

MCB Transcript

FALL 2008 • VOL. 11, NO. 2

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

FROM MICRO RNAs TO STAR-NOSED MOLES:

THE RESEARCH OF THE NEW MCB FACULTY

A TOUCHING TALE

If you have never experience the odd sensations of Szechuan peppercorns, go try them now. Crunch a few of the reddish pods in your teeth and let them rest in your mouth. You'll feel your tongue go numb, and, a few seconds later, you'll taste something peppery and lemony. Soon you'll sense both cool and hot temperatures and feel an unusual tingling, buzzing sensation. What gives Szechuan peppercorns such strange effects? New MCB Assistant Professor Diana Bautista is figuring it out.

Bautista completed her postdoc in David Julius's lab at UCSF, where the first temperature-sensitive pain receptor, *trpv1*, was identified as the target for capsaicin, the burning, hot molecule from chili peppers. This receptor is one of many pain and touch receptors that allow somatosensory neurons detect environmental stimuli such as temperature, pressure, and chemical irritation. Capsaicin from chili peppers is able to bind sites on *trpv1* that would normally be triggered by an endogenous molecule. This ability to hijack the system protects the plants: most mammals will find the heat-inducing sensation of capsaicin unpleasant and quickly learn to avoid eating peppers.



Assistant Professor Diana Bautista

Despite their central importance to our quality of life, we don't know much about the molecular mechanisms of touch and pain. How are pain thresholds set? At what point does a light touch begin to hurt? And why do these thresholds sometimes not reset? How do we learn special touch sensitivity, such as reading Braille? The answers could lead to an understanding of—and treatments for—such conditions as chronic pain or pain insensitivity.

In Julius's lab, Bautista studied another pain receptor, *trpa1*, which is sensitive to wasabi. She noticed that most of the receptors being studied were pain receptors, even though about half of the somatosensory neurons are dedicated to sensing light touch.

In her own lab, Bautista is identifying touch receptors through studying spices and herbal remedies. "I really liked David Julius's



Star-nosed mole (*Condylura cristata*)

CONTINUED ON PAGE 2 . . .

approach," says Bautista. "In my own lab, I thought I could apply a lot of the same approaches to understanding touch transduction."

It's been working. From Szechuan peppercorns, used traditionally to numb toothaches, she identified several members of the KCNK channel family that may play an important role in the detection of light touch. [Nature Neuroscience 11, 772 - 779 (2008)].

Bautista's lab is currently deciphering the molecular mechanisms of these channels and investigating how hydroxy-alpha-sanshool, the compound from Szechuan peppercorns, can lead to pain relief. She is also continuing to test other plants to find new types of touch receptors.

To look at cellular mechanisms of touch, Bautista is developing systems to mechanically stimulate different types of touch-sensitive neurons in culture. For example, stretching neurons grown on elastic membranes can mimic the stretch of skin. Low amounts of stretch stimulate light touch receptors, but stretch the membrane further and pain fibers will fire. Using this diagnostic, she may find genes and molecules that mediate touch transduction *in vivo*.

Rounding out her approach, Bautista aims to recruit the star-nosed mole as an animal model for touch receptors. These blind moles have 22 fleshy protrusions, collectively termed the "star," around their noses that allow the moles to quickly find food, such as earthworms, by texture. "It looks like a weird starfish," says Bautista. And it does.

"This is the world's most sensitive touch organ," says Bautista, while showing a movie of the moles gobbling up pieces of earthworm at lightning speeds. "The nose is really small, but innervated ten times more than the human hand. Think about our ability to read Braille, and this small organ is much more sensitive."

While the mole's star has similar types of neurons as other mammals have, its percentage of pain and touch receptors is remarkable: the star has 95% touch receptors.

Preliminary work demonstrated that the same basic neural structures in the mole's star and human skin are the same, but the mole has them in much higher densities. Bautista plans to discover basic molecules and mechanisms involved in touch sensitivity by identifying the types of molecules that are enriched in the mole's star versus skin cells of other mammals.

