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Beyond the Symptom: The Biology of Fatigue

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Approaches to study the biology of fatigue in preclinical models: how we study cancer-related fatigue in mice

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Disclaimer and Disclosures

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This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure
This certifies that I, Robert Dantzer, have no financial relationship that is relevant to the subject matter of this presentation.

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Why study fatigue in cancer patients?

Cancer-related fatigue is the most prominent symptom in cancer patients. It is present in 10-20% of patients at time of diagnosis, increases in prevalence and intensity during cancer therapy and persists in up to 20% patients after completion of treatment.

Its mechanisms are still disputed

nature REVIEWS CLINICAL ONCOLOGY

Review Article | Published: 12 August 2014

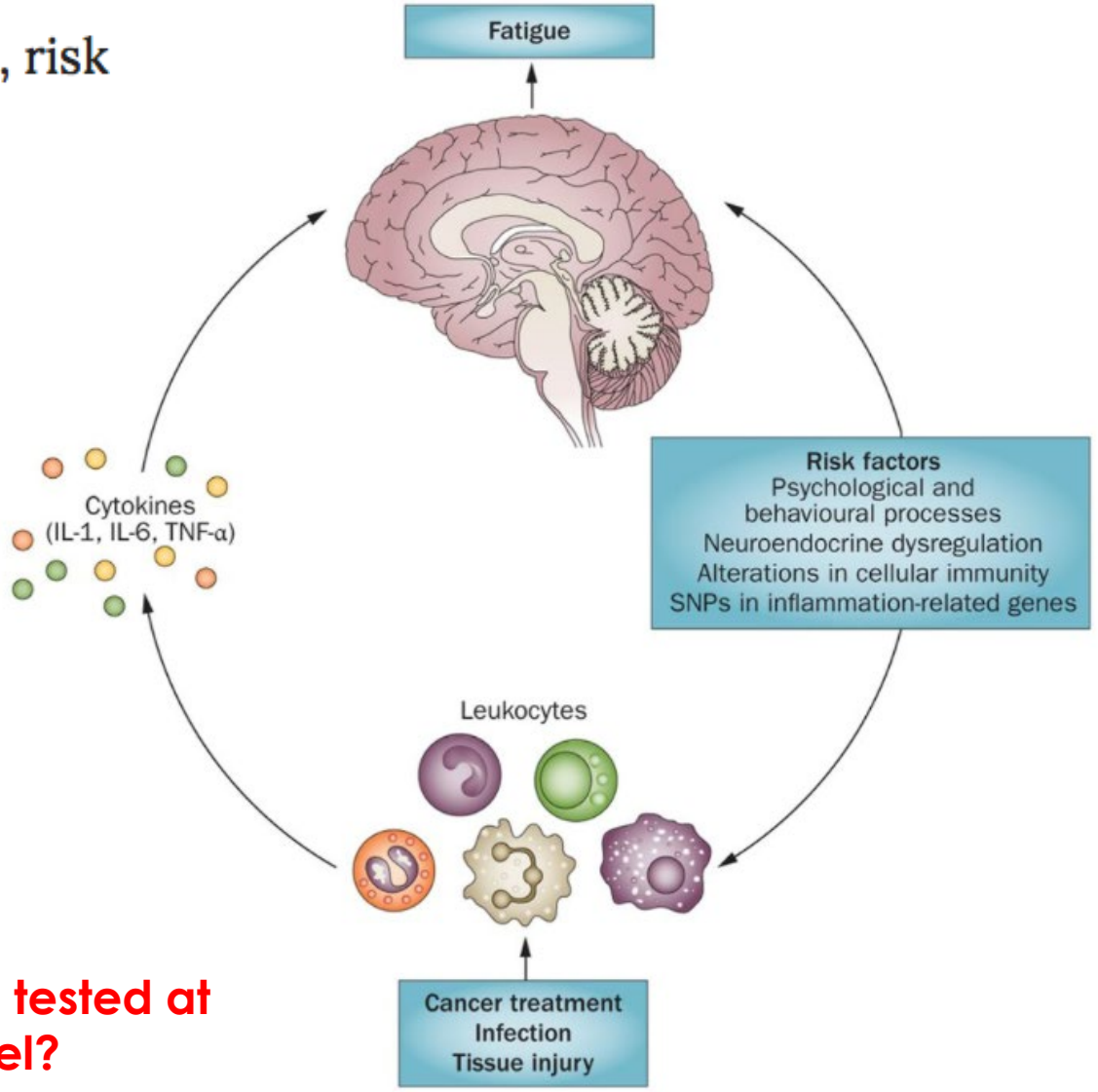
Cancer-related fatigue—mechanisms, risk factors, and treatments

Julienne E. Bower

Nature Reviews Clinical Oncology **11**, 597–609 (2014) | Download Citation

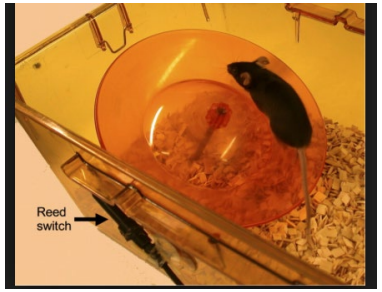
In terms of mechanisms, cancer-related fatigue is currently presented as the result of the propagation of tumor-associated inflammation to the brain

Can this theory be tested at the preclinical level?



