COLLEEN COSGROVE HEGG

Pharmacology and Toxicology
Michigan State University
B439 Life Sciences
East Lansing, MI 48824

EDUCATION

1990 **B.A., Kalamazoo College, Kalamazoo, Michigan**
Major: Chemistry
Research Advisor, Senior Thesis: Professor Peter Cobbett at Michigan State University
Thesis Project: Characterized the physiological differentiation of N1E-115 cells.

1996 **Ph.D., Environmental Toxicology, University of Wisconsin - Madison**
Focal Area: Neurotoxicology
Advisor: Professor Vjekoslav Miletic
Thesis Project: Examined the neurotoxic effects of lead on voltage-gated calcium currents.

1996 - 1999 **NIH Postdoctoral Training Grant Recipient, University of Minnesota-Minneapolis**
Focal Area: Neuropharmacology
Advisor: Professor Stanley A. Thayer
Research Area: Studied glial-induced AIDS neurotoxicity.

GRANT SUPPORT

CURRENT

7/1/04-6/30/09 Grant: Injury-Evoked Regeneration Mechanism in Olfactory System
Studies the role of extracellular ATP in regeneration of olfactory receptor neurons.
Principal Investigator: Colleen C. Hegg, Ph.D.
Agency: National Institute on Deafness and other Communication Disorders
Type: R01 (DC0006897) Direct cost $175,000/year, Total cost $336,625/year

PAST

8/1/01-7/31/04 Grant: Purinergic Receptors in the Mammalian Olfactory System
Studies the role of purinergic receptors in olfactory receptor neurons.
Principal Investigator: Colleen C. Hegg, Ph.D.
Agency: National Institute on Deafness and other Communication Disorders
Type: R03 (DC04953) Direct cost $50,000/year, Total cost $75,000/year

PROFESSIONAL EXPERIENCE

2006 - present ***Assistant Professor*; Pharmacology & Toxicology Department, Michigan State University**
Currently investigating whether ATP acts as a neurotrophic factor during injury-evoked neuronal regeneration in the olfactory system.

General Research Interests

- Mechanisms of neurogenesis and neuroregeneration
- The physiological effects of bioactive peptides on olfactory receptor neurons and glial-like sustentacular cells
- Glial-neuronal interactions in the peripheral olfactory system
- Cellular mechanisms of neurotoxicity

2003 - 2006 ***Research Assistant Professor*; Department of Physiology, University of Utah**

- Determined that ATP is released in the olfactory epithelium by noxious stimulation.

2000 - 2003 ***Research Associate*; Department of Physiology, University of Utah**

- Developed a mouse olfactory epithelial slice preparation to examine dopaminergic modulation of odor responses visualized using confocal imaging.
- Determined that exogenous and endogenous ATP and dopamine act as neuromodulators for odor reception, and examined the effects of PACAP in the peripheral olfactory system.

1996 - 1999 ***NIH Postdoctoral Fellow*; Department of Pharmacology, University of Minnesota**

- Characterized the effects of HIV-1 proteins, chemokines and drugs of abuse on glutamatergic synaptic transmission and calcium signaling pathways in rat hippocampal neurons and human microglia.
- Demonstrated that HIV-1 proteins and β-chemokines desensitize chemokine receptors.

1991 - 1996 ***Graduate Student*; Environmental Toxicology Center, University of Wisconsin-Madison**

- Examined how chronic exposure to lead alters neural function and produces neurotoxicity.
- Evaluated the acute and chronic effects of low-level lead on voltage-gated calcium currents.
- Demonstrated that chronic lead exposure results in notable increases in calcium current that may impair normal cellular function.

1991 ***Summer Intern*; Chemical Industry Institute of Toxicology, Research Triangle Park, NC**

- Investigated biochemical mechanisms of furan-induced cytolethality.
- Isolated rat hepatocytes and measured glutathione levels and lactate dehydrogenase release.

1990 ***Research Assistant*; Department of Medicine, University of Chicago, IL**

- Examined interactions between lipoproteins.
- Maintained primary human hepatocytes and developed a gel electrophoretic separation system to detect both apo(a) and Lp(a) lipoproteins.

