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Newsletter for Members and Alumni of
the Department of Molecular & Cell Biology
at the University of California, Berkeley

Brain Puzzle:

*MCB Neurobiologists are
Figuring It Out*



Only recently have neuroscientists realized that our brains can grow and change in response to use and environment. This theory of brain plasticity fundamentally changes the way we understand the brain. Not long ago, we were all taught that brain cells don't replicate, but we now know that brain cells are constantly being created. It's not the creation but it's the culling of these cells that's important for learning and function. There is still so much we don't understand about brain function and development. As these puzzles of the mind and brain are solved, the science of neurobiology becomes more and more intriguing.

The following articles highlight MCB neurobiology research that is revolutionizing our view of neuron function and communication. Professor Richard Kramer is overturning old paradigms about eye function and paving the way to new vision technologies. Professor Ehud Isacoff is poking zebrafish to probe the secrets of a very unusual neuron. Professor Yang Dan subjects mice to a short movie on repeat to understand attentive brain states.

Each of these laboratories use a new technique called optogenetics, which is described on page 2.

MCB Welcomes David Savage

MCB welcomes David Savage to the faculty, as Assistant Professor of Biochemistry and Molecular Biology. His research combines biochemistry, biophysics, and systems biology to understand how metabolic reactions function in the context of the cellular system. He is interested in building synthetic biology tools to discover new ways of curing disease and new forms of environmentally friendly chemistry.



OPTOGENETICS

Illuminating cellular function

If the new technique called optogenetics hasn't impacted the research in your field of study, yet, it's likely to do so soon. Named the Method of the Year in 2010 by *Nature Methods*, optogenetics is allowing scientists to control the behavior of cells by shining light on them.

"It's been an explosive revolution," says MCB Professor Ehud Isacoff. "The impact has been huge."

Isacoff and fellow MCB Professor Richard Kramer have developed optogenetics techniques for neurobiology experiments.

"Optogenetics is not the best term because it sounds like light affecting genes," says Isacoff. "It's actually genes encoding proteins that can be controlled by light."

Light-activated molecules that act as switches for a cellular function provide researchers with precise spatial and temporal control of the process they are studying. The experiments can be designed for use noninvasively *in vivo*.

Kramer and Isacoff, working with former Berkeley Chemist Dirk Trauner, now in Munich, are using an approach in which a small synthetic version of a biologically active molecule, such as a neurotransmitter or a modulator or blocker, can be engineered to attach to a protein of interest in a site-specific manner and to photoisomerize in such a way that one wavelength of light causes it to bind and another to unbind, thereby rapidly and reversibly activating, modulating, or blocking the function of the protein. This makes it possible to obtain optical control over the function of a specific protein.

An alternative approach for remotely controlling cellular functions with light is to use naturally occurring light-activated ion channels that pump proteins in microbes. These use the vitamin A derivative retinal, which is biologically available in vertebrates, as their photoswitch.

Optogenetics techniques are especially suited for studying single neurons, their synaptic connections, and the complex circuits that assemblies of these neurons form, which have very rapid action potential change and neurotransmitter release. Light-sensitive proteins can be targeted to specific ion channels or ion pumps that excite or inhibit the cell. Researchers can focus lasers on specific parts of neurons, like an axon or a dendrite, in very short pulses to mimic the brief local signals that occur physiologically. Additionally, because these switches can be designed to be triggered by specific wavelengths of light, experimental systems can have multiple switches that respond to different light signals.

In a sense, these techniques allows researchers to "drive" a nervous system, to see what consequences come from changing the normal function of individual neurons or to "play back" to the nervous system different patterns of natural activity in order to determine their meanings. Following a neuronal process at this level of detail would be practically impossible using other techniques.

"You can point light very selectively," says Isacoff. "You can point it at one cell at a time or groups of cells, or even a little area within a cell. And then you can give very brief pulses of light that will turn the protein on and off. You can therefore recapitulate how the nervous system normally signals, except that now you are the driver."

In the short time it has been around, optogenetics has become an unparalleled tool for many types of research. As the capabilities of optogenetics grow, the potential applications are likely to expand as well. The use of optogenetics techniques is a commonality among the research highlighted in the following articles.

