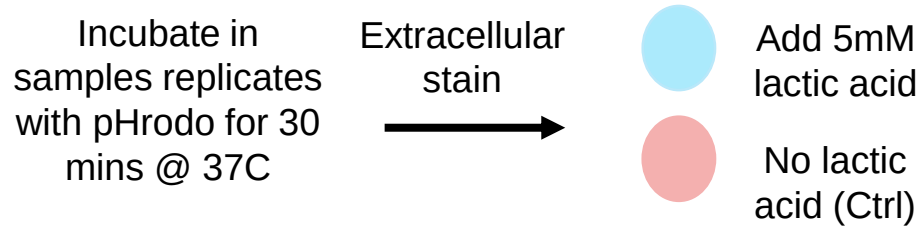
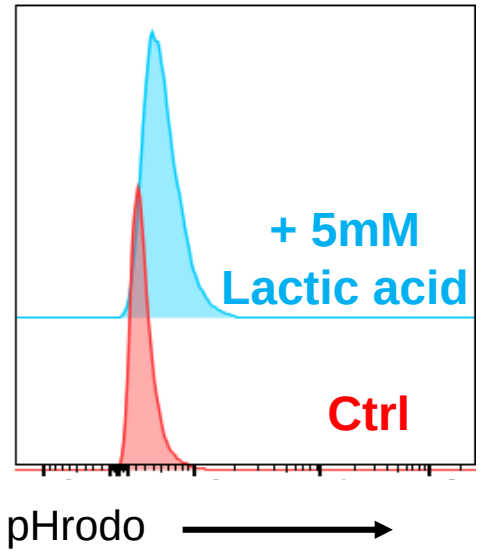
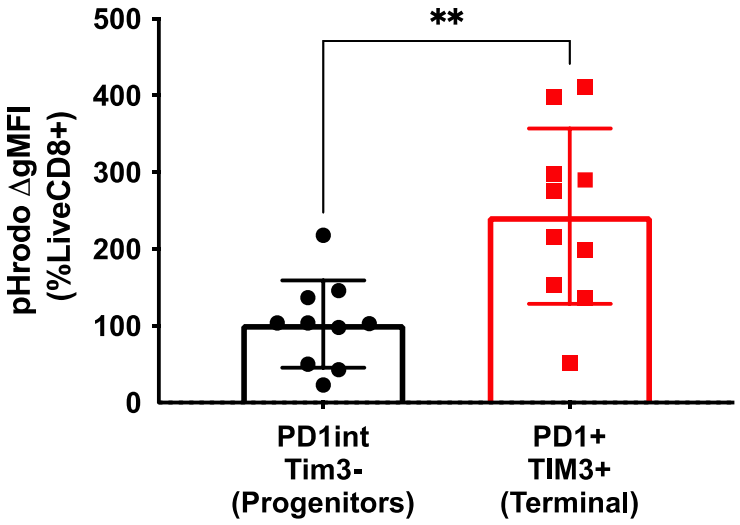


Lactic acid pHrodo gMFI – Ctrl pHrodo gMFI = ΔpHrodo gMFI





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- to cell surface by CD147 (basigin)
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- **Do exhausted T cells from the TME take up lactic acid?**

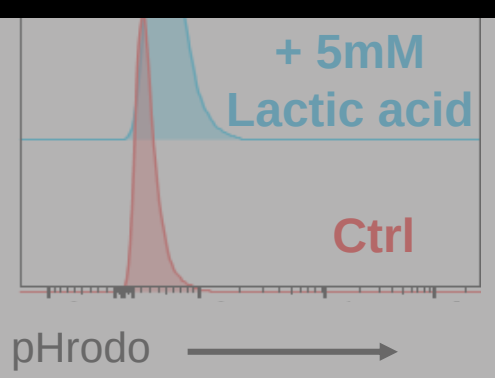
Incubate in samples replicates with pHrodo for 30 mins @ 37C → Extracellular stain

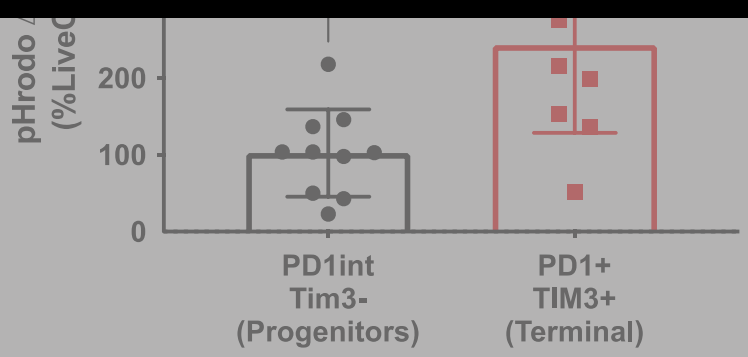
Add 5mM lactic acid

No lactic acid (Ctrl)

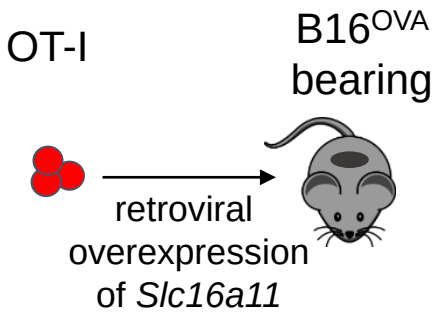
Lactic acid pHrodo gMFI – Ctrl pHrodo gMFI = ∆pHrodo gMFI

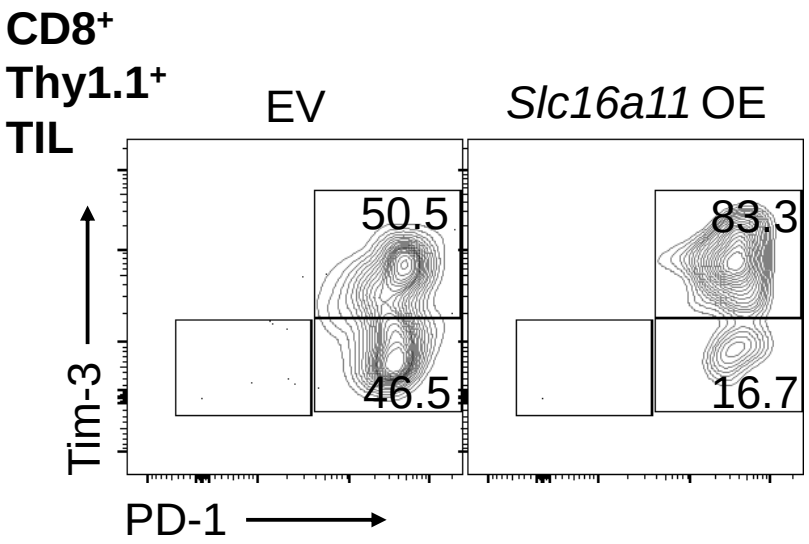
Exhausted T cells can take up lactic acid

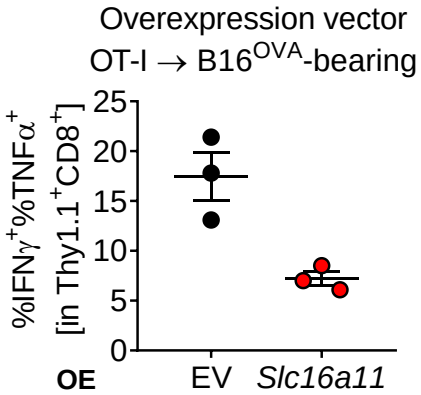




Does MCT11 promote or alleviate exhaustion?