1990 ***Undergraduate*; Pharmacology and Toxicology Department, Michigan State University**

- Conducted an independent research project that received Biology Departmental Honors.
- Characterized the physiological differentiation of N1E-115 cells using the patch clamp technique.

1988 ***Undergraduate Intern*; The Upjohn Company, Kalamazoo, MI**

- Responsible for running potency and impurity assays on many Upjohn products and materials using high performance liquid chromatography.

SCHOLASTIC HONORS

2007 New Investigator Award, Central Nervous System Section, American Physiological Society
1996 - 1999 NIH-Neuroscience Drug Abuse Research Training Grant Recipient, University of Minnesota
1993 - 1996 NIH-Environmental Toxicology Training Grant Recipient, University of Wisconsin
1990 Honors for Independent Research, Biology Department, Kalamazoo College
1990 Catherine A. Smith Prize, Kalamazoo College
1986 - 1990 Kalamazoo College Honors Scholarship

BIBLIOGRAPHY

PUBLICATIONS

1. S Kanekar, and CC Hegg. **2007**. Purinergic receptor activation evokes neurotrophic factor NPY release from mouse olfactory epithelial slices. *Neuroscience*, submitted October 2007.

2. CC Hegg, M Irwin, and MT Lucero. **2007**. Calcium store-mediated signaling in sustentacular cells of the mouse olfactory epithelium. *Glia*, submitted, July 2007 (currently in revision).

3. CC Hegg, and MT Lucero. **2006**. Purinergic receptor antagonists inhibit odorant-evoked heat shock protein 25 induction in mouse olfactory epithelium. *Glia*, 53:182-190.

4. F Vogalis, CC Hegg, and MT Lucero. **2005**. Electrical coupling in sustentacular cells of the mouse olfactory epithelium. *J. Neurophysiol.*, 94:1001-1012.

5. F Vogalis, CC Hegg, and MT Lucero. **2005**. Ionic conductances in sustentacular cells of the mouse olfactory epithelium. *J. Physiol.,* 562:785-799.

6. CC Hegg and MT Lucero. **2004**. Dopamine reduces odor- and elevated K^+-induced calcium responses in mouse olfactory receptor neurons in situ. *J. Neurophysiol.,* 91:1492-1499.

7. CC Hegg, E Au, AJ Roskams and MT Lucero. **2003**. PACAP is present in the olfactory system and elicits calcium transients in olfactory receptor neurons. *J. Neurophysiol.*, 90:2711-2719.

8. CC Hegg, D Greenwood, W Huang, P Han and MT Lucero. **2003**. ATP differentially modulates odor responsiveness through purinergic receptor activation**.** *J. Neuroscience*, 23:8291-301.

9. JR Lokensgard, S Hu, CC Hegg, SA Thayer, G Gekker and PK Peterson. **2001**. Diazepam inhibits HIV-1 Tat-induced migration of human microglia. *J. Neurovirol.*, 7: 481-486.

10. WS Sheng, S Hu, CC Hegg, SA Thayer and PK Peterson. **2000**. Activation of human microglial cells by HIV-1 gp41 and Tat proteins. *Clin. Immunol.,* 96: 243-251.

11. CC Hegg, S Hu, PK Peterson and SA Thayer. **2000**. β-chemokines and HIV-1 proteins evoke intracellular calcium increases in human microglia. *Neuroscience*, 98:191-199.

12. S Hu, CC Chao, CC Hegg, SA Thayer and PK Peterson. **2000**. Morphine inhibits human microglial cell production of and migration toward RANTES. *J. Psychopharmacol.,* 14: 238-243.

13. CC Hegg and SA Thayer. **1999**. Monocytic cells secrete factors that evoke excitatory synaptic activity in rat hippocampal cultures. *Eur. J. Pharmacol*., 385:231-237.

14. CC Hegg and V Miletic. **1998**. Diminished blocking effect of acute lead exposure on high-threshold voltage-gated calcium currents in rat PC12 cells chronically exposed to the heavy metal. *Neurotoxicol*., 19:413-420.

