

## Concept Clearance

Branch: GEHB

Council Period: 201910

Concept Title: Functionally Inferred G x E Discovery/Validation

### Introduction

#### Limited G x E Discovery and Validation in Human Studies:

Many complex human diseases are known to involve multiple potentially interacting genetic and environmental factors. However, studies directly interrogating the gene-environment (G x E) interplay in human genetic epidemiology studies have been hampered by genetic and phenotypic heterogeneity, underpowered study designs, and the complexities of measuring environmental exposures. Furthermore, the limited number of intriguing gene-environment (G x E) interactions that have been identified as associated with potential risk for some complex diseases (through both the basic and epidemiological grant awards that NIEHS has supported in recent years) have not been validated or replicated.

#### Recent Relevant Efforts to Address this Problem:

A variety of recent efforts have focused on the need to advance G x E discovery and validation and the functional role of genetic variants in human disease outcomes using multiple exciting advances in functional genomics tools, technologies, and biological knowledge:

-A workshop presented by the National Academies of Sciences in 2018 discussed "The Promise of Genome Editing Tools to Advance Environmental Health Research". Recommendations from this workshop included the need for more *proof of concept and pilot studies* using the next generation of gene editing tools to quickly identify those genetic variants that predispose to differential environmental responses, as well as further development of assay technology that facilitates expansion of functional endpoints beyond cell viability.<sup>1</sup>

-A recent NHGRI strategic planning workshop emphasized the application of functional genomics at scale, animal models, and predictive modeling from integrated omics data and polygenic risk score models for understanding gene-environment interactions.<sup>2</sup>

-Recent RFAs from NHGRI support novel functional genomics approaches and development of new assays and technologies that can assist in relating genetic variation to function and disease.<sup>3</sup>

### Research Goals and Scope

#### Proof of Principle for Use of Functional Genomics Tools/Technologies for G x E:

The overall goal of this NIEHS initiative would be to generate proof of principle studies for the utilization of more recent developments in functional genomics tools, *in vitro* approaches, and biological knowledge, together with well characterized exposures, for G x E discovery and/or validation. Recent advances in functional genomics applications provide novel avenues to functionally validate, experimentally characterize, and interpret both

newly identified as well as existing G x E hits. A variety of approaches, resources, and strategies could be utilized to achieve these goals including:

- sophisticated model organism resources (including population-based model organism and single cell analyses) and induced pluripotent stem cells from relevant cell types (including from patient-derived tissues) to allow more detailed endpoints to be tested and defined that may help elucidate underlying G x E mechanisms driving disease pathogenesis
- *CRISPR/Cas9* and other genome editing tools for robust high-content genome-wide screens in combination with environmental exposures of interest
- organoid models, tissue-chip platforms, and other innovative culture systems and microfluidics for *in vitro* approaches which more accurately model *in vivo* disease systems and delineate tissue-specific and organ-specific dysfunction relevant to gene-environment interactions for complex disease outcomes
- the integration of omics data using various annotation information (including DNase I hypersensitive sites, ENCODE, Roadmap Epigenomics, and GTEx data) as well as computational approaches using biological knowledge to better inform predictions and associations of G x E interactions relevant to human disease outcomes

This initiative would fit under the NIEHS strategic plan goal of “Advancing Environmental Health Sciences through Basic Biological Research and Individual Susceptibility”. This extramural funding opportunity will complement efforts currently being developed through Tox21 (Toxicity Testing in the 21<sup>st</sup> Century) and the National Chemical Genomics Center at NCATS (National Center for Advancing Translational Science) for high-throughput screening of toxicants and further development of cell and biochemical based *in vitro* phenotypic assays. In addition, several ongoing NIEHS and other NIH IC-supported SBIR (Small Business Innovation Research) efforts are being developed to improve on the use of genetic diversity and organoid cultures/models for *in vitro* toxicology applications.

### Mechanism and Justification

There is currently a need to stimulate this field as a preliminary portfolio analysis suggests an underutilization of these advanced functional genomics technologies and tools to explore G x E at the NIEHS. The small number of unsolicited NIEHS applications that have been received to date related to this area of science have struggled for an appropriate NIH study section home. A funding announcement focused on this subject matter is needed to allow these resources to be more firmly established as mainstream in the environmental health science field and stimulate the potential use of these technologies for environmental health questions, particularly the exploration of G X E interplay and the identification and understanding of genetic susceptibility to environmental exposures. This FOA will be reviewed by a Specialized Emphasis Panel convened by the NIEHS Scientific Review Branch and will include reviewers with expertise in gene editing tools, high content screens, and *in silico* approaches as well as environmental health science expertise. The R01 mechanism will likely be utilized due to the need for extensive preliminary data to justify the strategy and the substantial time and cost required to implement the approaches. Several other NIH Institutes have expressed an interest in joining this solicitation (including NHLBI, NCI, and NHGRI), which could allow a larger trans-NIH effort.

### References:

1. “The Promise of Genome Editing Tools to Advance Environmental Health Research”, A Workshop presented by the Standing Committee on Emerging Science for Environmental Health Decisions, January 10-11, 2018. National Academies of Sciences, Engineering, and Medicine.
2. “From Genome to Phenotype: Genomic Variation Identification, Association, and Function in Human Health and Disease”, NHGRI Planning Workshop, January 22-24, 2019.
3. Novel Approaches for Relating Genetic Variation to Function and Disease (R43/R44/R01/R21)  
<https://grants.nih.gov/grants/guide/pa-files/pa-19-043.html>  
<https://grants.nih.gov/grants/guide/pa-files/PA-18-868.html> <https://grants.nih.gov/grants/guide/pa-files/PA-18-867.html>