

## James & Esther King Biomedical Research Program

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2007 Program  
New Investigator (3-year project)

**Project Title:** Mechanisms of Nicotine Reinforcement in Rats: An RNA Interference Approach

**Project Summary:** Nicotine is the active ingredient in tobacco smoke most likely responsible for the addictive properties of tobacco and the persistence of the harmful tobacco habit in human smokers. The aim of this grant is to investigate the mechanisms by which nicotine acts in the brain to produce its addictive properties. Nicotine activates proteins in the brain termed *nicotinic acetylcholine receptors* (nAChRs) that are located in brain reward pathways or “pleasure centers.” By activating these nAChRs, nicotine stimulates pleasure centers in the brain, which ultimately results in the development of tobacco addiction. There are many different subtypes of nAChRs, each constructed from different combinations of subunits that are the building blocks of nAChRs. Importantly, very little is known regarding the precise subunits that combine to form the nAChRs at which nicotine acts to stimulate brain pleasure centers—the fundamental first step in the chain of events that ultimately results in tobacco addiction and which contributes to the persistence of the smoking habit. If we can determine the distinct subunits at which nicotine acts, we may be able to design better drugs to control the actions of nicotine at these receptors and thereby help break the smoking habit. In this project, the expression of different nAChR subunits likely to regulate the addictive actions of nicotine will be decreased in a specific region of the rat brain that has been widely implicated in regulating the pleasurable/addictive properties of nicotine. To “knock down” targeted nAChR subunits, we will inject a virus (lentivirus, similar to human immunodeficiency virus, HIV) into this region of the rat brain that can infect brain cells in this area, and make a molecule called a short interfering RNA (siRNA) inside the brain cells. We can design this siRNA such that it binds to specific (RNA) targets within the infected brain cells. Upon binding to their targets, siRNAs activate machinery within the cell to destroy the target to which it has bound, by a process termed RNA interference. So, by targeting siRNAs to individual nAChR subunits, we can knock down the expression of these nAChR subunits in brain cells important for the development of nicotine addiction. We plan to examine the effects of knocking down discrete nAChR subunits in rat brain on the ability of nicotine to produce its pleasurable effects and on the desire to consume nicotine, compared with control rats with intact nAChRs. It is predicted that, if nAChR subunits that regulate the actions of nicotine are knocked down, the excitatory effects of nicotine on brain pleasure centers will be decreased, as will the amount of nicotine that rats will consume.