MCB Transcript

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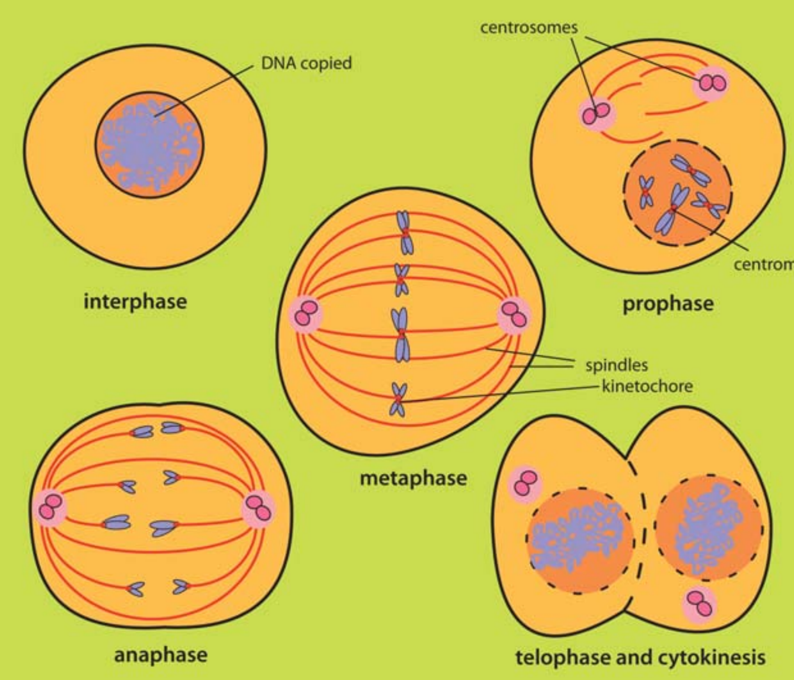
Newsletter for Members and Alumni of the Department of Molecular & Cell Biology at the University of California, Berkeley

DEMYSTIFYING METAPHASE: MCB Scientists Collaborate and Confer to Understand the Processes of Chromosome Separation



Eukaryotic cell division is a coordinated and regulated process. It begins in the nucleus, where DNA is copied during the S phase of interphase. In prophase, centrosomes form outside the nucleus and the chromatin in the nucleus condenses. The chromosomes align in metaphase and attach to the centrosomes via spindles. The nuclear envelope breaks down, and, in anaphase, the two half spindles shorten, drawing the chomatids toward the centrosomes and into separate halves of the cell. Nuclear membranes form around each set of chromosomes forming two nuclei in telophase as cytokinesis begins to separate the daughter cells.

Like a great artist, Nature sometimes invokes complex techniques to achieve an elegant and deceptively simple result. Watson and Crick were the first to appreciate the elegant beauty of the relationship between DNA's form and function. Because the double strands hold redundant information, the DNA can faithfully replicate its information. A cinch, yes? While a simple idea at its core, the copying of DNA and its separation into two equivalent daughter cells is complex.

One of the most complicated processes in eukaryotic cell division is encountered during metaphase. The processes of metaphase ensure that each daughter cell must receive exactly one of the two copies of each chromosome. The cells don't leave this to chance. They employ a system of ropes and pulleys to haul the chromosomes to their destinations.

A central part of this machinery is the kinetochore, which assembles on the centromere of the chromosome, connecting the DNA to the spindles. After chromosome duplication in the S phase of mitosis, each sister chromatid gains a kinetochore at its centromere.

The kinetochore connects the centromere of the chromosome to a microtubule spindle. The spindle connects to one of the two centrosome poles. As described in the first article following, research from Professor Rebecca Heald's laboratory has shed light on the mechanisms of spindle size and formation.

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The Aurora complex of the kinetochore is essential for making sure the chromosomes are aligned (or bioriented) at the center of the cell with each sister chromatid attached to a different pole. The ability of the cell to determine that all of the chromatids are set and ready for separation seems a bit mind-boggling, and, indeed, it is a complex process. The laboratories of Professors Georjana Barnes & David Drubin are working to understand how the kinetochore's Dam1 ring allows the chromatids and the spindle microtubules to maintain a connection even as the spindle shortens, and how this connection is regulated by the Aurora complex, as described in the second article below.

The third article covers Professor Eva Nogales's visualizations of the machinery of the kinetochore at a molecular level. This work analyzes the structural underpinnings for the kinetochore machinery. The Nogales lab's work has also given insights into how an aspect of the checkpoint activity could be determined by the structure of the Ndc80 subcomplex of the kinetocore.

