MCB AT BERKELEY

SPRING 1998

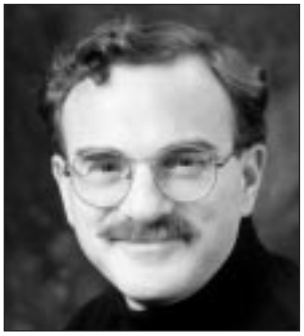
Newsletter for Members and Alumni of the Department of Molecular & Cell Biology at the University of California, Berkeley

Message from the Chair

I hope you enjoy our inaugural edition of the MCB at Berkeley Newsletter. MCB was born almost ten years ago, and we have grown to such an extent that I felt it was necessary to create a vehicle of communication connecting the Divisions of our far-flung enterprise. In addition, we have trained a generation of students and fellows who have gone on to their own careers and who may be interested in the current affairs of our Department. We intend to publish the Newsletter once a semester to provide a survey of the Department's student and faculty research and training activities that have made this Department the largest academic unit on campus. This first issue covers the news from the 1997-98 academic year.

Among the highlights of the year are the significant honors and achievements that our students and faculty have garnered (see pages 9-12). Also, MCB is expanding its interactions with other departments on campus. Two of the new MCB faculty have joint appointments (see pages 2-3), and MCB is leading the effort to establish a Center for Neuroscience which will unite faculty from various departments (see page 8).

We have had a tremendous year recruiting graduate students and new faculty. Our Graduate Admissions Committee, under the academic and administrative leadership of David Drubin and Eileen Bell, has enrolled a new class of 45 students, 10 of whom have independent fellowships (NSF, HHMI, DOD, and University). Congratulations to the faculty and student members of the Graduate Admissions Committee and the Graduate Affairs Unit staff for another outstanding year. Although it is premature to make a public announcement, we have every indication that our faculty recruitment for 1998-99 will also be a smashing success. As of this writing, it appears that we will secure 4 or 5 new faculty, each one the top choice of the relevant faculty search committees. Our success in recruiting comes, in part, from the enthusiasm we communicate to our prospective students and faculty. Thanks to all who have pitched in.



I particularly wish to acknowledge my predecessors, Co-Chairs John Gerhart and Alex Glazer and before them Gunther Stent, who led the Department through the worst days of the California recession. Each year of their term brought a shrinking state budget and a declining faculty census brought about by early retirements. In spite of these limiting financial and personnel resources, they managed to staff courses and provide administrative services for an increased undergraduate enrollment and for an expanding effort to secure extramural support. Now that the recession is over and the State and the University are being more generous with resources, I look back with respect at the ability of John, Alex, and Gunther not only to keep us afloat, but to allow us to prosper as a department.

We were all greatly saddened by the loss of our dear friend and colleague, Marian Koshland (see page 4-5). Marian represented the best of citizenship and scholarship here at Cal and in the larger academic arena. She continued to teach, supervise research, and serve as Head of the Graduate Affairs Unit even as she labored in declining health. I must recount a personal anecdote concerning my initial encounter with Marian. The Koshland's invited me to a party at their home shortly after I arrived in Berkeley in 1976. The Biochemistry Department had just returned from its annual Asilomar retreat where Dan and I had enjoyed our first encounter of the humorous kind on stage in front of our colleagues. Marian's first words to me were: "Dan tells me you're funny; OK, Schekman, make me laugh!" I knew from that moment that Marian would expect nothing less than precision in my science and my humor! We remember her fondly, and applaud the decision of our campus administration to rename the Bioscience and Natural Resources Library in her honor.

Finally, I want to thank Laura Williams, our Newsletter editor. Laura is a PhD graduate of ours from the Kane/Chamberlin lab who has decided to make a career in scientific publishing. Laura gained experience as the editor of the Women in Cell Biology column in the American Society for Cell Biology Newsletter. I am certain that her efforts here will set high standards for future MCB at Berkeley Newsletters.

Have a good summer.

RANDY SCHEKMAN
MCB Co-Chair

MCB at Berkeley is a publication of the Department of Molecular and Cell Biology at the University of California, Berkeley.
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NEW FACULTY

Rebecca Heald, CDB

Rebecca Heald became an Assistant Professor of Molecular and Cell Biology in July, 1997.

Education:
- B.A. in Chemistry, 1985, Hamilton College, Clinton, NY.
- Ph.D., 1993, Harvard Medical School, Thesis Advisor: Frank McKeon.
- *Thesis project:* I identified phosphorylation sites in the nuclear lamin proteins that when mutated prevent nuclear lamina breakdown in mitosis. These results showed that phosphorylation just outside of the large coiled-coil domain controls the assembly dynamics of these intermediate filament-type proteins. I also showed that overexpression of positive cell cycle regulatory proteins could cause premature entry into mitosis in the absence of complete DNA replication and that this could be rescued by overexpression of a negative regulator. These results showed that cell cycle progression in vertebrate cells is regulated by a balance between positive and negative regulators, just as in yeast.

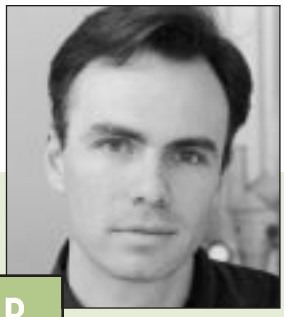
Postdoc:
- 1993-97, European Molecular Biology Laboratory (EMBL), Heidelberg, Germany, American Cancer Society Postdoctoral Fellowship, Advisor: Eric Karsenti.
- *Project:* I developed a system in which plasmid DNA-coated beads were sufficient to induce the assembly of bipolar mitotic spindles in *Xenopus* egg extracts. These results showed that spindle assembly can occur in the absence of centrosomes or kinetochores. I also showed that spindle pole formation was dependent on the microtubule-based motor, cytoplasmic dynein, both in the presence and absence of centrosomes, but that centrosomes, when present, constitute dominant sites for spindle pole assembly.

Current Projects: I am following up on my postdoctoral project to study mitotic spindle assembly. We would like to identify proteins on mitotic chromatin that stabilize microtubules. We would also like to reconstitute kinetochore function on beads.

Why are you excited to be working at Berkeley? There are so many interesting people and projects; the place is both diverse and friendly.