Behavioral phenotype of fatigue in mice

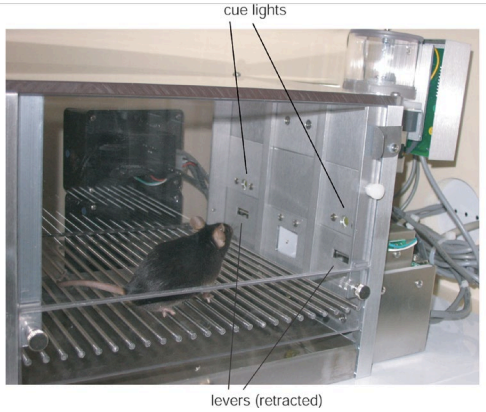
Physical aspect of fatigue (*This requires too much effort, I cannot do it any longer*): measured by decreased ability to engage in an effortful activity



Wheel running behavior

Postulate: Fatigue has to do with perception and valuation of effort

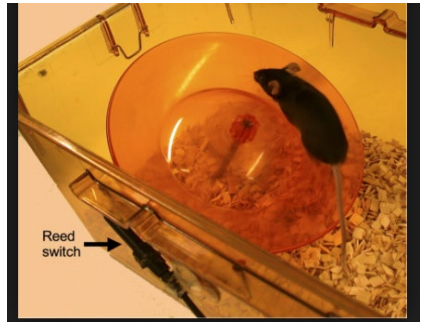
Motivational aspect of fatigue (*This requires too much effort in view of what I get from it, it is not worth doing it any longer):* measured by decreased willingness to engage in a motivated behavior in proportion of the effort needed to obtain the expected reward

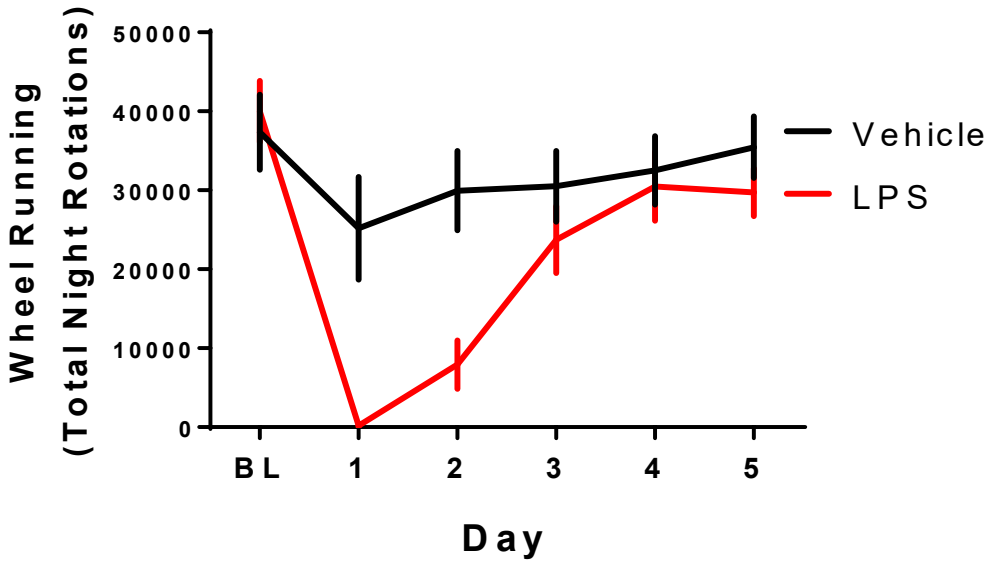


Operant responding (with various schedules of reinforcement)

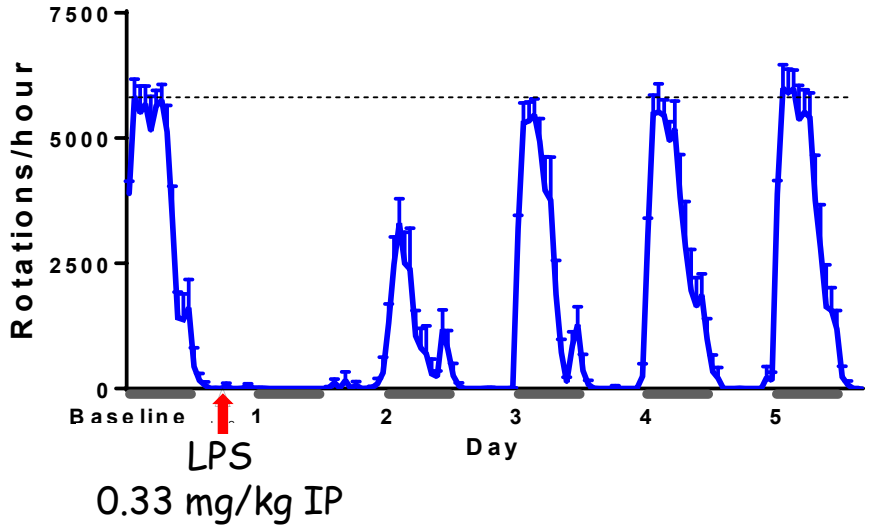
Objective: Are the behavioral phenotypes of inflammation and cancer similar?

