A Nanomedicine Based Combinatorial Approach for the Treatment of Ovarian Cancer Using Gene and Chemotherapy

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Introduction

Ovarian cancer is the fifth leading cause of cancer death in women and is known as the “silent killer” due to the fact that very few to any symptoms present until the later stages of the cancers development (John Hopkins). Every year approximately 22,000 women will be diagnosed and out of that population roughly 14,000 (~50%) of women will die because of it. Treatment for ovarian cancer is dependent on the stage that the disease has progressed. Unfortunately, >70% of women are diagnosed in the later stages, Stage III and IV, where the cancer has spread to distal organs as well as the peritoneal cavity. This late stage diagnosis is harder to treat, due to metastases of the tumor, and relies on the use of first line chemotherapeutic agents like cisplatin and taxanes for clinically effective therapeutic outcomes. A combinational therapeutic approach for cancer has been shown to be the most effective in vivo if the drug combination provides an additive or synergistic effect. Finding a drug combination that complement each other’s cytotoxic mechanism of action or block multiple pathways that may either confer chemoresistance or drive the cancers proliferation and growth is imperative in providing patients with the best chance for survival after diagnosis.

Hypothesis/Purpose

Develop and implement a synergistic therapeutic approach for the treatment of ovarian cancer using gene and chemotherapies. Through the synthesis of a targeted nanomedicine delivery platform capable of delivering siRNA targeted to a key oncogenic protein, DJ-1, we hypothesize that the suppression of DJ-1 along with the administration of the first line chemotherapeutic agent cisplatin we can: 1) elicit a synergistic cytotoxic response 2) reduce the amount of chemotherapy being administered while retaining therapy efficiency, thereby reducing dose dependent side effects 3) increase patient quality of life while reducing patient mortality.

DDS Synthesis

Problems:
- Rapid clearance (small size)
- Poor retention (large size)
- Difficult degradation
- Little penetration

Solutions:
- Increase in size (PEG)
- Targeting (folic acid, LHRH)
- Improved stability (SPG4, PIG4)
- Increased stability (PEG, SPG4)
- Enhanced degradation (SPG4, PIG4)

Drug Delivery System

 DDS Characterization

xCELLigence Real Time Cell Proliferation

Cell Cycle

Cell Index

Conclusion

This study sheds light on the need for a personalized medicinal approach when treating patients clinically. An overexpression of DJ-1 has been shown to be a poor prognosis marker as well as increasing proliferation and overall cell survival. To be able to biopsy and determine what is the driving force behind a particular cancer gives medical professionals a very powerful tool for formulating a therapeutic strategy to overcome those drivers. Very little in the way of therapeutic strategies have been employed targeting DJ-1, but in this work we have shown that after successful targeted delivery of our DJ-1 DDS that suppression of DJ-1 is more efficacious in shutting down proliferation, causing cell cycle arrest and increasing intracellular ROS than cisplatin alone. To be able to use this approach for the treatment of ovarian cancer where DJ-1 levels are high along with a decreased dose of our chemotherapeutic agent and still remain more efficacious than a single therapy alone is a promising therapeutic approach. There is still much to be done but this is a good platform to start from in the pursuit of better patient care and quality of life.

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