The fundamental mechanisms cells use to faithfully divide are as complicated as they are intriguing. Through a variety of techniques, several organismal models, and a network of collaborations, MCB researchers are unraveling the mysteries of metaphase.

SIZE MATTERS: Spindle Formation in Frog Egg Extracts

Cell division involves a lot of biochemistry where the use of space is central. When forming a bipolar microtubule spindle capable of segregating chromosomes to opposite ends of the cell, the locations and sizes of all the components must be coordinated. How the spindle adjusts its size to a steady state at metaphase is of interest to Professor Rebecca Heald.

"Our lab is interested in mechanisms of morphogenesis within the cell and also scaling," says Heald. "How do structures within the cell know to be a certain size? How do they get to be that size? Is that determined by the size of the cell or are there other activities that set the size?"

Heald's laboratory is studying spindle size and scaling using extract from *Xenopus laevis* eggs. Arrested in the metaphase stage of meiosis II, the extracts contain all of the cellular components, like membranes, organelles, and enzymes, but they lack chromosomes. Added DNA, such as in the form of frog sperm nuclei, will trigger spindle formation. Adding fluorescently-labeled tubulin allows researchers to directly visualize and measure microtubule dynamics and spindle formation in real time.

"It all happens *in vitro* pretty much the way it happens *in vivo*," says Heald. This includes the sizing of the spindles. "They are so incredibly uniform in size. Their scale is not being determined by extrinsic factors like being constrained within a certain size cell so; therefore, they have to be a certain size. It's something intrinsic to the structure itself."

Like many discoveries in science, their breakthrough originated from an unexpected observation while they were looking for something else. Professor Richard Harland loaned his *Xenopus tropicalis* frogs, a closely related but smaller species than *X. laevis,* to compare the cell biology and biochemistry through their egg extracts.

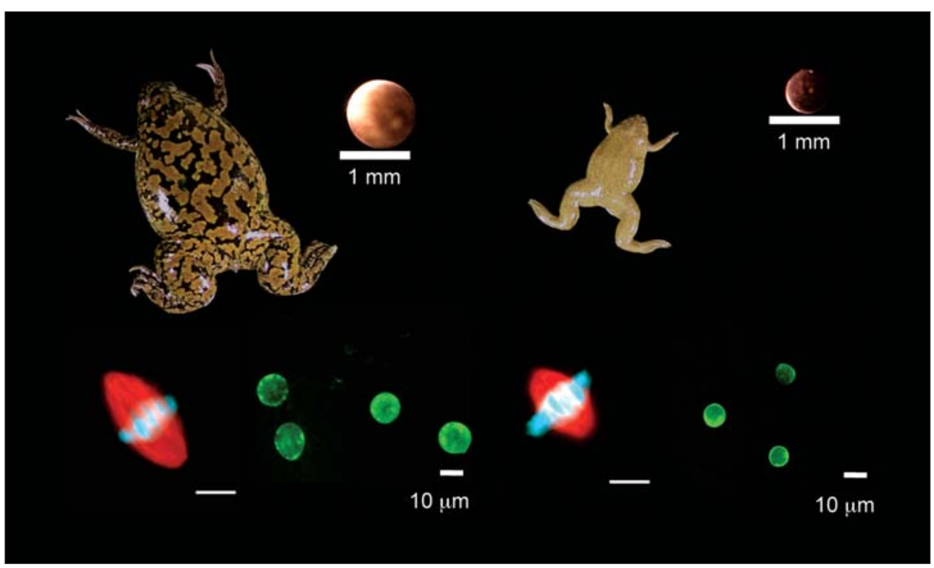
"We haven't really made headway on that project because we were just stunned by the fact that when we made these egg extracts from the *X. tropicalis*, [we noticed that] the spindles are smaller," says Heald. "And this is with the same source of chromosomes. So this told us right away that there's some intrinsic mechanism in the cytoplasm that's scaling the spindle.

Professor Rebecca Heald

It doesn't depend on the number of chromosomes or the amount of chromosomes. It doesn't depend on the size of the cell. It's some scaling activity."

Rose Loughlin, a graduate student in Heald's group, has been investigating why egg extract from *X. tropicalis* forms spindles that are much smaller than those formed in the *X. laevis* extract. When they mixed the two extracts together, the resulting spindles were an intermediate size. Loughlin has identified one of the enzymes responsible for this difference: katanin, which severs microtubules. The evidence points to a difference in regulation of katanin activity in the two frog species. Heald's lab is currently deciphering what is responsible for the regulatory difference as well as looking for other factors that might have an effect.

