NIH NATIONAL CANCER INSTITUTE | PURDUE UNIVERSITY CENTER FOR CANCER RESEARCH | INDIANA UNIVERSITY MELVIN AND BREN SIMON COMPREHENSIVE CANCER CENTER | BIG GR 2021

Big Data Training for Cancer Research

Special Lecture Series

Translating basic science discoveries for patients: Use of bioinformatics to discover new pathways for targeting APE1/Ref-1 for cancer treatments

Dr. Mark R. Kelley

June 17, 2021, 1:00 – 2:30 PM (EDT)

Abstract: Comprehensive molecular characterization of the APE1/Ref-1 enzyme and its functions. The Base Excision Repair (BER) pathway is the body's main defense in repairing oxidative damage to DNA. The most singular 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). 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/Ref-1 occurs in many solid cancers (pancreatic, colon, bladder, sarcomas, etc), contributing to therapeutic resistance. Inhibition of APE1/Ref-1'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 in cancer patients (NCT03375086). APX3330 has also advanced to Phase II clinical trials in diabetic retinopathy (DR) and diabetic macular edema (DME) with a trial currently accruing patients (NCT04692688). We are also developing new, second generation molecules to advance to the clinic. Recently, using bioinformatics we have identified new pathways where APE1/Ref-1 plays a role. Previously published single cell (sc) RNA-seq analysis of low passage pancreatic patient derived Pa03C cells transfected with scrambled or siAPE revealed novel pathways to be downregulated with APE1/Ref-1 knockdown. Under hypoxia, a cluster within scRef-1 cells was found to have high expression of HIF1α-regulated genes while a cluster within the siRef-1 cells corresponded to consistently down-regulated genes that were downstream of HIF1α. Analysis of the same data for a comparison between normoxia and hypoxia identified glycolysis, TCA cycle, and OXPHOS to be downregulated with APE1/Ref-1 knockdown especially under hypoxia. Data in non-cancer cells and comparison to cancer cells will also be discussed. 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 based on these new findings.

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 including ocular diseases. A phase II trial using APX3330 in diabetic retinopathy (DR) and diabetic macular edema (DME) recently began accruing patients (NCT04692688). 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. He is also directing the Cancer Drug Discovery and Development (CDDD) program in the IU Simon Comprehensive Cancer Center (IUSCCC) and is a member of the CTSA drug discovery "think-tank" at IUSM. His current h-index is 73. 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://purdue-edu.zoom.us/webinar/register/WN_PuK61jbhSWWHdFIK3jGLyQ