Ellen Rothenberg, California Institute of Technology: *"Remembrance of Things Past, and Constructive Forgetting: Transcription Factor-Directed Remodeling of Epigenetic Marks in Development"*

ABSTRACT: In any given cell type of a complex organism, a sequence-specific transcription factor may not have equal access to all its potential binding sites across the genome. As a result, the same transcription factor can be used to help control the expression of different target genes in one cell type as it does in another. A number of mechanisms contribute to the selective access to some sites as opposed to others in a given cell type. One mechanism is the effect of local modifications to chromatin structure or DNA methylation which impede transcription factor binding, modifications which by default may be passed along through cell division. These "epigenetic mechanisms" have become popular to consider as if they represented a source of information for development and physiology separate from the information in the genome itself. However, this is a mistaken view, based on "snapshot" assessments of cells which do not take into account their histories of development and prior transcription factor activity. In fact, longitudinal tracking of epigenetic marks and transcription factor binding through a major developmental transition such as T-lymphocyte lineage commitment shows that epigenetic marks are emplaced and removed at specific sites across the genome as a result of dynamic changes in transcription factor expression and binding. Silencing marks do not mandate permanent silence and are not the mechanism through which active genes are turned off. Instead, they are emplaced during development to create a steep, nonlinear dependence of future target gene activation rates on transcription factor levels in the cell's descendants. Stage-to-stage tracking of RNA expression vs. epigenetic marking across the genome clearly reveals the magnitude and ordering of these effects. Crucial to an understanding of what is happening is the fact that most transcriptional regulation in complex organisms depends on concurrent binding of several, different transcription factors within close proximity. Not all transcription factors are equally blocked by "silencing" marks, and those that disregard silencing marks can

act as pioneers for recruitment of others. Gene loci then become activated as combinatorial action of transcription factors recruit enzymes that remove repressive marks, and the default propagation of these marks sets a new “normal” state of access for the future. Thus, epigenetic marks reflect the regulatory state history of the ancestors of a given cell, and like human history, they can cast a shadow but also be rewritten in the future.