

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

NAME OF PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: **Gutian Xiao**

Project Title: **Studies of the proto-oncoprotein Cot in leukemia**

Description: **Using various biochemical, genetic and molecular biological techniques, the studies proposed in this grant proposal will address the oncogenic mechanism of Cot in conjunction with the Tax oncoprotein encoded by the human T-cell leukemia virus type 1 (HTLV-1), the etiologic agent of Adult T-cell leukemia (ATL).**

Tumor formation involves activation of proto-oncogenes or inactivation of tumor suppressor genes. The products of these genes usually play critical roles in regulating cell growth and survival. Understanding the molecular mechanisms that mediate the function and oncogenic alteration of these genetic factors are important for the design of effective cancer therapies. The studies proposed in the present application investigate the oncogenic mechanisms of a proto-oncoprotein, Cot, which is associated with both human and animal cancers. In normal cells, Cot is expressed in an inducible manner along with cell growth triggered by extra-cellular signals and appears to regulate cell cycle progression. Increasing evidence suggests that deregulated expression and function of Cot contributes to the induction of cell transformation and development of cancers. For example, Cot gene is over-expressed in about 40% of breast cancers.

We have obtained strong evidence showing that Cot can consistently be over-expressed and activated by infection of the human T-cell leukemia virus type 1 (HTLV-1). HTLV-1 is a sexually transmitted virus, which can also spread through blood transfusion and from mother to baby (during labor or via breast-feeding). HTLV-1 infection is associated with the development of an acute and often fatal T-cell malignancy, termed adult T-cell leukemia (ATL). Currently, though over 20-30 million of people worldwide are infected with HTLV-1, the prognosis for ATL patients is extremely poor, largely due to the lack of knowledge on how the virus induces T-cell transformation. The studies proposed here will provide important insights into the molecular mechanisms mediating the development of both ATL and other Cot-associated cancers.

We have found that Cot is both over-expressed and functionally activated in HTLV-1-infected T cells. An HTLV-1-produced viral protein, Tax, mediates the over-expression and activation of Cot. Cot and Tax appear to functionally cooperate in deregulating the growth and survival of T cells. Thus, the molecular interplay between the viral Tax oncoprotein and the cellular proto-oncoprotein Cot may be an important part of the mechanism underlying HTLV-1-induced T-cell malignancy. The **overall objective** of this grant application is to understand how Tax stimulates the activity of and functionally cooperates with Cot, and the role of this molecular interplay in the induction of human T-cell transformation.