MCB Transcript

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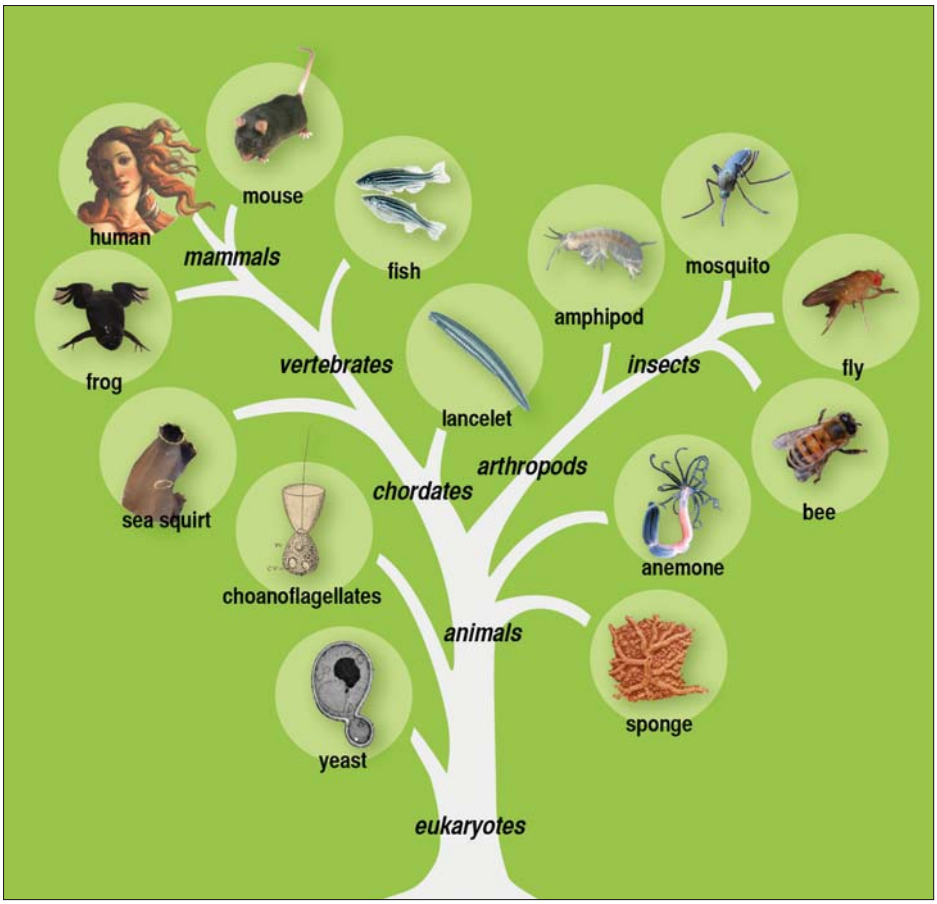
Newsletter for Members and Alumni of the Department of Molecular & Cell Biology at the University of California, Berkeley

THE DEEP INNER LIFE OF ANEMONES...

AND OTHER TALES OF SURPRISING SEA CREATURES



The scientists of the Center for Integrated Genomics compare sequences from a variety of species to answer questions about evolution and animal development.

CREDIT: RUSTY HOWSON, REDOX DESIGN

Mike Levine cheerfully admits that his sea squirts are not typical lab animals. Nor have sea anemones, sea sponges, or beach hoppers often seen the inside of a test tube. Yet, these odd sea creatures are exactly the type that interest MCB Professor Levine and his colleagues. These largely overlooked animals hold clues that are helping unravel the mysteries of animal evolution and development.

Levine and other MCB professors formed the Center for Integrated Genomics to use one of the newest tools in a molecular biologist's toolbox, genomic sequencing, to answer some of biology's oldest questions. The Center, now about five years old, has received funding from the Gordon and Betty More Foundation, an organization that funds research to explore and preserve organismal diversity.

