A. SPECIFIC AIMS

Although animal models have demonstrated great promise for the benefits of circadian timing of chemotherapy, important knowledge gaps remain before this work can be translated in clinical practice. While mouse models work with genetically identical mice closely monitored under controlled circadian conditions, humans have significant variability in genetics and circadian rhythms, both of which may influence efficacy and tolerability of chemotherapy. There is a dire need to identify patient-specific factors driving this variability to determine the optimal time to administer chemotherapy in humans. This will ultimately enhance treatment tolerability and efficacy, while improving quality of life.

One important barrier in determining the optimal treatment time is the significant variability in when daytime begins for individual patients. Studies have shown that the hours after light onset (HALO) have a significant effect on circadian dynamics. While patients can self-report this information via surveys, actigraphy devices can be used to tract rest-activity periods and provide a more objective measure of when a patient's day begins. Patient-reported outcomes (PROs) and actigraphy data can also provide important information regarding treatment toxicity and tolerability, which ultimately determine the long-term success of any optimal therapy. Patients who experience low tolerability and higher toxicity struggle to comply with treatment demands and consequently progress earlier than those who do not.

Our *long-term goal* is to improve treatment response by determining patient-specific drivers of circadian differences that can be modulated through alternative treatment timings. We propose to conduct a retrospective analysis of actigraphy, PRO, blood, and tumor volume data from N = 132 gynecological patients undergoing chemotherapy at multiple infusion times. Pre- and post-infusion actigraphy and PRO data will be used to extract important sleep parameters that can ultimately determine patient-specific circadian dynamics. These data will also be used to determine toxicity and quality of life related parameters that are important for long-term treatment compliance. **We hypothesize that circadian dynamics can be leveraged to predict the optimal time to administer treatment to enhance treatment tolerability, reduce treatment toxicities and improve quality of life.** To test our hypothesis, we propose the following aims.

Aim 1: To explore associations between circadian timing of chemotherapy and chemotherapy-related toxicities and quality of life. Hypothesis 1: Patients receiving chemotherapy infusions at the optimal circadian time of day will experience less chemotherapy-related toxicity and better quality of life than patients infused at suboptimal circadian time of day.

1a: Carry out additional chart review on this cohort on timing of treatment, toxicity, and treatment efficacy. Collect infusion times, lymphocyte counts, details on adverse events, tumor volume data and genetic data.

1b: Use statistical analysis to test for impact of treatment time on tolerability, toxicity, and treatment efficacy patient, and explore factors that influence a patient's sensitivity, such as age, menopausal status, and ethnicity.

Aim 2: To develop an innovative mathematical model of circadian dynamics to determine the optimal time to administer chemotherapy to maximize efficacy and quality of life while minimizing toxicity. Hypothesis 2: Drivers of circadian differences can be modulated via mathematical modeling to determine the optimal treatment time.

2a: Develop, calibrate, and validate a mechanistic mathematical model to optimize patient-specific chronotherapy

2b: Carry out in silico study to determine possible benefit of our proposed framework.

The successful execution of this project will provide important evidence regarding the effects of misaligning chemotherapy infusion time with patients' circadian time of day and effective ways to bypass this. We anticipate that this methodology can be extended to additional cancer types and treatment modalities by accounting for differences in efficacy and toxicity relationships.