Eye Sensations: *Seeing Beyond Rods and Cones*

MCB Professor Richard Kramer is interested in the biochemistry of neural synapses and information processing, focusing on the neurons in the retina of the eye. Kramer's recent research has changed our understanding of how we see, as well as provided the first steps to some important, potential applications.

"Your eye is not a camera that faithfully transmits light and dark downstream and that's what you see," says Kramer. "Instead there are comparisons. That has a big influence on what we see."

The layers of neurons in our retinas do not simply pass information on, but are involved in processing the information before it reaches the brain. Many of the classic optical illusions take advantage of oddities caused by the functions our neurons use to enhance our vision beyond the simple transmission of light and dark.

For example, photoreceptors, including the rod and cone neural cells in the retina, communicate with one another through horizontal cells, the next layer. For fifty years, this communication was thought to be restricted to a negative feedback system caused by a voltage change in the horizontal cell. The voltage of the entire cell changes, affecting the transmitted signal of many photoreceptors at once. The problem with this theory is that, although the negative feedback system explains why we are good at picking out object's edges, it does not allow for our ability to see point light sources.

Recently, Kramer's lab discovered an additional biochemical response in the horizontal cells: a localized calcium gradient that affects a synapse back to the photoreceptor cells. This system can accentuate the signal of a single photoreceptor through a positive feedback mechanism. Their model explains both our ability to find an object's edges and to see point light sources. This discovery changes the long-accepted paradigm in the field.

Another aspect of Kramer's lab's research involves the layers of cells in the retina. Using the optogenetic approaches he developed with MCB Professor Ehud Isacoff, the lab is engineering molecules that allow the neurons positioned in the layers behind the photoreceptors, such as the horizontal cells that are normally blind to light, to be light-responsive. This could lead to devices that allow blind people to sense visual signals.

"The reasoning is that if you could somehow make the second or the third order cells sensitive to light, the neural code would not be completely correct, but at least there would be light sensitivity, and maybe you can make devices that could use wavelengths that would paint images on the retina," says Kramer.

He envisions that such a device might be a pair of goggles, not dissimilar to those the blind character Geordi La Forge used in the *Star Trek: The Next Generation* TV series. This might be analogous to the cochlear implants currently used to give deaf people some ability to hear. In that case, the plasticity of the brain allows for nerve cells to rewire over time to make sense of the artificial signals.

Kramer stresses that this work is at an early stage, but early experiments show promise. Injection of the light-responsive molecule into the eyes of blind mice is able to restore the pupillary dilation reflex and the animal's light-responsive behavior.

Another potential medical application of optogenetic techniques is very localized and timed anesthesia. It was by chance, says Kramer, that one of the photoisomerizable chemical derivatives his lab created has structural similarity to two local anesthetics connected together. They found that the molecule, called QAQ, isomerizes in such a way that it allows for the light-controlled blockage of signaling in pain-sensing neurons.

QAQ can't cross the cell membrane, so the Kramer lab has found a way to get it into the cytoplasm of cells using pain-sensing membrane channels such as TRPV1, which are activated by heat or the chili-pepper molecule capsaicin.

"We can get QAQ into neurons if we open up their TRP channels," says Kramer. "We can optically regulate the sensation of pain at its source. Essentially this molecule is a light-sensitive analgesic."

Along with its potential for medical applications, QAQ is a helpful tool for basic research. The Kramer lab is using it to investigate the self-perpetuation process of pain—in other words, why your finger continues to hurt after the hammer that hit it has long been taken away.

[Thank you to Tzu-Ming Wang, Kramer Lab postdoc, for editing this article.]



MCB Professor
Richard Kramer



Just Keep Swimming

Tracking An Unusual Neuron



MCB Professor
Ehud Isacoff

Locomotion for most animals involves coordination of repetitive, alternating motions on the two sides of the animal, whether they are slithering, swimming, or walking. Imagine walking if you had to think about each step, alternating left, right, left, right, left, right.

“This is not the marines,” says MCB Professor Ehud Isacoff. “When you run or walk you need to be able to not have to think about every step you take.”