Not only do spindle lengths vary between species, they can also vary within a species. *X. laevis* eggs are about a millimeter in diameter when they start dividing. Within



Xenopus laevis, *shown on the left, has larger eggs and larger spindles than* Xenopus tropicalis, *shown on the right.*

four hours the individual cells are too small to see. Therefore, spindles in the earliest rounds of cell division will be much larger than those in the later rounds, as seen both *in vivo* and in the embryo extracts made by Jeremy Wilbur, a postdoctoral researcher in the Heald group. Suspecting that regulators of microtubule dynamics may also play a role in determining the different intra-species spindle sizes during development, the group is currently investigating this possibility.

Rebecca Heald's research points toward an intrinsic metric for size and scaling of some cellular components. The spindles are not a certain size because they are constrained by the size of a cell. Instead their size most likely results from the complex, dynamic processes of their formation and the many factors that control these processes.

CHECKS AND BALANCES: Yeast's Checkpoint Mechanisms

Professors Georjana Barnes and David Drubin are intrigued by cells' ability to detect when all of the chromotids are properly attached and aligned during metaphase, triggering the chromatid separation process of anaphase. At the heart of this checkpoint activity is the kinetochore, a complex of over 70 proteins that attaches the chromatid's centromere to the spindle. In a process full of unknowns, the complexity of the kinetochore is one of the biggest mysteries.

"No one understands why you need that level of complexity, and it's really daunting to figure out how these proteins are linked together," says Drubin. Barnes and Drubin's groups are using the powerful genetic tools of the yeast system to research this process. "A new technique came up called tap tagging, where you could put an affinity tag on a protein and express it in yeast and pull out that protein plus whatever it was attached to."

Barnes's student Iain Cheeseman (now an Assistant Professor at MIT) performed a tap tagging experiment on the kinetochore, finding a number of subcomplexes [Cheeseman, I. M., *et al.*, *Cell* **111**, 163-172; 2002]. One is the chromosomal passenger complex, which is responsible for the checkpoint activity that ensures that chromosomes are properly attached and bioriented before the cell enters anaphase.

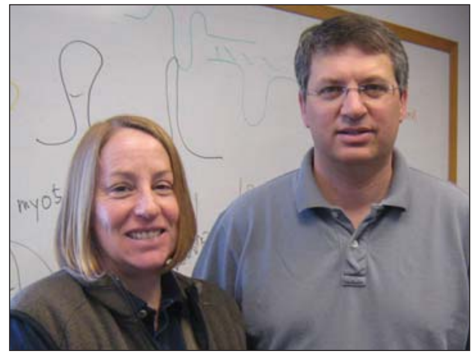
The CPC includes a kinase, called Aurora kinase, which, by phosphorylating the Dam1 complex, causes the chromosome to let go of the spindle. The CPC keeps the connections between the spindle fibers, also called microtubules, and the centromeres in a state of flux until each sister chromatid is bioriented and attached to different pole. The CPC's checkpoint activity senses that all kinetochores are attached to microtubules and that all the attachments have the proper tension. At this point, the signals that inhibit anaphase cease, and the cell continues to the next step of mitosis.

The CPC is not just interesting for its fundamental role in proper cell division. Several pharmaceutical companies are exploring its potential as a target for cancer treatments, because it is only active in dividing cells and is over-expressed in many cancer cells.

Performing a critical function in the process of mitosis, the CPC is well conserved in animals, but it hadn't yet been found in fungi. When Cheeseman did find it in yeast, it seemed to have only three of the four conserved subunits. Especially puzzling was its lack of a subunit critical to form a stable structure.

Yuko Nakajima, a current student, solved the mystery. The reason that the fourth subunit couldn't be found was that the yeast version of this protein is unexpectedly small and showed very little homology to its mammalian counterparts. The yeast protein contains only the region critical for stabilizing the structure of the complex. Furthermore, only the structure, not the sequence, is conserved [Nakajima, Y., *et al.*, *Mol. Biol. Cell* **20**, 1772-1784; 2009].

"People searched the yeast genome with the sequence of the fourth subunit of the yeast complex using the mammalian protein and never found anything by sequence



Professors Georjana Barnes and David Drubin

homology that looked like the yeast protein," says Barnes. "So even by sequence it still doesn't look like the mammalian subunit, but structurally it looks like it."

Not only does this work confirm that the CPC is conserved throughout eukaryotes, but having the fourth subunit allows reconstitution of the stable complex *in vitro*, making the system ripe for studying biorientation and the check-point activity in a cell-free system.