Having arrived in January, Bautista says she is enjoying her Berkeley experience so far. "I love the campus, and I love the department," she says. "The department is so diverse. It's great to be exposed to a lot of different approaches and questions, and I think it helps you come up with creative ways to address the question that you are interested in."

Diversity is a theme for Bautista, who draws on a history of diverse scientific experiences and interests.

"I went to University of Oregon to study environmental science and ecology," says Bautista. "But I took a neuroscience class

and after that I was totally hooked." She researched visual system in *Drosophila*, and changed her focus to signal transduction mechanisms during her graduate studies at Stanford with Rich Lewis. She went back to sensory systems for her postdoctoral work at UCSF.

She is happy to continue living in the Bay Area, where she takes advantage of its cultural and natural offerings. When she's not in lab, you may find her in Chinatown, enjoying a traditional meal with a palate-buzzing dose of Szechuan peppercorns.

TINY RNAs WITH HUGE POTENTIAL

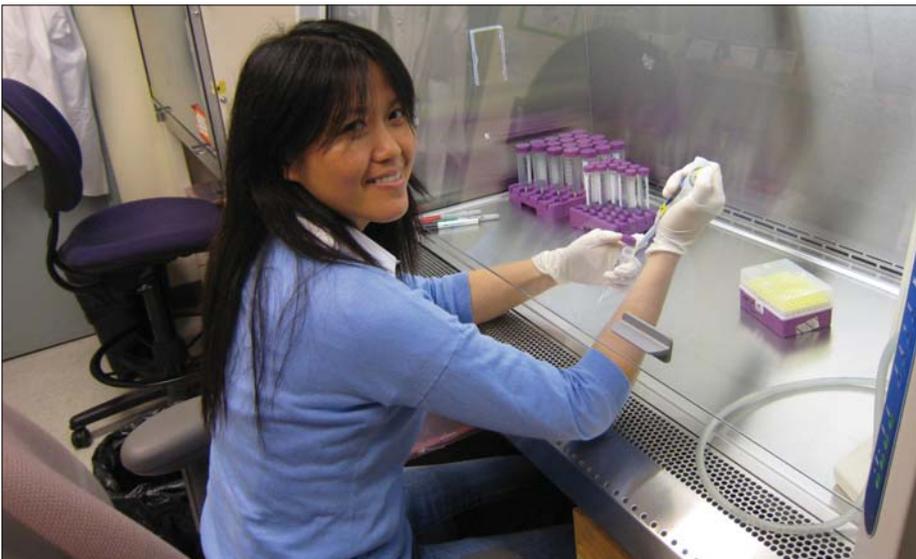
You may think those small RNA molecules couldn't possibly be important, so you let them run off the end of your gel. New MCB Assistant Professor Lin He might advise you not to do that. Her recent findings suggest that you may be missing something interesting.

Lin He works on micro RNAs (miRNAs), which are so named because of their tiny size, usually about 20-24 nucleotides. Still, they pack a punch. In that short length, they fold into a secondary structure and imperfectly match messenger RNAs to effectively regulate gene expression.

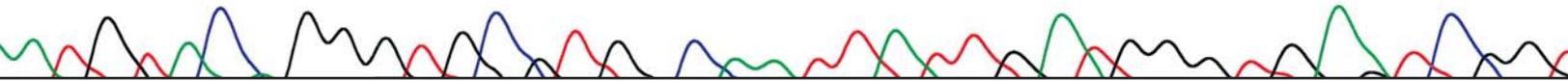
miRNAs were first discovered in 1993 in *C. elegans*, by Victor Ambros and Gary Ruvkun, using classic genetics screens. Because no homologues were found in other animals, they were assumed to be a worm quirk. But, seven years later, when researchers started screening other animals, they found the miRNAs everywhere.

"To everyone's surprise, there's a huge repertoire of these RNAs in almost all model organisms," says He. Almost 500 miRNAs are identified in humans. He and others believe that studying this newly discovered, abundant class of genes will shed light on how and when gene expression is regulated.

miRNAs recognize their targets by imperfect base pairing. This trick allows one miRNA to target multiple genes, resulting in the post-transcriptional regulation of a fleet of genes at the same time. It's thought that these targeted messenger RNAs become sequestered in the processing body in the cytoplasm and then can undergo partial degradation, in a similar pathway to RNAi-induced degradation. The sequestered



Assistant Professor Lin He



mRNAs may also be re-released and translated into proteins.

