

**2024 RACHMIEL LEVINE-ARTHUR RIGGS**

# Diabetes Research Symposium

## A New Metabolic Approach to Cancer-Related Fatigue: Implications for Inactivity in Obesity and Diabetes

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Yale University



# Disclosures

- I do not have any relevant financial relationships.

*This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.*

**The off-label/investigational use of Dichloroacetate will be addressed.**

# Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

## STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

*The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.*

## **EXEMPTION:**

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

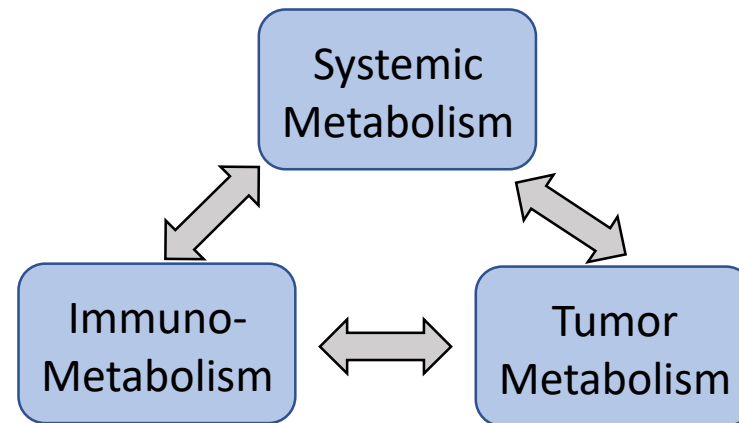
***This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.***

# Perry lab mission

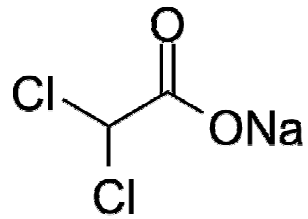
- We study how systemic and local metabolism intersects with tumor metabolism, with the goal to develop metabolism-targeting, precision medicine approaches for various tumor types

## Overarching Goal

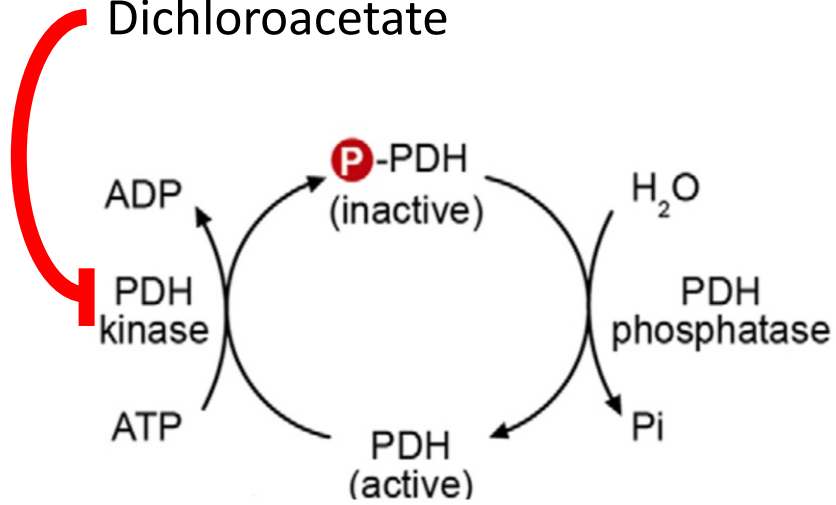
To define and therapeutically modulate each of these interrelationships:



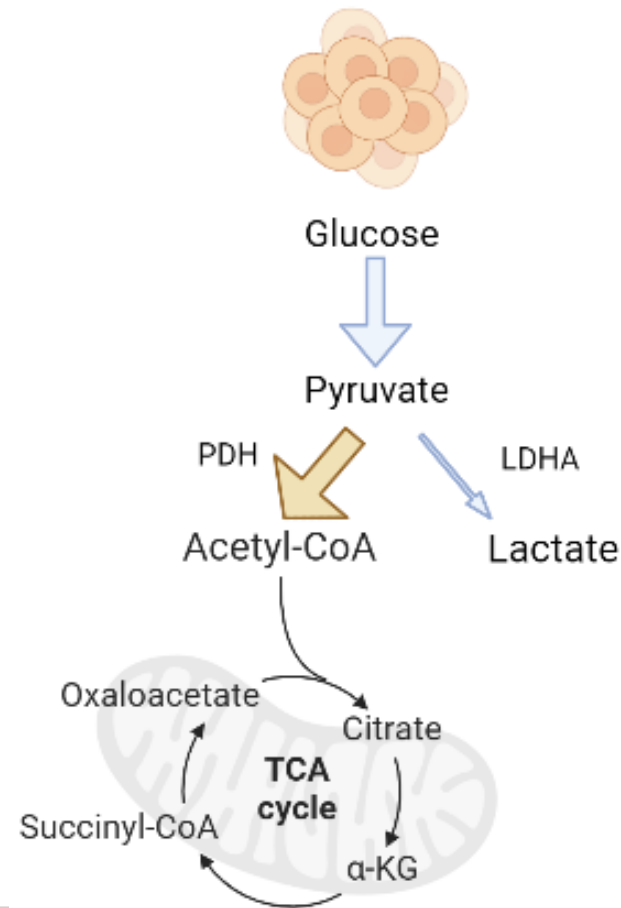
Dichloroacetate (DCA) is a small molecule activator of **glucose oxidation** that has been proposed as a tumor suppressor *in vitro* and in preclinical cancer models



