# Developing a pre-clinical model of cancer associated cachexia

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## Significance

In the last three decades, significant breakthroughs in cancer therapeutics have resulted in a 26% decrease in cancer related mortality in the U.S.[1] Yet, as cancer survival rates plateau, select studies project that over the next decade years of life with a disability will increase by close to 25%[2]. These data indicate that, in cancer patients, medical prognosis and functional prognosis need be addressed with distinct clinical approaches. In more recent years, cancer dedicated rehabilitation clinicians have identified the importance of rehabilitation interventions in efforts to improve ability, pain, treatment tolerance, and quality of life related to cancer sequelae[3,4]. Current rehabilitation strategies for cancer patients are primarily rooted in general or neuro-rehabilitation principles. However, in order to optimize functional outcomes in patients with cancer, more knowledge is needed regarding the broad mechanisms by which patients acquire disabilities and are capable of regaining function. For example, our recent unpublished work, within the Shirley Ryan AbilityLab (SRAlab) cancer inpatient rehabilitation population, demonstrates that decreased functional independence measure gains are associated with markers of poor nutritional status and decreased muscle mass, such as low serum creatinine and albumin ($p=0.0029$ and $p<0.0001$, respectively).

Muscle loss despite adequate nutrition that results in progressive functional decline is defined as cachexia - this condition that effects a large fraction of patients across all cancers. For example, in the SRAlab inpatient rehabilitation population, our data shows that a majority of cancer patients have cachexia on admission (Figure 1). Additionally, others have demonstrated that, independent of stage, the lifetime prevalence of cachexia ranges from 50% to 80%% with specific cancers[5]. Cachexia is driven by a number of pathophysiologic mechanisms, including systemic inflammation, that affect muscle and a wide variety of organ systems. To date, no single pharmaceutical strategy has had a significant impact on reversing cachexia or improving quality of life in the cancer population[6], suggesting a multidisciplinary approach is needed[7].

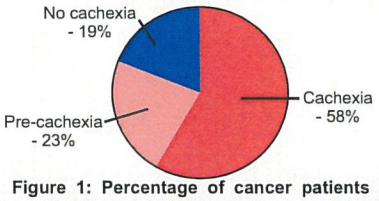


**Figure 1: Percentage of cancer patients with cachexia, pre-cachexia, and no cachexia on admission to SRAlab using consensus criteria for cachexia**

Our long-term goal is the development of translatable rehabilitative interventions for cancer associated cachexia to regain ability and improve quality of life for patients with cancer. In the clinical setting, precise exercise interventions for cachexia have not been rigorously tested[8]. Likewise, in model systems, the effects of exercise on cachexia have not been definitively quantified. Conventional animal models of cancer are not adequate for recapitulating cachexia, as these models were designed to develop robust tumor pathophysiology, leading to animals rapidly succumbing to tumor burden and preventing the investigation of systemic physiology sequalae. The few current animal models of cachexia use rare tumor phenotypes[9–12], limiting translational value. Additionally, these models have not been longitudinally characterized from a functional perspective. As a result, the sequence of change in molecular, metabolic, musculoskeletal, and functional mechanisms during cachexia are unknown. The determination of this sequence is critical prior to the development of targeted exercise or rehabilitation interventions that will prevent or reverse cancer associated cachexia.

## Specific Aim:

**Define a preclinical window for future rehabilitation interventions in a model of cancer-associated cachexia.** Given our prior experience in animal models of cancer[13,14], we propose using one of our novel models of murine cancer-driven cachexia to determine the time course of pathophysiological and functional changes. We will track changes in molecular and metabolic mechanisms during cachexia using standardized inflammatory and catabolic serum markers. In parallel, *in vivo* changes in muscle will be monitored by MR imaging, while functional status will be tracked over time with serial grip strength and activity monitoring. Using the data collected, we will define a window during which pathophysiologic changes occur prior to functional decline. This window will provide an optimized timeframe to target rehabilitation interventions for cachexia (Figure 2).

## Innovations:

1. **Development of a novel pre-clinical rehabilitation model of cancer:** To our knowledge, no prior studies have attempted to specifically design a pre-clinical animal model of cancer that is optimized for the investigation of functional impairments rather than tumor burden. Based on expert recommendations, emerging studies have described novel models of cancer that demonstrate pathophysiologic and translationally relevant cachexia[15,16]. However, these models have not been longitudinally examined for functional outcomes.
2. **Multidisciplinary team-based approach to translational cancer rehabilitation research:** The investigators in our proposed study represent a new collaborative effort. Dr. Jayabalan, a well-established musculoskeletal physiatrist and Dr. Roy, a cancer rehabilitation physiatrist-in-training, have previously collaborated to define cachexia as a clinical problem affecting cancer patients at SRAlab (Figure 1). Now, in order to translate these clinical findings to basic science investigation, a new collaboration with Dr. Binder-Markey, a physical therapist and post-doctoral fellow, will be formed. As Drs. Jayabalan, Roy, and Binder-Markey are experts in exercise science, cancer biology, and muscle physiology,

respectively, all three investigators have distinct areas of clinical and research expertise. This diversity of clinical and research backgrounds is essential to the complex nature of cancer rehabilitation related investigation.

