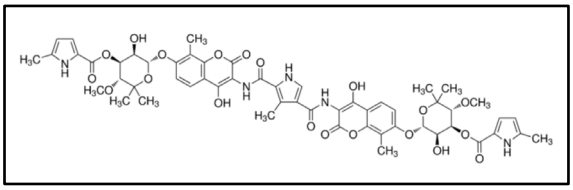
Novel Use for Aminocoumarins as HPV Helicase E1 Inhibitors to Treat Cancer

The naturally occurring Aminocoumarin compounds coumermycin-A1, clorobiocin, and novobiocin have been found to be inhibitors of the Human Papilloma Virus (HPV) E1 helicase. This HPV helicase is important for both infection, as well as replication and spreading of the virus. HPV infection is linked with several cancers such as cancer of the cervix, vagina, vulva, head and neck, anal, and penile carcinomas. These drugs can inhibit the human CMG helicase, SV40 virus Large T Antigen helicase and the high-risk HPV16/18 E1 helicase in purified systems. The drugs show cellular IC_{50}s of between 0.5-3μM. They act by blocking ATP binding and hydrolysis of hexameric helicases. These cellular IC_{50}s are comparable to approved standard of care chemotherapy drugs. These drugs have also already been in human Phase 1 clinical trials as antibiotics that inhibit the bacterial DNA gyrase and topo IV, where they were found to be bioavailable and without serious adverse events. These drugs represent a first-in-class set of anti-virals targeting HPV replication, and offer novel anti-neoplastic potential.



COMMERCIAL OPPORTUNITY

- HPV accounts for approximately 600,000 cases of cancers of the cervix, oropharyngeal cancers, anal cancers, vulvovaginal and penile cancers, as well as a genital wart and recurrent papillomatosis of the lungs worldwide. HPV type 16 and 18 are the most common oncogenic viruses among the HPVs that cause cancer. Uterine cervical cancer, the third most common cancer in women worldwide and the second most common cancer in Indian women, is caused by infection with one of these oncogenic types. In general, HPV has been associated with more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, 70% of oropharyngeal cancers and more than 60% of penile cancers. [Int J Appl Basic Med Res v.6(2); Apr-Jun 2016]
- While Novobiocin only inhibits the HPV helicase, coumermycin-A1 and clorobiocin were found to inhibit both the HPV helicase and the human CMG helicase. As such, coumermycin-A1 and clorobiocin may directly affect cancer cells in addition to inhibiting HPV replication because healthy cells have an excess or reserve of the MCM hexamer subunit of the human CMG helicase. In contrast, tumor cells lack a proper number of unused reserve MCM hexamers and cannot easily create new CMG helicases as needed, for example in recovering from chemotherapy drugs.
- Of the aminocoumarins, Novobiocin was FDA approved and used primarily for bacterial infections caused by penicillin-resistant S. aureus. Novobiocin was administered to patients in high oral doses of 3−9 g/day and reached high μM plasma levels. Cases of treatment failure were reported because of spontaneous resistance to novobiocin. Rash, sometimes severe, was the most commonly reported adverse effect, and occasionally hematological disorders and gastrointestinal intolerance were also seen. In 1969, a combined panel of the National Academy of Science and National Research Council reviewed efficacy claims for over 3000 marketed drug products, and stated that oral novobiocin should be taken off the market because of the “development of safer and more effective drugs.” [ACS Infect. Dis. 2015, 1, 4−41]. As such, the SAEs associated with the aminocoumarins may be more similar to anti-neoplastics than antibiotics.

TECHNOLOGY

A class of compounds/drugs has been identified through biochemical screening of chemical libraries for inhibitors of the purified replicative Cdc45-MCM-GINS (CMG) helicase, which also inhibit related helicases from SV40 (TAg helicase) and high-risk HPV16/18 (E1 helicase) in purified systems. Human osteosarcoma 143B and OS252 cells were assayed in a cell viability experiment showing IC50s of between 0.5-3μM. NCI-tested tumor lines showed similar low-μM IC50s (BC, CRC, NSCLC, PDAC, SCLC, melanoma). This IC50 range for OS tumor cells is equal to or below that seen with standard-of-care chemotherapy drugs in vitro (0.4-8μM; cis, dox, etoposide, gem). The mode of action of the drugs is by blocking ATP binding and hydrolysis of the hexameric helicases. The drugs (coumermycin-A1, clorobiocin, novobiocin) display differential inhibition of the CMG and E1 helicases, with novobiocin being specific for the E1 enzyme.

PUBLICATION/PATENT

- Provisional Patent application filed October 5, 2020 for Dr. Alexandrow.

CONTACT
Haskell Adler PhD MBA
Senior Licensing Manager
Haskell.Adler@Moffitt.org
(813) 745-6596

LICENSING OPPORTUNITY

MOFFITT CANCER CENTER