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Mapping the Protein *Universe*

photo courtesy Sung-Hou Kim

Professor Sung-Hou Kim has created the first map of the protein folding universe.

Astronomers aren't the only scientists with the challenge and excitement of mapping the universe, since not all "universes" are made of stars and planets. Chemistry professor **Sung-Hou Kim** and his colleagues have produced the first three-dimensional map of the protein structure universe. This universe is comprised of the various folds (patterns) that the amino acid chains assume as they put themselves together.

"We have found that protein folds are broadly grouped into four different classes that correspond to the four classes of protein structures defined by the Structural Classification System of Proteins (SCOP)," Kim says. "Some researchers have argued that there are only three classes of protein fold structures, but we can now mathematically prove there are four."

This map, published in the online early edition of the *Proceedings of the National Academy of Sciences* in February, compares the four classes of protein folds. The folds represent recurring structural motifs or "domains" that make up all protein architecture. Scientists can use the map to see all of the possible twists and turns that the protein backbone can take. Since protein function arises from the conformation of the protein, solving how a protein is folded in space helps scientists understand what that protein does and how it interacts with other proteins and biological molecules.

Now that the approximately 40,000 genes in the human genome have been sequenced, scientists are working to identify the coding genes and the molecular and cellular functions of the proteins associated with them. Coding genes are DNA sequences that translate into sequences of amino acids, which RNA assembles into proteins.

Structural biology is increasingly important in the pharmaceutical industry since protein folding is the link between what the genome codes for and what the proteins actually do. For example, enzymes that catalyze reactions important for cancer growth could be controlled with a specifically designed inhibitor, if the structure of the enzymatic protein is known. Using structural biology techniques, scientists can also predict which biological functions known drugs would inadvertently affect.

The prevailing technique for predicting the function of a newly discovered protein is to compare the sequence of its amino acids to the amino acid sequences of proteins whose functions are already

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Inside

Stanley in Transition

Stanley Hall has a date with the wrecking ball in mid-March to make way for the new Center for Health Sciences and Quantitative Bioengineering. The new building is a highlight of the Health Sciences Initiative and will serve as an interdisciplinary hub for scientific research. The facility will house part of the Department of Molecular and Cell Biology, the Department of Bioengineering, and research programs in the Departments of Chemistry and Physics that have interdisciplinary ties to molecular and cell biology and bioengineering.

The current Stanley building was constructed in 1952 and named for biochemist Wendell Stanley. He received a Nobel Prize in Chemistry for his work on the tobacco mosaic virus, which he crystallized in 1935. The demonstration of the molecular properties of the virus opened up a new field of research: the study of viruses as large molecules.

With a groundbreaking ceremony tentatively scheduled for May 30, Berkeley's next generation Stanley Hall will house state-of-the-art laboratories and should be completed by the spring of 2006. ▲

The current Stanley Hall

Teaching the Teachers

Eileen Lewis

Eileen Lewis is helping to change the way undergraduates learn chemistry. "We take advantage of the students' natural curiosity about the world around them to teach chemistry. They behave like scientists as they engage in hands-on activities, data analysis, hypothesis testing, or concept generation," said Lewis, the principal investigator and project director of the Multi-Initiative Dissemination (MID) Project that is housed within the college. This NSF-funded project disseminates the materials and methods from all of the five NSF-funded chemistry systemic reform projects (ModularCHEM Consortium, based here at the college, ChemLinks, Molecular Science, New Traditions, and Peer-Led Team Learning).

Faculty as students

"Our goal is to help faculty learn about the latest research findings on teaching, learning, and assessment as well as have them experience what has been developed by each of the chemistry reform initiatives," said Lewis. "Since all of the projects share an active-learning, student-centered perspective, our workshops for faculty allow them to experience their own learning processes and explore which materials and methods would be most useful for their courses and institutions. We provide faculty with lots of ideas and materials to take back to their own institutions." They are also in the process of evaluating the impact the MID Project has had on faculty over the last two years' workshops.

The faculty represent a broad distribution from research universities, four year comprehensive colleges, and community colleges.

The faculty interest is impressive, Lewis noted. "We've given about 18 workshops, which have increased in size over time. Our average attendance now is capped at 50 faculty and there can be 20 or more colleges and universities represented at each workshop. More than 650 faculty members have attended the workshops to date."

To really learn chemistry, according to Lewis, "students must reflect on their own understanding, building on those ideas that are the beginnings of good science, and construct a more robust understanding of concepts where they are confused. Giving explanations is a key component of students' developing deeper understanding. The students learn to modify and to reject models in favor of better models."