3. **Investigation of an unaddressed and poor understood functional impairment:** While cachexia has been recognized by clinicians as having a significant burden on the chronic disease population[5], including cancer, it has yet to be addressed by rehabilitation scientists. Previous studies of cachexia have been approached from a cancer biology or palliative care approach, with limited expertise from a functional perspective. Our study will be the first to approach cachexia as a primary functional impairment of cancer, with the intent to ultimately design novel exercise and rehabilitative therapies tailored to the underlying biologic mechanisms that drive this condition.

## Approach: Methods & Outcome Measures

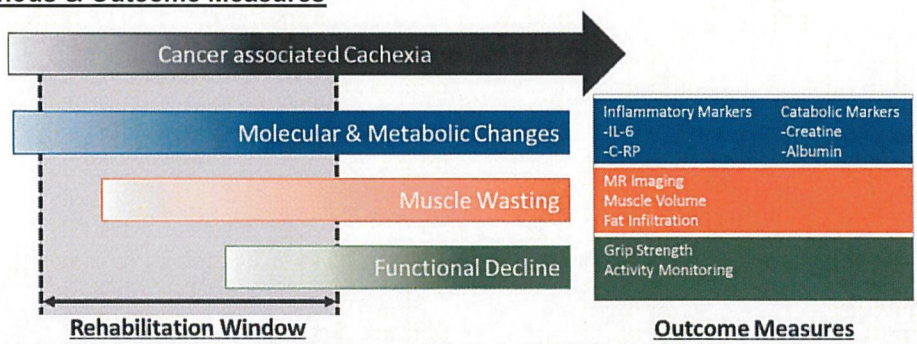


**Figure 2: Schematic of approach to determine preclinical rehabilitation window of cancer-associated cachexia.**

Experts in cachexia biology have identified pancreatic cancer as a novel candidate for basic science modeling of cachexia[15]. Preliminary studies in pancreatic cancer have demonstrated pathologic evidence of cachexia, but have not examined functional outcomes[17,18]. In pilot studies, we have recapitulated muscle wasting in our murine models of pancreatic cancer, and optimized this model in terms of longitudinal functional observation without excess tumor burden, using techniques described previously[19]. Briefly, adult mice will be orthotopically implanted with syngeneic pancreatic tumor cells. A single cohort of mice (6 experimental and 4 control) will be followed for an 8-10 week time course. To monitor cachexia progression *in vivo*, we will use high resolution MR imaging at timed intervals within a single cohort of animals. Due to the spontaneous nature of cancer models, a longitudinal approach will control for tumor and animal related variation over time. These data will be collected in collaboration with the Small Animal Imaging Group at the Center for Translational Imaging at Northwestern University, who are experienced in acquisition and analysis of imaging related to both tumor and muscle pathology. MR imaging analysis will include tumor burden, muscle volume, and fat composition. In tandem, at the molecular level, we will monitor clinically validated markers of inflammation and catabolism that have been tied to cachexia[20], using blood draws at the time of imaging. Specifically we will focus on interleukin-6 and C-reactive protein to track inflammatory burden; and we will use serum albumin and creatinine to monitor protein catabolism. Functional decline will be assessed weekly with grip strength and cage-based running wheels to monitor both strength and basal physical activity, respectively.

## Study Timeline & Deliverables

As outlined in Table 1, the time line of deliverables for this study will include completion of data acquisition and analysis within the first six months, followed by local and national presentations of the preliminary findings, publication of the development of the final pre-clinical model, and ultimately R-award NIH grant applications to investigate the basic science underpinnings of functional decline due to cachexia and mechanism driven rehabilitative therapies for cachexia. The long-term impact of this study will be the development of a pre-clinical cancer rehabilitation animal model of cancer and the characterization of a window of opportunity for treatment of cancer associated cachexia.

**Table 1: Timeline of deliverables and impact**

| | 0-3 months | 3-6 months | 6-12 months | 12-18 months |
|---|---|---|---|---|
| **Deliverables** | -Data acquisition<br>-Data analysis | -Data analysis<br>-Local presentation of findings | -National presentation of findings<br>-Publication submission | NIH R-award applications for rehab mechanisms and targeted therapies |
| **Impact** | -First ever development of a pre-clinical rehabilitation-centered animal model of cancer<br>-Characterization of window for rehabilitation based on pathophysiologic and functional decline due to cancer-associated cachexia | | | |

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