

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

### DO HOLIDAY BUBBLES TICKLE

#### YOUR TONGUE AS WELL AS YOUR NOSE?

In elementary school we learned about the four basic tastes: sweet, salty, sour, and bitter. Then came a fifth, umami, the glutamate "meaty" taste. Well, be forewarned: there may be another, and this one may explain why we prefer bubbles in our beer and soda.



Walter Fischler, a graduate student in MCB Associate Professor Kristin Scott's laboratory, had finished his qualifying exam and was ready to dive into his thesis project. Interested in sense perception, he was looking for taste cells in fruit flies beyond the two that the lab had previously found.

"We had identified sugar and bitter sensing cells in the fly, and we were looking for new taste cells that recognize different taste compounds," says Scott. "It was actually a long and hard struggle to figure out what these cells responded to, because they didn't respond to any of the classic taste modalities. And we sort of naively assumed that there would be a salt-sensing cell or a sour-sensing cell."

After a long search in which they tried the usual suspects (sweet and salty) and some unusual suspects (just about anything on the shelf), Fischler got creative and found something truly unexpected.

"There was an element of serendipity," says Fischler. "Once I exhausted all of the things in the chemical room, I decided to try the fridge." And in the lab refrigerator was a bottle of Sam Adams, left over from Fischler's qualifying exam celebration.

A dab of the beer on the fly's long, tubular proboscis gave him what he was looking for. It wasn't the alcohol in the beer that the flies wanted; it was the carbonation.

## **EXPLORE PERCEPTION**



**NEW PROFS** 

A pair of dye-filled neurons in rodent somatosensory cortex, the brain's main touch center.

#### **DAN FELDMAN**

The human brain has the remarkable ability to rewire quickly in response to new information. You may have noticed, for instance, if a head cold has ever blocked the hearing in one ear, that the problem seems to correct itself in a couple of hours. Or when a new pair of eyeglasses makes the world swim at first, before long your crystal-clear view returns.

These are examples of your brain adapting to new situations. Noticing a



change in perceptual input, it responds with a change in perception. Every day, your neural pathways are changing, but how? And how does the brain turn stimuli into perception, anyway?

These are topics of interest for new MCB professor and Helen Wills Neuroscience Institute member Dan Feldman.

"We are very interested in two questions," says Feldman. "One is how your brain processes sensory information to give you that internal perception of things happening in the world around you. And the second thing is how your brain learns new information and responds to changes in your environment in a way that helps you process information better."

The answers to these questions aren't just fundamentally fascinating, but could be useful in finding treatments for neurological disorders such as Alzheimer's disease, mental retardation, and many learning disabilities.

Feldman uses rodents as a model system. Rat whiskers are like our fingers—

they project into the world, bumping against objects and transmitting information about the world to the brain. But unlike our fingers, whiskers occasionally fall off. When this happens, the rat brain must adapt to the lack of information received from those neurons. The neurons or the neural connections are altered to learn how to interpret this new situation.

The classic model of learning, proposed by Donald Hebb in 1949, suggests two ways neural circuits can change. A neuron that is deprived of its normal input or is giving unhelpful information can either be rewired or its output to other neurons dampened, a process called long term synaptic depression (LTD). These processes can be likened to a computer circuit board: to affect a circuit you can disconnect and move the wire or you can change the voltage on the wire.

"Those theories have had remarkable sticking power without enough data behind them to know whether they are really true," says Feldman. The persistence of Hebb's ideas is largely due to how well these



This reconstruction of two neuron cells from the rat somatosensory cortex shows the far-reaching connections with which they transmit information about whisker contacts from the thalamus using their dendrites (black and green) to other cortical layers of the brain using their axons (blue and red).

processes can explain the adaptive behavior and plasticity of the brain.

Feldman set out to test Hebb's theories. His recent research has demonstrated experimentally that rat neurons do exhibit LTD in response to trimming a whisker (*Nat. Neurosci.* **6**, 291–299; 2003 & *Journal of Neurosci.* **26**, 4155-4165; 2006). He found that the neurons corresponding to whiskers that had been trimmed showed the physiological hallmarks of LTD, including weaker synaptic responses.

