**UNIVERSITY OF CINCINNATI**
**Department of Pharmacy**

# SUMMER RESEARCH OPPORTUNITIES FOR UNDERGRADUATE WOMEN

## APPLICATION DEADLINE: MARCH 1, 2005

*The Department of Pharmacy is pleased to offer the following research project for the summer of 2005. Interested students are urged to contact the faculty member(s) directing the project that most interests them. By contacting the faculty member, you can discover more about the project, learn what your responsibilities will be and if possible, develop a timetable for the twelve-week research period.*

## Prolactin (PRL) and the profound effects on Female Fertility

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Prolactin (PRL), a hormone produced by anterior pituitary lactotrophs, has profound effects on female fertility. Hypersecretion of prolactin by pituitary adenomas is the major neuroendocrine-related pathology associated with female infertility and tumor growth is associated with multiple endocrine and visual complications due to compression of the brain. The underlying defects that lead to the common hypersecretion of PRL and hyperproliferation of lactotrophs remain ill defined. Usually, both the secretion of PRL and the proliferation of lactotrophs are under tonic inhibition by hypothalamic dopamine (DA). The fact that reduced responsiveness to DA is a hallmark of hyperprolactinemic syndromes demands that we focus attention on the cellular and molecular basis of DA actions on the lactotroph.

We have discovered and extensively characterized a DA-activated potassium channel ($K_{DA}$) in normal female lactotrophs. DA regulates lactotroph membrane excitability through activation of $K_{DA}$ and both *in vitro* and *in vivo* studies have demonstrated a critical role for this $K_{DA}$ channel in the regulation of PRL secretion by DA. The possible role of the $K_{DA}$ channel in DA's antiproliferative actions on lactotrophs is unknown. This proposal is part of our approach to examine this question. We have made two genetically engineered mouse models in which to study the role of $K_{DA}$ in the control of lactotroph proliferation. The first model carries a dominant—negative mutant of the $K_{DA}$ channel, specifically expressed in pituitary lactotrophs. These animals have demonstrated a disrupted ability of DA to inhibit PRL secretion ("*Loss of function*" model). The second transgenic model carries a constitutively active K channel, with the same biophysical properties as $K_{DA}$, over expressed in pituitary lactotrophs. These animals have an enhanced inhibition of PRL secretion compared to wild type animals ("*Gain of function*" model). We have found that anterior pituitary wet weight in our transgenic dominant-negative mice ("*Loss of function*" model) is slightly larger than wild type controls even though disruption of the $K_{DA}$ channel leads to hyperprolactinemia only on proestrus. The anterior pituitaries of our female "*Gain of function*" (Kir2.1 mice) mice are significantly smaller than age-matched wild type controls. Taken together these findings make a compelling argument for a role of $K_{DA}$ and inhibited membrane excitability in the antiproliferative action of DA.

We are testing this hypothesis by crossing our mice with another line of mice that spontaneously develops PRL adenomas. These studies will determine if the $K_{DA}$ channel and lactotroph membrane excitability play a role in the antiproliferative actions of DA. These studies may have considerably broader implications regarding proliferation and adenomatous transformation in general. Students participating in this study will be involved in some animal handling and will learn immunocytochemical techniques for the identification of proliferating lactotrophs in the anterior pituitary glands and mRNA analysis.