Isacoff’s lab studies the how the nervous system is able to time and send signals that drive orderly locomotion. Because muscles on each side of the body need to alternate, some sort of clock is needed for coordination. This timing mechanism is named the central pattern generator (CPG), but how it works is unknown. The CPG could be driven by a neuron or group of neurons in the spinal chord or by a command from the brain. To find out how the CPG works, the lab looked for CPG driver neurons in the spinal cord of the zebrafish.

Since the zebrafish larva is transparent, optogenetic techniques can easily be employed to search for candidate neurons. In collaboration with Dirk Trauner, a synthetic chemist previously at UC Berkeley and now at LMU Munich, and Herwig Baier, at UCSF, Isacoff’s lab designed a specific photoswitch protein. From a library of animals expressing the photoswitch randomly in the genome, the researchers focused on 30 fish that showed photoswitch expression in distinct sets of spinal cord neurons.

“And then we can ask a very simple question that you otherwise couldn’t ask, which is: ‘Can I shine light on the spinal cord of this animal and turn on swim behavior?’” says Isacoff.

A negative result might only mean that the cell of interest wasn’t affected in the random search. But Isacoff’s lab did find a cell that triggered swimming behavior when stimulated. That marked it as a great candidate for involvement with CPG function.

The story grew even more interesting when they discovered that the cell they identified is quite unusual. It has all of the hallmarks of a sensory neuron, but it is located in the middle of the spinal cord. Normally sensory neurons sample the external world (they smell chemicals in the nose, they feel vibrations in the ear, or they capture photons in the eye) and are therefore exposed to the outer world. Just what this neuron might be sensing in the middle of the animal is unknown.

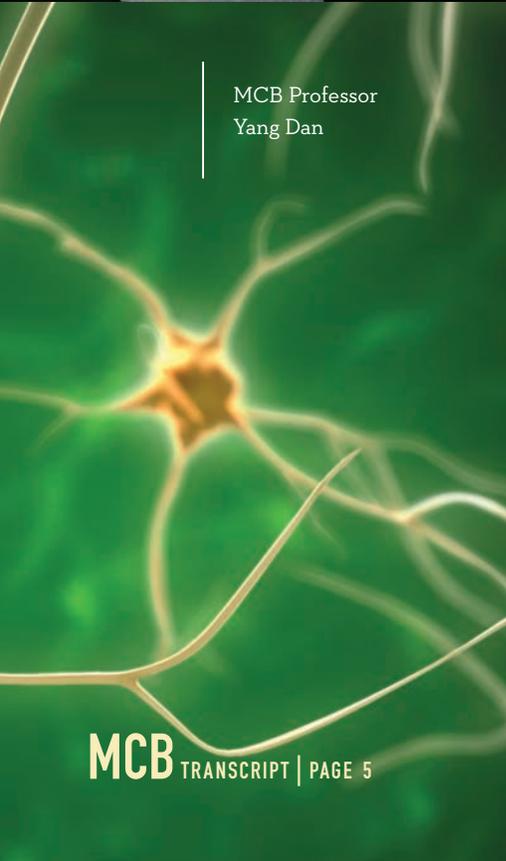
Isacoff wonders if the neuron might be sensing a change in force, the bending of the spinal cord. It is this bend that may trigger a swimming pattern. Such a control mechanism would provide a tidy explanation for the startle behavior of the zebrafish. When you tap the fish on the side, it whips its tail to turn away from the stimulus and then dashes in a straight swim to distance itself from the disturbance. If the instruction for this behavior came completely from the brain, two commands would be necessary: first “turn,” then “swim straight.” The neuron in the spinal cord may allow the brain to send just one command: “bend,” and the bend would trigger the swim movement.

Like much of the nervous system, this neuron of interest was described morphologically 75 years ago, but its function had remained unknown. Isacoff points out that it was only through using optogenetic techniques that the neuron was linked to an activity of interest, the CPG.

“You can come to the nervous system blind as a bat, without preconceived notions and fish out blindly things that are involved in certain behavioral circuits,” Isacoff says. “I randomly plop this thing into different neurons, find neurons that when activated drive a behavior or modify a behavior, and try to identify which neuron it was. Now I know a circuit element that maybe I never would have come to before.”