MCB Professor Dan Rokhsar spearheads the genomic quests. In collaboration with the Department of Energy's Joint Genome Institute, Rokhsar and his colleagues use sequencing machines and techniques developed for the human genome sequencing project. The first step is finding the sequence of A, T, C, and G bases, which is then computationally scanned to find the genes and other features. The Center has recruited scientists in other fields, such as biostatistics and math, to aid in mining as much information as possible from the sequences.

CONTINUED ON PAGE 2. . .

ANEMONES FROM PAGE 1. . .

Genomes assembled through the resources of the Center to date include the sea squirt, sea anemone, sea sponge, *Xenopus* frog, a Hawaiian segmented worm, a local Californian leech and limpet, Monosiga (an animal-like protozoan), lancelet (a primitive filter feeding cousin of vertebrates), and *Trichoplax* (a simple animal resembling a multicellular amoeba).

These genomes are treasure troves of surprises and information. First, they divulge what genes the organism has and how they are arranged. For example, the genome of the sea anemone revealed a complexity that was not expected based on its relatively simple form. Another surprise was the arrangement of the anemone genes, which was much more like human genes than that found in the favored model animals of *C. elegans* (worm) and *D. melanogaster* (fruit fly). This "synteny" suggests that the last common ancestor of anemones and humans had these same gene arrangements. Somewhere down the road, *C. elegans* and *D. melanogaster* lost this arrangement, but humans and the anemones retained it. The genome has shown that humans and anemones have much more in common than one would suspect.

While the list of favored organisms may appear motley, they have been carefully chosen by the researchers in the Center to help clarify evolutionary questions. Scientists infer what historical creatures like the first animals or the first vertebrates were like by comparing the traits of their modern ancestors. If two organisms share a trait, it is likely their last common ancestor did, too. Researchers compare genes and genetic organization to glean information about long extinct creatures.

For example, sea squirts and lancelets are chordates but not vertebrates, so comparing their genome with the sequence of vertebrates provides information on the common ancestor that evolved into vertebrates and suggests how vertebrate traits may have arisen. Similarly, the beach hopper crustacean could give insights into animal body plan development. And looking way back in evolution, the single-celled *Monosiga* may be key in understanding how multi-celled animals arose. The power of this comparative technique increases with the number of examples. As more genomes are solved, the emerging picture of the evolutionary process that created humans and all other modern organisms becomes more and more refined.

While the genomes contain answers, they also lead to intriguing questions. The Center scientists follow up on the initial conclusions with genetic experiments to further explore their findings. For example, the genome of the limpet (a marine snail) revealed genes associated with segmentation in *D. melanogaster* flies. What are those genes doing in the unsegmented snails? The answer is currently being pursued in Dan Rokhsar and Nipam Patel's laboratory with experiments made possible by knowledge of the gene sequences.

This work highlights one of the emerging themes of the evolutionary field: the general conservation of the molecular machinery itself but not necessarily the conservation of ultimate function. The genomes abound with familiar genes serving unfamiliar functions. The Center's researchers use genetics experiments to discover what those functions are.

THE BEACH HOPPER: DISCOVERING EVOLUTION'S TOOLBOX

"One of the beauties of a lobster is that, if you try to feed one (that doesn't have rubber bands on it), it can attack you, run away, eat food, and do all of these things at the same time because every segment has a specialized pair of appendages with different functions," says MCB professor Nipam Patel.

Arthropods, including lobsters, insects, spiders, and millipedes, could be considered the most successful type of animal, far outnumbering other phyla. Evolution has endowed arthropods with diverse appendages for swimming, walking, eating, flying, and fighting within a segmented body plan. Patel and his group are interested in how these segments develop and how evolution allows for changes and specializations of these segments. Through his work with a small crustacean, he has uncovered one of evolution's tools.