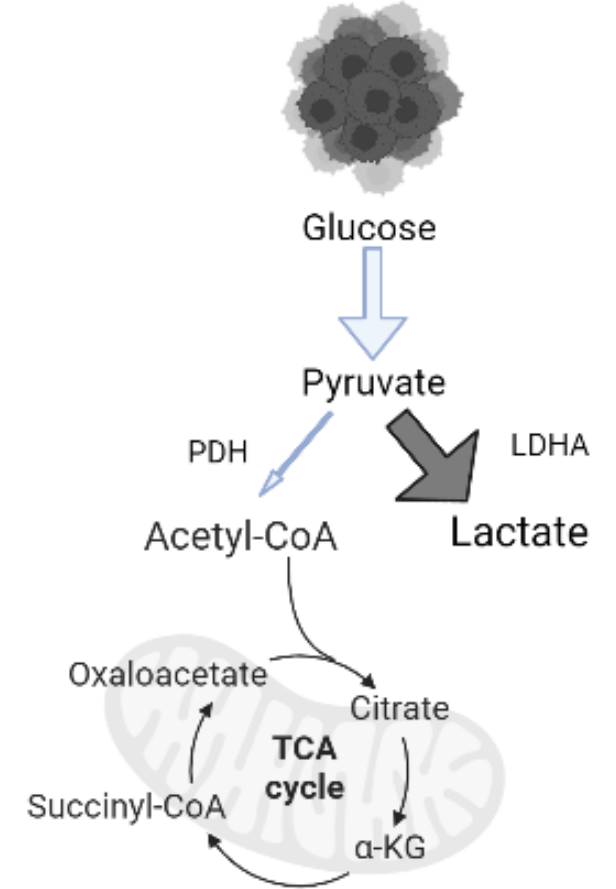
Dichloroacetate



Normal tissue

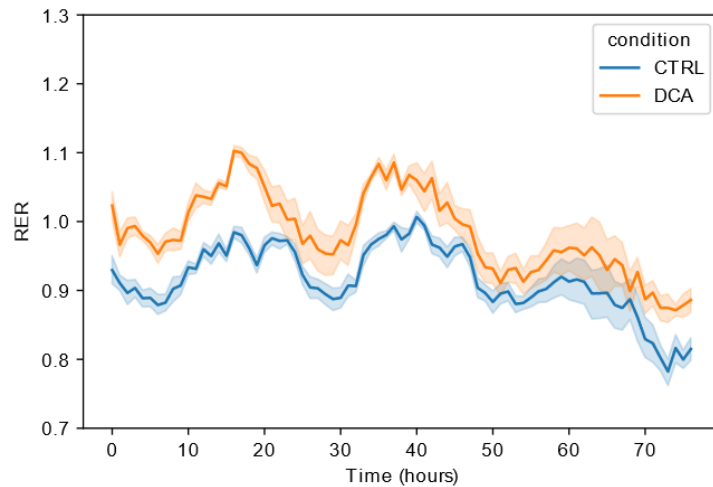


Tumor

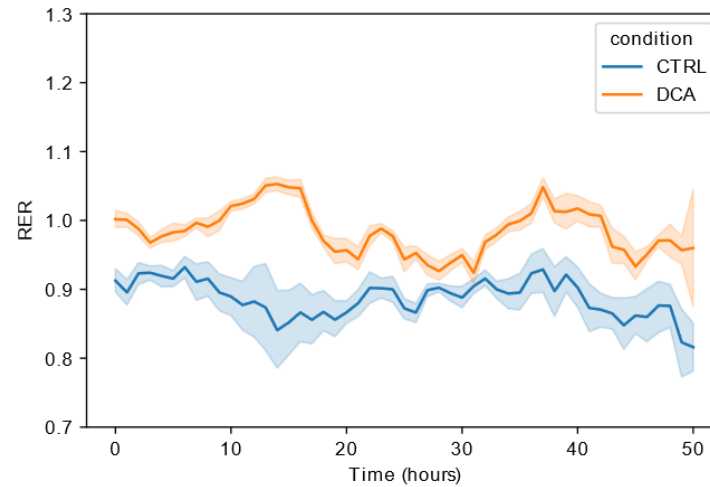


# As expected, DCA increases systemic glucose oxidation in mice with melanoma

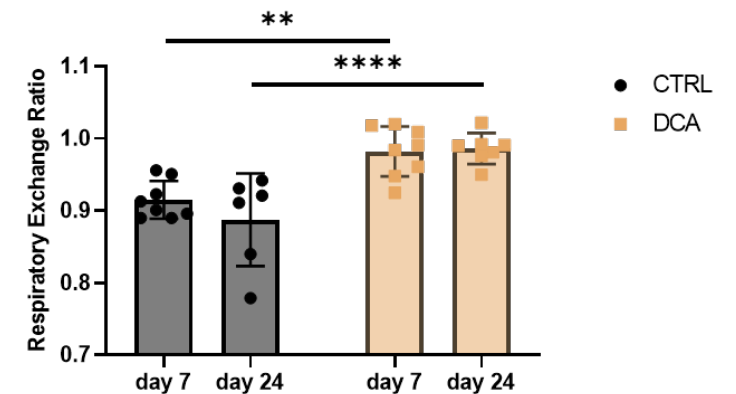
### Week 0 (Early Stage)



### Week 3 (Late Stage)



### Respiratory Exchange Ratio

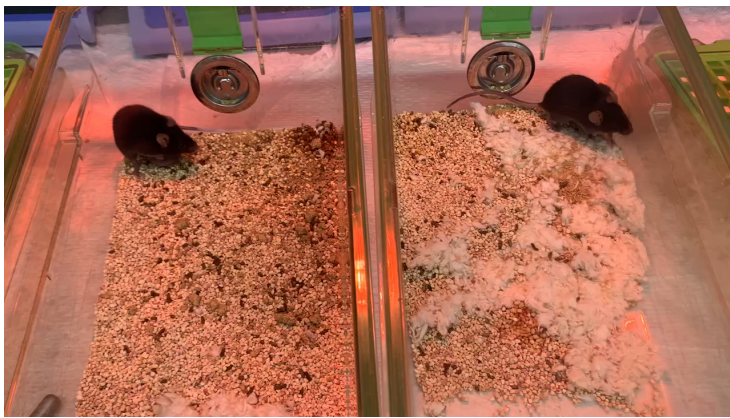
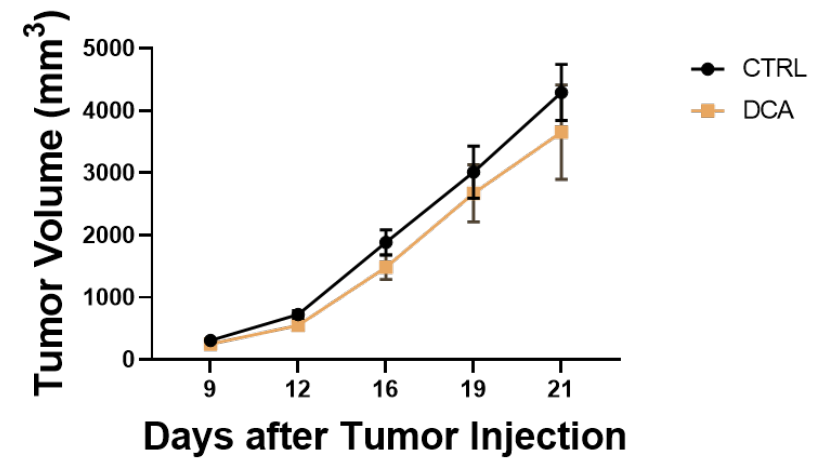
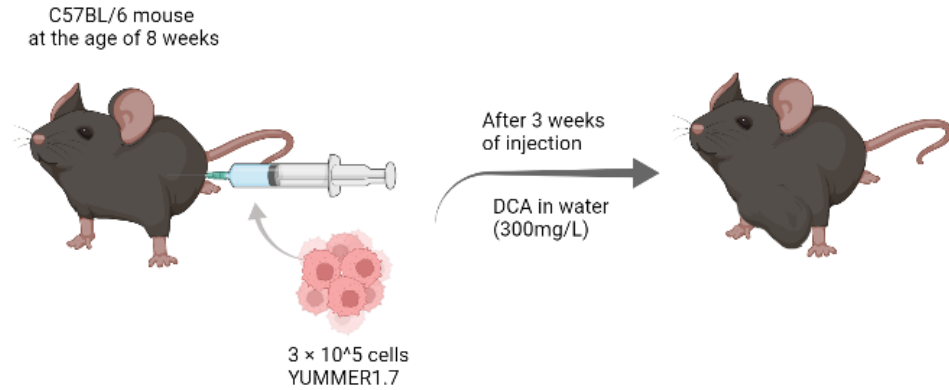
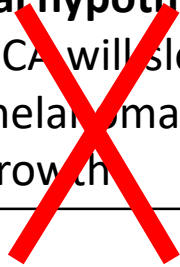


Zhang et al., *AJP Endo* 2023

# DCA does not slow tumor growth, but increases activity in tumor-bearing mice

**Initial hypothesis:**

- DCA will slow melanoma tumor growth



Tumor +  
No treatment

Tumor +  
DCA treatment



Xinyi Zhang

CITY OF HOPE



November 2023

The American Physiological Society

acknowledges

Xinyi Zhang, Won D. Lee, Brooks P. Leitner, Wanling Zhu, Andin Fosam, Zongyu Li, Rafael C. Gaspar, Alexandra A. Halberstam, Briana Robles, Joshua D. Rabinowitz, and Rachel J. Perry for distinction in scholarship in the *American Journal of Physiology-Endocrinology and Metabolism* for the article

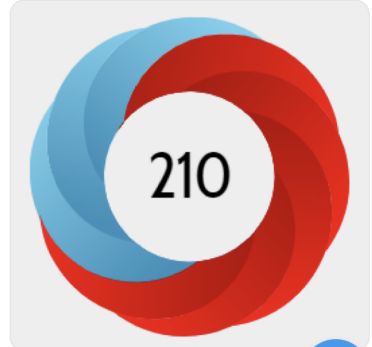
**Dichloroacetate as a novel pharmaceutical treatment for cancer-related fatigue in melanoma**

10.1152/ajpendo.00105.2023

APS Publications @APSPublicatio... · 6h ...  
Last week's most mentioned article is from @ajpendo:

Dichloroacetate as a novel pharmaceutical treatment for cancer-related fatigue in melanoma (Xinyi Zhang et al.)

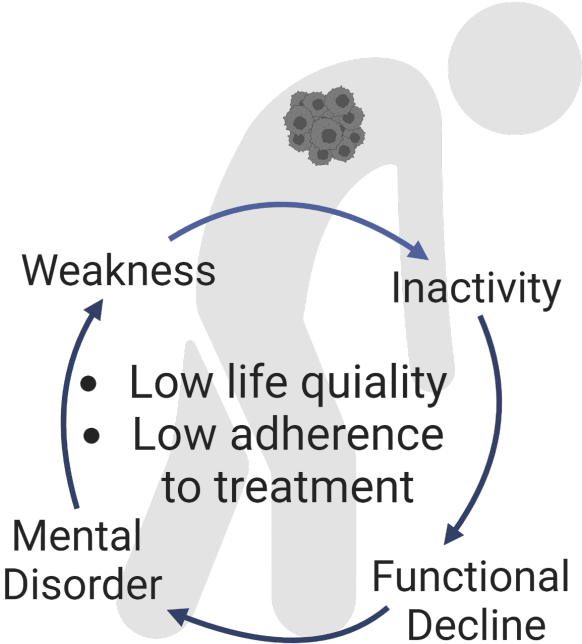
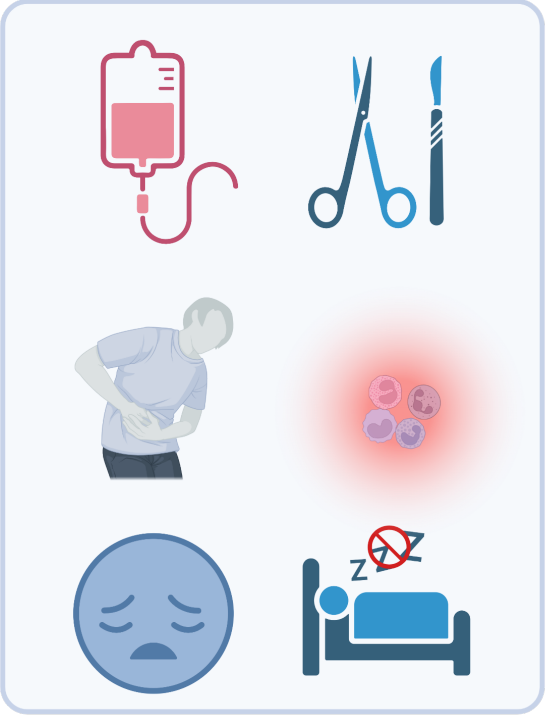
[ow.ly/6qAo50PUAes](https://ow.ly/6qAo50PUAes)



