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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

May 26, 2022, 1:00 – 2:30 PM (EDT)

Abstract: 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 in 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 IIb clinical trials in diabetic retinopathy (DR) and diabetic macular edema (DME) with the trial completing enrollment and will report data in late 2022 (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. Additionally, we have new data on the MOA of the APX compounds and their interaction with the APE1/Ref-1 protein as well as a method to determine the redox status of APE1/Ref-1 in cells with and without addition of APX compounds. This will be discussed along with the redox signaling interactions of PRDX-APE1/Ref-1-TRX axis. The path from bench to clinical trial as well as future directions and indications for the clinical use of APE1/Ref-1 inhibitors based on these new findings will be presented.

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 1991, 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-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 concentrated 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 Officer and co-Founder 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. A Phase IIb trial in diabetic retinopathy (DR) and diabetic macular edema (DME) will report data in late 2022 (NCT04692688). He is developing new APE1/Ref-1 APX inhibitors for not only cancer and ocular treatments, but for other diseases that have shown a role of APE1/Ref-1 such as Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis). In broader terms, all the academic positions 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 and other disease treatments. In his leadership positions, he helps equip the next generation of researchers by training and mentoring junior faculty, postdoctorates, fellows, MD students and others. He is the Associate Director of Basic Science in the IU Simon Comprehensive Cancer Center (IUSCCC) and is also co-directing the Cancer Drug Discovery and Development (CDDD) program in the IUSCCC and is a member of the CTSA drug discovery "think-tank" at IUSM. He was recently made an AAAS Science Fellow. His current h-index is 73. All of the discoveries during his career have culminated in 21 patents and over 194 articles in peer reviewed journals as well as 36 review articles/book chapters (complete Bibliography at https://www.ncbi.nlm.nih.gov/myncbi/mark.kelley.1/bibliography/public/

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