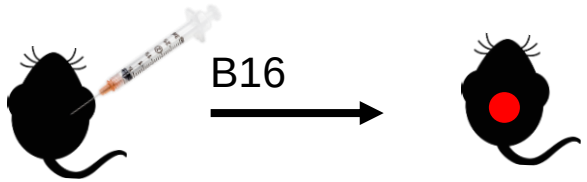




MCT11 overexpression increases PD1⁺Tim3⁺ population and decreases cytokine production

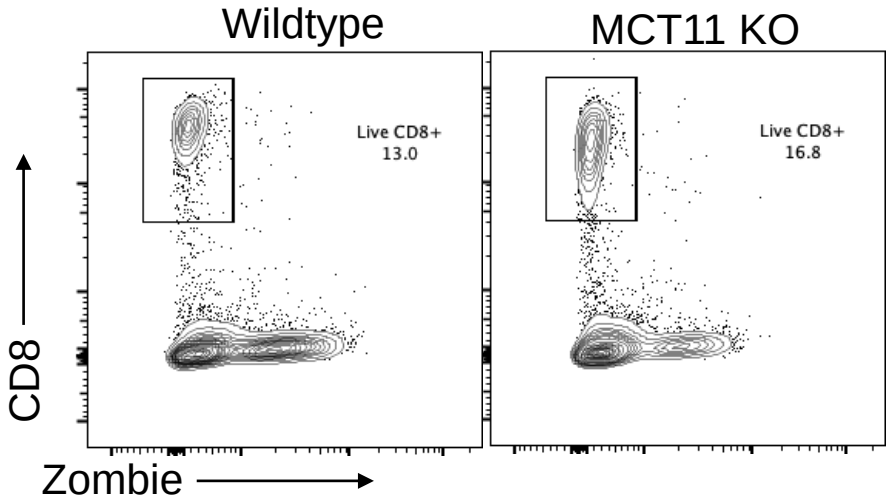
Does MCT11 promote exhaustion in endogenous TIL?