Whether or not neurons are rewired is still unknown. "We've looked very hard to see whether experience disconnects synapses and so far we haven't found it—that's not to say it doesn't occur," says Feldman.

Most likely, Feldman says, LTD is just one of many processes at work to support learning and adaptation. Figuring out these processes and how they work together is a current challenge to the field.

Now that he has demonstrated that LTD is important for adaptation and learning, Feldman's next experiments will focus on the molecular level to find the chemicals involved in the neurons or synapses that mediate experience-dependent weakening of synapses. His laboratory is studying endocannabinoid receptors, which are highly expressed in many synaptic terminals and seem to have a role in decreasing synaptic function. He will also continue to study how the neural signals generated by the whiskers turn into a perception of the world.

Dan Feldman moved his laboratory to Berkeley in August after seven years at UC San Diego. He completed his undergraduate work at Brown University, his doctoral work at Stanford, and postdoctoral appointments at UCSF and the NIH.

#### MARLA FELLER

If you have stayed up late to watch television, you might have noticed a static screen of blocks of color that make up the "test pattern" many stations transmit when they are not broadcasting a program. These patterns are used to align and calibrate the signal. They insure that the output on the screen matches the input recorded by the camera. It turns out that our visual system may calibrate itself in a similar way.

Before ever being exposed to light, our eyes create their own version of test patterns that allows our brains to hone an accurate, sharp picture.



The spots of color represent six individual waves observed in a mouse retina during a minute. The direction of wave propagation is indicated by the intensity of the color, dark to light.

New MCB professor and Helen Wills Neuroscience Institute member Marla Feller studies these test patterns in her research on how vision develops.

While a nascent UC Berkeley faculty member, Feller is no stranger to the UC Berkeley community. She earned her PhD in the Berkeley physics department working in solid-state physics with Ron Shen. "I did a lot with lasers and I knew a lot about optics and light, but I didn't know anything about biology," Feller recalls.

Feller was offered a postdoctoral position at Bell Labs, where she was asked if she would apply her optics skills to study action potential propagation in an axon. "I said, 'Sure! What's an axon?'" Feller remembers. This research whetted her interest in neurobiology, and she pursued a second postdoc in a neurobiology lab. She chose to come back to Berkeley to work with Carla Shatz on retinal waves.

She continued her postdoctoral work in her own lab at the NIH. Two years later, she took her neurobiological expertise to UC San Diego, where she stayed for seven years before arriving here in August.

Feller's research uses the example of vision to investigate how the circuits in our brains assemble during development. In order to see images sharply, the neural cells that neighbor each other in the retinas of our eyes must continue to neighbor each other while they travel throughout the visual relay system, which includes the superior colliculus, a target in the brain that coordinates eye-driven reflexes, and the thalamus and the visual cortex, the pathway for our "conscious" vision.

The cells don't naturally grow in this organized manner. A newborn mouse's eyes and brain lack this coordination—cells that neighbor each other in the retina make connections that are widely dispersed in the superior colliculus and in the thalamus. Yet within a week and a half, the system has become coordinated. The mouse's brain has pruned and tended the connections between neurons until they are in their proper orderly place. How does it do that?

It uses test patterns. Mice are born with their eyes closed and their light-sensing neural circuitry off. During this time, their retinas produce spontaneous neural waves. When a cell fires during one of these events, it causes the cells around it to fire. In order to watch the process, Feller's team mounts the retinas of mice under a microscope and uses a calcium-sensitive dye to reveal firing stations. Discovering how it works is Feller's aim.

Feller's group is using two approaches to identify the components of this test pattern alignment. They measure the correlation of firing strength and frequency between tens or hundreds of individual neuron cells using multi-electrode arrays. And they observe the visual circuit organizations of transgenic mice that lack genes necessary for wave propagation and compare those to the wildtype.

The implications for human vision are tremendous. Human fetuses undergo the same retinal wave behavior as mice in the late second or early third trimester of gestation (*Clin Perinatol.* **31**, 199-216; 2004). Feller believes, understanding this process in mice may lead to methods of re-training brains of adults who have damaged or scrambled connections. For instance, it might be possible to recreate the waves, conceivably with



The Feller Lab at Joshua Tree. Clockwise from left: Anastasia Anishchenko, Tim Dunn, Justin Elstrott, Shiloh Guerrero, Marla Feller, Aaron Blankenship, Will Barkis, Kevin Ford, Ethan Hua.

neurons and record the progression of the waves. "We can take movies of them for hours. They are never the same," she says.

