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ALSO FEATURING
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Front cover: Artist’s impression of an astrocyte with multiple branches showing Ca2+ flashes.  
Khakh lab/UCLA
Dear Friends and Colleagues,

It has been both a challenging and rewarding year for the BRI, with strong accomplishments that highlight the wide spectrum of neuroscience research by our faculty.

Despite the constant challenges of shrinking state and federal budgets, we are ending 2014 having maintained our spectacular national and international standings. In the areas of mental health (the NIH’s National Institute of Mental Health - NIMH) and drug abuse (the NIH’s National Institute on Drug Abuse - NIDA), UCLA is close to the top in the US, with a rank of 2nd and 4th respectively. This clearly shows the high impact we are making in these areas of neuroscience, which consistently outperform most benchmark institutions.

In the recent US News & World Report, UCLA was ranked 8th in the world, highlighting the university’s overall standing as a very prominent, world-renowned institution. The same report placed UCLA Neuroscience and Behavior 6th in the world, and Psychiatry and Psychology 4th in the world.

Despite these impressive statistics, UCLA neuroscience revenues are down. Funding received from the NIMH and NIDA has decreased over the past couple of years and, though we’re ranked 7th in the country for grant awards from the NIH’s National Institute of Neurological Disorders and Stroke (NINDS), we’ve lost approximately $9million in funding from this NIH institute.

In fact, funding is down for almost all UCLA neuroscience entities. However, the very high departmental rankings reflect the quality of our research and education. They serve as evidence of an ability to collaborate and share resources across departments and institutes, and the sheer tenacity of our outstanding faculty.

The BRI is a key infrastructure for maintaining and enhancing the degree to which we share skills, ideas, and resources. This year, the BRI Integrative Center for Neural Repair (ICNR) held its first symposium, which featured 13 speakers from across California, and was attended by hundreds. Dr. Ming Guo, whose ground breaking work in cell biology has led to new insights into Parkinson’s disease, was a featured speaker. The ICNR joins two other established Integrative Centers -- the Integrative Centers for Learning and Memory, and Neurogenetics

Additional BRI Integrative Centers will be established in the coming months, including an integrative center for addiction biology that will provide an interdisciplinary forum to brainstorm and explore multiple approaches to addiction research at UCLA.

This edition’s feature article is a reminder of the historical and contemporary significance of the work BRI physiologists have accomplished, and the value of taking risks in exploring new scientific questions, even knowing that these risks may be too ‘out there’ for traditional scientific funding agencies to embrace.

Alan Grinnell’s generation of physiologists came to UCLA partially because the Brain Research Institute was one of the first of its kind in the US. Its existence at the time provided an infrastructure in which zoologists, biologists, biophysicists and chemists could collaborate in the then nascent field of neuroscience. (The Society for Neuroscience had less than 1000 members in the early 60s. Now it has over 40,000.)

Our early dominance in neuroscience and the establishment of one of the first brain research institutes in the world has evolved a culture of non-competitive collaboration that characterizes BRI neuroscience to this day. Part of the institute’s role is to give researchers the support necessary to embolden them to ask brand new questions and challenge scientific dogma.

During the next year, I hope to grow BRI support efforts to incubate new collaborations in exciting areas of neuroscience, including engineering, physics, and chemistry. These efforts may not immediately result in large funding awards, but they will lay the foundation for future cross-disciplinary excellence that may eventually lead to a breakthrough in understanding of the brain, and advancement in human health.

As we move these groundbreaking endeavors forward, we are reliant on the support of individual and foundation donors who see the value in new areas of research and who are more free to embrace risky endeavors.

I am excited for what the new year may bring us.

[Image]
Since the 1950s there has been a plethora of disciplines that have evolved into "neuro" versions of their former selves. Now, on a campus that is populated with exceptional neuroscientists ranging the full gamut of basic through clinical research, it is easy to forget the absolute necessities of fundamental knowledge. Physiology—the study of living mechanisms from the molecular bases of cell function to integrated analyses of the behavior of the entire body—is an essential driving force of contemporary neuroscience as much as it has ever been.

UCLA Physiology, from its foundations in the 1960s to the present, has consistently asked the big questions, creating new realms of investigation.

Formed around the same time as the Brain Research Institute, the Physiology Department has been a key collaborator with the BRI for decades. It is responsible for solving some of the biggest puzzles in neuroscience, empowering it to significantly increase our understanding of the human brain in health and disease.

Baljit Khakh, PhD, Professor of Physiology and Neurobiology and the BRI's Associate Director for Research sums it up: "Physiology is important because it offers a biophysical, mechanistically satisfying understanding essential to neurobiology. The department at UCLA has been particularly strong in the area of mechanisms and biophysics, with its roots lying in the biophysics of membrane channels and membrane transporters."

Khakh is alluding to the groundbreaking work that UCLA researchers accomplished when the department was in its infancy. Distinguished Professor of Physiology, Alan Grinnell, PhD, was both a witness and participant in these endeavors. Last year, the BRI sponsored a celebration of Grinnell’s 50 year career here: “From the Frog Neuromuscular Junction to Bats & Beyond: a symposium to honor Alan Grinnell.” Speakers from Puerto Rico, Oslo, and across the US participated.

In the fall of 1964, Grinnell came to UCLA as a member of the zoology department, and one of the early members of the BRI. "At the time, neuroscience was a tiny discipline. Even Harvard College didn’t have a neuroscientist in its faculty. But UCLA had the Brain Research Institute which pulled in scientists from a diverse group of disciplines to participate in neuroscience research," Grinnell recounts. “I was also attracted here by the chance to collaborate with Ted Bullock, a leading comparative neurophysiologist and one of the co-founders of the BRI, and Susumu “Hagi” Hagihara.”

Neuroscience was a fledgling discipline. “One could look at the world around you and find endless examples of interesting phenomena that hadn’t yet been explained,” Grinnell says.