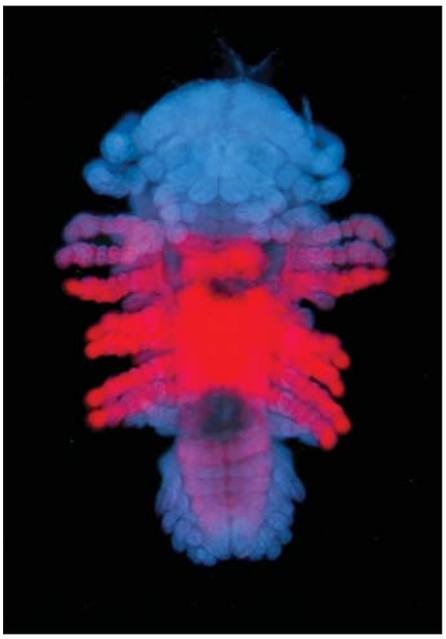
While the model arthropod, the fruit fly *Drosophila melanogaster*, has revealed much about its genetics and development, it has turned out to have its own particular system for segmentation that is not used by other types of arthropods. To understand segmentation in crustaceans like lobsters, Patel needed a different animal model.

That animal turned out to be the amphipod crustacean *Parhyale hawaiensis*, a beach hopper, chosen party because it is easy to grow—Patel's student collected specimens from an aquarium where they were happily living in the filtration system. The shrimp-like *Parhyale* is about twice the size of a fly and has a diversity of appendages.

Never having been used as a lab animal before, *Parhyale* did not have the rich history of genetics like the fruit fly. When interested in genes of an organism about which little is known, a geneticist will often put those genetic sequences into a model system like

A native of of tropical beaches worldwide, the amphipod crustacean Parhyale hawaiensis *can reach 1.5 centimeters in length.*

PHOTO: ALIVIA PRICE



A Parhyale *embryo showing the expression of Ubx, lit up in red.*
PHOTO: DANIELLE LIUBICICH

Drosophila. But Patel wanted to research the genes in the context of the animal they came from. Using the resources of the Center for Integrated Genomics, Patel's group was able to devise techniques to study the genes and the upstream regulatory elements within *Parhyale*, itself.

Patel started by looking at homeotic genes, which are responsible for head to tail patterning and are well conserved and well studied among animals. One of these genes is called Ultrabithorax (Ubx), which was shown in fruit flies to play a role in segment identity through experiments that resulted in remarkable transformations, including the generation of four-winged flies.

In *Parhyale*, Ubx also plays a role in segment identity. It is expressed in the second thoracic segment through the tail of the animal and marks the division between jaw-like feeding appendages and leg appendages. In other crusteacean species, the boundary of Ubx expression depends on the species examined, ranging from the first to the fourth thoracic segment, but in all cases correlates with the transition from jaw-like to leg-like appendages. Patel's group, led by graduate student Danielle Liubicich, lowered the expression of Ubx in Parhayle and created a creature with extra sets of feeding appendages and fewer walking legs. In collaboration with the lab of Michalis Averof of the Institute of Molecular Biology and Biotechnology in Greece, they also found that moving the expression of Ubx forward created more walking leg appendages and fewer feeding appendages.

"What's really interesting is that just by manipulating the levels of Ubx we've recreated what evolution has also done, which is not to get absolutely identical segments but to get a gradation of morphology," says Patel.

Patel's group will next explore whether the change in the expression of Ubx comes from changes in the surrounding regulatory DNA of the Ubx gene, or from changes in genes upstream of Ubx.

Parhyale the little beach hopper has turned out to have other interesting characteristics. For example, it performs a trick not seen before in an animal: it's able to replace its germ line cells, those that make sperm and eggs, as an adult. This could have implications for stem cell technologies.

"This highlights one of the really neat things about picking these non-model species to study," says Patel, "Because any animal you pick up has interesting biology to it." You just have to look.