"We are really at the very beginning of understanding the realm of non-coding RNA," says He. "These small RNAs provide a nice entry point for us to probe the function of non-coding RNAs and how they interact with coding genes to achieve very complicated regulation of gene expression."

Furthermore, miRNAs seem to play a regulatory role in human tumor formation and tumor maintenance. A number of miRNAs are located in regions of the genome that show alteration, such as amplifications, deletions, or translocations, in human cancer cells. Micro RNAs also show changes in expression patterns in tumor versus normal human cells and/or tissues: some miRNAs are depleted while others are enhanced.

He's lab is researching the function of miRNAs involved in human cancer using animal tumor models and cell culture systems. They are focusing on a miRNA that has a very high expression in B cell lymphoma cells versus control cells. Putting this micro RNA into a mouse model confirmed that the miRNA is oncogenic, the first miRNA implicated in tumorigenesis [Nature (2005) **435**:828-33]. It turns out that this is not an isolated case, many more miRNAs have now been found that are important for many types of tumors.

He is also interested in tumor suppressor miRNAs, which can suppress tumor formation and/or maintenance. Her team identified a key miRNA component in the p53 pathway and is currently uncovering how it works at the molecular level.

He's lab will continue to screen for novel miRNAs that either promote or suppress tumor formation and growth in various model systems.

"I would not be surprised if miRNA functions are involved in almost all aspects of developmental and physiological processes," says He. "It's a really big family of genes. I'm sure that that there are a lot more to be discovered."

Viewing the broader picture, He would like to understand how the unique properties of miRNAs affect their function, making them so adept at their regulatory tasks. Beyond basic science, there may be application for miRNAs to diagnostic or therapeutic uses for tumors, since they are natural, small, and relatively easy to deliver.

Lin He grew up in China where she enjoyed math and science from a very early

age. She participated in special programs for school children who excelled in these subjects. She fondly remembers solving puzzles in the weekly math camp. Through these programs she developed a love for experimentation and, especially, chemistry.

Her high school biology teacher is responsible for turning her interest to living systems. As an undergrad in China, she majored in biology, where she studied basic molecular biology.

As a graduate student at Stanford University, she focused on genetics. Her thesis research involved classic mouse genetics experiments, working on coat color genes with Greg Barsh. "I always liked genetics because it sparks a lot of intellectual thinking and it often presents really interesting problems that need a lot of deciphering," she says.

He started working on miRNAs as a side project during her postdoc in Gregory Hannon's RNAi-focused lab at Cold Spring Harbor.

"I did a side project on miRNA." Says He. "I took several miRNA genes that was over-expressed in cancer and I put it into a mouse tumor model. To my great surprise, it worked much better than some of the protein oncogenes that I was planning to work on. I immediately was fascinated by the fact that you can put in such a small RNA species into an animal tumor model and have a tumorigenic activity comparable to some of the famous known protein oncogenes."

Almost five years later, He is still fascinated by the interesting puzzles miRNA provides—and these small RNAs are likely to keep her occupied for years to come.

BREAKING IT DOWN

The protein folding problem is famous: how does a string of residues find its one functional, stable 3D shape out of a staggeringly large set of possible confirmations? New MCB assistant professor Andreas Martin was intrigued by this question as a graduate student, studying the folding kinetics and the thermodynamic stability of proteins. More recently, Martin's attention turned to a different, yet related problem: how do cells break down these stable structures when they are no longer needed?

"My main focus was on protein folding," says Martin. "Then I switched to destroying them."



Assistant Professor Andreas Martin

To degrade misfolded, damaged, or unneeded proteins, cells employ molecular machines that transform the chemical energy stored in ATP into mechanical work aimed at unfolding proteins and making them accessible to degradation by a protease. Martin is interested in how these unfoldases recognize a target and how they channel energy for unfolding.

