

## The Jane Coffin Childs

MEMORIAL FUND FOR  
MEDICAL RESEARCH

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## Meet the New JCC Fellows

*This spring the Jane Coffin Childs Fund awarded fellowships to 24 outstanding young biomedical scientists. Here we profile five, chosen to represent a cross-section of interests and backgrounds.*

### Zev Gartner

When JCC fellow Zev Gartner joined Carolyn Bertozzi's lab at the University of California, Berkeley, last fall, his plan was to study the sulfated glycolipids on the outer envelope of the bacterium that causes tuberculosis. But a chance connection has since led him down a very different path.

As a graduate student with chemical biologist David Liu at Harvard University, Gartner had found a way to drive organic reactions by linking the

reagents to complementary DNA oligonucleotides. The DNA strands would hybridize, bringing the reagents close together. When he got to the Bertozzi lab, he met a graduate student who had learned how to attach oligonucleotides to cells. The original purpose was to stick cells to specific surfaces, but Gartner saw another opportunity.

Cell biologists would love to find a way to get different cell types to associate with each other in a dish. While many cells can be cultured alone, controlled mixing would open the door to building models of whole tissues like skin or liver. Gartner wondered if the same principles he used to bring molecules together would work with whole cells. "The idea was to take the nanoscale stuff I did in grad school and apply it at the micro-scale," he says.

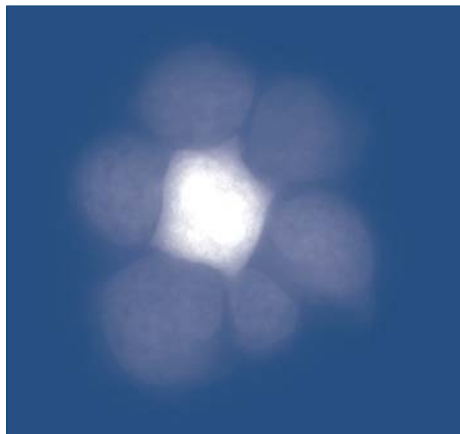
He began by linking complementary strands to two populations of Jurkat cells, a T-cell leukemia line that normally sticks to nothing. "If you get any adhesion, you know it's working," he says. When he mixed these together, he got a stunning



*Zev Gartner*

array of cell complexes from simple pairs to cells of one type surrounded by five or six of the other. By varying the DNA concentration and the cell density, he found he could alter the kinds of cell complexes that formed.

As with most new findings, there are still more questions than answers, and Gartner excitedly enumerates them. Will this work with other cells? What happens when the cells start to divide? How many cell types can be linked? Will they talk to each other? Is it possible, for instance, to guide the differentiation of stem cells by bringing them in contact with mature cells? "This is just the coolest



*Group hug: Jurkat cells decorated with single-stranded DNA adhere to a cell (bright, center) bearing the complementary strand.*

CONTINUED FROM PAGE 1

thing I have ever seen,” Gartner says.

He is also quite happy to be closer to his home town of Santa Cruz, not least because of the Pacific Ocean. He grew up surfing and still goes out nearly every day. Before starting in the Bertozzi lab last fall, he spent a year traveling the world with his board in tow, surfing exotic locations like Chile, New Zealand, Thailand and South Africa, with time out for a surf contest in Nova Scotia. “I finally got tired of lugging my board bag around,” he says.

## Robert Johnston

Einstein denied that “God plays dice with the world,” but that was before much was known about cell fate choice. Chance influences numerous biological decisions, from whether hemopoietic stem cells become erythrocytes or leukocytes to the selection of mating type in yeast. So how do biological systems incorporate chance while still executing a well-regulated developmental program?

Robert Johnston, a post-doctoral fellow in Claude Desplan’s lab at New York University in Manhattan, is tackling this broad question through



Robert Johnston

the study of a particular stochastic event in the development of the fruit fly eye. Flies distinguish colors through a pair of cells at the center of each of the eye’s 800 facets, or ommatidia. During pupation, 30% of the cell pairs specialize for short wavelengths (“pale” type) and the rest for longer wavelengths (“yellow” type). The choice comes down to the action of the transcription factor Spineless, a dioxin receptor homolog that drives the cells toward the yellow type.

