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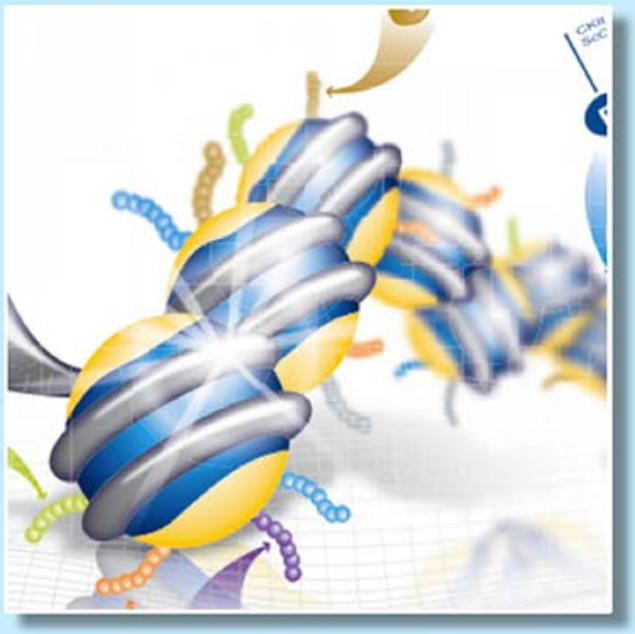

DNA Wraps Around Histone Cores to Create Nucleosomes
(Image credit: Tony Kouzarides, Andy Bannister, and Abcam. Epigenetic Modifications. Abcam. 2011.)

Developing Small Molecule Probes to Inhibit Transcriptional Repression by Long Noncoding RNAs

Sex determination by the XY chromosome system is found in numerous organisms. In both mice and humans, females have two X chromosomes, while males have one X and one Y chromosome. It is vital to balance the gene expression in females. This balancing is achieved through the epigenetic inactivation of one of the two X chromosomes. This inactivation is regulated in part by X-inactive specific transcript, *Xist*, a long noncoding RNA that induces silencing by binding to one of the X chromosomes. *Xist* has been shown to recruit proteins that read, write, and erase histone modifications and DNA methylation; however, the mechanistic role of these proteins in *Xist*-mediated silencing is poorly understood. The purpose of this study is to understand how epigenetic modifications such as histone methylation and deacetylation are involved in *Xist* silencing of the X chromosome. We employed TETRIS cells, mouse embryonic stem cells that express *Xist* in a doxycycline-inducible manner. When activated, *Xist* represses an adjacent luciferase reporter gene. We treated TETRIS cells with a library of small molecules targeting specific histone reader, writer, and eraser proteins. We hypothesized that inhibition of any proteins known to be involved in *Xist*-mediated repression result in a failure to silence luciferase. Our preliminary results indicated that inhibitors of histone deacetylase enzymes participate in the repression of luciferase. Small molecules that inhibit *Xist* function could be used as chemical tools for biological pathway discovery or potential therapeutics for X-linked diseases or misregulation of genes targeted for silencing.