

3rd International Conference on

Molecular Biology & Nucleic Acids

August 27-28, 2018 | Toronto, Canada

Molecular approaches using small molecule compounds and RNA interference oligonucleotides to investigate mechanistic aspects and therapeutic strategies involving DNA helicases

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Statement of the Problem: The Section on DNA Helicases, NIA-NIH investigates the roles of human DNA helicases in genomic stability, prompted by the findings of hereditary helicase disorders characterized by accelerated aging and cancer.

Methodology & Theoretical Orientation: Building on our discovery of small molecule inhibitors of the WRN helicase defective in Werner syndrome, we are conducting studies with compounds to target human helicases for inhibition (or activation) in cell-based model systems as a novel approach to assign specific helicase functions *in vivo* that may pave the way for development of therapeutic strategies. Of particular interest are helicase-interacting compounds that accentuate the effects of anti-cancer drugs based on a DNA damaging paradigm in genetically defined mutant backgrounds. Development of preclinical models is underway to evaluate the efficacy of helicase-targeted drugs for personalized medicine. In a parallel effort, we are conducting RNA interference screens with isogenic helicase-deficient and helicase-proficient cell lines to identify novel interactions between human helicases and target genes.

Conclusion & Significance: These studies are built upon the premise that DNA helicases exhibit a network of synthetic lethal interactions that may be exploited to overcome resistance to existing anti-cancer therapies.

Biography

Dr Robert Brosh Jr received his PhD in Biology from the University of North Carolina at Chapel Hill, MS in Biochemistry from Texas A&M University, and BS in Chemistry from Bethany College. He conducted postdoctoral training at the Laboratory of Molecular Genetics (NIA, NIH) before assuming his position as a Principal Investigator where he leads the Section on DNA Helicases. In 2015, Dr Brosh received the NIH-NIA Post Baccalaureate Distinguished Mentor Award and in 2017 the NIH-NIA Director's Merit Award. He is Associate Editor of Ageing Research Reviews. He serves on several editorial boards including the Journal of Biological Chemistry, Aging, and Genes and international grant review boards including NIH, Italian Telethon, and German Research Foundation. He is a member of the American Federation of Aging Research National Scientific Advisory Council, lectures at Johns Hopkins University, and is involved in Outreach Programs to provide children hands-on learning opportunities in science.

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