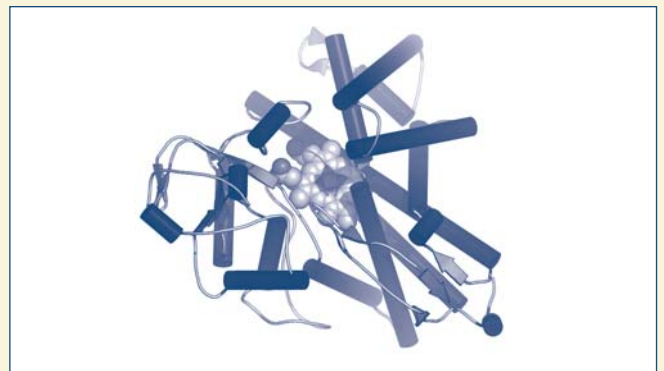
Whether this protein is produced in a developing ommatidium appears to be entirely stochastic, so Johnston has set out to understand the regulation of the *spineless* gene. Flies with extra copies of the *spineless* promoter produce less Spineless and end up with fewer yellow receptors, suggesting that the added sequences are sopping up a limiting factor. Johnston hopes

to identify this factor and others and to determine how they collaborate at the promoter.

Johnston was a graduate student in Oliver Hobert’s lab at Columbia University where he studied how microRNAs influence left-right neuronal asymmetry in *C. elegans*. Originally from Philadelphia, Johnston says he got turned on to science in a high school genetics class. “Geeky as it sounds, I really liked Punnett squares,” he says.

from its sequence alone. To that end, some research groups are solving the crystal structure of every variant they can get their hands on. But with so many versions out there (4500 across all species found so far), they won’t be done anytime soon.

Christopher Snow is planning another approach. When he takes up his JCC fellowship with bioengineer Frances Arnold at Cal Tech in September, he will begin developing algorithms for



Model of a cytochrome P450

## Christopher Snow

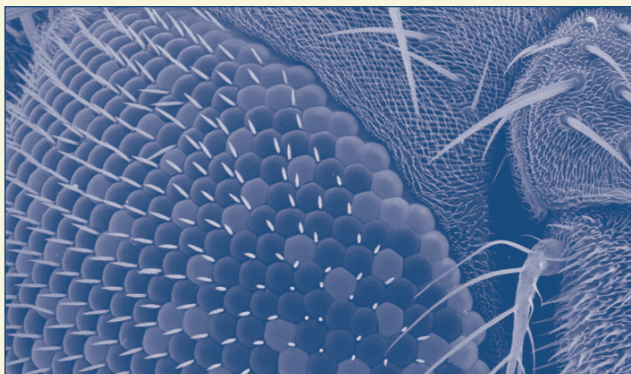
Why do some people need a double dose of sleeping pills to feel groggy? Why do others cut ibuprofen tablets in half to avoid side effects? Cytochrome P450 oxidases are a big part of the answer. These enzymes, found mainly in the liver, catalyze the initial breakdown of drugs and other foreign compounds in the body. The human genome encodes 59 P450s, each with subtly different versions, resulting in an endless variety of drug sensitivities in the population. Pharmaceutical companies would love to understand P450 biochemistry better, both to develop better drugs and to identify patients who will benefit the most.

The holy grail of P450 research is to predict an enzyme’s rate and specificity



Christopher Snow

predicting a P450’s structure directly from its amino acid sequence. Despite decades of effort, such predictions have proven to be extremely hard. Perhaps the most successful algorithm to date, known as Rosetta, can predict the folded structure of an 80-amino-acid peptide to within one angstrom. That’s impressive, yet it still can’t handle a P450, which is



Multi-faceted: the ommatidia of a fly eye specialize in seeing a subset of colors by a stochastic process.

Photo credit: M. Wernet

some five times bigger. The key, Snow says, is that P450s end up looking very much like one another, despite their low sequence similarity. This will allow him to assume a basic shape for each new sequence and then to refine the structure by adapting algorithms like Rosetta. "Refinement, to my mind, is one of the greatest challenges in computational biology today," he says.

