atorium of the Laboratory of Assoc. Prof. Dan Llano, who has been installed as the first Goldberg Professorial Scholar. The Newsletter also offers a snapshot of our Annual Departmental Retreat—held in the beautiful Allerton Park in May 2018—which featured a talk by former MIP Head (1997–2007) Phil Best, undoubtedly, one of the MIP faculty members who have had the largest impact on my own career. This year’s Newsletter also features a description of the Illinois Cancer Center, a new initiative on Campus with strong MIP presence through the membership of Assistant Prof. Erik Nelson. Furthermore, we also highlight the success of our Departmental trainees and faculty in terms of publications, grants awarded, and milestones.

Most importantly, however, this year’s Newsletter remembers the life and scientific accomplishments of our colleague and friend Ann Nardulli, who passed away this past June from ovarian cancer. We include an excerpt from an interview with Ann conducted by Assistant Prof. Catherine Christian that vividly reminds us of the freshness, spontaneity, and wisdom that characterized Ann both as a scientist and friend.

However exciting these times are to conduct research, the funding climate remains uncertain, which poses a serious challenge to scientific progress. We hope that our alumni and friends will remain actively committed to our Department so as to buttress our continued growth and sustain our rank as one of the most prestigious places to do research and receive education in modern Physiology.
The Role of Top-down Corticocollicular Projections in the Mouse Auditory System

Updates from Daniel Llano’s Lab
by Jeanne Bullock Goldberg, M.D.

We live in an environment characterized by a multitude of complex, diverse sounds. The ability to filter, select and understand specific sounds from this rich environment can impact learning, speech, and even our survival. Just imagine driving your car in heavy traffic while listening intently to a radio interview when, in the distance, you hear a siren. That sound will automatically and immediately cause you to focus on the road, ignore the sound emanating from the radio, and take aversive action if necessary.

The cues that enable us to function optimally in our noisy, often cacophonous, world are central to the exciting research that is being performed in the laboratory of Dr. Daniel Llano, an associate professor in the University of Illinois Department of Molecular and Integrative Physiology (MIP) and a full-time faculty member at the Beckman Institute. Dr. Llano, who is also an M. D. with a subspecialty in neurology, has a clinical appointment at Carle Foundation Hospital and cares for patients with age-related auditory dysfunction and cognitive disorders. Thus, his research and clinical responsibilities are intimately linked.

The central auditory system, outlined in the graphic illustration below, is composed of pathways that ascend from sensory neurons in the auditory nerve to a succession of other key processing centers in the brainstem, midbrain and thalamus, with termination in the auditory cortex. Traditionally the ascending pathway has been emphasized, but studies utilizing tracers have demonstrated that descending neural fibers (projections) from the auditory portion of the cerebral cortex to lower processing centers greatly outnumber ascending projections in the central auditory system.

The descending projections that contribute to this “top-down” organization are critical in the process of interpretation and modulation of complex sounds with diverse characteristics. These sounds may also occur simultaneously, thereby being superimposed upon each other. One of the largest top-down pathways is the corticocollicular pathway (CC), which extends from the auditory cortex to the inferior colliculus (IC). The IC, located in the midbrain, is regarded as a major integrative center as it receives ascending signals from the auditory brainstem in addition to extensive descending signal input from the auditory cortex (AC). Its architecture is complex, consisting of a lateral cortex, a dorsal cortex and a central nucleus, each with different cell types which exhibit a variety of electrophysiological, morphological and molecular characteristics. The corticocollicular neurons have been shown to tune (or adjust the sensitivity of) IC neurons for frequency, amplitude and duration.

The importance of top-down modulation of response properties of neurons in lower auditory centers and a special interest in the massive corticocollicular pathway has led Dr. Llano’s laboratory to study the anatomical and also the functional (molecular and circuit level) organization of these descending neural projections. Tools utilized for these studies include electrophysiologic recording instrumentation in addition to novel optical and molecular techniques.

The auditory cortex is located on the superior temporal gyrus in the temporal lobe, and studies have shown that almost all regions of it project to the IC located on the same side, as opposed to the other IC that is located on the opposite side. The AC is composed of six layers (see figure below), each with specific types of cells. Descending projections, whether they are corticothalamic or corticocollicular, for example, arise from layers 5 and 6 of the AC, and the cell morphology (configuration) differs in each layer. Layer 5 corticocollicular cells are large, pyramidal cells with a long apical dendrite (the cell structure that receives information) projecting toward layer 1 whereas layer 6 cells are smaller, have long, thin, densely branching dendrites and are oriented horizontally as opposed to the layer 5 cells.

