Design and Testing of Organometallic, Targeting Anticancer Drugs

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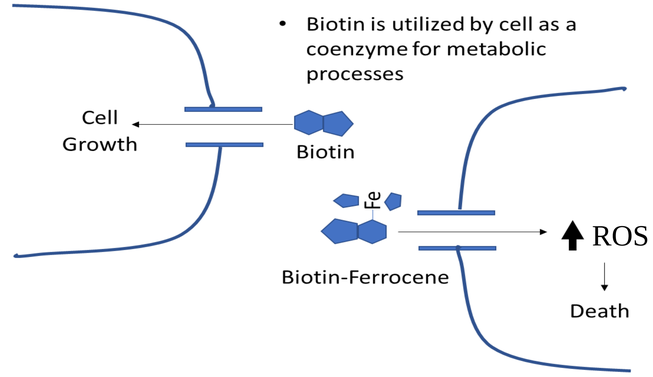
Abstract

Cancer is the second leading cause of death and will directly affect approximately 40% of the people in the United States over the course of their life. Chemotherapy has been shown to be an effective therapeutic strategy, but it lacks specificity, resulting in a multitude of negative side effects. Targeted therapies such as Herceptin, Iressa, and Nivolumab have shown increased effectiveness against cancer by attacking specific molecules in the target cell. For example, Herceptin inhibits the HER2 protein, which is overproduced in some breast cancer cells, and stops cell division. Biotin is an innate coenzyme for carbohydrate, lipid and protein metabolism. Certain cancer types overexpress biotin transporters on the surface of each cancer cell in order to increase biotin absorption necessary for metabolic processes. Furthermore, the intracellular environment in cancer cells is more reducing compared to non-cancer cells due to increased metabolism. Ferrocene is an iron-based organometallic molecule that has been shown to generate reactive oxygen species (ROS) in the reducing environment of cancer cells. Given that certain cancer cells absorb biotin with a higher efficiency, we hypothesize that linking biotin to ferrocene will increase the efficiency of ferrocene entering the cell and result in selective cancer cell death. Therefore, we have produced a library of biotin-ferrocene conjugates to selectively target cancer cell lines that over express biotin receptor sites. Experiments were conducted utilizing ferrocene and a variety of ferrocene-biotin conjugates (C1, C2, 2) in both cancer (MCF-7) and noncancer (HEK 293) cell lines in order to compare the relative toxicity between compounds.

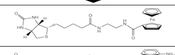
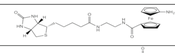
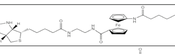
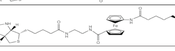
Hypothesis

Conjugating ferrocene and ferrocenyl-derivatives to biotin will result in increased absorption in cancer cells which will result in increased ROS and cell death.

Mode of Action

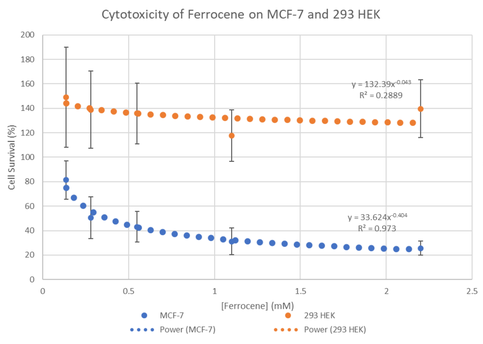


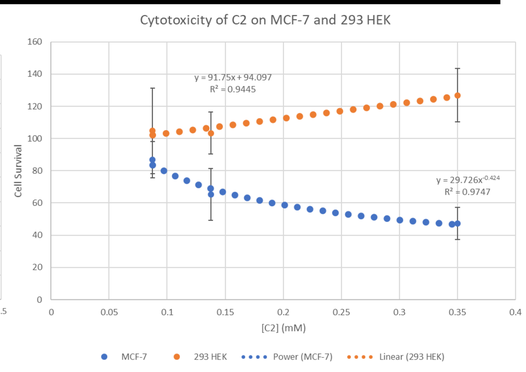
Compounds

Compound	Structure
Ferrocene	
C1	
C2	
2	
3A	

Synthesized by Dr. Green and Marianne Burnett, Department of Chemistry

Results





Discussion

Due to the increased metabolic rate in cancer, cancer cells are susceptible to the production of free radicals ROS. Compounds such as ferrocene have shown to increase levels of ROS and cell death in cancer cells in comparison to noncancer cells. Furthermore, cancer cells requirement of biotin and overexpression of the biotin transporter provides a novel mechanism for targeted cancer treatment. The overexpression of the biotin transporter allows for an increased efficiency of absorption of biotin in cancer cells. By conjugating ferrocene, ferrocenyl derivatives and biotin it is predicted that there will be an increased absorption f the compounds by cancer cells and will result in higher levels of ROS and cell death.

Conclusions

- Ferrocene has shown to increase levels of ROS in cancer cells
- C2 has also shown to result in increased levels of cell death in cancer cells (MCF-7) in comparison to noncancer (293 HEK) cell lines.