

MCB Transcript

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

A NEW CENTER BRINGS TOGETHER DIVERSE INTERESTS

Malaria, tuberculosis, and other diseases that have a disproportionate effect on populations in developing countries are termed “neglected” diseases. Because the people and countries affected are poor, these diseases have traditionally given most scientists and pharmaceutical companies little financial incentive to work on them. Not only is basic research on neglected diseases often underfunded, but discoveries are rarely translated into useable vaccines, treatments, and diagnosis tools that could save people’s lives. UC Berkeley researchers are exploring whether the university could have a role in bridging these gaps.



CEND's Executive Director Temina Madon (left) participating in a workshop in Nigeria

In 2005, Geoffrey Owen, then the dean of the Biological Sciences Division, convened a meeting to gauge interest among UC Berkeley faculty members in forming a center for neglected diseases. Owen conceived that such a center might not only support basic research into neglected diseases but also support the translation of academic discoveries into therapies and vaccines. The idea took hold, culminating in the Center for Emerging and Neglected Diseases.

“People who are doing neglected disease research want to solve scientific problems, but they wouldn’t be working on these areas unless millions of people were getting sick,” says CEND faculty director and MCB professor Tom Alber. “A major aim [of the center] is to foster the process of translating some of the discoveries into significant impacts in the world.”

CEND is a campus-wide organization made possible by a gift from Henry Wheeler. It launched in March of 2008 as one of two organizations under the Berkeley Alliance for Public Health. CEND includes over 50 faculty members from 14 departments.

“What’s unique about us is the interdisciplinarity, that we are bringing in chemists, bio-engineers, chemical engineers, molecular biologists, as well as environmental scientists to collaborate,” says Dr. Temina Madon, who was hired in 2007 as CEND’s first employee. It is Madon’s task to bring the diverse groups together into one community.

Both CEND’s advantage and its challenge lie in the diversity of its members.

FOR A COMMON GOAL



MCB Professor and CEND faculty director Tom Alber (right) with Prasant Kumar, an undergraduate from the Indian Institute of technology at Kharagpur, who was hosted in a summer research exchange program.

Although cross-pollination of ideas across fields can spark ideas for research, getting people to take time out for such encounters isn’t always easy. To encourage in cross-mingling, CEND invites a wide range of investigators as well as people from non-academic professions to participate in its seminars, symposia, and lunches.

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As faculty director, Alber's vision for CEND includes four major goals: training students in new ways, fostering original research defined by disease burden, developing top-tier research facilities, and building community interactions locally and internationally. While some CEND investigators have decades-long collaborations in South Asia, Africa and Latin America, others are making new connections through the Center. For the last two years, CEND has hosted a summer undergraduate research program for students from the Indian Institute of Technology, creating new links between U.S. and Indian faculty members. To bring Berkeley innovations to scale, the Center is brokering campus alliances with organizations that have large international operations—including Gilead Sciences, Google.org, Celera Diagnostics, and the Novartis Vaccines Institute for Global Health.

"I think there's a growing understanding in the US, and in our area, of the important connection between global health and peace," says Alber.

The following articles share some of the research and experiences of MCB researchers involved in CEND.

A BACTERIUM BRIDGES THE GAP BETWEEN BASIC RESEARCH AND USEFUL THERAPIES

That his model organism *Listeria monocytogenes* might make a good vector for vaccines occurred to MCB and School of Public Health Professor Dan Portnoy many years ago. After some initial positive results, he decided to put the idea aside not knowing that, almost two decades later, he would be contacted by a local biotechnology company wanting his help to do just that.

Listeria monocytogenes is the model organism Portnoy uses to study the molecular and cell biology of intracellular pathogens. The bacterium can cause listeriosis, a potentially lethal infection, when ingested in contaminated food. When *Listeria* first infects a cell, it is sequestered in a phagosome. This should be the end of the infection, but *Listeria* is able to escape



Professor Dan Portnoy

from the phagosome. As a free agent in the host cell's cytoplasm, it hijacks the host's cytoskeleton to mobilize and ultimately infect other cells.

Immunity to *Listeria* and other intracellular pathogens requires what is called cell-mediated immunity that involves antigen-specific killer T-cells. Antibodies play no role in this type of immunity. At least in mice, *Listeria* is the champion at inducing cell-mediated immunity, which led investigators to consider engineering *Listeria* as a vector for the induction of immunity to other pathogens and even cancer. An ideal vaccine strain must be safe, but still effectively trigger an immune response. Overly attenuated strains not only fail to immunize, but Portnoy has shown that they can even block immunization.