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Zhang et al., *AJP Endo* 2023

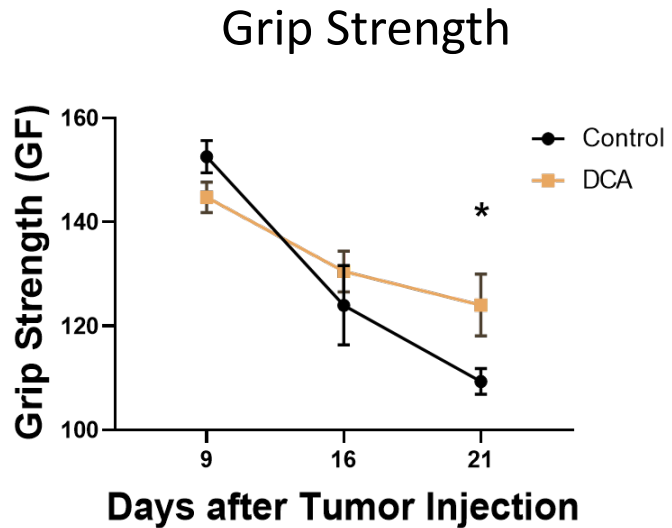
# Cancer related fatigue is common, debilitating, and often overlooked and undertreated





Untreated tumor-bearing mice had decreased physical performance, but DCA rescued this decline

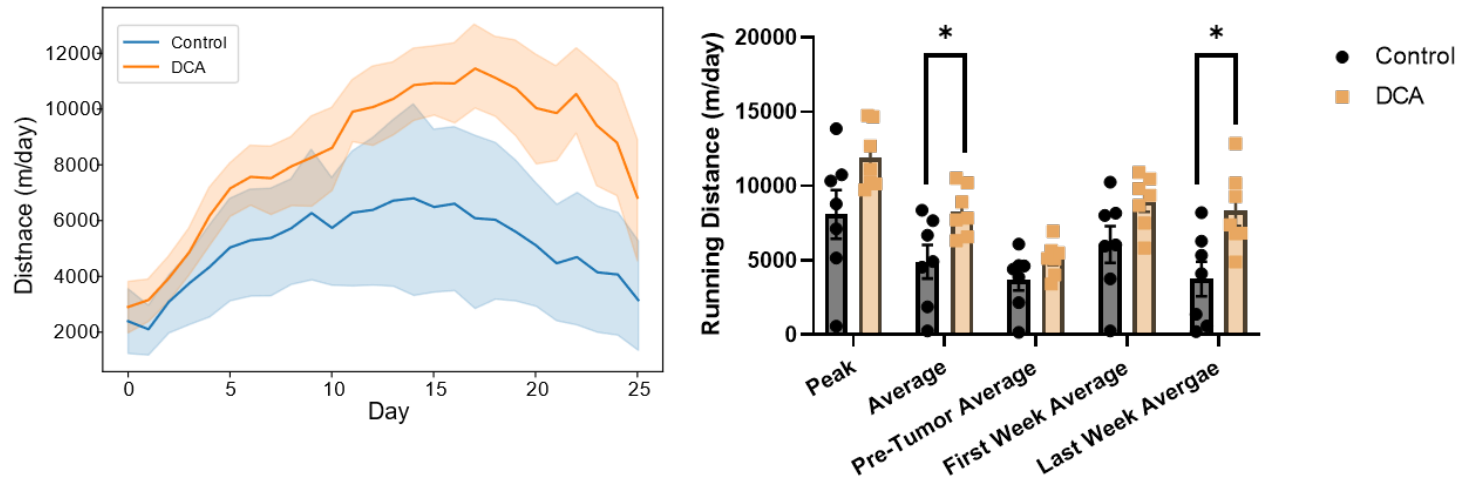
## Physical Performance



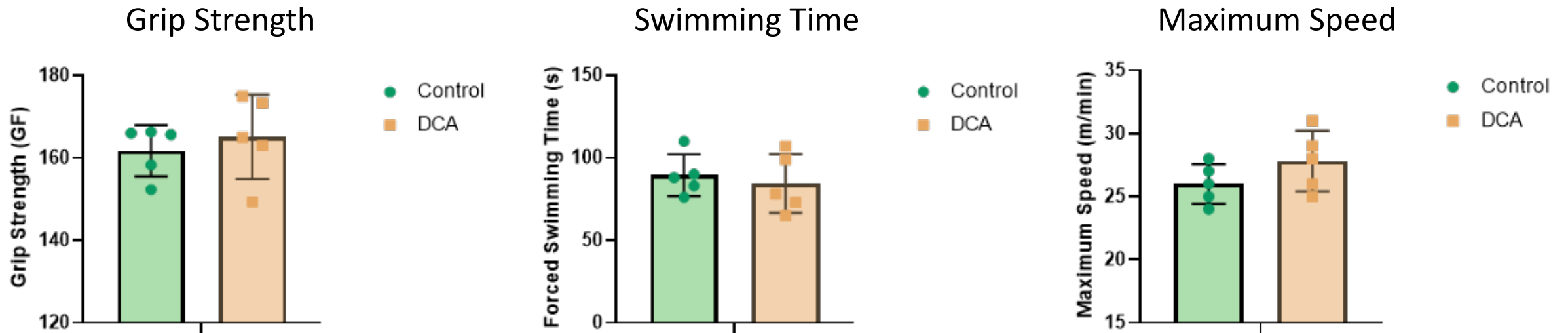
# Untreated tumor-bearing mice had decreased physical performance, but DCA rescued this decline

