

2011

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 Note from the Chairs of MCB

In travels around the world a frequently posed question we hear is: "Will Molecular and Cell Biology at UC Berkeley survive?" Now we appreciate that misery loves company, and with endowments cut to bare bones all over and 401Ks dropping to 201's, it is hard to say "Well, we are not only surviving, but perhaps doing better than we have ever done." Of course, budget cuts from the state were terrible for our staff, because we have to struggle to do more with fewer staff. Undergraduate education suffers with less money

for labs and overcrowding in the classroom is indeed ugly. However, our research and graduate programs are as strong and perhaps stronger than ever, using any measure we apply. A few examples: We have had at

least 12 faculty offered extravagant offers from prominent institutions during the last 4 years, and despite this feeding frenzy from competitors who think they sense a sinking ship, MCB has suffered only one loss, and that for personal family reasons. As documented in the pages of this newsletter, our faculty have in the past 2-3 years won MacArthur, HHMI and Cancer Society faculty awards from private sources, received Pioneer and Eureka awards from NIH, and been elected to honorific societies such as the AAAS and the NAS. We are presently involved in new faculty searches for 4 positions, and have a new building, the Li Ka Shing center for bio-medical sciences, that will be ready by early 2012 to house some of these new recruits. Last but perhaps not least, the recent NRC ratings for graduate programs in science list all of our divisions in the top categories. Like Avis we must be trying harder.

But these are hard times and it is a challenge to keep up with falling NIH budgets. Many are predicting a big shake out in research support from the federal government, after which only the truly exceptional centers will be left standing. On top of this we understand that State support for Cal will never go back to where it was during the salad days of the early 80's. But at the risk of being called "Pollyannas"—or worse—we do find the challenge exciting. Many may be aware of the recent "Operational Excellence" programs being put forward and studied by campus. Some of this is "Animal Farm"-speak for cut and contract. On the other hand through the initiative of Dean Schissel we look forward to a merging of administrative staff with IB that we hope will bring these two departments closer together. We will survive!



— Michael Botchan & G. Steven Martin

Innate Immunity:

MCB labs analyze our front line of defense

Ask most people what they know about immunity and they are likely to mention T-cells, antibodies, and other parts of the adaptive immune system. However, our first line of defense against infectious agents is the innate immune system, an evolutionarily older collection of receptors and cells that recognizes more general features of bacteria, viruses, and even our own cancerous cells.

MCB faculty members are studying various aspects of this critical system. The following articles represent just some of the work on innate immunity being done by members of the department. Greg Barton studies innate immune receptors that detect potential threats in the fluid between cells. Russell Vance focuses on how infectious agents within cells are detected. David Raulet is discovering how the innate immune system responds to our own cells gone awry. A common thread in all of these stories is the problem of how to distinguish what is self from not-self, as well as what is harmful versus benign.

The professors point out that a critical element to their labs' successes is the close community among those researching innate immunity and related systems.

"There's a ton of synergy," says MCB Assistant Professor Greg Barton. "It's almost like every grad student has at least two if not three PIs who they can go to get help. That makes this a very nice place for people to train, and it makes it great for us, too."

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Interrogation Chambers: *How Compartmentalization Aids Discrimination*



MCB Assistant Professor
Greg Barton with graduate
student Maria Mouchess

The adaptive immune system makes millions of different antigen receptors to identify specific disease agents. The innate immune system, often the first to respond to signs of disease, uses a different strategy. Multiple general receptors on a single cell allow the recognition of many potential threats. Coded for in the genome, these receptors have evolved to respond to the most informative general targets.

“The interesting thing is that evolution had to make very hard choices about what those receptors should see, because with twelve receptors they have to see many different microbes,” says MCB Assistant Professor Greg Barton. “They evolved to recognize very conserved features on microbes.”

Barton is interested in understanding what the innate immune system’s strategies for general microbial recognition are and what trade-offs are tolerated because of these choices. His lab focuses on the Toll-like receptors (TLRs), which monitor the contents of the extracellular space. Some TLRs look for molecules that are common in bacteria but not made by mammalian cells, such as lipopolysaccharides. The presence of such molecules is a telltale sign that something foreign is present. Other TLRs detect molecules that are found in mammalian cells, like DNA and RNA.

