

PROTAC – Based Combination Therapy for the Treatment of Cancer

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Background

PROTACs (Proteolysis-Targeting Chimeras) represent a promising new class of drugs that selectively degrade proteins of interest from cells. PROTACs are small molecules with two functional ends, a small-molecule end that binds to the protein of interest and the other end that binds to an E3 ubiquitin ligase. The PROTAC component recruits the ubiquitin ligase to the target protein, leading to its ubiquitination and subsequent degradation by the proteasome. PROTACs have been developed for a variety of cancer targets including oncogenic kinases, epigenetic targets and recently KRAS^{G12C} proteins, with several currently being tested in clinical trials for various cancers. Acquired resistance to PROTACs has been reported in pre-clinical cancer models, suggesting PROTAC therapies may have limited long-term benefits in cancer. Accordingly, there is a need for therapeutic approaches that overcome resistance to PROTACs providing durable drug responses.

Summary of the Invention

Dr. James Duncan, Associate Professor in the Epigenetics in Signaling Program at Fox Chase Cancer Center has discovered a method for overcoming drug resistance to PROTACs in cancer patients undergoing PROTAC treatment. This approach is based on a surprising and unexpected discovery that resistance of cancer to PROTAC therapeutic regimens can be overcome by inhibiting one or more cell signaling pathways. Without being limited to any particular theory, it is believed that chronic exposure of cancer cells to PROTACs triggers reprogramming of cell signaling that promotes PROTAC resistance. Inhibition of particular cell signaling pathways may represent a general therapeutic strategy to overcome resistance and improve the durability of PROTAC treatments leading to better therapeutic responses. Moreover, this therapy can improve efficacy of PROTACs by minimizing the concentrations of PROTACs required to degrade protein targets in cells. Accordingly, inhibiting cell signaling pathways with one or more kinase inhibitors, KRAS inhibitors, or autophagy inhibitors will suppress this resistance mechanism thereby restoring cancer cell sensitivity to the PROTAC therapy.

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