Cleveland Clinic Innovations

PRODUCT
Nanogel delivery system for chemotherapeutic drugs

INDICATION
Cancer, drug delivery

VALUE PROPOSITION
Nanogel-based drug delivery system allows for sequential delivery of chemotherapeutic agents which can prevent effects of drug resistance in cancer.

DEVELOPMENT STAGE
In vivo validation

INTELLECTUAL PROPERTY
Issued Patent (US10729659B2) (US)

RELATED PUBLICATIONS
Vijayaraghavalu S, Labhasetwar V. “Efficacy of decitabine-loaded nanogels in overcoming cancer drug resistance is mediated via sustained DNA methyltransferase 1 (DNMT1) depletion”. Cancer Lett. 2013 Apr 30;331(1):122-9.

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Nanogel Mediated Chemotherapy Delivery to Prevent Drug Resistance in Cancer

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UNMET NEED

Epigenetic mechanisms such as DNA hypermethylation can silence tumor suppressor genes and cell cycle regulators which can influence the efficacy of anticancer drugs. This epigenetic silencing influences tumorigenesis, tumor response to drug therapy, and is also the main cause of acquired drug resistance.. The epigenetic drug, decitabine (DAC) is a potent hypomethylating agent, but its effect is transient because of its instability. The major disadvantage of DAC is its instability, both in vitro (half-life in aqueous solution is ~4 h, in cell culture medium ~17 h) and in vivo (half-life 10-35 min). Therefore, there is an urgent unmet need to develop novel delivery mechanisms that can protect DAC (and other drugs) while increasing its half-life to treat solid tumors.

SOLUTION

Cleveland Clinic inventors have developed a nanogel-based delivery system which allows for sequential delivery of DAC to overcome chemotherapy-induced drug resistance in cancer. The nanogel is generated using poly-N-isopropylacrylamide (PNIPAM) which can be loaded with a wide range of epigenetic drugs and chemotherapeutic agents. A sequential method of nanogel drug loading was used, wherein the chemotherapeutic drug doxorubicin (DOX) was added first to the aqueous nanogel dispersion which resulted in partition of the drug to the core of the nanogel due to its hydrophobic nature. Next, following nanogel formation, the epigenetic drug DAC was loaded and was preferentially partitioned into the corona of the nanogel. When the nanogel was implanted at the tumor site it began to degrade, releasing DAC first followed by doxorubicin, thereby effectively inhibiting DNA hypermethylation before killing the tumor cells.

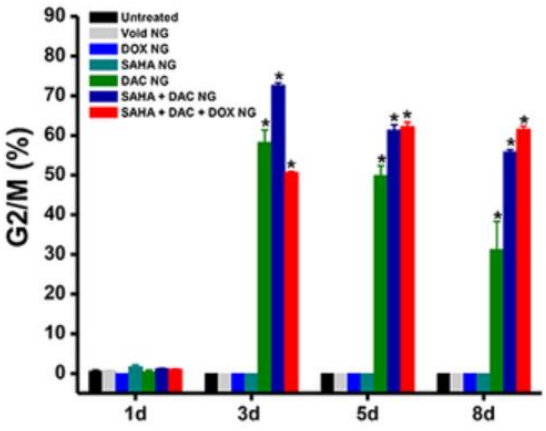

Fig 1. Quantification of percentage of cells in G2/M arrest phase treated with a combination of drugs loaded in NGs and analyzed at different time periods suggests the combination of SAHA/DAC and/or SAHA/DAC/DOX are most effective with the current nanogels developed.

In conclusion, this approach allows for novel chemotherapeutic treatment strategies which can reduce drug resistance and improve patient outcomes.