James & Esther King Biomedical Research Program

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Basic Biomedical Sciences — *2008 Program*
Florida Atlantic University — *Team Science (2-year project)*

Project Title: A Rat Model of Individual Differences in Neuro-immune Responses to Nicotine and Stress

Project Summary: Human beings differ in their vulnerability for smoking addiction. This grant uses a rat model of individual differences in nicotine craving. The individual difference is the novelty-seeking phenotype, where rats are categorized as showing high reactivity (HRs) or low reactivity (LRs) to novelty based on their free exploration of a novel environment. The grant consists of three interrelated projects.

Preliminary research for Project 1 showed regulation of this phenotype with two chronic stress regimens: chronic, variable physical stress (CVP) and social stress (CVS). We observed a phenotype shift with the chronic physical stress; it promoted high reactivity-like vulnerability to nicotine in the low reactivity group. However, the social stress regimen inhibited the pre-existing vulnerability in the high reactivity group. Project 1 investigates a switch in neural activational patterns underlying this phenotype shift in the low and high reactivity rats.

Project 2's preliminary work showed that the immune system of high reactivity rats is vulnerable to nicotine-induced overproduction of the pro-inflammatory cytokine, tumor necrosis factor alpha (TNF-a). This indicates induction of a "disease state" in the high reactivity rats with nicotine. Project 2 investigates the cytokine profiles of different subpopulations of the immune cells in the low and high reactivity animals with nicotine.

Project 3 elaborated on molecular modulators of increased TNF-a production in high reactivity rats and showed that the TNF-a converting enzyme (TACE) levels are increased. Effective inhibitor of TACE, the tissue inhibitor of metalloproteinase-3 (TIMP-3) levels are decreased in T-cells. Project 3 employs TACE inhibitors and TIMP 3 mutants to reverse nicotine effects in high reactivity rats.