Staying Strong Through Chemo

Does electrical stimulation protect skeletal muscle from Doxorubicin toxicity?

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June 24th, 2022

I have no conflicts or competing interests to declare.

Funding for this study was provided by Dr. MacLean's René Guilbeault Research Award

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Université Laurentienne

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What is Doxorubicin?

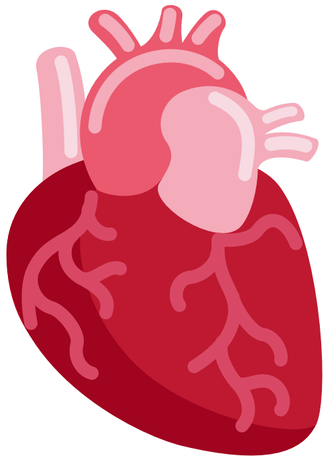
Risks and Benefits

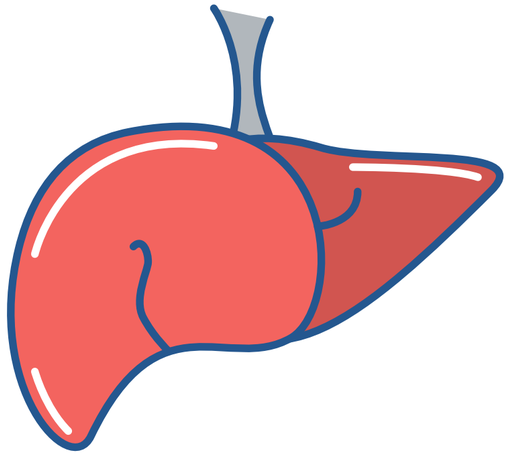
Effective anti-cancer tool

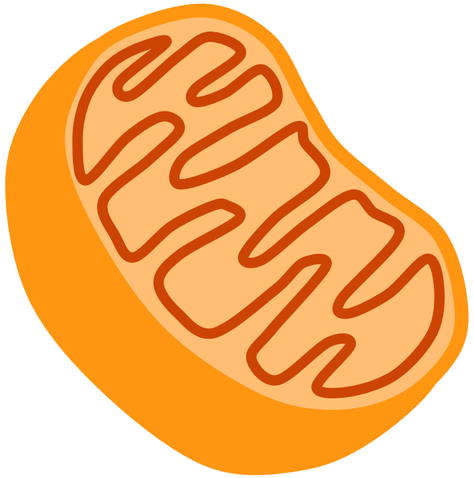
Non-specific + Dose Limited

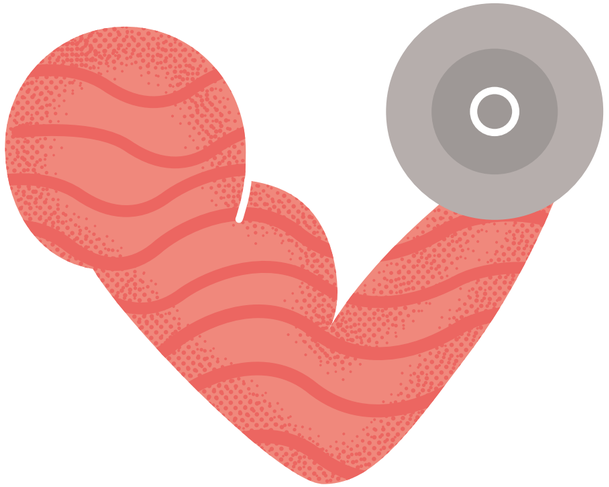
Toxic to healthy tissues

What tissues are most effected?