Wildtype or MCT11$^{f/f}$xCD4^{cre} mice

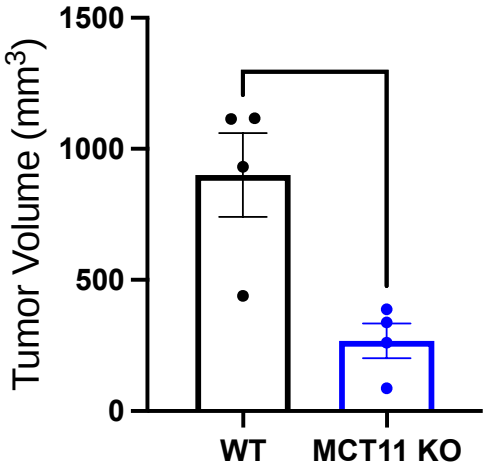


B16

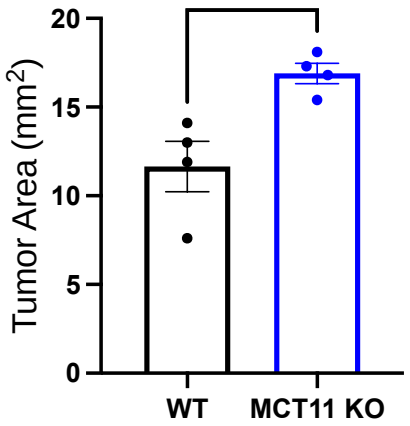
D0 **D14**



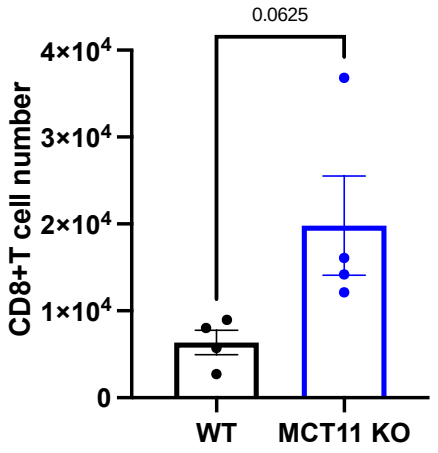
Tumor Volume



Percent Live CD8+

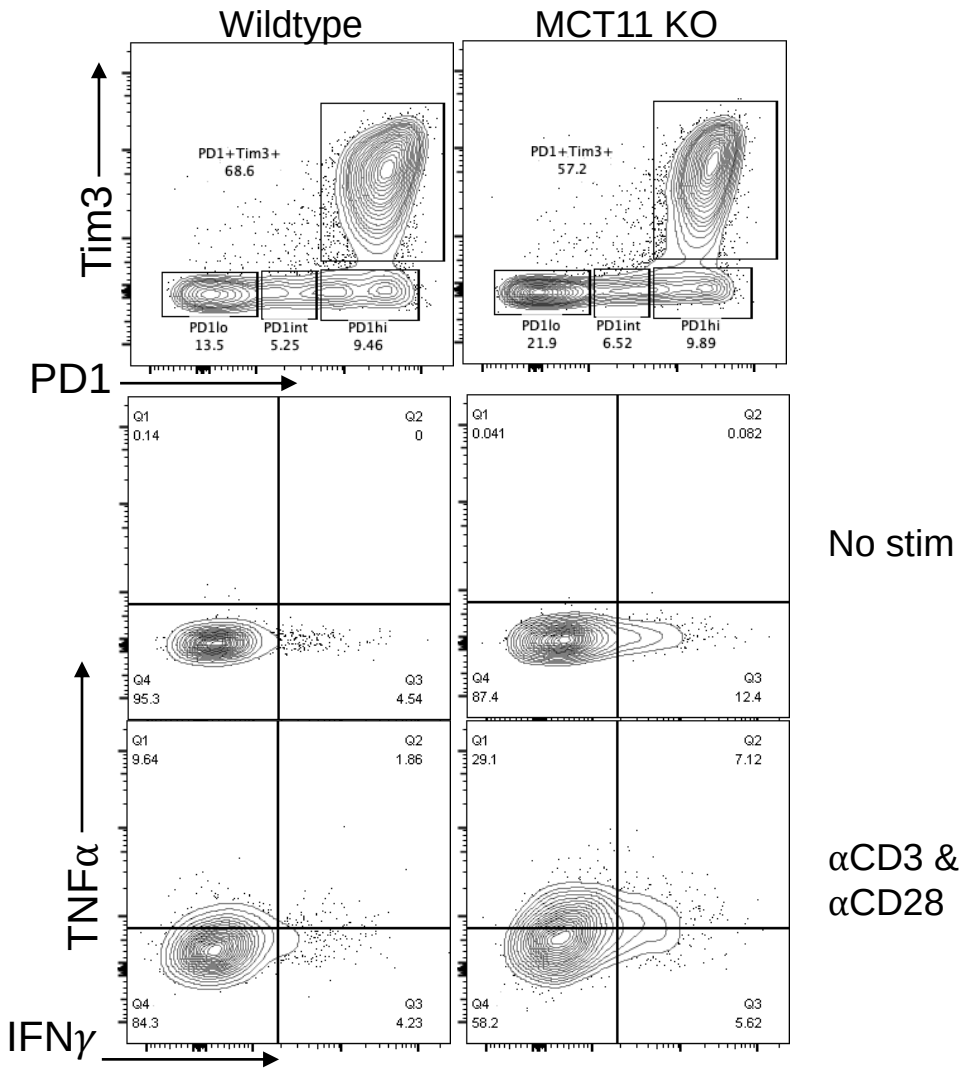


Counts CD8 /vol



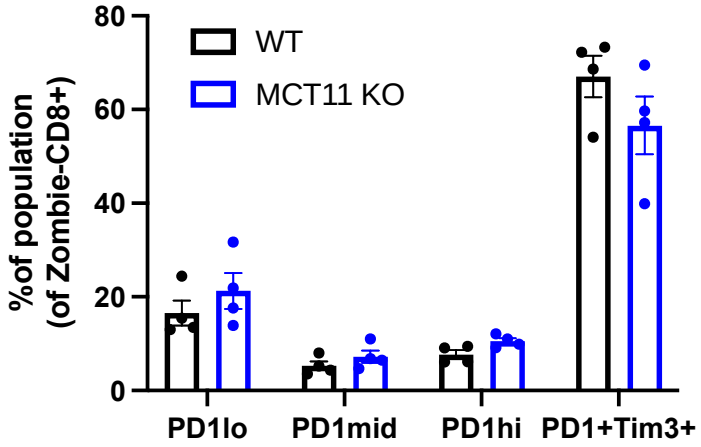
- Conditional T cell knockout of MCT11 reduces tumor burden
- Conditional T cell knockout of MCT11 increases CD8+ TIL

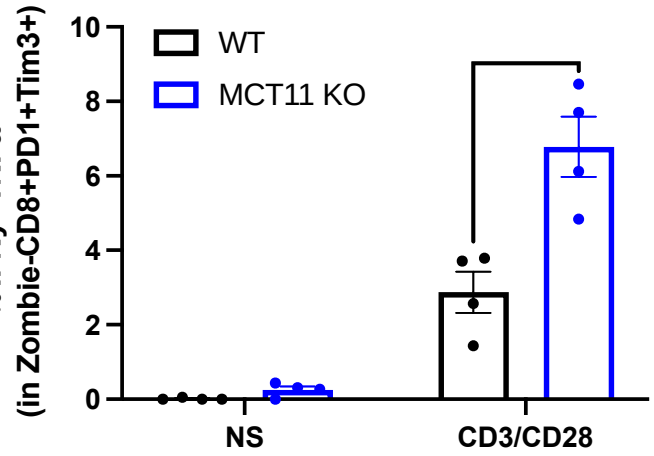
Does MCT11 promote exhaustion in endogenous TIL?



No stim

αCD3 & αCD28





- Conditional T cell knockout of MCT11 decreases coinhibitory marker expression in T cells
- Conditional T cell knockout of MCT11 increases exhausted T cell cytokine production

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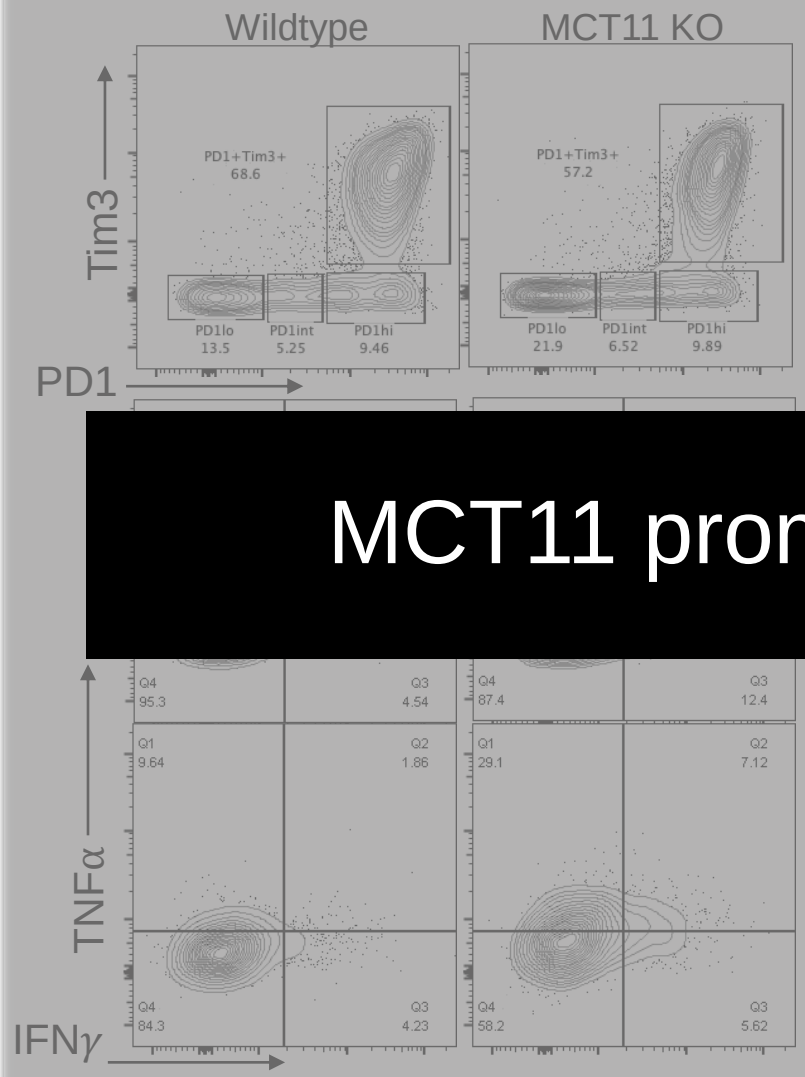
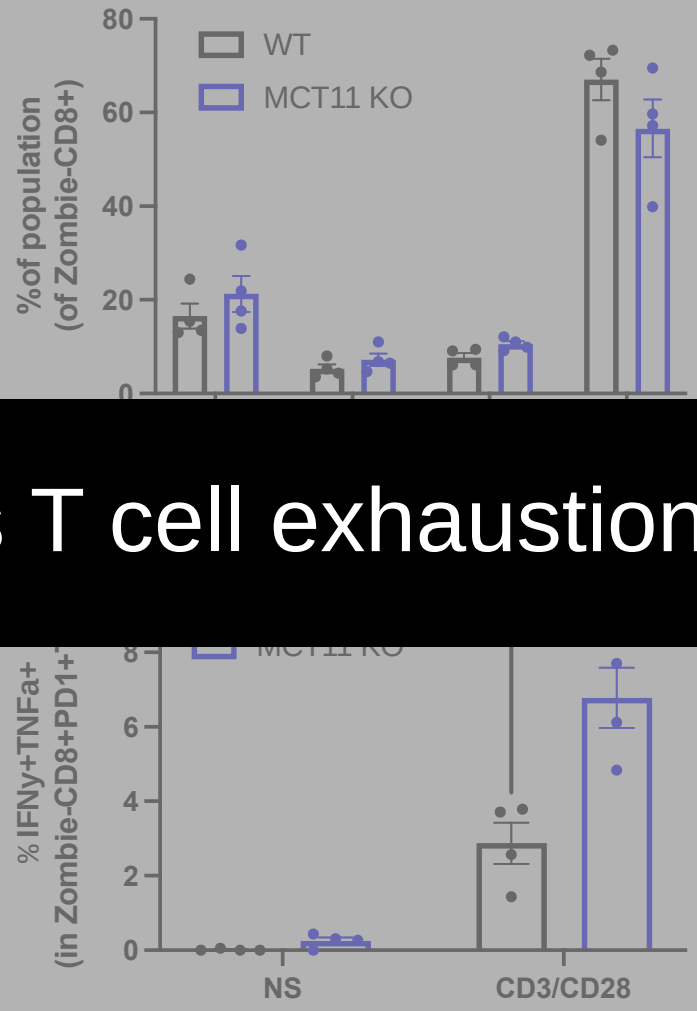