Although the anatomy and the functional roles of the corticothalamic projections have been extensively studied and delineated, knowledge of the role of the corticocollicular projections is limited. Dr. Llano’s laboratory, however, is making significant strides in providing an understanding of this critical information pathway.

In a publication in Hearing Research in 2014, Drs. Llano, Stebbings and Lesicko summarized their research findings, utilizing mice as mammalian subjects, which clearly demonstrate the heterogeneity of the descending CC pathway. Some of the neural projections from the auditory cortex to the IC respect what is known as a tonotopic relationship, meaning that neurons in the auditory cortex that have sensitivity to tones of a given frequency or frequency range project onto neurons in the IC that display the same frequency sensitivity. The AC, however, can modulate or shift the tuning functions of IC neurons toward the tuning functions of the AC source. The CC pathway can also decrease responses to sound by the IC neurons via frequency-specific inhibition. Specific local circuit interactions in the IC may be either stimulated or suppressed, representing another mechanism by which the AC modulates IC neurons. Some regions of the IC are characterized by the above-described tonotopic configuration, but the laboratory
has discovered other projections that are nontonotopic. Dr. Llano and his staff postulate that the tonotopically arranged projections from the AC can support frequency sensitivity adjustments (stimulatory or inhibitory) of neurons in the IC (i.e. “tuning”), but that perhaps the nontonotopic projections might play a role in modulating duration or temporal tuning.

Dr. Llano’s laboratory has shown that the descending input to the IC is primarily derived from cortical layer 5 neurons, but a spatially distinct pathway derived from layer 6 neurons also exists. Interestingly, layer 5 corticothalamic neurons are very similar to layer 5 corticocollicular neurons and single layer 5 cells may actually branch to many subcortical regions. Of importance is the fact that these layer 5 cells also exhibit bursting and receive both local excitatory and inhibitory cortical inputs from near the cell body as well as from upper cortical layers, as opposed to the layer 6 cells, which are non-bursting and also differ in additional electrophysiological metrics. Layer 6 cells differ in additional electrophysiological metrics too. The layer 6 CC cells are also very different from their corticothalamic counterparts. Thus, it is likely that each separate pathway emanating from levels 5 and 6 respectively play distinct roles in processing auditory information in the midbrain.

The Llano laboratory has further explored the microarchitecture of the IC, and some fascinating findings have resulted from this research. They have discovered, utilizing immunostaining techniques, that the lateral cortex (LC) of the IC receives information not only from auditory structures but also, in multiple processing streams, information from somatosensory structures. In addition, the lateral cortex and the dorsal cortex areas of the IC receive considerably more projections from the auditory cortex than the central nucleus of the IC. Modular areas in the LC, which stains positively for a variety of neurochemicals, in particular the inhibitory neurotransmitter GABA, exist as early as day 8 in the mouse, before the onset of hearing, and these modules receive somatosensory input which probably drives their formation. The LC also receives input from the visual cortex, basal ganglia, hypothalamus, and deep layers of the superior colliculus (SC). (The superior colliculi are paired structures which play an important role in orienting eye and head movements to visual stimuli and in generating escape and defense behaviors.)

Shared characteristics of cells in the SC and LC of the IC suggest related functional roles.

Therefore, multisensory integration (i.e., auditory, somatosensory and visual) occurs at each level of the ascending auditory pathway (cochlear nucleus, IC, medial geniculate body of the thalamus, and the auditory cortex). The findings that have emerged from Dr. Llano’s laboratory, however, have greatly enlarged our understanding of the multisensory connections to the descending CC pathway and, in his words, “will likely lead to broader insights about top-down modulatory pathways in general.”

For a deeper understanding of how the auditory cortex modulates the IC, the Llano laboratory has used optical stimulation and other sophisticated tools to study the integration of corticocollicular neurons in local cortical and corticothalamic networks. Previous studies have advanced the view that the thalamus provides input primarily to layer 4 of the cerebral cortex, but thalamocortical neurons also contact layers 5 and 6. The Llano laboratory has shown that layer 5 corticocollicular neurons receive prominent excitatory and inhibitory input from layer 5 to the pia (the innermost layer of the meninges which adheres to the surface of the brain and spinal cord) in a vertical fashion; however, layer 6 corticocollicular neurons receive inputs primarily from layer 6 in a horizontal orientation.

