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Our research is aimed at identifying and understanding the genes that modulate genomic instability in development, aging and carcinogenesis. Strategies used include RNAi knockdown, transgenic over-expression and both constitutive and conditional knock-out models in a variety of systems including *Drosophila* and mammalian tissue culture and *in vivo* mouse models. Our preferred method of assessing genomic instability is by measuring homologous recombination (HR). HR repair is a significant component of the cellular repair process in a replicating cell, and most importantly, responds to the widest variety of DNA damages, from oxidative stress, alkylation damage, bulky adducts on DNA as well as cross-links and ionizing radiation.

Homologous recombination is an important process of genetic alteration in the generation of cancers. Certain genetic deficiencies result in higher than normal levels of genomic instability during development, including a higher frequency of HR and a higher probability of developing cancers. Environmental exposures often exasperate these effects. In the last decade several researchers have demonstrated that spontaneous deletions can be mediated by HR between repeated DNA fragments and that the frequency of such events are elevated following exposure to carcinogens. Conversely, a higher level of HR can result in a greater resistance to certain chemotherapeutic agents, making some cancers refractory to these treatments.

Over the last few years we have established several systems to begin to ask key questions in the field of DNA damage response and we have used these systems to examine the role of DNA damage response pathway components Atm, p53, Gadd45 and p21 on HR and cancer development *in vivo* in the mouse. From these studies we developed the hypothesis that there are additional cellular components that affect genomic stability through development and over age. It is these modulators of genomic stability that we are trying to determine and would like to characterize.

To identify novel factors involved in DNA repair and damage response we have taken advantage of a *Drosophila* genome library of RNAi. We have taken a bioinformatics approach to mine the data obtained and develop novel hypotheses. We then examine the functional conservation of identified mammalian homologues. These studies have revealed not only novel genes but also novel functions of known genes. Our long-term goal is to understand how these relate to one another and cancer development.