Presenter: Matt Simon

Authors: Matthew Simon, Jiping Yang, Eric, Early, Maria Zagorulya, Greg Tombline, Michael Van Meter, Stephan Emmrich, Paul D. Robbins, Jan Vijg, Andrei Seluanov, Yousin Suh, and Vera Gorbunova

Title: A CENTENARIAN VARIANT OF SIRT6 ENHANCES GENOME MAINTENANCE ACTIVITY

Abstract:
Sirtuin 6 (SIRT6) is a deacylase and mono-ADP ribosyl transferase (mADPr) enzyme involved in multiple cellular pathways implicated in the regulation of aging and metabolism. Targeted sequencing identified a SIRT6 allele containing two linked substitutions (N308K/A313S) enriched in Ashkenazi Jewish (AJ) centenarians, compared to AJ control individuals. Characterization of this SIRT6 (centSIRT6) allele demonstrated it to be a stronger suppressor of LINE1 retrotransposons, confer enhanced stimulation of DNA double strand break repair, and more robust cancer cell killing compared to the wild type. Surprisingly, centSIRT6 displayed weaker deacetylase activity, but stronger mADPr activity, over a range of NAD+ concentrations and substrates. Additionally, centSIRT6 displayed a stronger interaction with Lamin A/C (LMNA), which correlated with enhanced ribosylation of LMNA. Our results suggest that enhanced SIRT6 function contributes to human longevity by improving genome maintenance via increased mADPr activity and enhanced interaction with LMNA.