

## James & Esther King Biomedical Research Program

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*2006 Program  
New Investigator (3-year project)*

**Project Title:** Telomere Susceptibility to Cigarette Smoke-Associated Chromosomal Abnormalities in Embryos

**Project Summary:** Cigarette smoking is a major risk factor for the development of severe pulmonary and cardiovascular diseases and the induction of a variety of neoplasias and carcinogenesis. Smoking also affects female fecundity and reduces fertility. Telomere shortening and erosion, and chromosomal instability are common elements of many pathologies, including carcinogenesis and infertility. However, only a small fraction of individuals with tobacco exposure develop cancer and infertility. The underlying mechanisms still remain to be determined although smoking is known to induce oxidative stress, damage mitochondrial function and nuclear DNA, and cause aneuploidy and/or apoptosis. Telomeres consist of repetitive G-rich sequences and associated proteins, which cap the ends of linear chromosomes. Capping maintains chromosomal stability; preventing nucleolytic degradation, end-to-end fusion, and irregular recombination which are associated with carcinogenesis. Our previous work has identified a link between oxidative stress, mitochondrial dysfunction, and telomere dysfunction, leading to chromosome instability and apoptosis. We also have shown that long telomere length is associated with successful pregnancy from eggs that have undergone in vitro fertilization. Since telomere dysfunction leads to genetic instability, individuals with shorter telomeres may be more likely to have increased chromosomal instability and therefore be at a higher risk for infertility-associated embryonic developmental abnormalities. Shorter telomeres may render certain smokers more susceptible to oxidative stress and chromosomal instability than others.

We hypothesize that smoking and oxidative stress may operate through telomere shortening and dysfunction to increase genetic instability and susceptibility to infertility. This research uses early embryo development and embryonic stem (ES) cell model systems, as well as transgenic and short-telomere mouse models to investigate whether smoking induces oxidative stress and leads to telomere shortening and dysfunction, and thus chromosomal instability, and whether telomere function plays a critical role in smoking associated defects in embryo development. Moreover, the potential role of antioxidants in preventing oxidative stress and telomere erosion, thus recovering normal embryo development, will be determined in these model systems. This project will provide new insights into how smoking causes aneuploidy or apoptosis in embryos, which can lead to pregnancy loss or birth defects. Understanding these mechanisms will help develop novel methods to prevent or treat smoking related infertility in women, and may have general implications for understanding and prevention of other smoking-associated diseases, particularly carcinogenesis which occurs more frequently in humans at an advanced age.