"Mitosis is understood better in yeast than anywhere because the tools are so good and there's an intensive effort to study it," says Drubin. "So it provides a great opportunity to fit all the pieces together."

Barnes and Drubin will continue researching the structure, activity, and regulation of the yeast CPC to shed light in the black box of one of eukaryotic life's most fundamental and complex processes. In addition to biochemical and genetic experiments, they are collaborating with Eva Nogales's laboratory to find the structure of the CPC bound to microtubules. Because of the high conservation among eukaryotic CPCs, findings gleaned through the yeast system will likely be applicable to the human system.

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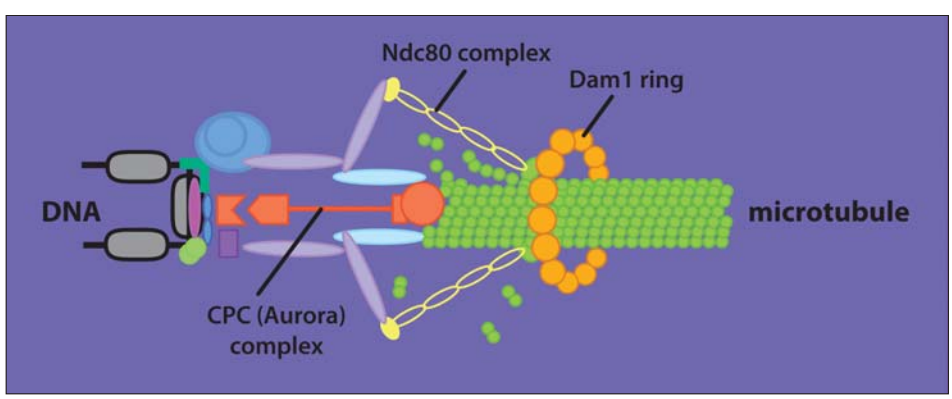

A cartoon of the yeast kinetochore based on a diagram made by S. Westermann.

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FITTING THE PIECES: A Structural Perspective on Kinetochore Subcomplexes

While discerning the stages of cell division at the cellular level is critical, the mysteries of how mitosis works must ultimately be solved at the molecular level. And, often, nothing is so satisfying as actually seeing the molecules at work.

Professor Eva Nogales's laboratory visualizes the molecules involved in yeast metaphase using cryo-electron microscopy. Using this technique, macromolecular complexes can be visualized in a closer to native state than in some other structural techniques. In collaboration with other MCB researchers, the Nogales lab is providing visuals that illuminate the fundamental processes of metaphase.

The spindle microtubules connect to the kinetochore perpendicularly, and this connection must stay intact while the microtubule grows or shrinks. If the kinetochore was binding very tightly on the microtubule surface, as microtubules in the spindle shorten by depolymerization at that kinetochore-engaged end, contact would be lost and the kinetochore would fall off the spindle. Instead of this tight, fixed mode of binding, a component of the kinetochore called the Dam1 complex assembles into a ring that wraps around the spindle microtubule, like a washer on a screw, with multiple weak connections that can quickly reorganize. Thus, the Dam1 ring can diffuse along the microtubule and can move with the shortening microtubule end while maintaining a robust connection.

About sixteen copies of the ten-protein Dam1 complex are assembled into a ring around each spindle microtubule at metaphase. As the spindle microtubules get smaller in anaphase by splaying out their protofilaments, they force the Dam1 ring closer to the spindle poles and pull the chromatides with it. Nogales's cryo-EM work on the Dam1 ring gave a picture at about 30Å resolution of both the monomers and of the complex assembled around the microtubule [Wang, H.-W., *et al.*, *Nat. Struct. Mol. Biol.* **14**, 894-903; 2008]. They found that contact with the microtubules is likely to cause a conformational change in the Dam1 subunits that triggers ring assembly.

When sites on the Dam1 C-terminus are phosphorylated by the Aurora B kinase, the Dam1 ring is likely to disassemble. This is part of the chromosomal passenger complex's checkpoint activity. The Aurora B kinase activity keeps the attachments between the spindle and the chromatids in flux until all chromatids are properly connected and aligned.

