Concept Clearance

Branch: GEHB

Council Period: 201701

Concept Title: Population-Based Model Organism Research for G X E Exploration in Complex Disease

Introduction

Most human diseases result from a complex interplay of multiple genetic, epigenetic, and environmental factors, yet studies of complex trait associations are inherently difficult in human populations. Until now, most laboratory mouse strains were inbred or outbred from a small group of founder animals. Thus, mapping complex traits in mice was also very challenging. New mouse resources, such as those derived from randomized eight-way outcrosses, have produced advance intercross recombinant inbred strains, the Collaborative Cross (CC) and a random breeding population, the Diversity Outbred (DO) mice. These genetically-diverse mouse resources were developed to simulate the genetic diversity found in human populations and overcome many of limitations of linkage mapping in the human population in an experimental model system. Furthermore, it is now possible to develop a complementary resource of cells and cell lines derived from the CC and DO strains, enabling researchers to perform population-level studies *in vitro*. These unique resources have proven to be powerful tools for identifying individual quantitative trait loci (QTL) and candidate genes for validation for hypothesis generation related to gene-environment interplay in complex human diseases. Other recently developed population-based model organism resources that could significantly advance the understanding of genetic susceptibility to environmental exposures include the Drosophila Genetic Reference Panel and the Rat Hybrid Diversity Panel. Using controlled exposure studies *in vivo* and *in vitro* with these rodent and other organism resources will allow us to better model the differential responses in humans to environmental exposures.

Research Goals and Scope

A meeting exploring the use of the rodent population-based resources to model environmental exposures and gene-environment interactions in human disease was held on March 18-19, 2015. This meeting (with NIEHS DIR, DERT, NTP, as well as EPA representation) included presentations by most current users of these rodent models in the field of environmental health and toxicology and a range of environmental health projects using the CC and DO mice were discussed. The overwhelming consensus from this meeting was that these resources were being underutilized to address hypotheses relevant to the impact of environmental exposures for models of complex human disease outcomes. The overall goal of an NIEHS initiative would therefore be to further stimulate the potential of these new powerful population-based model organism resources for environmental health science questions, particularly the exploration of G X E interplay and the identification and understanding of genetic susceptibility to environmental exposures. This research would support NIEHS strategic plan goals 1 (*Identify and understand fundamental shared mechanisms or common biological pathways*) and 3 (*Transform exposure science by enabling consideration of the totality of human exposures and links to biological pathways, and create a blueprint for incorporating exposure science into human health studies*).

Current NIEHS investments in the use of population-based model organism resources have resulted in increased interest in this area, and a few NIEHS grants have been funded in recent years that have focused on the use of these resources. However, there is still a general limited use of these resources in the environmental health science community due to a lack of recognition and awareness of the resources and issues associated with NIH study section review. A funding announcement specifically focused on this area is needed to allow these resources to be more firmly established as mainstream in the environmental health science field.

Mechanism and Justification

An FOA would allow "proof of principle" studies to be funded in this area to accelerate the impact of this emerging field for the understanding of gene-environment interactions relevant to complex human disease outcomes. This FOA will be reviewed by a Specialized Emphasis Panel convened by the NIEHS Scientific Review Branch and will include reviewers with expertise in the population-based model organism resources, genetics, and environmental exposures. It is

anticipated that 5 or 6 larger R01 applications would be awarded. Several other NIH Institutes have expressed an interest in joining this initiative (including NIDA, NIAID, NCI). This initiative would also incorporate the requirement of a strong data management plan and sharing expectations so that these studies could be made readily available to the scientific community in a timely fashion.