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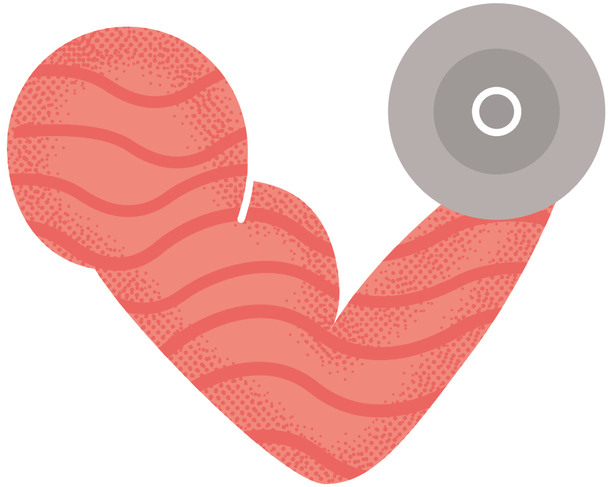


Skeletal Muscle

40% of human body

Required for basic function + metabolism

Indicator of prognosis

Dox-induced myotoxicity

Oxidative stress

Mitochondrial dysfunction

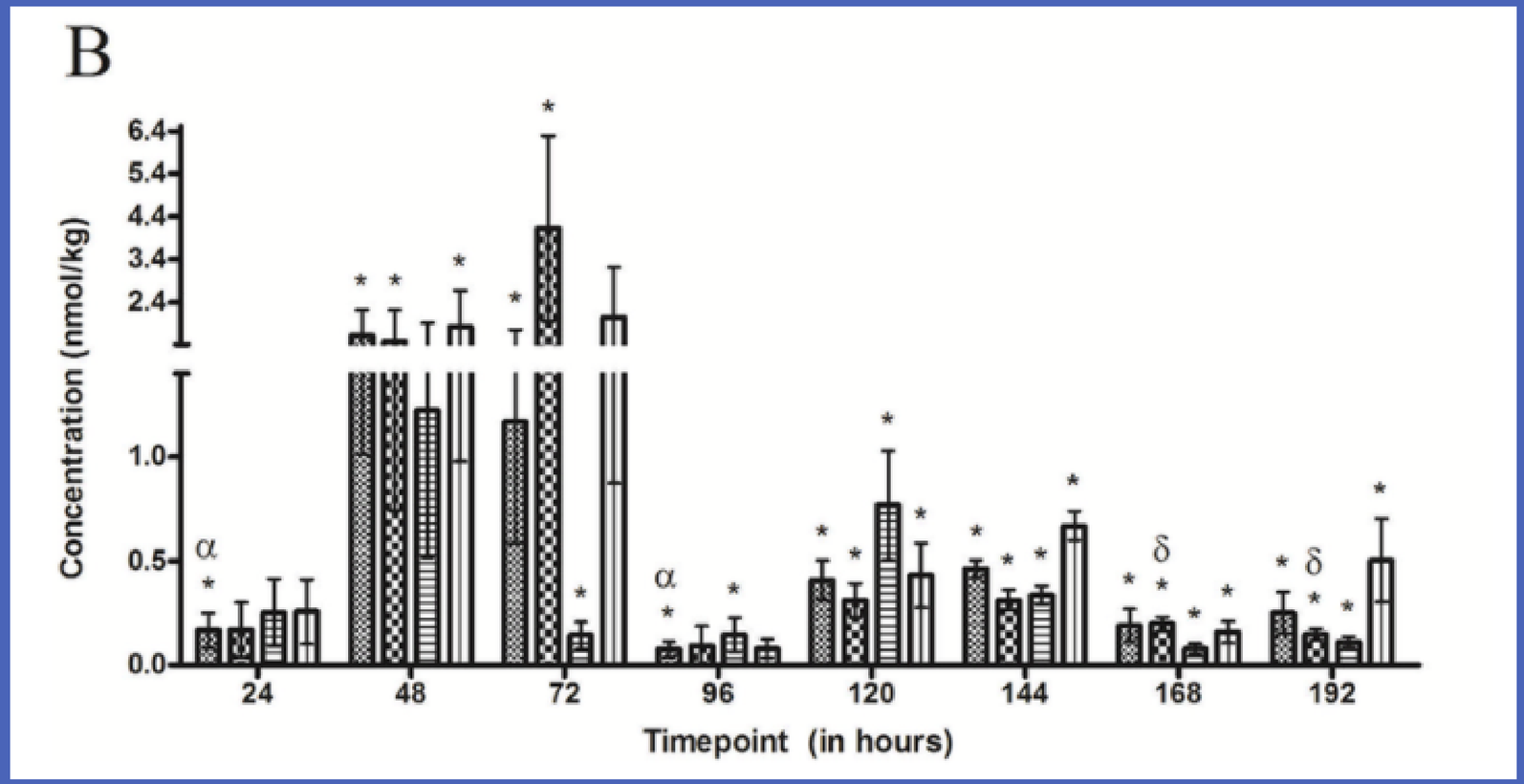
Muscle breakdown

Impaired glucose metabolism

Weakness, exercise intolerance

Gilliam et al., 2013;
Hayward et al., 2013;
Hiensch et al., 2019

To add to basic toxicity... Skeletal muscle is an active site of Dox sequestration



Fabris and MacLean, 2015

How do we protect muscle?

Exercise

Stimulates glucose metabolism

Prevents atrophy, stimulates muscle growth

Reduces intramuscular accumulation?

