



GREETINGS FROM THE HEAD

Milan Bagchi

For the past 67 years since its formal establishment as an independent academic unit in 1949, the Department of Molecular and Integrative Physiology (MIP) has continued to thrive as one of the best physiology departments in the country. During the past two decades, the discipline of physiology has undergone a sea change, entering an exciting new era that melds our knowledge of molecular and cellular processes with the principles of systems biology and translational approaches, allowing us to gain new mechanistic insights at the organismal level. To keep pace with this rapidly evolving field, we have envisioned an MIP Department that will maintain its strength in traditional core areas, such as neuroscience, endocrinology, metabolism, and cancer cell signaling, as well as build in emerging areas, such as genomic medicine. The MIP Department aspires to position itself at the center of progress in basic research in biology at the University of Illinois and to become an indispensable partner of the new Carle-Illinois College of Medicine in performing translational research to advance human health. The challenge is to determine how our faculty can maximize their productivity by synergistically interacting with the faculty in other disciplines, such as bioengineering, where individuals are eager to collaborate to expand use of their technologies and approaches in needed biomedical applications.

This year, as a first step to evaluate and solidify this departmental vision, we underwent an Academic Program Review conducted by an external team of eminent biologists. I am pleased to report that the external reviewers concluded that “the Department of Molecular and Integrative Physiology is doing remarkably well” and is “on the right path and should continue in that direction”. They appreciated that “the department is continuing to establish the paradigm for the “new physiology”, which is “clearly central to the research and educational missions of the School of Molecular and Cellular Biology and College of Liberal Arts and Sciences.” They also provided specific recommendations and urged the campus leadership to act on those so that the department can “take a significant leap forward in stature, with further growth and new investment” and “synergize tightly with the new Carle-Illinois College of Medicine”. These are encouraging comments that extend unequivocal support to our proposal to build our faculty in emerging areas in order to maintain our position at the forefront of modern physiology.

Throughout 2016, we encountered a very difficult financial climate because of the budgetary impasse created at the State level. Like many other departments in the College of LAS, MIP had to accommodate a painful recurring reduction in our State budget. In spite of these difficulties, our faculty continues to run highly visible research programs, publish high impact research articles and secure competitive federal research grants. Our doctoral students are receiving first-rate training in modern physiology that enables them to be placed successfully in postdoctoral positions. As we embark on 2017, we fervently hope that the budget nightmare will end, restoring certainty and stability that will allow us to maintain excellence in our academic mission.

DECEMBER 2016 NEWSLETTER

IN THIS ISSUE

Greetings from the Head by Milan Bagchi	1
Neuronal Excitability in Health and Disease by Jeanne Bullock Goldberg	2-3
Milan Bagchi Receives Deb Paul Professorship	4
MIP Retreat	4
My Experience at MIP by Victor Ramirez, MD, Emeritus Prof.	5
Awards & Grants	5
Students, Alumni & Retirements	6
Recent Publications	7

ABOUT THE NEWSLETTER

The Molecular and Integrative Physiology Newsletter is an annual publication of the Department of Molecular and Integrative Physiology in the School of Molecular and Cellular Biology at the University of Illinois, Urbana-Champaign. The newsletter is written by MIP faculty and friends, and designed by MCB Communications.

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NEURONAL EXCITABILITY IN HEALTH AND DISEASE

Jeanne Bullock Goldberg, M.D.

A new era has dawned in understanding neuropathological disorders such as epilepsy, schizophrenia, depression, and autism spectrum disorders. These disorders, traditionally classified in the Diagnostic and Statistical Manual of Mental Disorders by the American Psychiatric Society, are now being re-examined through the lens of molecular and cellular physiology. As a result of novel research techniques, they are increasingly being regarded as neurophysiological disorders, and the stigmatization directed towards those diagnosed with these disorders is decreasing.