15. CC Hegg and V Miletic. **1997**. Chronic exposure to inorganic lead increases high-threshold voltage-gated calcium currents in rat PC12 cells. *Brain Res*., 772:63-70.

16. CC Hegg and V Miletic. **1996**. Acute exposure to inorganic lead modifies high-threshold voltage-gated calcium currents in rat PC12 cells. *Brain Res.*, 738:333-336.

17. C Cosgrove and P Cobbett. **1991**. Induction of temporally dissociated morphological and physiological differentiation of N1E-115 cells. *Brain Res. Bulletin*, 27:53-58.

ORAL PRESENTATIONS AT SCIENTIFIC CONFERENCES

1. *Invited Speaker* at Symposium: "Gainfully Employed: From Launching a Job Search to Navigating Negotiations". CC Hegg. **2008**. Launching a successful job search. Experimental Biology Annual Meeting, San Diego, CA, April 5-9.
2. *Abstract selected for oral presentation* in the Featured Topic "Disorders of the enteric nervous system". S. Kanekar, CC Hegg. **2007**. Purinergic receptor activation evokes neurotrophic factor NPY release from mouse olfactory epithelial slices. Experimental Biology Annual Meeting, Washington, D.C, April 28-May 2.
3. *Invited Speaker* at Symposium: "Non-neuronal cells in olfactory system in development". CC Hegg, F Vogalis, and MT Lucero. **2004**. Sustentacular cells- More active than we ever imagined. Association for Chemoreception Sciences 24th Annual Meeting, (*Chem. Senses,* in press (A254).
4. CC Hegg and MT Lucero. **2001**. Purinergic receptors in the peripheral mammalian olfactory system. Sponsored by University of Utah Neuroscience program. Neurobiology of Disease-Neuroscience Mini-Symposium, Snowbird Resort, UT, November 2-3.
5. CC Hegg and MT Lucero. **2001**. ATP evokes Ca^{2+} increases and inward currents in mouse olfactory receptor neurons. Association for Chemoreception Sciences 23rd Annual Meeting, (*Chem. Senses,* 26:1073).
6. CC Hegg and MT Lucero. **2001**. Visualization of purinergic receptors in the mammalian olfactory system. Sponsored by NIH-NIDCD. New Strategies for Functional Visualization of Peripheral and Central Chemosensory Cells Conference, Jackson, WY, February 9-12.

POSTER PRESENTATIONS AT SCIENTIFIC CONFERENCES

1. S. Kanekar, CC Hegg. **2007**. Purinergic receptor activation evokes neurotrophic factor NPY release from mouse olfactory epithelial slices. Experimental Biology Annual Meeting, Washington, D.C, April 28-May 2.
2. S. Kanekar, CC Hegg. **2007**. Purinergic receptor activation evokes neurotrophic factor NPY release from mouse olfactory epithelial slices. Keystone Symposium, Snowbird, Utah January 19-23.
3. S Kanekar, CC Hegg. **2006**. Purinergic receptor activation evokes neurotrophic factor NPY release from mouse olfactory epithelial slices. Association for Chemoreception Sciences 28th Annual Meeting, (*Chem. Senses,* in press)
4. Hegg CC. **2005**. The role of transporter proteins in the release of neuromodulators in the olfactory epithelium. Conference on Chemosensory Modulation, Jackson, WY, January 21-24.
5. B Brown B, CC Hegg. **2005**. The role of transporter proteins in release of the neuromodulator ATP in the mouse olfactory epithelium. Association for Chemoreception Sciences 27th Annual Meeting, Sarasota, FL, April 13-17. *Chem. Senses,* in press (A201).
6. CC Hegg. **2004**. Purinergic Receptor Activation Modulates Odor Sensitivity And Purinergic Receptor Antagonism Blocks Heat Shock Protein Induction - Novel Neuroprotection Mechanisms In The Mouse Olfactory System? Purines, Chapel Hill, NC.
7. CC Hegg, F Vogalis, and MT Lucero. **2004.** Sustentacular cells- More active than we ever imagined. Association for Chemoreception Sciences 24th Annual Meeting, (*Chem. Senses,* in press (A254).
8. F Vogalis, CC Hegg, and MT Lucero. **2004**. Electrophysiology of sustentacular cells in mouse olfactory epithelium (OE). Association for Chemoreception Sciences 26th Annual Meeting, Sarasota, FL, April 21-25. *Chem. Senses,* in press (A285).
9. CC Hegg, K Davis and MT Lucero. **2003**. Inhibition of heat shock protein induction in mouse olfactory epithelium by in vivo administration of purinergic receptor antagonists. Association for Chemoreception Sciences 25th Annual Meeting, Sarasota, FL, April 9 -13. *Chem. Senses,* 28:561.