What is the most rewarding achievement in your career so far? It has been extremely rewarding to get the lab started and to have students to interact with and to teach.

Personal information: I enjoy bicycling, reading, and music.



James Berger, BMB

James Berger will join the Biochemistry and Molecular Biology Division as an Assistant Professor on July 1, 1998. He is currently a Fellow at the Whitehead Institute at MIT.

Education:
- B.S. in Biology, 1990, University of Utah.
- Ph.D., 1995, Harvard University, Thesis Advisors: James C. Wang and Stephen C. Harrison.
- *Thesis Project:* My thesis involved using X-ray crystallography to determine the three-dimensional structure of a type II DNA topoisomerase, an enzyme that untangles and unknots DNA in the cell. The structure provided a molecular model for demonstrating how the enzyme can physically transport one DNA through another.

Current Project: While a Fellow at the Whitehead Institute, the focus of my work has been to understand the structural basis by which proteins convert cellular energy into motion and work. In particular, we study enzymes that unwind, move, and manipulate DNA and RNA in the cell.

Future Projects at Berkeley: My lab will continue in these areas, studying the structure and function of enzymes and enzyme complexes involved in replication and chromosome structure.

Why are you excited about working at Berkeley? Berkeley offers the opportunity to interact with students and faculty in numerous and diverse areas of science, all within an environment known for scientific excellence.

What is the most rewarding achievement in your career so far? Determining the structure of a protein. The process is similar to building a jigsaw puzzle in three dimensions, and it yields a vast amount of biochemical information about a protein's function in a short time.

Personal information: Married to Marian Feldman who will graduate this June with a Ph.D. in Art History from Harvard.

Dan Portnoy, BMB

Dan Portnoy is a Professor of Biochemistry and Molecular Biology, and he has a joint appointment with the School of Public Health. In July, 1997, he moved his lab from the University of Pennsylvania where he was in the Department of Microbiology since 1988. Before that he had been a faculty member at Washington University in St. Louis from 1986 to 1988.

Education:
- B.A. in Bacteriology, 1978, University of California, Los Angeles.
- Ph.D. in Microbiology & Immunology, 1983, University of Washington, Seattle, Thesis Advisor: Stanley Falkow.
- *Thesis Project:* We discovered that a plasmid shared by all pathogenic *Yersiniae* (including *Yersina pestis*, the causative agent of bubonic plague) encoded a number of secreted proteins (Yops) which were essential for virulence. Years later, it became clear that many other animal and plant pathogens also secrete Yops directly into their host cells.

Postdoc:
- 1983-86, Rockefeller University, Damon Runyon Walter Winchell Cancer Fund Fellowship and NIAID National Research Service Award, Advisor: Jay Unkeless.
- Project: We cloned and characterized a lysosomal protease, cathepsin L, and a macrophage Fc Receptor. One key aspect of my training is that I went from the premiere bacterial pathogenesis lab (Falkow's) to a lab dedicated to aspects of the host.

Selected Awards and Honors:
- Eli Lilly Award in Microbiology and Immunology, 1996.
- MERIT Award from NIAID, NIH, 1995.

Current Projects: I started working on the intracellular bacterial pathogen *Listeria monocytogenes* in 1986 after my postdoc, and I have been ever since. I view *L. monocytogenes* as the bacteriophage Lambda of intracellular pathogens. We are analyzing every detail of the intracellular life style of this organism which, surprisingly, only needs five proteins to escape from a vacuole, exploit a host system of actin-based motility and spread cell-to-cell.

Why are you excited about working at Berkeley?
- The commitment to graduate education.
- The commitment to first-rate, cutting edge science among my colleagues.
- The breadth and diversity of science in the department and on campus.
- The opportunity to be part of the rebirth of microbial biology on campus.

What are the benefits of your joint appointment both to you and to the departments? The benefits of the joint appointment are that I can bring together groups of scientists and students who previously did not interact. To do this, I have organized a well-attended seminar series in Microbial Biology, and I am starting a new course on bacterial pathogenesis.

What is the most rewarding achievement in your career so far? Watching the development of systems I initiated. I started both the *Yersinia* and *Listeria* systems from scratch. It is very gratifying to see the *Listeria* system develop as one of the premiere systems for the study of the actin-based cytoskeleton.

Personal Information: My wife is Suzanne Jacks Portnoy. She s staying home to raise our 2-year-old daughter, Eleanor.

Carlos Bustamante, BMB

Carlos Bustamante will begin a joint appointment as a Professor of Biochemistry and Molecular Biology and Physics on July 1, 1998. He is currently a Professor at the University of Oregon where he has been since 1991. From 1982 to 1990, he was on the faculty of the University of New Mexico.

Education:
- B.S. in Biology, 1973, Universidad Peruana Cayetano Heredia, Peru.
- M.S. in Biochemistry, 1975, Universidad Nacional Mayor de San Marcos.
- Ph.D. in Biophysics, 1981, UC Berkeley, Thesis Advisor: Ignacio Tinoco, Jr.
- *Thesis Project:* Two effects were known previously in the optical activity of chiral (handed) molecules: circular dichroism and optical rotatory dispersion. We characterized a third effect, i.e., the ability of chiral molecules to scatter the two circular polarizations with different efficiency in all directions of space.

Postdoc:
- 1981-82, Lawrence Berkeley Laboratory, Advisors: Marcos F. Maestre and Ignacio Tinoco, Jr.
- *Project:* We built an instrument to measure circular differential scattering, and we made the first direct measurement of this effect on nuclei of sperm cells. This method has since been used to discriminate between different pathogenic and non-pathogenic bacteria.

Selected Awards and Honors:
- Elected Fellow of American Physical Society, 1995.
- Howard Hughes Medical Institute Investigator, 1994.
- Alfred P. Sloan Fellow, 1985.
- Searle Scholar, 1984.

Current and Future Projects: At Berkeley, we will continue developing the methods of single molecule manipulation that we started at the University of Oregon. In particular, we want to investigate the mechanical folding and unfolding of single protein molecules to try to map, for the first time, the potential energy function of globular proteins. In addition, we will be investigating the behavior of DNA and RNA polymerases as molecular motors by using laser tweezers. Finally, we will continue the development and application of the Scanning Force Microscope (SFM) to investigate multiprotein-DNA complexes involved in transcription regulation both in prokaryotes and eukaryotes.