Inflammation decreases voluntary wheel running





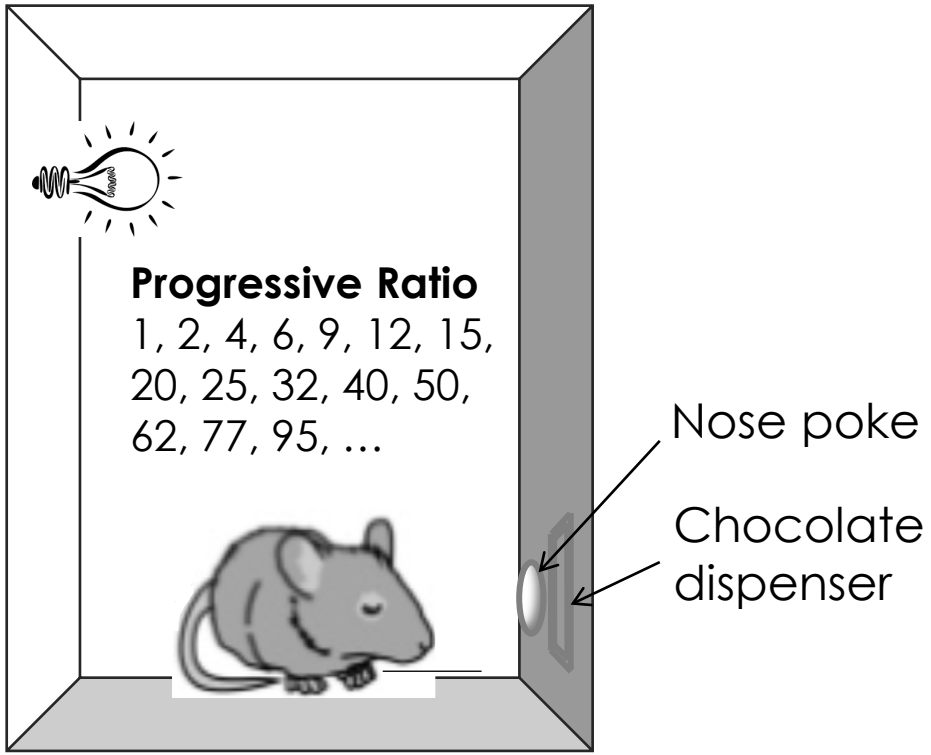
Hourly wheel running

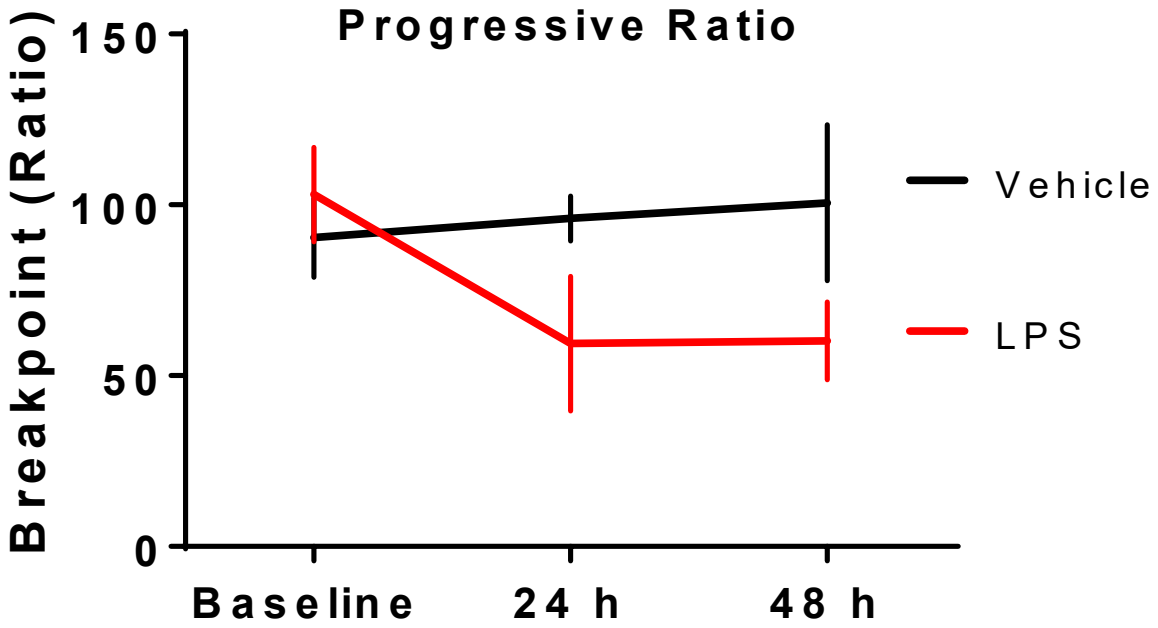


(Vichaya et al., 2019)

Inflammation decrease incentive motivation measured by performance in a progressive ratio schedule of food reinforcement (reward valuation)

Progressive Ratio Schedule of Food Reinforcement

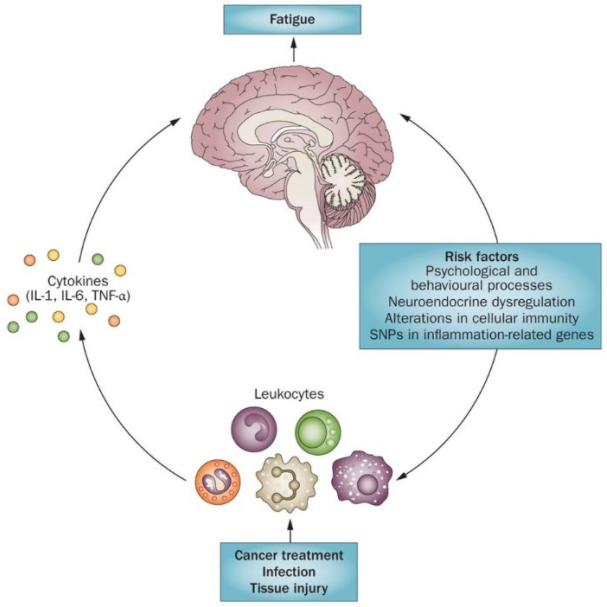




1. Inflammation induces a behavioral phenotype characterized by physical and motivational fatigue

2. Is the behavioral phenotype of cancer similar to the behavioral phenotype of inflammation?

Working hypothesis and experimental design



Tumor/Cancer therapy

↓

Inflammation

- *Cytokines*
- *DAMPs*

↓

Brain

↓

Behavioral fatigue

- Non-inflammatory tumor: HPV-positive head and neck cancer
- Inflammatory tumor: Lewis lung carcinoma