The presence of four nucleic acid detecting TLRs in humans suggests that there is an adaptive advantage, perhaps the recognition of viruses, that outweighs potential complications in discriminating between similar molecules found in both host cells and foreign agents. While the DNA of healthy mammalian cells is safely tucked away in the nucleus where the TLRs cannot see it, DNA from dead cells can be in the extracellular space and should not trigger alarm by the TLRs.

Part of the answer as to how this self-discrimination takes place, says Barton, is that the cells internalize samples of the extracellular medium into compartments. The TLRs that recognize nucleic acids, like TLR9 that recognizes DNA, are only active within the compartments and not on the cell surface. For reasons not completely understood, virus DNA is much more likely to be found in these vacuoles than self-DNA. Barton’s first graduate student Sarah Ewald, who was awarded the Cozzarelli Prize when she graduated last spring, uncovered the biochemistry of how TLR9 is activated, by a proteolytic cleavage, in the intracellular compartments. In this way, the cells ensure that TLR9 will not respond to self-DNA in the extracellular space.

Another graduate student, Maria Mouchess, found mutations that allow TLR9 to be always active, even when not cleaved. This allowed her to test the theory that compartmentalization is important for successful self-discrimination. She found that mice who have active TLR9 mutants on the cell surface succumb to an aggressive auto-inflammatory disease, having become sensitive to their own DNA.

“This result is exciting because it supports very strongly the idea that compartmentalization is really key for enabling the innate immune system to use nucleic acids as a way of seeing foreign [entities],” says Barton.

Barton’s lab is currently working to understand the specifics of how this system works, for example how the receptor localization is controlled and whether the break-down of this system has different consequences in different cell types. Answering these questions can give insight into the mechanisms of auto-immune diseases in humans.

“I think this is a general theme in biology,” says Barton. “There’s a huge amount of information that comes from compartmentalization. We have a lot of evidence for that in innate immunity, and there’s lots of evidence for it in other aspects of biology, too, that a way of generating information is to route something someplace and then special signaling components that are there or not there generates differential information. We think that’s basically how the TLR9 system works.”

A Cancer's Barcode:

How NK Cells Find Distressed Cells

Like the adaptive immune system's more famous killer T cells, the innate immune system has its own sniper cells that find and destroy infected cells. For 20 years MCB Professor David Raulet has been studying these natural killer or NK cells, which target cancerous and virus-infected cells.

Part of Raulet's research focuses on how NK cells distinguish healthy versus diseased cells, which has led him to the receptor NKG2D. This receptor resides in the membranes of NK cells and can activate the killer pathways when it recognizes certain features of diseased cells. Raulet's lab found a family of cell surface proteins that are recognized by the NKG2D receptor.

"These were not foreign ligands; they were all proteins that we have—that humans and mice both have," says Raulet. "What's fascinating about them is that they are expressed on cancer cells but not on many normal cells. They are displayed on the surface of disease cells and enable NK cells to recognize the cell and kill it."

Raulet's lab found that cancer cells produce and display these ligands like a flags to recruit NK cells to come destroy them, and the NK cells are like a roving cancer and infection surveillance system. Further experiments with cancer susceptible mice demonstrated that genetic deficiency of NKG2D receptors resulted in a higher incidence of more malignant cancers. Interestingly, analysis of the cancers from the knockout mice showed that all these cells displayed the NKG2D ligands, but with no NKG2D receptors to recognize them, while none of the cancers tested from the wild type mice displayed the ligands. Raulet hypothesizes that natural mutations that might arise in some cancers to foil the self-flagging pathway would allow a cancer to evade detection by the NK cells.

But how does a cell know that it is not normal and needs to be removed? Cancer cells do many of the same things normal cells do, like proliferate and move; the difference is that they do these things at the wrong time or place. The triggers that cause cells to flag themselves as cancerous may not be linked to just one activity, but an array of different information together—like data in a barcode used to identify consumer products.

"Like a barcode in a supermarket, where each bar is a different kind of information, our idea is that cells need to have the right combination of signals to get expression of the NKG2D ligands," says Raulet.

For example, part of the information from a cell's cancer-ID barcode is from the DNA damage response. DNA may be damaged many different ways, most of which are not due to cancer. But the rapid replication of cancer cells is known to trigger a cell's DNA damage response, so its activation is a suggestive, but not indicative, sign that something might be wrong. Ongoing research by Heiyoun Jung, a grad student in Raulet's lab, shows that cell proliferation is another signal tied to expression of NKG2D ligands.

