Project Summary

Drug addiction is a fundamental threat to public safety and health. Its pathobiology has therefore been under intense study. The nucleus accumbens (NAc) is a brain region that plays a key role in normal reward learning and in addiction. Gene expression microarrays have been employed to elucidate the molecular basis of NAc neuroplasticity in addiction, revealing a complex landscape of distinct and drug-specific gene expression patterns in animal models and human postmortem brain. While such microarrays predominantly measure mRNA levels of protein-coding genes, major recent studies demonstrate that non-protein-coding RNA classes, including microRNA and long noncoding RNA (lncRNA), are abundantly expressed in the brain within specific spatiotemporally restricted contexts, and can directly regulate protein-coding genes. Nevertheless, nothing is known about human brain lncRNA expression in drug addiction. The proposed project will fill this important gap in our knowledge of brain gene expression and function. Insights emergent from the proposed analysis of lncRNA expression in the addicted and normal brain will further our understanding of addiction mechanisms and may facilitate the development of anti-addiction therapies.

Specific Aim 1 will construct a comprehensive catalog of human lncRNA genes, and will build upon that catalog to design a custom genome-wide lncRNA expression analysis microarray. This is a fundamental necessity, since there is no universally accepted reference annotation of the human lncRNA transcriptome, and since prefabricated microarrays exist to profile protein-coding and microRNA transcripts but not lncRNA. Specific Aim 2 will use the arrays created in Aim 1 to identify lncRNAs differentially expressed in the NAc of cocaine abusers, heroin abusers, and pair-matched controls, and will validate the microarray results using RT-PCR. The outcome, a catalog of lncRNAs whose NAc expression is altered significantly by chronic drug exposure, will provide a foundation for functional studies of lncRNA action mechanisms in drug addiction. Specific Aim 3 will begin to elucidate the regulation of the differentially expressed lncRNAs by combining public transcription factor binding site datasets with lncRNA genomic mappings, thereby identifying neurally-expressed transcription factors with potential binding sites at promoters of specific lncRNA genes. Fitting specific lncRNAs into known transcription regulatory networks will begin to elucidate the regulation of lncRNA expression, potentially highlighting signaling pathways amenable as therapy targets for drug abuse.