MCB Transcript

Spring 2004 • Vol. 7, No. 1

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

MCB Research Keeps on Humming

Previous newsletters have featured major developments in the department, such as the establishment of the Center for Integrative Genomics (Spring, 2003) and the Helen Wills Neuroscience Institute (Spring, 2001). Lest we forget why MCB consistently attracts the resources needed to grow in this way, it is time for a reminder of the important contributions to biological knowledge that flow steadily from MCB laboratories. A Medline search reveals that in the first four months of 2004, MCB faculty published 82 papers, including 17 reviews and commentaries. Here we provide a quick survey of eight fresh MCB research articles, chosen both for general interest and diversity. Only space prevented the inclusion of more.

Eat your vegetables

Cabbage, collards, broccoli, kale and other *Brassica* vegetables produce indole compounds that inhibit the growth of human breast cancer cells. Understanding how these natural molecules exert this effect is likely to lead to new anti-cancer drugs, and Gary Firestone's group, in collaboration with Leonard Bjeldanes' group in Nutritional Sciences and Toxicology, has been hard at work on the process for several years. Now Urmi Chatterji, a postdoc in the Firestone lab, and colleagues have worked out a key step in the process. Microarray analysis showed that the compound, indole-3-carbinol (I3C), increases expression of the interferon gamma receptor 1 in human breast

cancer cells. As part of this process, I3C also enhances the interferon receptor mediated response. Interferons damp down the cellular mechanisms that lead to cell division. This mechanism and the growth inhibitory effects of I3C suggest that natural indoles can potentially be used in new therapeutic strategies for the control of reproductive cancers.

— Chatterji, U. et al. *Carcinogenesis,* published online February 26, 2004, DOI: 10.1093/carcin/bgh121.

Noise reduction

Gene expression is noisy. Apparently random fluctuations in this complex processes—brought about by changes in the amount or state of cellular factors and external signals—influence everything from the color of a calico cat's fur to the loss of synchrony in a population of dividing cells. But noise in gene expression is more than a bit of static to be ignored. According to a new paper from Michael Eisen's group, noise has affected the course of evolution.

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Department Student Wins Weintraub . . . Again

MCB just can't stop winning. The Harold M. Weintraub Graduate Student Award was established in 2000 to recognize high-quality original research by graduate students in molecular biology from around the world. Although only around 17 students are chosen, every year at least one has been from MCB.

This year's MCB recipient is Zev Bryant for his work on the physics of DNA and DNA associated enzymes. As a graduate student in Carlos Bustamante's lab at the Lawrence Berkeley National Laboratory, Bryant and his colleagues have developed new methods of manipulating individual DNA molecules in order to

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. . . MCB Research continued from page 1

Eisen's graduate student Hunter Fraser and colleagues at Stanford University came to this conclusion after looking at expression data for thousands of yeast genes. They found that expression strategies that minimize noise were much more likely to occur in essential genes and genes that participate in large protein complexes. The authors conclude that noise is a generally detrimental biological variable which has been subject to natural selection in yeast. At the same time, the energetic cost of minimizing noise means that it will tend to be low only when the consequences are significant.

— Fraser, H. B., Hirsh, A. E., Giaever, G., Kumm, J. & Eisen, M. B. *PLoS Biology* , June 2004 DOI: 10.1371/journal.pbio.0020137.

A new twist

If DNA were left to its own devices, it would be about as useful as a pile of string, full of twists, tangles and knots. Fortunately, cells carry a set of remarkable enzymes that keep DNA tidy by untwisting strands and even passing one strand through another. Previous work has revealed much about the mechanics of these topoisomerases, but one enzyme, bacterial DNA gyrase, has a unique ability that was poorly understood until now. Only gyrase can braid a simple loop of DNA into a tight negative supercoil by repeatedly breaking one strand and passing another through it. This process takes energy, just as it takes energy to squeeze a spring. Now James Berger's group has produced a crystal structure of the region of gyrase that helps add the supertwists.