It is difficult to assess the total impact of neuropathological disorders. One study, for example, found that the economic cost of depression in America is \$210 billion per year and that for every dollar spent in its treatment, about \$6.60 is spent on costs of related illnesses, reduced workplace productivity and suicide (Greenberg, *Scientific American*, 2015). Epilepsy, the most common neurologic condition after headache, is associated with a risk of death which is 2-3 times higher overall than in the general population (Wiebe, *Goldman's Cecil Medicine 24th edition*, 2012) and is also frequently associated with depression, reproductive dysfunction and generally poor psychological and physical outcomes. In 1990 the total economic cost of schizophrenia was estimated to be \$32.5 billion and \$46.6 billion for anxiety disorders. (Rice, *J Clin Psychiatry*, 1999) These data just brush the surface of the total impact of these disorders and of others such as autism spectrum disorders.

Altered neuronal excitability is the common denominator in this wide spectrum of neuropathological disorders, and scientists in the University of Illinois Department of Molecular and Integrative Physiology (MIP) are in the forefront



of this research activity. Utilizing a multidisciplinary approach, the laboratories of Drs. Catherine A. Christian, Nien-Pei Tsai, and Hee Jung Chung are studying neurobiological phenomena that are not only important in disease but also are essential in learning and memory.

The diagram below, demonstrating the anatomy of a neuron, the cell which processes information in the central nervous system, is basic to understanding this research. The neuron has processes which receive and transmit information, the dendrites and the axons, respectively. The tiny gap between neurons through which information signals flow is known as the synapse, truly a key area in information processing. The inside of the neuron is electrically negative with respect to its outside, with a resting membrane potential of approximately -60 mV. When an action potential is generated, it depolarizes the neuronal cell membrane and is transmitted down the axon and through the synapse. The cell body of the neuron manufactures chemical neurotransmitters which are transported to the axon terminal, and these are released in the synapse as a

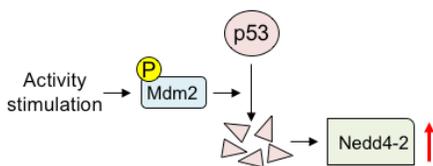


Figure 1. Mdm2-p53-Nedd4-2 signaling (Modified from Jewett et al., 2016, *Molecular Brain*)

result of the conduction of electrical signals along the axon. There are two types of synapses, those which transmit electrical signals only, and the much more common chemical synapse. When neurotransmitters are released, they bind to receptors on the postsynaptic neuron and influence the activity of ion channels, essential elements in synaptic transmission. The membrane potential of the

postsynaptic neuron is changed as a result, and depending on the receptors activated by the neurotransmitters, can either raise or decrease the level of activity of the postsynaptic neuron.

Neurons are able to monitor their activity (i.e. firing rates) through calcium-dependent sensors which actually regulate the number of neurotransmitter receptor sites at synapses in addition to the amount of neurotransmitter that is released. (Turrigiano, *Cold Spring Harbor Perspect Biol*, 2012). To add to the complexity of this feedback system, there are additional mechanisms that the nervous system utilizes to modify firing rates not only at local synaptic sites but also globally at network-wide locations.

The capacity of self-monitoring and self-regulation of the central nervous system's activity is known as synaptic plasticity, a truly exciting concept (Whalley, *Nat Rev Neurosci.*, 2007). The synapse, once regarded as fixed and unchangeable in recent decades, has actually been proven to be plastic, accommodating to various environmental conditions by reacting to neurotransmitters that are released to strengthen or weaken neuronal activity. Dr. Tsai is studying the role of protein translation and degradation in plasticity. Neuronal activity modulate the dynamics of proteins which are involved in neurodevelopmental events, and when this process is dysfunctional various neurodevelopmental disorders can result. Synchronous (global) firing of neurons is critical to learning and memory, but abnormalities in control of this synchrony are associated with a spectrum of disorders, including epilepsy, depression, autism spectrum disorders, and schizophrenia.

One of the challenges in studying neuropathological disorders has been the identification of specific genes and signaling pathways associated with the disorders and the articulation of gene-environment interactions. A recent paper published in the journal *Molecular Brain* by Dr. Tsai's lab in collaboration with Dr. Christian,

however, describes, for the first time in the literature, a molecular signaling feedback pathway critical to understanding epilepsy (Jewett et al., *Mol Brain*, 2016). They have pharmacologically stimulated neuronal activity and demonstrated that this triggers an enzyme (Mdm2) to degrade a transcription factor p53. p53 normally suppresses an epilepsy-associated gene Nedd4-2 to produce messenger RNA, which results in enhanced seizure susceptibility. Through in vitro and in vivo mouse studies, they have demonstrated that when p53 is inhibited, seizure susceptibility in mice is inhibited. However, Dr. Tsai's lab has demonstrated that when the degradation of p53 is blocked neural network synchrony is enhanced. When p53 is inhibited, neural network synchrony is reduced. These data demonstrate a specific molecular regulatory feedback loop controlling neuronal excitation in the healthy state (Figure 1).