αCD3 &
αCD28



- Conditional T cell knockout of MCT11 decreases coinhibitory marker expression in T cells

MCT11 promotes T cell exhaustion in the TME

- Conditional T cell knockout of MCT11 increases exhausted T cell cytokine production

Could lactic acid uptake be blocked with anti-MCT11 antibody?

Incubate TIL samples in triplicates with pHrodo for 30 mins @ 37C

Extracellular stain

No lactate (Ctrl)

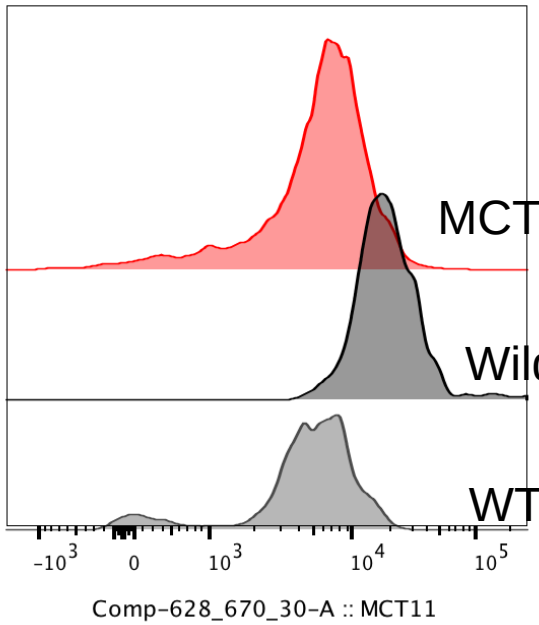
Add 5mM lactate

Add 5mM lactate +2µg anti-MCT11

Wait 30 mins

Flow cytometry

B16 CD8+ TIL



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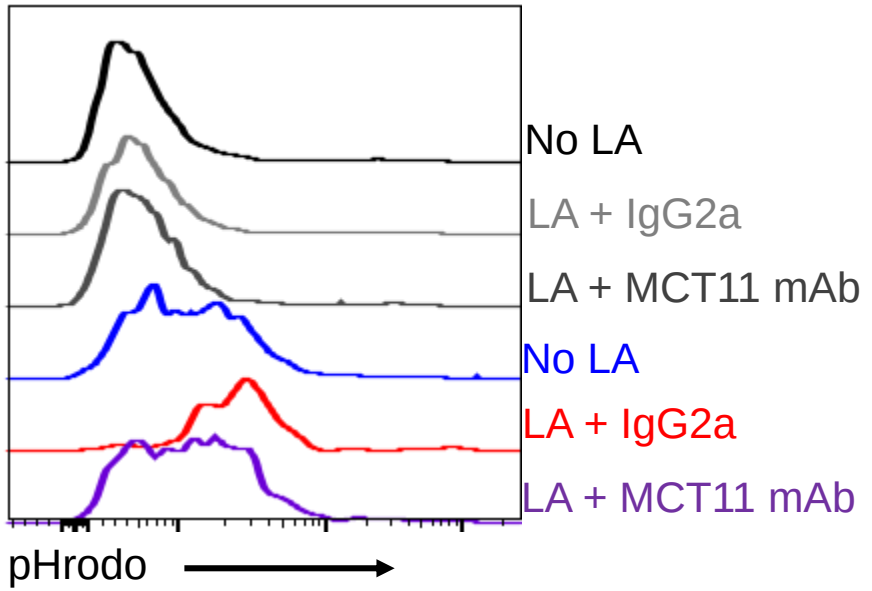

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Add 5mM lactate +2µg anti-MCT11

