Title:
*Rearrangement-Associated Activation of Telomerase Integrative Analysis of a Rare Cancer Type*

About Dr. Davis:
Dr. Davis earned his bachelor of science degree in biochemical and biophysical sciences from the University of Houston in 2005. He then went on to receive his Ph.D. through the Structural and Computational Biology & Molecular Biophysics graduate program at Baylor College of Medicine, under the guidance of Dr. Ching Lau. He is currently a postdoctoral fellow in the lab of Dr. Richard Gibbs at the Human Genome Sequencing Center at Baylor College of Medicine.

Abstract:
Rare tumor types offer a unique opportunity to investigate and discover previously unrecognized mechanisms of tumorigenesis. Representing ~5% of renal cell carcinomas, Chromophobe renal cell carcinoma (ChRCC) is a kidney malignancy which has been poorly characterized on a genetic and molecular level. In this study, we performed comprehensive molecular analysis of tumor and matched blood from 66 ChRCC cases, including analyses of whole exome sequencing, whole genome sequencing (WGS), RNA sequencing, and DNA copy number profiling. We observed genomic alterations previously associated with ChRCC, including loss of one copy of the entire chromosome, for most or all of chromosomes 1, 2, 6, 10, 13, and 17, in the majority of cases (86%), and recurrent mutations involving P53 and PTEN pathways (n=26 and n=15, respectively). WGS analysis identified novel genomic rearrangements involving the promoter region of TERT, a key component of the telomerase enzyme whose activity is known to facilitate the unlimited proliferation of cancerous cells. The rearrangements resulted in breakpoints within the TERT promoter region in six out of 50 ChRCC cases; these cases also had the highest levels of TERT expression (p < 1 x 10⁻²⁰, t test), even compared to cases with the recently identified TERT promoter activating point mutation, C228T. Three of these six cases also showed the strongest manifestation of localized hypermutation, or kataegis, commonly associated with genomic rearrangements.

In five ChRCC cases, the TERT-associated rearrangements were intrachromosomal (one involving part of PDCD6), while the sixth case involved NEK5 on chromosome 13. When considering intratumor heterogeneity, in most cases, these variants were estimated to reside in nearly all of the cells, which would indicate that the TERT-associated rearrangements represent early events and therefore possible drivers. Of the seven rearrangements identified by WGS, we confirmed six (involving six cases) by PCR, by designing primers that spanned both sides of the breakpoint junction, allowing amplification of DNA spanning the breakpoint region in the tumor sample; subsequent sequencing of the PCR product independently confirmed the junction in each case.

Although point mutations in the TERT promoter (leading to upregulation of TERT) were recently reported in cancers such as melanoma, our results represent another phenomenon, of recurrent genomic rearrangement breakpoints in the TERT promoter associated with elevated TERT expression in cancer. The precise mechanism is unknown, though, as a result of rearrangement, a number of cis-regulatory elements were in close proximity to the core promoter of TERT. Future applications of the information presented here will include comparative analysis with other cancer types, for the possible existence elsewhere of structural rearrangements involving promoters for TERT or for other key drivers of cancer.