## Motivation for Movement

### Daily Running Distance

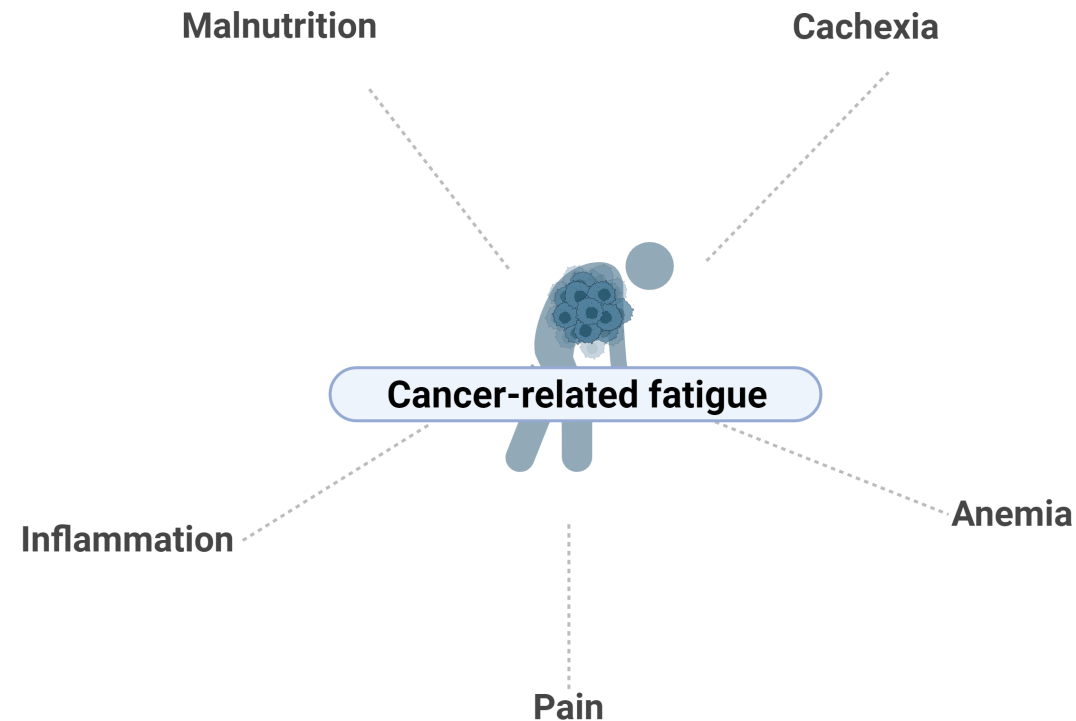


# DCA did not change physical performance in healthy control mice

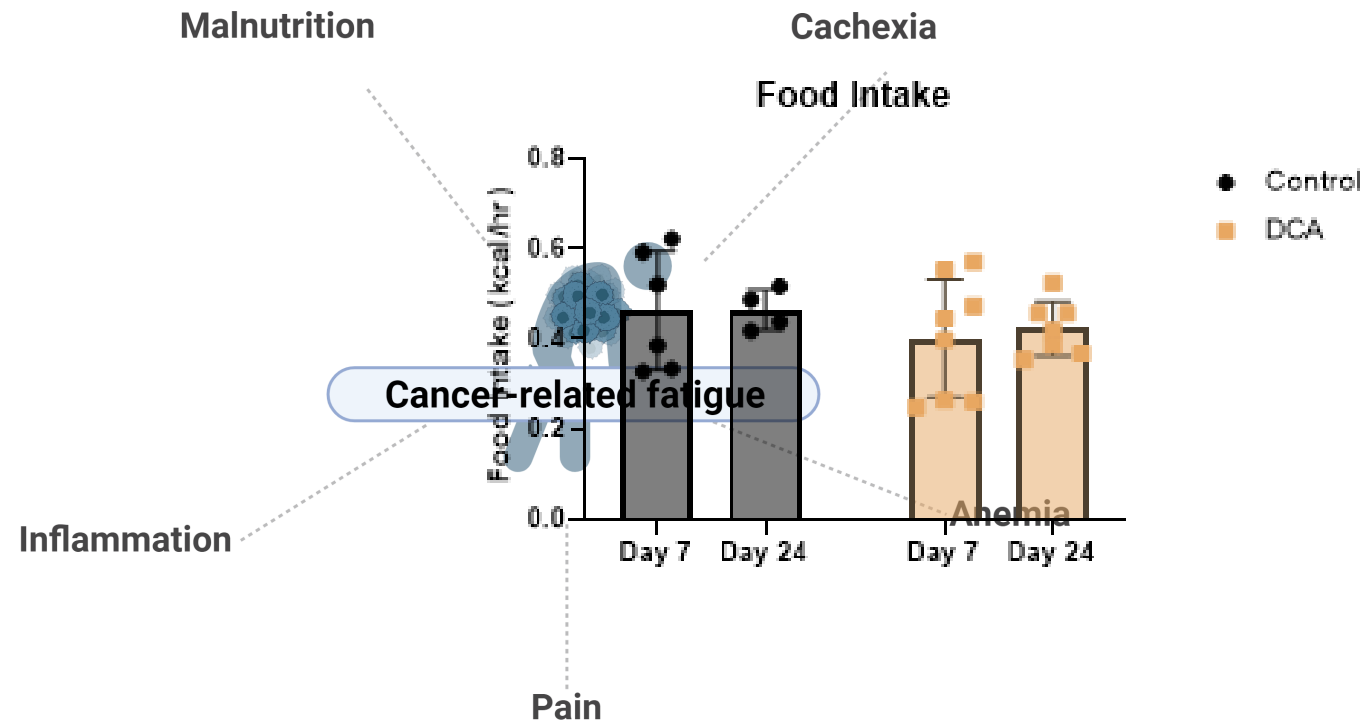


# Why does DCA protect against cancer-related fatigue?

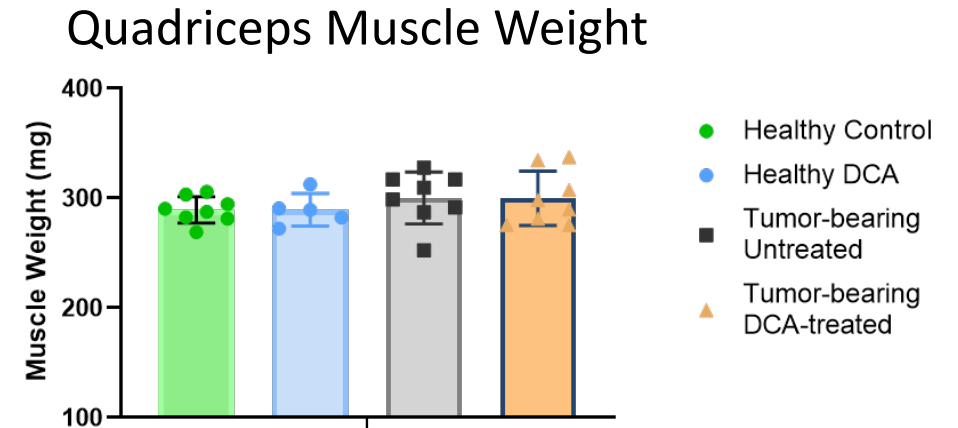
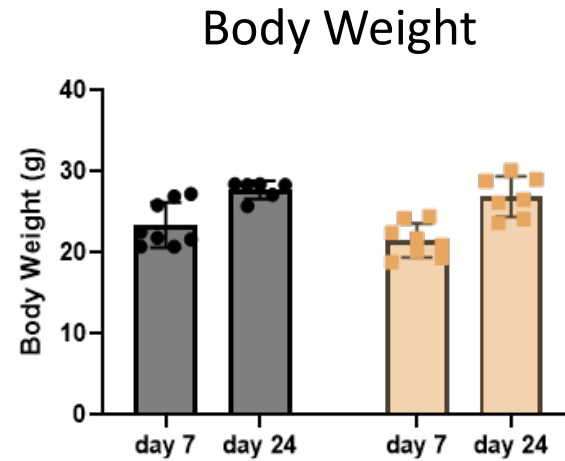
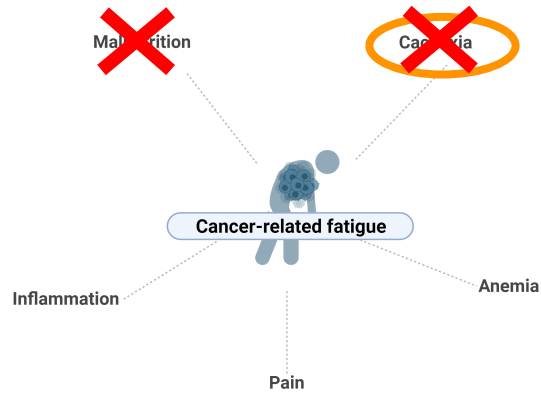
## Proposed Causes of Cancer-Related Fatigue



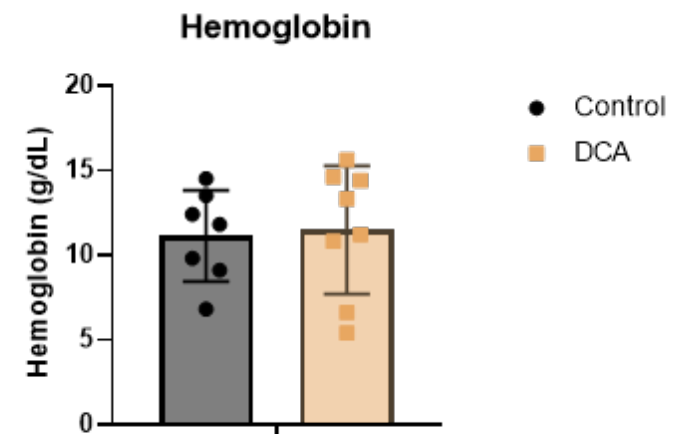
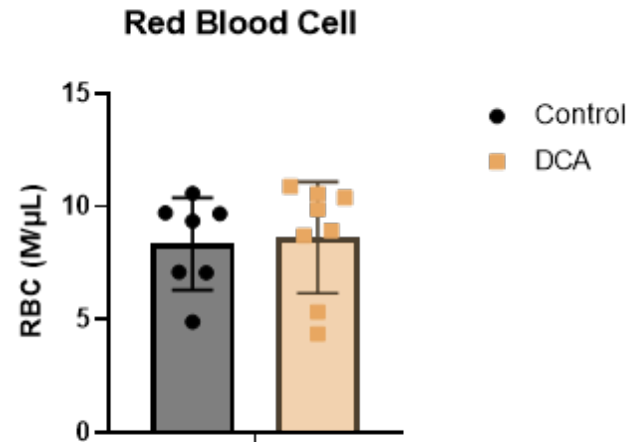
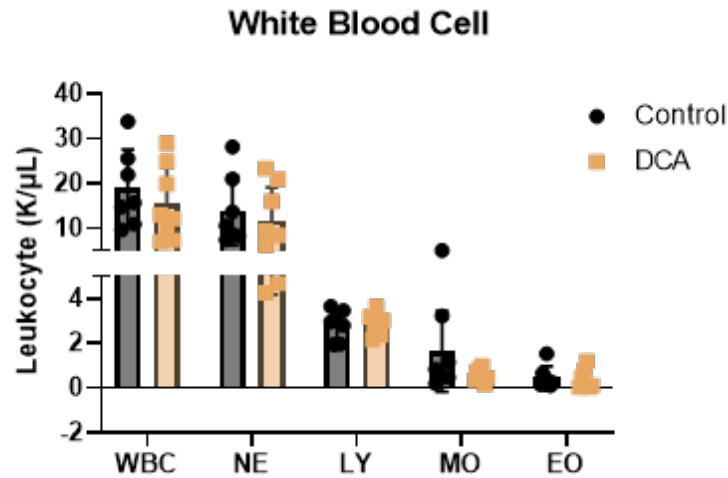
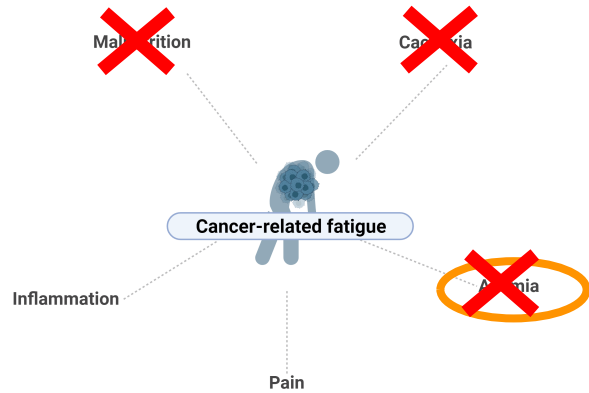
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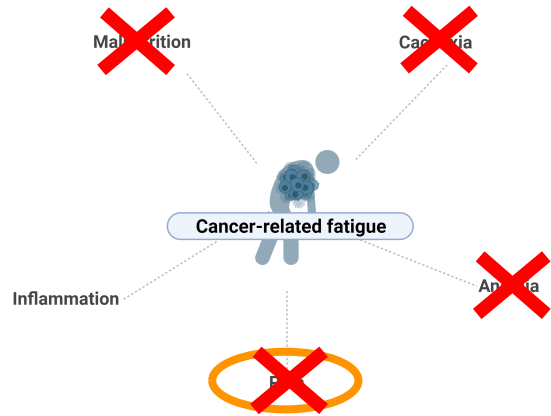
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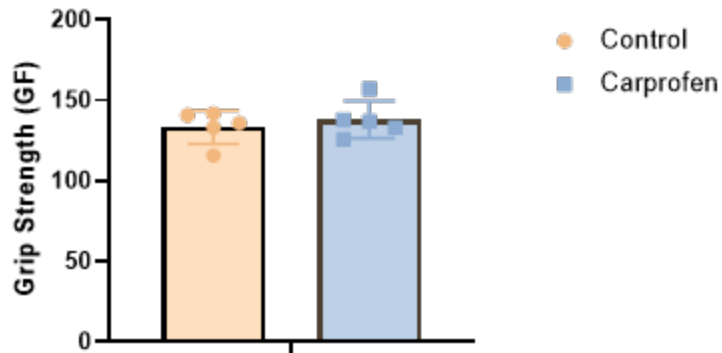
# Why does DCA protect against cancer-related fatigue?