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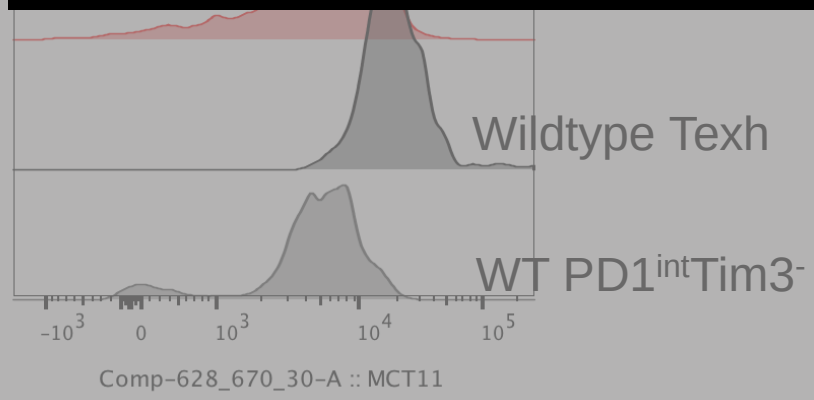
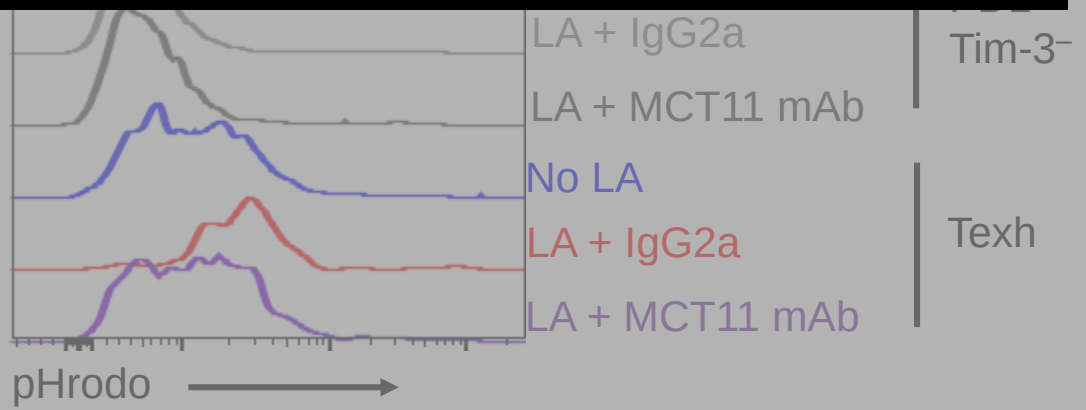
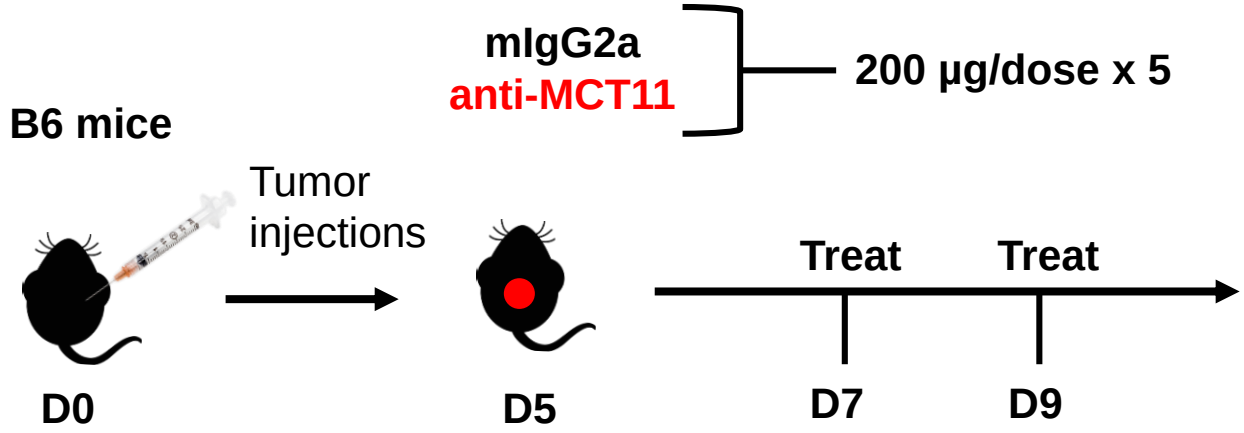
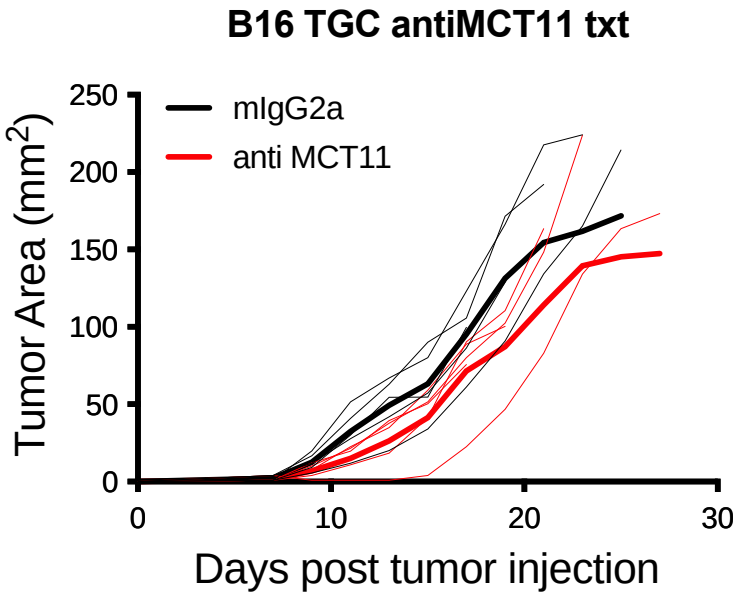
MCT11 enables lactic acid uptake in exhausted T cells from the TME