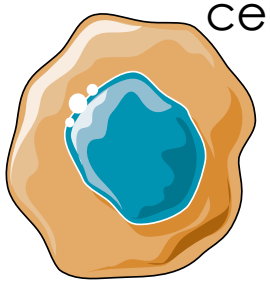
- Blockade by IL-1R1, Myd-88 or TLR4 genetic deletion
- Blockade by CSF1 receptor antagonist (depletes macrophages/microglia)

- Measured by decreased voluntary wheel running ("I cannot do it")
- Measured by reduced motivation ("The reward is not worth the effort")

Tumor growth decreases wheel running activity in a murine model of HPV-related head and neck cancer

Murine tonsil epithelial cells

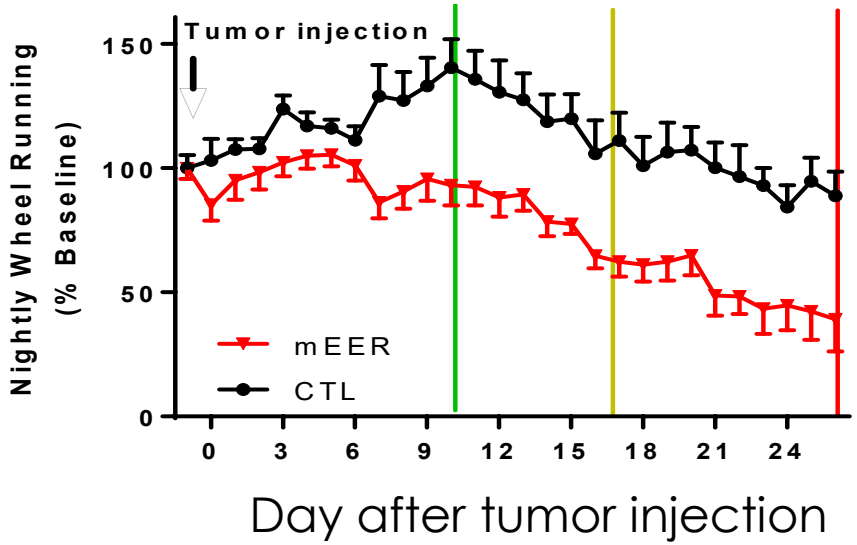
HPV16 E6/E7 + hRas

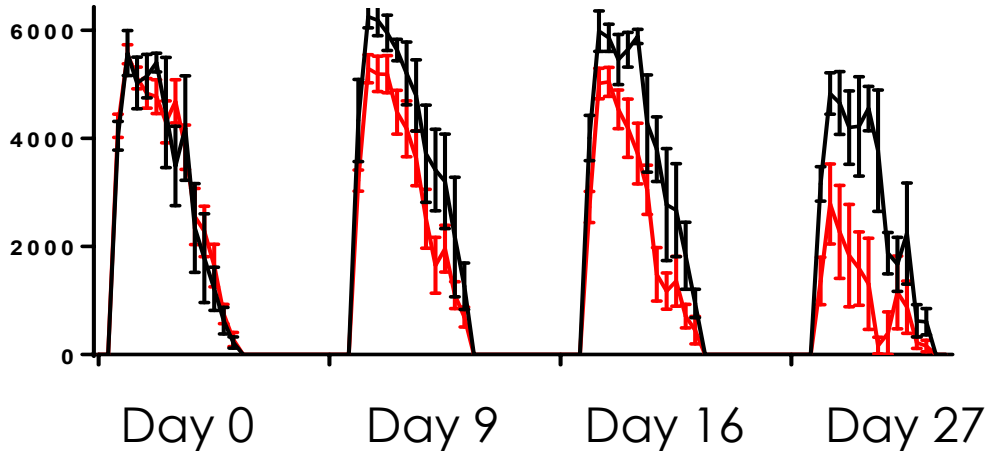


mEER cell line

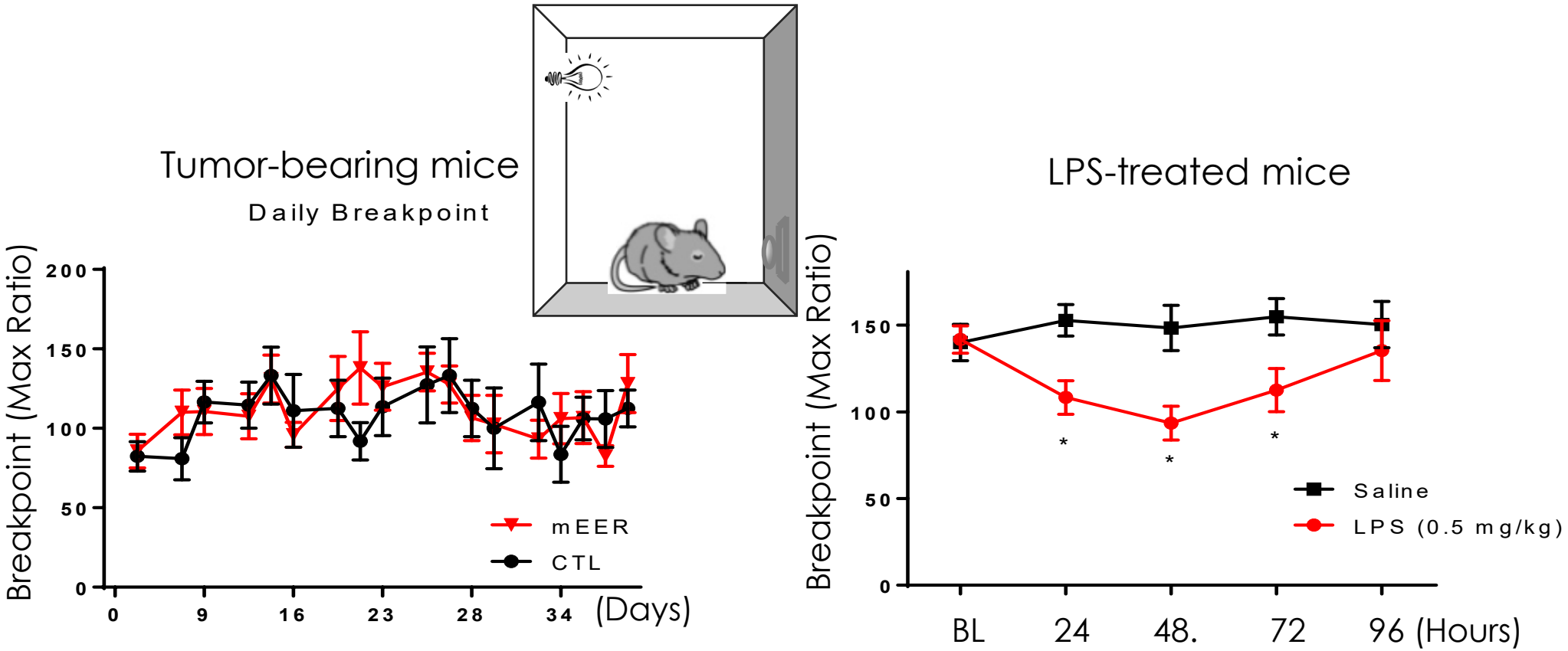
Wheel running

Nightly wheel running (% baseline)





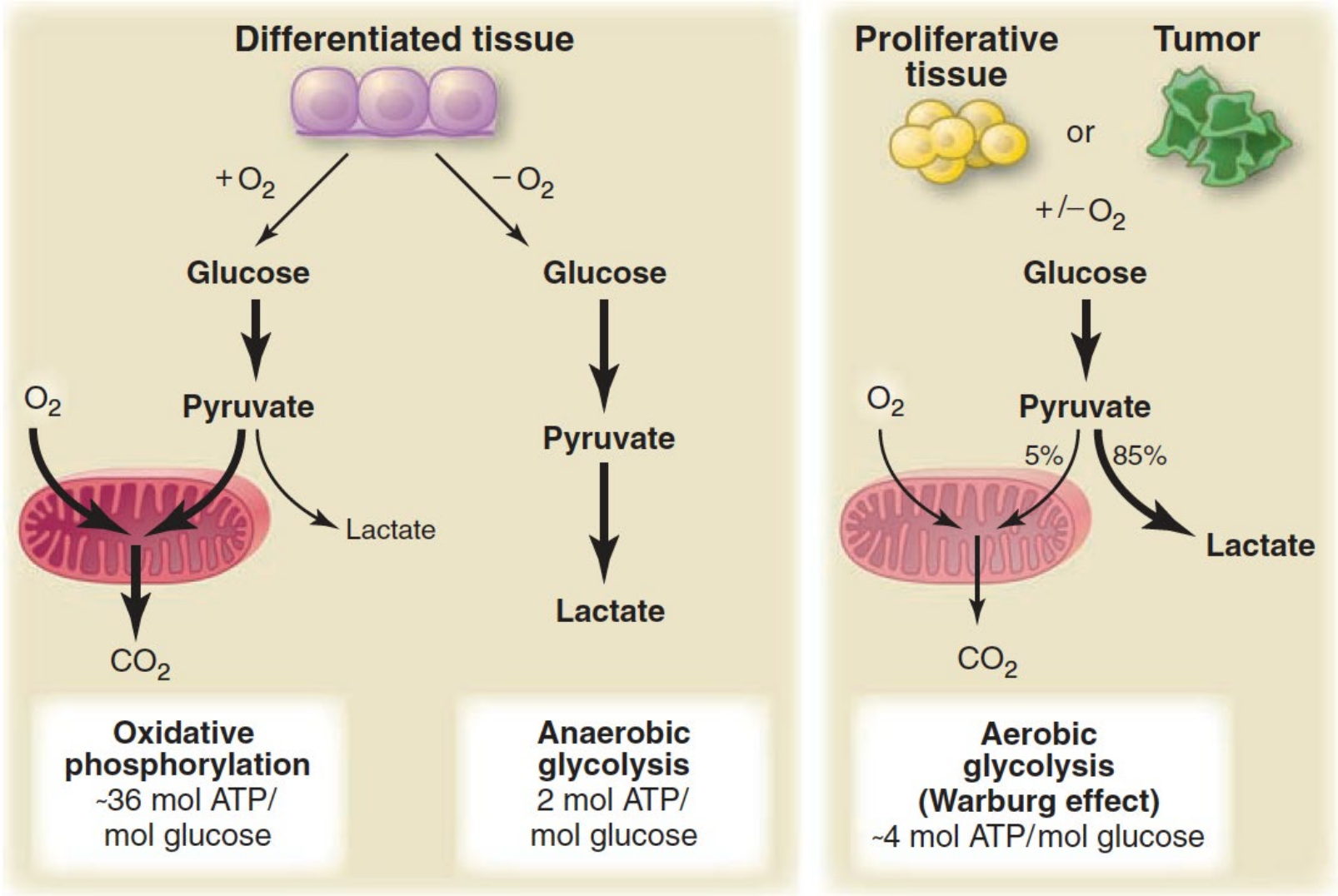
In contrast to LPS tumor growth has no effect on reward valuation