A few years ago, Portnoy and MCB Professor Matt Welch studied how a single bacterial surface protein, ActA, was able to nucleate actin polymerization and drive the intra and intercellular movement of the bacteria from cell to cell. It was later found that ActA-minus mutants were highly attenuated, yet fully immunogenic. This is the base strain being used in clinical trials for cancer immunotherapy. Recent research from the Portnoy lab has identified a collection of *Listeria* mutants that activate different arms to the immune system and may provide more potent vaccines or vaccines for different applications.

The attenuated bacteria can be engineered to express antigens that will stimulate the immune system to protect against intracellular infections or provide immunotherapy to fight an existing disease, such as cancer.

"Immunity to cancer and intracellular pathogens is overlapping," says Portnoy. "In both cases you are trying to eliminate self, host. So these vaccines may work for both."

Portnoy provides his expertise as a consultant for Berkeley-based Aduro

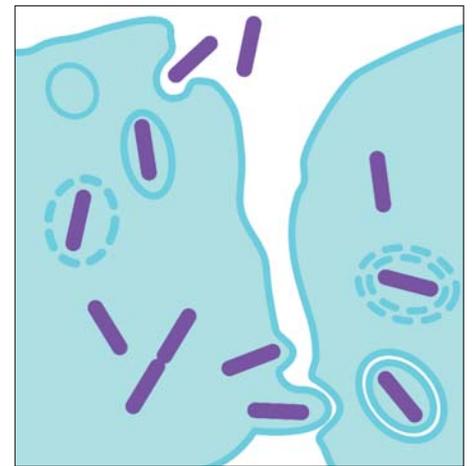
BioTech, which has developed *Listeria*-based immunotherapy for cancer and hepatitis C virus. They are also developing vaccines for HIV, malaria, and tuberculosis.

"We are doing the basic science and the biotech company is translating it into vaccines," says Portnoy regarding his role at Aduro. "The question comes up of what should be done in academia and what should be done in a company. I think that is one of the issues that we are debating within the Berkeley Center for Emerging and Neglected Diseases (CEND). In this case, there are so many issues related to manufacturing, quality control, and analysis that, in my opinion, it's better served to do this in the private sector."

Portnoy is pleased, and somewhat surprised, in reflecting that his experiences with a biotech company have amounted to much more than a one-way flow of information. The researchers in the company have developed reagents and experimental protocols useful for Portnoy's lab.

The relationship also provided a more unexpected benefit. "They modeled how a group of investigators could work together for a common goal, where in academia it tends to be more individual," says Portnoy. "I've used that [model] to try to encourage people to work together in my own lab. So, I feel it's helped my research program."

"Although I am a basic scientist at heart, it is gratifying to see one's research translated into products that may benefit the human condition," says Portnoy.



Life cycle of the Listeria monocytogenes. When Listeria enters a host cell, it is sequestered in a phagosome. It escapes the phagosome and uses the host's cytoskeleton to move across the cell and into neighboring cells.

COXING HIV OUT OF HIDING

Long gone are the days when the diagnosis of HIV in the USA was tantamount to a death sentence. Through a complex “cocktail” of medicines that target several viral functions simultaneously, the AIDS can be managed well enough to allow many people to live long and mostly normal lives.

Although this treatment is an amazing success, there is still room for improvement. Because the cocktail is expensive, it is out of reach for most in economically depressed countries. Even for people in wealthy countries, treating HIV/AIDS as a chronic disease is less than ideal.

“Because the patient needs to take the cocktail every day for a very long time, there is a risk of virus having resistance to the therapy,” says MCB Professor Qiang Zhou. “There are some other complications because the drugs are fairly toxic and inhibit a lot of the normal functions of cells. So the idea is to find new therapies, new targets, for treatment and also for making vaccines. That’s what we are doing.”

Zhou’s laboratory is researching the transition between the latent stage of the HIV virus, when the RNA genome has been reverse transcribed into DNA that is inserted into a host chromosome and remains silent, and the active stage, when the integrated viral DNA is actively transcribed to make fresh HIV proteins and RNAs for efficient replication and infection of other cells. The latent viral DNA, hidden from the immune system, can wait for years until some trigger causes its genes to start being expressed. When this happens, the virus goes into full production mode.

