Comparative Study of Chemotherapy Drug Combinations

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Introduction
The use of polymeric nanoparticles to deliver imaging and therapeutic agents has become an active area of research. These amphiphilic particles have the ability to encapsulate hydrophobic molecules, while exposing a hydrophilic layer that is more soluble in the blood. Many chemotherapy drugs have to be altered in order to be soluble in the blood. These analogs are sometimes less potent than the original molecule. In addition to increasing solubility of drugs, these particles offer sustained release and can be conjugated with proteins that allow cell-specific delivery [1,2].

The success of these nanoparticles as a cancer treatment depends not only on their delivery, but the specific cancer cell type and therapeutic agents that are being delivered. Paclitaxel (PX) is an anti-mitotic agent. It binds to microtubules during mitosis, stabilizing them preventing further cell division [3]. Doxorubicin (DOX) has two mechanisms of action. It is an anthracycline antibiotic that prevents DNA synthesis and transcription. It also inhibits topoisomerase II [4]. Methotrexate (MTX) prevents DNA synthesis by inhibiting the enzyme dihydrofolate reductase, thus preventing the production of folic acid which is necessary for the synthesis of new purine bases [3]. MTX has also been shown to interfere with topoisomerase II [4]. Camptothecin (CPT) binds DNA in complex with topoisomerase I creating a cleavable conformation [4]. A great difficulty in the treatment of cancer is the recurrence of tumors after the initial treatment because of drug resistance. Combining chemotherapy drugs is a common practice in cancer therapy. The screening of drugs in vitro will give insight into what drug combinations might be most effective when encapsulated into nanoparticles in vivo.

Methods
- 48 well plates prepared with HeLa Cells

Dosage Curve Generation
- Dosage curves were created to determine EC₅₀ values for each drug.

Drug Combination Screening
- Preparation of 0.3 µM doses of each, determined from dosage curves.
- First treatment (red) applied and incubated for 20 hours.
- Second treatment (blue) applied and incubated for 20 hours.
- Cell viability was determined by crystal violet assay.

Results: Dosage Curves

Results: Encapsulation

Results: Drug Combinations

Conclusions
- PX and DOX in either order produced similar results, both rendering low cell viability and very similar resulting cell morphology.
- PX and CPT yielded very different results based on the order of delivery. PX followed by CPT was one of the most potent combinations in this investigation, whereas CPT followed by PX produced a significantly lower response.
- DOX and CPT effectiveness was also dependent on the order of delivery, CPT followed by DOX was a more potent combination than DOX followed by CPT.
- MTX did not prove very effective against this line of cancer cells. MTX and DOX have similar functionalities, so it is not surprising this combination was not highly effective. When combined with PX and DOX, MTX actually killed less cells than repeat treatments of the first drug.
- Overall, PX seemed to be the most potent drug against this line of cancer cells.
- Each of the drugs produces markedly different cell morphologies after treatment. Further investigations into the implications of the different cell morphologies could prove useful.

References

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