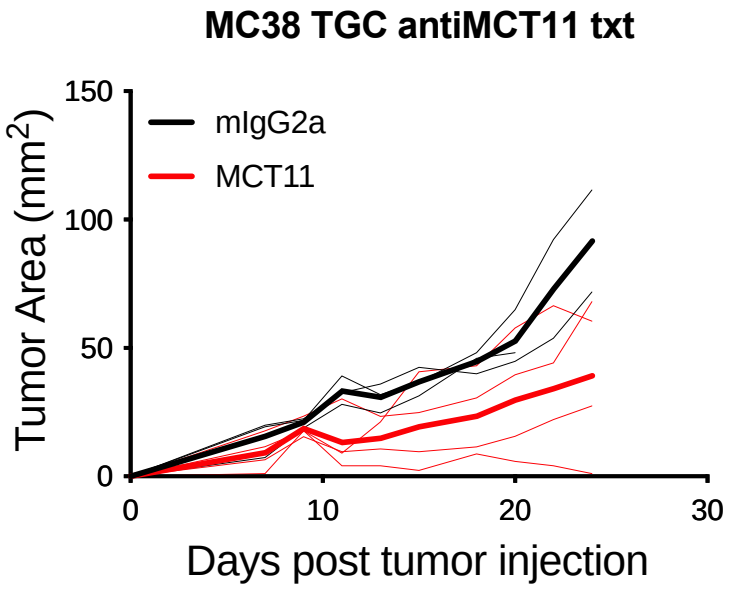


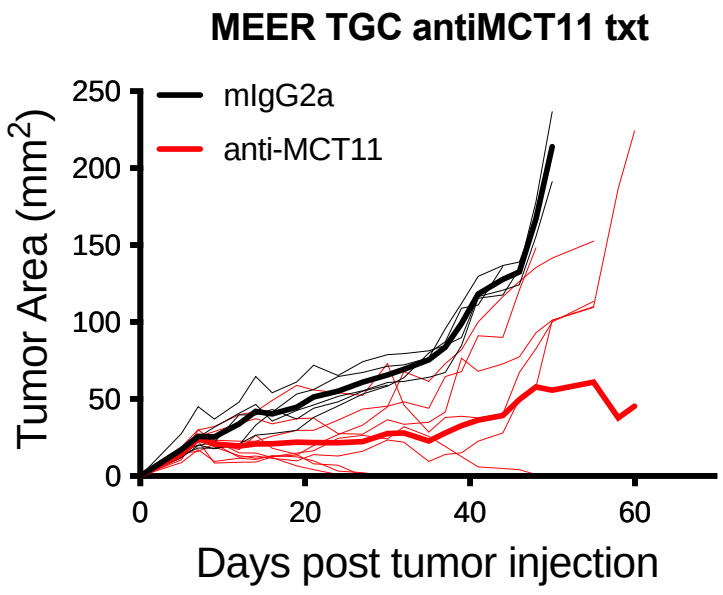


Can anti-MCT11 be used therapeutically?

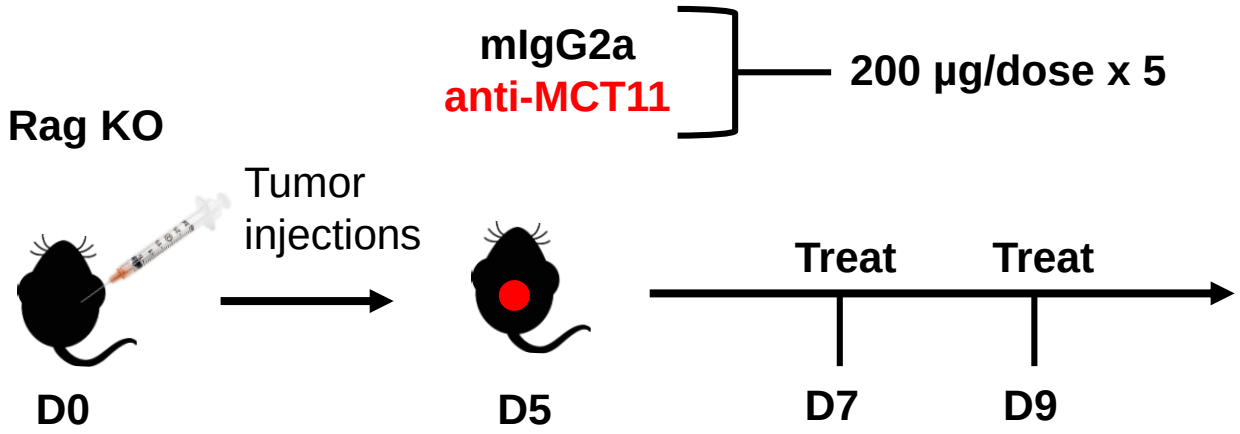


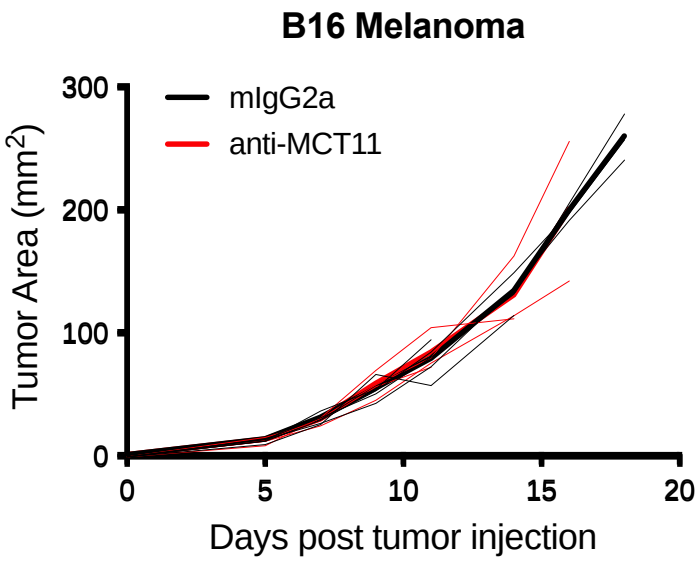


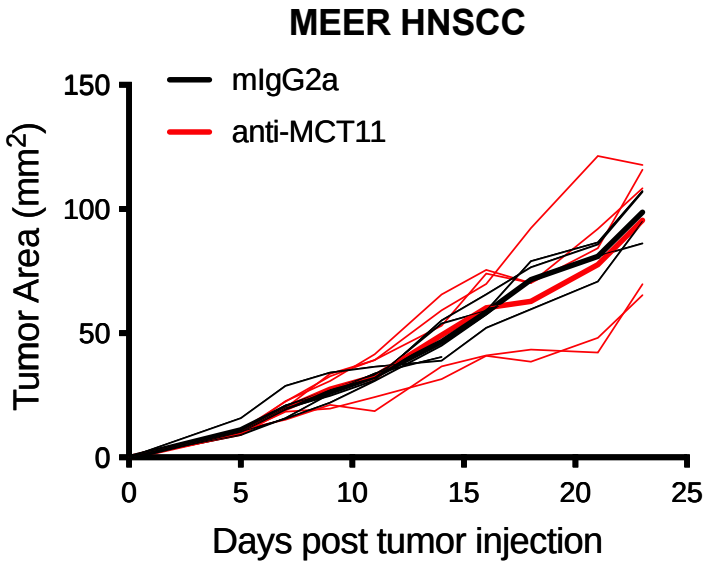




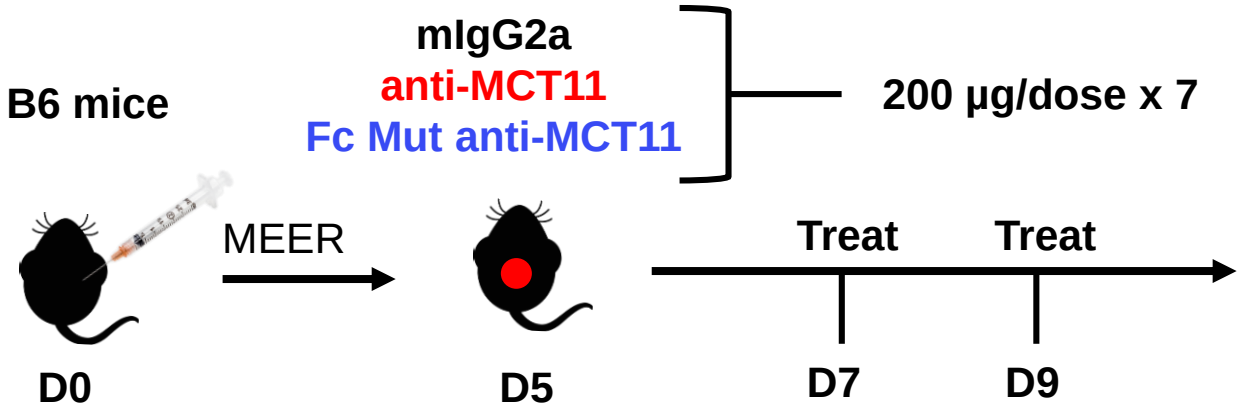
Does anti-MCT11 therapy require adaptive immunity?