10. P Han, CC Hegg, and MT Lucero. **2003**. PACAP inhibits ORN apoptosis and reduces transient K current through different intracellular pathways. Association for Chemoreception Sciences 25th Annual Meeting, Sarasota, FL, April 9 -13. *Chem. Senses*, 28:551.
11. CC Hegg, K Davis and MT Lucero. **2003**. Inhibition of heat shock protein induction in mouse olfactory epithelium by in vivo administration of purinergic receptor antagonists. Society of Toxicology 42nd annual meeting, Salt Lake City, UT, March 9-13. *Toxicologist,* 72:292.
12. P Han, CC Hegg, AJ Roskams and MT Lucero. **2002**. PACAP modulates potassium currents and promotes survival of olfactory receptor neurons. *Chem. Senses,* 27:669.
13. CC Hegg and MT Lucero. **2002**. Dopamine inhibits odor responsiveness and excitability in mouse ORNs. *Chem. Senses*, 27:670.
14. CC Hegg and MT Lucero. **2002**. Activation of purinergic receptor subtypes differentially modulates mouse ORN odor responsiveness. *Chem. Senses*, 27:670.
15. EW Johnson, CC Hegg and MT Lucero. **2002**. Immuno-localization of PACAP in the developing and mature rodent VNO. *Chem. Senses,* 27:662.
16. MT Lucero and CC Hegg**. 2001**. Immunocytochemical and functional identification of PACAP in developing and adult olfactory epithelium. *Chem. Senses,* 26:1090.
17. JR Lokensgard, S Hu, CC Hegg, SA Thayer, G Gekker and PK Peterson. **2001**. Diazepam inhibits Tat-induced migration and intracellular calcium mobilization in human microglia. Society on Neuroimmune Pharmacology, Emory University, Atlanta, Georgia, March 21-25.
18. CC Hegg, S Hu, CC Chao, PK Peterson and SA Thayer. **1998**. β-Chemokine (RANTES) evoked increases in intracellular calcium in human microglia cells. *Soc. Neurosci. Abstr.*, 24:2007.
19. CC Hegg and V Miletic. **1995**. Chronic low level lead exposure alters calcium current in pheochromocytoma (PC12) cells. *Soc. Neurosci. Abstr.*, 21:1986.
20. CC Hegg and V Miletic. **1994**. Acute low level lead alters calcium current in pheochromocytoma (PC12) cells. *Soc. Neurosci. Abstr.*, 20:1720.
21. MA Carfagna, SD Held, C Cosgrove and GL Kedderis. **1992**. Furan-induced glutathione depletion and cytolethality in freshly isolated rat hepatocytes. *Toxicologist,* 12:396.
22. P Cobbett, C Cosgrove and I Tien. **1990**. Induction of morphological and physiological differentiation of N1E-115 cells in serum-free medium. *Soc. Neurosci. Abstr.,* 16:990.

PATENTS

MT Lucero and CC Hegg. **2002**. Provisional Patent 60/428140. Purinergic Modulation of Smell.