Dr. Tsai's lab has shown the crucial importance of the Mdm2-p53-Nedd4-2 signaling pathway as a feedback loop in controlling neuronal excitation and synchrony. The evidence that both p53 and the epilepsy-associated gene Nedd4-2 are linked to seizure susceptibility affords a potential for novel therapeutic strategies. Their focus on dysregulated neuronal excitation, specifically related to Mdm2, also has potential importance in understanding and treating other conditions such as autism spectrum disorders.

An interesting facet of Dr. Christian's epilepsy research focuses on the association of female reproductive dysfunction with epilepsy. Using mouse seizure models, her laboratory was able to show an association between estrous cycle disruption and abnormally elevated neuronal activity in the hypothalamic gonadotropin-releasing hormone neurons, the central neurons that control reproduction. Further research concerning hormone production in males and females will further our understanding of the relationship between seizures and reproductive

function and lead to new therapeutic targets.

A fascinating area of research centers on the role of astrocytes, a type of glial cell that have traditionally been regarded simply as cells that support neurons (Halassa et al., *Trends Mol Med*, 2007). Interestingly, the cellular processes of astrocytes make contact with both the pre- and the post-synaptic neurons, allowing not only assessment of vascular supply but also of neuronal activity. In recent years, the role of astrocytes in actively enhancing or reducing synaptic transmission is being recognized (the "astrocytes activation spectrum"), contributing to epilepsy and schizophrenia, respectively. This is accomplished through calcium signaling and variable levels of release of gliotransmitters such as glutamate and D-serine. Dr. Christian's laboratory is focusing on the role of astrocytes in modulating synaptic inhibition by studying GABA receptors, key inhibitors in the vertebrate central nervous system. The goal of these studies is to promote understanding of how these receptors and specific endogenous peptides (short sequences of amino acids) influence abnormal behaviors.

Dr. Hee Jung Chung's research centers on the role of ion channels, key elements in controlling neuronal excitability and synaptic communication. Dr. Chung's epilepsy research focuses on mutations in KCNQ potassium (K⁺) channels that cause mild-symptomatic to drug resistant epilepsy in children. These potassium channels localized at the neuronal axon are inhibitory since they keep the membrane potential more negative than the threshold potential for action potential firing. Dr. Chung's research discovered that epilepsy mutations block the channel expression at the neuronal axon as well as channel opening, leading to excessive firing of hippocampal neurons.

Dr. Chung's laboratory

also studies the normal role of ion channels in maintaining the dynamic control of neuronal excitability and synaptic communication. Adaptation to a constantly changing environment requires plastic but also stable neuronal circuits. Dr. Chung's lab has identified a rich gene network that control such adaptation and that are regulated by NMDA-type glutamate receptors that mediate Ca²⁺ ions to move into the neuron (Lee et al., *Mol Brain*, 2015). NMDA receptor-dependent sensing of the activity level of the hippocampal neurons in turn leads to regulation of the genes that produce multiple K⁺ channels. The resulting current through these K⁺ channels modifies the rate of firing of the neurons in the network (Figure 2). The fact that mutations in specific K⁺ ion channels are associated with epilepsy strongly suggests that Dr. Chung's work could point to potential therapeutic targets. In addition, her laboratory's discovery of novel genes that influence synaptic strength and calcium sensors could add to the armamentarium of therapeutic agents.

The research projects highlighted in this article illuminate various mechanisms which achieve this balance through accurate sensing of network activity (e.g. Ca²⁺-dependent sensors), controlling the types and amounts of proteins produced by specific genes, and controlling ion channel activities. The type and quality of research studying neuronal excitability in health and disease that is underway in our department perfectly embodies our acronym (MIP)... it is truly *molecular and integrative*.