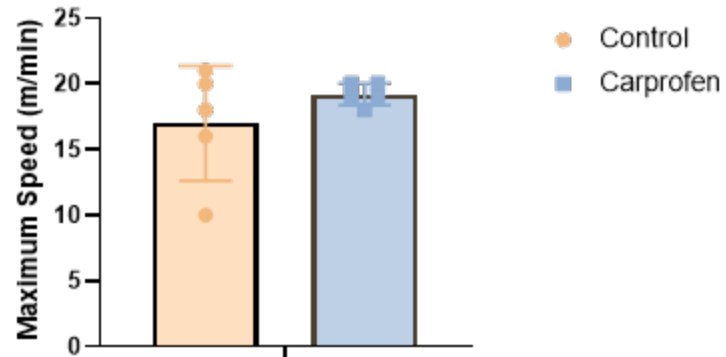
# Why does DCA protect against cancer-related fatigue?



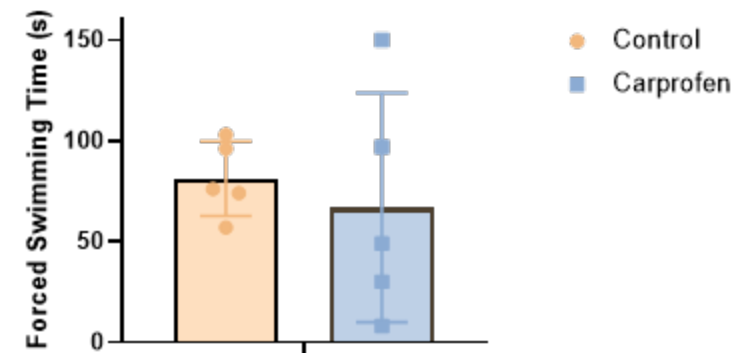
### Grip Strength



### Maximum Speed

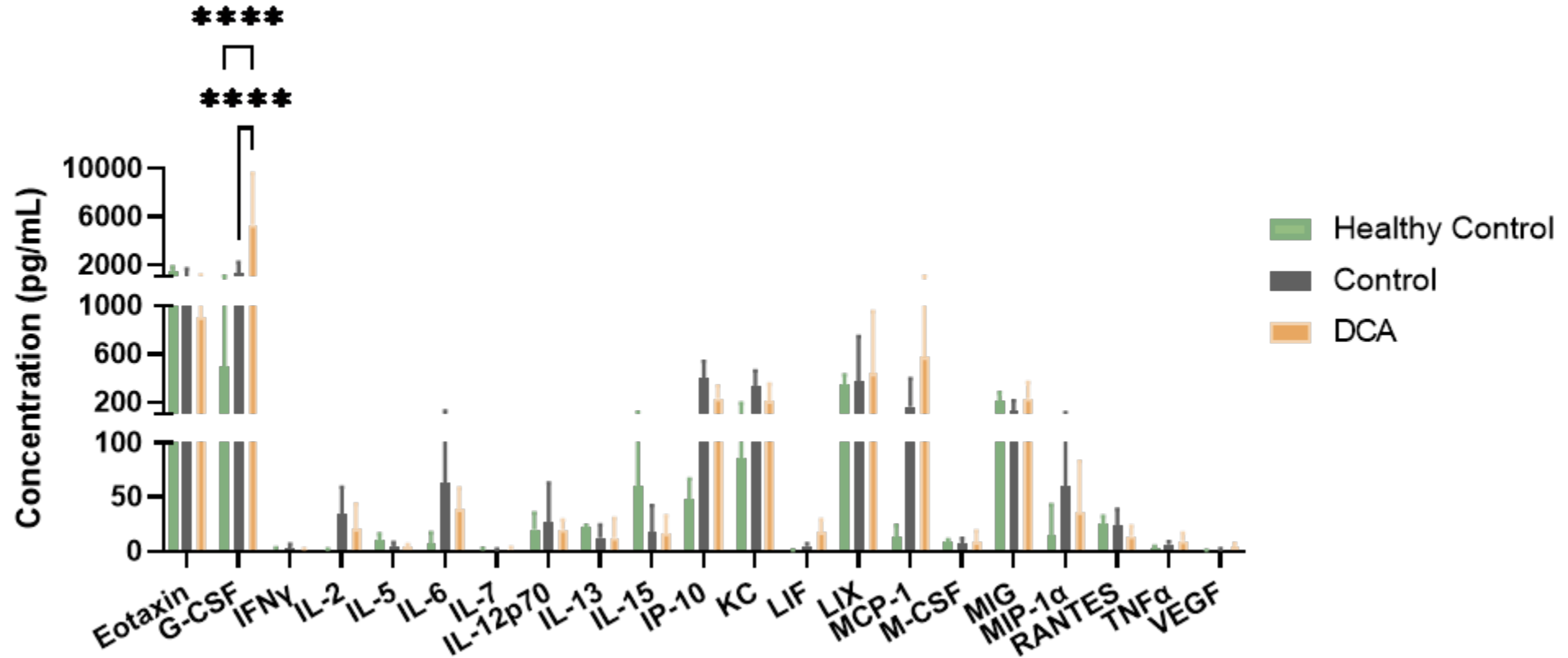
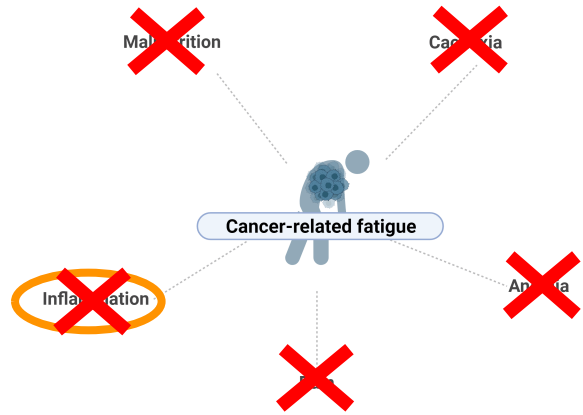


