Tao Lu, J Cancer Sci Ther 2017, 9:10 (Suppl)
DOI: 10.4172/1948-5956-C1-114

AlphaLISA high throughput screen discovers a novel small-molecule inhibitor to target protein arginine methyltransferase 5 in pancreatic and colorectal cancers

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Pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer (CRC) are notoriously challenging for treatment. Hyperactive nuclear factor κB (NF-κB) is a common culprit in both cancers. Previously, we discovered that protein arginine methyltransferase 5 (PRMT5) methylated and activated NF-κB. Here, we show that PRMT5 is highly expressed in PDAC and CRC. Overexpression of PRMT5 promoted cancer progression, while shRNA knockdown showed an opposite effect. Using an innovative AlphaLISA high throughput screen, we discovered a lead compound, PR5-LL-CM01, which exhibited robust tumor inhibition effects in both cancers. An in silico structure prediction suggests that PR5-LL-CM01 inhibits PRMT5 by binding with its active pocket. Importantly, PR5-LL-CM01 showed higher antitumor efficacy than the commercial PRMT5 inhibitor, EPZ015666, in both PDAC and CRC. This study clearly highlights the significant potential of PRMT5 as a therapeutic target in PDAC and CRC, and establishes PR5-LL-CM01 as a promising basis for new drug development in the future.

Biography

Tao Lu is a tenure-track Assistant Professor and Principle Investigator at Department of Pharmacology and Toxicology and a member of Simon Cancer Center at Indiana University School of Medicine. She obtained her PhD degree from University of Toledo, School of Medicine and finished her Post-doctoral training with the world renowned scientist Dr. George Stark at Cleveland Clinic, Ohio. Her research focuses on the discovery of novel regulators of NF-kB, particularly, on the epigenetic regulation of NF-kB and its role in cancer therapeutics. She won multiple awards at international scientific meetings. She has published near 50 papers with 2 being highlighted by F1000 Prime. She currently holds 2 provisional patents regarding NF-kB regulation and serves as the board member of 5 scientific journals.

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