Graduate students Kevin Corbett and Ryan Shultzaberger crystallized the C-terminal domain of the gyrase from *Borrelia burgdorferi*, the bacterium that causes lyme disease, and solved its structure from the X-ray diffraction pattern. Based on the sequence, they had expected to see a shape called a β-propeller. But the arrangement of the folded protein proved to be distinctly different resembling more of a pinwheel. Four of the blades carry a positive charge, apparently to aid in binding and bending DNA, which is negatively charged. Different versions of the gyrase C-terminal domain appear in several families of proteins, the authors say, suggesting that cells have subtly tuned the structure and function of the pinwheel motif over evolution to carry out specialized tasks.

— Corbett, K. D., Shultzaberger, R. K. & Berger, J. M. *Proc. Natl. Acad. Sci.* **101**, 7293-7298 (2004).

GAG reflex

Inflammation, the immune system's first response to injury, is also a factor in numerous maladies, from arthritis to heart disease, so unraveling the details of the inflammatory response has been an important goal in biomedicine. Hence the recent surge of interest in chemokines, small proteins that control the migration of white blood cells, or leukocytes, to a site of injury. Critical to the process are complex carbohydrate molecules called glycosaminoglycans (GAGs). GAGs bind to chemokines and appear to mediate chemokine interactions with their receptors on leukocytes.

How does it all work? The complexity of the question is hard to overstate, since there are 45 known human chemokines and 18 receptors. Elaine Lau, a graduate student in Tracy Handel's lab, along with colleagues here and in Europe, have now worked out how GAGs bind to a particular chemokine called MCP-1. They describe the likely role of GAGs in retaining chemokines at the site of production, and how GAGs may modulate chemokine activity.

— Lau, E. K. et al. *Journal of Biological Chemistry*, published online 18 March, 2004, DOI: 0.1074/jbc.M311224200.

A pinwheel structure helps DNA gyrase add supertwists

A frog neural tube closing normally

Reaching closure

Spina bifida, a birth defect in which the neural tube fails to close, is the most common congenital disability, affecting around one in a thousand newborns. Neural tube defects appear to result from multiple factors, none of which is well understood. One reason the causes are so hard to grapple with is the large number of genes—upwards of 50—involved in closing the neural tube by pushing up, curving and sealing layers of cells that start out as a flat sheet of tissue called the neural plate.

Research from Richard Harland's lab has now helped to simplify the picture with the discovery that a particular protein is essential for closure. In work on frogs, Undergraduate Saori Haigo and postdoc John Wallingford found that the actin binding protein Shroom, first identified in mice, somehow induces cells in the neural plate to become wedge shaped, which in turn causes the tissue to curl. Without this apical constriction, the other pushing and folding forces acting on the neural plate are incapable of closing the tube. Harland speculates that polymorphisms of

Shroom may contribute to neural tube defects in humans.

— Haigo, S. L., Hildebrand, J. D., Harland, R. M. & Wallingford, J. B. *Current Biology* **13**, 2125-2137 (2003).

Seeing the light

In a sense, the retina works backwards. Most neurons transmit signals only intermittently by releasing neurotransmitter in a burst. Cone photoreceptors in the retina, on the other hand, release neurotransmitter continuously in the dark and respond to light by releasing less. But how cones maintain this continuous flow of neurotransmitter has been something of a mystery.

Ruth Rea, a postdoc in Richard Kramer's group, found that cones have two unique features that help them do this. Whereas most neurons hold a large portion of their neurotransmitter in a reserve pool that cannot be quickly released, cones have less than 15% of neurotransmitter in reserve. Most of the neurotransmitter remains near the nerve terminal carried by an unusually large number of neurotransmitter-lade vesicles that are always in rapid motion. These features help explain the unusual capacity of photoreceptors for releasing neurotransmitter.

— Rea, R. et al. *Neuron* **41**, 755-766 (2004).