### Forced Swim Time

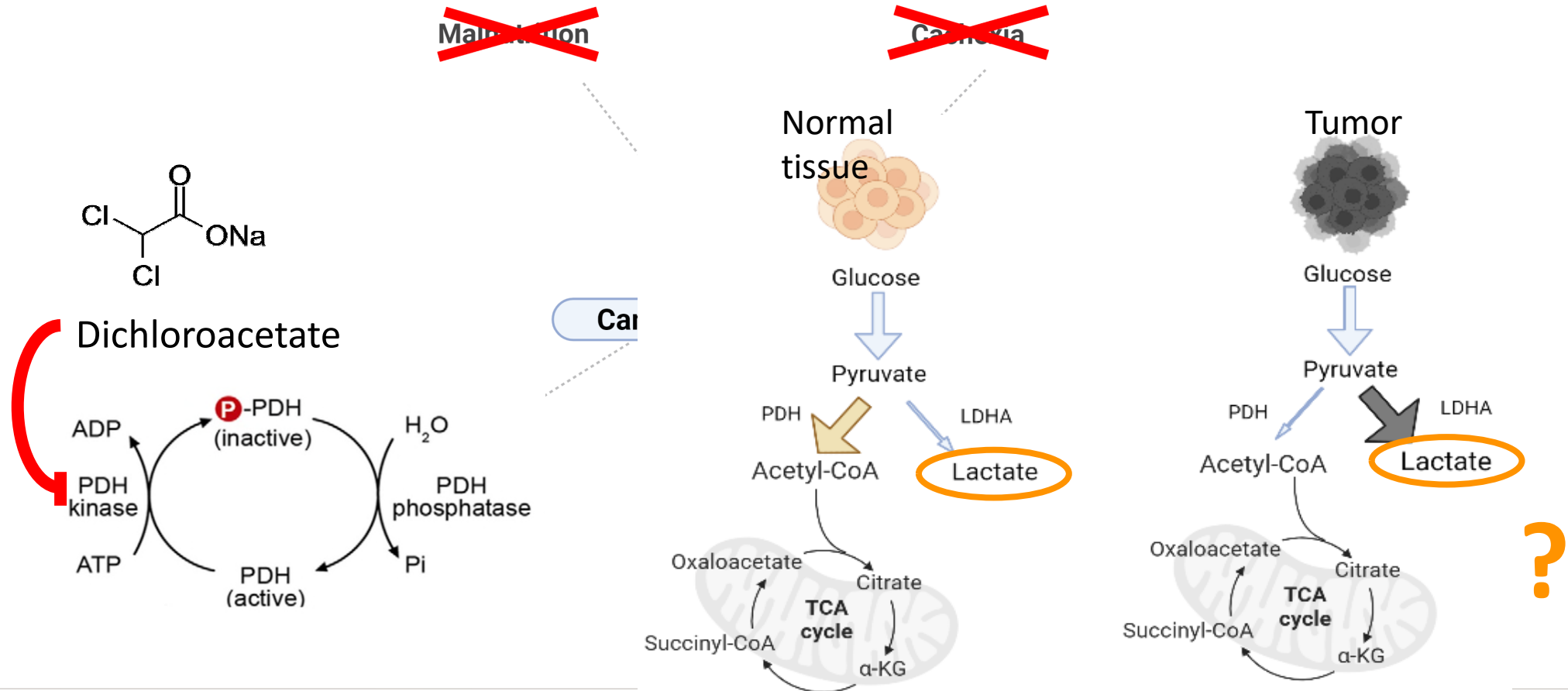




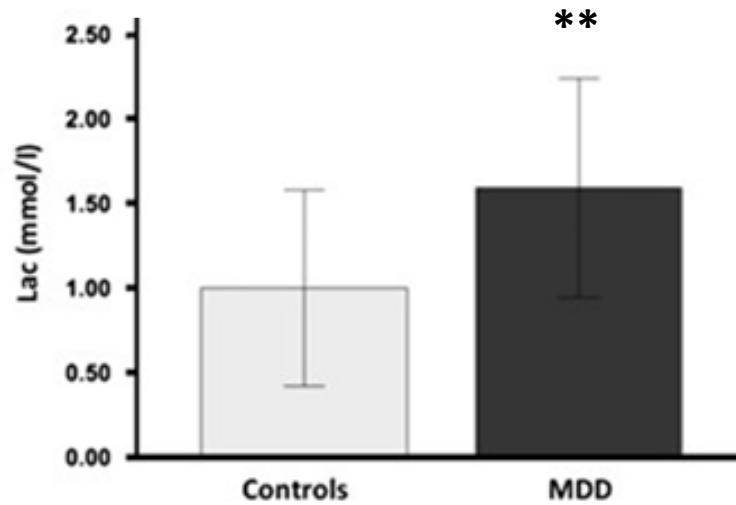
# Why does DCA protect against cancer-related fatigue?