As a postdoc in Bob Sauer's lab at MIT, Martin worked on the bacterial ClpXP system, which is composed of an unfoldase (ClpX) and a peptidase (ClpP). ClpX uses energy from ATP to unfold proteins and feed them into a degradation chamber of ClpP. Martin's work covered substrate recognition, unfolding, translocation, and the mechanisms of ATP hydrolysis.

Martin's research led to a deeper understanding of the mechanical aspects of this molecular machine. For instance, he found that the six ATPase subunits in ClpX, which he likens to six cylinders in an engine, contribute additively to degradation activity by hydrolyzing ATP and changing their conformation one at a time, but not necessarily sequentially. Additionally, mutating certain residues in the central pore that loosen the unfoldase's grip on a substrate polypeptide increases the amount of ATP consumed.

"It's like making the gas mileage worse, like if you have a slipping clutch or transmission," says Martin. "We use a lot of these machine analogies to explain these molecular motors."

After unpacking the boxes in his new lab in MCB, Martin will focus on the 26S proteasome from eukaryotes, a more complicated unfolding and degrading machine. Like the ClpXP system, it has two parts. The 19S unfoldase subcomplex recognizes appropriate substrates, unfolds them, and feeds the

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polypeptides into a 20S peptidase for degradation. Unlike the ClpXP system that has just two different proteins forming the two parts, the proteasome has at least 32 different subunits. Adding to the complexity, the proteasome system integrates a large number of associated proteins that are active for instance in substrate delivery.

The proteasome recognizes its targets through a polyubiquitin tag, added in a three step process by other enzymes. The story is a bit more complicated, though, since the proteasome must often prioritize its efforts to degrade some proteins before others, although each have a polyubiquitin tag. Also, some proteins must only be clipped or partially degraded, and not completely destroyed. In some cases these functions may be regulated by associated adaptors, in other cases intrinsic features of the substrate polypeptide may be responsible.

The unfoldase part of the proteasome threads the unfolded protein through a central pore. Some protein sequences, such as those containing glycine-alanine repeats, may be slippery or unable to be threaded, causing the translocation process to stop. Some viruses use this feature to their advantage, coding for protein sequences that are resistant to proteasome degradation.

"Many groups are working on the proteasome, but most of them focus on more cell biological aspects." Says Martin. "A lot of components of the ubiquitin-proteasome system have been identified, but the detailed molecular mechanisms are largely unknown. I want to use biochemical approaches to understand the mechanisms of substrate recognition, how ATP is utilized to exert unfolding forces, and how substrate is translocated."

Martin is attacking these problems from several angles.

"First, I will primarily focus on in-vitro biochemistry using purified components," says Martin. He'll use the proteasome from yeast as the model system, because it is relatively easy to manipulate, purify and handle, and it has high homology to the mammalian systems. He will also develop an *E. coli* expression system, which will allow proteasome mutations that would be lethal to eukaryotic cells.

Spectroscopy will allow real-time measurements of substrate degradation and ATP utilization. Single molecule FRET experiments, for instance, can detect conformational changes within the protease or the substrate. Martin will also pursue the determination of high-resolution structures of the



Associate Professor Henk Roelink

19S cap or its subunits to address the question of how the unfoldase machine works.

Because the proteasome's ATPases belong to the large family of AAA+ enzymes that are active for instance in helicases, chaperones, and motor proteins, understanding their detailed mechanisms may also give important insight into operating principles of other molecular machines.

When exploring protein unfolding, Martin draws upon his experiences in protein folding as a graduate student in Franz Schmid's lab in Germany. "In enzymatic protein unfolding and processing, the same rules apply as in protein folding," he says.

Martin says he has always been interested in science and biochemistry in particular. "Biochemistry was the right choice for me because you can describe biological processes in quantitative detail, with equations," says Martin.

When not exploring the inner workings of molecular machines, Martin likes to be active through sports, cross-country and downhill skiing, snowboarding, biking, and, most recently, kite surfing.

NERVE BEGINNINGS

"Nature works in very clever ways," says new MCB Associate Professor Henk Roelink, clearly delighted by the prospect of solving its puzzles.