“Hagi, Ted and I fell in love with the freedom and atmosphere here. It allowed us to push the envelope and ask new questions. It was a very ‘yeasty’ time. Bullock was focusing on comparative neurophysiology. He loved finding exceptions to the rules, examples that were different to the conventional wisdom. It’s these exceptions that can show us how biological mechanisms work because a particular animal has specifically adapted to a certain lifestyle or circuitry system.”

Grinnell’s research dovetailed well with Bullock’s interests. While much of Grinnell’s career had been centered on synaptic biophysics and nerve-muscle trophic interactions, his other major interest was in bats, the only order of
BRI physiologists challenge traditional neuroscience in the past and present

mammals that have successfully adapted to the niche of nighttime air by evolving the ability to use sound as a substitute for vision.

The question of how the brain “visualizes” sound is one that Grinnell still investigates. He now works with the one genus of old world “flying foxes” that echolocate as well as having excellent night vision. In collaboration at UCLA with Walter Metzner, he is studying the degree to which a real visual picture is equivalent to the image formed by acoustic data. “In total darkness, these old world flying foxes echolocate by analyzing the echoes of sounds produced by clicking the tongue; but how much like a visual map is the mental image they are creating?” If these bats can be trained to discriminate between visual and auditory information and transfer seamlessly from one sensory modality to the other, then echolocation must be creating a picture that the animals interpret in the same way as visual information. If the bats can’t be trained to discriminate between the two modalities, then information must be transmitted through a complicated computational process in the brainstem that prompts them to behave as if they were seeing.

Grinnell’s work may result in practical assistance in designing guidance devices for the blind but, he explains, “the principal applied value of echolocation studies is increased knowledge of how the nervous system works.”

Major advances by other UCLA physiologists during the 1960s are responsible for establishing a set of tools and principles that neuroscientists now take for granted. The function of ion channels is a basic concept in cell biology. Without an understanding of the fundamental laws that govern the structure and mechanisms of these channels, including the means by which ions can enter or exit a cell, many disciplines would be hamstrung.

A major emphasis on ion channel biophysics was first established in the BRI through the research of George Eisenman, who was defining the detailed mechanisms of selectivity of ion channels: the interactions between charged ions; the cloud of water molecules surrounding the ions in solution; and the charges in the pores of ion selective channels in glass membranes and, later, in channels formed by antibiotics in lipid membranes. This groundbreaking research led to an explosion of interest in details of structure-function relationships in ion channels. “Then”, Grinnell says, “Jared Diamond joined the faculty. His work ignited the field further.”

Diamond, at the time a young physiologist, is perhaps now best known as a Pulitzer Prize winner for his geo-historical non-fiction work, Guns, Germs and Steel. In 1969, he co-wrote a paradigmatic review article with Ernest Wright, in which he interpreted Eisenman’s principals of ion channel selectivity in terms more familiar to physiologists, and extrapolated the principles that explain selectivity for singly charged anions. That review “strongly influenced all of us working on ion channels,” Grinnell explains. “It gave us a new set of working tools for ways in which we could interfere with conductance, and summarized the reasons that channels are selective.” It is worth noting that the Diamond/Wright review article was based on a careful reading of the physical chemistry of proteins, and thus served to enlarge the context of neuroscience at UCLA.

Grinnell in his lab, circa 1970. BRI Archives/UCLA
"Like me, Hagi had also come to UCLA because of Ted Bullock. He shared Bullock’s love of the diversity of interesting preparations, but while Bullock was interested in neural circuitry and animal behavior, Hagi was interested in the diversity of ion channels and their roles on cell behavior." Hagi became particularly well known as a pioneer in the characterization of calcium channels and their many roles in neurotransmitter release, muscle contraction, neurosecretion, and multiple other effector systems. He is also famous in the field for groundbreaking work on multiple types of potassium, sodium, and chloride channels. With a lab populated by a constant stream of talented students and postdocs from around the world, Hagi’s distinguished career at UCLA made the Physiology Department and the BRI a world center for the study of ion channels.

In the 1980’s the department’s strength in ion channel structure-function relationships took another great step forward. Francisco (Pancho) Bezanilla, who had earlier co-discovered gating charge movements in ion channels came to UCLA. Together with Julio Vergara, who was an expert on muscle physiology and excitation-contraction coupling, Bezanilla was key in the foundation of the Ahmanson Laboratory of Neurobiology within the BRI. These scientists and their collaborators made many major advances in understanding the structural basis of gating and other aspects of channel function.

BRI member and Professor of Physiology, Diane Papazian, PhD, came to UCLA to build on the foundation of the earlier physiologists. Papazian focuses on membrane biophysics, and studies the structure and function of potassium channels in particular. Her work is emblematic of the department’s gradual elaboration of membrane biophysics, ion channels and the roles of different kinds of these channels in health and disease.

Papazian’s research trajectory is typical of BRI physiologists. She first took on the challenge of analyzing voltage dependent channel gating – the process by which small voltage changes across the membrane open “gates” in ion channels, allowing charged ions to permeate. “We now understand quite a bit about how channel proteins sense changes in voltage and how that is coupled to opening and closing of the gate that controls ion conduction through the pore,” she says. “Over the past few years, the field has matured significantly. That is when I started looking for other challenges.”

Papazian began to investigate the ways that changes in gating lead to specific diseases. She now focuses on rare diseases caused by single mutations. “One mutation can affect a very specialized type of gating, producing infant onset ataxia associated with intellectual disability, whereas a mutation that alters a different kind of specialized gating in another channel protein is associated with autism and epilepsy.”

"Disease models of autism, epilepsy and infant onset ataxia are striking examples of the way that the physiological understanding of channel gating at a detailed level is important for human health."