Progressive ratio schedule of food reinforcement

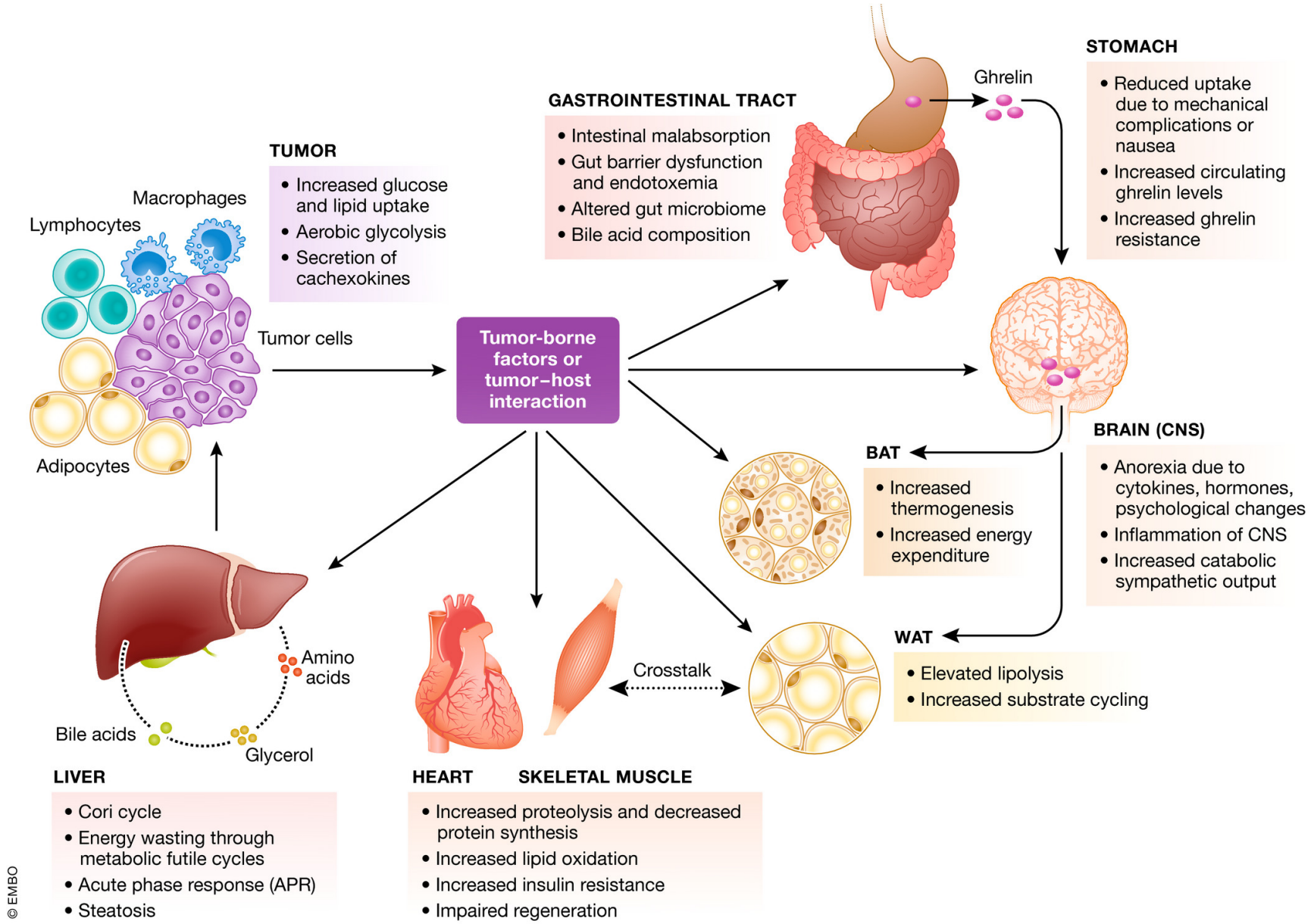
(Grossberg, Vichaya et al., Tumor-associated fatigue in cancer patients develops independently of IL-1 signaling, Cancer Research, 2018, 78, 695-705)

If it is not inflammation, what is it?



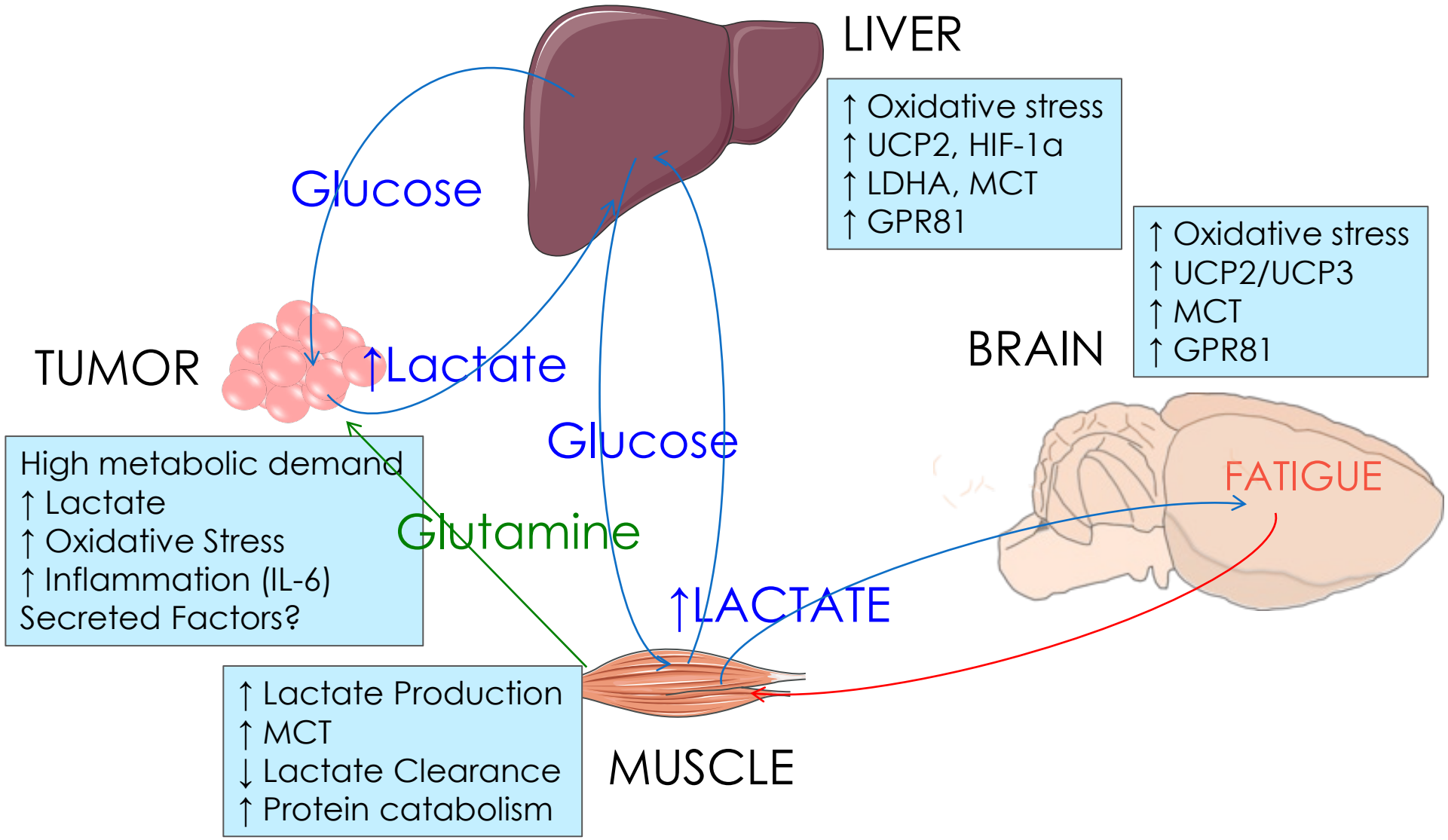
MG Vander Heiden, LC Cantley, CB Thompson, Understanding the Warburg effect: the metabolic requirements of cell proliferation, Science, 2009, 324, 1029-1033

