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## Inducible, Lung-Specific Deletion of the NADPH-cytochrome P450 Reductase Gene: a Model for Studying the Role of Pulmonary P450s in NNK-Induced Lung Cancer

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NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone] is a potent tobacco-specific carcinogen, which is believed to play a significant role in smoking-induced human lung cancer. Our hypothesis is that target tissue bioactivation of NNK by microsomal cytochrome P450 (CYP or P450) are required for NNK-induced lung tumorigenesis. The aim of the current research was to test this hypothesis in a mouse model with lung-specific, inducible deletion of the cytochrome P450 reductase (*Cpr*) gene, which is essential for the function of all microsomal P450 enzymes. This mouse model was generated by cross-breeding three single transgenic mice: the *Cpr*<sup>lox</sup> mouse with a floxed *Cpr* gene, the CCSP-rtTA (Clara cell secretary protein-reverse tetracycline-controlled transactivator) mouse with lung -specific expression of the rtTA transgene, and the tetO-Cre mouse which requires tetracycline (or doxycycline) and the rtTA protein for Cre expression. Here we report preliminary characterization of doxycycline-induced, site-specific deletion of the *Cpr* gene in the triple transgenic (3-tg) mice. Cre protein was detected by immunoblotting in the lungs of 3-tg mice after doxycycline treatment, but was not detected in mice treated with sucrose (vehicle). However, deletion of the *Cpr* gene was detected by PCR in the lungs of both groups of mice, which indicated leakiness of Cre expression in the control animals. Nevertheless, quantitation analysis, with use of real-time PCR, showed that *Cpr* gene deletion occurred in 5-15% of lung cells in doxycycline-treated 3-tg mice, which is consistent with the proportion of Clara cells in mouse lung, but only 3-4% of lung cells in sucrose-treated 3-tg mice. Thus, this mouse model can be used for the planned studies on the function of pulmonary P450s in NNK-induced lung tumorigenesis.