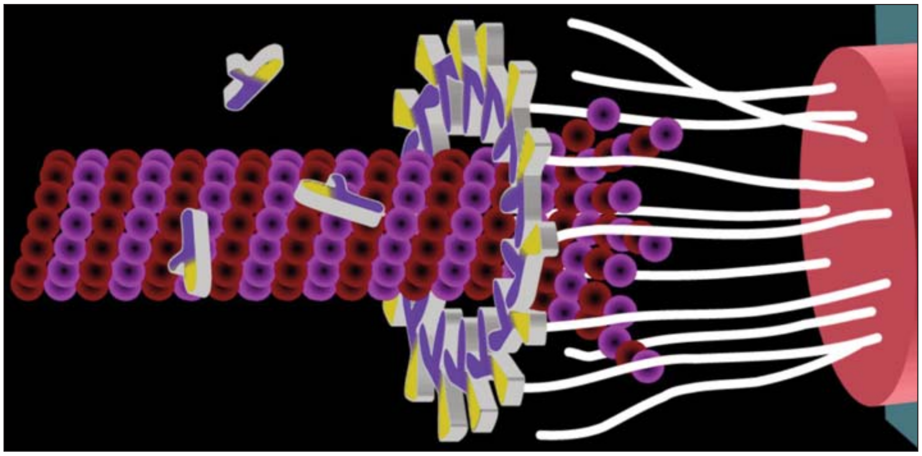
While the Dam1 ring makes multiple weak contacts with flexible regions in the microtubule surface due to its special geometry, another highly conserved component of the yeast kinetochore, Ndc80, is expected to bind very differently. The Ndc80 complex is composed of four different proteins and is shaped somewhat like a barbell, with a long, thin region flanked by globular domains. One globular end contacts the microtubule and the other binds the kinetochore.

Professor Eva Nogales
photo credit: Paul Fetters for *HHMI*

The EM studies from the Nogales lab revealed a kink in the long region of the Ndc80 complex [Wang, H.-W., *et al.*, *J. Mol. Biol.* **383**, 721-726; 2007]. The kink maps to a sequence break in a predominantly coiled-coil structure. In the micrographs, the angle of this "elbow" varied from completely extended to bent at about 120°. This bending capability could enable the free end of kinetochore-bound Ndc80 to find and bind to a microtubule.

The structure's inherent flexibility may also contribute to the checkpoint mechanism that makes sure all of the chromatids are properly attached to microtubules in metaphase. When the sister chromatids are attached to opposite spindle poles, tension is exerted on the kinetochore-microtubule connection. Under this condition, the Ndc80 complex would exist in its extended form. Nogales's group hypothesizes that factors binding to either the bent or extended form could signal whether the chromatids are properly aligned and connected to spindle poles. When these signals give the go-ahead, the cell can start anaphase.

Nogales's cryo-EM work not only gives a visual context to the complex processes of mitosis, it also suggests how critical cellular behaviors emerge from interactions at the molecular level. The results confirm that Nature often employs elegant solutions of form-meets-function to create complex behaviors.



This schematic of a yeast microtubule-kinetochore attachment based on cryo-EM micrographs shows a depolymerizing microtubule, a Dam1 ring, and connections of the ring with the rest of the kinetochore via fibrous structures likely corresponding to the Ndc80 complex.

FACULTY NEWS

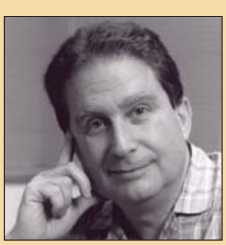
- **Diana Bautista** received the 2009 Pew Scholar award in Biomedical Sciences, awarded to "young investigators of outstanding promise in science relevant to the advancement of human health." It provides four years of support for research projects. She also received a 2009 Scholar Award from the McKnight Endowment Fund for Neuroscience, which provides three years of support to promising young faculty whose research could have immediate implications for treatment of disorders of learning and memory.

- **James Berger** received the David A. Shirley Award for Outstanding Scientific Achievement at the Advanced Light Source, Lawrence Berkeley National Laboratory

- **Carolyn R. Bertozzi** brought home gold this year for her work in cell surface glycosylation in relationship to disease. She was awarded the 2008 Willard Gibbs Medal of the Chicago ACS section, the 103rd Nichols Medal of the New York ACS section, and the 2009 Albert Hofmann Medal from University of Zurich. In addition, she has been honored with the Harrison Howe Award of the Rochester ACS section.

- **Steven Brenner, Jennifer Doudna, Susan Marqusee, Barbara Meyer,** and **Nipam Patel** were elected 2008 AAAS Fellows.

- **Mike Botchan** was elected as a fellow of the American Academy of Microbiology.



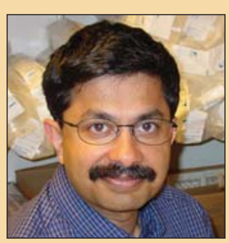
- **Richard Calendar** will be retiring on July 1. He will be a Professor in the Graduate School and still head a lab studying phages, especially those of pathogenic bacteria. He will also teach MCB110L in the fall, working with staff to raise its ATPase turnover number.