SEA SQUIRTS: NOT SO FAR FROM HUMAN

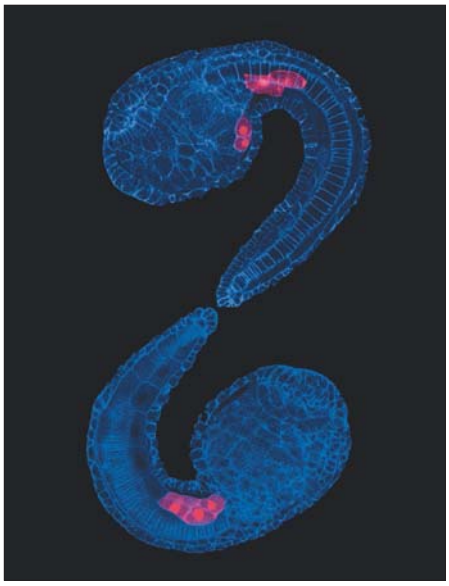
The oceans contain many weird and wonderful forms of life, some complex and some simple. A sea squirt is one of the more simple animals. The sea squirts (*Ciona intestinalis*) living on rocks in the shallow waters of Half Moon Bay are a few inches long and translucent. They consist mainly of two tubes, one for drawing water in and one for spitting it out. Between these tubes they filter the seawater to gather food. Although the adult sea squirt looks rather alien, the hatchlings look much more familiar. The immature sea squirt is a tiny tadpole that has remarkable resemblance to a chordate embryo.

Sea squirts are not vertebrates, but they are chordates. Like fish and birds and hamsters and humans, they have a notochord, a dorsal hollow neural tube, and a compartmentalized brain. The common ancestor that humans share with sea squirts lived about 550 million years ago, just before the budding of the vertebrate branch, which hosts the animals that developed spines. Understanding more about the genes and traits this long extinct common ancestor possessed will further illuminate the evolutionary processes that gave rise to vertebrates and, eventually, humans.

Its notable position on the evolutionary tree made the sea squirt a prime candidate for genetic sequencing. MCB professors Dan Rakhsar and Mike Levine headed the group to sequence and analyze the sea squirt genome [*Science* **298**: 2157-67]. Levine's laboratory took it from there, using the genome as a springboard and tool to address specific questions, such as the evolutionary pathway of heart development.

"We were starting to work on this without the genome but we made really slow progress," says Levine. "When the genome was determined at the end of 2002, things have really been moving fast. And it's attracted a lot of good young people into the field."

While sea squirts can be called spineless, they can't be called heartless. Many invertebrates have a simple, one-chambered heart, but the sea squirt's heart is different. It is one-chambered, but it is made of muscle tissue similar to that of a mammalian heart and beats about once per second.



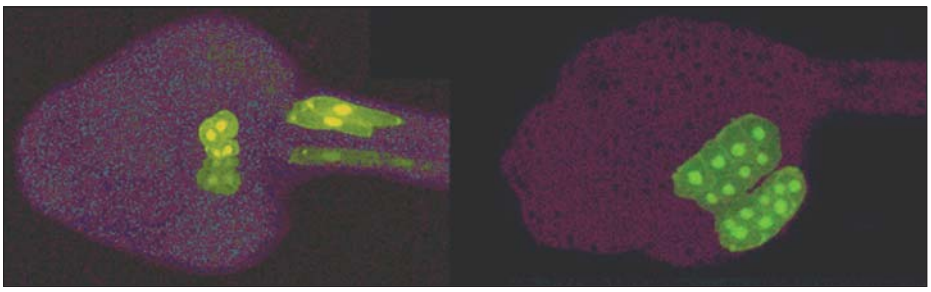
The normal sea squirt tadpole shown at top shows two highlighted cells have migrated to the head to make heart cells and two remain in the tail to become muscle cells. The lower tadpole will have no heart; all four cells remain in the tail to become muscle cells.
PHOTO: BRAD DAVIDSON AND MIKE LEVINE

"First of all that tells you that the very first vertebrates definitely had muscular, rhythmic beating hearts," says Levine. He wondered if the sea squirt's one chambered vertebrate-like heart can give insight into how fish developed their two-chamber heart, reptiles their three-chambered heart, and birds and humans a four-chambered heart. Understanding the process by which evolution adds complexity to organisms is tricky, and Levine hoped to gain insight into this process. His lab investigated the early evolution of the chordate heart by using molecular biology techniques as the vehicle and the genome as a map.

Next to the sea squirt's heart muscles are tail muscles. Levine's group found a simple way to transform the heart muscles into tail muscles and vice versa. The sea squirts genetically manipulated to have all tail muscles die from their lack of a heart. The ones that have all heart muscles survive and show interesting behavior. A doubled heart looks like it has two chambers. The blood is pumped into one heart area, then into the other. [Genes Dev**. 20**: 2728-2738.]