Why are you excited about working at Berkeley? I am excited by the enthusiasm and drive for research that one finds everywhere at Berkeley and by the unlimited potential for new collaborations.

What are the benefits of your joint appointment both to you and to the departments? Tapping into the knowledge and expertise from faculty in both departments will be an enormous benefit to our research program. In addition, I will be able to interact with and to train students with two widely different backgrounds. I believe that there is a trend in biology towards quantification and that, in the near future, biology students will need more training in the physical sciences in order to make their impact in research.

What is the most rewarding achievement in your career so far? I feel that most of the satisfaction in scientific work is in the act of research itself, in the quest for that which we do not understand. Because the latter is a constantly moving target, perhaps the best answer to this question is 'that which we are doing right now.'

Personal Information: My wife, Silvia, is a speech pathologist. We have two kids, Fernanda (18 yrs.) and Carlos Jr. (15 yrs.). My main interests outside science are history, music, and soccer.

Remembering

MARIAN KOSHLAND

1921–1997

MCB Professor of Immunology Marian Elliott Koshland died on October 28, 1997. Her career at UC Berkeley spanned 32 years. She came to Berkeley in 1965 as a researcher and a lecturer, and she joined the faculty in 1970. She later served as Chair of the Department of Microbiology and Immunology and, until the time of her death, was the Head of the MCB Graduate Affairs Office. In recognition of her distinguished service to the campus and outstanding achievements in her field, Marian Koshland was posthumously awarded the Berkeley Citation, the University's highest honor. Professor Koshland is survived by her husband of 52 years, MCB Professor Daniel E. Koshland, Jr., five children, and nine grandchildren. She is remembered here in the words of her students and of her colleague, Jim Allison.

Donations in Marian Koshland's memory may be sent to the Graduate Fund, University of California at Berkeley, Department of Molecular and Cell Biology, 597 Life Sciences Addition #3200, Berkeley, CA 94720-3200. Checks should be made payable to the UC Regents.

Memories of Her Students

Marcy Blackman (PhD, '85), a former graduate student of Marian Koshland's and now an Associate Member in the Immunology Department at St. Jude's Children's Research Hospital in Memphis, shares her memories: "I was in Marian's lab when she came back from a sabbatical in David Baltimore's lab at MIT. She turned the lab around with the new molecular techniques she had learned, and it was an exciting place to be. Marian was in her late 50's, but I remember Marian saying that she felt like a postdoc again. Such enthusiasm for science was characteristic of Marian, and it rubbed off on those around her."

Jeff Wallin was Marian Koshland's last graduate student and is still in MCB working toward his Ph.D. Up to a week before she passed away, they were working on a paper which was published in a recent issue of *Science* (March 20, 1998). Jeff has these thoughts: "As a mentor, Marian listened to my ideas about my project and let me approach it my way, but she knew what help to give me in order to advance the project. Over time, I became more of an independent thinker. As a scientist, her longevity alone is impressive, but her landmark discoveries were so seminal that they are taken for granted today." When asked what he will remember about her, he replied: "People say she was worldly and she loved art, but what I will remember is her love for sports. She could talk about sports as well as anybody I have known."

Blackman, Wallin, and Allison participated in the "The Status of Women Symposium: Mechanisms of Immune Regulation" dedicated to the memory of Marian Koshland at the Annual Meeting of the American Association of Immunologists in San Francisco on April 21, 1998.

MARIAN KOSHLAND

Remarks of a Colleague

MCB Professor of Immunology James Allison gave the following remarks about Marian (Bunny) Koshland's impressive scientific career at her memorial service at the University Art Museum on December 1, 1997.

Good evening. My name is Jim Allison. I am an Immunologist who has known of Bunny's work since I became an immunologist, and knew her as a friend and colleague since she recruited me to Berkeley in 1985. I would like to make a few comments on her contributions to our field.

It would not be at all an exaggeration to say that Bunny's career as a scientist was spectacular. She made very important contributions to our understanding of the immune system in every decade for the past half century. In the 1940's, she studied the development of immunity to Asiatic cholera. Not only was the information she obtained used in the development of vaccines, but, by the early 1950's, Bunny had shown that secreted and serum-borne forms of antibodies were discrete molecules. This was considerably before the formal definition of antibody classes.

By the 1960s, Bunny began to address one of the central problems in immunology—the origin of antibody specificity. There was a raging debate between instructive models, which held that antibody proteins were all the same and just folded around their target antigens, and selective models, which argued that they were the products of different cells. Bunny, in the early 60's, published a series of papers showing that the chemical composition of antibodies directed against different antigens were in fact different, thus arguing for selection. Legend has it that at the annual meeting of the American Association of Immunology where she first presented her data, her talk was received by a standing ovation—quite high praise indeed. By the end of the 60's, her work had become part of the mainstream of an emerging idea that is now one of the cornerstones of immunology, that is that antigen receptors, both of T cells and B cells, are encoded by multiple rearranging gene segments. Bunny's work in this area was seminal. Charlie Janeway, who is currently the president of the American Association of Immunologists, recently commented that he had a clear memory of the time in medical school when he first read Marian's papers in this area, and that it was for him a defining moment that motivated him to embark on a career in immunology.

By the 70's, Marian had returned to her studies of secreted vs. serum-borne antibodies. She identified a novel antibody subunit called the J chain, characterized it, showed that it played a central role in antibody assembly and secretion, and that the beginning of its expression marked a clear, discrete step in the maturation of B cells. This work led to the central theme of the remainder of her scientific career—understanding the way in which a B cell becomes an active player in the immune response.

In the late 1970's, she did a sabbatical stay in David Baltimore's lab at MIT to learn molecular biology, as she felt that the future of the field lay in this area. While at MIT, she collaborated in obtaining the gene encoding the J chain, and she brought the gene and her knowledge of this new technology back to Berkeley. In the 1980's, she turned her attention to regulation of transcription of the J chain gene by B cell growth factors. By the 1990's, her work had extended to the more general area of events that accompany and direct B cell activation and maturation. In an invited talk at the national meeting of the American Association of Immunologists this past February, she presented a wonderful description of recent work from her lab. They demonstrated that the action of a transcription factor, BSAP, was very complex and dynamic, and that it could have both positive and negative effects—extinguishing some genes whose products were no longer needed while turning on new genes with roles important to the emerging antibody-producing arm of the immune system. This talk was a marvel, and it put together complex biochemical phenomena in an understandable context of biological function. It was a testament not only to the quality and timeliness of her own work, but also to how far the field has come in a detailed understanding of the workings of the immune system in the half century since Marian entered it.