These spontaneous waves must be important for visual alignment, because blocking the waves prevents proper ordering of neurons, resulting in blurry vision. The waves are somehow honing the visual circuits by making sure that the cells that lie next to each other in the retina remain neighbors all along their pathway into the brain. This alignment verification is analogous to the test pattern used at television light pulses, to help the brain re-establish its orderliness.

Feller also looks to other applications for her work. Understanding development of the visual system could lead to a better picture of how environment affects development in general. She is also investigating how the brain uses and interprets the signals sent through neurons.

When asked how it is to be back in Berkeley, Feller says, "Each time I come back it feels different, but it also feels like being home."

## Mannandana

This discovery surprised both Fischler and his mentor. It had already been determined that flies can smell  $CO_2$  and avoid it, but this new experiment showed that flies are attracted to  $CO_2$  when they taste it (*Nature* **448**, 1054-1057; 2007). So the same molecule was not only both a taste and a smell, but the fly's reaction to the molecule was opposite depending on whether it was tasted or smelled.

The difference between a smell and a taste is a bit fuzzy, but certainly has a lot to do with how and where signals are interpreted by the brain. When a fly smells  $CO_2$  through cells in its antenna, the antennal lobes in the brain issue avoidance orders. When a fly tastes  $CO_2$  through the bristles on its body or its proboscis, its subesophageal ganglion urges the fly to eat.

While it is unknown why this system evolved, Fischler and Scott believe it may be a technique to find the best food sources.

"Maybe it's a way for the fly to find the right amount of rottenness in a fruit," says Scott. "So when the fruit contains growing



Kristen Scott sorts some of her flies.



This live fly is prepared for **in vivo** functional imaging experiments. It has been immobilized in parafilm and the top of its head cut open to reveal its subesophageal ganglion, the taste center of the brain. The brain is green due to a GFP-based dye. The bright green is the bitter taste area.

micro-organisms and is a little bit rotten, that's great. Flies love it. But if it gets overly ripe and they sense too much CO<sub>2</sub>, they'll avoid it." Overly rotten fruit may not have enough nutrients left to be worth the fly's effort.

The cells that detect carbonation are very specific. In neural imaging studies, they did not respond to any of the more than 50 other compounds tested.

"So now we are trying to go further to understand the molecular mechanisms," says Fischler. "We already know the molecular receptors for the  $CO_2$  detection (as a smell). And we already know that those aren't expressed in these cells. It's exciting that there's a potential new mechanism for detecting  $CO_2$ ."

Because of the similarity between fly and mammal taste cells, the discovery of  $CO_2$  sensing cells in *Drosophila* has other researchers looking for a similar taste in humans.

"We are waiting to see whether or not the taste of carbonation will be similar between flies and man," says Scott. "From personal experience, I wouldn't be surprised. People drink carbonated water, and you don't usually choose to drink things that you can't taste."

So prepare yourselves for basic taste number six: carbonation.

## FACULTY NEWS

## **IN MEMORIAM**

Robert K. Mortimer, widely credited as the father of yeast genetics, died August 10 from complications of Alzheimer's and Parkinson's diseases. He was 79. Mortimer began championing Saccharomyces cerevisiae as a convenient model organism in the 1950s when maize and fruit flies reigned supreme. He developed many of the standard techniques for working with yeast, including methods of gene replacement and the enzyme digestion of the tough coat on yeast spores that allows sexual progeny to be separated. He also acquired a vast collection of yeast strains which he made available to anyone who asked. By the mid-1970s, Mortimer had mapped the organism's 16 chromosomes and identified numerous genetic markers, firmly establishing yeast as a pre-eminant research tool in genetics. Mortimer joined the genetics faculty at UC Berkeley in 1956 and became full professor in 1966. After he retired in 1991, he continued to study yeast, this time comparing wild strains found in the vineyards of California and Italy, where he was a visiting scholar at the University of Bologna, to better understand the organism's contribution to aroma in wine.