Collaborations with MCB Associate Professor Laurent Coscoy and grad student Maria Tokuyama are uncovering how herpes virus infection triggers cells to make the NKG2D ligands. But the virus has evolved to fight back by down-regulating expression of these proteins. They are finding strong parallels between regulation of NKG2D ligand expression in cancerous and virus-infected cells.

Next, says Raulet, is fitting the big picture together by understanding how individual pathways make up the barcoding system. He is also interested in exploring the potential link between NK cells and inflammatory diseases.

"This system seems a little dangerous when you think of it," says Raulet. "Basically the system is mounting a response that is meant to be protective, but when conditions conspire the NKG2D ligands may be expressed inappropriately. There's now a lot of emerging evidence that NKG2D plays a role in inflammatory and autoimmune diseases."

Understanding this aspect of the innate immune system could have far-reaching implications for many human diseases.



MCB Professor
David Raulet



Friend or Foe:

How Microphages Read Microbe's Intentions



Legionella pneumophila,
the bacterium that causes
Legionnaires' disease

In the ecosystem of a human organism that includes more microbial cells than human cells, the immune system is faced with the problem of destroying bacteria that are potentially harmful, while ignoring those that are harmless. MCB Assistant Professor Russell Vance's work focuses on this problem.

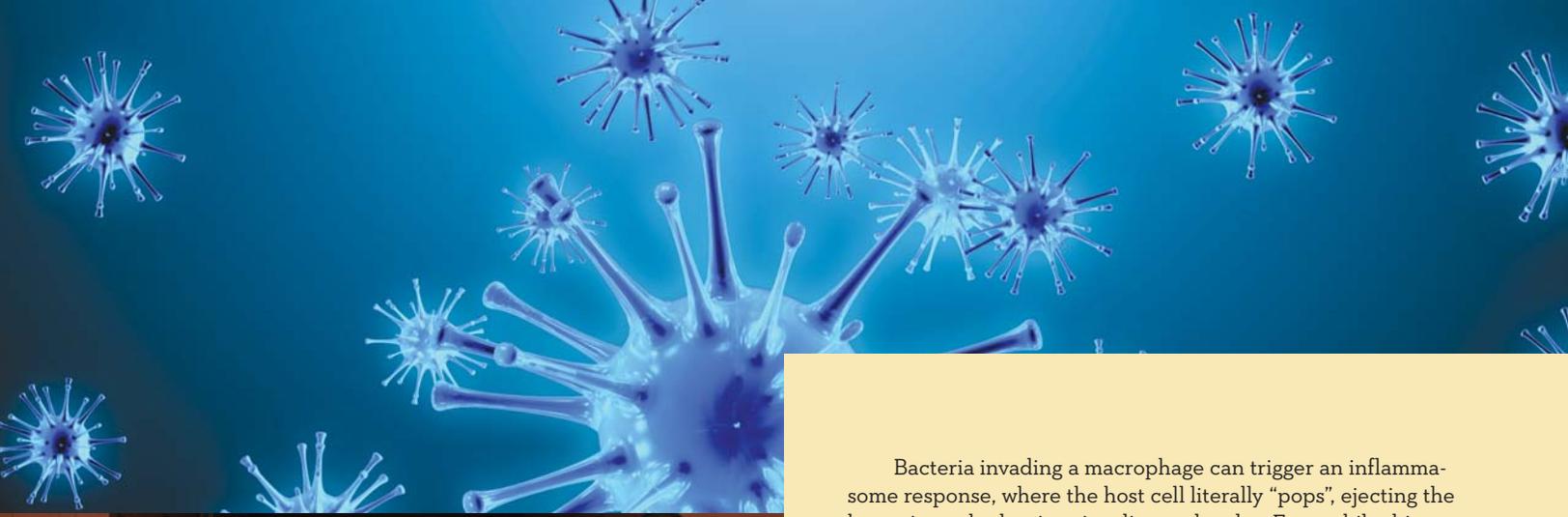
"How does the innate immune system discriminate pathogenic bacteria that are likely to cause us harm and nonpathogenic bacteria, which we should just ignore?" asks Vance.

To address this question, Vance studies an infectious bacterium that has not co-evolved with humans. To *Legionella pneumophila*, humans are an accidental host and a dead-end. While infection can cause a severe pneumonia in humans, the bacterium can not spread from a human host, having evolved to infect and spread primarily in the environment within amoeba. Therefore, the innate immune response to this bacterial intruder must be a general response, with neither organism having had the opportunity for evolutionary refinement. Through studying how the mouse innate immune system responds to *Legionella*, Vance is interested in understanding the general properties of the innate immune system that might be relevant for many different infectious diseases.