“Within a relatively short period of time, the virus reactivates in an explosive manner,” says Zhou. “Reactivation requires a really fast response.”

The viral transcription factor Tat is critical for the reactivation of latency. Tat forms a complex with the human transcription elongation factor P-TEFb, which is a focus of Zhou’s laboratory.

“We have been studying how you can target the Tat protein and its interaction with P-TEFb to perhaps control viral replication,” says Zhou. “A newer way of

thinking in the field is, perhaps, to activate Tat function through activating one of its co-factors such as P-TEFb (to wake up the virus) in the presence of the combination of the drug cocktail. This may lead to the eradication of the virus and to obtaining a final cure of HIV infection.”

Zhou’s lab found that P-TEFb activity is tightly regulated. It can exist in either an active state or an inactive state, the ratio between the two changing depending on the needs of the cell. Because P-TEFb is involved in controlling cell growth, its activity has also been implicated as contributing to some cancers.

bifunctional complex to achieve synergistic activation explains why Tat is such an incredibly powerful activator of HIV gene expression and plays such an important role, especially during latency reactivation.”

This work was accomplished in collaboration with MCB professor Tom Alber’s laboratory and has been submitted for publication. They will continue their collaboration as Alber’s lab determines the crystal structures of these complexes and Zhou’s lab continues to search for other factors that may control their activities and uncover ways to affect latency reactivation.



Qiang Zhou (front, second from left) with collaborator Dr. Ruichuan Chen (front left) with Chen’s laboratory members at Xiamen University.

Using affinity purification techniques, members of Zhou’s group recently searched for other factors involved in the Tat and P-TEFb interaction. To their surprise, they found that Tat mediates the interaction of another human elongation factor with P-TEFb. This discovery was unexpected because the two transcription factors usually work separately and through different mechanisms.

“This provides the first evidence that P-TEFb actually works together with another elongation factor because of Tat,” says Zhou. “The ability of Tat to recruit two different classes of elongation factors into a

Zhou is also engaged in a long-term collaboration with a laboratory in China. Together they wrote an advertisement to attract undergraduate and graduate students to a new HIV/AIDS research program sponsored by CEND. This summer, the chosen students will spend a few weeks starting a research project at UC Berkeley and then will travel to China to complete the project.

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BEYOND THE BENCH

Last year, MCB graduate student Lisa Prach boarded an airplane for South Africa to find out if her research topic could be relevant to real people affected by disease. Prach, who is a member of MCB professor Tom Alber's laboratory, was interested in a small group of lipids unique to the tuberculosis bacterium. The scientific literature suggested the lipids might be interesting, but no one knew if they play an important role in human disease.

In her two-month residence in the laboratory of Paul van Helden and Rob Warren at the University of Stellenbosch in Cape Town, South Africa, Prach had access to clinical isolates organized by strain history and associated with patient histories. She grew the strains, isolated the lipids, and analyzed the abundance of different lipid types in collaboration with the Keasling group. She found a few lipids that may contribute to TB in people.

"If these lipids were just playing a structural role, for instance, the abundance would probably be relatively uniform across all of the different strains," says Prach. "However, the particular lipids that I am interested in show up to a 35-fold change in abundance between different strains. So that could indicate that there's positive selection for their production within certain strain families. Does it give selective advantage for these strains? That's a future avenue of research."

Prach's travel was sponsored by a fellowship from CEND, which encourages international collaborations as opportunities to make unique basic discoveries and to give researchers insights into the research questions most relevant in disease-endemic communities. This is certainly true for Prach, who values her experiences in South Africa as much as her experiences in the laboratory.

"It was truly eye-opening to go to a country where the disease prevalence is so high," says Prach. "Pretty much everyone I talked to knew someone who had TB at some point. Think about that. Do you know anyone in the US that's ever had TB? It's big



Lisa Prach (right) with colleagues in South Africa

news when that happens here, but in South Africa it's an every day occurrence." One of the first two students to be sent abroad using their travel grants, CEND views her trip as an unqualified success and an example for others.

"She deserves all of the credit," says Alber, who in addition to being Prach's thesis advisor is the director of CEND. "She figured out on her own that this would be a good thing to do. She made the contacts and she went to South Africa and met people. She set up this project on her own. It's really great to have a mechanism to support that. And I assure you that she has inspired other people to try to do the same thing."