If there is any single feature that marked Bunny's work, it was this ability to reduce complex phenomena to experimentally addressable components. She did this by putting a very high emphasis on experimental rigor and absolute scientific integrity. She was not affected by fads in science, but only in the bottom line that should be of interest to all scientists—how well hypotheses hold up to hard experimental scrutiny.

Speaking for myself, and I suspect for many of her fellows and students, I can attest to her quickness to challenge weak, half-baked ideas. I can also attest to the fact that she was willing to make helpful suggestions—once an idea passed her test, you could be more confident in presenting it to the wider community.

In honor of all of her accomplishments, Marian received awards that are much too numerous for me to itemize completely. She was, of course, elected to the National Academy of Sciences, the American Association of Arts and Sciences, and the Council of the American Association of Immunologists, of which she served as President in 1982-83. She served on many committees involved in setting national scientific policy. She was noted for her courage and straightforwardness in speaking her mind, and for her honorable positions on emerging issues.

Another area for which Marian was much admired was her status as a role model for women. In addition to being a pioneer for women in science in a field that was clearly dominated by men during the early stages of her career, she also demonstrated that a woman could have a spectacular career while successfully managing to raise a family. It is in part for this achievement that she will be honored by the Committee for the Status of Women in Science at a special symposium to be held at the upcoming Annual Meeting of the American Association of Immunologists.

Reading back over some of Marian's works recently, I noted that in a memoir she stated that she chose science as a career because of her conviction that it is a way of making a lasting contribution, and, in a sense, is immortal. The legacy that Marian has left us is in many ways immortal, in terms of her own scientific achievements, those of the students and the fellows that she has trained, and those of her colleagues like myself on whom she had a strong and lasting influence. For these things, she will long be remembered and honored.

Editor's Note: I highly recommend Marian Koshland's illuminating and inspiring memoir entitled, "Sheer Luck Made Me an Immunologist," published in *Annual Reviews of Immunology* (1996) **14**: ix-xv.

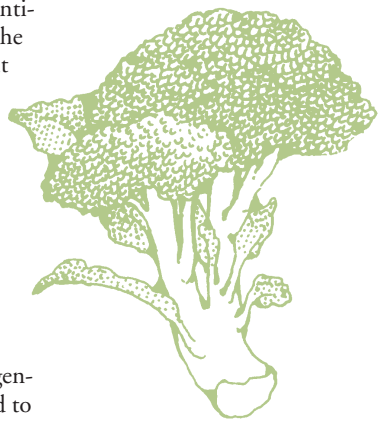
RESEARCH HIGHLIGHTS

Gary Firestone

Professor of Cell and Developmental Biology

Gary Firestone's group has discovered that indole-3-carbinol (I3C), a chemical which occurs naturally in broccoli and other *Brassica* vegetables, inhibits the growth of cultured human breast cancer cells. Specifically, I3C inhibits the expression of cyclin-dependent kinase-6 (CDK6) and causes a G1 cell cycle arrest. The project was a collaboration with fellow UC Berkeley Professor Leonard Bjeldanes in the Department of Nutritional Sciences.

These effects of I3C on the cell cycle were found to be independent of estrogen receptor signaling, although I3C and related compounds are known to have anti-estrogenic effects. Conversely, it was found that the breast cancer drug tamoxifen, which is dependent on estrogen receptor signaling, has no effect on CDK6 expression. Finally, a combination of I3C and tamoxifen was found to inhibit cell growth more efficiently than either one alone, consistent with the different modes of action of each agent.



These results suggest that, theoretically, a combination therapy with I3C and tamoxifen may be highly effective in breast cancer patients with estrogen-responsive tumors. Two-thirds of patients with metastatic breast cancer have estrogen-responsive tumors, but only half of those respond to tamoxifen therapy. Thus, only one-third of patients initially respond to tamoxifen, and those who do will eventually develop tamoxifen resistance. In combination with I3C, lower doses of tamoxifen could, in theory, be used to avoid tamoxifen resistance and to lessen its side effects

I3C alone is promising as a cancer drug because it has no reported side effects, and it has been shown to be a chemopreventative agent in rodents. Firestone sees a potential role for I3C as a post-surgical treatment to prevent tumor regrowth or new tumors. Firestone points out, "What's especially nice about this research is that one doesn't have to be a visionary to see the potential for human health."

But as a cell biologist and molecular endocrinologist, Firestone is interested in how I3C works at the cellular and molecular level. Firestone suggests that I3C may bind a target receptor which then affects the transcription of a network of genes including the gene for CDK6. His model is based on steroid receptors and their signaling, a subject he has studied for years.

REFERENCE:
C.M. Cover, S.J. Hsieh, S.H. Tran, G. Hallden, G.S. Kim, L.F. Bjeldanes, and G.L. Firestone (1998) *Journal of Biological Chemistry* 273(7): 3838-3847.

Ellen Robey

Assistant Professor of Immunology

Ellen Robey's lab is elucidating the role of the Notch receptor in immune cell fate decisions. A T cell precursor has two possible fates: it may become a killer T cell which fights viral infections or a helper T cell involved in an antibody response. If the antigen receptor expressed by a T cell precursor recognizes a MHC Class I ligand, then the precursor cell becomes a killer T cell. But if, instead, its antigen receptor recognizes a MHC Class II ligand, then the precursor cell becomes a helper T cell.

From nematodes to humans, the cell surface receptor Notch is involved in differentiation and cell fate decisions. Since Notch is present on immune precursor cells, Robey investigated whether it might be involved in T cell lineage choice.

Robey's team made transgenic mice with a constitutively active Notch receptor. They found that precursor cells become killer T cells, regardless of the ligand recognized by the antigen receptor. In other words, cells that normally would become helper T cells become killer T cells. Robey explains, "The constitutive Notch receptor is overriding the normal recognition, suggesting that it is acting downstream of the antigen receptor to control cell fate determination." Normally, the Notch receptor is present, but not active, in cells destined to be helper T cells. Thus, the presence or absence of Notch ligands may be regulating Notch signaling. They have identified some Notch ligands and are now trying to figure out how they are regulated in the thymus.

