U-RISE@NSU
Mentee Research Project Description

Mentors, please provide a description of the work you mentee will be engaged with. The description should be arranged into seven sections, as described below. This document has several purposes and you will use it to describe the research you will be having the mentee perform, in reporting to NIH, for webpage information, etc. Please construct this document accordingly. The sections needed and a brief description of the section provided below. An example is also provided.

**Title**: Provide a descriptive title for the research. Avoid run-on sentences. Note, titles do not end with a period.

**Background**: Brief background of the problem to be studied. The information provided should be limited to what is needed to understand the problem, significance of the problem, the gap in knowledge to be address, and how the proposed work will potentially lead to a solution.

**Hypothesis/Objective**: The hypothesis/objective should follow from the information provided in the background. The hypothesis/objective should largely stand on its own and there should be very little other text. If you find that you need to add text here to explain your hypothesis, it probably belongs in the Background section.

**Specific Aim(s)**: The specific aim(s) of the project should be described here. Remember that these should be designed to prove (or not) the hypothesis and therefore need to clearly relate to the hypothesis. Try to avoid having aims being written as what your mentee will do, rather, write them with an eye for what will learned. What the mentee will do is in the next section, Project Design.

**Project Design**: First provide an overview of the experimental approach the mentee will take toward addressing the overarching hypothesis. Then, describe the key components of the experimental approaches that will be taken to address each specific aim you have listed and the key result anticipated. You may want to add how the pieces fit together to address the hypothesis but keep it short.

**Innovation**: Clearly identify the innovation associated with the research plan. This can be a new approach to solving a problem, a collection of established methods put together in a novel way, etc. You should be able to clearly state the innovation in one or two sentences, perhaps with a lead in sentence of two.

**Impact**: The background should have provided some information regarding what problem you are trying to solve and potentially the magnitude of the problem. Here, you want to state how this work will address the problem, likely lead to a solution, and the resulting impact – e.g., saving of human life, treatment of a disease state, savings in terms of dollars thus pointing out the broader scope of the work (relevance to other problems, diseases, etc., is very helpful).

Below is an example that may help guide you in preparing this description.

**Background**: Poly(ADP-ribose) polymerase 1 (PARP-1) is an abundant and ubiquitous nuclear enzyme which, when active, assembles long and branching molecules of Poly(ADP-ribose), thereby modifying itself, as well as surrounding proteins. Although DNA repair is commonly accepted as its main function, recent findings indicate that PARP-1 also participates in numerous nuclear processes. Mutations in the phosphatase and tensin homolog (PTEN) gene and loss of PTEN expression have both been associated with a wide range of human tumors. Loss of PTEN expression is observed in 27% of primary prostatic tumors and in 79% of castration-resistant prostate cancer (PC) samples. Recent studies reveal that PTEN deficiency dramatically sensitizes tumor cells to PARP inhibitors. The rationale behind these phenomena is that PTEN deficiency causes a homologous recombination (HR) defect in tumor cells. In turn, the HR defect sensitizes tumor cells to PARP-1 inhibitors. Most of the current NAD-dependent PARP inhibitors cause undesired side effects since NAD is commonly utilized by many other pathways. To address these limitations, this proposal aims to test a novel class of PARP inhibitors that block a specific step of PARP-1 activation, i.e., the interaction of PARP-1 protein with histone H4 (non-NAD-like). Our preliminary studies demonstrate the high sensitivity of PC cells to these novel inhibitors both in vitro and in vivo.

**Hypothesis/Objective**: The first hypothesis is that novel non-NAD-like PARP-1 inhibitors will be highly effective against advanced PTEN-negative prostate tumors. The second hypothesis is that these specific PARP-1 inhibitors will be less likely to cause side effects due to the lack of inhibitory effect on other enzymes.

**Specific Aims**: 1. To examine the antitumor efficacy of non-NAD-like PARP-1 inhibitors using primary prostate cancer cell lines and a xenograft model of human prostate cancer. 2. To examine the effect of non-NAD-like PARP-1 inhibitors on prostate tumorigenesis in a PTEN-deficient transgenic mouse model. 3. To identify biomarkers and investigate the molecular mechanism that explains how PARP-1 contributes to prostate cancer malignancy.

**Project Design**: Aim 1. PTEN expression is lost in a vast majority of castration-resistant PC tumors. The preliminary and published data demonstrate that PTEN deficiency dramatically increases sensitivity of tumor cells to PARP-1 inhibitors. Experiments in this aim will compare the antitumor efficacy of conventional and novel non-NAD-like PARP-1 inhibitors against PTEN-negative and PTEN-positive prostate cancer cells in cell culture and xenograft animal models. Aim 2. These experiments will test the potential therapeutic efficacy of non-NAD-like PARP-1 inhibitors against androgen-dependent and castration-resistant tumors using a PTEN-deficient transgenic mouse model of PC. Aim 3. We will examine how PARP-1-dependent expression of PC-specific genes controls prostate carcinogenesis. PARP-1 occupancy in promoters of these genes will be tested in normal and malignant prostate cells using the conventional ChIP approach and genome-wide ChIP-seq analysis. The role of other components of the pADPr pathway, such as PARG, will also be tested.

**Innovation**: Traditionally, research on cancer epigenetics is focused on investigating either histone or DNA modifications. The principal novelty of this proposal is that by targeting PARP-1, the research project focuses on a protein that simultaneously functions as an effector and as an epigenetic mark. Furthermore, novel class of PARP-1 inhibitors will be tested in cell culture as well as xenograft and transgenic animal models of PC. Identification of cancer related genes that are targets of PARP-1 using the genome-wide approach is another novelty.

**Impact**: At any given time, more than 2.5 million men in the United States are diagnosed with PC. We aim to explore the therapeutic efficacy of novel non-NAD-like PARP-1 inhibitors for the treatment of advanced PC. These inhibitors are expected to possess minimal secondary toxicity, as they target an activation mechanism unique to PARP-1 enzyme, rather than a broad spectrum of pathways involving NAD. Additionally, data and reagents obtained during the proposed project will benefit the biomedical research community studying PARP-1 roles in development, pathogenesis, and aging. The proposed studies will integrate methods developed in three distinct areas of biology and design new procedures and reagents that will have wide applicability.