Of particular interest to Snow is a set of some 3000 novel P450 enzymes generated in the Arnold lab by mixing and matching naturally-occurring protein regions. Most of these "unnatural" proteins are thought to be functional, but their exact activities are unknown. Snow hopes his models will be a first step to predicting the chemistry that each is capable of. This would allow chemical engineers to sift through the library for enzymes that carry out reactions not possible with standard organic chemistry, opening new doors for compound synthesis. "If I could have the opportunity to help guide some of these projects, that would be super cool," Snow enthuses.

## Ahmet Yildiz

To keep a cell running takes a lot of work. Organelles must be moved, vesicles sorted, and chromosomes corralled. Much of the labor is done by tiny protein motors known as kinesins which carry cargo along the microtubule scaffolding that makes up a cell's internal skeleton. These slender robots actually appear to walk. They take one 8-nanometer step at a time by alternately catching and releasing a pair of "heads" (to use the admittedly upside-down jargon), burning up ATP for fuel as they go. Kinesins have been filmed striding down



Ahmet Yildiz

microtubules on glass coverslips, and the energetics of their motion in a cell-free environment has been measured with great precision.

But Ahmet Yildiz would very much like to know how relevant these results are in the living cell. "All this biophysical work has been done *in vitro*," he says, "but we don't know the importance of these parameters biologically."

Yildiz has generated a kinesin with an elongated neck-linker (the portion that connects to the head) such that it could theoretically take a 16-nanometer step. He has found that the protein still moves, albeit more slowly than the wild-type. Now, as a postdoctoral fellow in Ron Vale's lab at the University of California, San Francisco, Yildiz is measuring its actual step size using FIONA, a high-resolution microscopy technique he developed as a graduate student. Ultimately, he would like to test the function of the protein in a living organism.

As a first step towards *in vivo* work with kinesin mutants, Yildiz hopes to resolve a debate over whether a particular kinesin, encoded by *unc 104* in the roundworm *C. elegans*, must form a dimer in order to function. To test this, Yildiz will collaborate with Cynthia Kenyon's lab at UCSF to generate worms that express two versions of Unc 104, each attached to a

different fluorophore. Exciting one of these will cause the other to fluoresce only if the two are intimately close, as in a protein dimer, so that energy transfer can occur.

Yildiz also plans to introduce other kinesin mutants into worms. This should enable him to measure for the first time the effects of changing the normal parameters of kinesin motion at both the whole-animal and cellular level.

## Dianne Schwarz

The life of wild yeast is feast or famine—mostly famine. Lucky cells that land on a fallen apple, for instance, can ferment away happily only until the fruit has rotted and dried. Then it's time to conserve energy until the next windfall. An essential component of yeast's low-nutrient austerity plan is the strict limitation of ribosome production. In fat times, the job of transcribing the cell's 137 ribosomal protein genes consumes half the total effort of RNA polymerase II, the main protein gene reader, so turning the thermostat down on the RP genes can amount to real savings.

Dianne Schwarz, a JCC fellow in biochemist Erin O'Shea's lab at Harvard University, would like to work out just how yeast carry out this RP gene shutdown. Her initial focus is on the Sfp1 protein, a transcription factor found at active RP promoters. Under nutrient stress, Sfp1 leaves these promoters and the nucleus entirely, but just how it gets evicted is an open question.

One of Schwarz's first projects is to identify upstream regulators of Sfp1's localization. She has tagged Sfp1 with green fluorescent protein so she can tell whether it's in the nucleus



Dianne Schwarz

or the cytoplasm by fluorescent microscopy. She plans to introduce this construct into yeast with deletions in various kinase genes (kinases are cellular enzymes often involved in gene regulation) and look for cells in which Sfp1 behaves abnormally. She will also troll yeast extracts for proteins that bind directly to Sfp1 and other RP regulators. One of the big unanswered questions is whether Sfp1 binds directly to the promoter or via some other factor. With answers to these questions in hand, it should ultimately be possible to reconstruct the molecular events that shut down RP genes during stress and send Sfp1 packing to the cytoplasm.