Daniel E. Koshland, biochemist, institution builder and outspoken champion of science, died July 23 in Walnut Creek following a stroke. He was 87. A member of the UC Berkeley faculty since 1965, Koshland was the original proponent of the "induced fit" model of substrate binding by enzymes. Later he went on to discover how bacteria use surface receptors and internal signalling proteins to sense and respond to environmental cues as well as to create a rudementary form of memory. In the mid-1980s, Koshland spearheaded a massive reorganization of the biological sciences at Berkeley, merging 11 departments into three—of which MCB was one—that better matched the convergence of many research areas on the underlying interactions of genes and proteins. The result catapulted Berkeley to a leadership position in the biological sciences. Koshland's role as scientific statesman grew out of his editorship of Science, the once stodgy journal he helmed from 1985 to 1995. Under his guidance, and often as a result of the timely and forceful opinions he penned, the journal became an influential voice in public policy. An heir to the Levi Strauss fortune, Koshland gave generously to the campus. He also endowed the Marian Koshland Science Museum in Washington, DC, in memory of his first wife, also an MCB professor, who died in 1997. A campuswide memorial celebrating Koshland's life and contributions was held September 16 in Zellerbach Hall.

- Gregory Barton was one of 17 UC Berkeley faculty to receive an award from the Hellman Family Faculty Fund, which supports the research of promising assistant professors who show capacity for great distinction in their research. Barton studies the roll of Toll-like receptors in immunity and auto-immune disease.
- For continuing to push back the frontier of cell surface glycobiology, Carolyn Bertozzi this fall added to her accolades the Ernst Schering Prize, given by the Ernst Schering Research Foundation for outstanding basic research. She received the award, worth 50,000 euros, at a September ceremony in Berlin.
- Rich Calendar will be off to Turkey in August 2008 to co-chair a symposium entitled "Phage Evolution and Genomics" at the XIVth International Congress of Virology in Istanbul.
- Jennifer Doudna and Carolyn Bertozzi will share one half of a \$1.8 million, four-year grant from Gilead Sciences, Inc., a drug company in Foster City. The funds are intended to further Doudna's pursuit of drug treatments for hepatitis C and Bertozzi's research on the bacterium that causes tuberculosis. The remaining half of the Gilead grant will benefit the Berkeley Health Sciences Initiative.
- Michael Rape was one of 29 recipients of the National Institutes of Health New Innovator award. The five-year grant of \$1.5 million will help fund Rape's work on ubiquitin ligases, enzymes whose role in regulating cell division makes them potential targets for cancer drugs. This is the first year the award has been given.
- Randy Schekman and Judith Klinman were elected AAAS fellows this year. Schekman also received the van Deenen Medal of the Institute of Biomembranes at Utrecht University in The Netherlands.
- Qing Zhong picked up a New Scholar Award from the Ellison Medical Foundation for his work on the role of autophagy in aging (see Spring 2007 *Transcript*, p. 3).

## <u>2006-2007 GRADUATES</u>

#### **FALL 2006**

- Daniel R. Ballon (Thorner) DEP Domains; functional characterization and target identification in the yeast Saccharomyces cerevisiae.
- Benjamin P. Berman (Rubin) Gene expression diversity and *cis*-regulatory sequence models in the transcriptional network of *Drosophila* embryogenesis
- Ken H. Cadwell (Coscoy) Characterization of a novel form of ubiquitination by the viral E3 ligase MIR1
- Jason F. Cellitti (Marqusee) The role of intermediates and subdomains in the folding and unfolding of T4 lysozyme
- Cynthia D. Duggan (Ngai) Molecular determinants of olfactory placode development and formation of the olfactory topographic map
- Daniel S. Evans (Cline) The control of oogenesis and female sexual behavior by somatic gene targets of sex-lethal
- Foster C. Gonsalves (Weisblat) Signaling transcription and transcript stability during early embryonic development of the leech *Helobdella robusta*
- Gianna E. Hammer (Shastri) Antigen processing in the endoplasmic reticulum for MHC class 1 molecules
- Andro R. Hsu (Handel) Structure and function of the chemokine CTACK/CCL27:CCR10 signaling and glycosaminoglycan-induced aggregation
- Tereza Kolesnikov (Beckendorf) Invagination and migration of salivary glands in Drosophila melanogaster
- Patrick E. McDonel (Meyer) Recruitment of the C. elegans dosage compensation complex to the X chromosome
- Catherine M. O'Connor (Collins)
  Hierarchical assembly of the Tetrahymena telomerase holoenzyme
- Kira E. O'Day (Patel) Notch signaling and segmentation in Parhyale hawaiensis
- Daniel D. Roche (Harland) Regulation of premigratory cell populations in Xenopus embryogenesis
- Jonathan A. Scolnick (Ngai) Olfactory development: molecular biology of glomerulus formation