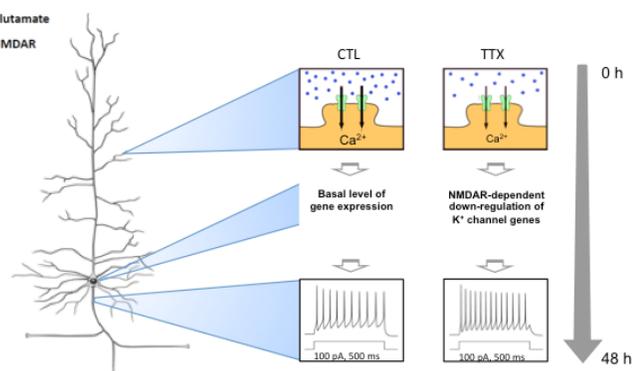


Figure 2. Model for K⁺ channel regulation during induction of homeostatic intrinsic plasticity (Modified from Lee et al., 2015, *Molecular Brain*)

MILAN BAGCHI RECEIVES DEBORAH PAUL PROFESSORSHIP

The School of Molecular and Cellular Biology is honored to announce that Professor Milan Bagchi, Department of Molecular and Integrative Physiology, has been named the Deborah Paul Professor of Molecular and Cellular Biology. An official investiture ceremony was held in the fall semester of 2016.

The position was made possible by a generous gift from the Deb and Tim Paul Endowment Fund. Deborah Paul, Ph.D. received her Masters in Biology from the University of Illinois in 1979 and then went on to have a distinguished career at Abbott Laboratories. There she is credited with pioneering work leading to the identification of HIV antigen in the serum of infected patients, enabling tests used in the diagnosis and monitoring of HIV infection.

Through her gift, Dr. Paul wishes to recognize an outstanding professor in the School of Molecular and Cellular Biology with demonstrated strengths in translational science, as well as linkages to the new College of Medicine.



Vice Provost for Undergraduate Education and Innovation Charles Tucker, Professor Milan Bagchi, Exec VP and VP for Academic Affairs Barbara Wilson, Director, School of MCB Steve Sligar

2016 MIP RETREAT

The 2016 MIP Annual Retreat was held at the Allerton Park and Retreat Center in Monticello on April 29 to great success. In addition to the stimulating poster and talk sessions highlighting the breadth of current work in MIP labs, we were delighted to have two keynote lectures. The first was given by MIP alumnus Dr. David Mead, who presented “Metagenomics, Commercial Biotech, and the Elusive Money Gene.” Dr. Mead, who obtained his PhD in the lab of Dr. Byron Kemper, discussed his experiences applying his groundbreaking discoveries



Dr. David Mead

in cloning and genomics in the arenas of industrial and commercial biotechnology. The second keynote speaker, Dr. Dennis Buetow, entertained us with “Notes on My Career in Research,” a memoir of his long and very successful time at Illinois. Bhoomika Mathur (Anakk Lab) and Sisi He (E. Nelson Lab) received awards for best oral presentations, and the poster awards went to Janelle Mapes (Bagchi Lab) and Gisele Cymes (Grosman Lab), with honorable mentions to Ramona Haji Seyed Javadi (Wildman Lab) and Demilade Akinrotimi (Anakk Lab). The scientific sessions were enhanced by a scavenger hunt sending MIP students and faculty exploring the beautiful Allerton grounds to track down sites and statues with creative clues invoking “fish in a sea of green,” “a modest maiden,” “Chinese musicians,” “a travel overseas,” and “the Japanese symbol of friendship.” To provide evidence of finding each treasure on the hunt, each team had to take “selfie” pictures of themselves in each locale. It was a great bonding

experience and a fun way to learn more about the lovely Allerton Park.



Rose Zhu (Tsai lab) and Ramona Haji Seyed Javadi (Wildman lab)



Selfie with Dr. Hee Jung Chung and Chung lab members, Shuwei Wang, Amanda Weiss, Sung-Soo Jang, Nickolas Broches

MY EXPERIENCE AT MIP

Victor Ramirez, MD, Emeritus Professor, MIP

I arrived in 1974 as full professor to the Department of Physiology and Biophysics, as it was known at that time. As expected I did research, teaching and mentoring and my letter today will focus on Teaching as one of the most rewarding experiences I had. I have selected 10 of the many students I have mentored to highlight the three major layers that comprise higher learning: undergraduates, masters and PhDs.

