Title of proposed program: Epigenomic Pharmacology

Submitting Source: NIH

What is the major obstacle/challenge/opportunity that the Common Fund should address? What would the goals of the program be? A previous Common Fund initiative demonstrated the importance of the epigenome for normal development, response to environmental factors, and cell-specific transcriptional regulation. During the previous five years the field has moved from selective epigenetic changes to tools for unbiased epigenomic screening. While the field of epigenomics has progressed by demonstrating the importance of these mechanisms, the field lacks tools to manipulate the epigenome with precision. To be sure, there are drugs such as valproic acid that influence methylation broadly and shRNAs that have been used to modify specific histone deacetylases (Graff et al., Nature 483:222-6, 2012). But cell-specific, sequence-specific intervention remains an aspiration and a scientific gap to be filled if the science is to transition from descriptive to mechanistic studies and ultimately be translated to clinical efforts. Because most of the key epigenomic modifiers are governed by enzymes (demethylases and histone deacetylases), the epigenome is a tractable target for pharmacology. While this has led to many projects in industry, drugs from the private effort will likely not be available to academic scientists. A small project for public tools is underway via the Structural Genomics Consortium, but this will not have the scale and scope of what is needed: a broad innovative effort to create next-generation tools for manipulating the epigenome with cellular and sequence specificity.

Why is a trans-NIH strategy needed to achieve these goals? What initiatives might form the strategic plan for this topic? This program will develop molecules with a very broad array of potential targets that will be operative in many different diseases relevant to many different ICs. Therefore, a trans-NIH strategy is required for the program to meet its potential. The initiatives that would form a strategic plan would include (a) an exploratory approach to develop new approaches for altering methylation, acetylation, and other modifications of DNA and accompanying histones and (b) a program to test these molecules in cellular or model organism assays as a precursor to creating medicines for the epigenome.

If a Common Fund program on this topic achieved its objectives, what would be the impact? This program would (a) catalyze the understanding of how environmental effects influence gene expression and (b) open the pathway to a new pharmacology of epigenomics with potentially a new domain of therapeutics.