How worms do it

Sex poses all sorts of challenges for the organisms that use it. One of the biggest, on the molecular level at least, is how to deal with the different number of sex chromosomes that males and females have. In mammals, certain insects and roundworms, males have one X chromosome and females (hermaphrodites in the case of worms) have two. Unless something is done, the females will end up with a double dose of X chromosome gene products compared to males.

Various solutions exist. Female mammals handle dosage compensation by shutting down one X in every cell. Male fruit flies, in contrast, increase transcription from their one X to match the female dose of two. In the roundworm *Caenorhabditis elegans*, the organism Barbara Meyer's group studies, the hermaphrodites bring their X gene dosage in line with the males by reducing expression by half on both copies of the X.

In all three cases, the process involves a dosage compensation complex (DCC) which binds to one or both X chromosomes. In worms, the DCC binds to both, but until this year just how it bound was unknown. Now postdoc Györgyi Csankovszki and graduate student Patrick McDonel in Meyer's lab have determined that DCC binding works by spreading. Initially, the complex attaches to a number of recognition elements throughout the X and then recruits other DCCs to coat the remaining X DNA which can't bring in DCCs on its own. In a sense, this is a hybrid of the way mammals and flies do it. The mammalian X has only a single recognition site that initiates spreading, and fly X chromosomes have recently been shown to contain so many recognition sites that spreading is not obviously needed.

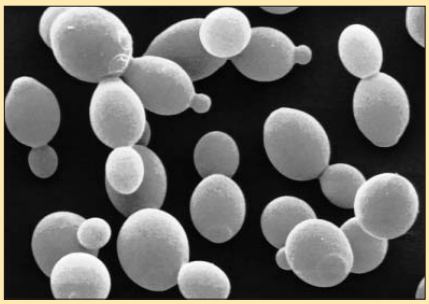
— Csankovszki, G., McDonel, P. & Meyer, B. J. *Science* **303**, 1182-1185 (2004).

Nipped in the bud

A crucial step in the cell division of budding yeast (*Saccharomyces cerevisiae*) is the formation of a collar of septin proteins at the point where the bud emerges. This septin collar keeps bud-specific proteins from diffusing into the mother cell, and its splitting into two rings just before cell division may help in the final pinching off of the daughter cell. The septin collar is also a crucial checkpoint in cell division. If it doesn't form properly, a checkpoint protein blocks entry into mitosis. Only when the collar is completely assembled is the blockage relieved.

Exactly how the collar forms has been a difficult problem, and previous results have produced conflicting models. Matthias Versele, a postdoc in Jeremy Thorner's lab, has now published an elegant series of genetic and biochemical experiments that resolve these conflicting accounts and demonstrate the crucial role of GTP binding and direct phosphorylation in assembling the collar.

— Versele, M. & Thorner, J. *The Journal of Cell Biology* **164**, 701-715 (2004).



S. cerevisiae *divide by budding*

. . . *Weintraub Award continued from page 1*

measure torque, the rotational force applied by a twisted or stretched DNA double helix.

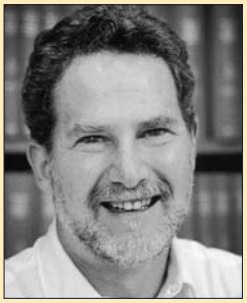
The award is in honor of molecular biologist Harold Weintraub, who died of complications from a brain tumor in 1995 at the prime of his career. He was 49. Weintraub was a founding member of the Basic Sciences Division of Seattle's Fred Hutchinson Cancer Research Center, which established and now administers the award. His numerous achievements in the study of cell differentiation earned him wide recognition as a leader in the field. He was also well known for his humility. "He delighted in others' ideas and accomplishments," wrote Harvard biologist Marc Kirschner in a memorial essay soon after Weintraub's death (*Mol. Biol. Cell* **6**, 757-758; 1995).

In 2000, the first year of the award, two MCB students were among the winners. Russell Vance who described a novel signaling pathway in the natural killer cells of the immune system as part of his graduate work in David Raulet's lab. The other winner, James (Jay) Mitchell, did his thesis work in Kathleen Collins' lab where he discovered new components of human telomerase, the enzyme that maintains chromosome ends. He also made the first connection between a telomerase defect and human disease by linking dyskeratosis congenita, which causes a rash and abnormal finger and toenails, to a failure of the enzyme complex.

