**Project Description**

**HYPOTHESIS:**

The long-term objective of this work is to investigate the hypothesis that the growth inhibitory properties of naltrindole and other opioids on multiple myeloma cells can be exploited for the treatment of this disorder. We present evidence that naltrindole does indeed inhibit the growth of human multiple myeloma cells in culture. We propose to use human multiple myeloma cells as a model to investigate the growth inhibitory properties of naltrindole, as well as the effects of combining naltrindole treatment with other anti-myeloma therapeutic agents.

Development of tolerance to opioids is a problem during prolonged opioid therapy for pain relief, which most multiple myeloma patients require. Antagonism of δ-opioid receptors with naltrindole can attenuate the development of tolerance to morphine as well as decrease withdrawal symptoms (Abdelhamid et al., 1991). We propose that naltrindole has the potential to be an important addition to current multiple myeloma therapies, based on its dual action to inhibit multiple myeloma cell proliferation and its ability to attenuate the development of tolerance to the analgesic effects of morphine. We hope these studies will lead to enhanced treatment regimens of current and future multiple myeloma therapies.

**PROJECT DESCRIPTION** (Include design, methodology, data collection, techniques, data analysis to be employed and evaluation and interpretation methodology)

**Specific Aim 1.** *Investigation of additivity/synergy in the growth inhibitory properties of naltrindole with other anti-myeloma therapeutic agents using a human multiple myeloma cell model.* We have found that naltrindole inhibits growth of human multiple myeloma cells in a concentration dependent manner. We have also observed additivity in inhibition of multiple myeloma cell growth when naltrindole treatment was combined the HDAC inhibitor, valproic acid, or the proteasome inhibitor, bortezomib. The combination therapies will be studied further with the use of comprehensive concentration-response analysis. We will also investigate combinations of naltrindole with other known antineoplastic agents currently in use or under investigation for the treatment of multiple myeloma, such as lenalidomide, dexamethasone, and suberoylanilide hydroxamic acid (SAHA). We will use a tetrazolium salt-based method and bromodeoxyuridine incorporation to monitor cell proliferation. Apoptosis will be assessed by assaying levels of activated caspase 3 by western blotting and flow cytometry, and annexinV and propidium iodide staining will be determined by flow cytometry, in collaboration with Dr. Pat Fitzgerald-Bocarsly.

**Specific Aim 2.** *Investigation of antiproliferative properties of naltrindole alone and in combination with other antineoplastic agents in human multiple myeloma cells co-cultured with bone marrow stromal cells and in an in vivo xenograft mouse model of multiple myeloma.* The interplay between multiple myeloma cells and the cells of the bone marrow plays a major role in proliferation and survival of the myeloma cells, their resistance to chemotherapy, as well as destruction of the bone and overall disease progression. Direct cell-cell interactions as well as secreted cytokines and growth factors are believed to play a role. Thus we will study the effects of naltrindole and its combinations with other agents on the
Summer Student Research Program

Project Description

multiple myeloma cells in the presence of H-5 human bone marrow stromal cells to determine the effect of direct cell to cell contact, as well as in the presence of the culture medium conditioned by H-5 cells to determine the role of the secreted factors. To assess the antiproliferative properties of naltrindole in vivo, a subcutaneous mouse xenograft model of the human multiple myeloma will be used. These in vivo studies will be carried out in collaboration with and at the site of Washington Biotechnology, Columbia, MD.

SPONSOR'S MOST RECENT PUBLICATIONS RELEVANT TO THIS RESEARCH:


IS THIS PROJECT SUPPORTED BY EXTRAMURAL FUNDS? 

Yes [ ] or No [ ]

(IF YES, PLEASE SUPPLY THE GRANTING AGENCY’S NAME)

Foundation of UMDNJ

THIS PROJECT IS:  [ ] Clinical  ☒Laboratory  [ ] Behavioral  [ ] Other
Summer Student Research Program
Project Description

THIS PROJECT EMPLOYS RADIOISOTOPES

THIS PROJECT INVOLVES THE USE OF ANIMALS

PENDING  □   APPROVED  □   IACUC PROTOCOL #

THIS PROJECT INVOLVES THE USE OF HUMAN SUBJECTS

PENDING  □   APPROVED  □   IRB PROTOCOL # M

WHAT WILL THE STUDENT LEARN FROM THIS EXPERIENCE?

The student will become fully acquainted with the biology and treatment of multiple myeloma, in addition to gaining valuable laboratory experience utilizing techniques such as radioreceptor binding assays, cell proliferation assays, cell culture techniques, FACS analysis and western blotting. The student will also learn about the use of opioids as analgesic agents for the treatment of pain in cancer patients, and will gain first-hand experience in the concept of diminishing tolerance to morphine with naltrindole.