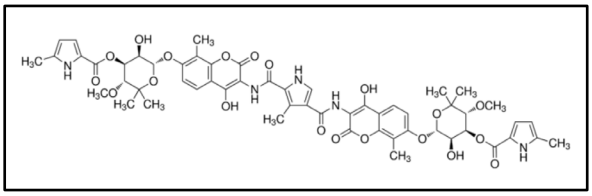
Novel Replicative CMG Helicase Inhibitors (CMGi) to Treat Solid Tumors

A new use for the aminocoumarin compounds coumermycin-A1 and clorobiocin has been identified as potent inhibitors of the human Cdc45-MCM-GINS (CMG) replicative helicase. This CMG helicase is important for DNA replication and recovering from fork-stalling chemotherapy. A molecular vulnerability in the CMG helicase exists in cancers that is derived from oncogene-driven weaknesses in CMG assembly and function (e.g., Myc and Cyclin E, which are overexpressed in the majority of human malignancies). Several cancers such as Small-Cell Lung Cancer, Osteosarcoma, Pancreatic Ductal Adenocarcinoma, and Colorectal Carcinomas have selective sensitivity to inhibition of the CMG. These drugs can inhibit the CMG helicase and the high-risk HPV16/18/31 E1 helicases in purified biochemical assays. They act by blocking ATP binding and hydrolysis of human and viral hexameric helicases, and SAR knowledge is available to facilitate the rationale design of improved versions. The drugs show cellular IC_{50}s of between 0.5-6μM against OS, SCLC, NSCLC, CRC, and PDAC. These cellular IC_{50}s are comparable to approved standard of care chemotherapy drugs. Human PK/PD data are available from earlier Phase 1 clinical trials where these compounds were tested as potential antibiotics. They were were found to be bioavailable and with SAEs similar to anti-neoplastics. These drugs represent a first-in-class set of CMG inhibitors, and offer novel CMG-targeting potential to treat solid tumors.



COMMERCIAL OPPORTUNITY

- OS, PDAC, and SCLC represent tumor types with limited available clinical options. OS is the most common bone cancer in teens and young adults, with a high morbidity once tumors spread. In the U.S., PDAC is estimated to be diagnosed in ~60,000 people, with ~48,000 deaths per year. Pancreatic cancers represent ~3% of all cancers in the U.S. Lung cancer is a leading cause of death in men and women, making up ~25% of all cancer deaths. SCLC represents ~13% and NSCLC ~84% of lung cancers. SCLC is typically associated with smoking, and certain oncogenes such as Myc are drivers of more aggressive subtypes of SCLC (data from ACS).
- Cancer cells are selectively sensitized to CMG inhibition because healthy cells have an excess, or reserve, of the CMG helicase that is used to recover from replicative stresses such as chemotherapy, but tumor cells have a diminished number of unused reserve CMGs due to oncogene-driven reduction in reserve levels. This occurs, for example, when Myc or Cyclin E are overexpressed in cancers, which over-uses or reduces their CMG reserves. Coumermycin-A1 or clorobiocin target the remaining CMG enzymes, weakening the ability of tumor cells to respond to and recover from chemotherapy or other fork-stresses.
- SAR knowledge with the hCMG indicate that these aminocoumarins use a ‘wine cork’ mechanism in which a head group dependent on a 2-methylpyrrole noviose sugar enters channels in the CMG through which ATP traverses into one of its six discrete catalytic clefts. The coumarin group occupies the channel and the head group interacts with the cleft, thus ‘corking’ the CMG from ATP entry or exit. This SAR allows for commercial opportunities to use rationale drug design to further improve these compounds for clinical use.

TECHNOLOGY

A class of compounds/drugs has been identified through biochemical screening of chemical libraries for inhibitors of the purified human Cdc45-MCM-GINS (hCMG) helicase, which also inhibit related hexameric helicases from HPV16/18/31 (E1 helicase). Human osteosarcoma 143B and OS252 cells were assayed in a cell viability experiment showing IC50s of between 0.5-3μM. SCLC, NSCLC, CRC, and PDAC tumor cells show similar low IC50s between 1-6μM. This IC50 range for tumor cells is similar to that seen with other chemotherapy drugs *in vitro* (dox, etoposide, gem, AZD6738/ATRi, BMN673/PARPi). Aminocoumarins block ATP binding/hydrolysis of the hCMG, and successfully target the hCMG in cells. SAR information is known and will facilitate rationale design of improved CMGi for clinical use. These aminocoumarins are a first-in-class set of CMGi with the capacity to treat multiple solid tumor types.

PUBLICATION/PATENT

- Provisional Patent application filed March 5, 2021 for Dr. Alexandrow.

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