Tumor growth has a metabolic cost

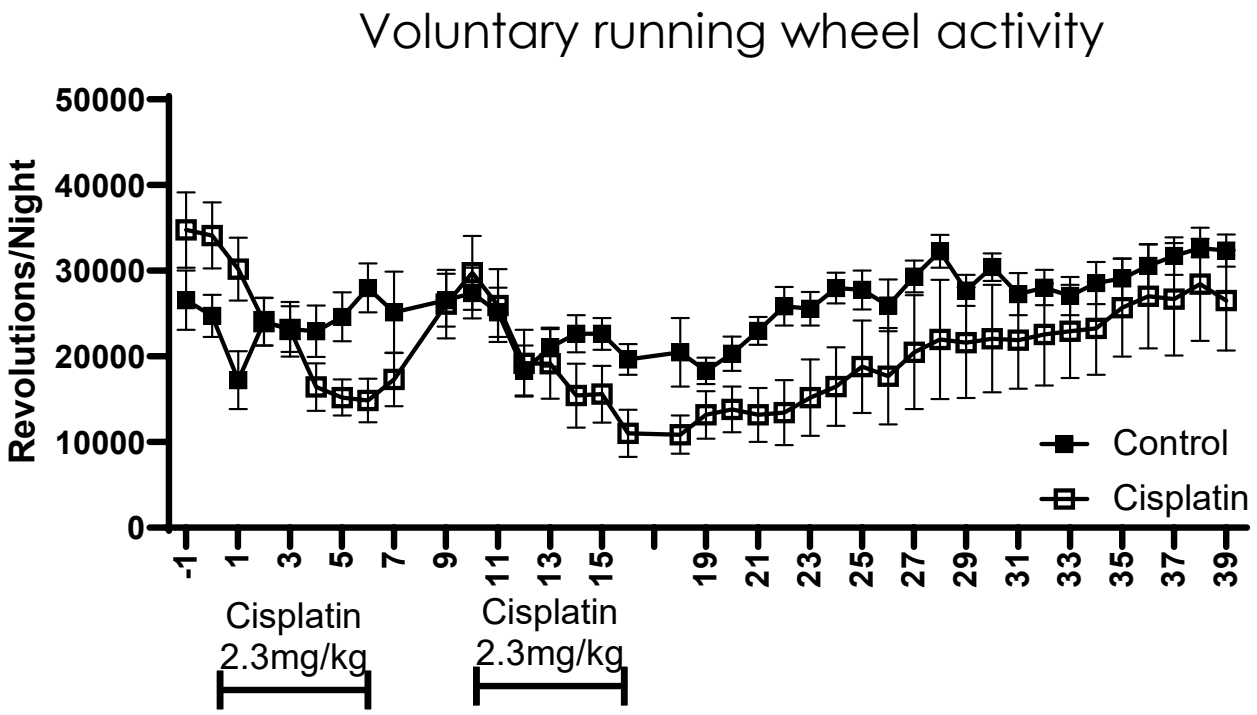


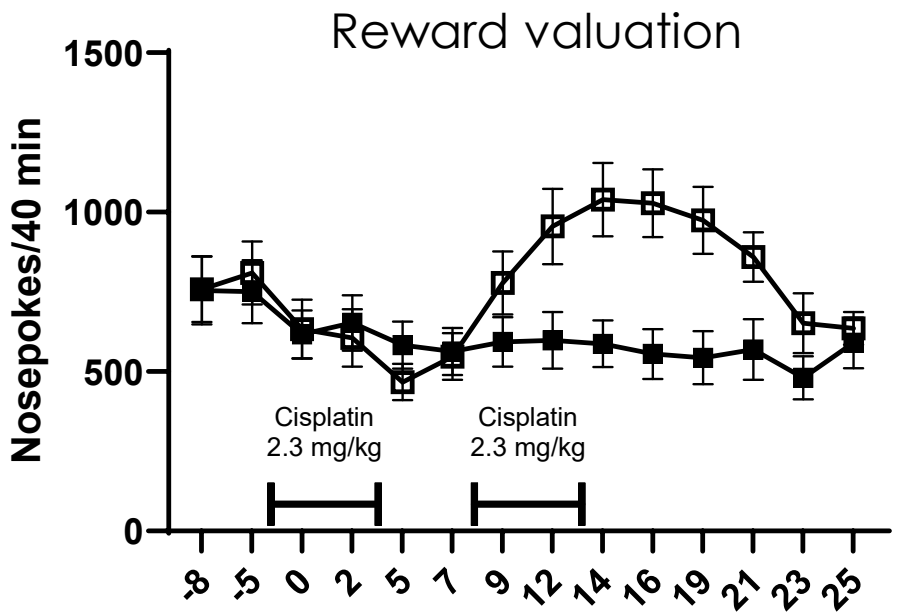
(Rohm M et al., Energy metabolism in cachexia, Embo Rep, 2019)

