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

NAME OF PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: **Dessislava Dimova**

Project Title: **Genomic study of CDK-independent functions of RB proteins**

Description: **We will use Drosophila as a system to study unusual aspects of retinoblastoma gene function with the aim of generating hypotheses that would be easily testable in human tumor cell lines.**

Retinoblastoma (RB) was the first gene that was identified to predispose to cancer formation when an individual inherits a defective copy. The Rb gene is frequently inactivated in many types of human cancer, however, its role in tumorigenesis is still poorly understood. One of the reasons for this is that RB has many cellular functions. To this date all mutations in the Rb gene found in cancer patients destroy every function of the RB protein. This makes it difficult to determine which functions are important for tumor suppression.

Cyclin-dependent kinases (CDKs) control cellular proliferation and are frequently aberrantly activated in cancer cells. They function in part by inhibiting retinoblastoma proteins, and activating mutations in CDKs are often equated with loss of RB function. We and others have recently found that RB has functions that are not inhibited by CDKs. This means that in a cancer cell with an activating CDK mutation, RB retains some functions, while others are inhibited. It is important to understand what functions are retained by RB in such a setting and what their significance is in regard to tumor formation. This will go a long way towards determining which cellular functions of RB are important for tumor suppression.

The goal of this research project is to study these CDK-independent functions of RB. We use Drosophila (fruit fly) as a model organism for these studies for several reasons. The functions of RB, RB related proteins, their partners and their regulators (commonly referred to as the RB-pathway) are very well conserved, very similar in flies (some of the pathway functions were first elucidated in flies), however the pathway is much simpler making it much easier for study. The major advantage of flies however, is that it is technically very simple to turn genes on and off. We will identify functions of RB that are CDK independent using Genomics. Specifically, we will monitor the changes in gene expression of every gene in flies (approximately 18 000 genes) simultaneously in response to perturbations in CDK function using both "knock-down" and activating mutations and compare these changes to the ones that occur when we perturb the function of RB. Furthermore, we will study the mechanisms that allow some functions of RB to be inhibited by CDKs while others escape this inactivation. An analysis of such scale would be difficult and impractical to perform in human cells. We hope to narrow down the number of genes affected by RB, but not by CDK activity in order to provide a framework for the analysis of the RB pathway in human cancer cells. The importance of such studies is underscored by the recent advances in cancer treatment that are aimed to tailor medicines towards patients with specific mutations, perturbations in specific cellular functions. In order for such tailored treatments to work we need to know what are the specific functions perturbed in a given cancer. This is especially important for genes like Rb, that have many different (sometimes) opposing functions.