

## **Fontoura, Beatriz Marina Avilia**

Department of Molecular and Cellular Pharmacology  
University of Miami School of Medicine

2001 Program  
New Investigator (3-year project)

**Project Title:** Abnormal nuclear transport and cancer

**Project Summary:** The laboratory works on the mechanisms that determine how molecules move between two major compartments in the cell called the nucleus and the cytoplasm. Mislocalization of molecules in the cell is implicated in cancer. After synthesis, molecules have to be targeted to the right compartment to exert their function and also at a specific time. A wall called nuclear envelope surrounds the nucleus. In order to transverse this wall, molecules have to pass through gates termed nuclear pore complexes (NPCs). The NPCs are constituted of molecules or "guards" called nucleoporins or Nups, which control nuclear entry and exit of molecules that in turn regulate genes, cell growth and cancer. Nups are targets of viral proteins and disruption of Nup function is involved in cancer. The project identified and characterized three major Nups, Nup98, Nup96 and Sec13, which are key controllers of nuclear entry and exit of molecules involved in cancer. The Nup98-Nup96 pathway is highly regulated by the cellular environment, is a target of viral proteins, and is involved in tumorigenesis. The project goal is to understand the molecular mechanisms of this nuclear transport machinery to be able to regulate cell growth and cancer. The additional discoveries of novel mechanisms or molecules of this pathway are important for controlling cell growth and to serve as therapeutic targets. Recently, the project discovered that the interaction of Nup98 with another molecule called Rae1 is important in viral oncolysis, which is a new therapy being considered for several types of cancer.

**Project Successes:** The project identified an interacting partner of Nup96, Sec13, which is a component of the nuclear pore complex and the endoplasmic reticulum. The project results indicate that Sec13 is a key mediator of a cross-talk between the nucleus and the cytoplasm to regulate major cellular functions such as cell growth. It was mentioned, in the previous progress report that a manuscript had been submitted to *Mol. Cell. Biol.* The project is now glad to inform the Program that the project manuscript was accepted and published: "*Sec13 shuttles between the nucleus and the cytoplasm and stably interacts with Nup96 at the Nuclear Pore Complex.. Enninga, J., Levay A., and Fontoura B.M.A. Mol Cell. Biol. 23: 7271-7284, 2003.*" Importantly, Dr. Fontoura presented this work in a International Meeting: *EMBO Workshop, Mechanisms of Nuclear Transport, Italy, November 2003*, which was highlighted this week in *Nature Cell Biology*: "*Nuclear Transport erupts on the slopes of Mount Etna.*" *Nature Cell Biology February 2004*. These are very prestigious scientific journals.

The project findings on the effect of DNA damage in Nup expression are crucial for understanding the role of nucleoporins in cancer. The observation that expression of nucleoporins is up-regulated during DNA damage which then regulates nucleocytoplasmic transport of proteins involved in DNA repair and RNAs. This may constitute a key step for controlling cell growth and differentiation.

**Publications from BRP funded research in Peer Reviewed Journals:**

Enninga J, Levay A, Fontoura BMA. Sec13 shuttles between the nucleus and the cytoplasm and stably interacts with Nup96 at the Nuclear Pore Complex. *Mol Cell Biol.* 2003;23:7271-7284.

Enninga J, Levy DE, Blobel G, Fontoura BMA. Role of nucleoporin induction in releasing an mRNA nuclear export block. *Science.* 2002;295:1523-1525.

**Selected presentations from BRP funded research:**

Invited speaker: EMBO Workshop, Mechanisms of Nuclear Transport, Italy, November 2003, which was highlighted this week in *Nature Cell Biology*; "Nuclear Transport erupts on the slopes of Mount Etna." *Nature Cell Biology* February 2004.

Invited speaker: Second Annual Landon-AACR Awards Lecture, 2004.

Invited speaker: Joint Cancer Conference of the Florida Universities.

Invited speaker: Nuclear Pore Complex Workshop, NIH, 2004.

Poster presentations by students: American Society of Cell Biology, December 2003, San Francisco.

Invited speaker: Department of Pharmacology, UT Southwestern, 2003, A.Gilman's Department of Pharmacology.

Abstract on the 2002 Cancer Research Poster Session held on June 13, 2002 at the Sylvester Cancer Center.

**New grants based in part on BRP-funded work:**

NIH

Title: Regulation of nucleoporins by interferon

Project period: 7/01/03 - 06/30/08

Award amount: \$1,348,350