INVITED SEMINARS

University of Michigan, Department of Pharmacology, February 28, 2007
University of Windsor, Department of Biological Sciences, February 9, 2007
Michigan State University, Department of Physiology, February 8, 2007
University of Utah, Department of Pharmacology and Toxicology, March 16, 2006
University of Pittsburgh, Department of Environmental and Occupational Health, March 2, 2006
Emory University, Department of Physiology, January 24, 2006
North Dakota State University, Department of Pharmaceutical Sciences, October 25, 2005
Michigan State University, Department of Pharmacology and Toxicology, June 30, 2005
Michigan State University, Department of Zoology, April 7, 2005
University of Utah, Department of Physiology, October 4, 2000

MANUSCRIPTS REFEREED

- Journal of Neurochemistry
- European Journal of Neuroscience
- Neurotoxicology
- Journal of Comparative Neurology

MEMBERSHIP IN PROFESSIONAL SOCIETIES

American Physiological Society
Association for Chemoreception Sciences
Society for Neuroscience

SERVICE TO MICHIGAN STATE UNIVERSITY

2007-2009 **Committee on Diversity and Affirmative Action,** College of Veterinary Medicine
2007-present **Course and Curriculum Committee**, Department of Pharmacology and Toxicology
2006-2007 **Ad hoc Committee to Revise Website,** Department of Pharmacology and Toxicology
2006-2007 **Graduate Committee**, Department of Pharmacology and Toxicology

SERVICE TO THE SCIENTIFIC COMMUNITY

2007-2009 **Women in Physiology Committee**, American Physiological Society
2008 **Symposium Co-Chair**, "Gainfully Employed: From Launching a Job Search to Navigating Negotiations". Sponsored by the American Physiological Society at Experimental Biology
2005-2008 **Finance Committee**, Association for Chemoreception Sciences

OUTREACH SERVICE TO THE COMMUNITY

2000-present Brain Awareness Week presentations to elementary and high schools, and to scout troops

TEACHING RESPONSIBILITIES TO DATE

Fall 2007 PDI 520 – Tissue Structure and Function (Cellular Neurobiology lectures)
Fall 2007 PHM 816 – Integrative Toxicology (Neurotoxicology lectures)
Spring 2007 PHM 810 – Synaptic Transmission (Chemical Senses lectures)

LABORATORY PERSONNEL

Current

Postdoctoral Students

11/07 – present	Sebastien Hayoz
11/07 – present	Cuihong Jia

Graduate Students

9/07 – 12/07	Jasmina Jacupovic (rotation)
1/08 – 5/08	Laura Hornung (rotation)

Undergraduates

4/07 – present	Sean Crudgington
4/07 – present	Eric Jones
10/07 – present	Benjamin Clark

Medical Students

6/07 – present	Jacob Januszewski
9/07 – present	Catherine Burger

Past

Research Associate

6/05-8/06	Shami Kanekar

Research Technician

4/07-8/07	James Doherty
11/05-3/05	Brienne Brown

Description of Current and Future Research Programs

Current Research Program

My currently funded research program investigates whether ATP has a role in regulating regeneration in the olfactory system in normal and injury-induced neurogenesis. The peripheral olfactory system is a good model to study neuroregeneration. Olfactory sensory neurons (OSNs) in the olfactory epithelium are continuously renewed throughout life by local restricted neuronal progenitor cells. Normally, in the mature olfactory epithelium, neurogenesis only occurs to replace the few OSNs that have been injured and are dying. When there is significant chemical, infectious or traumatic damage to the olfactory epithelium the rate of neurogenesis accelerates. The level of neurogenesis is tightly regulated by a multitude of chemical signals, or neurotrophic factors, produced by OSNs or sustentacular cells that influence the proliferation and differentiation of endogenous neuronal progenitors. Negative autoregulation of neurogenesis has been demonstrated. Destruction of OSNs removes the source of the inhibitory anti-proliferative signal, and thereby promotes neuronal regeneration. Numerous studies have also identified a number of factors that may positively regulate neurogenesis. Dead and dying OSNs or their neighboring sustentacular cells can release growth-promoting factors that initiate proliferation. I am currently examining the hypothesis that ATP, released by injured OSNs, may act as a positive regulator of neurogenesis.