Vance's research compares the innate immune system's response to wild-type pathogenic *Legionella* and non-pathogenic mutants, which are missing a key component of a system that allows them to be virulent. Vance's group found several distinct immune responses toward pathogenic *Legionella* only, demonstrating that the innate immune system can and does distinguish between virulent and non-virulent bacteria. To figure out how this works, Vance's lab took a closer look some of the immune responses.

continued on next page >





The members of the Vance Lab.
Left to Right: Jakob von Moltke,
Katia Sotelo-Troha,
Kate Monroe, Dara Burdette,
Russell Vance, Mary Fontana,
Janelle Ayres, Eric Kofoed,
Norver Trinidad, Kevin Barry

Bacteria invading a macrophage can trigger an inflammatory response, where the host cell literally “pops”, ejecting the bacteria, and releasing signaling molecules. For a while this response was misunderstood as the bacteria killing the cell, but it is actually an important feature of innate immunity that alerts the adaptive immune system to step in with pathogen-specific responses. Vance’s lab screened for bacterial mutants that can infect cells but do not trigger cell suicide, finding mutations in the protein flagellin, important for building bacterial flagella but not used by mammalian cells.

“*Legionella* is not evolved to evade the immune system so hasn’t learned that secretion of flagellin in the host cell cytosol is a bad idea, because amoeba don’t have this pathway,” says Vance. “So *Legionella* is secreting this flagellin into the host cell and there’s a detector which detects that and then triggers this inflammatory response.”

Vance’s lab went on to discover that knockout mice lacking the flagellin receptor do not launch an inflammasome response when infected with *Legionella* and are permissive for bacterial replication. The molecular events by which flagellin is detected remain poorly understood. To address this, a student in the lab, Eric Kofoed, is building and using a reconstituted inflammasome system in 293T-cells, a cell type that does not have its own inflammasome response, to determine the biochemical roles played by the individual factors.

Additionally, Vance has turned his attention to the interactions between immune cells and bacteria in the gut, which is host to many kinds of non-pathogenic bacteria, many of which have flagellin but do not cause the inflammasome response. The key, says Vance, is the location of the flagellin. Flagellin detected outside the cell activates it, while flagellin detected inside the cell triggers a rapid cell death response.

“The only way flagellin can get into the inside of the cell is if the bacterium has intentionally delivered it there, and the only bacteria that have the ability to intentionally deliver things into the cytosol of the host cell are probably pathogens,” says Vance. “So when the host cell sees flagellin in the cytosol it’s a sign to the host that, oh dear, there’s a pathogen present, and I should probably respond differently than I would if there was just a harmless bacterium there.”

Data from Janelle Ayres, a postdoctoral fellow in Vance’s lab, suggest that a breakdown of this process could be especially important in the gut and may be related to auto-immune disorders such as inflammatory bowel disease or Crohn’s disease. The ability of the innate immune system to distinguish friend from foe is critical to our maintenance of health in our own cells and our microbial communities.



FACULTY NEWS



◀ **DIANA BAUTISTA** received an NIH New Pioneer Award, which supports scientists with “exceptional creativity” who propose pioneering approaches to major challenges in biomedical and behavioral research. Bautista’s work involves finding novel touch and pain receptors.



◀ **CAROLYN BERTOZZI** was awarded the \$500,000 Lemelson-MIT Prize for her achievements in biotechnology.



TOM CLINE and **BARBARA MEYER** are both 2010 recipients of Genetics Society of America (GSA) awards for distinguished service to the field of genetics. Cline has been awarded the Edward Novitski Prize for exhibiting an extraordinary level of creativity and intellectual ingenuity in solving a significant problem in genetics. Meyer has been awarded the Genetics Society of America (GSA) Medal for outstanding contributions to the field of genetics in the last 15 years.



◀ **JENNIFER DOUDNA** has been elected a member of the Institute of Medicine, considered one of the highest honors in the fields of medicine and health.



◀ **ISWAR HARIHARAN** has been granted an American Cancer Society Research Professorship, their most prestigious award. The five-year grant will be used to study ways by which excessive tissue growth can be curtailed by manipulating cell metabolism in fruit flies.



