S9. Applications of Genetically-Engineered Mice for Cancer Prevention Studies

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Prevention studies in human populations are the ultimate determinant of whether a prevention strategy is effective in reducing cancer risk. However, given the generally long period of time required to conduct such expensive studies, the need to assemble large patient cohorts, and genetic diversity of the human population, high throughput strategies are needed to evaluate more rapidly potential chemopreventive agents. Genetically-engineered mouse (GEM) models of human cancers offer important opportunities for the testing of single or combination approaches for chemoprevention. GEM models have become increasing sophisticated in recapitulating many of the genetic abnormalities associated with human oncogenesis, including genomic instability, loss of cell cycle regulation, and dysregulation of growth factor and apoptosis pathways. Such models may be particularly well suited for determining whether the dynamic process of tumorigenesis and lesion progression can be inhibited by chemopreventive agents and, importantly, at what stages of tumor progression these agents may work. The study of stage-specific responses is quite problematic in human populations. Models that represent specific sub-types of human cancers are being identified through comprehensive biologic and genomic approaches. For instance, our lab has demonstrated that, depending upon the genetic lesion and design of the model, the major mouse models of mammary cancer can currently be categorized with one of three subtypes of human breast cancer. Responses to chemoprevention trials using the three newly defined classes of GEM models may help predict which sub-sets of patients or high-risk individuals would most likely benefit from particular prevention strategies. Examples of the use of GEM models for colon, breast and prostate cancer prevention studies will be given. Future strategies for the identification and validation of candidate molecular targets for chemoprevention using GEM models will be discussed. Determining the predictive power of GEM models in chemopreventive approaches, however, remains a major challenge.