When asked if she has inspired her peers, Prach replies, "I have been approached by several younger graduate students and they ask me about my

research experiences. I hope that maybe I've inspired them to go out and apply for these CEND fellowships that are available. It's been really amazing and incredibly influential in planning my future career."

Prach, who graduates at the end of this year, will bring her laboratory research expertise into a public health field through either earning a masters degree in public health or taking a postdoctoral fellowship in a public health related area. "You never know where the road is going to take you," she says. "When I came to grad school I had no idea I would be doing any of this. So who knows what the next five years will bring."

FACULTY NEWS

■ The Pew Charitable trust selected **Diana Bautista** as a 2009 Pew Scholar in the Biomedical Sciences. The award was given to 17 early-career scientists who display outstanding promise in research relevant to the advancement of human health.

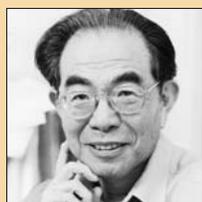
■ **Laurent Coscoy** was promoted to Associate Professor effective July 1, 2009.

▼ **Kunxin Luo** was promoted to Professor effective July 1, 2009.



■ **Andreas Martin** was selected as a 2009 Searle Scholar. The Searle Scholar Program awards 15 grants per year to selected universities and research centers to support the independent research of exceptional young faculty in the biomedical sciences and chemistry.

▼ **Hiroshi Nikaido** and **Mu-ming Poo** were elected to the National Academy of Sciences during the 146th annual meeting of the Academy this year. The National Academy of Sciences is a private organization of scientists and engineers established in 1863 by a congressional act signed by Abraham Lincoln. The Academy acts as an official adviser to the Federal Government, when requested.

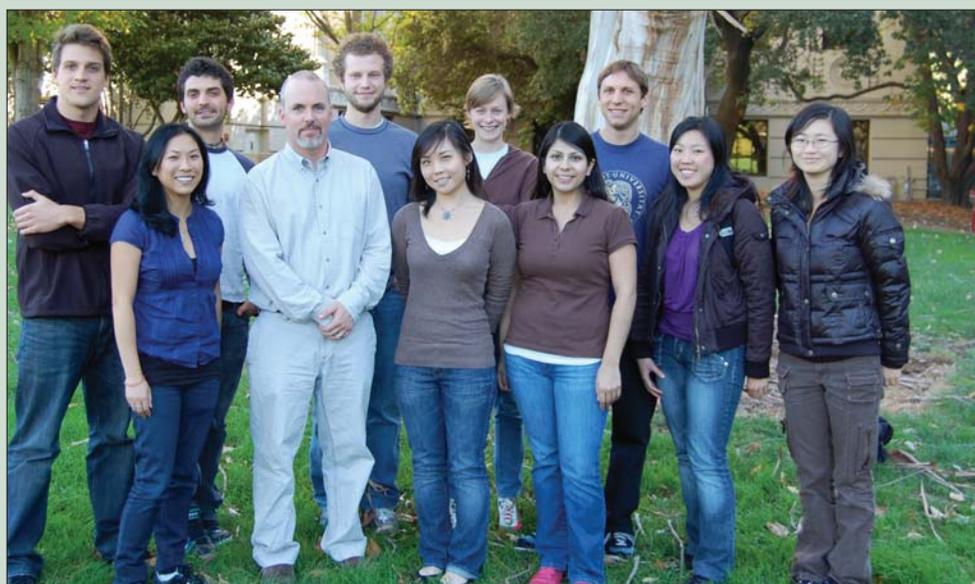


■ The Burroughs Wellcome Fund selected **Russell Vance** for a 2009 Investigators in the Pathogenesis of Infectious Disease award.



BOWES FELLOWSHIP

MCB welcomed **Woj Wojtowicz** in August as the first Bowes Fellowship recipient. The Bowes Fellowship program allows recent Ph.D. and M.D. graduates a chance to set up an independent lab rather than a more traditional postdoctoral appointment. Wojtowicz is researching the development of neural connections in the brain.



