[Billing Code 4140-01-P]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Request for Information: The National Institute of Environmental Health Sciences/National Toxicology Program requests the nomination and prioritization of environmentally responsive genes for use in screening large numbers of substances using toxicogenomic technologies.

SUMMARY: The National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP) is interested in the identification and prioritization of a comprehensive list of environmentally responsive genes that might be targets for screening cells or tissues obtained from humans, rats, mice, zebrafish, and Caenorhabditis elegans against large numbers of substances. The goal is to generate a minimum list of 1000 genes for each species that would provide the maximal toxicogenomic information on (1) effects that reflect general cellular responses, independent of cell type or species, and (2) gene expression changes that are specific by organ and/or cell type. The NIEHS/NTP also seeks recommendations on criteria to use for prioritizing the genes in order to identify those potentially most useful in a screening paradigm. Such a list of environmentally responsive genes may be useful also in biomarker development and basic research efforts.

DATES: The deadline for receipt of information is August 23, 2013.

ADDRESSES: Nominated genes and/or recommendations on prioritization criteria should be submitted electronically in Microsoft Excel or Word formats to Genelist@niehs.nih.gov.

FOR FURTHER INFORMATION CONTACT: Dr. Elizabeth Maull, NIEHS, P. O. Box 12233 (MD K2-17), Research Triangle Park, NC 27709; email: maull@niehs.nih.gov.

SUPPLEMENTARY INFORMATION:

Background:

In 2008, the NIEHS/NTP, the U.S. Environmental Protection Agency's (EPA) National Center for Computational Toxicology (NCCT), and the National Human Genome Research Institute (NHGRI)/NIH Chemical Genomics Center (NCGC) (now located within the National Center for Advancing Translational Sciences (NCATS)) entered into a formal agreement to develop a vision and devise an implementation strategy to shift the assessment of chemical hazards from traditional, experimental animal, toxicology studies to target-specific, mechanism-based, biological observations largely obtained using in vitro assays. In mid-2010, the U.S. Food and Drug Administration (FDA) joined the collaboration that is known informally as Tox21.

In Tox21, the agencies collaborate to research, develop, validate, and translate innovative testing methods for characterization of toxicity pathways; identify compounds, assays, informatic analyses, and targeted testing needed to support the development of

new methods; identify patterns of compound-induced biological response(s) in order to characterize toxicity pathways; facilitate cross-species and low-dose extrapolation; prioritize compounds for more extensive toxicological evaluation; and develop predictive models for biological response in humans. Currently, the primary Tox21 activity is the screening of a 10,000 compound library in a number of nuclear receptor agonist/antagonist and stress response pathway assays primarily using reporter gene platforms. In the next phase, the focus will be on assaying large numbers of chemicals in high content screens and mid to high throughput, targeted gene expression platforms.

To conduct the next phase, the NIEHS/NTP in collaboration with its Tox21 partners seeks to identify a prioritized set of at least 1000 genes that would provide comprehensive toxicogenomic information on (1) gene induction or repression reflecting general cellular responses that are largely independent of cell type or species, and (2) gene expression changes that are organ and/or cell type specific. Examples of processes likely to be cell-type independent include genes involved in stress-response pathways (e.g., DNA repair, hypoxia, heat shock), chromatin remodeling, and those that regulate cell division and death. Examples of processes more likely to be cell-type specific include induction or repression of expression of enzymes that modify or activate chemical toxicants, regulation of the hypothalamic-pituitary-adrenal axis, and inflammatory responses. In keeping with the Tox21 goal of facilitating cross-species extrapolation, the NIEHS/NTP is especially interested in the nomination of genes or gene sets specifically relevant for comparisons between humans, rats, mice, zebrafish, and C. elegans and especially those for which complementary functional pathways exist. Such a list of environmentally responsive genes may be useful also in biomarker development

and basic research efforts. To facilitate identification of the most useful genes to include in a screening paradigm, the NIEHS/NTP also requests recommendations on criteria to use for their prioritization.

Request for Information:

The NIEHS/NTP seeks to establish a prioritized list of environmentally responsive genes to screen cells/tissues from humans, rats, mice, zebrafish, and C. elegans for agent-induced alterations using mid to high throughput, targeted transcriptomics platforms. The goal is to screen a large number of compounds and obtain information useful for understanding the potential for adverse health outcomes. To that end, the NIEHS/NTP requests that respondents provide information for either or both of the following:

- Nominations of specific genes or gene sets. Nominated genes should be identified using Entrez and/or Ensembl gene IDs. Desirable supporting information for the nominated gene(s) would include the associated pathway(s) or biological process(s), the cellular context(s) where demonstrated, and the technology used to measure expression of the nominated gene. If available, please include relevant citations as a part of the supporting information.
- Criteria for prioritization of the genes or gene sets. The NIEHS/NTP is interested in criteria that could be used to develop a prioritized list of genes that would provide the greatest level of insight and discrimination of toxicological response in a variety of applications including cross-species comparisons and differential tissue responses.

The nominated genes and/or criteria recommendations should be submitted electronically in Microsoft Excel or Word format.

Respondents to this request for information are asked also to provide their name, affiliation, address, and contact information (including telephone and fax numbers, and email address). The deadline for receipt of the requested information is August 23, 2013.

Responses to this request are voluntary. This notice does not obligate the U.S. Government to award a contract or otherwise pay for the information provided in response to this request. The U.S. Government reserves the right to use information provided by respondents for any purpose deemed necessary and legally appropriate. Any organization responding to this request should ensure that its response is complete and sufficiently detailed. Respondents are advised that the U.S. Government is under no obligation to acknowledge receipt of the information received or provide feedback to respondents with respect to any information submitted. No proprietary, classified, confidential, or sensitive information should be included in your response.

Background Information on the NTP: The NTP is an interagency program established in 1978 (43 FR 53060) to strengthen the Department's activities in toxicology research and testing, and develop and validate new and better testing methods. Other activities of the program focus on strengthening the science base in toxicology and providing information about potentially toxic chemicals to health regulatory and research agencies, scientific and medical communities, and the public. The NTP is located administratively at the NIEHS. Information about the NTP and NIEHS is found at

http://www.niehs.nih.gov and http://ntp.niehs.nih.gov, respectively.

Dated: July 23, 2013

John R. Bucher, Ph.D.

Associate Director, National Toxicology Program

[FR Doc. 2013-18058 Filed 07/26/2013 at 8:45 am; Publication Date: 07/29/2013]