MCB Professor
Yang Dan



Paying Attention: *Sorting Out Brain States*

When sleeping, we have two major states, REM (dreaming) sleep and non-REM sleep. When we are awake the array of potential brain states grows more complicated. We can be alert and attentive to our environment, truly observing and reacting to what is around us, or exist in a world in our minds, lost in thought, daydreaming, or zoning out. These behaviors are linked to different brain states. MCB Professor Yang Dan researches the neural mechanisms that determine brain states.

To investigate how brain states are controlled, Dan's lab focuses on cholinergic neurons, which release acetylcholine, in the basal forebrain. Acetylcholine can act as a neuromodulator that when released causes a cellular cascade of reactions that change the global brain state. These neurons are active when we are awake and attentive and shut down when we are in non-dreaming sleep. They are some of the first neurons to fail in the early stages of Alzheimer's disease, says Dan, and most of the drugs approved for Alzheimer's target the acetylcholine system.

"You can think of these neurons as being important for being awake and attentive and functional," says Dan. "We wanted to take a closer look."

The cholinergic neurons in a mouse's basal forebrain release acetylcholine when electrically stimulated. The effects of the acetylcholine release can be measured in distant sensory neurons, in this case those in the visual cortex. Dan's lab used optogenetic approaches to measure the response of single sensory neurons to a 5 second movie both in the stimulated and unstimulated brain states. The movies were repeated multiple times to measure the reliability of the responses.

The 30th time you see the same short video, you might not pay as much attention as the first time, but your neurons don't get bored—they react to the images the same way each time. A sensory neuron's job is to report its experiences, not to judge how novel the experiences are.

Dan found that when the cholinergic neurons were stimulated to release acetylcholine, the sensory neuron gave a much more reliable account of the sensory input than in the unstimulated, control state.

"If the neurons are telling your brain about what's out there reliably, when you play the same movie over and over again you expect them to react the same way," says Dan. "To the extent that they don't respond the same way means that they are noisy. Even though each neuron is noisy, we have so many of them we can average out the noise. But still if you can make each neuron more reliable, that's a good thing for central processing."

Another effect of acetylcholine release is that the signals of individual neurons become less correlated with each other. Since the signals from two perfectly correlated neurons are redundant, that each neuron is acting independently ensures that noise can be canceled out when the signals are averaged. In previous work, Dan has shown that de-correlation of neuronal signal improves visual coding.

"After stimulation each neuron becomes more reliable, and, after you average more neurons, you can average out even more noise," says Dan. "Before stimulation, they are not doing a good job, and they are all saying the same thing. They are two separate effects but they are both affecting visual processing in the same direction."

Does this mean that when their brains are flooded with acetylcholine, the animals are more attentive? Not necessarily, says Dan. These experiments support that theory, but they still need more data to draw any conclusions.

The experiments described were performed on an anesthetized animal, and currently they are working with awake animals. The mice are trained to lick when they see certain stimuli. The animals' mistake rate at this task will give a better indication of the attentiveness of their mental state.

FACULTY NEWS



GREG BARTON received the Burroughs Wellcome Fund Investigators Award in the Pathogenesis of Infectious Disease.

JAMES BERGER is a recipient of the NAS Award in Molecular Biology. Berger is honored for elucidating the structures of topoisomerases and helicases and providing insights into the biochemical mechanisms that mediate the replication and transcription of DNA.

◀ **ABBY DERNBURG** has been awarded the 2011 Edward Novitski prize by the Genetics Society of America (GSA).



MARLA B. FELLER will be on sabbatical during to for Fall 2011. She will be working with Prof. David diGregorio at Institut Pasteur to apply novel imaging methods to her studies in retinal development. She will also be giving a Special Lecture, entitled “The development of functional circuits in the retina” at the annual Society for Neuroscience Meeting to be held in November in Washington, DC.

RICHARD HARLAND has agreed to serve as interim MCB co-Chair (2011-2012).

◀ **DOUGLAS KOSHLAND** has agreed to serve as Division Head of GGD.



◀ **G. STEVEN MARTIN**, MCB Professor and co-Chair, has been appointed interim dean of biological sciences in the College of Letters and Science, effective July 1, 2011. He takes over for Mark Schlissel, who was recently named provost of Brown University.

