

DATE: January 14, 2009

TO: Howard Hendrickson, Ph.D.
Chairman, Voldeng Fellowship Selection Committee

FROM: Dwight R. Pierce, Ph.D. and
Kim Edward Light, Ph.D.
Department of Pharmaceutical Sciences

Re: Voldeng Fellowship Research Proposal

Title: “Development of Surviving Purkinje Neurons and Climbing Fibers Following Postnatal Ethanol-Induced Neuron Death”

One of the most extensively studied aspects of neural toxicity is the specific loss of Purkinje cells of the cerebellum induced by alcohol and possibly other drug exposures. The consequences of Purkinje cell loss are involved in the deficiencies of motor coordination and gait exhibited by children born to mothers with alcohol and drug use during pregnancy. Recent studies in our laboratory have characterized the manner of Purkinje neuron death after alcohol exposure as apoptotic.

In spite of extensive studies into the mechanisms of neural developmental damage induced by fetal alcohol or other drug exposure, virtually no systematic hypotheses have addressed the fate and developmental sequencing of the neurons that survive the toxicity. **We hypothesize that the surviving neurons exhibit developmental alterations expressed as morphologically stunted and underdeveloped structures with incomplete synaptic connections compared to neurons from non-exposed conditions.** We focus on the Purkinje neurons of the cerebellum using rat and primate model systems. For the rat model, exposure to ethanol occurs during one of three postnatal periods: postnatal day (PN) 4, PN4-6 or PN7-9. For the primate model, vervet monkeys (*Chlorocebus aethiops sabeus*) consume alcohol in a naturalistic environment during the third trimester of pregnancy with analysis of the offspring either immediately at birth or at 2 years of age.

We have developed data from immunofluorescence and confocal microscopy with 3D reconstruction and quantitative analysis to identify significant deficits of proteins uniquely expressed in climbing fibers and Purkinje neurons. Additionally, we have early indications of alterations in the architecture of the dendritic tree and the electrophysiological functioning of these neurons. We will work to extend these analyses to include key proteins of interest and to develop additional analytical tools to address related questions.

Opportunities

The Voldeng Fellow will focus primarily on learning tissue preparation for histological analyses along with the immunofluorescence and electrophysiological analysis of single neurons. The Voldeng Fellow will work as part of a team consisting of

three Ph.D. investigators, a research technologist, and one or more other students. Work in this laboratory provides the Voldeng Fellow with an opportunity to learn modern molecular biological techniques and sophisticated microscopic imaging analyses applied to address research questions of critical importance. This team approach will allow the Voldeng Fellow to experience research in a basic science laboratory as well as glimpse of the nature of the graduate education atmosphere, the collaborative nature of modern research, and the relationships between basic and translational research activities.

Funds for supplies are available from investigator resources.