REBECCA HEALD is the first recipient of the Faculty Award for Excellence in Postdoctoral Mentoring.

CRAIG MILLER was named a 2010 Pew Scholar in the Biomedical Sciences.



◀ **DAVID RAULET** and **ELLEN ROBEY** received funding from The Governing Board of the California Institute for Regenerative Medicine, the state stem cell agency created by proposition 71.



◀ **DONALD RIO** was awarded a EUREKA award from the National Institute of General Medical Sciences, which supports “exceptionally innovative” research.

JASPER RINE was named the Winde-Lindgren Lecturer by the Genetics Society of America.



RANDY SCHEKMAN was awarded the 2010 Massry Prize, given by the Meira and Shaul G. Massry Foundation, and the E. B. Wilson Award, the highest honor of the American Society for Cell Biology. He was also elected as Foreign Associate of the Accademia Nazionale Dei Lincei, the oldest scientific academy in the world.

JEREMY THORNER would like to acknowledge, with pride, the honors his recent graduates received on their work.

LINDSAY S. GARRENTON (Ph.D., 2007), now a staff scientist at Genentech, had a paper about her thesis work highlighted in the “Editor’s Choice” section of the 23 July 2010 issue of *Science* under the Cell Biology category.

RAYMOND E. CHEN (Ph.D., 2008), now a postdoctoral research fellow in the lab of Prof. Patrick O. Brown at Stanford University, had a paper about his thesis work highlighted as being of significant interest in the “Spotlight” section of the second September 2010 issue (#17) of *Molecular and Cellular Biology*.

JESSE C. PATTERSON and **EVGUENIA (“JANE”) S. KLIMENKO** (Ph.D.s, expected 2011), had a paper about their thesis work highlighted in the on-line Faculty of 1000 system as being in “the top 2% of published articles in biology and medicine.”