"I'd like to understand how an embryo develops and how information contained in a genome and an egg leads to an organism that is thinking and walking around," says Roelink. "It's a very big question."

To answer this question, Roelink is using a bottom-up approach to understand the early fundamental processes that are likely to take place reiteratively throughout development. He is studying differentiation in the neural tube, the developmental precursor to an animal's nervous system.

The neural tube begins as a homogeneous sheet of cells that acquires differences along its various axes, allowing the region that develops into the head to be different than that which develops into the tail, for example. Roelink is interested in understanding how signal molecules, which come from adjacent sources, cause the differentiation. "It's a very interesting, but very complex phenomena," he says.

The young neural tube cells can measure the concentration of signaling molecules present and acquire a phenotype based on that concentration. In essence, the cell can count how many of its signal receptors are occupied. Roelink's favorite signaling molecule Sonic Hedgehog (Shh) is a protein involved in many developmental processes, including neural tube patterning.

"We're trying to find out how cells can read a distinct concentration and differentiate accordingly," says Roelink. "An equally big problem is that we don't even know how this molecule that's released from the notochord gets far away into the epithelium. It's a very difficult question because the signal Sonic Hedgehog is non-soluble and membrane bound, so you would not expect it to travel 10 or 15 cell diameters away. But it does."

While signaling molecules were thought to travel via simple diffusion,

FACULTY NEWS

▼ **Rachel Brem** received a 2008 New Scholar Award in Aging by the Ellison Medical Foundation for her work in signaling behaviors of the unfolded protein response in aging.



▼ **Beth Burnside** received the Berkeley Citation from the Chancellor for her contributions as Vice Chancellor for Research.



■ The Protein Society has awarded **Jamie Doudna Cate** their 2008 Irving Sigal Young Investigator Award, which is given to an early career scientist who has contributed to protein research.

▼ **David Drubin** received the Ira Herskowitz Award at the Genetics Society of America/ Yeast Genetics and Molecular Biology meeting last summer in Toronto, Canada.



■ **Richard Harland** was elected President-elect of the Society for Developmental Biology.

■ **Lin He** was awarded a New Faculty Award from the California Institute for Regenerative Medicine (CIRM), the state's stem cell research funding program.

■ The December 2008 issue of *Discover* magazine features **Nicole King** as one of the "Best Brains in Science." The article describes the research of 20 scientists under the age of 40.

■ **John Kuriyan** received the American Society for Biochemistry and Molecular Biology (ASBMB)'s 2009 Merck Award, which recognizes outstanding contributions to research in biochemistry and molecular biology. He was also elected to the American Academy of Arts and Sciences.

■ UC Berkeley Extension named **David Presti** an Honored Instructor for his exceptional and inspiring teaching.

■ **Randy Schekman** was appointed the first Senior Fellow of the UC Berkeley Miller Institute. This five year appointment is awarded to accomplished tenured faculty members at a rate of about one per year. It comes with an annual \$50,000 in discretionary research funds. The Miller Institute website states: "The appointment of Randy Schekman illustrates the high standard that we seek for Senior Fellows. Randy's scientific stature and citizenry on campus and around world are well known and admired."

■ **Robert Tjian** was elected as the new president of the Howard Hughes Medical Institute. (See story below.)

■ **Russell Vance** received an Investigatorship from the Cancer Research Institute. This provides funds to study inflammasome activation in Naip5-deficient mice.

■ **Gerald Westheimer** was elected to an honorary membership of the Royal Society of New South Wales, the oldest academy of science in Australia. He is a long-time Fellow of the Royal Society of London.

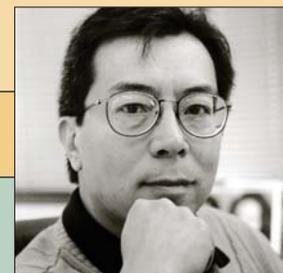
TJIAN TO HEAD HOWARD HUGHES MEDICAL INSTITUTE

MCB Professor Bob Tjian is the newly elected president of the Howard Hughes Medical Institute. HHMI, a private organization with an endowment of \$17.5 billion, supports the biomedical research of more than 350 investigators at over 60 universities and other research organizations throughout the United States. The MCB department hosts ten HHMI-supported faculty members.