Professor Greg Barton with his laboratory personnel

MCB RESEARCHERS AWARDED STIMULUS FUNDS

The NIH recently awarded funds specified by the 2009 American Recovery and Reinvestment Act (ARRA) to two projects headed MCB researchers. The UC Berkeley campus has received around \$65 million of the \$25.1 billion in stimulus funds promised to fund scientific research nationwide.

Gregory Barton was awarded a grant of \$400 thousand over two years. This will fund his investigations of the innate immune system, which is important in intracellular and autoimmune diseases. He will create a mouse model for toll-like gene receptor TLR9 gene function.

Daniel Portnoy is the PI of a P01 grant that received a \$5 million over two years. It includes MCB professors **Russell Vance** and **Gregory Barton** as well as researchers from UCSF and Stanford. The project is entitled, "Intracellular pathogens and innate immunity."

2008-2009 GRADUATES

FALL 2008

- **Raymond Chen** (Thorner) Function and Regulation of Nitrogen-Activated Protein Kinases in the Yeast *Saccharomyces cerevisiae*
- **Gregory Crimmins** (Portnoy) Interaction of *Listeria monocytogenes* with a Host Cytosolic
- **Luis Estevez** (Luo) Regulation of the TGF- β by the Inner Nuclear Membrane Proteins MAN1, Ski and SnoN: A Genomic Approach to Understand their Functions
- **Ming Yu Hsiung** (Raulet) Regulation of Genes Encoding Murine Rae 1 Natural Killer Cell Activating Ligands
- **Elsa Lee** (Forte) Characterization of *Caenorhabditis elegans* Mechanosensory Protein -6 (MEC-6), a Homolog for Human Paraoxonase 1(hPON1)
- **Nick Levinson** (Kuriyan) Structural Studies of Tyrosine Kinase Regulation and Substrate Specificity
- **Byungkook Lim** (Poo) EphrinB-Reverse Signaling Promotes Structural and Functional Maturation of Developing Retinotectal Synapses *In Vivo*
- **Yuko Nakajima** (Barnes/Drubin) Organization and Regulation of the Chromosomal Passenger Complex in *Saccharomyces cerevisiae*
- **Christine Nam** (Chen) Extracellular Interaction Defines AMPA Receptor Trafficking Checkpoint Regulated by Stargazin
- **Ronald Parchem, Jr.** (Patel) Segmentation in *Parhyale hawaiiensis*
- **Elizabeth Quezada** (Kane) *In Vitro* Studies of Hepatitis C Virus (HCV) RNA Dependent RNA Polymerase NS5B: The Impact of the NS5A Protein on Replication
- **Bertrand Vick** (Tjian) Roles for Combgap Ad GAGA-Factor in Long-Range Enhancement of the *Drosophila melanogaster* Gene Sex Combs Reduced
- **Rebecca Waitz** (Allison) Enhancement of T Cell Responses Through CTLA-4 Blockade Combination Therapy in Mouse Model of Prostate Cancer
- **Joyce Wei** (Allison) The Role of B7x in Maintaining Peripheral Tolerance
- **Mary Wilson** (Schlissel) The role of TRAIL Suppression, CD19 Signaling, and CARMA1 Interference in the Survival of Abelson Transformed Cells
- **Zhiyuan Yang** (Zhou) Controlling RNA polymerase II Transcriptional Elongation Through Positive and Negative Regulation of P-TEFb

