

## **Report 40: Environmental Epigenomics**

**Convener:** Brad Bernstein

**Brief History:** disease susceptibility is a function of genetic and environmental influences. Genome sequencing studies have gained increasing insight into the genetic bases of human disease, but in nearly all cases the genetic components explain only a fraction of disease prevalence. Importantly, a large body of epidemiological data has identified diverse environmental exposures that also contribute to disease. However, the mechanisms remain obscure.

### **Discussion Highlights:**

**VISION:** The participants in this session identified the broad area of connecting environmental influences to disease through the study of epigenomics and epigenetic mechanism as an opportunity and important long-term goal for NIEHS.

ENVIRONMENT → EPIGENOME (+GENETICS) → MANIFESTATION OF DISEASE

**TIMING:** Experimental and computational technologies have advanced to the point that comprehensive study of human epigenomes is now feasible. Coordinated efforts by Common Fund, NHGRI and international consortia are now mapping human epigenomes and functional genomic elements at unprecedented rate. The technologies and infrastructures developed in these contexts provide an opportunity for expanded synergistic – for example, related technologies have been embraced by the Cancer Genome Atlas to characterize epigenomic aberrations in human cancer.

**HOWEVER,** none of the ongoing studies are considering the role of environmental perturbagens and how such agents may alter the epigenome. Such information could provide insight into the mechanisms of action of disease-relevant environmental exposures, and identify relevant biomarkers that could be applied more broadly in population-based studies.

The participants sought to define a relatively focused scientific project that would leverage existing infrastructure and resources within NIEHS (DIR, DERT, NTP) and ongoing large-scale epigenome mapping projects.

### **Recommendations:**

- *In vitro* cell assays to identify the influences of toxic exposures on the epigenome. Cell models would include state-of-the-art human stem cell models, derivatives, artificial tissues
- Toxic exposures would be identified with a disease-driven strategy to ensure maximal relevance, and would prioritize compounds deemed likely to confer stable (long-term) consequences. This would dovetail with ongoing projects and vital expertise at NIEHS.
- Readouts would leverage existing high-throughput technologies for DNA methylation, histone modifications, chromatin accessibility, RNAs.

- Key goal will be to distinguish short-term and long-term epigenomic changes; the latter 'stable' markers are of particular interest for understanding environmental contributions and biomarkers of disease susceptibility.
- In parallel, the strategy would be applied to key mouse experimental models of exposure through coordination with NTP. Though lower throughput, these studies will provide critical *in vivo* validations.
- The project could lead to multiple follow-up studies on the mechanisms of action of environmental insults. Such studies would be ongoing and supported in parallel.
- The project will identify biomarkers of environmental insults which would be validated and applied in cohort studies to examine predictive value for disease susceptibility (in concert with genetic analysis)

**Discussion Participants:**

Karen Adelman, Trevor Archer, Brad Bernstein, Geraldine Dawson, David Fargo, Richard Finnell, Frank Gilliland, Shuk-Mei Ho, John Hollingsworth, Steve Kleeberger, George Leikauf, Stephanie London, David Miller, Sheila Newton, Jonathan Pollock, Robert Sills, Jack Taylor, Fred Tyson, Leroy Worth, Mike Waalkes