REFERENCES:
E.A. Robey, D. Chang, A. Itano, D. Cado, H. Alexander, D. Lans, G. Weinmaster, and P. Salmon (1996) *Cell* 87 (3): 483-492.
T. Washburn, E. Schweighoffer, T. Gridley, D. Chang, B.J. Fowlkes, D. Cado, P. Salmon, and E. Robey (1997) *Cell* 88 (6): 833-843.

Udi Isacoff

Assistant Professor of Neurobiology

Udi Isacoff's lab has developed powerful new fluorescence techniques for studying the ion channels that control excitability and synaptic transmission in the nervous system, and, in the process, has found wider applications for the techniques. Isacoff's group used site-specific fluorescent labeling of the *Shaker* potassium channel protein in combination with voltage-clamping to observe the conformational changes induced by gating, that is opening and closing of the channel. As the labeled domain of the channel moves, the fluorescence changes because a fluorophore is sensitive to its local environment. Recently, they have begun an effort to use similar optical fluorescence techniques to observe structural events in single channels, rather than in populations of channels.

In addition to providing structural information, fluorescently labeled voltage-sensitive channels can optically report electrical activity. In a cell, labeled channels can be used to noninvasively measure the voltage across the membrane. Isacoff describes this as "harnessing signaling proteins and having them tell you when they are active."

When making such optical measurements in neural tissue, however, it is difficult to measure the signal from only the cells of interest, for instance, the neurons and not the glia. To solve this problem, Isacoff's group designed "a voltage sensor encoded into DNA" which, when placed under the control of various promoters, could be targeted to specific cell types as well as developmental stages, tissues, and subcellular compartments. To do this, they made use of the green fluorescent protein (GFP) which was originally isolated from a jellyfish. By fusing GFP to the *Shaker* potassium channel, they made an intrinsically fluorescent protein. Voltage-dependent gating of this chimeric channel causes large changes in its fluorescence. Thus, they created an optical probe to measure transmembrane voltage which, since it is genetically encoded, can be selectively expressed and localized. Isacoff has begun collaborating with other MCB labs to make similar optical sensors by fusing GFP to different channels and to other detector proteins such as receptors.

REFERENCES:
L.M. Mannuzzo, M.M. Morrone, and E.Y. Isacoff (1996) *Science* 271: 213-216.
M.S, Siegel and E.Y. Isacoff (1997) *Neuron* 19: 735-741.
K. Zito, R.D. Fetter, C.S. Goodman, and E.Y. Isacoff (1997) *Neuron* 19: 1007-1016.

Paul Kaufman

Adjunct Assistant Professor of Biochemistry and Molecular Biology

In the two years that Paul Kaufman has been at Berkeley, he has expanded his investigation of chromatin assembly which he began as a postdoctoral fellow. In Bruce Stillman's lab at Cold Spring Harbor, Kaufman characterized human chromatin assembly factor 1 (CAF-1), which performs the first step in chromatin assembly, depositing histones H3 and H4 onto DNA.

Genes encoding the three subunits of CAF-1 have been cloned from human cells, and, for the purpose of genetic analysis, from yeast cells. The three yeast genes are collectively referred to as *CAC* (Chromatin Assembly Complex) genes. Interestingly, the mammalian *in vitro* assay was used to purify and clone CAF-1 from *S. cerevisiae*, demonstrating a lack of species specificity.

The *CAC* genes are not essential for cell viability, but deletion of any of the *CAC* genes reduces position-dependent transcriptional silencing. Since chromatin proteins are involved in this silencing, these results suggest that CAF-1 affects chromatin structure *in vivo*.

Since the *CAC* genes are not essential, Kaufman reasons that they are either auxiliary players in chromatin assembly or are functionally redundant, and he has evidence for the latter. His group has observed that mutations in several genes implicated in transcriptional regulation have strong synthetic gene silencing defects when combined with *cac* mutations. "Perhaps severe phenotypes are only observed when multiple pillars holding up the structure are knocked out," Kaufman analogizes. "These synthetic interactions with other genes suggest that our strategy for finding other players in chromatin assembly is a good one," and synthetic lethality screens are in progress.

REFERENCE:
P. Kaufman, R. Kobayashi, and B. Stillman (1997) *Genes and Development* 11: 345-357

Donald Rio

Professor of Genetics

Donald Rio is studying the mechanism and regulation of *Drosophila* P-element transposition and finding similarities with other nucleic acid rearrangements, such as those that occur during immunoglobulin and T-cell receptor gene V(D)J recombination in the vertebrate immune system. Transposons are mobile genetic elements which are present in many organisms, and the *Drosophila* P element is one of the best characterized eukaryotic transposons. P-element transposition occurs by a cut-and-paste mechanism initiated with cleavage by the P-element-encoded transposase and followed by DNA repair by nonhomologous end joining involving host proteins.

Rio's group has found that the repair of the double-strand DNA breaks formed in the process of transposition involves DNA-dependent protein kinase (DNA-PK), a nuclear serine-threonine kinase. They have shown that mutations in one of the three subunits of DNA-PK result in large deletions and chromosome loss due to defective repair at P-element-induced breaks. Similarly in mice, mutations in another subunit of DNA-PK, the product of the scid (severe combined immunodeficiency) locus, cause defects in end processing and joining during V(D)J recombination. Scid mice are immunodeficient because they have very few undifferentiated B or T cells. In both transposition and V(D)J recombination, DNA-PK mutations lead to unrepaired double-strand breaks which may result in deletions, chromosome loss, and cell death.

Because of the severe consequences of unrepaired double-strand DNA breaks, transposition is carefully regulated. Recent work in Rio's lab has shown that DNA-PK may play a direct role in that regulation. They have found that P-element transposase is a substrate for DNA-PK and that the phosphorylation state of transposase affects its activity.

Rio explains that the role of phosphorylation of transposase by DNA-PK may be to restrict transposition to the G2 phase in the cell cycle when DNA-PK and other repair machinery is expressed so as not to leave unrepaired double-strand breaks. "The implication is clear," he says, "Signal transduction involving DNA-PK connects the cleavage event to the repair event. It may also act to transduce extracellular stimuli to trigger DNA rearrangements." He concludes, "Transposition is advantageous in terms of genome evolution because it introduces genetic variation, yet it can't be so unrestricted as to cause cell death."

