Title of proposed program: The Individual Exposome Project

Submitting Source: NIH

What is the major obstacle/challenge/opportunity that the Common Fund should address? What would the goals of the program be?

The concept of the exposome as first defined in a seminal paper by Christopher Wild (Wild 2005), "encompasses the life-course [of] environmental exposures (including lifestyle factors), from the prenatal period onwards." Since the exposome represents an untargeted, hypothesis-free, view of the totality of non-genetic factors that associate with disease endpoints, it represents a uniquely powerful tool for hypothesis generation in identifying the factors that interact with genetic susceptibility to create disease risk. The initial concept put forward by Wild has been advanced and discussed in a variety of international forums (Rappaport and Smith 2010). What is emerging as the concept becomes a reality is a view that the exposome is a highly dynamic, individual set of factors similar in concept to the genome or microbiome. As groups have begun to demonstrate the power of this approach, it has become evident that the major obstacle remains the development of methodology and tools for untargeted analysis of the exposome. Two approaches to measuring the exposome have been discussed; an approach building from characterization of variation in the personal environment (Chemical exposures, dietary intake, physical activity, psychosocial stress, pharmaceutical use) , and an approach focused on assessing the variation of the biological manifestation of the environment including both the direct measurement of endogenous and exogenously produced small molecules or through the measurement of biomarkers of biological response at the epigenome, transcriptome or proteome levels (Lioy and Rappaport 2011).

Why is a trans-NIH strategy needed to achieve these goals? What initiatives might form the strategic plan for this topic?

Regardless of the approach used to conceptualize the exposome, the critical element is a need to conduct a discovery driven interrogation of the non-genetic factors that contribute to disease risk and how those factors vary in time over the life course of an individual. Implementing the exposome on a scale that will allow adequate power to draw conclusions will require a significant investment of interdisciplinary expertise, including coordination not only across NIH but with international funding agencies. The specific elements of the program include:

- Development of technologies to enable untargeted characterization of variation of the personal environment including chemical exposures, dietary intake, physical activity and psychosocial stress in time and space. Activities will include not only the development of new devices but also their validation and manufacture and the development of strategies to facilitate translation into large scale studies.
- Development of technologies for untargeted analysis of non-genetic factors in biological samples including biomonitoring of chemical exposures, macro- and micro-nutrients, hormones and metabolites on an 'omic scale. This will include efforts to interface with existing efforts such as the common fund metabolomics program.

- The integration and application of these technologies in a consortium of existing epidemiological studies with large sample sets; such studies could include those conducting GWAS and other studies looking at multiple disease endpoints such as the Women's Health Initiative, the National Children's Study, or the UK Biobank.

If a Common Fund program on this topic achieved its objectives, what would be the impact?

The potential of achieving an understanding of the individual exposome cannot be understated; it will provide an unprecedented view of the factors that contribute to the risk for common, complex diseases. These associations can then be translated into hypothesis-driven studies to lead to new understanding of the mechanisms of disease, the identification of new therapeutic strategies and the identification of opportunities for disease prevention through the modification of the personal environment.

While the concept of the exposome is in its infancy, there are a small number of proof of principle reports that demonstrate the potential power of an untargeted approach in discovering unanticipated and powerful associations between non-genetic factors and important diseases such as diabetes and cardiovascular disease (Patel, Bhattacharya et al. 2010; Wang, Klipfell et al. 2011). Support of a comprehensive, focused, program to establish the capacity for measuring the exposome will provide unique and unprecedented insight into disease processes and point to new hypotheses for both therapeutic intervention and disease prevention.

Lioy, P. J. and S. M. Rappaport (2011). "Exposure science and the exposome: an opportunity for coherence in the environmental health sciences." Environmental health perspectives **119**(11): A466-467.

Patel, C. J., J. Bhattacharya, et al. (2010). "An Environment-Wide Association Study (EWAS) on type 2 diabetes mellitus." PloS one **5**(5): e10746.

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