- **Lu Chen** was promoted to Associate Professor with tenure, effective July 1, 2008.

- **Steven Chu** was confirmed by Senate as U.S. Secretary of Energy. Chu was also featured in the June 25th issue of Rolling Stone magazine.

- **David Drubin** has been selected as the Editor-in-Chief of the journal *Molecular Biology of the Cell.*

- **Iswar Hariharan** to become CDB Division Head effective July 1, 2009.

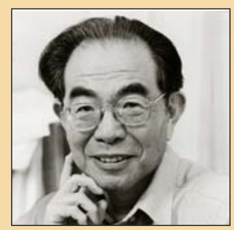


- Discover Magazine named **Nicole King** was named one of the "Best Brains in Science."

- **John Kuriyan** received the 2008 ASBMB-Merck Award.

- **Andreas Martin** was named one of the 2009 Searle Scholars, chosen for innovative research and future promise. The award delivers $100 thousand a year for three years.

- **Hiroshi Nikaido** was recently elected to the National Academy of Sciences. He will officially retire at the end of June but aims to continue teaching courses and directing his research lab.



- A conference on cell biophysics was held at UC Berkeley from May 29-31, 2009, to honor the pioneering research of **George Oster**. Called From Motors to Morphogenesis: Oster-Inspired Research, the conference included local and international speakers.

- Named Netherlands Biochemistry and Molecular Biology Society Speaker of the Year, **Randy Schekman** gave lectures about his protein sorting research at three Dutch universities in May.

- **Robert Tjian** received a CIRM stem cell research grant.

- The Queen's Birthday Honours List issued by the Governor-General of Australia appointed **Gerald Westheimer** as a member of the Order of Australia of "for service to vision science as a researcher, through optometric education and as a mentor." Established in 1975, the Order of Australia recognizes outstanding achievement and service.

- **Ahmet Yildiz** has been awarded a Sloan Fellowship, which is given to young faculty who show outstanding promise, and an Ellison Medical Foundation Award for New Scholars in Aging, which awards $400 thousand over 4 years.

2009 AWARDS

GRADUATE AWARDS

OUTSTANDING GRADUATE STUDENT INSTRUCTORS

The following GSIs for MCB courses were among those honored by the Graduate Division in a May 6 event at the Alumni House for outstanding teaching.

- **Asya Agulnik** [(Public Health)]
- **Nick Arpaia** [Schlissel lab]
- **Aaron Cheng** [Drubin lab]
- **Regina Choy** [Schekman lab]
- **Clara Coffman** [Riley lab (Public Health)]
- **Devin Coleman-Derr** [Dan Zilberman lab (Plant Biology)]
- **Emily Cooper** [Banks lab (Neuroscience)]
- **Emily Crane** [Meyer lab]
- **Abigail Gerhold** [Hariharan lab]
- **Rachel Haurwitz** [Doudna lab]
- **Hector Huang** [Groves lab]
- **Laura Lombardi** [Rine lab]
- **Allison Mackey** [Bunge lab (Neuroscience)]
- **Jesse Patterson** [Thorner lab]
- **Lars Plate** [Marletta lab]
- **Bryan Schmidt** [Berger lab]
- **Sarah Stern-Nezer** [Ahern lab (Public Health)]
- **Patrick Visperas** [Kuriyan lab]
- **Rachel Zunder** [Rine lab]

Pictured from left to right:
Regina Choy, Aaron Cheng, Jesse Patterson, Laura Lombardi, Nick Arpaia, Rachel Haurwitz, Bryan Schmidt, Patrick Visperas, and Lars Plate.

Photo credit: Eileen Bell

UNDERGRADUATE AWARDS

DEPARTMENTAL AWARDS

Departmental Citation
- **Chris Hsiung** [Jeremy Thorner lab]

Outstanding Scholar
- **Xiying Fan** [George Brooks lab (Integrative Biology)]

DIVISION OF BIOCHEMISTRY & MOLECULAR BIOLOGY

Grace Fimognari Memorial Prize
- **Wing Shing Vincent Yip** [Susan Marqusee lab]

Kazuo Gerald Yanaba & Ting Jung Memorial Prize
- **Anna Podgornaia** [Steven Brenner lab]

Jesse Rabinowitz Memorial Prize (for outstanding junior in BMB)
- **Aron Kamajaya** [Kathleen Ryan lab (Plant & Microbial Biology)]