# Why does DCA protect against cancer-related fatigue?

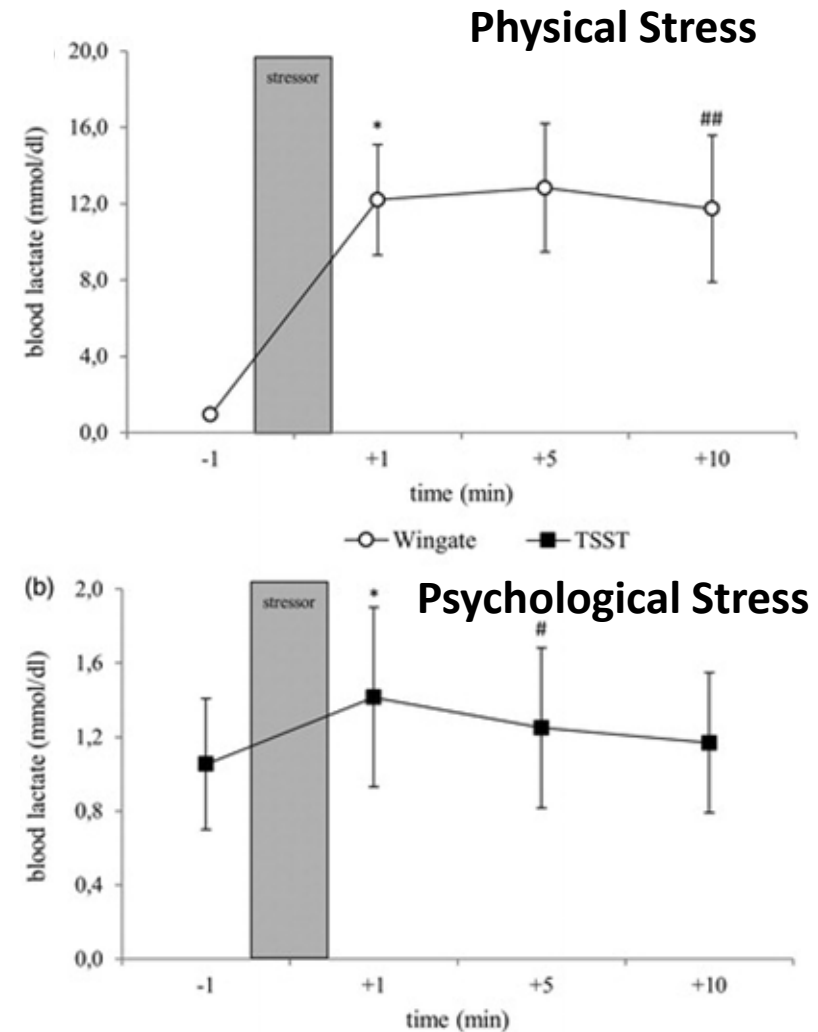


# Lactic acid is increased in individuals with psychiatric disease

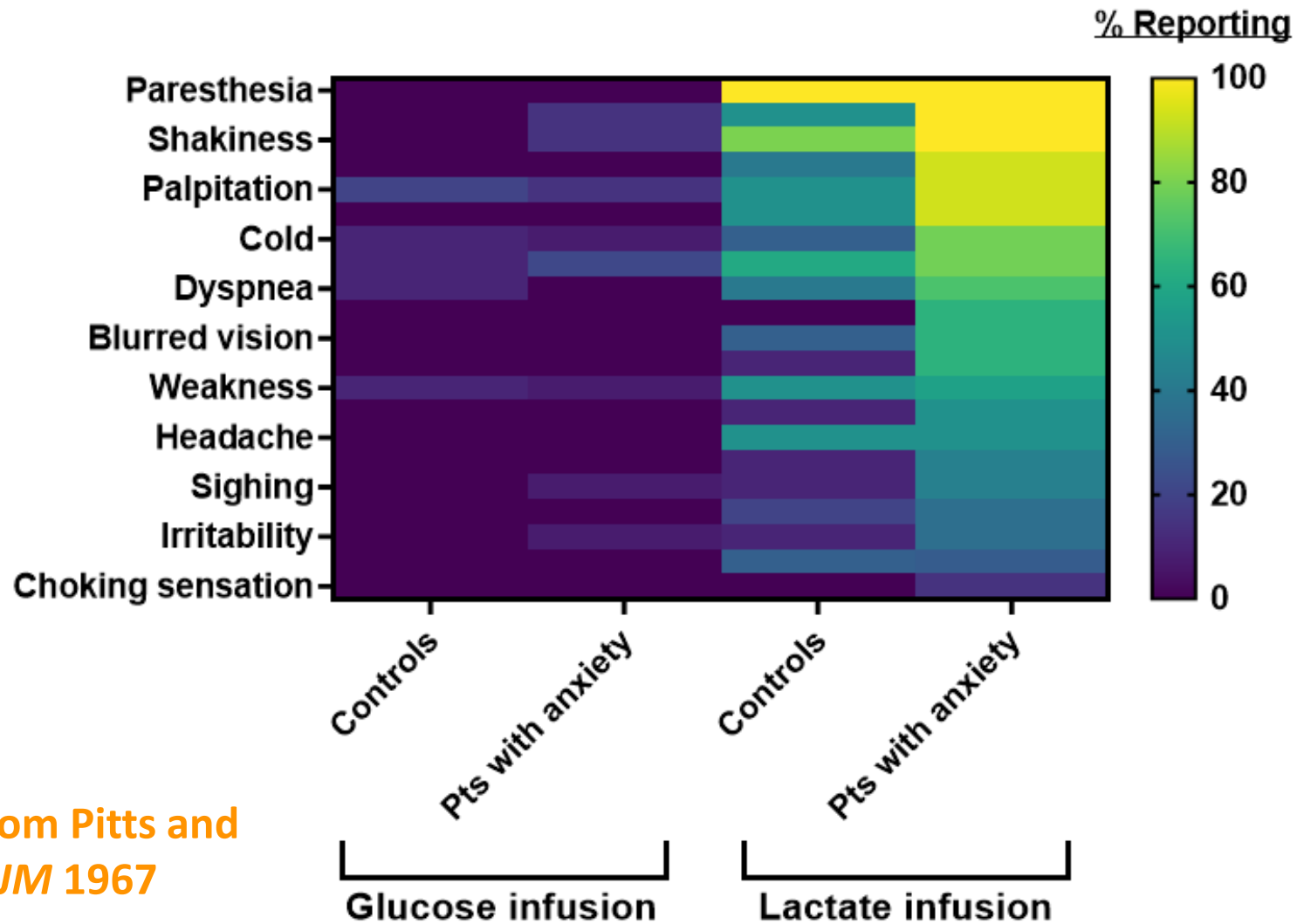


MDD: Major depressive disorder

Ernst et al., *Mol. Psych.* 2016



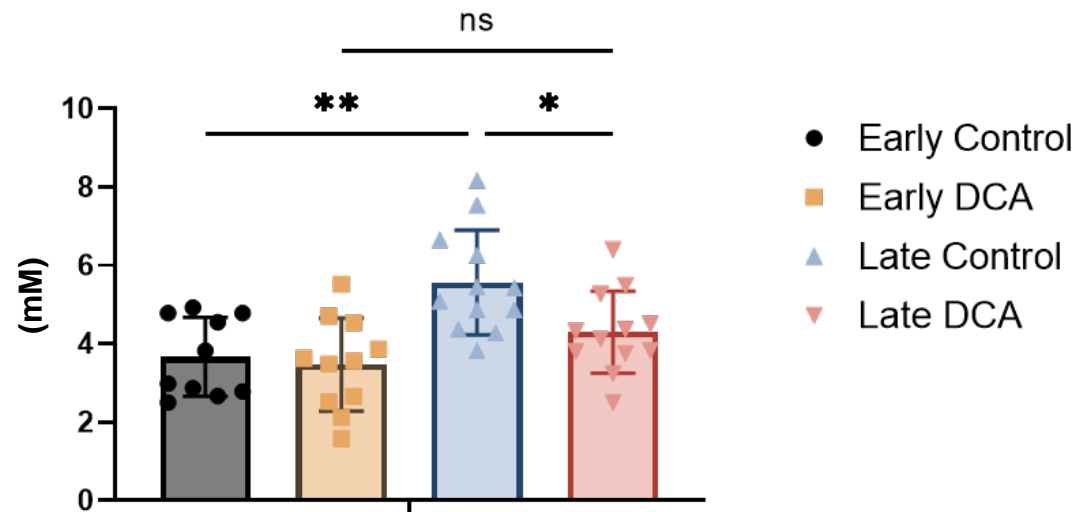
# Lactate infusion generates symptoms of anxiety in humans



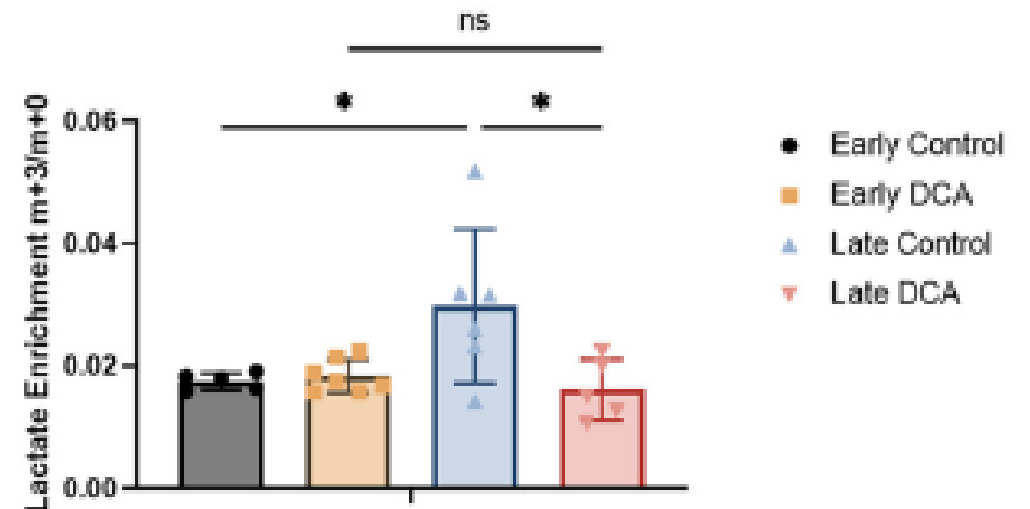
Reconstructed from Pitts and McClure, *NEJM* 1967

# DCA reduced plasma lactate derived from glucose in tumor-bearing mice

## Plasma Lactate Concentration



## $^{13}\text{C}$ Lactate from $^{13}\text{C}$ Glucose



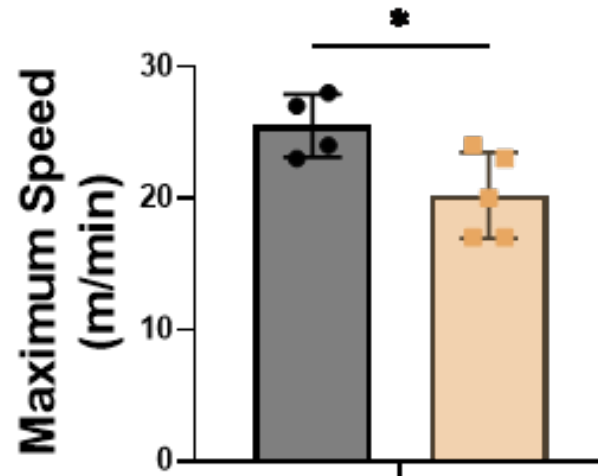
# Lactate impairs physical performance and motivation for movement in healthy mice

Healthy Control

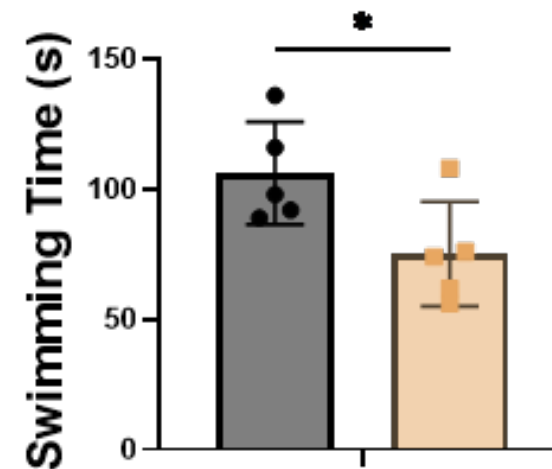


Sodium Lactate  
transient plasma lactate increase

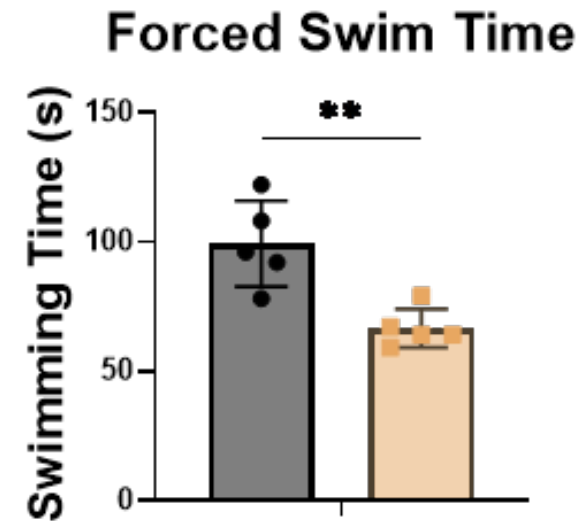
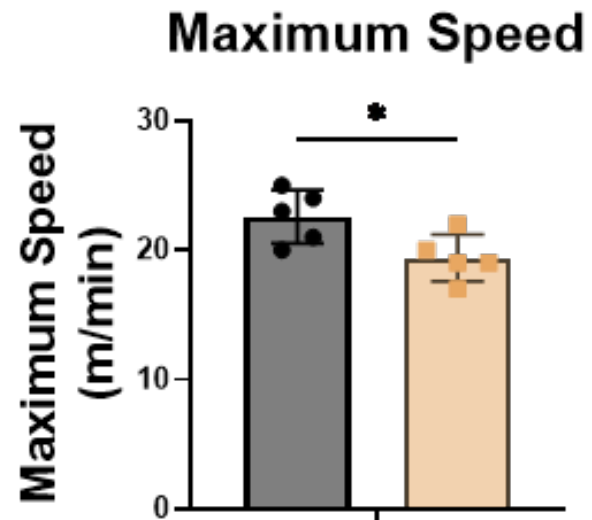
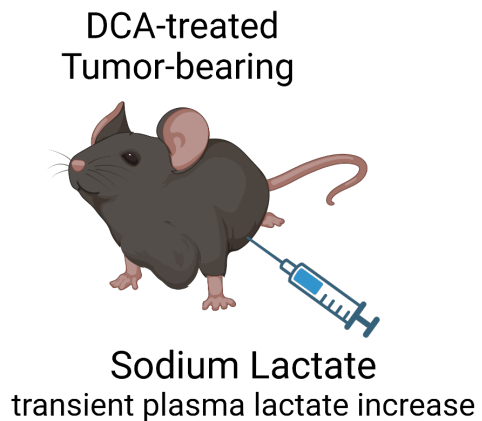
### Maximum Speed



