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Biochemical and biological assays for the discovery and characterization of DNA helicase inhibitors

The growing number of helicases implicated in hereditary disorders and cancer is indicative of their fundamentally essential roles in DNA transactions, genomic stability, and cellular homeostasis. Indeed, molecular and cellular evidence demonstrates that helicases catalytically unwind or remodel a variety of nucleic acid substrates and interact with numerous proteins to perform their functions in replication, DNA repair, recombination, and transcription. Understanding how helicases operate in unique and overlapping pathways is a great challenge to researchers. Identification and characterization of biologically active small molecules that modulate the catalytic activity of a target helicase represents a unique approach to studying helicase function in human cells. In this review, we describe a series of experimental approaches and methodologies to identify and characterize DNA helicase inhibitors which collectively provide an alternative and useful strategy to explore their biological significance in cell-based systems. These procedures were used in the discovery of biologically active compounds that inhibited the DNA unwinding function catalyzed by the human WRN helicase-nuclease defective in the premature aging disorder Werner syndrome. Our studies with newly discovered WRN-specific helicase inhibitors have provided proof-of-principle evidence for how these compounds can be used in synthetic lethal approaches with other pharmacological agents or in defined genetic mutant backgrounds. In this Nucleic Acids 2017 Workshop, I will describe in vitro and in vivo experimental approaches to characterize helicase inhibitors with WRN as the model, anticipating that these approaches may be extrapolated to other DNA helicases, particularly those implicated in DNA repair and/or the replication stress response. Helicase inhibitors provide an alternative strategy for investigating the molecular and cellular functions of their targets, and in a broader scope, the sophisticated orchestration of overlapping and intersecting DNA metabolic pathways. In addition, my lab and others visualize helicases as suitable small molecule targets that might enhance existing anti-cancer strategies or emerge as novel therapeutic treatments.

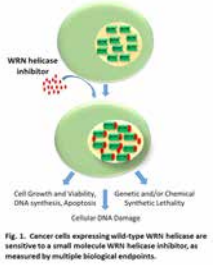

Fig. 1. Cancer cells expressing wild-type WRN helicase are sensitive to a small molecule WRN helicase inhibitor, as measured by multiple biological endpoints.

Biography

Robert M Brosh has his expertise in DNA Repair and Genome Stability Maintenance. He leads a Research group at the National Institute on Aging, NIH that is focused on characterizing the roles of clinically relevant human DNA helicases in cellular nucleic acid metabolism. This work has yielded insights into how DNA repair helicases promote phenotypes consistent with healthy aging and cancer resistance.

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