"It's an exciting opportunity," says Tjian. "I think that the head of HHMI is one of the most influential positions that a scientist can

have in terms of helping set the direction and policy of the educational and research program in the United States, and probably internationally."

Tjian will assume this position on April 1, 2009, succeeding Nobel Laureate Thomas R. Cech of the University of Colorado at Boulder. Tjian will continue to run his MCB lab, taking a portion of his research with him to Janelia farm, HHMI's research campus in Ashburn, Virginia.



Tjian has been an investigator with HHMI for 20 years and a professor at UC Berkeley since 1979. Born in Hong Kong, his distinguished career includes a B.S. in biochemistry from UC Berkeley in 1971, a Ph.D. from Harvard University in 1976, and post-doctoral work with Nobel Laureate James Watson at Cold Spring Harbor Laboratory.

2007-2008 GRADUATES

FALL 2007

- **Sonia Bakkour** (Sha) Characterization of ICOS-mediated B7h shedding
- **Veysel Berk** (Cate) Towards a model for ribosomal decoding
- **Jacob Corn** (Berger) Structure and function of the bacterial primase
- **Maria Divina Deato** (Tjian) Switching core promoter recognition complexes during myogenic differentiation
- **Todd Ferreira** (Ngai) Characterization of the development of the zebrafish olfactory system
- **Andrew Greenstein** (Alber) Structure, function, and regulation of eukaryotic-like serine/threonine protein kinases in *Mycobacterium tuberculosis*
- **Katie Gustavsen** (Gallant) Effects of attention on the responses of V4 neurons
- **Tiffany Juarez** (Raulet) Roles of the NKG2D receptor and its ligands in tumor surveillance and autoimmunity
- **Leonard Kusdra** (Martin) Multiple roles of src family kinases in mammary epithelial tumorigenesis.
- **Kevin Larimore** (Sha) Selective initiation and control of antibody responses by dendritic cell and B cell mediated ICOS Signaling
- **Hanson Lee** (Isacoff) Alternative splicing of neuroligin-1 regulates the rate of pre-synaptic differentiation
- **Venkataramanan Nandagopal** (Eisen) Experimental and computational analyses of early embryonic cis-regulatory elements in the diptera
- **Jerod Ptacin** (Bustamante) Mechanism of DNA transfer by the FtsK/SpoIIIE family of DNA translocases
- **Daniel Serna** (Raulet) Murine cytomegalovirus evasion of natural cell surveillance
- **Zejuan Sheng** (Kramer) Synaptic Ca²⁺ and information coding in vertebrate rods and cones
- **Jessica Shugart** (Shastri) Exploration of diverse antigen processing pathways that generate peptides for presentation by MHC I molecules
- **Jamin Willoughby** (Firestone) Artemisinin regulation of proliferation and disruption of androgen responsiveness of human prostate cancer cells

