CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP130054

Project Title:
Genes and Pathways Cooperating with p53 in LFS Tumorigenesis

Award Mechanism:
Individual Investigator

Principal Investigator:
Krahe, Ralf

Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Identification of the tumor suppressor gene TP53 (p53) ushered in a new era in cancer research. This gene alone has shaped many of our fundamental concepts in cancer biology. TP53 is now recognized as the single most altered gene in human cancers, and its central role in cancer biology has stood the test of time. The p53 pathway is a complex network that regulates cell growth and death, but its role in tumorigenesis is complex and our understanding is incomplete. Li-Fraumeni Syndrome (LFS) is an inherited childhood cancer caused by mutations in TP53. It has become increasingly clear that while TP53 mutations predispose LFS patients, additional genetic and epigenetic alterations are necessary for tumor development. LFS provides a unique opportunity to investigate the role of p53 as the earliest (inherited) alteration and to identify acquired changes as key downstream drivers of p53-mediated tumorigenesis. Our knowledge of what these critical alterations are and how they cooperate with mutant p53 is limited. This is an important problem, because without it, complete understanding of the role of p53 in tumorigenesis is highly unlikely. In this proposal, we seek to identify these additional changes through novel approaches and technologies resulting from the Human Genome Project and to understand their role in the development of LFS tumors. To this end, we are compiling an atlas of genetic and epigenetic changes commonly associated with LFS tumors in human patients and a mouse model. Candidate genes harboring recurrent changes will be tested in cell culture systems and mouse models. We are using these models to study the role of additional genomic and epigenomics changes and their significance in the development of LFS. We anticipate that our findings will have an impact on the understanding of inherited cancer risk, metastasis, and perhaps its therapy, not just for LFS, but also sporadic adulthood tumors that are part of the LFS spectrum.