Neurons in layers 5 and 6 receive both direct and indirect thalamic input, but layer 5 corticocollicular neurons receive significantly more direct input from the auditory thalamus than layer 6 neurons. In fact, only a minority of layer 6 corticocollicular cells receive direct thalamic input.

An exciting result of this work is the demonstration, for the first time, that there is a direct connection between the auditory thalamus and layer 5 corticocollicular neurons, thereby linking the ascending and descending pathways. An understanding of the mechanisms that govern modulation of auditory information is emerging, pointing towards a duplex system which addresses issues of differing time scales, different degrees of convergence or divergence and different degrees of inhibition and excitation.

The concept of top-down modulation is key to our understanding of the auditory system. How do we process sounds? How do memories and previous experiences influence how we react to sounds? By studying top-down modulation might we understand the aging process better or even influence neuroprosthetic device design? These are just a few of the unanswered but critical questions that Dr. Llano’s laboratory is illuminating with truly innovative research.
INTERVIEW WITH ANN NARDULLI, 1949 - 2018

Prof. Ann Nardulli, an endocrinologist and cherished MIP faculty member, passed away on June 27, 2018. To honor Ann’s memory, we present excerpts of a conversation between Ann and Assistant Prof. Catherine Christian, conducted in September 2016 on the occasion of her retirement.

Illinois has played a major role in your life, from graduate school through your faculty career. Could you please briefly describe your educational and career experiences here?

I decided to come back to school and initially was going to pursue a Master’s degree, because I had taught school for 4 years, had been at home for 6 years, and didn’t contemplate a Ph.D. at the time – it seemed a stretch to me. But then I came in and I talked to John Zehr, who was extraordinarily kind and so supportive. I started graduate school when my daughter was in Kindergarten. Once I started, there was no turning back and there was no question that I could do the work, or that I loved the work.

How did being part of the MIP department influence your work? Were there projects you pursued that you might not have done if you were somewhere else?

Absolutely! It really affected the trajectory of our work. I mainly did breast cancer, and then we were interested in proteins that interacted with the estrogen receptor, which mediates the effects of estrogen. And what was really interesting was that there were four oxidative stress proteins that had been shown to be protective in the brain if you cut off circulation to a region of the brain. And these experiments so closely paralleled the work that had been done in Phyllis Wise’s lab, where she showed that estrogen given to an ovariectomized rodent would protect that animal from subsequent ischemia. And so the thought was, “Wow, estrogen could be mediating the effects of these proteins in the brain.” And Lee Cox showed us how to do brain slices, and also Martha Gillette’s lab showed us how to do brain slices. Lori Raetzman showed us how to use microscopy to visualize these proteins. We got uteri from other faculty members so that we could practice doing the immunohistochemistry. Our lab changed directions totally, and it was because of the generosity of people here.

Which discovery that your lab has made was the most surprising to you?

Well, that was one of them. But we had also done some work early on – it was some work where we were trying to figure out which regions of the genome the estrogen receptor was associated with. At that time, there weren’t chromatin immunoprecipitation assays where you could look at the genome, and so what we did was immunoprecipitate the estrogen receptor, isolate the DNA, clone the DNA into plasmids, and then sequence the DNA. And what we found, we thought was gibberish, because there were only about 35 regions that we identified. They were not in regions that we had anticipated they would be located, within 500 base pairs of the transcription start site. They were hundreds of thousands of base pairs away from that! An investigator from Singapore came to visit here, and he said they had been using genomic processes that were just newly developed. And they had done a similar sort of experiment, and had identified over 300 regions of the genome that were associated with the estrogen receptor. I asked him, “Where did you find them?” And he said, “All over!” It really felt like we were trying to do something different, though we were doing it in a very primitive way.

What favorite pieces of advice do you have for students, postdocs, and junior faculty?

Especially at the level of a student, make sure you’re doing what you love. And for the faculty, follow wherever science leads you. Because even though you’ll feel like you’re in water that’s over your head, it just opens up a whole new world. I have always loved learning, and following whatever changes or new things we found in the lab was instrumental in getting everyone revved up and seemed to be the best way to go.

To honor Ann’s legacy, the Molecular and Integrative Physiology Department has established the Ann Nardulli Graduate Student Support Fund. Graduate education was very important to Ann and this fund will provide graduate students with support to enhance their education, such as travel support to present and discuss their research findings at scientific meetings. If Professor Nardulli has touched your life in some meaningful way, please consider donating to this fund.