"These tools give us the ability to investigate the effects of altered gating at several levels, starting with the channel protein. We can then put mutant proteins back in the neuron to see how they impact neuronal function and in turn, importantly, track how these changes in neuronal function lead to aspects of disease." The Papazian lab has a diverse arsenal of experimental approaches to explore these questions including electrophysiology, imaging, biochemistry, molecular biology, genetics and behavioral analysis tools.

Papazian’s work fits well into an emerging area of neuroscience. A growing body of researchers is suggesting that fundamental changes in neuronal activity – even if these changes are not the initial trigger of a disease – is a crucial part of pathogenesis. Epilepsies, neurodegenerative diseases, autism and mental retardation are particularly implicated.

"R1 in S4 occupies the gating charge transfer center in the resting state. (L) Cartoon of the resting conformation shows an arginine representing R1 in the gating charge transfer center. (L & R) Ribbons representing the backbone atoms of S2, S3, and S4 are shown in yellow, red, and blue, respectively. Backbone atoms and side chains corresponding to I287, F290, E2, D3, and F324 (mutated in silico from tryptophan) in Shaker were extracted from the Kv1.2/Kv2.1 paddle chimera x-ray structure (2r9r). (Long et al., 2007). (R) Cartoon of the penultimate closed state shows arginines representing R1 in the vicinity of I287 and R2 in the gating charge transfer center. Meng-Chin A. Lin/UCLA"
“There are no examples to prove this yet,” Papazian explains, “but I believe some of these functional mechanisms may be a point of convergence. Let’s say we study a disease with a complex mix of triggers such as autism or Alzheimer’s. It is difficult to conceive of therapies directed at individual triggers because each one could contribute to a small fraction of the affected population.”

“But if several triggers cause a similar functional change in a certain type of neuron, then rather than target each of the initial triggers separately, it might be possible to target the area where the mechanisms converge. If that were feasible – and there are no documented cases yet – there will be hope for effective treatments for a broad range of the patient population.”

Papazian hopes that her perspective as a basic scientist and physiologist will lead to an understanding of how a tiny change in channel function leads to wide-ranging and devastating consequences in a living organism. “My ultimate goal is to take one of these mutations and track its natural history from the most basic level, its impact on channel function, to its in vivo consequence at several levels of analysis. This could range from changes in excitability, to downstream effectors, to organismal consequences.” It is this functional perspective which exemplifies the fundamental value of physiology in neuroscience.

Thomas O’Dell, PhD, is Professor of Physiology, the BRI’s Assistant Director for Education, and Vice-Chair of the UCLA Interdepartmental Graduate Program for Neuroscience. “Physiology is a driving force in neuroscience,” he says. “It has to be.”

O’Dell continues, “The first neurobiologists were physiologists. It was physiology that drove early advances in terms of understanding mechanisms of excitability in neurons and axons, and found processes of synaptic communication.”

“In a sense, now, everybody has become a physiologist. The study of the structure and function of biology, from the atomic level through the whole organism, is occurring not just throughout neuroscience, but in other fields ranging from cardiovascular research to biochemistry.”

O’Dell has always been a physiologist and neuroscientist with an abiding interest in glutamate receptors, which mediate fast excitatory synaptic transmission in the central nervous system and are localized on neuronal and non-neuronal cells.

As a post-doctoral researcher in the lab of legendary Columbia University neuroscientist, Eric Kandel, O’Dell began to focus on learning and memory – how glutamate acts as a transmitter and stores information in the brain during memory formation. At first, he worked on comparative mechanisms of plasticity. Could mechanisms for learning and memory in invertebrates translate to mammalian model systems? “At the time, we had problems with this question. It wasn’t clear if the models were translatable or if there were technical problems. But there was freedom in the Kandel lab. And I got very interested in something else.”

O’Dell began to notice tyrosine kinases which are a subclass of protein kinases – enzymes that phosphorylate proteins to change their function. Tyrosine kinases (TKs) transfer a phosphate from Adenosine Triphosphate (ATP) to a protein in a cell. Since TKs can phosphorylate a large number of cellular proteins, these kinases can regulate many cellular functions. “When I started looking at them, no one knew if TKs were involved in learning and memory formation. It was a totally new question.”

O’Dell first started to use pharmacological techniques to study what happens if TKs are blocked, but these techniques necessitated blocking out all TKs. Pharmacology didn’t allow for selective blocking. “It was when we started using genetic techniques to introduce mutations to knock out specific TKs that things became really interesting. Along with Alcino Silva [UCLA Professor and BRI member] and Seth Grant [Professor at the University of Edinburgh] we were the first to use transgenic molecular genetic approaches to study synaptic plasticity. We were totally surprised by the findings. They were nothing like we were anticipating.”

Perhaps the biggest surprise came from experiments using molecular genetic techniques to study the role of N-Methyl-D-aspartate receptors (NMDARs), a subtype of glutamate receptor in synaptic plasticity. Activation of NMDARs allows a lot of calcium to enter the cell. This in turn activates enzymes, makes synapses stronger, and helps form a memory and store the information in the brain. “Early in my career, the textbook view of NMDA was erroneously simplistic. Contrary to the standard view at the time, these receptors bind to another protein, which in turn acts as a little adapter that will then bind to other proteins, bringing them together in a cluster. We visualized this complex of proteins associated with NMDARs as a little signaling molecular machine.”

O’Dell then wanted to know if these signaling machines impact learning, memory and plasticity. “Working with Seth Grant, we knocked out Post Synaptic Density (PSD95) – an NMDAR adaptor protein that is found in the postsynaptic density – the thick, dark structure underneath the membrane where two cells intersect. The prediction was that this would mess up the ability of synapses to get stronger when NMDA is activated. In other words, the organism’s neural plasticity would diminish. But the opposite occurred. Long term
because ATP was shown to be co-released with other transmitters. This belief dominated neuroscience for each particular neuron, and unchangeable."

