Study Protocol

Official Title: The effect of peri-surgery blue and amber light exposure in subjects undergoing medical and surgical treatment of cancer.

ClinicalTrials.gov ID (NCT number): 06164691

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Scientific Background: The 5-year survival for pancreatic cancer (all SEER stages combined) is 11%; for those with Stage IV disease, fewer than 3% survive 5 years. Though the biology of this disease, specifically its chemoresistance and ability to evade immune defenses, is complex and just being elucidated, an emerging theme is the generation of neutrophil extracellular traps (NETS). There are now 7 basic, preclinical and translational studies highlighting the role of NETS in accelerating tumor growth, metastasis, and hypercoagulability; notably, in many of those studies methods to reduce NETS (e,g., administration of DNAse) are therapeutic, restoring innate and adaptive immunity in the tumor microenvironment and attenuating tumor growth.

https://pubmed.ncbi.nlm.nih.gov/?term=pancreatic+cancer%5BTitle%5D+AND+neutrophil+extracellular+traps%5BTitle%5D&sort=date

For cancers in general, the list of publications is 75.

Undoubtedly there are mechanisms in addition to NETosis (i.e., generation of NETS) by which this cancer and others can thwart immunosurveillance, including dysfunction in immune cell (monocytes, macrophages, lymphocytes) antigen processing, MHC class I and II, and antigen presentation. Regardless there is immense interest and active research in developing methods to restore immune competence and even specifically targeted immunotherapy, for the treatment of a variety of cancers.

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Related is the field of study entitled chronotherapy. More and more human observational and clinical trials underscore the relationship between circadian rhythms and outcomes agnostic to the specific disease of study. For cancer alone, there are now N=63 studies that highlight the dependence of medical and surgical outcomes in the treatment of cancer on the time of day at which the therapy is delivered.

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Specifically, the collective evidence for cancer have created a biological and clinical conceptual paradigm in which the delivery of therapy during the active circadian phase (i.e., day for diurnal mammals, night for nocturnal mammals) reduces the side effects from chemotherapy (e.g., gastrointestinal), enhances completion of the full chemotherapeutic regimen, and reduces tumor growth, metastasis, and survival. The circadian mechanisms regulating this benefit have yet to be defined. However, recent studies identify the importance of the circadian clock protein Rev-Erbα (NR1D1). In this studies, pharmacological enhancement of Rev-Erbα activity was observed to be lethal in cancer and oncogene senescence in cell and small animal based studies.1,2 The authors conclude that means by which to augment Rev-Erbα should be further studied in cancer biology and treatment.

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Within each cell is a circadian clockwork of proteins that dovetails with the molecular machinery regulating cell phenotype. These peripheral clocks are synchronized across the entire organism by the master central clock of the suprachiasmatic nucleus (SCN). Each day, light travels in

through the eye to the SCN, and via the autonomic nervous system (ANS), pineal gland, and hypothalamic-pituitary adrenal (HPA) axis, coordinates a temporal program of physiologies, such as enhancing immune competence. This system is maximally entrained by the short wavelength visible blue spectrum. Our lab has been studying circadian rhythms and clock biology for nearly a decade. We have applied blue light in 4 distinct models to reduce tissue injury: ischemia/reperfusion of the liver and kidney3, intraabdominal sepsis4, and pneumonia.5 In our studies of sepsis, we identified an optic-parasympathetic pathway through which blue light elevated the expression of the clock protein Rev-Erbα within the spleen and bolstered a splenic population of CCR2+ inflammatory monocytes.4,5 Tissue resident macrophages (e.g., the lung) also exhibited increased Rev-Erbα in mice exposed to blue light. This enhanced bacterial clearance and increased survival 4-fold. Notably, a Rev-Erbα agonist (SR9009) replicated the effects of blue light, augmenting bacterial clearance and prolonging survival, whereas mice deficient in Rev-Erbα were no longer protected by blue light, nor were mice that had undergone splenectomy.4,5 In both I/R and sepsis the enhanced immune competence was accompanied by reduced neutrophilic inflammation, the formation of NETS, and bystander tissue injury. More preliminary data from single cell RNA seq and gene ontology (GO) enrichment analyses direct our attention to unique populations of monocytes and B cells that emerge predominantly in mice exposed to blue light. From these data an innovative paradigm emerges, integrated at the molecular, cellular, and organismal levels, in which neurophysiologic pathways converge on the bone marrow and spleen and tissue resident immune cell population to set the clock protein machinery of immune cells to an 'active day,' characterized by elevated Rev-Erbα. This recruits a highly functional population of monocytes enriched in Major Histocompatibility Complex class II (MHC II) and antigen presentation, Type I Interferon (IFN-I) responses, and cellular defense. This also induces development of a cluster of B cells, expressing a cluster of genes enriched in MHC II, actin assembly and associated signaling pathways, including PI3K-AKT, and immunoglobulin production. These support an immune cell phenotype vital to an efficient immune response to a variety of stimuli.

