Pharmacy Student Summer Research Fellowship Proposal for 2020

FACULTY INFORMATION:

NAME: Darin E. Jones, Ph.D.
DEPARTMENT: Pharmaceutical Sciences

LOCATION: Bio Med1 B238C

PROJECT INFORMATION:

TITLE: Pharmacological Modulation of Poly(ADP-ribose) Metabolism

LOCATION OF THE PROJECT: Bio Med1 B238C

BRIEF DESCRIPTION OF THE PROJECT:

Molecularly-targeted cancer therapies have revolutionized the treatment of this heterogeneous and increasingly prevalent disease. Genetic instability is a hallmark of many cancers that generates mutations to support uncontrolled tumor growth and resistance to chemotherapies. The underlying DNA repair defects in these tumors can be exploited in tumor-selective therapies that block critical remaining DNA repair functions to trigger catastrophic damage and cell death. This idea is borne out by the clinical successes of inhibitors of poly(ADP-ribose) polymerase 1 (PARP1) to treat breast and ovarian cancers with mutations in BRCA1 or BRCA2. However, these BRCA-deficient tumors account for a minority of cancers so it is important to identify other physiological defects of tumors that are synthetically lethal in combination with molecularly targeted therapies. Additionally, the current PARP inhibitors suffer from dose-limiting toxicities, which may result from off-target effects on other members of the large PARP superfamily. As an alternative to PARP inhibitors, we used high-throughput screening to identify selective inhibitors of the human poly(ADP-ribose) glycohydrolase PARG. PARG is a monogenic enzyme that removes the poly(ADP-ribose) posttranslational modification of proteins modified by PARP1. A genetic knockdown of PARG sensitizes cancer cells to DNA damaging agents and radiation and phenocopies the tumor-specific killing effects of PARP1 enzymatic inhibitors in BRCA- deficient cancer cells. We utilize structure-guided chemical synthesis and in vitro testing, to improve the potency and selectivity of small molecule PARG inhibitors. Selected compounds are advanced to preclinical trials of tumor killing activity in cultured cells and xenograft models of breast cancer. We design and synthesize focused libraries of analogs that exploit unique features of the PARG active site and screen small molecule fragment library to identify new chemotypes and interactions that are incorporated into our inhibitor design strategy. Selective inhibitors of PARG will be useful probes of cellular responses to cancer chemotherapeutics that damage DNA, and may be useful cancer therapies in their own right by exploiting the genomic instability phenotype of many tumors.

STUDENT'S RESPONSIBILITIES-DUTIES IN THE PROPOSED PROJECT:

Student design, synthesize, and purify novel compounds for biological evaluation. Student will also aid in preparation of presentations and manuscripts for publication.

ESTIMATED TIME FOR PROJECT COMPLETION: _____ weeks

DOES THE WORK INVOLVE ANIMAL RESEARCH? YES –-------
NO **---NO--**

ORAL/POSTER PRESENTATION OPPORTUNITY:
Yes, several potential venues in the fall; American Chemical Society, American Association for Cancer Research, MCBIOS

MANUSCRIPT SUBMISSION: Possible journal names for this work to be submitted:
Journal of Medicinal Chemistry
Bioorganic and Medicinal Chemistry
Molecules