And the Weintraubs kept coming. In 2001 it was Michael Miller, also in the Collins lab, for his work on telomerase in the ciliate *Tetrahymena thermophila*. The following year Åsa Engqvist-Goldstein (Drubin Lab) earned the prize for discovering a protein link between the actin cytoskeleton and endocytosis, a process by which cells selectively take up things from their environment. And last year's winner was Iain Cheeseman (Barnes Lab) for his work on chromosome segregation during cell division.

Bryant's work will make it possible to study the physical forces exerted on DNA by enzymes that copy or unravel the molecule, a project he says he is actively pursuing. As for next year's Weintraub award, watch this space.

FACULTY NEWS



▲ **Tom Alber** (BMB), **Jasper Rine** (G&D) and **Tom Cline** (G&D) were all elected Fellows of the American Academy for the Advancement of Science.

▲ **Carolyn Bertozzi** (BMB) received the 2004 Iota Sigma Pi Agnes Fay Morgan Research Award, given each year to a woman under 40 for research achievement in chemistry or biochemistry. She also joined the editorial board of *Chemistry & Biology*.

▲ **Rich Calendar** (BMB) has been made an editor of *Plasmid*. In April, he was elected to the American Academy of Microbiology.

Dernberg receives her PECASE from Raynard Kington, deputy director of the National Institutes of Health

▲ **Abby Dernburg** (CDB) received a Presidential Early Career Award for Scientists and Engineers (PECASE). The honor was bestowed at the White House on May 4. Dernburg studies meiosis, the type of cell division that produces eggs and sperm. Errors in meiosis can lead to diseases such as Down and Kleinfelter Syndromes. Dernburg is a Staff Scientist at LBNL and Assistant Professor in Residence with MCB.

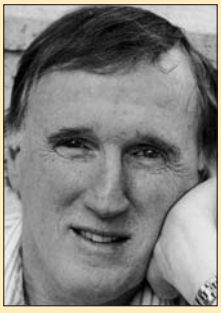
David Drubin (G&D) will become Division Head of Cell and Developmental Biology on July 1. He will also give a plenary lecture at the annual meeting of the American Society for Cell Biology in December in Washington, DC.

Alex Glazer (BMB) gave the keynote lecture on genetically engineered luminescent probes at Photonics West, a conference of the International Society for Optical Engineering, in San Jose in January.

Nicole King (G&D) was selected for the Pew Scholars Program in the Biomedical Sciences, which provides funding to assist outstanding junior faculty in establishing and developing their laboratories.

▲ **Michael Eisen** (G&D) received a 2004 Rave Award from Wired Magazine "for cracking the spine of the science cartel" by virtue of helping to found the Public Library of Science (www.plos.org). His co-recipients were PLoS co-founders Harold Varmus, President of the Memorial Sloan-Kettering Cancer Center in New York, and Patrick Brown, Professor of Biochemistry at Stanford University. PLoS seeks to promote the open access model of research publication. The San Francisco organization launched its first journal, *PLoS Biology*, in October 2003.

Jack Kirsch (BMB) gave the Nathan Kaplan Lecture at Brandeis University in March.



▲ **George Oster** (CDB) was elected to the National Academy of Sciences.

Reorganization Helps MCB Weather the Budget Storm

First, the bad news. In January, Governor Arnold Schwarzenegger proposed a 13% reduction in the UC system operating budget for 2004-2005. If the budget is approved by the legislature over the summer, it will be the second year in a row of deep cuts for the University, and the third year of budget stress. About half the shortfall will be made up by student fee hikes. The rest will come from academic departments and administrative units, which have been asked to scrutinize every dollar for possible savings and to reduce their spending by between 5 and 8.5 percent. MCB is no exception.