DIVISION OF GENETICS & DEVELOPMENT

Edward Blount Award
- **Devin Noblin** [Ellen Simms lab (Integrative Biology)]
- **Kathleen Pitz**

Spencer W. Brown Award
- **Lauren Barclay** [John Kuriyan lab]
- **Genevieve Gould** [Michael Eisen lab]
- **Alisa Moskaleva** [Tom Alber lab]
- **Kelly Nissen** [Damon Lisch lab (Plant & Microbial Biology)]
- **Jane O** [Jasper Rine lab]

DIVISION OF IMMUNOLOGY

Outstanding Immunologist
- **Kelly Mahuron** [Gary Firestone lab]

Distinction in Academic Achievement
- **Sepehr Keyhani** [Arash Komeili lab]

Excellence in Research
- **Jernej Godec** [Greg Barton lab]

DIVISIONS OF CELL & DEVELOPMENT BIOLOGY

Paola S. Timiras Memorial Prize
- **Philip Choi** [Ron Zuckerman lab (LBNL)]

I. L. Chaikoff Memorial Awards
- **Philip Choi** [Ron Zuckerman lab (LBNL)]
- **Brandon Endo** [Craig Moritz lab (Integrative Biology)]
- **Bianca Lee** [John Kuriyan lab]
- **James Lee** [Xiao Gong lab (School of Optometry)]
- **Viviana Ruiz Barros** [Janet King lab (Children's Hospital Oakland Research Institute)]
- **Graham Walmsley** [Patrick Brown lab (Stanford)]
- **Wiggin Wu** [Christine Wildsoet lab (School of Optometry)]

DIVISIONS OF NEUROSCIENCE

Jeffery A. Winer Memorial Prize
- **Yohan Song** [Jeffery Winer lab]

I.L. Chaikoff Memorial Award
- **Justine Hum** [Ronald Krauss lab (Children's Hospital Oakland Research Institute)]
- **Sarah Kaufman** [Richard Harland lab]
- **Alicia Nugent** [Richard Kramer lab]
- **Jasdeep Sabharwal** [Adam Gazzaley lab (UCSF)]
- **Yohan Song** [Jeffery Winer lab]

CLASS NOTES

■ **David Tom Cooke** [BA 1994] is an Assistant Professor in the Division of Cardiothoracic Surgery at the UC Davis Medical Center. He was the Administrative Chief Resident in Cardiothoracic Surgery at the University of Michigan Medical Center until 2008. He completed his general surgery residency in 2006 at the Massachusetts General Hospital. In 2004, he completed a research fellowship in experimental lung transplantation at Stanford's Department of Cardiothoracic Surgery. He received his MD from Harvard Medical School in 1999 after graduating from MCB (immunology) and completing a thesis with Marian Koshland. He specializes in non-cardiac general thoracic surgery, thoracic oncology, surgical treatment of esophageal disease, and video assisted thoracic surgery (VATS). His clinical studies include oncologic trials, surgical outcomes research, translational research, and surgical education. He is interested in forming research collaborations. "Go Bears!!" [Davidt.cooke@ucdmc.ucdavis.edu]

■ **Victor Da Costa** [BA 2001] finished medical school at UC Irvine and is in his second year of otolaryngology residency at Duke University. He is engaged to the Elizabeth Prada, a pediatric dentist at UNC. [victor.dacosta@duke.edu]

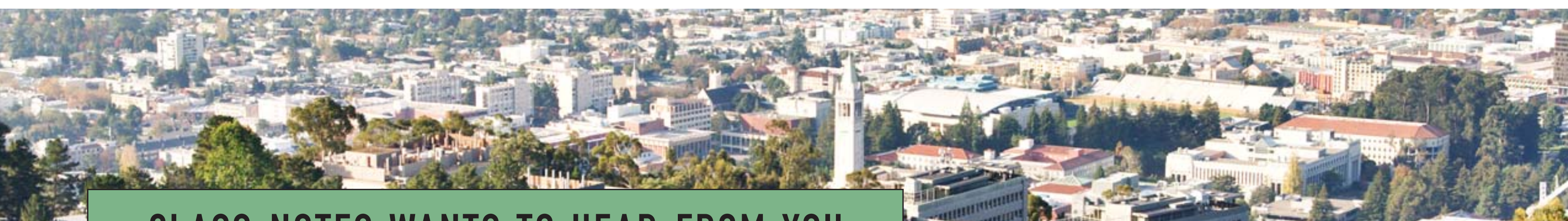
■ **Yu-Ming Chang** [BA 1999] received his M.D.Ph.D. degree from UC Davis School of Medicine and is now an Internal Medicine intern at Santa Clara Valley Medical Center. He is engaged to Karen Chiu [BA 2001].

