Big Data Training for Cancer Research

Special Lecture Series

Out of the Lab and into the Clinic: Translating Basic Science Discoveries into New Treatments for Patients

Dr. Mark Kelley

June 18, 2020, 1:00 – 2:30 PM (EST)

Abstract: The Base Excision Repair (BER) pathway is the body's main defense in repairing oxidative damage to DNA. The BER protein that has no "backup" or equivalent is APE1/Ref-1. Its dual name alludes to its unique dual functions as an AP endonuclease and as a redox effector factor (the "Ref" part of its name). While the fully folded protein performs its endonuclease function a locally unfolded configuration of the protein performs redox activities at its amino terminus. Unlike other redox proteins, APE1/Ref-1's cysteine residues are buried. Also, unlike other redox proteins that require two cysteine residues, APE1/Ref-1 requires three to perform its complex redox functions. Furthermore, APE1/Ref-1 is a master regulator of oxidative stress; and, as such, its redox activity maintains many transcription factors by keeping them in their active (reduced) state. Many of those factors are involved in cell growth, progression, proliferation, apoptosis, angiogenesis, and inflammation. We have shown that upregulation of APE1 occurs in many cancers (pancreatic, colon, bladder, sarcomas, etc), contributing to therapeutic resistance. Inhibition of APE1's redox activity blocks proliferation and migration by decreasing the transcription activity of NF-κB, AP-1, HIF-1α and STAT3— key factors involved survival, invasion, and metastasis. Based on these bench findings, we have developed small molecule inhibitors of the redox function of APE1/Ref-1. The first of these molecules, APX3330, has completed phase I clinical trials for safety and RP2D in cancer patients (NCT03375086). We are also developing new, second generation molecules to advance to the clinic. APE1 redox inhibition also holds promise as a potential treatment for inflammatory-based diseases, as well as situations where anti-angiogenic agents are used alone and to enhance the effectiveness of those agents. These indications include diabetic macular edema (DME), diabetic retinopathy (DR), age-related macular degeneration (AMD), as well as inflammatory bowel disease (IBD). The path from bench to clinical trial will be discussed as well as future directions and indications for the clinical use of APE1/Ref-1 inhibitors.

Series Schedule:

June 18: Dr. Mark Kelley – Indiana University
June 19: Dr. Warren Kibbe – Duke University

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Speaker Bio: Dr. Kelley's work has focused on translational research in DNA damage and repair, specifically, to determine how those activities can be exploited therapeutically to treat cancers and protect normal cells from oxidative and DNA base damage. Since 1993, he has focused specifically on the enzyme apurinic/apyrimidinic endonuclease 1/ Redox effector factor-1 (APE1/Ref-1)—mechanistically as well as a therapeutic target in cancers and other diseases that manifest cancer-like properties. APE1/Ref-1 is unique to the Base Excision Repair Pathway (BER), with dual repair and redox signaling functions that are crucial to cellular viability. His work has been focused on teasing apart these functions and in the process he has discovered and has been developing redox-specific inhibitors of APE1/Ref-1. This original work was the impetus for becoming Chief Scientific Founder and Officer of Apexian Pharmaceutical targeting APE1/Ref-1 to produce new therapeutics for some of the deadliest and hardest-to-treat cancers. Apexian recently completed a phase I clinical trial using oral APX3330 in solid tumor patients (NCT03375086). This trial established safety, expected PK, target engagement, and responses in patients in the trial. Phase II trials are being developed in cancer and other indications. In broader terms, all the academic chairs he has held and the program leader and director positions he currently holds are dedicated to fast-tracking collaboration and translational research to find more effective cancer treatments. In his leadership positions, he also helps equip the next generation of researchers by training and mentoring junior faculty, postdoctorates, fellows, MD students and others. All of the discoveries during his career have culminated in 21 patents and over 185 articles in peer reviewed journals as well as 31 review articles/book chapters.

A complete Bibliography can be found at
https://www.ncbi.nlm.nih.gov/myncbi/mark.kelley.1/bibliography/public/

Register at: https://us02web.zoom.us/webinar/register/WN_-db-p8RpQfOkTYBSTxLlzA