A Mouse Model of Cancer-Related Fatigue: Prostate Cancer

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Background

- Cancer-related fatigue (CRF) is a dominant symptom for men with prostate cancer related to the cancer and its treatment.[1]
- There are no specific treatments for CRF, attributed to a lack of knowledge of the biologic mechanisms contributing to this pathology.
- Results from preliminary prostate cancer clinical studies demonstrated associations between mitochondrial function and oxidative stress with CRF. [2-6]
- A mouse model is instrumental for controlled and standardized mechanistic studies of CRF, addressing many of the limitations of prior clinical research.[7]

Objective

- The objective of the proposed study is to elucidate biological mechanisms underlying cancer-related fatigue
- Primary Outcome: Determine the metabolic profile of fatigue in a preclinical model of CRF.
  - Target tissues (blood, muscle) will be used to investigate metabolic mechanisms of CRF (Figure 1) : mitochondrial quality and function, hypoxia, metabolomics, and oxidative stress.
  - Comprehensive assessment of these parameters combined with fatigue severity will allow us to identify specific tissues and parameters that may underlie CRF for future therapeutic targeting.

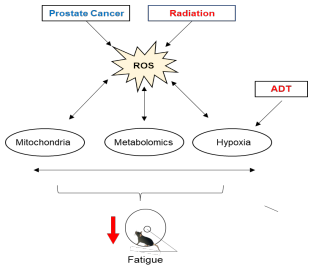

Figure 1. Overall schematic for metabolic mechanisms contributing to cancer-related fatigue. We hypothesize that metabolic dysfunction mediated by ROS secondary to the cancer and cancer treatment results in the fatigue.

Methods

- Male C57BL/6J mice, aged 5 weeks old upon arrival
- Implanted with RM-1 prostate tumor cells
- Randomized to receive prostate cancer treatment
  - Androgen Deprivation Therapy (ADT): enzalutamide (25 mg/kg) via intraperitoneal injection daily for 7 days
  - Radiation Therapy: pelvically irradiated with 8 Gy, 3 days in a row using image-guided irradiator (SARRP by Xstrahl).

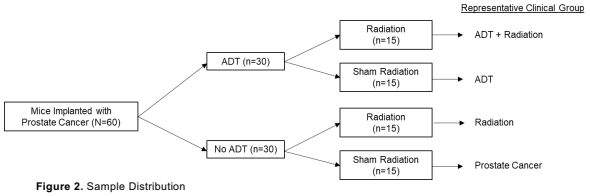

Figure 2. Sample Distribution

- Voluntary running wheels for assessment of fatigue

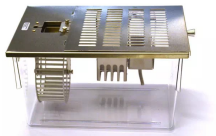

Figure 3. Scurry running wheel
https://lafayetteneuroscience.com/products/scurry-mouse-wheel

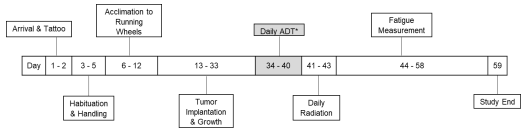

Figure 4. Study Timeline

- Target tissues will be used to investigate metabolic mechanisms. All biologic data will be correlated to our primary outcome of fatigue.

Current Progress

- Our initial model did not exhibit a fatigue effect
- We hypothesize that this occurred because we did not achieve complete testosterone depletion using enzalutamide
  - RM-1 cells represent an aggressive tumor line; therefore, a different approach to therapy may be needed
- Degarelix is used in the clinical setting for more aggressive prostate cancers
- Our preliminary experiments (Figure 4) have shown that one dose of Degarelix results in sustained testosterone depletion
- Next Steps: Repeat the ADT study arm using Degarelix

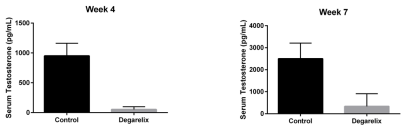

Figure 4. Testosterone Depletion from Degarelix

Expected Outcomes

- This study provides the unique opportunity to take the bedside (our previous clinical studies) back to the bench (animal model of CRF) to further understand the mechanistic underpinnings of CRF.

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