Schwarz did graduate work on RNA interference in Phil Zamore's lab at the University of Massachusetts Medical School in Worcester. She knew about O'Shea's reputation as a scientist (as did everyone else—the lecture hall overflowed when O'Shea came to talk), yet initially didn't consider her as an option for her postdoc because it would have entailed moving to San Francisco and far from her husband. Then the stars aligned in her favor. O'Shea moved just down the road to Harvard in 2005. "I had heard good things about her mentoring and her lab environment, and I was very interested in the research," Schwarz says. "It was a great opportunity." \*

## THE JANE COFFIN CHILDS MEMORIAL FUND FOR MEDICAL RESEARCH

## Fellows Awarded Spring 2006

- **Elio A. Abbondanzieri**  
A single-molecule study of reverse transcriptase, with Xiaowei Zhuang, Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts
- **Tal I. Arnon**  
Structure and function of the NKp30 killer receptor with Pamela Bjorkman, Division of Biology, California Institute of Technology, Pasadena, California
- **James M. Carothers**  
Controlling metabolic pathways with RNA aptamers, with Jay D. Keasling, Physical Biosciences Division, Lawrence Berkeley National Laboratory, University of California, Berkeley, California
- **Jason M. Casolari**  
Investigation of asymmetric RNA localization, with Patrick O. Brown, Department of Biochemistry, Stanford University School of Medicine, Stanford, California
- **Yunrong Chai**  
Multicellularity in *Bacillus subtilis*, with Richard M. Losick, Department of Molecular and Cellular Biology, Harvard University, Cambridge, Massachusetts
- **David W. Colby**  
Structural basis of synthetic prion infectivity, with Stanley B. Prusiner, Institute for Neurodegenerative Diseases and Neurology, University of California, San Francisco, California
- **Gregory A. Cope**  
Analysis of centrosome duplication in human cells, with Timothy Stearns, Department of Biological Sciences, Stanford University, Stanford, California
- **Rhiju Das**  
Prediction of novel protein folds at high resolution, with David Baker, Department of Biochemistry, University of Washington, Seattle, Washington
- **John G. Doench**  
Synthetic lethal interactions in cancer, with Ed Harlow, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts
- **Zev J. Gartner**  
The role of tuberculosis sulfatases in virulence, with Carolyn Bertozzi, Department of Chemistry, University of California, Berkeley, California
- **Stephanie L. Gupton**  
Adhesion and cytoskeletal dynamics in neuron guidance, with Frank B. Gertler, Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts
- **Jun R. Huh**  
Epigenetic nature of CD4 silencing in fully committed cytotoxic T cells, with Dan R. Littman, Memorial Sloan-Kettering Cancer Center, New York, New York
- **Robert J. Johnston**  
Stochastic fate choice generating the retinal mosaic, with Claude Desplan, Center for Developmental Genetics, Department of Biology, New York University, New York, New York
- **Jon A. Kenniston**  
Investigating dynamin as a model for functionally important low-affinity PH domain/phosphoinositide interactions, with Mark A. Lemmon, Department of Biochemistry and Biophysics, University of Pennsylvania, Philadelphia, Pennsylvania
- **Peter J. Mikulecky**  
Kinetic analysis of 30S ribosomal subunit assembly, with James R. Williamson, Departments of Molecular Biology and Chemistry, The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, California
- **Saskia B. Neher**  
Study of mechanisms ensuring productive SRP targeting, with Peter Walter, Department of Biochemistry and Biophysics, University of California, San Francisco, California
- **Matthew Y. Pecot**  
Specificity of neuronal wiring in *Drosophila*, with S. Lawrence Zipursky, Department of Biological Chemistry, University of California, Los Angeles, California
- **Ying Peng**  
Systems biology approach to dissecting a hierarchical signaling network, with Jeffery Axelrod, Department of Pathology, Stanford University, Stanford, California
- **Dianne S. Schwarz**  
Regulation of ribosomal protein gene expression, with Erin O'Shea, Department of Molecular and Cellular Biology, Harvard University, Cambridge, Massachusetts
- **Maria L. Scimone**  
Investigation of stem cell-potential and regulation in planarian regeneration, with Peter W. Reddien, Department of Biology, Whitehead Institute for Biomedical Research, Cambridge, Massachusetts
- **Christopher D. Snow**  
Modeling the cytochrome P450 enzyme superfamily, with Frances Arnold, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California
- **Michael Strong**  
Development of integrated genomic maps, with George Church, Department of Genetics, Harvard Medical School, Boston, Massachusetts
- **Ahmet Yildiz**  
Molecular engineering of kinesin motors, with Ronald D. Vale, Department of Cellular and Molecular Pharmacology, University of California, San Francisco, California
- **Calvin K. Yip**  
Structural characterization of gene silencing complexes, with Thomas Walz, Department of Cell Biology, Harvard Medical School, Boston, Massachusetts