Smuder et al., 2011; Dickinson et al., 2017; Hinkley et al., 2019; Park et al., 2019

Exercise is HARD! Especially during aggressive chemotherapy

Is there a reasonable alternative?

Electrical Stimulation

Passive “exercise” of muscle

Isolated effects of muscle activity

Viable option for bed-ridden or extremely ill patients

Do various electrical stimulation protocols impact Doxorubicin accumulation and toxicity in skeletal muscle?

Study Aims

- Use electrical stimulation to see if muscle contraction induces Dox efflux

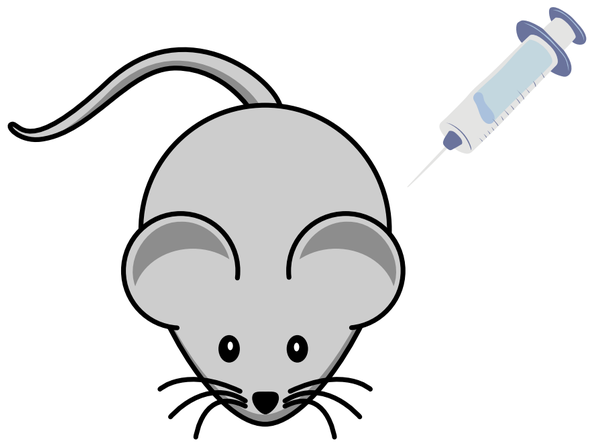
Study Aims

- Use electrical stimulation to see if muscle contraction induces Dox efflux

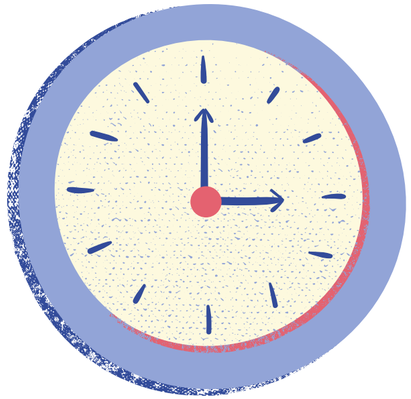
- Does electrical stimulation impact **glucose metabolism** and **muscle breakdown** pathways?