SPRING 2009

- **Jessica Cande** (Levine) Evolution of Insect Dorsoventral Gene Networks
- **Zain Dossani** (Weis) mRNP Remodeling at the Nuclear Pore Complex: Studies in *Saccharomyces cerevisiae*
- **Walter Fischler** (Scott) Taste Modalities in *Drosophila*
- **Benjamin Freedman** (Heald) Linker Histone Structure, Function, and Dynamics in *Xenopus* Egg Extracts and Embryos
- **Jodi Gureasko** (Kuriyan) Membrane-dependent Control of the Ras Activator Son of Sevenless
- **Giao Hang** (Dan) Interactions of Synaptic Inputs from Multiple Cortical Pathways in the Visual Cortex
- **Shirley Huang** (Marletta) Biochemical Characterization of Oxygen Regulated Soluble Guanylate Cyclases: Ligand Binding and Enzymatic Activity
- **Nicole Meyer-Morse** (Portnoy) The Cellular and Immunological Consequences of Listeriolysin O Mediated Vacuolar Escape
- **Melissa Mott** (Berger) Structural and Biochemical Studies of Bacterial DNA Replication Initiation
- **Voytek Okreglak** (Drubin) Actin dynamics in *S. corovisiae*
- **Stephanie Osborn** (Winoto) The non-Apoptotic Roles of the Fas-Associated Death Domain (FADD) Protein in the Immune Response
- **Bilge Ozaydin** (Rine) The Interplay Between the Replication Proteins and Silencing Proteins in *Saccharomyces cerevisiae*
- **Stacia Rodenbusch** (Dernburg) The Regulation of Synaptonemal Complex Assembly During Meiosis in *C. elegans*
- **Ryan Shultzaberger** (Eisen) Functional Variability in Transcriptional Initiation Complexes
- **Mansi Srivastava** (Rokhsar) Early Animal Evolution: Insights from the Genomes and Embryos of Cnidarians, Placozoans and Sponges
- **Brian Sullivan** (Coscoy) Immune Modulation by Human Resoecoloviruses
- **Leonid Teytelman** (Eisen/Rine) Evolution of Silencers and Silenced DNA in Budding Yeasts
- **Jennifer Thompson** (Winoto) The Molecular Mechanism of Nur77/Nor-1 Induced Apoptosis of Thymocytes Undergoing Negative Selection
- **Mario Vargas-Vila** (Patel) Single-Cell Laser Ablations and Dorsoventral Patterning in the Amphipod *Parhyale hawaiiensis*
- **Andrea Wills** (Harland) BMP Signaling and Antagonism in *Xenopus* Development
- **Jason Zemansky** (Portnoy) Development of a Mariner based Transposon and Identification of *Listeria monocytogenes* Determinants, Including the Peptidyl-prolyl Isomerase PrsA2, that Contribute to its Hemolytic Phenotype

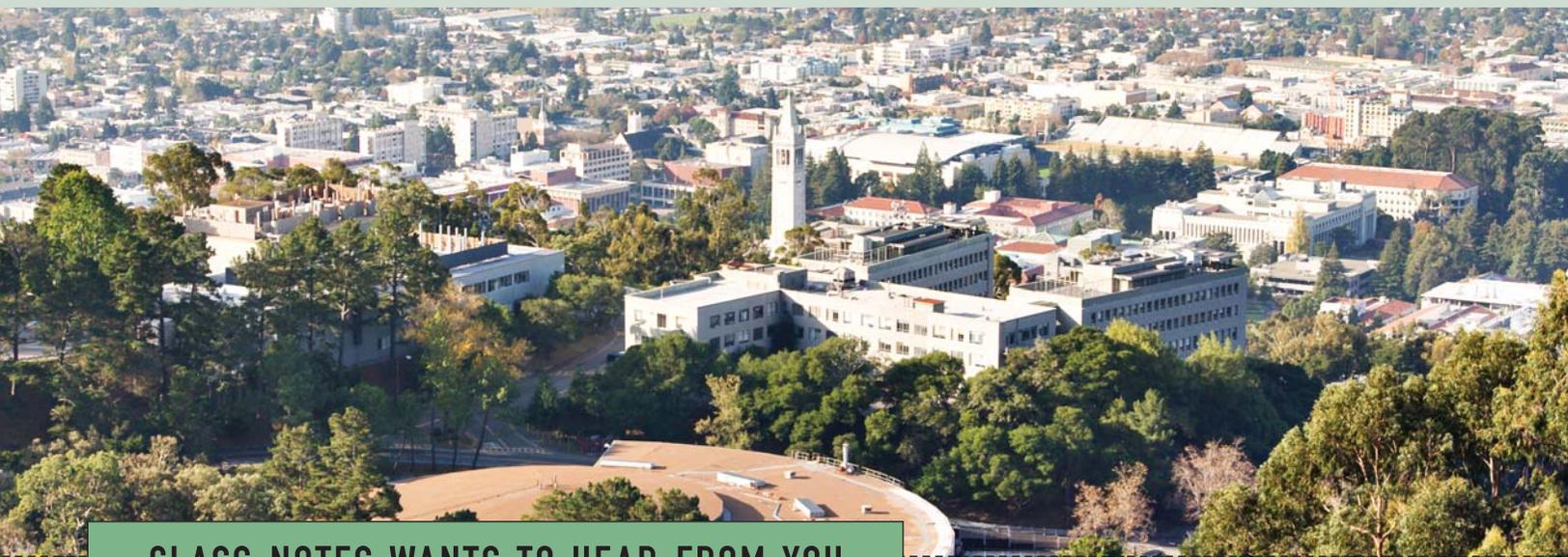
CLASS NOTES



■ Adjunct Professor **Mark Alper** [PhD 1973] has retired after 42 years with the Department. He will, however, continue to teach his MCB classes. He was also Deputy Director of the Materials Sciences Division, Director of the Biomolecular Materials Program, and Deputy Director of the Molecular Foundry, all at LBNL.