"So this suggests in evolution maybe you just have to expand the number of precursor cells required to make a heart to start getting this increase in complexity from one to two, two to three, and three to four chambers," hypothesizes Levine. He's quick to state that this theory is not proven, but it is tantalizing. Could something as simple as doubling an organ lead to specialization and complexity?

Levine attributes much of his success with the sea squirts as a lab organism to the availability of its genome. "It had been studied as a classical organism over 100 years ago, then it lost favor because of the creatures like fruit flies where genetics had passed them by," says Levine. "The advent of the genome has given this creature new life."



The sea squirt tadpole on the left is normal, with 8 heart cells in its head and 4 muscle cells in its tail. The tadpole on the right has twice as many heart cells and no tail muscle cells.

PHOTO: BRAD DAVIDSON AND MIKE LEVINE

STARLET SEA ANEMONE: MORE NERVOUS THAN WE THOUGHT

Back before our ancestors had brains, they had nerves. Before that they had cell signaling. MCB professor Dan Rokhsar is exploring the genomes of animals with simple or unrecognizable nervous systems, such as a sea anemone, to reconstruct the evolution of nervous systems.

Sea anemones, along with other sea animals like sea stars, jellyfish, and urchins, have radial symmetry. Such a body plan is fundamentally different from that of most of the animals you encounter, including mammals, birds, insects, and worms, which are bilaterially symmetrical (bilaterians). Although these two animal groups diverged about 600 million years ago, comparisons between the sea anemone genome and genomes of bilaterians suggest that their common ancestor was likely to have had most of the ingredients of a nervous system already in place.

The starlet sea anemone *Nematostella vectensis* burrows into the muddy bottom of brackish water. Usually less than an inch long, its column ends in a mouth disk surrounded by translucent tentacles that catch zooplankton. This anemone was chosen for genomic sequencing because it is relatively easy to grow in the lab.

Sea anemones have neurons that look like the classic textbook photos of human nerve cells, with an axon and dendrites. With no distinct center or brain, the neurons form a diffuse network throughout the

The mouth and tentacles of an adult Nematostella *sea anemone.*

PHOTO: MANSI SRIVASTAVA AND RUSSELL HOWSON

anemone. Before Rokhsar's group assembled the anemone genome [*Science* **317**: 86-94; 2007], it was assumed that the anemones had no complexity in its neural network. Analysis of the genome has produced a different picture.

"The common ancestor of sea anemones and bilaterians had already a pretty complicated neural genome, in the sense of having the genes involved in the nervous system," says Rokhsar. "It hadn't just invented neurons–the nervous system was already at some stage of organization."

To understand the origin of this complexity, Rokhsar's group is looking to the genomes of other organisms that share older common ancestors with humans, such as the very simple animal *Trichoplax* [paper submitted to Nature] that does not seem to have any nervous system yet carries some nervous system related genes.

"If *Trichoplax* is a biological relic of the earliest animals, it could represent what those genes were doing before the neuron was invented," says Rokhsar, who hypothesizes that the nervous system might have evolved from an endocrine-like cell signaling system. This theory isn't new, but the use of genome-based techniques to study the question is.

Rokhsar's research has shown that the common ancestor of anemones and humans already had many of the gene families that that give modern animals their complexity and diversity.

"We are used to thinking about humans as being particularly advanced, but I think what we are learning is that in their own way, those animals from 600 million years ago were already pretty advanced compared to their unicellular relatives," says Rokhsar.

FACULTY NEWS

- **Bruce N. Ames** received the first annual Senior Investigator Mary Swartz Rose Award from the American Society of Nutrition (ASN), sponsored by the Council for Responsible Nutrition (CRN).

- **Michael Botchan** and **Jasper Rine** were elected to the National Academy of Sciences. Rine has also been elected to the American Academy of Arts and Sciences, along with **John Kuriyan**.

- **Georjana Barnes** was selected as a Keith R. Porter Fellow by the American Society for Cell Biology.