## DIRECTOR'S CORNER

## Keeping the Promise Alive



In the year since our last newsletter, the Childs fellowship program has grown to attract even more than the usual number of applicants. This year we received approximately 380 applications for only 24 awards. The new fellows are stunningly successful and bring added luster to our program. We continue to search for new funding opportunities because so many other outstanding candidates on our alternate list remain just beyond the reach of our endowment.

Although we were forced to offer one award fewer this year after the Agouron Institute (which has supported two new fellow a year since 2000) decided to change its funding priorities, a new model for private underwriting of fellows promises to help reverse that trend. Beginning in 2007, the Howard Hughes Medical Institute has agreed to pay the fellowship of any postdoc at its Janelia Farm campus in Virginia who competes successfully for a Childs award. This will effectively increase the number of fellowships available in any given year, so long as someone from that research center is ranked near the top. We have presented this option to other private agencies, and we hope to be able to announce new partners in the promotion of excellent science soon.

Such private support of science is becoming ever more critical these days, at all levels. As our senior fellows launch into independent research positions in the real world they will encounter a mixed funding situation. A survey we conducted some years ago found that over 80% of the Childs fellows gravitate to research and teaching positions. For those who opt for positions in biotechnology and the pharmaceutical industry, the horizons are bright and varied. Many others will choose academic teaching and research at universities or research institutes. Here the job prospects remain strong, particularly for Childs fellows, but funding, at least at the federal level, is stagnant. Fortunately, our fellows compete quite successfully for the best such positions, many of which come with ample set-up support and access to select funds from private foundations. However, extramural funding at the NIH is tough with low pay lines and an overall budget that is seriously impacted by other federal priorities. The situation does not appear likely to change in the near future.

During this period it is crucial that our teaching and research institutions raise private capital to sustain beginning investigators through a critical phase in their careers. Those of us in a position to help raise funds for this purpose have an obligation to pitch in to keep the enterprise healthy and attractive to the next generation of biomedical scientists.

Of course there are many ways to help out, and so before I close I would like to acknowledge the service of Tom Steitz (Yale) and Larry Zipursky (UCLA), whose terms on the Board of Scientific Advisors have come to an end, but whose contributions will remain with us at least through the next few years as the fellows they helped select progress beyond their postdoctoral training. Fortunately, two other notable scholars, Susan McConnell of Stanford and Tom Pollard of Yale, have agreed to join the BSA with terms beginning this year (see their profiles beginning on p. 6). \*

— Randy Schekman, Director of the Board of Scientific Advisers

## Pollard and McConnell Join BSA

*The JCC Fund welcomes two distinguished researchers to its Board of Scientific Advisors this year. Yale biochemist Thomas Pollard and Stanford neurobiologist Susan McConnell will replace two retiring members, Thomas Steitz of Yale and Larry Zipursky of UCLA.*



Thomas Pollard

**Thomas Pollard**, Sterling Professor of Molecular, Cell & Developmental Biology at Yale University in New Haven, Connecticut, has devoted his career to discovering how eukaryotic cells move and divide. Over the past 30 years, much of the biochemistry and physical dynamics of the actin cytoskeleton, which controls cell shape and motility, has yielded to his efforts. His seminal contributions include the basis of actin's directional polymerization into microfilaments, the biochemistry of filament nucleation and capping, and the discovery of specialized myosins that transport vesicles along the filaments.