Let's start with one of the undergraduates, Daniel Becker, who graduated with distinction in our School, went on to pursue a MD-PhD at Michigan School of Medicine and later did an internship at Harvard and Brigham and Women's Hospital, also with distinction. Currently, as an Associate at New LeafVenture Partners, he monitors funds for health-related companies.

Two of the 10 selected students received a Master's in Physiology working in my laboratory. One is Daniel Llano, MD-PhD, presently a promising assistant professor in MIP, and also a physician at Carle Hospital. The other happens to be my son, Andres Ramirez, who is a Research Associate at Merck with 28+ years of extensive research experience in Neuroscience in both academia and the pharmaceutical industry, focusing his research on neurodegenerative diseases of the CNS.

Of the several PhDs trained in my lab I have chosen seven because they represent diverse disciplines in which they have pursued their dreams. Jon Levine, one of my first graduates, is now Director of the Wisconsin National Primate Research Center. Jill Becker is a Senior Scientist and professor of Psychology and Psychiatry and Senior Neuroscience Scholar in the Reproductive

Science Program at the University of Michigan. Nicholas Laping is Director of Pharmacology and Biology at GlaxoSmithKline with 18 years of drug discovery experience at SmithKline Beecham and Endo Pharmaceuticals. Kyunjiinn Kim is currently Chair and Distinguished Professor in the Department of Brain and Cognitive Sciences at the Institute of Science and Technology, Daegu, Korea. Robert Michaelson, a very successful MD-PhD, is owner of a private surgery clinic, Northwest Weight Loss Surgery in Washington. Jianbiao Zheng is now VP of Research and Development at Sequentia, Inc. Last but not least, Sean Smith, one of my last graduates before I retired as Emeritus Professor, is currently Executive Director of Neuroscience at Merck.

I hope my recounting of my mentoring experiences and the diversity of paths that my former students have taken will encourage current students in our Department to take advantage of all the opportunities and technical facilities offered by the Department and the School. Best wishes to all of you in your future endeavors.



Victor Ramirez
in Viña del Mar, Chile.

FACULTY AWARDS AND MILESTONES

Eric Bolton, James E. Heath Award for Excellence in Teaching in Physiology from School of MCB, University of Illinois-Urbana-Champaign.

Claudio Grosman, Faculty Excellence Award from School of MCB, University of Illinois-Urbana-Champaign.

FACULTY GRANTS NEWLY AWARDED IN 2016

Tom Anastasio, CART-Coins for Alzheimer's Research Trust, entitled: Computational Identification of Possible Combinations of Existing Drugs that Reduce Inflammation in AD with Minimal Side Effects.

Eric Bolton, Research Board RB16156, entitled: GFR α 1-Mediated Glial Cell Line-Derived Neurotrophic Factor Signaling in Prostate Development.

Eric Bolton, NIH R56 entitled: AR and GDNF signaling tune growth and differentiation in the developing prostate.

Catherine Christian, Brain Research Foundation, entitled: Optogliai modulation of inhibition and seizure susceptibility.

Hee Jung Chung, NIH R01 (with Drs. Andrew Smith and Paul Selvin), entitled: Super-resolution microscopy of small quantum dots to elucidate the mechanisms of Alzheimer's Disease.

Hee Jung Chung and Graham Huesmann, Carle/IL Seed grant, entitled: Biochemical and electrophysiological analyses to identify the early biomarkers and pathogenic mechanisms for human temporal lobe epilepsy.

Benita Katzenellenbogen, Breast Cancer Research Foundation, entitled: Development of novel antagonist ligands for metastatic breast cancers driven by estrogen receptors (ERs) with activating mutations

Derek Wildman, NIH R21, entitled: Placental RNA Expression as a Function of Gestational Age and Environmental Exposures

Derek Wildman, National Science Foundation (with Dr. Malhi), entitled: Epigenomic Effects of European Colonization of Alaskan Natives

Derek Wildman, Duke Lemur Center Director's Fund Award, entitled: Evolution of Progesterone Withdrawal in Strepsirrhine Primates.