Now the good news. Through a combination of foresight and good luck, MCB had already begun taking steps to streamline its operations when the budget crisis hit two years ago. As a result, MCB is standing up remarkably well in the face of the largest cuts the UC system has ever endured. A completely reorganized administration combined with numerous small cuts—cheaper recruiting dinners for prospective students, for instance—have left the department's teaching and research missions intact. At least so far.

Handling the reorganization at the heart of the savings is MCB's Director of Operations and Administration Iris Shaver, who joined the department in 2002 with more than 20 year's experience in academic administration under her belt. When she arrived, each administrative unit in the department—Barker/Koshland, LSA and Stanley Hall—had its own staff. Shaver's charge was to consolidate all three into one unit serving the entire faculty from a central location in Giannini Hall.

The process took more than a year and has produced remarkable improvements in efficiency, saving the department some $540,000 this year out of its $13.4 million budget. The streamlining has generated two Excellence in Management awards, given by the Berkeley Staff Assembly. One was presented last year to Leslie Ross, who supervises extramural funds accounting, and the other was given to Shaver in May for her handling of the reorganization.

One reason is the new structure saves money is its economy of scale. Every administrative function—from hiring new employees to managing extramural funds—involves a certain amount of set-up and organizing time, no matter how many laboratories it is performed for. So it's more efficient for one staff member to handle a task for everyone than to split the job up among several staff.

Operations director Iris Shaver oversaw MCB's reorganization

Big savings also come from keeping everyone together in one office. In February, 2003, all but a few MCB administrative staff moved from their disparate locations to a newly renovated space in the basement of Giannini Hall. That instantly improved communication and eliminated redundancy. And over the longer term, it has improved staff efficiency by allowing them to cover for each other more readily. Since people's work cycles peak at different times in the semester, those who temporarily have less to do are able to help others meet looming deadlines.

Besides saving money, the streamlining has also brought everyday benefits to the faculty. In the past, routine procedures were different in different buildings. Where one administrative unit produced finance reports every month, for instance, another did them every six months. Now, a newly automated accounting system produces consistent and accurate financial statements to chairs, division heads, managers and faculty. "There was no standardization, so the faculty were never sure what to expect," Shaver says

Remarkably, in all of this streamlining no one has been laid off. This is partly because changes have been introduced gradually. As staff members retired or moved on, they were simply not replaced. Instead, their jobs were redistributed among the remaining staff. In two years, 13 staff positions out of about 80 have been eliminated from attrition alone.

The most recent departures were by academic services manager Marilyn Tiaven, who has been with the department since 1990, and Becky Osborn-Coolidge, who has run lab support for CDB, Immunology and Neurobiology since 1991. Both retired in April. Neither will be replaced, and other staff are now sharing their duties.

Of course, such redistribution cannot continue forever. Eventually people simply have too much to do. It's a situation Shaver is carefully guarding against. "We are always reviewing to make sure our staffing needs are met," she says.

Although the staff reduction has covered most of MCB's recent budget decreases, savings have been found in other areas as well. Extraneous phone lines have been

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AWARD WINNERS

Outstanding GSI Awards

This year, 14 MCB instructors received Outstanding Graduate Student Instructor Awards.

Sonia Bakkour (Sha Lab)

Alexander Ding (Health & Medical Sciences)

Natalia Caporale (Neuroscience Grad Group)

Sophie Dumont (Biophysics)

Kevin Corbett (Berger Lab)

Erin Goley (Welch Lab)

Andrew Greenstein (Alber Lab)

Shyam Sundar (Firesone Lab – Endocrinology Grad Group)

Margaret Jow (Meyer Lab)

Claire Weer (Edward Rubin Lab, LBL)

Peter Lewis (Botchan Lab)

Brian Weinert (Rio Lab)

Ansley Scott (Zusman Lab)

Tanya Weitze (Kuriyan Lab)

