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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Request for Comments: The National Institute of Environmental Health Sciences/National Toxicology Program requests comments on a list of environmentally responsive human genes selected for use in screening large numbers of substances using toxicogenomic approaches.

SUMMARY: The National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP) requests comments on a set of human genes that have been identified and prioritized as environmentally responsive genes. These genes will be used in toxicogenomics approaches to screen cells or tissues obtained from humans against large numbers of chemicals. The goal was to generate a set of approximately 1500 human genes to evaluate transcriptional changes in response to chemical exposures. Similar gene sets will be developed for screening cells or tissues from other species such as rats, mice, zebrafish, and Caenorhabditis elegans. The human gene set should provide maximal toxicogenomic information on effects from chemical exposures that reflect general cellular responses, independent of cell type or species, and gene expression changes that are specific by organ and/or cell type. Such a list of environmentally

responsive genes may also be useful in biomarker development and basic research efforts. This list of genes, referred to as the "S1500" gene list, or gene set, is available for public comment.

DATES: The deadline for receipt of comments is May 15, 2015.

ADDRESSES: Comments on the human S1500 gene set should be submitted electronically in Microsoft Excel or Word formats to Genelist@niehs.nih.gov. Nominations for genes to be added to the S1500 must be accompanied with a strong scientific justification for inclusion.

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, 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.

Tox21 partner 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. The primary activity of Tox21 Phase I was the development of a quantitative high throughput screening (qHTS) approach for toxicology. The goal of Phase II was the implementation of the qHTS approach in screening a 10,000 compound library through a variety of nuclear receptor agonist/antagonist and stress response pathway assays, utilizing primarily reporter gene platforms. In Phase III, the focus is on assaying chemicals in high-content screens and mid to high throughput transcriptomic screens. High throughput gene expression changes will be the primary metric that is employed in Phase III to measure biological effects from chemical exposures.

To conduct Tox21 Phase III, Tox21 partners initiated the "S1500 Genes High Throughput Transcriptomics" project to capture information from the whole transcriptome (i.e., the entirety of all expressed RNA molecules in a cell or biological sample). This project will use a targeted subset of genes in a HTS or semi-HTS platform to gain insight into how biological systems respond to chemical exposures. Neither the

actual number of genes to be utilized, nor the specific transcriptomics platform(s) needed to carry out the project, have been finalized.

In an effort to select an appropriate subset of key representative or "sentinel" genes, the NTP previously requested input from the scientific community (78 FR 45542, July 29, 2013) on the "Nomination and Prioritization of Environmentally Responsive Genes for Use in Screening Large Numbers of Substances Using Toxicogenomic Technologies." An interagency working group composed of members of the Tox21 partnership considered the input provided in response to the Federal Register notice as they developed a consensus strategy to select appropriate genes.

The working group's goal was to select the most relevant and biologically diverse set of sentinel genes to represent transcriptomic responses to injury. Criteria for the selection and evaluation of an appropriate gene set are: (1) representative of highly diverse gene expression changes reported to date, (2) capable of predicting the gene expression changes observed across the transcriptome, and (3) coverage of all major biological pathways.

The current version of the human S1500 gene set can be found at http://ntp.niehs.nih.gov/go/S1500. This site will be updated as changes to the list are made. The consensus strategy for selection of an appropriate sentinel gene set can be accessed at the same site.

Comments on the human S1500 gene set should be submitted electronically in Microsoft Excel or Word format to Genelist@niehs.nih.gov.

Respondents to this request are asked to provide their name, affiliation, address, and contact information (including telephone and fax numbers, and email address). The deadline for receipt of comments is May 15, 2015.

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 to 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 NTP and NIEHS is available at http://ntp.niehs.nih.gov and http://www.niehs.nih.gov, respectively.

Dated: April 8, 2015

John R. Bucher, Ph.D.

Associate Director, National Toxicology Program

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