

Abstract: Pharmacogenetics of nicotine addiction treatment

PI: Caryn Lerman

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This application is in response to Funding Opportunity Announcement PAR-12-011, NIH Competitive Revision Applications for Research Relevant to the Family Smoking Prevention Control Act. The parent project of this application, U01-DA020830, Pharmacogenetics of Nicotine Addiction Treatment (PNAT) seeks to optimize pharmacotherapy options for people trying to quit smoking by conducting a prospective placebo-controlled clinical trial of several therapeutic options. A critical component of the parent grant is to characterize genetic variants that may identify serve as a predictor of successful response to pharmacotherapy. Research from PNAT has previously identified a genetically-informed biomarker of *CYP2A6* activity, the nicotine metabolism ratio (NMR) that has successful predictive validity in clinical trials of smoking cessation. The NMR, the ratio of 3-hydroxycotinine to cotinine, has been shown to be reliable, stable, and independent of time of assessment or time since last smoking.

The PNAT team has also demonstrated an association between NMR and smoking behaviors and toxin exposures, such that rapid metabolizers of nicotine will smoke a cigarette more intensely than a slow metabolizer; and, rapid metabolizers have greater levels of toxin exposure than slow metabolizers. Results from this study suggest that rapid metabolizers may be a sub-group at increased risk for cigarette toxin exposures. What remains unknown is how these people may smoke the proposed new low nicotine content cigarettes that are being introduced as part of FDA's efforts to reduce addiction and harm, as mandated in the Family Smoking Prevention and Control Act (FSPCA).

This revision application builds upon the utility of the NMR in trying to better characterize smokers, but is novel in that it is focused on the behavioral and toxin exposure effects when smoking low nicotine cigarettes and little cigars. Low nicotine content cigarettes have been developed to identify levels of nicotine that will not sustain addiction and lead to lower toxin exposure. This requires thorough examination, and the proposed application will rigorously assess smoking behaviors during a 35-day period while assessing toxin exposures using a thorough panel of biomarkers. We hypothesize that differences in NMR may identify sub-groups of smokers that may be at increased risk when smoking low nicotine content cigarettes.

A second study in this application proposes to examine the effect of switching to little cigars on smoking patterns and toxin exposures. Sales of little cigars have significantly increased in the past few years yet have received little research attention. Little cigar smoking is an important emerging market, and due to the lower taxes may be a cheap source of nicotine for low socio-economic status smokers. Further evidence suggests the little cigar market requires closer examination. First, several little cigar manufacturers increased their weights to a less taxed and regulated weight class, presumably aware of the need to provide cheap nicotine. Second, Philip Morris bought Black and Mild little cigars just prior to the FSPCA being enacted, and now this brand is the best selling and most popular among youth in the United States. We propose to examine smoking use patterns and toxin exposures when switching to two of the most popular brands of little cigars, and will examine how NMR may identify sub-groups at increased risk when smoking this tobacco product.

This revision application is responsive to the stated objectives of PAR-12-011, and will specifically address:

1) how reduced nicotine content in cigarettes affects use patterns and toxin exposure; 2) how sub-populations may be affected by reduced nicotine content cigarettes; 3) what effect switching to alternative tobacco products has on smokers; and, 4) identifying measures to best characterize relevant changes in exposure to harmful constituents.

This revision application will build upon the success of the parent U01, and will be led by Drs. Lerman and Tyndale, and include Dr. Benowitz, an international leader in nicotine pharmacokinetics; Dr. Kozlowski, an expert in cigarette and cigar smoking behaviors, smoking policy and regulatory efforts; and Dr. Strasser, an expert in research on potentially reduced exposure tobacco products.