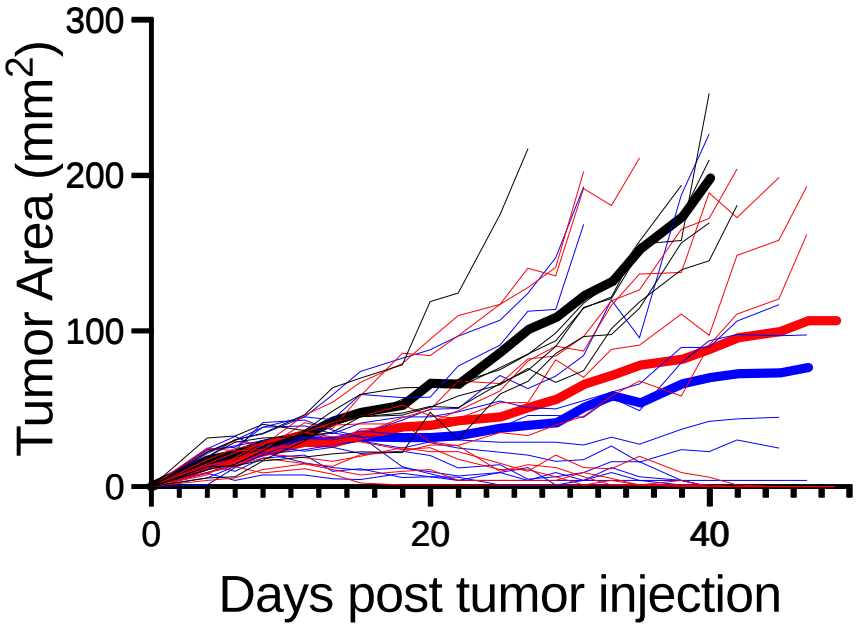


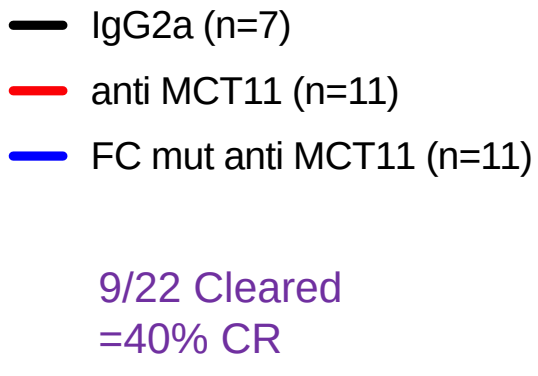




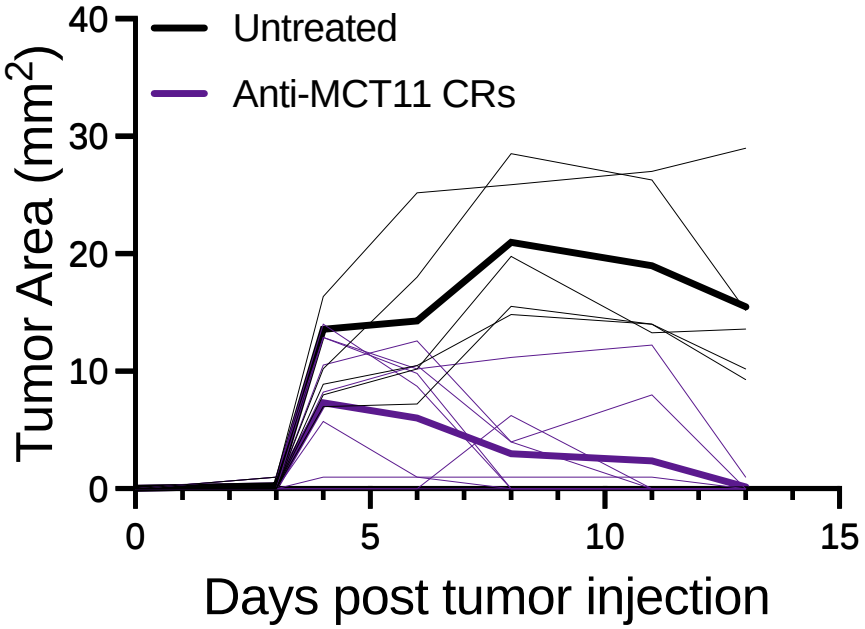
Does anti-MCT11 deplete T cells by ADCC or block MCT11 function?