2009-2010 Graduates

Spring 2010

Fall 2009

- **Jason Aoto** (Chen) Molecular Mechanisms Underlying Excitatory Shaft-Synapse Formation and Homeostatic Synaptic Scaling
- **Katherine Brown** (Amacher) Molecular Mechanisms of Vertebrate Segmentation
- **Salvatore Cilia** (Kane) *In Vitro* Biochemical Studies of NS5B, the HCV RNA Dependent RNA Polymerase
- **Joseph D'Alessio** (Tjian) Core Promoter Recognition Complex Switching in Liver Development & Regeneration
- **Elizabeth Flynn** (Alber) Structural and Functional Characterization of the *Mycobacterium tuberculosis* Virulence Factor Protein Tyrosine Phosphase B (PtpB)
- **Sarah Gilmore** (Bertozzi) The Role of Sulfated Metabolites in the Pathogenesis of *Mycobacterium tuberculosis*
- **Jeffrey Halley** (Rine) The Role of H2A.Z and H2A.Z Acetylation in Gene Regulation and Gene Expression in *Saccharomyces cerevisiae*
- **Kathleen Kolstad** (Flannery) Development and Assessment of Gene Therapies for Inherited Blinding Diseases
- **Crystal Marconett** (Firestone) Phytochemical Disruption of Hormone Receptor Expression and Intracellular Signaling in Human Reproductive Cancer Cells
- **Bosun Min** (Collins) Telomerase Holoenzyme Proteins and Processivity Subunit in *Tetrahymena thermophila*
- **Sarah Munchel** (Weis) Genome-wide Profiling of mRNA Turnover in *Saccharomyces cerevisiae*
- **Timothy Nice** (Raulet) Post-translational Regulation of the NKG2D Ligand Multi1 in Response to Cell Stress
- **Lisa Prach** (Alber) Diterpene Production in *Mycobacterium tuberculosis*
- **Melanie Prasol** (Ngai) Mechanisms of Neurogenesis and Adult Stem Cell Function in the Murine Olfactory Epithelium
- **Alejandro Sabogal** (Rio) Structural Studies on the P-element Transposase of *Drosophila Melanogaster*
- **Allyn Schoeffler** (Berger) Structural Specialization of Bacterial Type IIA Topoisomerases
- **John Tran** (Schekman) Mechanism of multivesicular body formation
- **James Walker** (Harland) Expression and function of microRNAs during *Xenopus* development
- **Monika Abedin** (King) Cadherin Evolution and the Origins of Animals
- **Luke Chao** (Kuriyan) Structural Studies of Calcium/Calmodulin Dependent Protein Kinase II Activation
- **Shannon DeMaria** (Ngai) Role of the Broadly Expressed Olfactory Receptor OlfCc1 in Mediating Amino Acid Detection in Zebrafish
- **Sarah Ewald** (Barton) Activation of Nucleic Acid-sensing Toll-like Receptors Cleavage by Endolysosomal Proteases: a Mechanism to Avoid Autoimmunity
- **Nathaniel Fernhoff** (Marletta) On the Molecular Mechanisms of Function and Dysfunction NO signaling in Mammalian Physiology
- **Lillian Fritz-Laylin** (Cande) The Genome and Cytoskeleton of *Naegleria gruberi*, an Amoeboflagellate
- **Stephanie Gline** (Weisblat) Evolution and Development in Spiralia: Early Progeny of the Mesodermal Lineage in the Leech *Helobdella sp.* (Austin)
- **Geoffrey Horner** (Marqusee) Investigating Protein Folding and Function by Manipulating Rare and Partially-Folded Conformations
- **Devon Jensen** (Schekman) COPII Specificity and the Regulation of Anterograde Transport for Planar Cell Polarity Proteins in Neural Tube Development
- **Roshni Kasad** (Dernburg) Characterizing Meiotic Mechanisms in *C. elegans*
- **Ryan Klimczak** (Flannery/Schaffer) Molecular Evolution of Adeno-associated Virus for Improved Retinal Gene Therapies
- **Sasha Langley** (Karpen) The Role of Sequence, Gene Orientation, and Intergenic Distance in Chromatin Structure and Function
- **Jasmine McCammon** (Amacher) Using Zinc Finger Nucleases for Targeted Genome Modification in the Zebrafish
- **Holly Morrison** (Bilder) Epithelial Cell Polarity and Proliferation Control in *Drosophila melanogaster*
- **Charles Olea** (Marletta) Chemical Consequences of Heme Distortion and the Role of Heme Distortion in Signal Transduction of H-NOX Proteins
- **Jessica Piel** (Levine) Non-coding RNAs of the Bithorax Complex in the Developing *Drosophila* Embryo
- **Aya Sato** (Dernburg) The Role of the Pairing Center and its Interaction with the Nuclear Envelope During Meiosis in *C. elegans*
- **E. Danae Schulz** (Schlüssel) Gfi1b Negatively Regulates the V (D)J Recombinase
- **Kyle Simonetta** (Kuriyan) Structural Studies of the Mechanism of Clamp Loading by Clamp Loader Complexes.
- **Leslie Stanton** (Weis) Development of a Novel Assay to Monitor Nuclear Pore Complex in *Saccharomyces cerevisiae*
- **Nathan Thomsen** (Berger) Structural Studies of Translocation Mechanism and Chemomechanical Coupling in Hexameric Helicases
- **Dina Weilhammer** (Sha) Host Factor Regulation of *Toxoplasma gondii* Growth and Differentiation
- **David Wynne** (Dernburg) The Role and Mechanism of Meiotic Chromosome Motion in *C. elegans*
- **Susan Young** (King) The Unicellular Ancestry of the Proto-oncogene Mye
- **Oliver Zill** (Rine) Evolutionary Genetic Studies of Mating Type and Silencing in *Saccharomyces*



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PRODUCTION: Raven Hanna
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MCB Newsletter
University of California
Department of Molecular and Cell Biology
142 Life Sciences Addition #3200
Berkeley, CA 94720-3200

tscript@berkeley.edu

Send address changes to:
Alumni Records
2440 Bancroft Way
University of California
Berkeley, CA 94720-4200

Or e-mail ursa@berkeley.edu

Current and past issues of the newsletter are available on the MCB web site (<http://mcb.berkeley.edu/news>).

Class Notes

Yen-Michael Hsu [BA 2000] completed MD/PhD training at University of Texas Medical School at Houston and University of Texas M.D. Anderson Cancer Center in May 2010. He began Clinical Pathology residency training at Washington University in St. Louis School of Medicine and Barnes-Jewish Hospital in July of 2010. [yhsu@path.wustl.edu]

Vu Nguyen [BA 2003] is Assistant Professor in the Division of Biological Sciences at the University of Chicago. He is studying the immunological mechanisms of graft-versus-host disease. [vnguyen@medicine.bsd.uchicago.edu]

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