If you would like to make a contribution to the Ann Nardulli Graduate Student Support Fund or another MIP fund, please visit: mcb.illinois.edu/giving/
MIP FACULTY PARTICIPATING IN NEW CANCER CENTER AT ILLINOIS

The Department of Molecular and Integrative Physiology looks forward to its interactions with the newly formed Cancer Center at Illinois (CCII). Organizational efforts started in 2011 with the formation of the working group known as the Cancer Community at Illinois. The CCII has emerged from this group as a central interdisciplinary hub for researchers with interests in cancer research.

With over 75 faculty members from a range of departments across campus, one of the main missions of the CCII is to unite world-class faculty to uncover fundamental knowledge, innovate new technologies, and enable cancer-free lives. The goal is to facilitate interactions between faculty with diverse expertise in order to spark novel discoveries that would not have been envisioned otherwise.

Four MIP faculty members are part of the CCII: Sayee Anakk, Benita Katzenellenbogen, Erik Nelson, and Edward Roy. Dr. Anakk’s research focuses on bile acid signaling and liver cancer. Dr. Katzenellenbogen has contributed significantly to our understanding of how the estrogen receptor contributes to breast cancer progression. Her current work is focusing on understanding the biology of mutant estrogen receptors and developing drugs to target these forms. In this regard, it has been shown that 30-40% of patients with estrogen receptor-positive breast cancer who have recurrent or metastatic disease also express one of these mutant estrogen receptor forms, which are resistant to current therapies. Dr. Nelson’s group is interested in how cholesterol metabolism impacts the tumor microenvironment, especially the immune system, to promote the progression and spread of breast cancer. Dr. Roy is developing different therapies to target the immune system, with the goal of retraining it to attack various forms of brain cancer.

Under the framework of the CCII, MIP faculty look forward to collaborating with investigators across campus, and continuing to perform cutting-edge cancer research.

THE 2018 MIP ANNUAL RETREAT

The 2018 MIP Annual Retreat was once again held at the Allerton Park and Retreat Center in May. The slight change in the calendar scheduling, which moved the retreat after the end of the spring semester, afforded wonderful weather and an opportunity for both faculty and students to spend the full day at Allerton.

This year’s keynote addresses were delivered by MIP alumna Dr. Erika Piedras-Renteria and her PhD advisor, MIP professor emeritus Dr. Philip Best. Dr. Piedras-Renteria is currently an Associate Professor of Cell and Molecular Physiology at Loyola University Chicago. Dr. Piedras-Renteria’s presentation focused on recent work from her lab, which investigates how Kelch-like protein 1 (KLHL1) modulates T-type calcium channels, and the relationship of this modulation to the effects of leptin on proopiomelanocortin (POMC) neurons in the hypothalamus.

Dr. Best led us on a very entertaining “Random Walk” down memory lane of his time in MIP. Special reminiscences included the many trainees in his lab, as well as his time as Department Head from 1997-2000 and his later stint as Associate Dean of the College of Liberal Arts & Sciences from 2007-2010.

The excellent poster and oral presentations of ongoing work in MIP labs were punctuated throughout the day by a “Sherlock Holmes”-style game (led by Sisi He of the Nelson lab) to find the physiological culprit of a “murder” and a scavenger hunt through the grounds of Allerton. Whitney Edwards (Raetzman lab) and Sangwon Byun (Kemper lab) received awards for the best oral presentations, and the poster awards went to James Nguyen (Anakk lab), Hao Sun (Kemper lab), and Jinjing Chen (Kemper lab).
STUDENT NEWS

Brian Baculis, a graduate student of Dr. Hee Jung Chung, was appointed to the NSF-supported training grant in Engineering and Deciphering of Miniature Brain Machinery.

Rachel Gonzalez, a graduate student of Dr. Lori Raetzman, was appointed to the NIH-supported training grant in Interdisciplinary Environmental Toxicology.

Sayyed Hamed Shahoei, a graduate student of Dr. Erik Nelson, was awarded a 2018 Endocrine Society Outstanding Abstract Award.

Sisi He, a graduate student of Dr. Erik Nelson, was awarded a 2018 Endocrine Society Outstanding Abstract Award and an AACR Scholar-in-Training Award.

Sung-Soo Jang, a graduate student of Dr. Hee Jung Chung, was awarded a predoctoral fellowship from the American Epilepsy Society.

Jiang Li, a graduate student of Dr. Catherine Christian, was awarded the 2018 Epilepsia Open Basic Science Prize, and was selected for the Investigators Workshop Poster Session of outstanding abstracts at the 2018 American Epilepsy Society Meeting.