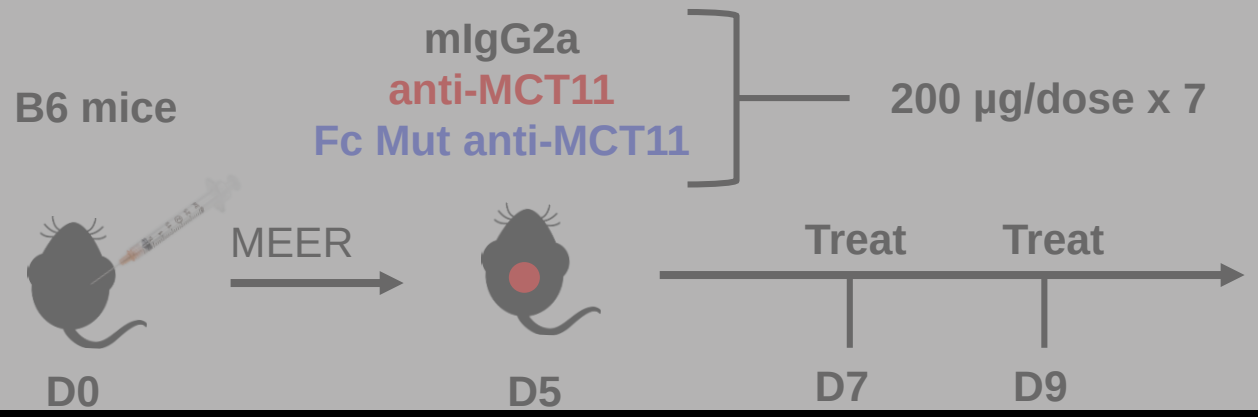




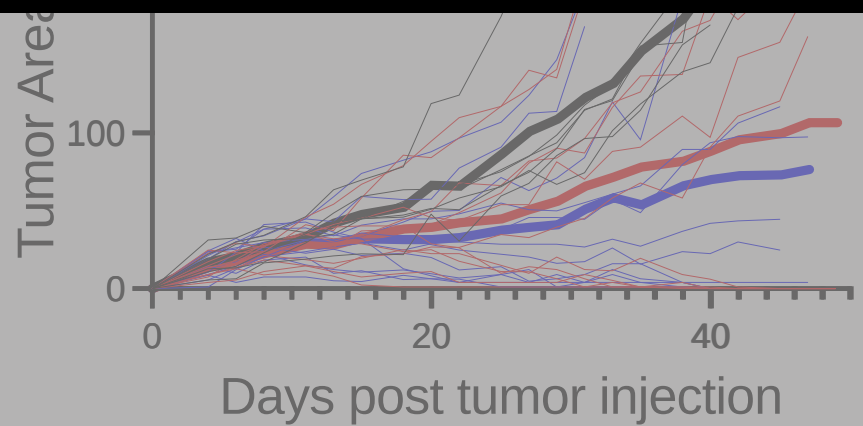
9/22 Cleared
=40% CR



Does anti-MCT11 deplete T cells by ADCC or block MCT11 function?



Single agent Anti-MCT11 therapy reduces tumor burden by blocking T cell lactic acid uptake & promotes memory



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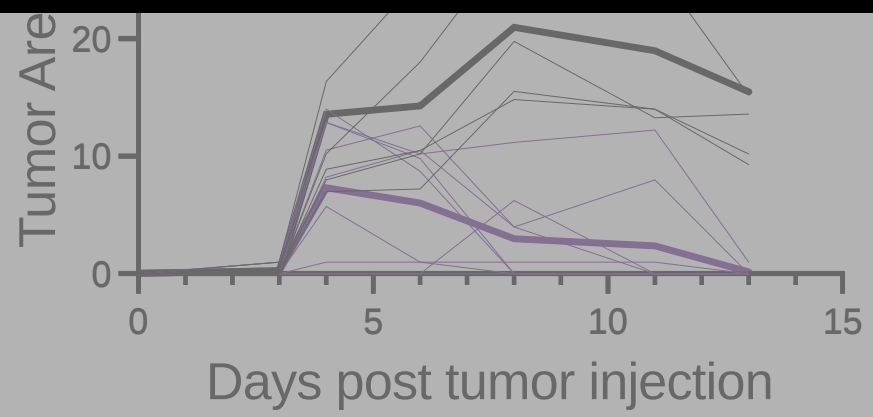
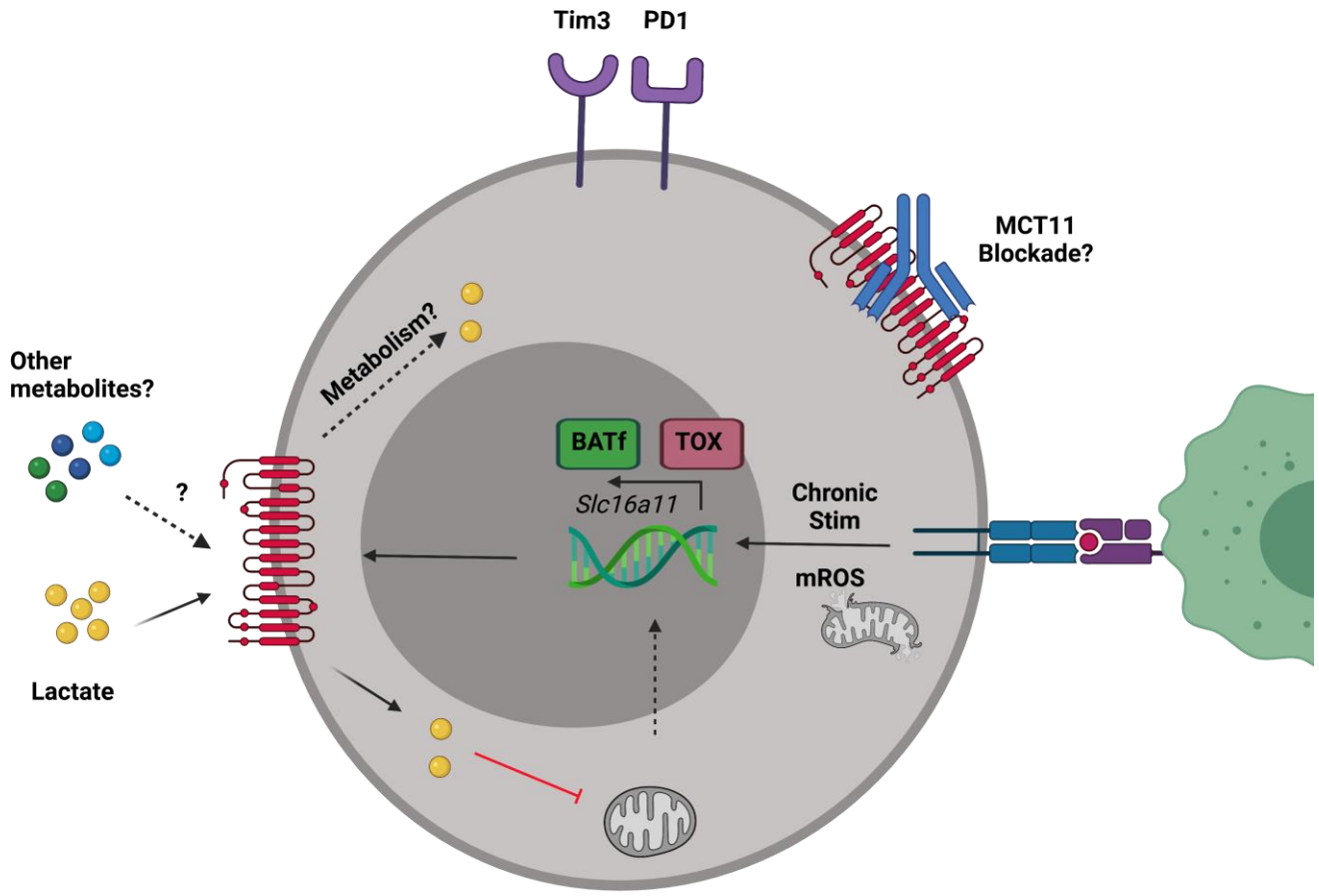


Conclusions & Future Directions

- MCT11 is highly and uniquely expressed by exhausted CD8+ TIL
- **Exhausted CD8+ TIL are sensitized to toxic lactic acid through MCT11**
- MCT11 enforces CD8+ T cell exhaustion in the TME
- **Single-agent antibody therapy against MCT11 reduces tumor burden in mice**



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