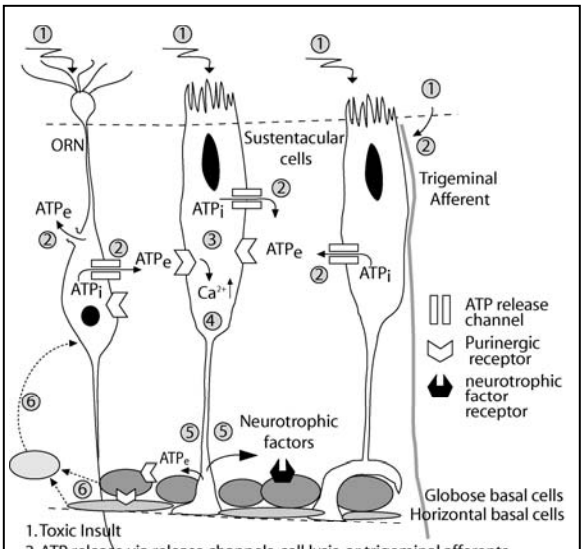

Figure 1. Schematic of the proposed purinergic signal cascade promoting regeneration of OE.

My research focuses on purinergic nucleotides as important local environmental trophic factors in neuronal regeneration. In the central nervous system (CNS), ATP mediates cell proliferation, differentiation, and stimulation of neurotrophic factor synthesis, release, or both in a wide range of cell types. The potential role of ATP, alone or in concert with various signaling molecules, in normal and injury-induced neurogenesis remains to be determined in the olfactory epithelium (OE). ***My general hypothesis is that noxious insult to the OE triggers an extracellular ATP signaling cascade that initiates regeneration of the neuroepithelium (Figure 1).***

The specific aims of my NIH-funded grant are to measure evoked ATP release, measure the subsequent release of growth factors, and measure the resulting proliferation. Thus far I have demonstrated evoked release of ATP from olfactory epithelium due to noxious stimuli and identified physiological stimuli for ATP release. As such, ATP may be a feedback signal which stimulates basal cell proliferation under normal conditions, as well as during injury-evoked regeneration. To determine if ATP and purinergic receptor activation triggers the release of neurotrophic factors in the OE, I will measure ATP-induced vesicular ATP release from sustentacular cells, and measure ATP-induced secretion of putative OE neurotrophic factors. To determine if ATP acts as a neurotrophic factor in the OE, I will (1) measure *in vitro* and *in vivo* proliferation in the presence of purinergic receptor agonists and antagonists, (2) determine if ATP acts synergistically with known neurotrophic factors to promote proliferation, and (3) measure the *in vivo* effects of purinergic receptor antagonists on injury-induced regeneration. Identification of factors such as ATP that control and regulate regeneration will have important implications on injury and repair therapeutics in both olfactory and neuronal tissue.

Future Research Directions

Although stem cell biologists, using a reductionist approach, have made great strides in elucidating the individual signals that play a role in regulating neuroregeneration, oftentimes, what occurs in cell culture is not reflected in whole animal studies. For instance, neuronal progenitor cells transplanted into the central nervous system can become either neurons or astrocytes depending on the transplant location. Although it is now recognized that the microenvironment is important in determining the fate of neuronal progenitor cells, we do not have much information regarding the chemical and physical signals responsible for fate decisions. Thus, my future research program will take advantage of the distinctive strengths offered by both whole animals and cultured olfactory epithelial slice preparations to monitor proliferation and differentiation with an intact endogenous microenvironment.

