

## **Method of Regulating Transcription in a Cell and of Modulating Gene Expression**

### **Inventors:**

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### **Applications:**

Drug Discovery, Regulation of Gene Expression, Chromatin Remodeling  
Chromatin based technology to define novel and highly specific protein targets for selective gene modulation

Appropriate differentiation and development of higher organisms require precisely regulated expression of multiple genes. The packaging of DNA into chromatin within the eukaryotic nucleus is highly organized and plays a critical role in regulating gene expression. The various types of chromatin structures that form on individual genes determine whether a gene is turned on or off. Regulation of chromatin structure is a critical component of gene regulation which affects tissue differentiation and cell function related to aging, cancer and a variety of diseases caused by changes in gene expression. Drug discovery related to modulation of gene expression, either to down regulate an overexpressed gene or to up regulate a silenced gene cannot be done at the DNA level alone. Chromatin based assays allow for the natural state of DNA regulation and provide optimal targets for therapeutic intervention. One important family of mammalian chromatin remodeling complexes, SWI/SNF (switch/sniff) is targeted to individual genes to specifically regulate its expression. SWI/SNF interacts with only certain classes of transcription factors and this property enables SWI/SNF to be selectively recruited to particular promoters. For example, proteins containing zinc finger DNA-binding domains (ZF DBDs), which is the largest class of eukaryotic transcription factors, interact with the BRG1 subunit of human SWI/SNF complex and recruit this complex to target promoters rather than the other catalytic subunit of SWI/SNF, BRM complexes. One invention provides for screening assays that identify small molecules that enhance or block the association between chromatin remodeling complexes and the specific transcription factors with which they interact. Specifically, the assays utilize several families of chromatin remodeling complexes which play key roles in facilitating the binding of specific transcription factors to nucleosomal DNA in diverse organisms from yeast to man. These in vitro assays can be developed for high-throughput screening to identify small molecule drugs that alleviate specific diseases caused by gene over or under expression. The second invention relates to three new findings of commercial potential. First, ZF DBDs or peptides are sufficient to direct SWI/SNF to a repressed promoter and create an accessible chromatin structure which enables other transcription factors to interact and activate the gene. In the absence of the ZF DBD, SWI/SNF and the other factors do not interact and the gene remains silent. Second, SWI/SNF BRG1 complexes, but not BRM, bind to the CREB transcription factor only when phosphorylated. CREB is the critical regulator of cAMP-response genes and thus a direct link between this signaling pathway and targeted chromosomal binding and gene activation by a specific form of SWI/SNF is established. Third, the opposite specificity exists for another type of signaling pathway. In this case, BRM SWI/SNF, but not BRG1, interacts with critical regulators of the Notch signaling pathway and is recruited to Notch target genes. Thus it is possible to identify drugs that selectively inhibit one type of pathway without affecting others.

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### **References:**

S00004: Cell 95(1):93-104(October 1998)  
S02019: Molecular Cell 11:377-389 (February 2003)

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### **License Terms:**

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