◀ **MICHAEL RAPE** received a CIRM Basic Biology Award to support stem cell work.



DAVID SAVAGE has been awarded the 2011 Alfred P. Sloan Research Fellowship. The two-year fellowship seeks to stimulate fundamental research by early-career scientists and scholars of outstanding promise. He also received a Department of Energy Early Career Research Program grant.

RANDY SCHEKMAN received the inaugural Arthur Kornberg-Paul Berg lifetime achievement award of the Stanford Medical School Alumni Association.



◀ **JEREMY THORNER** was awarded an American Asthma Foundation (formerly the Sandler Foundation) Senior Investigator Award. He will receive \$250,000 per year for three years for transitional research applying observations in yeast to understand the molecular basis of asthma in collaboration with Greg Barton.



◀ **ROBERT TJIAN**, MCB Professor and HHMI President, received the 2010 Glenn T. Seaborg Medal from the University of California, Los Angeles for outstanding accomplishments in chemistry or biochemistry. He was also awarded the 2010 Grand Prix Charles Léopold Mayer from the French Academy of Sciences for outstanding work in the biological sciences.



◀ **RUSSELL VANCE** has been selected as one of two recipients of the 2011 Merck Irving S. Sigal Memorial Award by the American Society for Microbiology. The award recognizes excellence in basic research in medical microbiology and infectious diseases.



AHMET YILDIZ received the National Science Foundation Career Award and the Helmann Faculty Award.

Graduate Awards

OUTSTANDING GRADUATE STUDENT INSTRUCTORS

The following GSIs for MCB courses were among the graduate students honored for outstanding teaching by the Graduate Division in a May 5 event at the International House.

- **Dahlia An**
- **Robert Calderon** [Krishna Niyogi Lab]
- **Kwan Chow** [Mark Schlissel Lab]
- **Allison Craney** [Micha Rape Lab]
- **Alejandra Figueroa-Clarevega** [David Bilder Lab]
- **Wendy Ingram** [Mike Eisen/Ellen Robey Labs]
- **Teresa Lee** [Barbara Meyer Lab]
- **Kristin Lind** [Nilabh Shastri Lab]
- **Kevin Mann** [Kristin Scott Lab]
- **Allan-Hermann Pool** [Kristin Scott Lab]
- **Joel Swenson** [Karpen Lab]
- **Jordan Turetsky**
- **Jakob von Moltke** [Russell Vance Lab]
- **Livia Wilz** [Qing Zhong Lab]
- **Lea Witkowsky** [Robert Tjian Lab]



Front Row: Kristin Lind, Teresa Lee, Alejandra Figueroa-Clarevega, Livia Wilz, Lea Witkowsky
 Back Row: Kwan Chow, Wendy Ingram, Allison Craney, Allan-Hermann Pool, Kevin Mann
 Not Pictured: Dahlia An, Robert Calderon, Joel Swenson, Jordan Turetsky, Jakob von Moltke

Photo credit: Christina Bianchi

Undergraduate Awards

DEPARTMENTAL AWARDS

Departmental Citation

- **Harvind (Harvey) Chahal**
[Brett Helms Lab, LBNL]

Outstanding Scholar

- **Albert Luong** [Craig T. Miller Lab]
- **Ankur Narain** [Jay Hollick Lab, Plant and Molecular Biology]

DIVISION OF BIOCHEMISTRY & MOLECULAR BIOLOGY

Grace Fimognari Memorial Prize

- **Patricia Deng** [John Kuriyan Lab]

Kazuo Gerald Yanaba & Ting Jung Memorial Prize

- **Brian Alford**
[Cynthia McMurray Lab, LBNL]

Jesse Rabinowitz Memorial Prize (for outstanding junior in BMB)

- **Timothy Roth**

DIVISION OF GENETICS & DEVELOPMENT

Edward Blount Award

- **Sophia Yenchuan Kuo Lewis**
[Xiao Lin Nan lab]