Study Outline

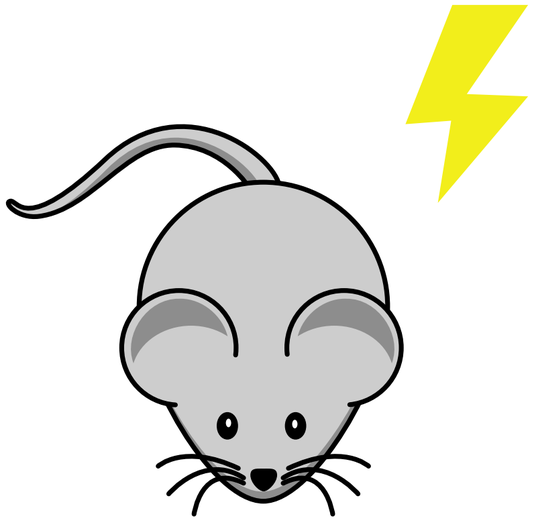
4.5 mg/kg IP Dox



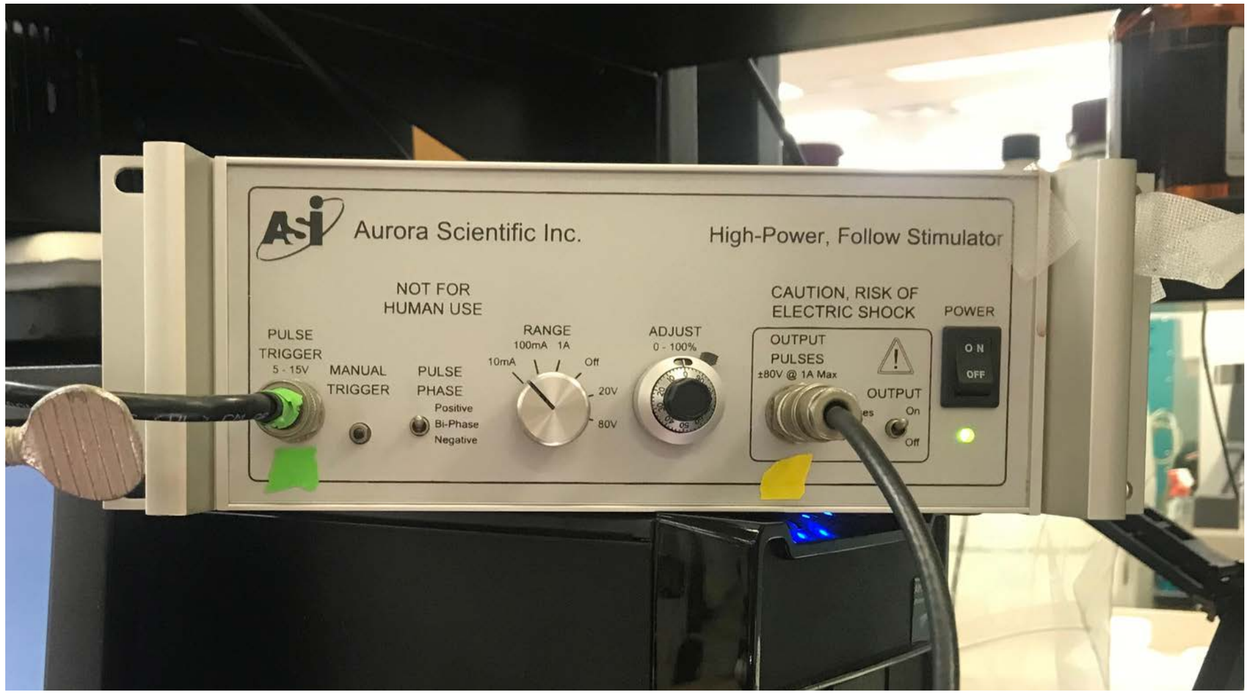
Wait 24 hours

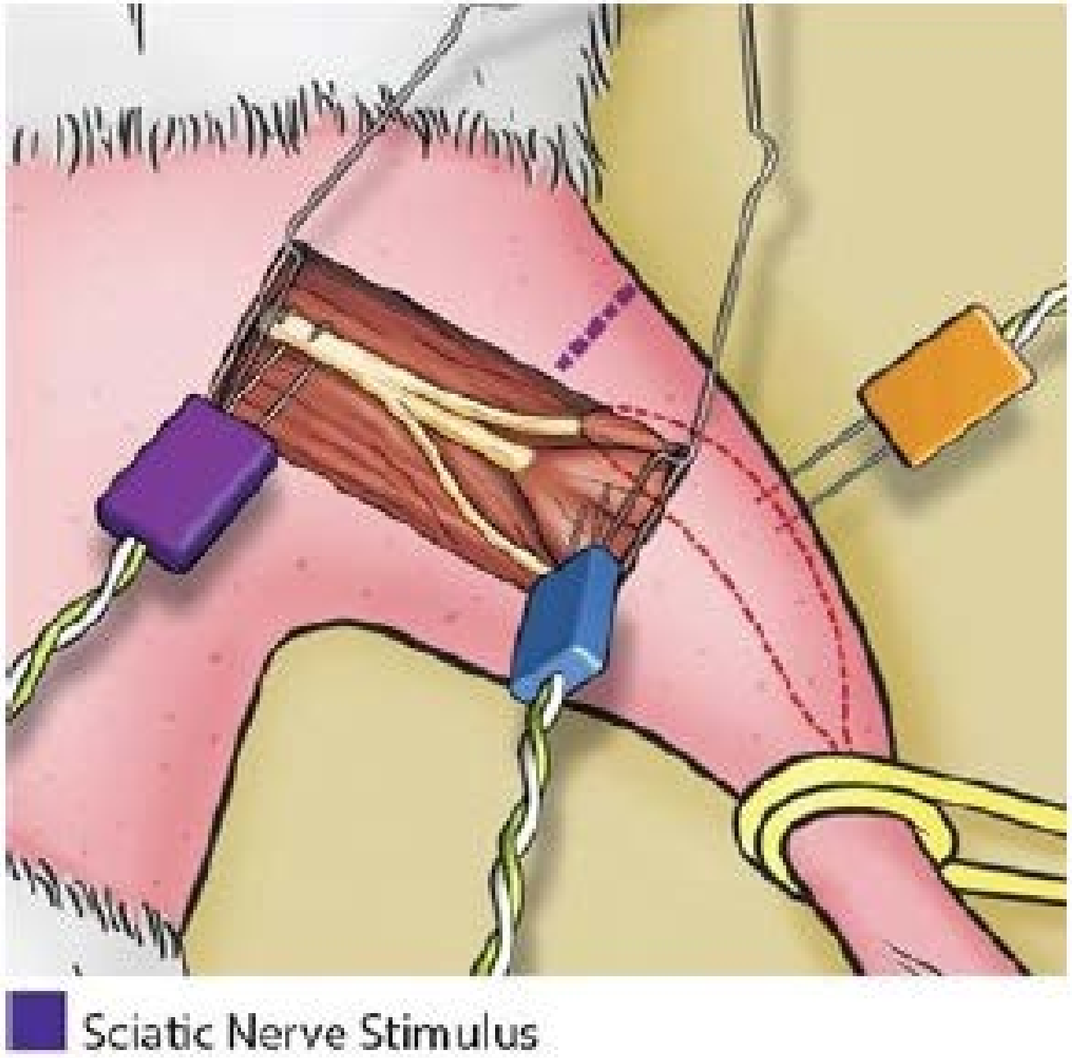


Hindlimb stimulation

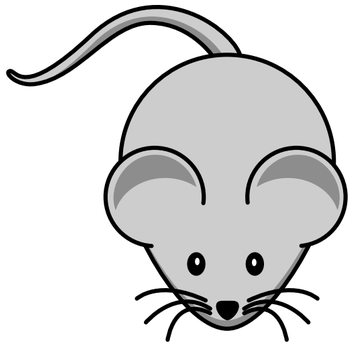


Stimulation on left leg ONLY





Nepomuceno et al., 2016



n= 6/group

1 Hz

3 Hz

5, 15, 30 minutes

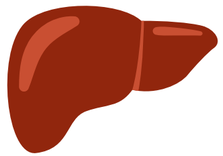
True control group: NO Doxorubicin, NO stimulation (n=6)