The implications of these initial experiments led O'Dell further down the rabbit hole. PSD95 is part of a larger family of NMDAR adaptor proteins that includes proteins like Synapse Associated Proteins (SAP102) and PSD-93. When O'Dell examined SAP102 mutants he found significant deficits in learning and memory. A few years after this discovery, a group of Canadian investigators found that humans with SAP102 mutations had x-linked intellectual disability. Similarly, another set of these adapters (PSD93), has been implicated in mutations found in a family in Scotland suffering from schizophrenia.

"Coming from a basic science perspective, asking fundamental questions on the way certain processes work and interrogating the proteins and molecules involved in memory foundation, gave us a head start on a real clinical problem. Mental retardation. Schizophrenia. Maybe more."

"In the case of NMDA receptors in general, I'm hoping to uncover insights into how activation of these receptors makes synapses stronger, weaker, and how they can trigger changes in the function of brain circuits. These same receptors might be very important targets for anti-depressants," O'Dell says.

O'Dell's journey, its ability to challenge commonly held neuroscientific belief and the surprises that may lead to clinical advances along the way, are typical of the physiology department's tendency to ask big, fundamental questions with startling, resonant results. "There's so much work to be done. We are still learning a lot about what we need to learn."

Like O'Dell, Baljit Khakh has asked big questions with important results. Early in his career, he was witness to the limitations of scientific dogma. In the 1920s, one of Khakh's greatest heroes, the English Nobel Laureate Henry Hallett Dale, stated the following: "In cases for which direct evidence is already available, the phenomena of regeneration appear to indicate that the nature of the chemical function... is characteristic for each particular neuron, and unchangeable." (PRSM 28 (3): 319-30). In other words, Dale’s principle proposed that a particular nerve could only release one transmitter. This belief dominated neuroscience until it was challenged in the 1960s to 1980s.

In the 1990s, Khakh became interested in ATP signaling, because ATP was shown to be co-released with other classical neurotransmitters in the periphery. "It turns out Dale was wrong – or at least largely misinterpreted. However, until the ATP-activated ion channel genes were cloned, most researchers didn’t even think that receptors for ATP existed on neurons. It turns out that there is a large family of ATP receptors, seven distinct genes for ion channels, and much more. If you look very broadly, it's not only one of the largest neurotransmitter receptor families there are, but also molecularly and structurally unique. And, the proteins are found throughout the nervous system. They are involved in many diseases, and seem to be critically involved in neuropathic pain."

For 9 years, Khakh focused on investigating this unique molecule (the P2X receptor) by studying how its ion channel pore forms and, once open, how it selects and rejects certain ions and why it was highly calcium permeable. "We couldn’t guess because the channel was so different from other ion channels. We had to go in there, clone isoforms, mutate subunits, swap domains around, make chimeric proteins, develop mutations and figure it out piece by piece. It was a very exciting and rewarding time." Khakh’s lab found that the channel was formed by Transmembrane Domain 2 (TM2) which was alpha helical. Specific residues in TM2 contributed to the selectivity filter, and the investigators found that the pore closed and dilated in the same region as well.

"We discovered ion selectivity dynamics in neurotransmitter-gated ion channels. After we did that, we spent a long time trying to measure conformational changes to see dynamics between ATP binding and channel opening, using several optical approaches. These data showed there were fast and slow conformational changes. Much of what we found with structure/function was completely confirmed when Eric Gouaux’s lab crystalized the protein". When Gouaux’s lab provided further proof of Khakh’s physiological interrogations into how P2X receptors worked, Khakh realized its key mysteries were solved and that others would fill in the gaps. He stepped up to another challenge, this one a largely blank slate in the neuroscience literature at the time. "We moved on to astrocytes. When I started studying ATP signaling, I was told the channels for them didn’t exist. The same is true now for astrocytes: people tell me they don’t do anything. One UCLA colleague even told me that astrocytes don’t exist in the cortex," he says.

"I’ve consistently been told by some colleagues that astrocytes do very little without any real evidence. Perhaps this is another example of dogma above all else? We became interested in astrocytes precisely because the field does not yet know what their functions are. There are many open questions that need to be answered."

“Fundamental questions on the way certain processes work and interrogating the proteins and molecules involved in memory foundation, gave us a head start on a real clinical problem. Mental retardation. Schizophrenia. Maybe more.”
Since astrocytes are glial cells that outnumber neurons, the previous lack of study in the field is a startling one. Khakh began exploring the basic biology of astrocytes in brain circuits. Along with BRI member Michael Sofroniew, he recently investigated the potential role of astrocytes in disease. He selected Huntington’s Disease (HD) because “it affected the striatum, and there wasn’t much information on what astrocytes did in the striatum, nor was there much information on what, if anything, astrocytes did in HD. Almost nothing was known.” At the same time, HD is a strong model because, unlike diseases like schizophrenia and epilepsy which have multiple causes, HD is caused by a known molecular defect.

“In the beginning, our goal was simple: study the function of astrocytes in HD and see what is different.” Khakh found that, in mouse models of this disease, expression of a potassium channel in the astrocyte (Kir4.1) is notably reduced. Since the channel usually siphons potassium and maintains extracellular potassium in the brain, the lack of Kir4.1 means that there is increased potassium around neurons in the striatum. “By fixing this deficit, we found that the outcome of the disease within mouse models was improved.” This suggested that loss of the channel is a contributing factor in HD. It also validated Khakh’s interest in astrocytes.

There are many large questions still to be explored, ranging from basic biology to disease mechanisms. “We know very little about the genes and proteins that regulate function in astrocytes.” Because they are so different from neurons developmentally and genetically, Khakh sees a great opportunity to identify the signaling molecules at work in order to produce desirable effects on key molecules within the astrocyte, which may benefit the circuit itself.

“We don’t know how astrocytes come together and operate in circuits of the brain. On a circuit level, there’s so much more to be discovered about what these fascinating cells do. The physiological perspective is crucial to arrive at the correct answers. We have to focus on understanding the mechanisms and, through this prism, try to explain what happens in the normal brain and in disease,” Khakh says.