STUDENT NEWS

Graduate Student and Postdoc Awards

Amy Baek, a postdoc of Dr. Erik Nelson, received a Postdoctoral Fellowship from Susan G. Komen Foundation, “Elucidating the mechanisms by which a cholesterol metabolite promotes metastasis”.

Congcong Chen, a graduate student of Dr. Eric Bolton, received a James Heath Award for Excellence in Teaching from School of MCB, University of Illinois-Urbana-Champaign.

Hanna Erickson, a graduate student of Dr. Sayee Anakk, received a Best Medical Student Research Poster Award from American College of Physicians at Internal Medicine Meeting, and a Hazel Craig Fellowship from University of Illinois at Urbana-Champaign.

Young-Chae Kim, a postdoc of Dr. Jongsook Kim Kemper, received a Scientist Development Grant from American Heart Association, “Role of Intestinal SHP and FGF19 in regulating cholesterol levels”.

Alexandria Lesicko, a graduate student of Dr. Dan Llano, received a predoctoral NRSA fellowship from National Institutes of Health, “Functional modularity and multisensory convergence in the lateral cortex of the mouse inferior colliculus”.

Jiang Li, a graduate student of Dr. Catherine Christian, received a Beckman Institute Graduate Fellowship.

Kevin Stebbings, a graduate student of Dr. Dan Llano, received a Beckman Institute Graduate Fellowship.

New Ph.D. 2015-2016

Congcong Chen (with Dr. Bolton), “Androgen Receptor-Mediated Growth Suppression and Apoptosis of Human Prostate Epithelial Cells”.

Itamar Livnat (with Dr. Sweedler), “Analysis of D-Amino Acid-Containing Neuropeptides in Mollusks and Rodents”.

Bernard (BJ) Slater (with Dr. Llano), “Layer specific differences in the mouse auditory corticocollicular system”.

ALUMNI UPDATES & RETIREMENTS

Ting Fu (Kemper lab), received the Salk Alumni Award and Hewitt Foundation post-doctoral fellowship at Salk.

Giovanni Gonzalez-Gutierrez (Grosman lab), is now the facility manager at the Macromolecular Crystallography Facility at Indiana University.

Tyler Harpole (Grosman lab), is now working as a post-doctoral researcher with Lucie Delemotte at the KTH Royal Institute of Technology, Stockholm, Sweden.

Ji Miao (Kemper lab), has started as a tenure-track Assistant Professor at Harvard Medical School.

Penny Morman: Penny Morman will be retiring from her position as Office Manager after serving the MIP Department with the highest level of professionalism and dedication for 18 years. She helped us every day on numerous things with a smiling face and her characteristic humor. She established deep personal bonds of friendship with many of our department faculty. It will be very hard to replace Penny. We congratulate her on a well-earned retirement.

Callie Els: We congratulate Dr. Callie Els on his retirement. Callie did his Masters in Biophysics and Physiology at UIUC in 1978. He returned to South Africa and established a very successful academic career there. He also collaborated with Professor Sandy Helman of the MIP department for many years, working on epithelial sodium channels. In 2001, Callie returned to UIUC to join the College of Medicine as a teaching faculty and assumed the responsibility of the coordinator of M1 Physiology. He also taught for many years in our Systems Physiology (MCB 402) course, a core requirement in the MIP graduate program. His deep knowledge of medical physiology and curriculum, and his passion for teaching and mentoring have marked him as an outstanding educator and invaluable member of the university community.

Ann Nardulli: Professor Ann Nardulli retired after a thirty year extraordinary career at the University of Illinois. She completed her graduate studies with Professor Benita Katzenellenbogen and her postdoctoral training with Professor David Shapiro before joining the MIP faculty. She established and led a vibrant and nationally recognized research program, studying estrogen receptor biology, which trained many graduate and undergraduate students. Ann has been an exceptional colleague. Her friendly spirit and genuine care for her students and colleagues, and a great sense of humor created a hospitable environment in the MIP department. One of her greatest attributes is her mentoring of younger women scientists in the campus. Ann continues to be associated with the MIP department as an Emeritus Professor.

RESEARCH PUBLICATIONS JAN - OCT 2016

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MOLECULAR & INTEGRATIVE PHYSIOLOGY

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