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SPEAKER ABSTRACTS

Transformative but not the way we planned: new approaches to centromere biology

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Awardee Institution: University of Michigan

Our work on Human Endogenous Retroviruses (HERVs), funded by a Transformative R01, led to our discovery of a previously unknown family of HERVs (termed K-111) that have spread throughout 15 centromeres in modern humans through a process resembling homologous recombination. More recently, we have discovered a second such virus, termed K-222, which has spread among pericentromeric sequences in distinct human chromosomes. The sequence of the human genome is not yet complete, and importantly, major gaps remain at the centromeric region of each chromosome. It would be naïve to believe that centromere sequences are functionally indolent, considering the fact that the centromere is responsible for the faithful segregation of chromosomes, and destabilization of this process results in genomic instability and aneuploidy. Therefore, the sequence of the centromere remains a last frontier of human genomics and genetics. The structure of each human centromere is, however, organized by specific alpha repeats that are distinct to the centromere of each individual human chromosome. We are now using the sequence information from alpha repeats and endogenous retroviruses to develop molecular, qPCR-based assays capable of specifically detecting and quantitating the centromeric material of each human chromosome. To initially address the applicability of these centromere assays to detecting aneuploidy, we have screened the DNA of humans with genetic defects. Using DNA from healthy humans as a control, our centromere assays were capable of detecting aneuploidy in autosomal chromosomal disorders such as trisomy 8 and trisomy 18. We were also capable of detecting sex-linked disorders and aneuploidy in the sex chromosomes. We are currently improving these rapid and reproducible quantitation methodologies to screen for genetic disorders in single cells and maternal plasma. In addition, the potential for centromeres to drive the pathogenesis of cancer has, surprisingly, remained very understudied, and our new methodology will allow us to directly assess whether specific patterns of centromeric evolution are seen in particular malignancies, as preliminary data would suggest. These tools can also be exploited to begin to examine whether centromere biology might directly guide malignant transformation. Thus, advances derived from our work on HERVs has led us to apply new technologies to begin to understand the mysteries of centromeres in health and disease.