- New faculty member **Diana Bautista** has been selected as an Alfred P. Sloan Research Fellow.

- **Jamie Cate** received The 2008 Irving Sigal Young Investigator Award, sponsored by Merck Research Laboratories. The award recognizes a significant contribution to the study of proteins by a scientist who is in the early stages of an independent career and, generally, not more than 40 years of age at the time of the award.

- **Yang Dan**, **Abby Dernburg** and **Michael Eisen** have been chosen by the Howard Hughes Medical Institute as HHMI investigators.

- **David Drubin** was selected to receive the Ira Herskowitz Award by the Genetics Society of America

- **John Forte** received the 2008 Distinguished Achievement Award from the American Gastroenterological Association, AGA's highest recognition for an investigator currently working in the field of gastro-intestinal and liver research. He also received an Excellence in Teaching Award from Phi Beta Kappa, Northern California Association.

- **Lin He** has been named a Searle Scholar for 2008-2010. This award provides funding for exceptional young faculty in the biomedical sciences, and given for He's work on the roles of microRNAs in tumor development.

- **Caroline Kane** retires on July 1st, but won't be spending all of her time golfing, hiking, and traveling with her husband. She will continue to work half time on projects related to equity and access to higher education in the sciences. She will also be volunteering with the Biology Scholars Program on campus, continue mentoring several thesis students, teaching MCB 110L this fall, and working with the UC Retirement Center. In her spare time, she will volunteer at the Lindsey Wildlife Museum in Walnut Creek. Best wishes to you!

- **Mike Levine** was named one of the two Faculty Research Lecturers by the Academic Senate for 2008/2009. Each year since 1913, one or two UC Berkeley professors "distinguished for scholarly research" are chosen to give a lecture on their research.

- **Michael Marletta** won the 2008 Murray Goodman Memorial Prize for "contributions towards a molecular understanding of nitric oxide signaling and gas sensing using chemical and biophysical methods."

- **Howard Schachman** received the 2008 Carl Brändén Award, sponsored by Rigaku Corporation. The award is given to an outstanding protein scientist who has also made exceptional contributions in the areas of education and/or service to the science. Schachman has also been selected as the "Distinguished Emeriti of the Year" by the UCB Emeritus Association.

- **Randy Schekman** is the winner of the 2008 Dickson Prize in Medicine and has been elected to the American Philosophical Society.

MCB WELCOMES THE NEW FACULTY MEMBERS:

- Assistant Professor **Lin He** (Cell & Developmental Biology)
- Associate Professor **Henk Roelink** (Genetics, Genomics and Development),
- Assistant Professor **Diana Bautista** (Cell & Developmental Biology)

The new faculty members' research will be featured in future issues.

2008 AWARDS

OUTSTANDING GRADUATE STUDENT INSTRUCTORS

The following GSIs for MCB courses were among those honored by the Graduate Division in a May 7 event at the Alumni House for outstanding teaching.

- Monika Abedin [King lab]
- Ryan Arant [Isacoff lab]
- Leah Byrne [Flannery lab]
- Venice Calinisan [Martin Lab]
- Seemay Chou [Meyer lab]
- Padma Gunda [Cate lab]
- Meghan Jones [Cline lab]
- Kihoon Kim [Comparative Biochemistry]
- Timothy Nice [Raulet lab]
- Vince Ramey [Nogales Lab]
- Daniel Richter [King Lab]
- Harshita Satija [Shastri lab]
- Erica Warp [Isacoff lab]
- Adam Williamson [Rape Lab]
- Edward Yang [Comparative Biochemistry]
- Susan Young [King lab]

UNDERGRADUATE AWARDS

▼ MCB student **Leslie Chung-Lei Sheu** [Carolyn Bertozzi lab] received the University Medal for 2008, given to the most distinguished undergraduate. The award comes with a $2,500 scholarship and the opportunity to speak at UC Berkeley's Commencement Convocation. She plans to begin medical school at UCSF this fall.

PHOTO: ANDY HSIEH

▼ MCB student **Angelica L. Zen** [Nilabh Shastri lab] was one of the five runners-up for the Medal. She will be attending medical school at UCLA this fall. Congratulations to you both!