REFERENCES:
E.L. Beall and D.C. Rio (1996) *Genes & Development* 10: 921-933.
E.L. Beall and D.C. Rio (1997) *Genes & Development* 11: 2137-2151.
E.L. Beall and D.C. Rio (1998) *EMBO Journal* 17: 2122-2136.

THE NEUROSCIENCE CENTER

An effort to create a Center for Neuroscience at UC Berkeley is being led by MCB Neurobiology Professors Corey Goodman and Carla Shatz. They provided their perspective on the development of the Neuroscience Center and an update on its current status.

We began working on the Neuroscience Center in April of 1993. In its initial conception, it was called the "Neuroscience Initiative," and it specifically proposed a fund-raising initiative to allow neuroscience research on campus to expand in directions that MCB alone would not go, that is the integrative, systems, cognitive, and computational ends of the field. The same vision for a broad-based neuroscience program drives the Neuroscience Center. Understanding how the human brain gets put together during development, how it works to control behavior and perception, and how it changes with learning and memory will require marshaling a broad range of technologies and approaches.

From the outset, we thought that MCB was doing a terrific job of hiring young molecular and cellular neurobiologists in not only the Neurobiology Division, but also in CDB and Genetics. However, we were concerned that no single department or unit on campus was making the same kind of effort at the systems and cognitive end of the field. Moreover, we believed that the most innovative work in the field was going to be interdisciplinary and at the interface of traditional definitions. We wanted a home—a Center—that fostered interactions amongst neuroscientists from across the campus. Thus, sprang the notion of the Neuroscience Center.

The initial members of the Neuroscience Center will be the current members of the Graduate Group in Neuroscience, which consists of faculty from MCB, Psychology, Vision Science, Environmental Science, Chemistry, Physics, and Integrative Biology. As for graduate students, the Graduate Program in Neuroscience, which was active before the departmental reorganization, will be reactivated once the Center is under way.

While waiting for the Neuroscience Center to get off the ground, we have already begun to build a strong campus-wide neuroscience community based on the strength of the Neurobiology Division in MCB. We invite all members of the campus-wide community to our divisional retreat each year. Similarly, we encourage other neuroscientists to suggest and to host speakers in our seminar series. Finally, we invite representatives from other areas of neuroscience to come to our faculty meetings.

We have received tremendous support from the neuroscience community across campus, from MCB and other departments, and from the administration, and, in the last year or so, the Neuroscience Center has begun to take shape. A search for a director is under way, and a promising candidate has been identified. The University has made a commitment for four to six new faculty positions for the Center. The administration has also begun formal discussions about where to house the Center. Finally, the Center has received two endowments. The Rauch family has endowed the Rauch Chair in memory of their son Evan, who was an undergraduate at UC Berkeley. The other endowment is from Helen Wills Moody Roark, a Cal alumnus and a tennis legend who won Wimbledon eight times. She left her entire estate to the University in the name of the Neuroscience Center because she was interested in biology, especially of the brain.

At this point, we are convinced that Berkeley is poised to build the top neuroscience program in the country. And after all, although we may be a bit biased, understanding the brain will be one of the great challenges for science in the twenty-first century.

Outstanding

GSI AWARD WINNERS

This year, the seven MCB students shown received Outstanding Graduate Student Instructor Awards along with the following students from other departments who taught MCB classes: Carrie Cowan and Cynthia Waters from Plant and Microbial Biology; Christine Eckels from Integrative Biology; Paul Woo from the Endocrinology Graduate Group; Ashild Vik from the Biophysics Graduate Group, Chai-Sue Lee, Jenny Way, and Kimberly Pothier from Health and Medical Sciences.

The winners were selected from the 151 graduate student instructors in Molecular and Cell Biology during the 1997 calendar year. The selections are made by MCB Divisional GSI Advisors with the concurrence of the Divisional faculty and are based on student and instructor evaluations. The GSI Advisors have noted that these GSIs performed at a very high level that was clearly a cut above our other GSIs who, as a whole, are dedicated teachers.

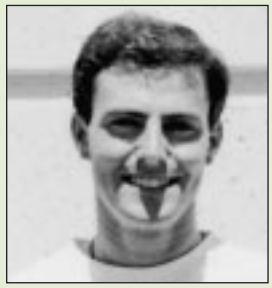
Winners received certificates of distinction from the campus GSI Teaching and Resource Center, and a reception was held in their honor at the Alumni House on May 7, 1998. Winners may submit an application for a Teaching Effectiveness Award which is designed to recognize exceptional teaching methods and includes a cash prize.

Julie Hollien, Marquesee Lab, for MCB 110L Biochemistry & Molecular Biology Laboratory

Heather Dawes, Meyer Lab, for MCB 140 Genetics

Pak Ming Lau, Bentley Lab, for MCB 160L Neurobiology Laboratory

Ben Eaton, Moore Lab, for MCB 130 Cell Biology



David Stellwagen, Shatz Lab, for MCB 160L Neurobiology Laboratory

Theresa Ho, Goodman Lab, for MCB 160 Neurobiology

Patricia Valdez, Robey Lab, for MCB 150L Molecular Immunology Laboratory

AWARD WINNERS

In recognition of outstanding achievements by MCB undergraduates, the following awards will be presented by the MCB Department during the MCB Commencement Ceremony at the Greek Theater on May 25, 1998. The following award descriptions are from the MCB Undergraduate Handbook.

DEPARTMENTAL CITATION

Roger Mar-Tang (CDB) wins the MCB Departmental Citation

The Departmental Citation represents the highest achievement each year by a graduating senior in the MCB Department, not only in terms of overall grade point average, but in major coursework, quality of research, and other such factors that indicate promise of great success in the student's career. The Citation is awarded by a vote of the Undergraduate Affairs Committee (UAC), after having examined the records of the nominees from each MCB Division. The winner receives $500 and a certificate.

DIVISION AWARDS

Jill Licht wins the BMB Divisional Citation

This Divisional Citation represents the highest achievement each year by a graduating senior in the BMB Division, not only in terms of overall grade point average, but in major coursework, quality of research, and other such factors that indicate promise of great success in the student's career. The winner receives $500 and a certificate.