Sometime in the future, the work of Grinnell, O’Dell, Papazian and Khakh will ultimately lead to clinical breakthroughs, but in a context of rapidly evolving and increasingly specialized sub-disciplines in neuroscience, physiology sometimes gets lost in the education of young scientists. O’Dell is faced with this question as he works on restructuring the curriculum for the Neuroscience Interdepartmental Graduate Program. “How broad should the foundation be? Do students still really need to know that the Nernst equation controls the flux of ions across an excitable cell’s membrane? There’s a growing trend at other universities to create a niche,” O’Dell says. “Physiological principles are still essential to neuroscience research. In some ways I think we’re getting ahead of ourselves. We assume that we have the fundamental building blocks and we don’t need to think about them anymore.” At UCLA, new physiological questions continue to be asked. O’Dell’s work on NMDA receptor complexes was a major revelation, and astrocytes, surely, can still be considered a largely blank slate. Grinnell and Papazian too have consciously steered themselves away from research areas that are too populated in order to ask brand new questions. It is a brave move, considering funding generally goes to the scientists who are incrementally building on known paradigms rather than exploring areas that may, or may not, yield fruit.

It is perhaps too easy, when thinking about the basic science work that UCLA physiologists are advancing, to focus on the end goal, the “hope for a cure” for the many terrible diseases afflicting humankind. For many of these researchers there seems to be a little distance between the biophysical, molecular and genetic levels of analyses they are accomplishing, and the development of viable clinical treatments. They hope to see the fruits of the building blocks they have created at the foundation of neuroscience. Perhaps one day soon they may get to shake the hand of a person whose health has been improved by the therapies developed from their constant quest to explore uncharted frontiers in the physiological world.
Parkinson’s Disease (PD) is an incurable brain disorder that causes symptoms such as gradual loss of motor control (tremor, rigidity, slowness in movement, inability to walk), and non-motor symptoms such as depression, anxiety, sleep difficulty and dementia. After Alzheimer’s disease, it is the most common neurodegenerative disorder, affecting about 5% of people age 80 and above. Each year, over 60,000 Americans are diagnosed with PD, with 5-10% of these cases occurring before age 50. As the population grows older, this devastating illness will be more prevalent, putting enormous financial, physical and emotional burdens on patients, families and society.

Thanks to groundbreaking researchers such as Ming Guo, MD, PhD, scientists are beginning to understand the cellular and molecular basis of Parkinson’s disease. Guo is a Professor of Neurology and Molecular & Medical Pharmacology at UCLA David Geffen School of Medicine. She is a practicing neurologist, who cares for patients with Alzheimer’s and Parkinson’s disease, and also a scientist, who runs a basic science research lab investigating the genetic basis and mechanisms of neurodegenerative disorders. When Guo entered the field, the dominant triggers of PD were widely believed to be “dopaminergic neuron degeneration in the substantia nigra, and the formation of intraneuronal protein aggregates called Lewy bodies, which trigger a cascade of motor symptoms”. Hence, since the 1970s, dopamine replacement has been the primary intervention. Dopamine replacement, however, does not halt the progression of the illness, has little effect on the ravages of PD’s motor symptoms such as gait (walking) problems, or non-motor symptoms including dementia. This has prompted Guo to seek new therapeutic strategies by approaching the disease from a different angle.

Recent studies suggest that a handful of genes, when mutated, lead to PD. Though this form of PD accounts for no more than 10% of all cases, by studying some of these genes Guo has identified a key effector in familial and sporadic PD – mitochondrial pathways.

In 2006, Guo’s research group was one of two groups in the world who first reported in the journal Nature that two of PD genes, PTEN-induced putative kinase 1 (PINK1) and parkin, work together to maintain healthy mitochondria.
Mitochondria are specialized compartments (organelles) that generate more than 90% of the energy required by the organism. Mitochondria are also important in controlling cell death and aging. This groundbreaking study indicated “that mitochondrial health is of central importance to prevent neurodegeneration,” she says. Her laboratory later reported that the PINK1/parkin pathway controls mitochondrial fusion and quality control, processes that constitute new therapeutic targets.

Most recently, Guo has found that alterations in the MUL1 gene are crucial in pathogenesis of PINK1 and parkin mutation-mediated PD pathology. Their 5-year study, performed on fruit flies, human cells and mice (with the help of collaborators), indicates that the dosage of MUL1 is key in PINK1/parkin mutation-mediated pathology. Providing extra MUL1 to damaged mitochondria that lack PINK1 or parkin reverses the pathology, and protects the tissue integrity. Conversely, the removal of MUL1 from PD neurons increased rates of neurodegeneration and unhealthy mitochondria. “MUL1 dosage is key, and optimizing its function is crucial to ward off Parkinson’s disease and for the general health of the brain. Finding a drug that can enhance MUL1 function would be of great benefit to patients,” she says.

In a larger sense, Guo’s work in cell biology and genetics broadens traditional definitions of Parkinson’s beyond its designation as a disease, suggesting it is a spectrum disease – a group of molecularly diverse disorders present in multiple tissues beyond dopaminergic neurons. Her work signifies hope to the estimated 1,000,000 people with PD in the US. It also suggests that, by boosting mitochondrial integrity and function, MUL1 may have wider roles as a factor that promotes neuronal health, and controls aging and neurodegeneration.
THE BRI WELCOMES NEW MEMBERS

ROBERT ASARNOW, Ph.D, PROFESSOR OF PSYCHIATRY & BIOBEHAVIORAL SCIENCES, AND PSYCHOLOGY

Dr. Asarnow investigates traumatic brain injury (TBI), schizophrenia, and cortical-striatal based learning with a special focus on children.