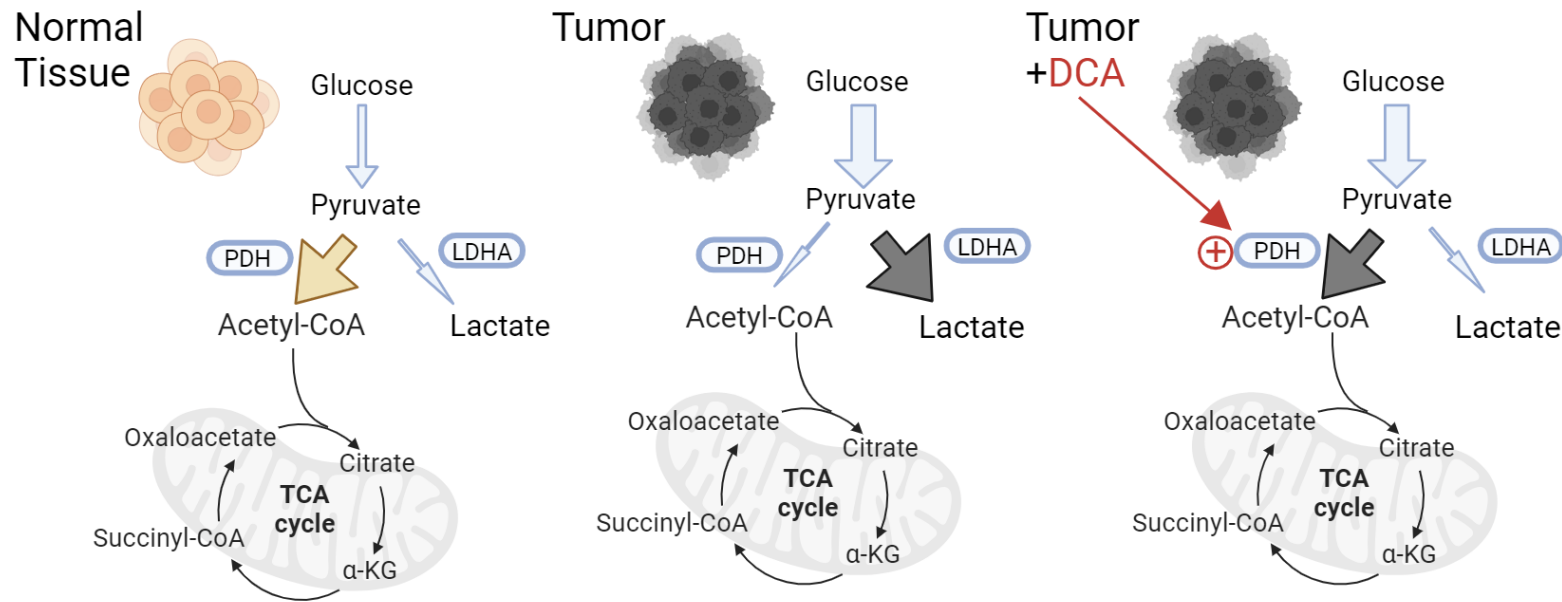
### Forced Swim Time



# Lactate reduces physical performance in DCA-treated, tumor-bearing mice



# Summary

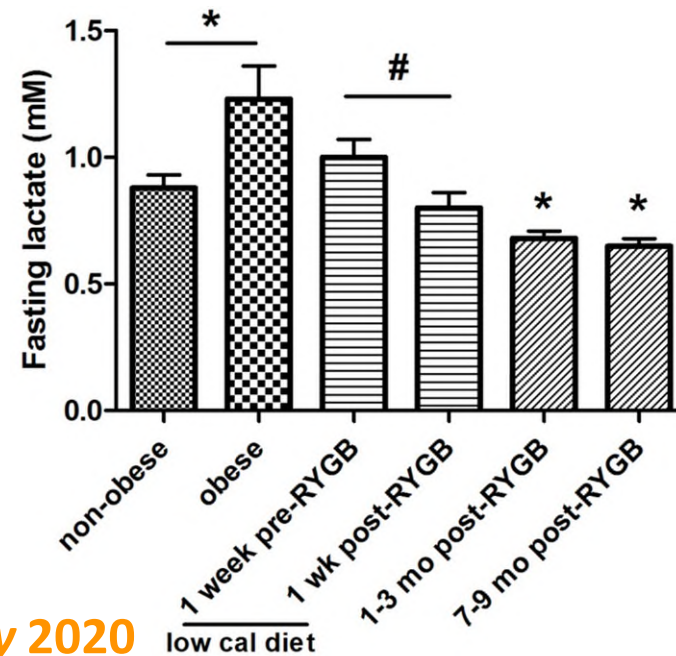


- DCA mitigates the decrease in physical performance observed in YUMMER1.7 murine melanoma (as well as in mice with chemotherapy- and immunotherapy-induced fatigue; not shown for the purposes of time)
- Increased plasma lactate is a key factor in inducing CRF
- DCA is safe and effective, having advanced to phase III trials for lactic acidosis and could move to clinical trials for cancer-related fatigue quickly

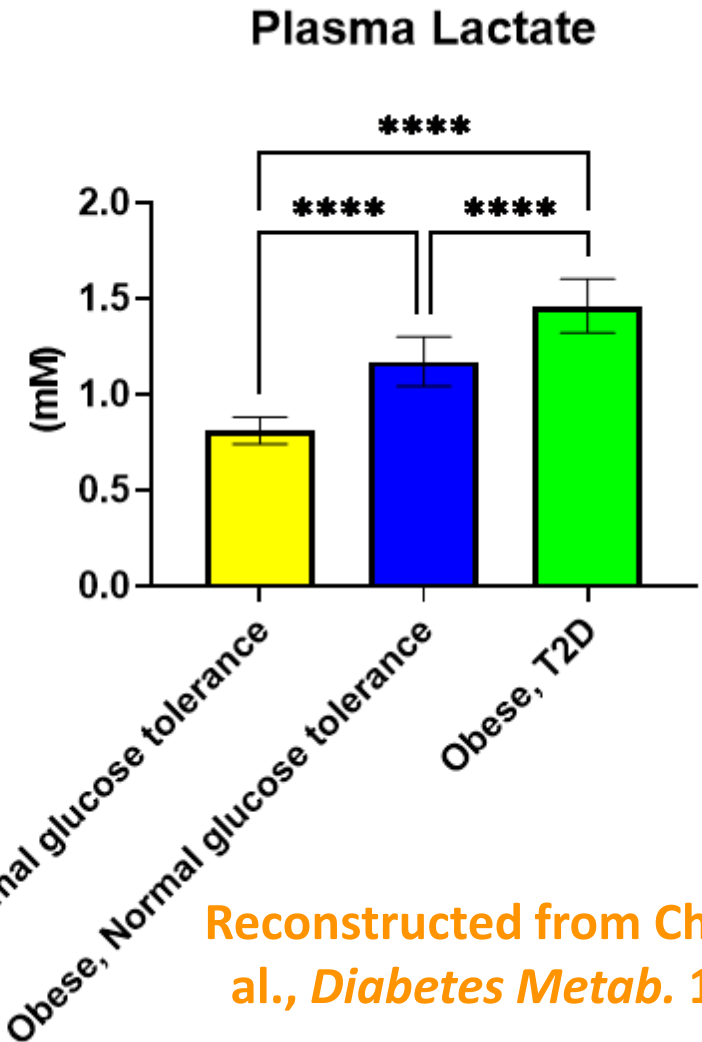


# Implications and potential next steps

- Lactate is elevated in individuals with obesity and type 2 diabetes



Jones et al., *Surgery* 2020



Reconstructed from Chen et al., *Diabetes Metab.* 1993

# Implications (pure speculation)

- Inactivity and poor cardiorespiratory fitness correlate with poor outcomes in individuals with obesity and/or type 2 diabetes
- Reducing circulating lactate in individuals with obesity and/or type 2 diabetes may enhance motivation for movement
- DCA merits consideration to address these issues – could it be an “exercise pill” in the making?

## Exercise in a Pill?



THE ECONOMIC TIMES | Panache

English Edition | Today's ePaper

There will soon be an 'exercise pill', so you don't have to hit the gym ever!

Is an “exercise pill” coming your way?

September 14, 2016



The Exercise Pill: One Swallow, Then Svelte

ANNALS OF SCIENCE

A PILL TO MAKE EXERCISE OBSOLETE

*What if a drug could give you all the benefits of a workout?*

By Nicola Twilley  
October 30, 2017



# Thank you

## Perry Lab

- Ngozi Akingbesote
- Andin Fosam
- Abigail Koomson
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- Zongyu Li, PhD
- Susana Nakandakari, PhD
- Yanitza Rodriguez
- Stephan Siebel, MD, PhD
- **Xinyi Zhang, PhD**

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