Intra-individual control: harvested muscles from the right leg prior to stimulation

Tissue Harvest

Gastrocneumis, Soleus, Plantaris 

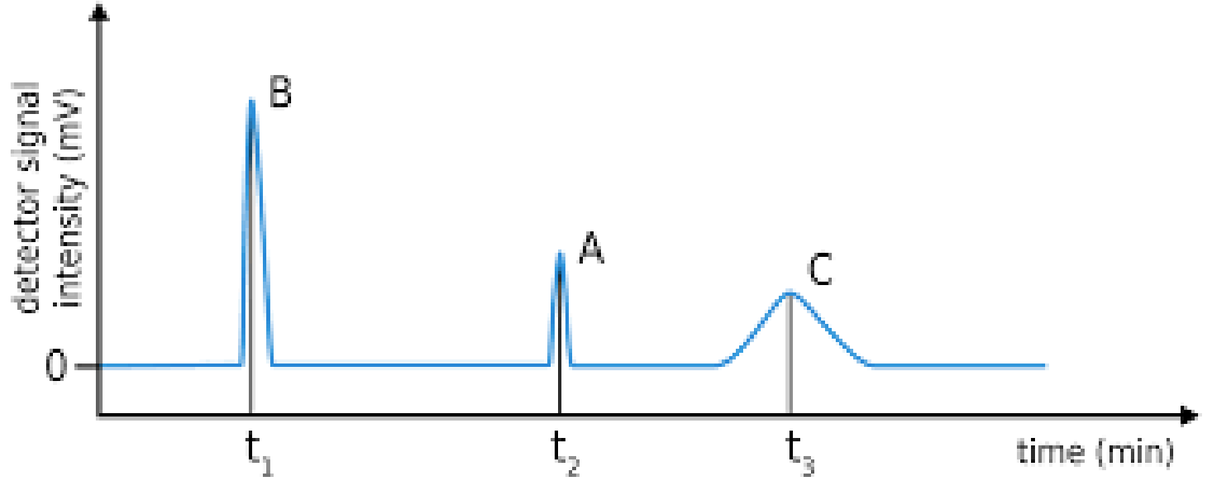
Mixed Venous Blood 

Heart + Liver  

Assays

Aim 1: Doxorubicin accumulation

Determine the quantity of Doxorubicin and Doxorubicinol in muscle and plasma using HPLC



Preliminary Results

Intramuscular Dox/Doxol

No apparent differences (pre vs. post stimulation)

Variability rat to rat

Exercise paradox?

Plasma Dox/Doxol

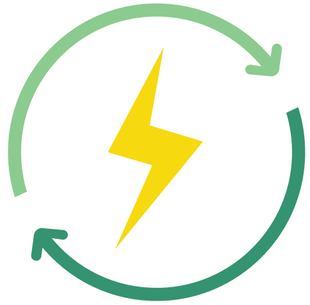
No apparent differences between groups (to be expected)

Variability rat to rat

Assays

Aim 2: Muscle Integrity

Investigate genes and markers that govern energy metabolism, muscle breakdown



Preliminary Results

Glucose Metabolism

No apparent differences across all groups for Glut-4 and AMPK or Rac1 mRNA expression

Need to evaluate transporter activity and location

Muscle Breakdown

Amino Acid profile, Nitric Oxide content, muscle atrophy pathways under investigation

Summary

No acute benefit of muscle contraction on Dox accumulation or **glucose metabolism genes**

Didn't see what we had hoped - but gained valuable insight

Still a ton of analysis left to go!

Next Steps?

- Change timeline
- Comparative Exercise
- Clinical Model

Questions?

Thank you for listening!

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