Branch: ERTB

Council Period: 201701

Concept Title: Expanding Genome Integrity Assays to Population Studies (U01)

Introduction

Genome integrity research is a cornerstone of environmental health sciences. More intimate knowledge of repair capacity – both overall and of specific cellular pathways – is needed to fulfill the field's promise of better predicting individuals at risk from exposures as well as directing disease treatment options. Significant advances in understanding the pathways involved in proper sequence maintenance following exposure – based damage have been achieved in the laboratory and a variety of diseases have been linked to genome integrity insufficiencies. For example, hypersensitivity of the skin and eyes to UV-radiation in individuals suffering from *Xeroderma pigmentosa* results from a defect in one of seven nucleoside excision repair genes or in the gene for polymerase η . Risk of head and neck cancer in tobacco and alcohol users appears to be higher for individuals with reduced double strand break repair capacity.

A select set of recent clinical and population studies invoke the recognition that insights on genome integrity pathways can inform measures of disease risk as well as treatment protocols. Although a handful of investigations report functional analyses on a small set of patients and/or subjects, for the most part studies are limited to cataloguing associations of genetic polymorphisms with disease risk. Newer clinical studies focus on the knowledge of individual repair capacity to predict which patients will respond positively to a pharmaceutical drug, such as the chemotherapeutic, temozolomide. However, translation of our knowledge from the laboratory to prevention strategies or the clinic has not been fully realized. This is likely due to the absence of epidemiology studies that have explored the functional variation among individuals or populations to respond to DNA damage, adducts, or mutagenesis and the relation to disease risk. Admittedly, the labor - intensive and costly procedures currently available likely contribute to the apparent reluctance of epidemiologists to integrate these potentially informative measures into their studies.

Through earlier initiatives, NIEHS has taken steps to bridge the gap from laboratory advances to population studies and application. For example, the announcement, PAR-10-016, Enabling Technologies in DNA Repair Research (R21), was designed to establish high throughput, efficient methods of detecting and determining DNA repair capacity and mutagenesis. The program resulted in several products successfully validated in the laboratory and at least one high-throughput, inexpensive model is now commercially available. Field testing in human populations is a critical next step.

Based on these compelling needs, NIEHS convened a Workshop on New Approaches for Detecting Environmentally-induced DNA Damage & Mutations in Population Studies (June 11 - 12, 2015). The goal was to construct a vision to guide translational genome integrity research by developing practical, reliable tools to interrogate differences in individuals and populations in genome error and damage correction. The Workshop included experts in environmental health, epidemiological approaches to genome integrity studies, and basic scientists who have been pioneering genome integrity assays. This program concept is based on their recommendations which are now being prepared as a commentary for publication.

Research Goals and Scope

This proposed FOA is highly technological in nature. The program would provide funds for technologists and epidemiologists to work together to improve on existing assays and approaches to produce practical tools to meet the needs of epidemiological studies. Teams would be formed to tailor assays to ongoing epidemiology studies or to form small subject or patient groups on which to pilot test the approaches. Collaborations will be fostered to clarify the interpretation of measures of DNA repair capacity for susceptibility and to expedite discovery of early disease biomarkers. NIH staff will work closely with the supported projects through the cooperative agreement mechanism to provide guidance on strategies to ensure sharing among the participants and that results are continually assessed for application. The results of eventual studies using such assays would be expected to lead to new insights into individual and population susceptibilities based on variation of genome maintenance capacity and provide an improved measure of risk on which to base prevention strategies. The results will also assist in directing disease treatment options based on repair capacity as well as the ability.

Successful applications will address all or most of the following guiding principles:

- Pilot testing and improvement of DNA repair or mutagenesis assays in populations at risk.
- Development or modification of existing assays as appropriate for epidemiology and population studies.
- Coordinated partnerships among basic scientists and epidemiologists to seek to improve measures of DNA repair capacity for individuals and population studies.

• Validation of assay results against currently accepted biomarkers and physiological parameters to advance studies of risk assessment in populations

• Further development of functional assays to improve on currently accepted biomarkers in terms of precision, labor demand, tissue specificity, cost, etc.

• Strengthening of interpretations of assay results in parallel studies on human tissue, human-derived stem cells or well established mammalian animal models versus levels of established biomarkers.

• Discovery of sentinel biomarkers in blood or tissue scrapings and determination of their reflection of DNA repair capacity or mutagenesis in target tissues of interest.

Mechanism and Justification

The Cooperative Agreement Mechanism (U01) will be used to ensure increased cooperation and sharing of advances among the projects. Regular conference calls and face-to-face meetings as well as guidance from NIH staff will assist in promoting development, applying best practices, and promoting wide availability of promising methodologies to the research and clinical communities.

The program cost is estimated at \$3.5M annually to support 5 – 6 U01 projects.