Our murine studies suggest that exposure to blue (442nm) light, by comparison to ambient white or amber (617nm) light, improves immune competence by augmenting immune cell Rev-Erbalpha expression and activity. A common theme in all of these preclinical models is an enhancement in immune competence with enhanced antigen processing, MHC class I expression, and antigen presentation; reduced neutrophilic inflammation and NET formation, and enhanced competence of mononuclear cells when animals or humans are exposed to blue light. Note that these physiological and biological pathways induced by blue light appear to converge on Rev-Erbα, and in preclinical studies, a Rev-Erbα agonist (SR9009), the same used in the aforementioned studies of cancer, perfectly replicated the effects of blue light (see references below). These are directly relevant to the current focus of this IRB application on cancer.

The ability to enhance the host response/tolerance to chemotherapy and major operations and directly augment the immune response to the cancer itself offers immense potential to improve patient care. Importantly, the risk of light is minimal; we and others have never identified an adverse event in either mice or humans exposed to bright blue light. Thus, the intervention of exposing a patient to a characteristic spectrum of light carries a very large benefit:risk ratio. The results of these studies may be directly applicable to a more generalized population of patients being treated for cancer.

Randomized Controlled Trial Crit Care Med. 2018 Aug;46(8):e779-e787.
doi: 10.1097/CCM.0000000000003190.

Blue Light Enhances Bacterial Clearance and Reduces Organ Injury During Sepsis
https://pubmed.ncbi.nlm.nih.gov/29727369/
https://pubmed.ncbi.nlm.nih.gov/?term=blue+light+AND+rosengart&sort=date

1 Shen, W. et al. SR9009 induces a REV-ERB dependent anti-small-cell lung cancer effect through inhibition of autophagy. Theranostics 10, 4466-4480, doi:10.7150/thno.42478 (2020).
2 Sulli, G. et al. Pharmacological activation of REV-ERBs is lethal in cancer and oncogene-induced senescence. Nature 553, 351-355, doi:10.1038/nature25170 (2018).
3 Yuan, D. et al. Blue light reduces organ injury from ischemia and reperfusion. Proc Natl Acad Sci U S A, doi:10.1073/pnas.1515296113 (2016).
4 Lewis, A. J. et al. Blue Light Enhances Bacterial Clearance and Reduces Organ Injury During Sepsis. Crit Care Med, doi:10.1097/CCM.0000000000003190 (2018).
5 Griepentrog, J. E. et al. Frontline Science: Rev-Erbalpha links blue light with enhanced bacterial clearance and improved survival in murine Klebsiella pneumoniae pneumonia. J Leukoc Biol, doi:10.1002/JLB.4HI0519-155R (2019).

Study Objectives: The primary purpose of this study is to test whether exposure to blue (442nm) light or amber (617nm) light, by comparison to ambient white fluorescent light, improves 1) the immune and oncological response to neoadjuvant chemoradiation therapy; 2) side effects and toleration to neoadjuvant chemoradiation therapy; 3) sleep (PSQI), pain control (BPI), functional status (Karnofsky), and quality of life (WHOQOL-BREF); and 3) survival in patients with 1) pancreatic cancer and 2) rectal cancer.

We incorporate appropriate control subjects: subjects matched by cancer type, stage, and age who undergo the same medical and surgical best practice care but are not exposed to any modulation of environmental light (i.e. ambient white fluorescent light).

We will analyze the blood (10mL) isolated from subjects for the following parameters: 1) monocyte function; 2) inflammatory markers; and 3) circadian clock markers. We will assess the following clinical outcomes of interest: 1) tolerance of neoadjuvant chemotherapy and radiation therapy; 2) sleep (PSQI), pain control (BPI), functional status (Karnofsky), and quality of life (WHOQOL-BREF); 3) clinical and pathological complete response; and 4) all-cause survival.