Development of Neuroregenerative Models

Over the next few years, **I plan to develop neuroregenerative models that will have varying degrees of neuronal progenitor cell proliferation and differentiation** by manipulating the local microenvironment within the olfactory epithelium. One objective is to develop models of both hyperproliferation and hypoproliferation. I will initiate the development of the models of regeneration using important and relevant models of disease, which will serve to not only develop useful research tools, but also to gain insight into complications associated with disease. The obese animal model may have altered local environments in the olfactory epithelium and will be utilized. The obese typically have low-level systemic inflammation characterized by the chronic presence of circulating cytokines, cytokine receptors, and chemokines, which appear to originate within the adipose tissue. Both cytokines and chemokines are important for regeneration in the olfactory system. When there is cell death in the olfactory epithelium, resident macrophages are activated to secrete cytokines and chemokines which recruit an infiltration of macrophages that phagocytose cellular debris and allow proliferation to occur. In mice lacking the specific chemokine MIP-1α (CCL3 by current nomenclature), the number of activated macrophages and proliferating cells decreases, suggesting that MIP-1α has a role in proliferation. I predict that the chronic elevated levels of chemokines and cytokines in an obese animal will lead to an increase in the number of proliferating cells. Thus, the obese model could be a hyperproliferative model of regeneration. Obese individuals are more likely to have olfactory dysfunction, and this proposed research could provide insight into that phenomenon. In contrast, the cytokine knock out mouse models may have hypoproliferation of neuronal progenitor cells. This novel approach will give insight into the fate and behavior of progenitor cells under a variety of physiological and pathophysiological states that could have important implications towards stem cell transplantation therapy. This research strategy could be extended in future studies to incorporate models of other pathophysiological disorders, including models of neurodegeneration, aging, and asthma.

Toxicological Studies Using Neuroregenerative Models

These models will be used to explore the interface between toxicology and stem cell biology by investigating how neurogenesis is affected by airborne pollutants under various physiological states. I will pharmacologically manipulate the system using activators and inhibitors of cellular pathways to interrogate the injury-related signals that accelerate proliferation following exposure to pollutants. Identification of factors that control and regulate regeneration will have important implications on injury and repair therapeutics in both olfactory and neuronal tissue. This innovative research project would provide essential information regarding neuroregenerative mechanisms and therapeutics both in general and in the obese, a potentially susceptible population.

An underlying goal is to develop and validate an in vitro model for nasal toxicity and a long term goal will be to develop a model to study nasal *neuro*toxicity. The nose has been described as a

"window to the brain", meaning that many inhaled substances, including viruses, metals, and toxins, are transported via axonal transport to the olfactory bulb and then to the cerebral cortex. Many metals associated with fossil fuel combustion are found on particulate matter and can be traced from the nasal tissue, through the olfactory bulb, and into the frontal lobe and hippocampus. These metals can foster damage by generating free radicals. It has been observed that dogs living in Mexico City, exposed to high levels of particulate pollutants, develop a plaque pathology characteristic of Alzheimer's disease after just 11 months, whereas dogs living in less polluted areas develop plaque-like pathology at 10 years, suggesting a correlation to airborne pollutants and neurodegenerative-like symptoms. Interestingly, olfactory loss is a common occurrence in neurodegenerative diseases such as Parkinson's disease or Alzheimer's disease. A nasal neurotoxicity model would allow correlation between the epidemiological and experimental studies on the potential association of environmental exposures and neurodegenerative diseases.

Investigating Glial-Neuronal Interactions

Another developing project examines the glial-neuronal interactions in the olfactory system. It is widely recognized that glial cells in the CNS have important support functions, including uptake of neurotransmitters and regulation of extracellular potassium and pH. However, during the past decade our understanding of the dynamic integrative capacity of glia has dramatically increased. Glia generate and propagate intracellular calcium signals as waves over long distances in response to synaptic activity. Glial calcium signaling has been implicated in a variety of physiological and pathological processes, including modulation of neuronal synaptic signaling, slowly propagated pathological phenomena such as spreading depression, and the multicellular response to localized injury. Preliminary studies show that sustentacular cells, the glial-like component of the olfactory epithelium, are capable of generating action potentials, calcium waves, and spontaneous increases in intracellular calcium. In this way, sustentacular cells are very similar to glia in the CNS. These previously understudied electrical and chemical activities in sustentacular cells led me to hypothesize that there are dynamic intra- and inter-cellular communications between sustentacular cells and olfactory neurons. **My long term objective is to understand the precise nature of sustentacular cell signals in response to neuronal activity and the consequence of such signals to neuronal function.**