SPRING 2008

- **Jennifer Beh** (Levine) Early heart development gene networks and morphogenesis in the *Clona intestinalis* chordate tadpole
- **Emily Cadera** (Schlissel) Regulation of receptor editing by NF- κ B
- **Megan Clarey** (Botchan/Nogales) Structural studies of the *Drosophila* origin recognition complex
- **Emily Derbyshire** (Marletta) Investigating the heme environment and mechanism of activation of soluble guanylate cyclase
- **Nathaniel Echols** (Alber) Molecular mechanisms of ser/thr kinase regulation in *Mycobacterium tuberculosis*
- **Aaron Garnett** (Amacher/Eisen) T-box transcriptional factors in zebrafish mesoderm development
- **Liana Lareau** (Brenner) Unproductive mRNA splicing and ultraconserved DNA elements
- **Twyla Lombana** (Alber) Structural and functional characterization of the regulation of PknB, an essential serine/threonine protein kinase of *Mycobacterium tuberculosis*
- **Deirdre Lyons** (Weisblat) Mechanisms controlling the asymmetric second cleavage of the *Helobdella* embryo
- **David Mets** (Meyer) Meiotic crossover position and frequency are regulated by chromosome structure in *C. elegans*
- **Yongkai Ow** (Shastri) Cryptic translation in immune surveillance under stress
- **Raj Pai** (Cate) Structural studies of the interaction of ribosome recycling factor with the ribosome
- **Brant Peterson** (Eisen/Levine) Harnessing natural sequence variation to explore cis-regulatory function and evolution
- **Mark Price** (Marletta) Investigation into a novel two component signaling pathway in *Shewanella oneidensis* MR-1
- **Adam Schindler** (Schekman) ATF6 transport from the endoplasmic reticulum to the golgi during the unfolded protein response
- **Mark Schramp** (Martin) The requirement for ERK5 in src-induced morphological transformation
- **Ansley Scott** (Zusman) Receptor methylation controls single cell and group behaviors in the social bacterium *Myxococcus xanthus*
- **Scott Siera** (Cline) Positive regulation of sex-lethal in the germline and soma of *Drosophila melanogaster*
- **Aakanksha Singhvi** (Garriga) Asymmetric cell divisions and cell fate specification in *C. elegans* neural development
- **Fai Yiu Siu** (Doudna) The role of 4.5S RNA in the *E. coli* SRP system
- **Christopher Toret** (Drubin) Comprehensive analysis of clathrin/actin mediated endocytosis in *S. cerevisiae*
- **Michael Whang** (Raulet) A novel NKG2D ligand expressed in the skin activates skin $\gamma\delta$ T cells
- **Tracy Young** (Marqusee) Investigation of the biophysical properties responsible for differences in the energy landscapes of homologous mesophilic phosphoglycerate kinases

CLASS NOTES



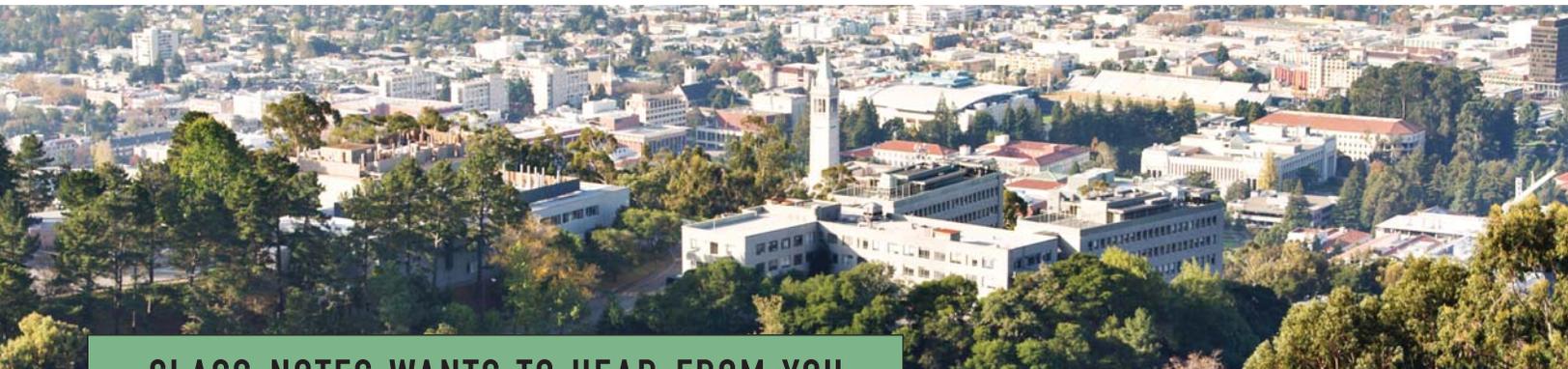
■ **Sarah L. Gaffen** [PhD 1994] has moved from SUNY Buffalo to an Associate Professor position at the University of Pittsburgh, Dept. of Medicine, Division of Rheumatology & Clinical Immunology. She'd love to hear from classmates. (sig65@pitt.edu)