One subject of current interest in the Pollard lab is the contractile ring, a complex assembly of proteins which pinches dividing cells in two. Through the study of fission yeast (*Schizosaccharomyces pombe*), Pollard's group has demonstrated how the various protein components of the ring assemble in a precisely-timed order relative to the cell cycle. The team continues to hunt for genes and proteins that regulate this process. Another hot area of research is the regulation and assembly of the Arp2/3 complex, which creates branching sites on actin filaments. Such branches are essential for numerous cellular processes including the extension of lamellipodia, phagocytosis and

wound healing. Arp2/3 activity also plays a role in intracellular transport of vesicles and endosomes.

Pollard earned his M.D. degree from Harvard Medical School in 1968. For 19 years he directed the Department of Cell Biology and Anatomy at Johns Hopkins Medical School where he founded a graduate program in cellular and molecular medicine and earned seven teaching awards. From 1996 to 2000 he served as president of the Salk Institute for Biological Studies in La Jolla, California, before moving to Yale in 2001.

Pollard's many honors include the Biophysical Society's Public Service Award, the University of Chicago's Howard T. Ricketts Award, and the American Society for Cell Biology's E.B. Wilson Medal. He is a member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences. He has also served as president of the American Society for Cell Biology (1987-1988) and the Biophysical Society (1992-1993).

Pollard's four-year term on the BSA will continue his long record of service to the scientific endeavor. "I look forward to helping the Jane Coffin Child Fund identify and support the most promising young people in the biomedical sciences," he says.

**Susan McConnell**, the Susan B. Ford Professor in the School of Humanities and Sciences at Stanford University, studies the development of the mammalian brain. In particular, she would like to understand how the cerebral cortex—the convoluted outer layer of the brain—emerges from a relatively uniform sheet of progenitor cells.

Although the adult cortex is only a few millimeters thick, it contains numerous specialized cells that make the billions of precise connections needed for higher functions like attention, memory and consciousness. The almost unimaginable complexity required starts off in the embryo as a monotonous layer of look-alike neural epithelial cells. As these progenitors divide, daughter cells migrate outward to form sequential layers in the developing cortex such that all cells within a given layer share roughly the same birthday. What's more, the neurons of each layer take on a unique function and morphology. Layer 5 cells send axons to the mid-brain and spinal cord, for instance, while layer 4 receives input from the thalamus.

McConnell's group has found a number of clues to the molecular regulation of daughter cell fates. As the cortex matures, the developmental potential of the progenitor cells becomes more restricted. Experiments such as subtractive



Susan McConnell

2006

hybridization of cDNA libraries made from early and late-stage progenitors have turned up a number of differentially-expressed genes whose regulation will likely give rise to a better understanding of the clock that governs daughter cell fates.

Another buzz in the McConnell lab comes from the discovery of a putative transcription factor that controls the fate choice between two types of cells that sit side-by-side in the same cortical layer. Certain cells in layer 5 need *Fez1* (fore-brain embryonic zinc-finger-like protein) to send connections to the tectum, pons and spinal cord. When the gene is mutated, they instead reach out to novel and inappropriate places like the other cerebral hemisphere. Efforts now are underway to learn how *Fez1* itself is regulated.

McConnell is the recipient of numerous research and teaching awards, including the

Searle Scholar award, the Alfred P. Sloan Research Fellowship, the National Science Foundation Presidential Young Investigator award, and McKnight Investigator award, the Walter J. Gores Award for Excellence in Teaching and the Hoagland Prize for Undergraduate Teaching at Stanford University.