Undergraduate Awards

Margaret Ann-Chia Chow earned high accolades this year as the recipient of both the MCB Department Citation and the University Medal, UC Berkeley's top honor for a graduating senior. While completing a double major in economics and MCB, Chow worked in the laboratory of Jack Kirsch (BMB), where her research earned her the 2003 F.H. Carpenter Memorial Prize. In his recommendation of Chow for the Medal, Kirsch wrote that she was "an unusually remarkable student who has shown outstanding judgment and prowess both in the classroom and in her research." Chow says she wishes to pursue a law degree in order to tackle issues in bioethics and public policy.

photo: Peg Skorpinski

University Medal Finalist

- David Matthew Young

Department of Molecular and Cell Biology

Outstanding Scholar

- Jim Boonyaratanakornkit (Hughes-Fulford, VA)
- Joanna Yeh (Harland Lab)

Division of Biochemistry & Molecular Biology

Grace Fimognari Memorial Prize

- Pradeep Natarajan (Bielicki Lab, LBL)

Kazuo Gerald Yanaba & Ting Jung Memorial Prize

- Jeremy Rock (Thorner Lab)

Division of Genetics & Development

Spencer W. Brown Award

- Keyan Salari (Burchard Lab)

Division of Immunology

Outstanding Undergraduate

- Cassie Chou (Liu Lab)

Division of Cell & Developmental Biology and Neurobiology

Chaikoff Memorial Awards

- Anu Agarwal (Nandi Lab)
- Sonny Batra (Jablons Lab, UCSF)
- Jonathan Gee (Nandi Lab)
- Cathy Hau (Cate Lab)
- Charles Liao (Ames Lab)
- Youssra Marjoua (Hayes Lab)
- Tresa McGranahan (Schaffer Lab, Chemistry)
- Christopher Peabody (Coscoy Lab)
- Jennifer Su (Forte Lab)
- Elaine Thung (Timiras Lab)

CLASS NOTES WANTS TO HEAR FROM YOU

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

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Biologist Named Provost

photo: Peg Skorpinski

A biologist has assumed the second-highest post in the UC system. UC Santa Cruz Chancellor M. R. C. Greenwood took over as provost and senior vice president of academic affairs on April 1. Before becoming chancellor, Greenwood was a professor of biology at UCSC, where her research involved the genetics of obesity. UC's president, physicist Robert Dynes, said Greenwood "brings the perfect credentials to this position." At a May 11 biotechnology summit on the Berkeley campus, Greenwood called for better science education as a way to increase the competitiveness of the US economy.

eliminated, for instance. Graduate student recruitment has been more of a budget affair for the past few years, with students enjoying dinner at a faculty member's house rather than aboard a party boat on the bay, as was once the practice.

Despite MCB's resilience to the crisis, some signs of the lean times are showing through. The campus facilities budget has been cut in half, so now the floors are cleaned much less often and floor polishing has been eliminated altogether. There is no longer routine maintenance of cold rooms and autoclaves, and repairs take much longer to complete. As a result, researchers may have to walk farther to find working equipment. The department has even hired outside contractors for emergency repairs.

And of course students are feeling the squeeze on their wallets. The Governor has proposed a 10% fee increase for undergrads and a 40% increase for graduate students for the coming fall. That's on top of last year's 30% hike for both. While MCB will continue to cover graduate student fees, the increase means a bigger bite out of the department's training grants. As a result, MCB will be able to train fewer students in coming years. Already the number of students accepted for the fall has been reduced to 45 from the usual 50. The end result will be a loss of research productivity.

How severely the next round of cuts will bite remains to be seen. Last year the Dean of Biological Sciences, neurobiology professor Geoffrey Owen, was able to ease the burden on the department by committing a portion of his discretionary reserve funds and may be able to do so again.

The department has also embarked on a fundraising effort called the MCB Fund for Education and Innovation. Initially, the fund is attempting to raise $250,000 from current faculty members, an average donation of $2500. A later phase will seek contributions from graduate and undergraduate MCB alumni as well.

Shaver says the way everyone has pulled together to stave off a budget crisis has left her cautiously optimistic. "Everyone has been quite cooperative in finding savings," she says. "But if we all have more reductions, who knows where this will go."

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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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