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## **An Exploration of the Mechanisms for Increased Resistance of Lateral Nasal Gland to Acetaminophen Toxicity in Cyp2g1-Null Mice**

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CYP2G1 is a cytochrome P450 monooxygenase expressed uniquely in the olfactory mucosa (OM). Our current Cyp2g1-null mouse showed increased resistance to acetaminophen (AP) toxicity in the lateral nasal gland (LNG), the largest anterior gland in the nasal cavity, even though CYP2G1 is not expressed in the organ. The aim of this study is to explore mechanisms that link CYP2G1 expression in the OM and AP toxicity in the LNG. We found that the increased resistance to AP toxicity was accompanied by reduced local AP and non-protein thiol (NPT) levels in the LNG. However, in vitro metabolic activation of AP by LNG microsomes was found previously to be unaltered in the Cyp2g1-null mouse, a finding that led to the hypothesis that OM CYP2G1, through a paracrine pathway, regulates LNG expression of genes involved in AP uptake, clearance, or post-bioactivation toxic response, and thus influences LNG resistance to AP toxicity (Zhuo et al., *J. Pharmacol. Expt. Ther.*, 308, 719-728, 2004). To test this hypothesis, microarray analysis will be performed to identify genes that are differentially expressed in the LNG and OM of Cyp2g1-null and wild-type mice. An alternative hypothesis, that the altered LNG AP toxicity is related to a tissue-selective neighboring effect of Cyp2g1 knockout on Cyp2a5 expression, will also be tested; the neighboring effects are believed to originate from the presence of a functional neo gene at the Cyp2g1 locus, upstream of Cyp2a5. In this regard, we are generating a new Cyp2g1-null mouse by disrupting the Cyp2g1 allele with a removable "floxed" neo. The new mouse model will be useful not only for exploring the mechanisms of increased LNG resistance to AP toxicity, but also for studying tissue specific chemical toxicities in the OM and even the relationships of odorant metabolism and olfaction.