NIH NATIONAL CANCER INSTITUTE | PURDUE UNIVERSITY Institute for Cancer Research | INDIANA UNIVERSITY MELVIN AND BREN SIMON COMPREHENSIVE CANCER CENTER | 2023

Big Data Training for Cancer Research

Special Lecture Series

What do Cancer, Retinal Diseases and Inflammatory Bowel Disease have in common? One target multiple diseases: A trip from the bench to biotech startup to clinical trials.

Dr. Mark R. Kelley

May 21, 2023, 1:00 – 2:15 PM (EDT)

Abstract: APE1/Ref-1 or 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 successfully completed phase I clinical trials in cancer patients (NCT03375086). APX3330 has also successfully completed a Phase II clinical trial in diabetic retinopathy (DR) and diabetic macular edema (DME) 2 (NCT04692688) and will have an End of Phase II (EOP2) meeting with the FDA later this year. 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. We have extended this analysis to human retinal endothelial cells (HRC) and compared alteration of APE1/ Ref-1 in HREC to cancer cells. 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. Additional studies have identified inflammatory bowel disease (IBD) which includes Crohn's and Ulcerative Colitis as a target for APE1/Ref-1 intervention using APX redox inhibitors. Discussion of how cancer, retinal disease and IBD are related through the APE1/Ref-1 protein, its functions and how inhibiting the redox function of Ref-1 can impinge on the difference diseases. 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 and redox signaling. He has focused specifically on the enzyme apurinic endonuclease 1/ Redox effector factor-1 (APE1/Ref-1), as a therapeutic target in cancers and other diseases where APE1/Ref-1 is involved. 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 II trial in diabetic retinopathy (DR) and diabetic macular edema (DME) was successful and clinical trial data reported in January, 2023 (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 Accelerator (C3DA) program in the IUSCCC and is a member of the CTSA drug discovery "think-tank" at IUSM. He is the PI of the IUSCCC ACS Institutional training grant in its 38th year and recently was awarded as PI an ACS Diversity in Cancer Research (DICR) post-baccalaureate award (1 of only 8 in the country) to augment our ACS DICR summer internship award (PI) to train the next generation of DEI cancer scientists. He is also an AAAS Science Fellow. His current h-index is 76. All of the discoveries during his career have culminated in 19 patents and over 201 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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