■ **Karen Chiu** [BA 2001] received her M.D. from UC Davis School of Medicine and completed a pediatric residency at Children's Hospital and Research Center Oakland. She is now a primary care pediatrician at Kaiser in Santa Clara, and will marry Yu-Ming Chang [BA 1999] on March 21, 2010.

■ **Andrew Holmes** [BA 2004] graduated from UC Hastings Law School magma cum laude in 2008. He married Annie [Business School '05]. He is an associate with the Mayer-Brown law firm in Menlo Park doing intellectual property litigation.

■ **Yen Hsu** [BA 2000] received a PhD in Immunology from the University of Texas Graduate School of Biomedical Sciences in August 2008. He returned to the 3rd year of medical school training at University of Texas Medical School at Houston and is expecting to finish the MD/PhD program in May 2010. [Yen-Michael.S.Hsu@uth.tmc.edu]

■ **Justin Liu M.D.** [BA 1995] is the newly appointed Medical Director for the Department of Physical Medicine & Rehabilitation at John Muir Medical Center in Walnut Creek, CA. He is also continuing his development of Wii-Hab Medicine. (www.WiiHabMedicine.com) [JustinLiuMD@stanfordmedalumni.org]



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

NAME

MCB DEGREE YEAR

E-MAIL

May we print your e-mail address? ❍ Yes ❍ No

Tell us what you have been up to:

Clip and mail form to:
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MCB NEWSLETTER
Department of Molecular and Cell Biology
142 LSA #3200
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Berkeley, CA 94720-3200

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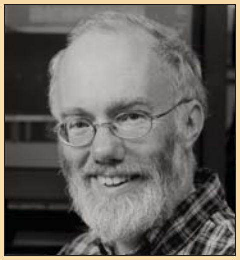
OUTSIDE THE BOX: Uncommon Knowledge From an Uncommonly Studied Organism

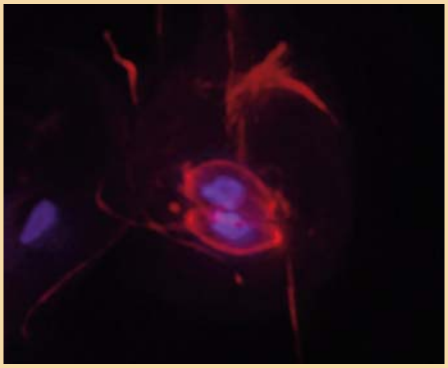


Professor Zac Cande

Professor Zac Cande's studies of cell division in a variety of organisms give insight into the evolutionary paths of eukaryotic cell division. *Giardia*, a single celled organism best known for the unpleasant and sometimes deadly diarrheal illness that results when it ends up in the human gut, is an early twig from the eukaryotic branch. With two nuclei and no mitochondria, *Giardia* doesn't quite fit into a typical model of a eukaryotic cell. Because *Giardia* diverged so long ago, similarities between it and other species like yeast and frogs give a sense of what cell division was like for early eukaryotes.

"*Giardia* is an interesting organism to study because of its deep phylogenic divergence from other organisms," says Cande. "If *Giardia* and mammalian cells do the same thing but yeast does not, it means that the process is highly conserved evolutionarily but has been lost in yeast."

Giardia and mammalian cells use similar mechanisms for chromosome segregation. Cande's studies found many of the same molecular motors at the kinetochores. One difference is the organization of spindles during metaphase. In mammalian cells, the nuclear envelope breaks down as spindles form. In *Giardia*, the spindles form around the nucleus and thread through small holes in the nuclear envelope to attach to the chromosomes. Cande's lab has found a connection between mitotic microtubular and flagellar formation in *Giardia* and hypothesizes that the depolymerization enzyme kinesin-13 plays a ancient and conserved function in these structures [Dawson, S.C., *et. al. Eukaryotic Cell* **6**, 2354-2364; 2007].



Giardia *in mitosis. The cell in the center is in the process of mitosis. The microtubules are stained red and the DNA appears blue. The two nuclei have formed spindles around the nuclear envelopes. The chromosomes, which don't appear to line up along a metaphase plate, will be pulled to the left and right while the cell divides along the vertical axis.*

In studying organisms from different branches on the phylogenic tree, Cande endeavors to not only aid understanding of evolutionary history but also to uncover unusual and fascinating mechanisms in Nature.

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