Competition for the Cori cycle between the tumor and the skeletal muscles



Cancer therapy induces a similar behavioral phenotype: Cisplatin decreases wheel running but increases reward valuation





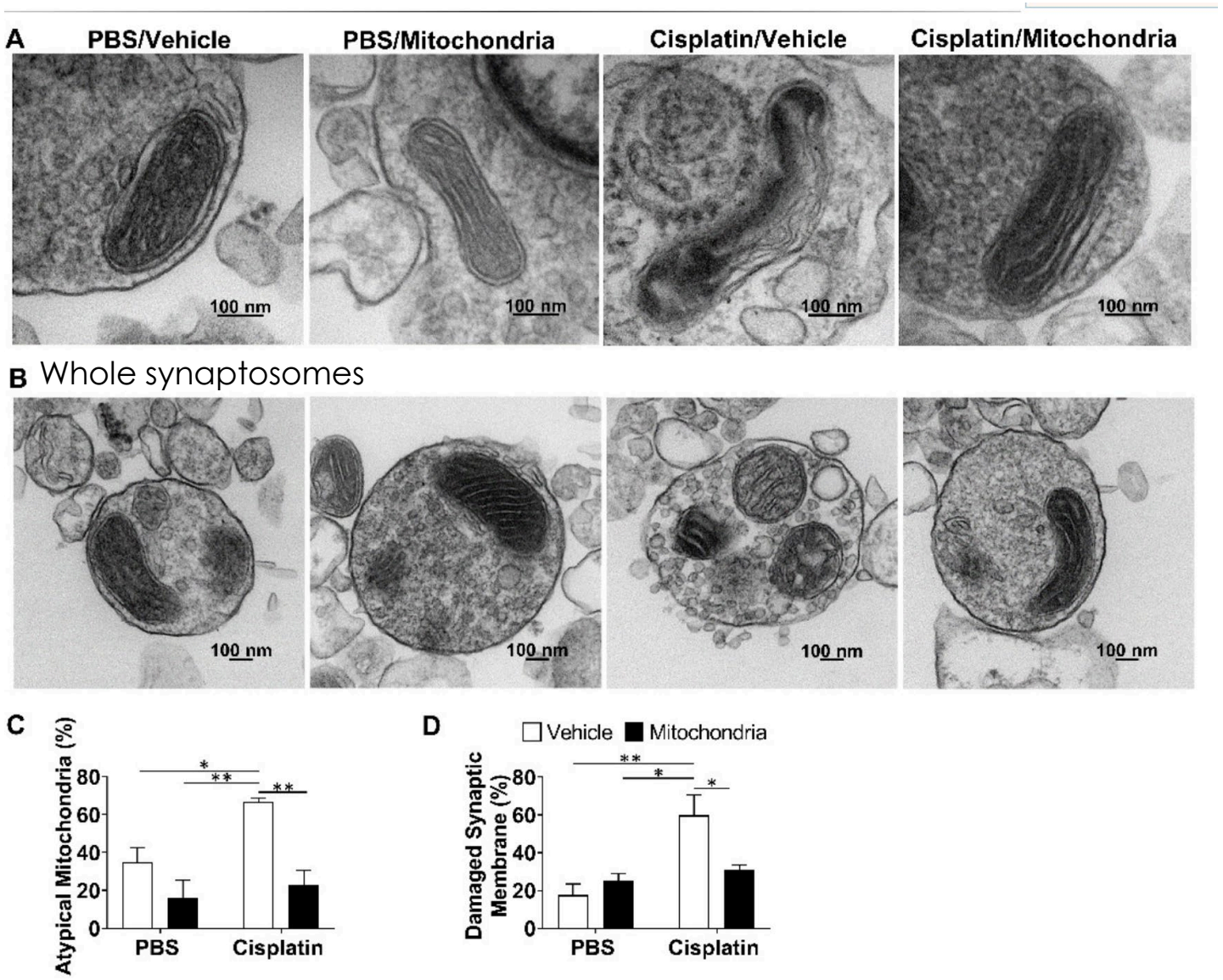
(KA Scott, Unpublished results)

Cisplatin induces mitochondrial dysfunction in metabolically active organs

Cisplatin induces mitochondrial alterations in synaptosomes that can be restored by intranasal administration of mitochondria isolated from human mesenchymal stem cells

(Alexander JF et al., Nasal administration of mitochondria reverses chemotherapy-induced cognitive deficits, Theranostics 2021, 11, 3109-30)

Mitochondria ultrastructure



Summary and perspectives

1. It is possible to study behavioral aspects of fatigue and its mechanisms at the preclinical level

2. Investigation of the full behavioral phenotype of fatigue is important as it shows that inflammation and cancer differ. Inflammation decreases both energy consuming activities and energy procuring activities whereas cancer and its treatment spare energy procuring activities

3. Current mechanistic studies focus on metabolic energy deficit and mitochondrial dysfunction