

## Bankhead-Coley Cancer Research Program

**Kato, Yoichi**

Department of Biomedical Sciences  
Florida State University

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**Project Title:** The Mechanism of Notch Signaling Pathway in Radial Glial Development

**Project Summary:** More than a century ago, the pathologist Julius Cohnheim noted the similarities between cancers and embryonic cells. Although some of the details of Cohnheim's theory differ from our current understanding of cancer formation, his recognition of the relationship between development and cancer was remarkably prescient. In the last ten years, striking parallels between cancer and development have begun to appear. Abnormal functions of genes or signal transduction pathways identified as regulators of body formation in invertebrates and vertebrates have been implicated in a variety of human cancers. Similarly, molecules originally discovered based on their role in cancer have now been shown to function as fundamental regulators of cell growth and differentiation during development. Therefore, exploring the mechanisms that control cell fate during development can yield important insights into the mechanisms of cancer formation and potentially yield new targets for therapy. In this grant, the research team will uncover the mechanism of development of the nervous system, in particular radial glia cells. Radial glia cells function as guiding cells for newborn neurons to reach their final destination and as a source of neural stem cells during brain development. Recently, radial glia cells have been indicated as candidate cancer stem cells of ependymoma, a type of brain cancer. Most cancer cells are generated by stem cell-like cancer cells called cancer stem cells that are similar to normal stem cells but exhibit dysfunctional patterns of self-renewal and differentiation. To date, radial glia cell formation has been reported to be regulated by several signals, and one of them is Notch. The Notch signaling pathway regulates multiple biological processes during development. Importantly, deregulated Notch activity is involved in the human cancer formation, such as T-cell leukemia, pancreatic cancer, and brain cancers. These two observations support the hypothesis that elucidating the mechanism of radial glia cell formation by Notch signaling will contribute to understanding the mechanism of cancer formation as well as developing diagnostic approaches and treatment. The team's data have shown that radial glia cell formation is regulated by Notch signaling, but this Notch signal is carried into the nucleus by both an unknown intracellular pathway and the well-characterized classical Notch pathway. This unknown pathway is called a Su(H)-independent Notch signaling pathway. However, the mechanism of this pathway is poorly understood. In this grant, the research plan is to identify missing components that are involved in a Su(H)-independent pathway and characterize their functions. Embryos of *Xenopus laevis*, frogs, will be used as model animals for the following reasons:

1. Notch signaling is well-conserved between human and frog at the molecular level.
2. *Xenopus* development is more rapid than mammals, so the team can obtain the results more quickly.
3. It is very easy to overexpress target proteins and deplete them to study their function. In particular, as the team presumes many candidate molecules will be obtained from our proposed screen, the functional analysis using *Xenopus* seems to

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be suitable for this purpose. In Aim 1, the function of Deltex-1 will be studied, which plays a crucial role in the protein degradation process and is reported to be involved in a Su(H)-independent pathway in other developmental processes, in radial glia cell formation. In Aim 2, the team proposes to identify the missing factors, which associate with the intracellular domain of Notch receptor (NICD) and regulate the gene expression under the Notch activation in the nucleus, in a Su(H)-independent Notch pathway. Next, the team will characterize the functions of candidate molecules to examine whether they are involved in radial glia cell formation. About 20,000 new primary brain tumors are diagnosed in the U.S. each year. Molecules identified from this research could be the products of genes responsible for brain cancer formation as well as targets for cancer treatment in the future.