We hypothesize that exposure to blue (442nm) spectrum light, by comparison to amber and ambient light, induces monocyte Rev-Erb alpha expression, improves tolerance of neoadjuvant chemoradiation therapy (e.g., reduced gastrointestinal complications), increases completion of the full neoadjuvant chemoradiation therapy, improves quality of sleep and quality of life, augments the biological (i.e., reduced NETS in the blood and specimen) and oncological response (i.e., greater rate of complete response) to neoadjuvant chemoradiation therapy and improves survival.

Study Design & Methods: Total number of subjects to be enrolled at this site: 238.
This study is an experimental investigation of exposure to blue (442nm) light, amber (617nm) light, or ambient white light in subjects undergoing neoadjuvant chemoradiation therapy and/or surgery for either pancreatic cancer or rectal cancer.

It is an open-label, unblinded, prospective study. There are six (6) different groups with two (2) different cancers and three (3) different lighting conditions.

There are a total of six (6) groups:

Pancreatic Cancer
1. Group 1 cohort will be exposed to bright (1700 lux) blue (peak 442 nm) light for 4 hours each morning for 3 days prior to and 3 days following each chemotherapy infusion.They will be exposed to bright (1700 lux) blue (peak 442 nm) light for 1 hour each morning during radiation treatments.

2. Group 2 will be exposed to bright (1700 lux) amber (peak 617 nm) light for 4 hours each morning for 3 days prior to and 3 days following each chemotherapy infusion.They will be exposed to bright (1700 lux) amber (peak 617 nm) light for 1 hour each morning during radiation treatments.

3. Group 3 will be exposed to usual, ambient white lighting of the environment during chemotherapy and radiation treatments.

Rectal Cancer
4. Group 1 cohort will be exposed to bright (1700 lux) blue (peak 442 nm) light for 4 hours each morning for 3 days prior to and 3 days following each chemotherapy infusion.They will be exposed to bright (1700 lux) blue (peak 442 nm) light for 1 hour each morning during radiation treatments.

5. Group 2 will be exposed to bright (1700 lux) amber (peak 617 nm) light for 4 hours each morning for 3 days prior to and 3 days following each chemotherapy infusion.They will be exposed to bright (1700 lux) amber (peak 617 nm) light for 1 hour each morning during radiation treatments.

6. Group 3 will be exposed to usual, ambient white lighting of the environment during chemotherapy and radiation treatments.

Randomization will achieved with block randomization on the following characteristics:
a. Type of cancer: group 1: pancreatic cancer; group 2: rectal cancer
b. Stage of cancer as defined by Tumor Node Metastasis classification
b. Age (<55 years, >/= 55 years)

Eligibility Criteria:

Inclusion criteria:
1. greater than 18 and less than 65 years of age
2. adenocarcinoma of the pancreas (unresectable) or adenocarcinoma of the rectum (stage II or III)

Exclusion criteria:

1. Prior chemotherapy (inability to determine the integrity of the immune response)
2. Autoimmune disorder, immunosuppression therapy, or immunocompromised state (inability to determine the integrity of the immune response)
3. Blindness or other significant vision disorder or prior traumatic brain injury (the inability to determine the integrity of functional optic and suprachiasmatic pathways)
4. Hematological disease - e.g., myelodysplastic syndrome, leukemia (inability to determine the integrity of the immune response)
5. Bipolar disorder or schizophrenia (potential heightened symptoms)
6. Refusal/ineligible to undergo neoadjuvant chemotherapy and/or radiation

Statistical Considerations:

1. Survival:

a. Assuming a median survival of 198 days for patients with stage IV pancreatic cancer who undergo chemotherapy, a two-sided alpha=0.05, and beta=0.20 (power of 80%), we will need n=36 participants in each group to detect an effect size of a Hazard Ratio of 2 for all-cause survival (doubling in survival rate).

2. Biological Parameters:

b. The recruitment of n=36 participants into each group will enable us to detect the following difference in proportion of participants experiencing a >90% reduction in serum CA19-9 and CEA concentrations: 23% vs. 55%.

We do anticipate approximately 10% attrition, and thus, will include a total of N=238 subjects into this study.