CALIFORNIA STATE SCIENCE FAIR
2016 PROJECT SUMMARY

Name(s)

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Project Number

S0538

Project Title

Investigation of Glucocorticoid Receptor Degradation and Its Antagonists to Address Cancer Drug Resistance

Abstract

Objectives/Goals

Prostate cancer treatment relies upon suppression of the androgen receptor (AR) pathway, but high levels of glucocorticoid receptor (GR) compensates for loss of AR activity, resulting in a drug-resistant tumor. Similarly, the default treatment method of chemotherapy for triple-negative breast cancer is only temporarily successful in the presence of high GR expression. To address the prevalent problem of cancer relapse, this project develops methods to lower GR level and identify suitable compounds to restore drug sensitivity and therapy effectiveness for prostate and breast cancer tumor-combative treatment.

Methods/Materials

A stable cell line was developed to evaluate compounds that can degrade GR. The cell line was transfected with a plasmid construct designed to express the GR linked to a fluorescent indicator. Protein expression and GR functionality were also tested with Western Blot and fluorescence microscope. A pharmacophore query was established by analyzing features of a known GR antagonist complex to mine a compound database.

Results

The stable cell line transfected with the plasmid was successfully created and in the presence of GR agonists, cell colonies express fluorescence concentration in the nucleus, indicating correct GR functionality. Molecular modeling identified 29 potential antagonists.

Conclusions/Discussion

The cell line has capability for high through-put screening of future GR antagonists, and compounds that degrade GR will be identifiable by loss of fluorescence. Multiple compounds were identified through modeling search for GR antagonists and five are promising for future testingon the stable cell line. The discovery and usage of these GR-degradative compounds has important implications for GR-directed cancer therapy to prevent drug resistance.

Summary Statement

Applying a glucocorticoid receptor (GR)-directed approach, I developed a stable cell line to evaluate GR level and identified potential GR antagonists with molecular modeling to address drug resistance in breast and prostate cancer.

Help Received

Laboratory experiments were carried out independently using equipment and facilities in the Dr. Ronald M. Evans Lab at the Salk Institute under the mentorship of Dr. Nanhai He. Molecular modeling procedures were designed and implemented by myself.