Liqian Ma, a graduate student of Dr. Erik Nelson, was awarded a 2018 AACR-Bristol Myers Squibb Oncology Scholar-in-Training Award.

2018 PHD GRADUATES AND DISSERTATION TITLES

Whitney Edwards (Raetzman Lab, MIP) “Uncovering Molecular Mechanisms of the Notch Signaling Pathway in the Regulation of Pituitary Gland Development”

Alexandria Lesicko (Llano Lab, Neuroscience) “Modularity of the microcircuitry of the lateral cortex of the mouse inferior colliculus”

Kevin Stebbings (Llano Lab, Neuroscience) “Quantifying effects of aging across structures of the mouse auditory system, with in-vitro slice preparations”

Hua-Chia Tai (Sweedler Lab, MIP) “Analysis of Enzymatic L/D-Peptide Isomerization in Animals”

ALUMNI UPDATES

Whitney Edwards (Raetzman Lab) is now a postdoc in the NIH-funded SPIRE program at UNC Chapel Hill.

Leah Nantie (Raetzman lab) is now a Research Scientist at miRagen Therapeutics.

Courtney Sobieski (Christian lab) is now a Medical Writer at R&Q Solutions.

FACULTY GRANTS NEWLY AWARDED IN 2018

Milan Bagchi, NIH R01 Co-PI (with Indrani Bagchi), “Role of Hypoxia in Regulating Stromal-Epithelial Communication during Pregnancy.”

Catherine Christian, NIH R03, “Lateralized targeting of hippocampus to model interactions between epilepsy and reproductive endocrine disorders.”

Catherine Christian, NIH R01, “Neural and pituitary mechanisms linking epilepsy to co-morbid reproductive endocrine dysfunction.”

Claudio Grosman, NIH R01, “Mechanisms of Neurotransmitter-Gated Ion Channels.”

Benita Katzenellenbogen, NIH R01 Co-PI (with John Katzenellenbogen and Kendall Nettles), “Chemical, structural and molecular rules for fully antagonizing the estrogen receptor.”


Benita Katzenellenbogen, Breast Cancer Research Foundation Co-I (John Katzenellenbogen, lead PI), “Antagonists for
**SELECTED MIP PAPERS NOV 2017-SEPT 2018**


Biehl MJ, Kaylan KB, Thompson RJ, Gonzalez RV, Weis KE, Underhill GH, Raetzman LT. Cellular fate decisions in the developing female anteroventral periventricular nucleus are regulated by canonical Notch signaling. *Developmental Biology* October 2018


Camacho MB, Anastasio TJ. Computational Model of Antidepressant Response Heterogeneity as Multi-pathway Neuroadaptation. *Frontiers in Pharmacology* December 2017

Courtney CD, Christian CA. Subregion-Specific Impacts of Genetic Loss of Diazepam Binding Inhibitor on Synaptic Inhibition in the Murine Hippocampus. *Neuroscience* September 2018


Gribkova ED, Ibrahim BAE, Llano DA. A novel mutual information estimator to measure spike train correlations in a model thalamocortical network. *Journal of Neurophysiology* September 2018

Jewett KA, Lee KY, Eagleman DE, Soriano S, Tsai NP. Dysregulation and restoration of homeostatic network plasticity in fragile X syndrome mice. *Neuropsychopharmacology* August 2018


Lee KY, Jewett KA, Chung HJ, Tsai NP. Loss of fragile X protein FMRP impairs homeostatic synaptic downscaling through tumor suppressor p53 and ubiquitin E3 ligase Nedd4-2. *Human Molecular Genetics* August 2018


Mapes J, Anandan L, Li Q, Neff A, Clevenger CV, Bagchi IC, Bagchi MK. Aberrantly high expression of the CUB and zona pellucida-like domain-containing protein 1 (CUZD1) in mammary epithelium leads to breast tumorigenesis. *Journal of Biological Chemistry* February 2018


Ujjainwala AL, Courtney CD, Rhoads SG, Rhodes JS, Christian CA. Genetic loss of diazepam binding inhibitor in mice impairs social interest. *Genes, Brain and Behavior* June 2018
MIP appreciates the support of our alumni and friends. If you would like to make a donation this year, use this form or visit: mcb.illinois.edu/giving/

I would like to make the following contribution to MIP:

$_________________ General Support LAS Development Fund - MIP (334866)
$_________________ Ann Nardulli Graduate Student Support Fund - (11342006)

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