McConnell says she considers it a privilege to join the JCC board, not least because of the opportunity to help support great young scientists. She also sees it as a chance to give something back, since she herself—and her field generally—have benefitted from private support of early-career research. “The people funded by JCC are among the most promising young biomedical scientists in the country,” she says. “These kinds of programs take on more and more value as funding gets tight.” \*

## Application Information

The Fund awards fellowships to qualified individuals for full-time postdoctoral research on cancer and related subject areas. Applicants should not have more than one year of postdoctoral experience and should hold either an M.D. or a Ph.D. in the field in which they propose to study. In some cases, evidence of equivalent training and experience will be accepted. The appointment normally lasts three years. The basic stipend for the 2007 recipients will be \$41,000 the first year, \$42,000 the second, and \$44,000 the third. Applications for 2007 must be received by Thursday, February 1, 2007.

**Applications must be submitted electronically.**

For details, please visit the Fund's website at [www.jccfund.org](http://www.jccfund.org)

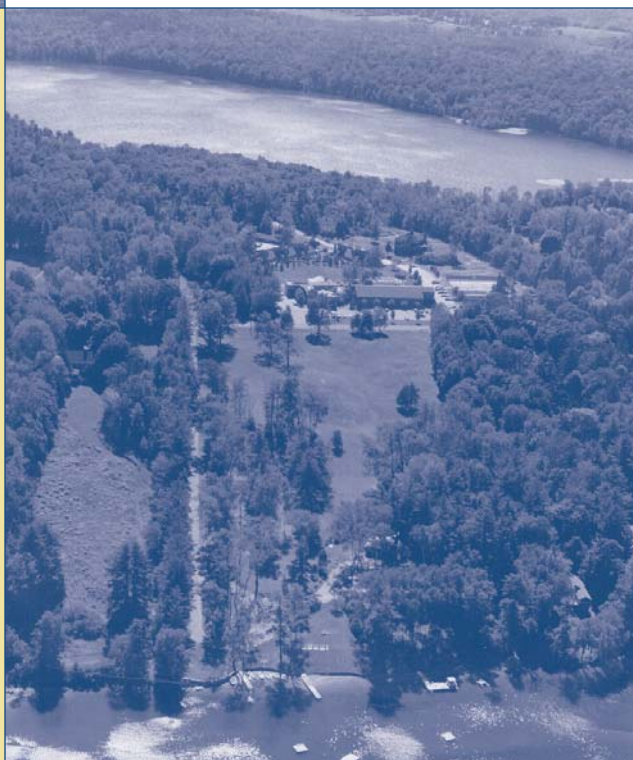
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Department of Biochemistry and Biophysics,  
University of California,  
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- **Dr. Susan McConnell**  
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# The 2006 Retreat

## Challenges in Biomedical Sciences: The Promise of Chemical Biology

October 20–22, 2006

Interlaken Inn, Lakeville, Connecticut

### HOSTED BY

Peter Cresswell and Tony Hunter

### SPEAKERS

**Ronald R. Breaker**

Department of Molecular,  
Cellular and  
Developmental Biology  
Yale University  
New Haven, Connecticut

**Virginia Cornish**

Department of Chemistry  
Columbia University  
New York, New York

**Timothy J. Mitchison**

Department of Systems Biology  
Harvard Medical School  
Boston, Massachusetts

**Barbara Imperiali**

Department of Chemistry  
Massachusetts Institute  
of Technology  
Cambridge, Massachusetts

**Hidde Ploegh**

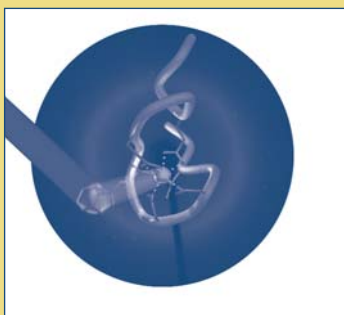
Whitehead Institute for  
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Cambridge, Massachusetts

**Joseph Noel**

Jack Skirball Chemical  
Biology and Proteomics  
Laboratory  
The Salk Institute for  
Biological Studies  
La Jolla, California

**Kevan Shokat**

Department of Cellular and  
Molecular Pharmacology  
University of California  
San Francisco, California



*Lanthanide binding tags (LBTs), developed in  
Barbara Imperiali's lab at MIT,  
are used for brightly labelling proteins*

## The Jane Coffin Childs

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