■ **Susan De Long** [BA 1999] earned an M.S.E. in Environmental Engineering from the University of Texas at Austin and recently also completed a Ph.D. She is an Assistant Professor at Colorado State University in the department of Civil and Environmental Engineering. She studies bacteria that degrade pollutants and does a lot of molecular biology. She says she is "still using all of the great stuff I learned in the MCB department at Cal!"
[Susan.De_Long@colostate.edu]

■ **Tom Serwold** [Ph.D 2000] was appointed as Assistant Professor at the Joslin Diabetes Center and Harvard Medical School.



CLASS NOTES WANTS TO HEAR FROM YOU

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

To send your Class Note, you can

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

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CEND'S TARGET COMPETITION

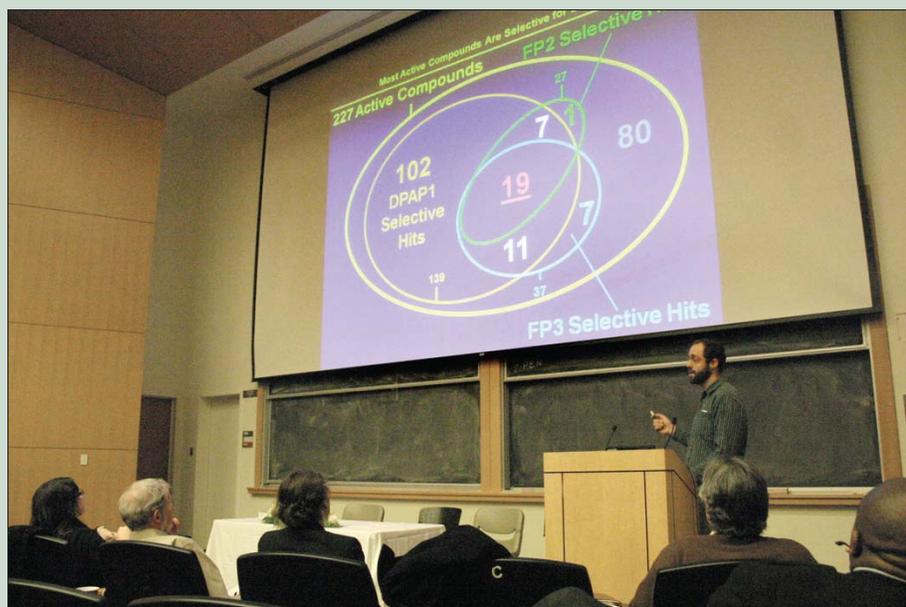
ENCOURAGES DRUG DISCOVERY RESEARCH

UC Berkeley's Center for Emerging and Neglected Diseases hosts a drug discovery competition as a part of their annual research symposium. This one-day event brings together a panel of venture capital and biotechnology industry judges to rate presentations of research proposals by graduate students, postdoctoral fellows, and faculty from UC Berkeley, UC San Francisco, and Stanford University. Each contestant has just 10 minutes to describe a pathogen or host behavior that, if disrupted by a drug-like molecule, could prevent or treat infectious disease. As in the TV show American Idol, the audience also has a chance to vote. The winning "drug target" will be tested against a library of drug-like molecules maintained by the Small Molecule Discovery Center at UCSF. The success of last year's maiden contest has encouraged CEND to make the competition an annual event.

"It's exciting and it's something that gets people roused and curious," says CEND's Temina Madon. "I think it also teaches people about the drug discovery process, which is something most academic scientists don't typically get involved in."



Professor Rafi Ahmed, Director of the Emory Vaccine Center, speaking at the CEND Symposium on December 10, 2009



Last years' contest winner Edgar Deu Sandoval, a Stanford postdoctoral fellow, explaining the progress on his project at the 2009 CEND symposium

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