New Jersey State Commission on Cancer Research
LAY ABSTRACT OF RESEARCH PROJECT

NAME OF PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: **Lorna Rodriguez-Rodriguez**

Project Title: **Regulation of Multidrug Resistance by CD44**

Description: **Molecular manipulation of cancer cells will be used to determine the mechanism(s) involved in the CD44 induction of multidrug resistance**

The major causes of treatment failure in cancer are the presence or development of metastatic disease and drug resistance. Although many types of cancer initially respond to drug treatment, acquired drug resistance is a major factor that limits the effectiveness of therapy in patients with advanced disease. Furthermore, patients whose cancers come back or recur are rarely cured. This is in part related to the development of cross-resistance to anti-cancer drugs. Additionally, some patients have intrinsically resistant tumors at the time of diagnosis and never respond to chemotherapy.

There is indirect evidence that the metastatic and drug resistance characteristics of the tumor may be functionally linked. We recently uncovered a functional relationship between two proteins involved in these tumor characteristics: P-gp (confers drug resistance to tumors) and CD44 gives tumors the potential to spread or metastasize. We found that these two proteins are present in the cancer cell membranes and that they bind tightly to each other. When we introduced the gene for the CD44 protein into cancer cells, unexpectedly the gene for P-gp also increased and the cancer cells became resistant to anti-cancer drugs.

We have identified parts of the CD44 protein that may be responsible for the increase in anti-cancer drug resistance, for instance, the tail of the molecule that is inside the cell (intracytoplasmic). This tail gets chemically modified after the cell is exposed to certain conditions by moving a phosphorus molecule from one part of the tail to another. When the phosphorus moves, the cell becomes drug resistant. The CD44 tail may also get cut-off or cleaved. This cut allows the small tail to travel or be transported into the cell nucleus. Once in the nucleus the tail has then access to the cell's machinery to make new proteins. We are going to test the hypothesis that the CD44 tail moves into the nucleus and stimulates the production of P-gp.

We hope that by understanding how CD44 induces the production of P-gp, we may be able to customize drugs to specifically avoid the interaction of the two proteins, and allow the anti-cancer drugs kill the cancer cells. This work is innovative and will help understand and hopefully circumvent the major roadblock in cancer treatment, drug resistance.

Relevance: Cancer remains a largely incurable disease, due to our inability to circumvent metastasis and drug resistance. The goal of the proposed studies is to explore a link between these phenotypes. By understanding the molecular basis and phenotypic consequences of the interaction between CD44 and P-gp, we hope to be able to define new strategies for intervention and treatment of this deadly disease.