# Cancer Driver Mutations in Experimental Rodents and Prediction for Human Cancer

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## Overview

Clonal expansion of cancer driver mutations (CDMs) is an intrinsic aspect of carcinogenesis. Our lab has been developing the tools and knowledge necessary to utilize measurements of CDMs as quantitative biomarkers of cancer risk, focusing on mutations that are highly-conserved across species and overrepresented in human cancers (i.e., hotspot CDMs). The goal is to measure panels of hotspot CDMs quantitatively and with high sensitivity in DNA from rodents subchronically-exposed to different doses of a test article, such that the output can predict the rodent tumor response due to chronic exposure and be translated into a human cancer risk.

Progress toward this goal includes demonstrating that Allele-specific Competitive Blocker PCR (ACB-PCR, sensitivity of 10-5) can detect the induction of CDMs in DNA isolated from rodent tissues after relatively short exposures (1 – 4 weeks) to model mutagenic carcinogens (azoxymethane, aristolochic acid, benzo[a]pyrene, ethylene oxide, or simulated solar light). In addition, we quantified hotspot CDMs in normal human tissues and tumors and related mutant fraction measurements to surrogates of cancer risk. We made the important observation that the magnitude of interindividual variability in hotspot cancer driver mutant fraction across normal human tissues is correlated with carcinogenic impact (percentages of tumors from each tissue carrying the relevant mutation). Thus, interindividual variation is likely due to stochastic clonal expansion and provides a metric for identifying the most important biomarkers to analyze for specific tissues.

Recently, we developed an error-corrected next-generation sequencing method with a sensitivity of 10-4 that can quantify >30 hotspot CDMs in 13 amplicons (973 bp target), while simultaneously discerning mutation spectra. The method reports expected tissues-specificities for cancer driver gene mutations in breast and lung cancers, as well as in normal breast and lung. Work is underway to validate analogous panels for rat and mouse, by comparing mutant fraction levels across strains that vary in terms of spontaneous mammary and lung tumor incidence.