Haidy Lee wins the F.H. Carpenter Memorial Prize in Biochemistry

This prize, made possible by the generosity of the family and friends of the late Professor Frederick H. Carpenter, is awarded annually to the outstanding junior MCB major in the Biochemistry & Molecular Biology emphasis, based on academic achievement in MCB courses and faculty recommendation. A stipend of $1200 is given to support the student's undergraduate research during the summer between junior and senior years with the MCB faculty member of his or her choice.

Emily Wood wins the Grace Fimognari Memorial Award

Established in 1969, this prize is awarded to an outstanding graduating senior in the BMB emphasis of the MCB major, based on the same criteria as the Departmental Citation. The awardee receives $500 and a certificate.

Ryan K. Louie wins the Kazuo Gerald Yanaba & Ting Jung Memorial Fund Prize

This prize is made possible by the generosity of family, friends, and associates of the late Kazuo Gerald Yanaba and Ting Jung, two graduates of the Microbiology and Immunology major and former employees of Cetus Corporation. Award of the prize is based on the students' oral presentation of their research at the annual BMB Undergraduate Honors Research Symposium and by their honors theses. The awardee receives $500 and a certificate.

Catharina Fu wins the Henke Award

This award is made possible through the generosity of the friends and family of James Henke, a neurobiology student who graduated in 1991. This award is given in recognition of outstanding achievement in the neurobiology emphasis. Recipients receive $200 and a certificate.

I.L. Chaikoff Award Winners

Harry Chang
Matthew Chang
Sumana Jothi
Wei Liu
Laurence Lu
Timothy Kubow
Kavita Patankar
Eric Williams

Dr. Chaikoff was a Professor of Physiology whose area of expertise was thyroid function measurement with radioactive iodine. He was also a pioneer in the study of hormones involved in lipid metabolism, which influences arteriosclerosis. Each year, several Chaikoff awards are given in recognition of outstanding achievement and excellence in the Cell & Developmental Biology and Neurobiology emphases. Awardees receive a $500 prize.

Erika Shor wins the Outstanding Undergraduate Geneticist Award

This prize is given each year to the student who has most distinguished himself or herself in genetics research. Award of the prize is based on the student's oral presentation of his or her research at the annual Genetics Undergraduate Research Symposium and by his or her honors thesis. The awardee receives $500 and a certificate.

Outstanding Immunologist Award

No selection made this year.

FACULTY NEWS

PROMOTIONS

- Tom Alber (BMB) promoted to Full Professor, effective 7/1/97.
- Georjana Barnes (Gen) promoted to Associate Adjunct Professor, effective 7/1/98.
- David Drubin (Gen) promoted to Full Professor, effective 7/1/98.
- Gian Garriga (Gen) promoted to Associate Professor, effective 7/1/98.
- Ellen Robey (Imm) promoted to Associate Professor, effective 7/1/98.

ADMINISTRATIVE APPOINTMENTS

- Randy Schekman and Jim Allison appointed Department Co-Chairs, effective 1/1/98.
- David Raulet appointed Immunology Division Head, effective 8/1/97.
- Hsiao-Ping Moore appointed Graduate Affairs Unit Head, effective 11/1/97.
- David Drubin appointed Graduate Affairs Unit Head, effective 7/1/98.

FACULTY AWARDS AND HONORS

RECEIVED SINCE JULY 1, 1997

Biochemistry and Molecular Biology Faculty

- Bruce Ames was given the Robert A. Kehoe Award of Merit for notable contributions to occupational medicine and was elected as an Honorary Member of the Japanese Pharmaceutical Society.
- Richard Calendar was appointed to the Evaluation Panel for HHMI Predoctoral Fellowships.
- Robert Glaeser was appointed to the U.S. National Committee for the International Union of Pure and Applied Biophysics for a 3-year term.
- Alex Glazer was the 1997-98 ASM Foundation for Microbiology Lecturer; gave the Keynote Lecture at the 1997 International Symposium on Marine Cyanobacteria and Related Organisms, Paris, France; and was appointed Director, University of California Natural Reserve System.
- Caroline Kane was appointed to the National Institutes of Health Advisory Board for the Office of Research into Minority Health, effective January 1, 1998.
- Judith Klinman was elected President of the American Society for Biochemistry and Molecular Biology.
- Sydney Kustu received a 10-year MERIT Award from the NIH and a Visiting Gauss Professorship at the University of Goettingen, Germany.
- Susan Marqusee received a Hellman Family Faculty Fund Award, was named Chair of the 1999 Proteins Gordon Conference, and was elected to the 1997-99 Nominating Committee of the Protein Society.
- Hiroshi Nikaido was elected Fellow of the American Academy of Microbiology.
- Dan Portnoy gave the Plenary Lecture at the 71st Annual Meeting of the Japanese Society for Bacteriology.
- Jesse Rabinowitz, professor emeritus, was elected Fellow of the American Academy of Microbiology.
- Randy Schekman is President-elect of the American Society for Cell Biology, and he delivered the Sonneborn Annual Lecture at Indiana University.
- Jeremy Thorner was appointed Research Professor of the Miller Institute for Basic Research in Science for 1999-2000, was elected Vice-Chair for 1998 and Chair for 1999 of the Gordon Research Conference on Second Messengers and Protein Phosphorylation, and was elected a Member of the 1998-99 Nominating Committee of the American Society for Biochemistry and Molecular Biology.
- Robert Tijan was elected to the American Academy of Arts and Sciences and was elected Fellow of the American Academy of Microbiology.

Genetics Faculty

- Thomas Cline was appointed to the Executive Council of the American Academy of Arts and Sciences.
- Michael Levine was elected to the National Academy of Sciences.
- Barbara Meyer was selected as Investigator of the Howard Hughes Medical Institute effective July, 1997.
- Jasper Rine received an endowed chair as the Richard and Rhoda E. Goldman Distinguished Professor of Biology.
- William Skarnes was named a 1998 Searle Scholar.