■ **Michael Galvez** [BA 2004] finished his pre-clinical years at Stanford University School of Medicine, and is now doing a year of full-time research as a Howard Hughes Medical Institute Medical Research Training Fellow in the Department of Surgery. (mgalvez@stanford.edu)

■ **Gor McCarter** [PhD 1996] is an Assistant Professor of Biological Sciences and newly appointed Assistant Dean for Student Services for the College of Pharmacy, Touro University - California in Vallejo, CA. (gmccarter@touro.edu)

■ **Jason Ng** [BA 1998] completed a Doctor of Optometry degree in 2003 and then spent a year practicing optometry before returning to UCB to complete a PhD in the Optometry School in 2008. Currently, he is an Assistant Professor at the Southern California College of Optometry. (jasonng@alum.calberkeley.org)

■ **Geoffrey Wool** [BA 2002] received a PhD in Pathology from the University of Chicago in August 2008. He is returning to the third year of medical school at Chicago and hopes to be back in the Bay Area in 2010. "Go Bears!" (gwool@cal.berkeley.edu)



CLASS NOTES WANTS TO HEAR FROM YOU

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Roelink argues that there must be an active "bucket brigade" transport from membrane to membrane between cells. In the epithelium, cells are packed very tightly together, which would inhibit free diffusion yet allow ample opportunity to actively transport molecules.

Signaling molecules originating at a single source would be passed along from cell to cell. If each cell passes a fraction of what it was passed, a gradient is formed, which can lead to differentiation into multiple cell types.

A recent breakthrough has enabled Roelink to turn embryonic stem cells into a tissue that resembles early neural tube cells. These can be used to study Shh movement and signaling. Not only is this method much more efficient than the previous method of hand-harvesting cells from chick embryos, it allows application of the vast library of mouse genetics.

"It feels like an embarrassment of riches," says Roelink. "Even three years ago the tissue we worked with was always the limiting factor. And it is no more."

Roelink sees potential to develop many different systems of different cell types and genotypes for testing a variety of signaling molecules. Through these systems, the question of how signaling molecules travel such long distances can be addressed.

Even with the cell culture method, Roelink isn't throwing out the eggs quite yet. Once interesting phenomena are found via the stem cell system, they will be tested in the much more complex environment of an embryo.

Roelink will also collaborate with MCB professor Bob Tjian's lab to decipher details

of transcriptional changes occurring in neural differentiation.

Roelink is originally from the Netherlands. He came to the United States during his graduate work, which started at the Netherlands Cancer Institute in Amsterdam and moved to Stanford Medical School in 1990. He worked on tumorigenesis in mammary cells in mice by using retroviruses to find tumor causing genes. He became interested in the normal functions of the genes he identified, which had interesting patterns of expression in the neural tube.

After finishing his graduate work at Stanford and defending his thesis in Amsterdam, Roelink started a postdoctoral position at Columbia University with Tom Jessell to learn how to measure the effects of inducing molecules in the neural tube. He remembers a "crazy period" when he was one of several scientists at different institutions who cloned the Shh gene.

Roelink started a laboratory at University of Washington in Seattle. There he investigated cyclopamine, a small molecule that causes cyclopia.

"Well if it causes cyclopia, it must have something to do with Sonic Hedgehog," Roelink remembers thinking, since Shh mutants often had a single midline eye. Indeed, cyclopamine blocks Shh signaling and is currently used therapeutically for Shh-induced cancers and as a laboratory tool.

He arrived in Berkeley at the start of the year. While acknowledging that Seattle is a hard place to leave, Roelink appreciates much about his new home: the scientific amenities, the broad biological research interests of his fellow professors, and a once long-distance, now local romance.

Roelink describes himself as having too many hobbies. He enjoys adventurous activities such as scuba diving and flying that involve a technological component. "I have a rational mind," says Roelink. "I like to know how things work, whether it's something simple as a car engine or complex as an organism."



The MCB Transcript is published twice a year by the Department of Molecular and Cell Biology at the University of California, Berkeley.

PRODUCTION: Raven Hanna
DESIGN: Betsy Joyce

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