I have discovered that two types of calcium signaling occur in sustentacular cells: non-propagating calcium oscillations and propagating intercellular calcium waves. Moreover, sustentacular cells respond to a variety of G-protein coupled receptor agonists with oscillatory increases in intracellular calcium that occur in individual cells. I hypothesize that calcium oscillations regulate individual cell function whereas propagating calcium waves coordinate multicellular activity and that the principles underlying these calcium signals are different. One very exciting aspect of this project is the occurrence of calcium waves in sustentacular cells *following* odorant-evoked increases in calcium in olfactory receptor neurons. This has led me to propose that neurons can modulate activity in sustentacular cells. Of great importance to me is understanding the physiological role of calcium signaling in the OE and the role of sustentacular cells in the direct modulation of neuronal activity. Continuing work on this project will initially focus on elucidating the mechanism by which calcium waves and spontaneous calcium oscillations are propagated in sustentacular cells and identifying natural stimuli that elicit calcium signals. Future research will test the hypothesis that spontaneous calcium oscillations in sustentacular cells modulate the activity of neighboring neurons, and in contrast, neuronal activity can modulate the functions of sustentacular cells, and characterize the physiological changes in sustentacular cells elicited by propagation of calcium waves.

Justification For How And Why The Applicant Meets The Intent Of The Award

Shih-Chun Wang's ground-breaking studies elucidated how the brain interacted with other organs to coordinate breathing, temperature regulation and reactions to motion. Just as Dr. Wang's research revealed how complex and integrated systems function, my research program strives to elucidate the mechanisms of neuroregeneration. In my relatively short research career I have made significant contributions to at least three fields of study using a research approach that is both neurophysiological and neuropharmacological. During my training, I examined the electrophysiological effects of heavy metals on calcium currents, the role of chemokines in HIV-1 AIDS dementia, olfaction, and neuroregeneration. I have morphed these fields of study into my current innovative research program that uses classical toxicity studies and stem cell physiology to gain information about neuronal repair therapeutics. One of my future research goals is to employ mechanistic physiological studies to investigate the correlation between environmental exposures to airborne particulates and neurodegenerative diseases with the ultimate goal of promoting therapeutic treatment and prevention of human neurotoxicity. My current and future research directions will facilitate the understanding of neuroregenerative mechanisms and lead the field of neurophysiology in new directions, as Wang's research did in brain stem control mechanisms. The esteem and recognition that goes with receiving the Shih-Chun Wang young investigator award will help to extend my own research and bring it to the forefront of the field, as well as help initiate this new and exciting research direction, in part by helping to recruit promising students and post-doctoral fellows into my laboratory.

ATP induces proliferation and neuroprotection in Swiss Webster mouse olfactory epithelium

Colleen Hegg, James Doherty, Sean Crudgington, Eric Jones.

Pharmacology and Toxicology, Michigan State University, East Lansing, MI

The olfactory epithelium (OE) is a good model to study neuroregeneration. Throughout life, progenitor cells proliferate, differentiate into neurons, and undergo apoptosis. In the CNS, ATP activation of purinergic receptors (P2R) induces proliferation. We tested the hypothesis that ATP can initiate proliferation in the OE. We measured BrdU incorporation in neonatal OE slices and adult mice 48 hours following treatment with ATP or ATPγS and/or P2R antagonists PPADS + suramin. Mice treated intranasally with ATPγS had significantly more BrdU-immunoreactive cells compared to control. Pre-treatment with P2R antagonists reduced the ATP-induced BrdU incorporation to control levels. Similar results were obtained with OE slices. These data suggest that P2R activation induces proliferation. To determine if the proliferation is related to cell survival, OE slices were treated with ATP or suramin and exposed to CaspACE FITC-VAD-FMK, a marker for activated caspase-3. 18 hr exposure to ATP decreased apoptosis, and suramin increased apoptosis, reversing the protective effect of ATP. These data suggest that ATP and P2R activation have a proliferative and a protective effect in the OE. Supported by NIDCD DC006897.