PHOTO: WENDY EDELSTEIN

DEPARTMENTAL AWARDS

Departmental Citation
- **Timothy W. Dunn** [Richard Kramer lab]

Outstanding Scholar
- **Vanessa Anne Van Voorhis** [Dan Portnoy lab]

DIVISION OF BIOCHEMISTRY & MOLECULAR BIOLOGY

Grace Fimognari Memorial Prize
- **Adam E. Singer**

Kazuo Gerald Yanaba & Ting Jung Memorial Prize
- **Heather Lovae Glasgow**

Jesse Rabinowitz Memorial Prize (for outstanding junior in BMB)
- **Panid Sharifnia**

DIVISION OF GENETICS & DEVELOPMENT

Edward Blount Award
- **Leslie C. Sheu** [Carolyn Bertozzi lab]

Spencer W. Brown Award
- **Joshua A. Arribere** [John Conboy lab, LBL]

DIVISION OF IMMUNOLOGY

Outstanding Undergraduates in the Division of Immunology
- **Eric A. Dunipace** [Russell Vance lab]
- **Ramses Monir El-Diwany**

DIVISIONS OF CELL & DEVELOPMENT BIOLOGY AND NEUROBIOLOGY

I. L. Chaikoff Memorial Awards
- **Vasiliki Irene Aivaliotis**
- **Tiffany Cheng**
- **Timothy W. Dunn** [Richard Kramer lab]
- **Kimberly Marie Iwaki**
- **Min Kyeong Jennifer Kim** [Silvia Bunge lab, Psychology]
- **Hank H. Lai** [George Bentley lab, IB]
- **Alexander H. Nguyen** [Iswar Hariharan lab]
- **Kevin Poon** [John Forte lab]
- **Amy Shen**
- **Joyce Lichi Yang**
- **Stephan Yoon**
- **Lily Zeng** [Robert Messing lab, UCSF]

CLASS NOTES

- **Miganoush Ghookasian** [BA 2004] is in his first year of dental school at NYU and is loving it. "Go Cal pre-dental society!" [mg1882@nyu.edu]

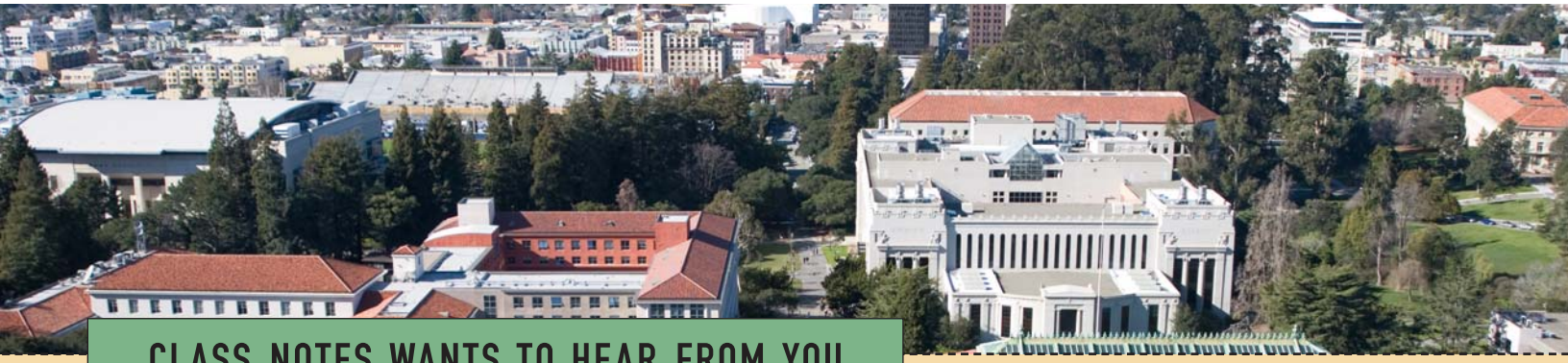
- **John Percival** [BA 1999] is currently a Project Manager in Technical Services Department at Baxter BioScience Los Angeles. [johnwpercival@hotmail.com]