He is currently conducting a longitudinal study of children with moderate to severe TBI, using multiple brain imaging methods and cognitive tests to determine the role of white matter in recovery following the first year post-injury. In this context, Asarnow also studies the NMDA agonist (D-Cycloserine) and its role in augmenting the effect of cognitive training in enhancing recovery.

Asarnow’s recent research endeavors also include a family genetic study of children with schizophrenia and attention deficit hyperactivity disorder. This study systematically evaluated alternative ways of measuring the schizophrenia phenotype. Results indicated an increased familial aggregation of schizophrenia, schizophrenia spectrum personality disorders, and certain neurocognitive impairments. In addition, the study identified an unusually early age of the onset of schizophrenia in family members who are related to early onset probands versus relatives of adult onset probands. Asarnow and his colleagues are now following up these results with association analyses to determine if certain genes involved in brain development are linked to cognitive impairments in the non-psychotic relatives of patients with childhood onset schizophrenia. His group also examines cortical-striatal networks in the non-psychotic relatives of patients with childhood onset schizophrenia, and collaborates with two other labs in using whole exome sequencing to identify de novo mutations in patients with childhood onset schizophrenia.

Asarnow received his PhD in Clinical Psychology, with a minor in Neuroscience, at Wayne State University. His many awards include the Dr. Alexander Gralnick Award from the Child Welfare League of America.

RACHELLE H. CROSBIE-WATSON, Ph.D, PROFESSOR OF INTEGRATIVE BIOLOGY & PHYSIOLOGY, AND NEUROLOGY

Dr. Crosbie-Watson studies Duchenne muscular dystrophy (DMD), an inherited muscle wasting disorder that affects all skeletal and cardiac muscles and is the most common lethal genetic disorder in children.

Loss of appropriate connection between the muscle cell membrane and its surrounding extracellular matrix is emerging as a critical initiating event in DMD, and Crosbie-Watson’s research group has identified mechanisms to restore cell surface-extracellular matrix connection that have the potential to ameliorate a broad range of muscle wasting disorders. In DMD, mutations in the dystrophin gene cause the absence of a dystrophin-associated glycoprotein complex that functions as the main connection between the muscle cell and the extracellular matrix. In normal skeletal muscle, two additional adhesion complexes are present at the neuromuscular junction. Crosbie-Watson found that overexpression of these complexes in DMD mice ameliorates muscular dystrophy.

In the process of her research, Crosbie-Watson’s lab has generated and validated more than 20 lines of genetically engineered mouse models, over 30 polyclonal antibodies, stable muscle cell lines, as well as viral, bacterial, and mammalian expression vectors.

Crosbie-Watson completed her PhD research in the laboratory of Professor and Dean Emeritus Emil Reisler in the Department of Biochemistry at UCLA. Her postdoctoral work at the Howard Hughes Medical Institute, University of Iowa College of Medicine, led to the isolation and characterization of a 25kDa core component of DGC, which she named “sarcospan” because of its multiple sarcolemma-spanning domains. In 2013, Crosbie-Watson was one of six faculty members at UCLA to receive the “UCLA Distinguished Teaching Award.”
WENTAI LIU, Ph.D, DISTINGUISHED PROFESSOR OF BIOENGINEERING, ELECTRICAL ENGINEERING, AND THE CALIFORNIA NANO SYSTEMS INSTITUTE, AND DIRECTOR OF THE CHAN SOON-SHIONG BIONIC ENGINEERING RESEARCH CENTER AT UCLA

Dr. Liu’s research areas include neuroengineering, bioelectronics, bio-signal processing, brain-machine interface, and personalized learning.

His investigations focus on the neural implants dealing with the nerves and muscles for the retina, muscles, eyelids, spinal cord, and bladder. The goal of Liu’s work is to regain eyesight for the blind, restore motor functions for spinal cord injury, and recover and enhance cognition for the impaired.

Since 1988, Liu has led the engineering efforts of the interdisciplinary retinal prosthesis project to restore vision. This culminated with successful implant trials and the Argus II Retinal Prosthesis System, a commercially available retinal implant device approved by the FDA in 2013. The Argus II operates by wirelessly transmitting images from a small, eyeglass-mounted camera to a microelectrode array implanted on a patient’s damaged retina. The array sends electrical signals via the optic nerve, enabling the brain to interpret a visual image.

Liu’s career has been characterized by interdisciplinary research from the conception of medical devices, through design, engineering, clinical trials, and FDA approval. He is an inventor of a wave pipelining technique that has been used to accelerate circuit performance in semiconductors and microprocessors, and is currently developing implantable technologies for the recovery of motor functions after spinal cord injury.

Liu received his PhD in Computer Engineering from the University of Michigan. He is founder of the International Conference on Neuroprosthetic Devices, and the 2010 recipient of Popular Mechanics Magazine’s Breakthrough Award.

NANTHIA SUTHANA, Ph.D, ASSISTANT PROFESSOR-IN-RESIDENCE, DEPARTMENT OF NEUROSURGERY

Dr. Suthana’s primary research focus is on the neural basis of human learning and memory. Specifically, she is interested in how the brain forms and retrieves memories for facts and everyday events, and how this process may be facilitated through invasive and non-invasive surgical methodologies.

Suthana’s research program combines high-resolution MRI and DTI with DBS, single neuron, and LFP recordings from the human medial temporal lobe (MTL) in epilepsy patients implanted with electrodes for clinical evaluation.

Suthana’s group is also part of a large multi-institutional effort to build a novel wireless implantable neuroprosthetic device that can restore memory in afflicted patient populations. Driven by the goal of understanding the neural mechanisms underlying different forms of memory, Suthana’s group uses high-resolution fMRI combined with novel real-world behavioral techniques including virtual reality to determine MTL subregional involvement in learning and memory.