Cell and Developmental Biology Faculty

- Zac Cande was appointed Research Professor of the Miller Institute for Basic Research in Science for 1999-2000.
- Lester Packer was awarded an honorary doctorate degree from the University of Rennes, France.
- Tito Serafini received a Searle Scholar Award, a Beckman Young Investigator Award, and the Mary Elisabeth Rennie Endowment for Epilepsy Research Grant.

Neurobiology Faculty

- Yang Dan was named a Sloan Fellow and received a Beckman Young Investigator Award.
- Corey Goodman won the Gairdner Foundation International Award for Achievement in Medical Sciences and the Ameritec Prize for basic research toward a cure for paralysis.

Immunology Faculty

- James Allison was selected as Investigator of the Howard Hughes Medical Institute effective July, 1997; won a Research Award from The Association for the Cure of Cancer of the Prostate, CapCure Foundation; and was elected Fellow of the American Academy of Microbiology.

1997-98 MCB

PhD GRADUATES

- **Melissa Adams** (Rio) Molecular Genetic and Biochemical Characterization of the P-element Somatic Inhibitor Protein, A *Drosophila* Alternative Splicing Factor.
- **Michael Albrecht** (Meyer) Analysis of Dosage Compensation and Chromosome Segregation in *C. elegans*.
- **Jeanne Baker** (Raulet) Elements That Control the Developmental Pattern of V(D)J Recombination and Transcription at the T Cell Receptor γ Locus.
- **Renee Baran** (Garriga) The Role of the *unc-42* Gene in Neuronal Differentiation and Axon Pathfinding in *C. elegans*.
- **Paul Baum** (Garriga) Molecular Genetic Analysis of the Migrations of the *Caenorhabditis elegans* Hermaphrodite Specific Neurons.
- **Eileen Beall** (Rio) Regulation of the P-Element Transposase Protein by the *Drosophila* DNA-dependent Protein Kinase.
- **Pierre Beaurang** (Tjian) Reconstitution of Chromatin Regulated Transcriptional Activation at the HIV LTR.
- **Victor Boyartchuk** (Rine) Prenylation-dependent Processing of Proteins in *Saccharomyces cerevisiae*.
- **Christine Brown** (Sachs) Messenger RNA Poly(A) Tail Metabolism in *Saccharomyces cerevisiae*: Roles for the Pab1p-dependent Poly(A) Nuclease.
- **Patricia Buse** (Firestone) Regulation of the Serum- and Glucocorticoid-Inducible Protein Kinase by Hormones and the Cell Cycle.
- **Aaron Chamberlain** (Marqusee) Partially Folded Conformations of *E. coli* Ribonuclease H.
- **John Chuang** (Schekman) Differential Trafficking and Timed Localization of Two Chitin Synthase Proteins, Chs2p and Chs3p, in *Saccharomyces cerevisiae*.
- **Laura Corral** (Raulet) Novel Monoclonal Antibodies Against Mouse NK Cell Receptors.
- **Gene Cutler** (Tjian) A Functional and Structural Characterization of the *Drosophila* Transcription Factor ADF-1.
- **Judith Davie** (Kane) Genetic Interactions of the Transcription Elongation Factor TFIIS from *Saccharomyces cerevisiae*.
- **Andrew Dillin** (Rine) Studies of the Origin Recognition Complex in the Yeast *Saccharomyces cerevisiae*.
- **Jason Dugas** (Ngai) Olfactory Receptor Genes: Genomic Organization and Transcriptional Regulation.
- **Eva Finney** (Shatz) Role of Subplate Neurons in Cortical Development.
- **Kenneth Frauwirth** (Shastri) Presentation of Endogenous Antigens by MHC Class II Molecules: Analysis of Processing Pathways and the Function of the Invariant Chain.
- **Balasubramanian Girish** (Miller, J.) Cricket Wind Detection: A Study of the Coding of Temporally Varying Vector Stimuli by a Well-Defined Neural Ensemble.
- **Richard Harris** (Isacoff) The Permeation Pathway of a Potassium Channel.
- **Christian Hofmann** (Drubin) Genetic Identification of Cytoskeletal Elements in *Saccharomyces cerevisiae*.
- **Deborah Isaksen** (Weisblat) The Identification of a TGF-Beta Class Gene and the Regulation of Endodermal Precursor Cell Fusion in the Leech.
- **Daniel Joo** (Calendar) Studies of the Interaction between the Heat Shock σ^{32} Factor and Core RNA Polymerase in *Escherichia coli*.
- **Andrew Kasarskis** (Harland) Isolation and characterization of ENU-induced Mutations Disrupting Normal Postimplantation Development in the Mouse.
- **Otis Littlefield** (Nelson/Thomas Ernest) Crystal Structures of the *Kluyveromyces lactis* Heat Shock Transcription Factor DNA-Binding Domain Complexed with DNA.
- **Kevin Mitchell** (Goodman) Combinatorial Mechanisms Involved in Commissure Formation and Motor Axon Target Selection in *Drosophila*.
- **Mario Pantoja** (Anderson) Molecular and Biochemical Studies of the Maternal Pathway Required for Embryonic Dorsoventral Polarity in *Drosophila melanogaster*.
- **Rhett Pascual** (Nandi) The Activation of the H-*ras* Gene in N-Methyl-N-Nitrosourea-Induced Rat Mammary Tumors is Regulated by the Ovarian Hormone Estradiol.
- **Sussan Paydar** (Jacobs) Anatomical and Functional Mapping of Primary Sensory Neurons in the Cricket Cercal System.
- **Elicia Penuel** (Martin) Characterization of Cellular Transformation by v-Src.
- **Carmen Robinett** (Dunaway) Identification and Analysis of an Insulator Element within the Intergenic Spacer of the *Xenopus* rRNA Genes.
- **Christine Rousseau** (King) Genetics of Perinatal HIV-1 Infection.
- **Nell Shimasaki** (Kane) Structure Function Analysis of the Eukaryotic Transcription Factor TFIIS.
- **Cheryl Smith** (Martin) Biochemical and Genetic Characterization of the *cdc18+* Gene of *Schizosaccaromyces pombe*.
- **Susan Uptain** (Chamberlin) Structural and Functional Characterization of *Escherichia coli* RNA Polymerase Ternary Complexes during Transcript Elongation and Termination.
- **Karen Zito** (Isacoff) Mechanisms Controlling Synapse Formation and Development at the *Drosophila* Neuromuscular Junction.

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