- Gareth G. Spor (Werblin) Amacrine cell inhibition refines the spatio-temporal filtering properties of ganglion cells
- Matthew D. Sweeney (Bertozzi) Chemokine-glycosaminoglycan interactions: binding oligomerization and insights into anti-inflammatory drug design
- Pamela Jacobs Vanderzalm (Garriga) The role of suppressors of unc-34/ena in C. elegans nervous system development
- Brian T. Weinert (Rio) Repair of P element-induced DNA double-strand breaks

#### SPRING 2007

- Rupesh H. Amin (Schlissel) Regulation of V(D)J recombinase expression and the role of germline transcription in recombinase targeting during mouse B-cell development
- Andrew J. Antczak (Berger) Biochemical and biophysical characterization of the histone chaperone protein Asf1
- Joshua E. Babiarz (Rine) An *in vitro* examination of silencing in *Saccharomyces cerevisiae*.
- Brian L. Carlson (Bertozzi) Investigating mycobacterial sulfatases.
- Andrew E. Douglas (Handel) Viral modulation of the immune system
- Kim L. Failor (Firestone) Glucocorticoid induction of apical junctional complex formation through regulation of cell signaling components in mammary epithelial cells
- **Tanya F. Freedman** (Kuriyan) Allostery in the Ras nucleotide exchange factors
- Erin M. Green (Weis) The dynamic nucleus: chromatin assembly and the control of gene expression in Saccharomyces cerevisiae
- Cyrus Harmon (Rubin) Spatial patterns of gene expression in *Drosophila* imaginal discs
- Katherine E. Harris (Beckendorf) Guidance and migration of embryonic salivary glands in *Drosophila melanogaster*
- Chris R. Kaffer (Schlissel) Analysis of overlapping transcripts in the rag locus: implications for mammalian gene regulation

- Suzanne R. Lee (Collins) Small non-coding RNAs and their biogenesis in *Tetrahymena* thermophila
- Han Lu (Bilder) Endocytic regulation of epithelial polarity proliferation control and signaling in *Drosophila melanogaster*
- Shelley E. Mettler (Forte) Modulatory role of phosphoinositide 3 kinase in gastric acid secretion
- Katherine E. Munckton (Kramer) Design and use of a light-gated potassium channel
- Lindsay G. (Garrenton) Odcikin (Thorner) Spatial and temporal regulation of the archetypal MAPK scaffold protein Ste5 in the budding yeast Saccharomyces cerevisiae
- Paul J. Pease (Bustamante) Singlemolecule studies of DNA translocation by a molecular motor
- Jamy C. Peng (Karpen) Local chromatin structure in heterochromatin regulates repeated DNA stability, nucleolus structure, and genome integrity
- Sara M. Peyrot (Harland) Dorsal midline patterning by notch and SHH signaling
- Carolyn M. Phillips (Dernburg) The role of pairing center during meiosis in C. elegans
- Michelle M. Pirruccello (Kuriyan) Conformational dynamics and activation of the p21-activated kinase
- Siraprapha Sanchatjate (Schekman) The roles of Chssp and Chsbp in anterograde transport of chitin synthase 3 (Chs3p) from the trans-Golgi network to the plasma membrane in budding yeast.
- Anosha D. Siripala (Welch) Regulation of Arp2/3 complex activation by nucleation promoting factors
- Andrea W. Tu (Luo) Regulation of the TGF-beta signaling pathway through the acetylation of Smad proteins
- Shellie R. Weisfield (Berger) Master's
- Peter J. Woodruff (Bertozzi) Trehalose metabolism in Mycobacterium smegmatis
- Kevin J. Wright (Tjian) In vivo role of TAF4 in TFIID structural integrity and co-activator function
- Bryan J. Zeitler (Weis) The role of nuclear pore complex architecture in nucleocytoplasmic transport and nuclear envelope structure
- Jennifer E. Zeitler (Bilder) Investigating the roles of Scribble and Discs-Large in epithelial polarity in *Drosophila* melanogaster

