Summer Research Fellowship Proposal for 2020

FACULTY INFORMATION:

NAME: Darin E. Jones
DEPARTMENT: Pharmaceutical Sciences

LOCATION: B238

PROJECT INFORMATION: Medicinal chemistry/drug discovery

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

LOCATION OF THE PROJECT: BM1 220 and 222

BRIEF DESCRIPTION OF THE PROJECT:
Molecularly-targeted cancer therapies have revolutionized the treatment of this heterogeneous and 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 for the development of tumor-selective therapies. For example, an acquired mutation in a DNA repair pathway together with a pharmacological blockade of a backup pathway for DNA repair creates a synergistic combination that is cytotoxic to the tumor. This principle 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 have identified selective inhibitors of poly(ADP-ribose) glycohydrolase (PARG), a monogenic enzyme that removes the poly(ADP-ribose) posttranslational modification of proteins modified by PARP1. A genetic knockdown of PARG sensitizes cells to DNA damage and phenocopies the effects of PARP1 enzymatic inhibitors in BRCA-deficient cells. In this project, we will improve the potency and selectivity of small molecule PARG inhibitors through structure-guided chemical synthesis and testing in vitro, and to advance selected compounds to preclinical trials of tumor killing activity in cultured cells and xenograft models of breast and ovarian cancer.

STUDENT'S RESPONSIBILITIES-DUTIES IN THE PROPOSED PROJECT:

This student will synthesize and purify novel compounds for biological evaluation. They will also fully characterize all new chemical entities using standard spectroscopic techniques. Student will attend and present research progress at research group meetings.

ESTIMATED TIME FOR PROJECT COMPLETION: ___~8-12_ weeks

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