- **John Pulliam** [BA 1999] earned his PhD in neuroscience from Emory University in December 2007. He is currently a postdoc at Morehouse School of Medicine. [JPulliam@msm.edu]

- **Minal Tapadia** [BA 2000] earned a law degree from University of California Hastings in 2003. She then researched birth defects at Stanford for a few years, and just started her first year of medical school at University of Toledo. She says, "I want to return to the Bay Area for summer clinical research in pediatrics or orthopedics, so if there are any Berkeley alumni looking for a good medical student to work on a project in their lab, I'm their girl." [tapadiam@yahoo.com]

CORN WINS WEINTRAUB

- **Jacob Corn**, who completed his Ph.D. last year in James Berger's lab, is one of 13 recipients of the Harold M. Weintraub Graduate Student Award sponsored by the Fred Hutchinson Cancer Research Center. Applications were solicited internationally and judged by the significance, originality, and quality of their research. Recipients participated in a symposium at the Hutchinson Center in Seattle on May 2 and received an honorarium.



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, you can

➜ Clip and mail this form
or
➜ go to mcb.berkeley.edu/alumni/survey.html
or
➜ Send e-mail to tscript@berkeley.edu

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MONOSIGA: CONNECTING WITH FRIENDS AND WITH FOOD

Even the most casual observer would notice at least one thing that separates us from our unicellular ancestors from 600 million years ago: size. By definition, animals are multi-cellular, yet they evolved from single-celled organisms.

To learn about the last single-celled ancestor that gave rise to multi-cellular animals, scientists look to unicellular organisms called choanoflagellates. These protozoans piqued the interest of MCB Professor Nicole King, who is interested in uncovering the molecular mechanisms that led to the origin of animals.

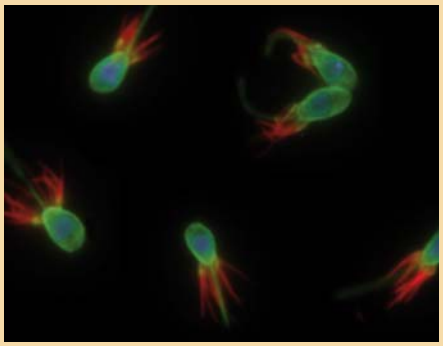
"We are more similar to choanoflagellates than we are to plants or fungi," King says. "And you can see it both in the genome and by looking at the basic cell biology."

Similar to the food gathering cells of sea sponges, choanoflagellates have a collar of actin filament microvilli that traps bacteria for food. A flagellum inside the collar beats back and forth, generating a water current to draw the bacteria into the trap.

Choanoflagellates are the only organisms other than animals that have proteins from a family called cadherins. Animal cells use these proteins to stick to one another, while other multi-cellular organisms like plants and fungi use other methods. Since genome comparisons show that cadherin genes are one of the genetic elements particular to animals, the presence of cadherins in choanoflagellates suggests an evolutionary relationship.

The genome of *Monosiga brevicollis* [*Nature* **451**:783-8; 2008], a choanoflagelate species that is easy to use in the laboratory, revealed 23 different cadherin genes, which is about equal to or more than any known animal species. Because a gene that is responsible for cell adhesion in multicellular organisms must have come from a gene that had a different role in unicellular organisms, King wondered what role the cadherins have in *Monosiga*. Her group found that one class of cadherin proteins localized to the collar region, which suggested that they might be used in feeding. Perhaps ancestors of the proteins that stick animal cells together were once used to catch bacterial cell prey.

King acknowledges the importance of having the genetic sequence. "All we had before the genome sequence was a little piece of DNA that had two or three cadherin repeats on it," she says. "We didn't even have the whole gene sequence for that one cadherin. And now we know the full sequence of every cadherin in the genome. It's because of this that we are able to make the types of comparisons that we've now made to reconstruct the history of this [cadherin gene] family."



A montage of Monosiga *cells stained in red for actin, blue for DNA, and green for tubulin.*

PHOTO: MONIKA ABEDIN

MCB Transcript

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