Suthana completed her Ph.D in Neuroscience at UCLA in the laboratory of Dr. Susan Bookheimer in collaboration with Dr. Barbara Knowlton, where she studied human medial temporal involvement during episodic memory formation. As a graduate student, she was twice the recipient of the UCLA Brain Research institute Travel Award, Society for Neuroscience, and received the UCLA Jeffrey L. Hanson Award for Distinguished Service.
BRI FACULTY KEY TO ADVANCING BRAIN INITIATIVE GOALS

Daniel Geschwind, MD, PhD, and X. William Yang, PhD, have each received a three-year award as part of the National Institute of Health’s Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which is aimed at revolutionizing understanding of the human brain.

Dr. Geschwind, Professor of Psychiatry, Neurology, and Genetics, and Dr. Yang, Professor of Psychiatry, received $2 million and $1.9 million, respectively, from the NIH’s first surge of investments into the BRAIN Initiative.

Both awards serve the initiative’s overarching objective: accelerate the development and application of innovative technologies in order to produce a revolutionary new dynamic picture of the brain—a picture that, for the first time, will capture how individual cells and complex neural circuits interact in time and space.

**The Geschwind Project**

Even after a century of brain research, the complexities of the cerebral cortex remains one of its major mysteries. Geschwind’s project will use genomic technologies to “drill down, and measure all of the genes expressed in a single human brain cell.” In this way, he says, “we can approach defining and identifying the major cell types in the developing human brain. This is an important step, as many developmental disorders such as autism and schizophrenia arise during the process of brain development.”

The investigation will measure up to 10,000 individual cells to obtain a representative sample of the cell types in the brain. Mathematical tools will then categorize these cells based on gene expression patterns. Following this, in collaboration with Dr. Katsushi Arisaka, UCLA Professor of Physics and Astronomy, new microscopy techniques will be developed that will allow high-resolution image capture of individual cells and their connections.

After using the revolutionary CLARITY technique to make the brain transparent, investigators will generate a three-dimensional map of each cell type in the circuits of the living brain. All cells will be visible.

“Understanding how brain cells develop will serve as a foundation for understanding how disease-causing mutations lead to brain disorders, as well as human brain evolution,” Geschwind said.

**The Yang Project**

Yang’s project will enhance understanding of the brain by developing new visualization methods. In collaboration with BRI members Dr. Larry Zipursky, Professor of Biological Chemistry, and Dr. Peyman Golshani, Assistant Professor of Neurology, Yang predicts the project will facilitate new understanding of the relationship between fine structures of specific neurons and global function of the brain.

The team will use relatively simple genetic methods to create a clear window into the elaborate morphology, activity, and synaptic connections of a wide range of neurons in the living brain. Yang plans to augment these methods with new brain mapping computer programs which will accelerate reconstruction of neuronal structures and allow them to be mapped onto a standard-reference brain atlas.

“These new tools may enable scientists to model brain disorders, discover new disease mechanisms, and test new therapies,” Yang said.
ERIC VILAIN AWARDED $7.2 MILLION TO UNLOCK GENETIC MYSTERIES OF UNDIAGNOSABLE DISEASES

Eric Vilain, PhD, Professor of Pediatrics, Urology, and Human Genetics, is one of the co-principal investigators leading UCLA’s mission to tackle the rarest and most difficult-to-solve medical cases involving patients with prolonged undiagnosed conditions.

The mission is part of the Undiagnosed Diseases Network (UDN), a $120 million National Institutes of Health initiative funding six clinical sites nationwide, and is aimed at supporting comprehensive “bedside-to-bench” clinical evaluation and scientific investigation of cases that involve mystery diseases.

The UDN builds on an NIH program that has thus far evaluated hundreds of patients, often using genomic tools for diagnoses of rare conditions. “Newly developed methods for genome sequencing now provide us [with] amazingly powerful approaches for deciphering the causes of undiagnosed diseases,” said Eric D. Greene, MD, PhD, director of the National Human Genome Research Institute.

UCLA’s site will bring patients to the Westwood campus where they will undergo weeklong assessments that include clinical evaluations, specialist consultations, and genome sequencing in order to identify genetic mutations. Network investigators will share resulting genomic and clinical data with UDN research colleagues nationwide to enhance the understanding of rare and unknown diseases.

“A vast number of children and adults suffer from severe, often fatal, undiagnosed disorders,” Vilain said. “This program will enable us to discover new genes causing ultra-rare medical conditions and identify environmental factors that lead to disease or interact with genes to cause disease.”

Co-principal investigators of the study are Drs. Katherine Dipple, Stanley Nelson, and Christina Palmer from the Department of Human Genetics.

Below: Exome sequencing reveals a DNA base insertion, indicated by a gaping hole (center), which is the likely explanation for a rare genetic disease.

Hane Lee/UCLA
ELISSA HALLEM RECEIVES NIH INNOVATOR AWARD FOR STEM CELL, NEUROSCIENCE RESEARCH

Dr. Elissa Hallem, Assistant Professor of Microbiology, Immunology, and Molecular Genetics, received the $2.3 million award for her investigations into interactions between animal parasites and their hosts. Understanding the processes at work in this context can advance understanding of human parasitic diseases.

Hallem’s innovations include investigations into the olfactory behavior of parasitic worms, a relatively unusual animal model, but one which poses a major threat to human health and are endemic in many parts of the developing world.

The award is designed to stimulate highly innovative research and support promising new ideas from unusually creative new investigators.

“To my knowledge, no one else is studying the sensory neurobiology of parasitic worms, and it’s invaluable to have the resources necessary to pursue riskier, less developed ideas in a relatively new area of study,” Hallem said.

A C. elegans larva expressing green fluorescent protein in a subset of sensory neurons. 
Elissa Hallem/UCLA

ACKNOWLEDGMENTS cont’d

PETER NARINS ELECTED INTERNATIONAL SOCIETY FOR NEUROETHOLOGY PRESIDENT

Dr. Peter Narins, Distinguished Professor of Integrative Biology & Physiology, Ecology & Evolutionary Biology, has been elected president of the International Society for Neuroethology (ISN), an academic organization composed of more than 500 scientists who are uncovering the neural mechanisms underlying natural behaviors.