Spencer W. Brown Award

- **Jennifer Cherone** [Fyodor Urnov Lab, Sangamo BioScience]
- **Steven K. Gore** [Doug Koshland Lab]
- **Eric Lu** [Xiaohua Gong Lab, School of Optometry]
- **Albert Luong** [Craig T. Miller Lab]
- **Joseph Magliocco** [Mike Levine Lab]
- **Carissa Ikka Pardamean** [Jasper Rine Lab]
- **Desirée Natasha Stanley** [Frank Harmon Lab, Plant and Microbial Biology/Plant Gene Expression Center]

DIVISION OF IMMUNOLOGY

Outstanding Immunologist

- **Lisa Brooke Noble**
[Nancy McNamara Lab, Proctor Foundation, UCSF]

Distinction in Academic Achievement

- **Ryan Christopher Kunitake**
[Gary Karpen Lab]

Excellence in Research

- **Kenneth Leung**
[Astar Winoto Lab]

DIVISION OF CELL & DEVELOPMENT BIOLOGY

Paola S. Timiras Memorial Prize

- **Albert Sae Yu**
[Iswar Hariharan Lab]

I. L. Chaikoff Memorial Awards

- **Neha Agarwal** [William Jagust Lab, LBNL/UCSF]
- **Amit Arunkumar** [Susana Chung Lab, Vision Science]
- **Lauren Hum** [Terry Machen Lab]
- **Sunil Kumar Joshi** [Jean M. J. Frechet Lab, Chemistry]
- **Susan Young Kim** [Dennis Levi Lab, School of Optometry]
- **Lee Ying**
[Gordon Watson, CHORI]
- **Albert Sae Yu**
[Iswar Hariharan Lab]

DIVISION OF NEUROSCIENCE

Jeffery A. Winer Memorial Prize

- **Kaili Zhou** [Maria Feller Lab]

I.L. Chaikoff Memorial Award

- **Aneesh Nitin Donde**
[William Jagust Lab, Hellen Wills Neuroscience Institute]
- **Gabriela Fragiadakis** [Carolyn Bertozzi Lab, Chemistry]
- **Zachary Grunwald**
[Robert Tjian Lab]
- **Samata Katta**
[Diana Bautista Lab]
- **Kaili Zhou** [Maria Feller Lab]



ADDRESS SERVICE REQUESTED

Class Notes

Ivan Cheng [BA 1993] earned an MD from Harvard Medical School and completed residency training in orthopaedic surgery at UC Davis. He went on to a Spine Surgery Fellowship at Washington University in St. Louis and is currently an Assistant Professor of Orthopaedic Surgery at Stanford University and the Residency Program Director. [ivan.cheng@stanford.edu]

Michael Galvez [BA 2004] will complete an M.D. degree at Stanford University School of Medicine in June 2011 and begin his surgical residency training in Plastic and Reconstructive Surgery at Stanford Hospital and Clinics. [mgalvez@stanford.edu]

Jennifer Lee [BA 1999] and **Hans Schoellhammer** [BA 1998] were married in 2010. Jennifer is a lawyer and Hans will be completing his residency in General Surgery. They live in Los Angeles.

Schuman Tam [BA 1983] received an MD in 1987 from the Medical College of Wisconsin. He completed a residency in internal medicine at St. Mary's Medical Center in San Francisco. After a fellowship in allergy and immunology at UCSF, he currently has a private practice in allergy and clinical immunology in San Francisco and Marin Counties. He is a Clinical Professor of Medicine at UC San Francisco.

Isaac Yang [BA 2000] is Assistant Professor in the Department of Neurosurgery at the University of California Los Angeles (UCLA). He is a neurosurgeon specializing in the surgical treatment and clinical outcomes of adult brain tumors at UCLA with an emphasis on acoustic neuromas, skull base tumors, and brain cancer vaccines. Happily married to **Nancy Huh**, M.D. [BA 2003]. [iyang@mednet.ucla.edu]

Class Notes wants to hear from you

Do you have a bachelor's, master's or Ph.D. in Molecular and Cell Biology from Berkeley? Let your classmates know what you are up to by sending in a Class Note for publication in the next issue.

To send your Class Note, go to mcb.berkeley.edu/alumni/survey.html or Send e-mail to tscript@berkeley.edu

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