## CLASS NOTES

- Laura Christie (MA 1993) earned her MD from Oregon Health & Science University in Portland in 2001. She returned to the San Francisco Bay Area for her pediatric residency at Children's Hospital Oakland and stayed for a fellowship in pediatric infectious disease, which involved research at the California Encephalitis Project of the California Department of Health Services. She joined the pediatric faculty of Kaiser Permanente at the Oakland Medical Center in summer 2007. She also serves as a pediatric forensic examiner for Children's Hospital Oakland.
- Sean Donrad (BA 1999) went to Golden Gate School of Law, and is currently a patent and general solo attorney. Sean was born in Iran and grew up in Sweden where he attended medical school for a couple of years before coming to Cal. He says he loves being an attorney and offers a discount to Cal students who need legal advice. (counselhelp@gmail.com)

- Sergio Hernandez (BA 2000) received an MD from the University at Buffalo School of Medicine in 2006. He was married in January of that year and continues to reside in Buffalo where he is a resident in psychiatry. (hernandezsergio@gmail.com)
- Brian Jonas (BA 1999) completed the MD/PhD program at the UC Davis School of Medicine in June 2007. He began a residency in internal medicine at Stanford University in June and plans to continue his training as a hematology/oncology fellow once residency is finished. (bajonas@gmail.com)
- Aras N. Mattis (BA 1998) earned his MD/PhD in biochemistry from the University of Illinois at Urbana-Champaign. He is currently a resident in the Department of Pathology at UC San Francisco. (aras.mattis@gmail.com)
- Panya Prachachalerm (BA 1998) moved to Manhattan in March 2005, where, after eight months, he landed a job as a portfolio administrator with the real estate finance company CharterMac. He survived a layoff and accepted a transfer offer to Irving, Texas,

outside of Dallas. Panya is currently an asset management analyst handling a small portfolio of government sponsored multi-family loans. "Life is good in Dallas," says Panya, "but it could be betta" if you e-mail him at pangya88@yahoo.com.

- Nishant Prasad (BA 2004) is a third-year medical student at The Ohio State University College of Medicine. (nprasad@cal.berkeley.edu)
- Jay Tung (BA 1984) was appointed Vice President of Drug Discovery for the Myelin Repair Foundation, a non-profit organization that seeks to accelerate the development of drug treatments for multiple sclerosis.

Correction: **Paolo Gabriel's** name was inadvertently omitted from the list of undergraduate award recipients in the Spring 2006 issue of the *Transcript*. Paolo, who worked in Eva Nogales' lab for two years, was the recipient of the Jesse Rabinowitz Memorial Prize for 2006-2007. We regret the error.

#### **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

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- → go to mcb.berkeley.edu/alumni/ survey.html or
- → Send e-mail to tscript@berkeley.edu

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## A MOTOR THAT

### **NEEDS NO GAS**

#### TOP:

The Dam1 kinetochore ring (modeled in yellow and purple) is made of 16 copies of a complex, itself comprised of 10 proteins. The ring slides along microtubules (modeled in pink and red) and works within the kinetochore to help separate the two copies of DNA during mitosis. The electrostatic interactions with the 13-fold symmetric microtubule, allow the ring to slide. The Dam1 ring could be seen as a novel type of molecular motor that does not use energy of its own, instead it is pushed along by mechanical forces when the protofilaments of the microtubule break apart. The background of this image is a fluorescence image of yeast mitotic spindles (DNA-blue, microtubules-red). This work results from a collaboration between MCB professors Eva Nogales, Georjana Barnes, and David Drubin.





# MCB Transcript

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

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An electron micrograph showing Dam1 ring complexes around microtubules.

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