Narins’ research primarily focuses on the question of how animals extract relevant sounds from the often highly noisy environments in which they live. His investigations in the lab and in situ use a range of qualitative, biophysical, and neurophysiological analysis tools, as well as direct behavioral observations in environments ranging from African deserts to temperate South American forests.

A recipient of many other accolades, including the Guggenheim and Fulbright Awards, Narins will take the ISN mantle in 2016.

Narins observes a Phyllomedusa treefrog, during a field trip to the rainforests of Aratai, French Guiana. 
Peter Narins/UCLA
Since 1958 when Advancing Science in America (ARCS) was founded in Los Angeles, the organization has been an invaluable partner in one of the key components of the BRI’s mission: to provide the resources and support necessary to maximize the academic abilities and research accomplishments of neuroscience graduate students. At the ARCS Los Angeles Founder Chapter 2014-15 Recognition Luncheon at the California Club Los Angeles, the BRI’s ARCS scholars were recognized in a meeting that included poster presentations, lectures, and interactions with the ARCS foundation members.

This year, Janelle Liu, graduate student in the UCLA Neuroscience Interdepartmental Program was awarded the inaugural Roche and ARCS Foundation Scholar Award in the Life Sciences, a unique collaboration between the ARCS foundation and the Roche Foundation providing financial support for Liu over the next three years. Liu received her BA in neuroscience and behavior from Columbia University. As an undergraduate, she investigated the role of serotonin in the neural circuit underlying vocal communication in the African clawed frog. Currently in her second year at UCLA, Liu works in the lab of BRI member Mirella Dapretto, PhD, where she is learning how to use neuroimaging tools to investigate the neural basis of language. Ultimately, Liu hopes to use a multimodal approach relating functional, structural, and genetic data to understand how language is learned.

Other 2014-15 ARCS scholars are: Ryan Guglietta, who studies regional differences in plasticity within the hippocampus in the lab of Tom O’Dell, PhD; Theresa Harrison, who studies cognitive aging and Alzheimer’s disease in the lab of Susan Bookheimer, PhD; Sarah Hersman, who studies neural substrates of learning and memory with Michael Faneslow, PhD; Donald Julien (Wallace and Rosemary Booth Scholar), who is working in the lab Alvaro Sagasti, PhD, where he studies the touch-sensing system and its relationship to neural development, degeneration and regeneration; Katherine Myers, who uses electrophysiological and imaging techniques to study molecular mechanisms which modulate synaptic transmission in the lab of Felix Schweizer, PhD; Anna Parievsky, who works in the lab of Michael Levine, PhD, where she aims to help understand the mechanisms and effects of neurodegeneration occurring in Huntington’s disease; Alexander Reeves, whose works in the lab of Bajit Khakh, PhD, focuses on the contribution of different cell types in the cerebellum to the process of motor learning where he evaluates efficacy of calcium dyes in imaging astrocyte fine processes; Matthew Schreiner, who researches the dysregulation of functional connectivity in individuals with neurodevelopmental disorders in the lab of Carrie Beardan, PhD; and Andrew Thompson, who works in the labs of David Jentsch, PhD, and Alicia Izquierdo, PhD, to understand the evolutionary origins of key mechanisms behind decision-making in the brain, and to investigate how these mechanisms are altered by exposure to drugs of abuse.

BRI Director Chris Evans, PhD predicts, “These students will contribute to future knowledge and cures for brain disorders and injury by training with UCLA faculty at the frontier of neuroscience research. The generosity of ARCS members inspires ARCS scholars as they develop the skills and knowledge they will need as future leaders in neuroscience research.”

Former ARCS scholar Kate Wassum, PhD, is now a BRI member and UCLA Assistant Professor in the Department of Psychology, where she is studying the neurochemistry of decision-making. At the time Wassum received the ARCS award, she was uncertain of what the focus of her research would be. But since the ARCS scholarship is not tied to a particular research question she was free to fully explore the options and research collaborations available to her. Eventually, Wassum focused on the mechanisms governing reward and motivation in the brain.

Jeffrey Bronstein, MD, PhD, is another former ARCS scholar. Now UCLA Professor of Molecular Toxicology, Neurology, Director of the UCLA Movement Clinic, and a BRI member, Bronstein’s work has been groundbreaking in the clinical and basic science of Parkinson’s disease. “I can think of no other organization that has contributed so unselfishly to foster and influence science and technology across the United States,” he says.
December 2nd, 2014, was an unusually cold, rainy Los Angeles day. Despite this over 300 undergraduate and graduate students, postdocs and faculty attended this year’s Neuroscience Poster Day, taking opportunity to present research to colleagues, faculty and visitors from across and outside campus. The Poster Session featured over 180 posters representing the increasingly diverse spectrum of neuroscience research occurring on campus (above).

Below: Graduate students Alden Huang (left) and Mochtar Pribadi, from the lab of Giovanni Coppola, present their poster, “Definition and Characterization of the Mu-Opioid Receptor in Hagfish.”
THE POSTER SESSION DISTINGUISHED LECTURE was presented by Dr. Rachel Wong, Professor in the Department of Biological Structure at the University of Washington, Seattle, Washington.

Dr. Wong presented “Circuit Assembly, Disassembly and Reassembly in the Vertebrate Retina.” She recounted a career-long interest in the retina with particular focus on her explorations of the highly stereotypic synaptic connectivity patterns of vertebrate retinal neurons, in zebrafish and mouse models.

Using a combination of transgenic methods, imaging techniques and electrophysiology, Dr. Wong investigates the cellular interactions and strategies that underlie normal circuit assembly as well as circuit reassembly during retinal regeneration.

This year’s Poster Session Distinguished Lecturer, Rachel Wong (left) and Alicia Izquierdo
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