"Chemistry teaches skills and knowledge that all college graduates need to learn to lead productive lives and to make informed decisions," added Lewis.

photo courtesy Eileen Lewis

Faculty members at an MID workshop. Participants from across the country learn new ideas in how to teach chemistry to undergraduates.

Since many undergraduate students at Berkeley take at least one course in chemistry, getting them interested and involved can be very rewarding. ▲

Brownie Invasion *by Monica Jackson-Tribble*

photos courtesy Monica Jackson-Tribble

The college was visited by Brownie Troop 2948 on Friday, February 7. **Jamie Ellis** and **Carolina Carvalho**, senior chemistry undergraduates, were the guest scientists. They led the group with a lively acid/base demonstration and each Brownie did a Swirling Colors experiment. Jamie and Carolina also gave an informal talk on preparing for careers in science. Special thanks to **Lonnie Martin**, **Sharon Mueller** and **Bob Lamoreaux** for making this event possible. A very special thanks to **Professor Judith Klinman** for donating her childhood picture for our flyer! ▲

Chemical Biology in the College of Chemistry

There is excitement in the air for chemistry undergraduates interested in pursuing a biological career. The Department of Chemistry is now developing a formal major in Chemical Biology leading to a Bachelor of Science degree. The proposed new Chemical Biology major is intended to provide a solid background in chemistry as it impacts on areas such as biochemistry, molecular biology, bioengineering, structural biology, drug design, pharmacology and medicine.

"We are always exploring ways to modify our curriculum in response to the increasingly collaborative nature of science," said **Dean Clayton Heathcock**.

Curriculum modifications

The motivation behind this new major is the fact that biology has changed enormously in the last 10 years, but the curriculum has not kept up. "The field is much more quantitative and molecular now," said chemistry professor emeritus **Ken Sauer**, who is leading the effort. "We would like to teach biology the way it is being used in research."

A recent National Research Council report supports the department's point of view, stating that biology should be taught in conjunction with physics, math, chemistry and engineering at the undergraduate level, and that students should perform team-oriented experiments and learn more about the huge databases of information (genetic sequencing, protein folding) at our disposal. "The Chemical Biology major will pioneer this effort on the Berkeley campus," said Sauer.

Chemical biology will probably be offered as a formal major in Fall 2004, although some students are currently pursuing it on an individual major basis. One requirement will be the new course Chemistry 135, which is taught by professors **Michael Marletta** and **Jamie Cate** and focuses on biochemistry with a specific emphasis on chemical principles.

Graduate Chemical Biology

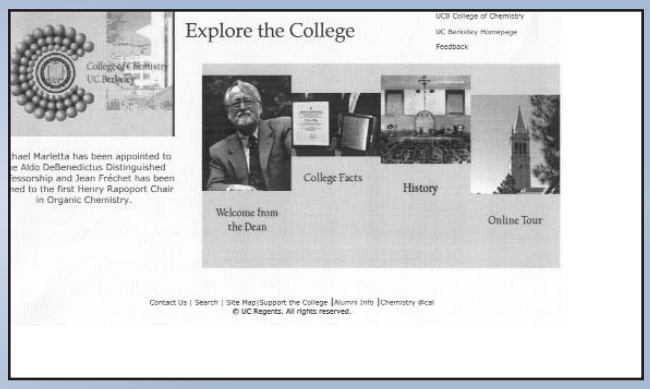
The undergraduate major in Chemical Biology will complement the recently introduced Chemical Biology Graduate Program. Directed by professors **Carolyn Bertozzi** and **Michael Marletta**, the program has approximately ten new students per year who rotate through three of the 35 participating laboratories during the first year of the Ph.D. program. These rotations, which last ten weeks, expose the students to the frontier research at the interface of chemistry and biology. "Students who learn both chemistry and biology will be prepared for the new directions that scientific research is taking," said Bertozzi. ▲

▼ Students in the chemical biology graduate program participate in a poster session.

photo by Carolyn Bertozzi

Explore the College Online

You can now learn all about the College of Chemistry at the new "Explore the College" website, located at http://www.cchem.berkeley.edu/editor/COC facts/. This site contains, among other items, a history of the college by chemistry professor **Rollie Myers**, information about awards and honors that our faculty members have received, and current facts and figures about the college. While you are there, you can take an online tour of the university and partake of the beauty and excitement of Berkeley. ▲



Mapping the Protein Universe (continued from page 1)

known. This method is flawed, however, since proteins in different organisms may have similar structure and function, but have drastically different amino acid sequences. The results from this technique did not make sense from an evolutionary point of view.

Kim has pushed for a different method of structure-function solving, one that groups proteins into classes on the basis of their fold structures and uses these structural similarities to help predict individual protein functions. While the protein universe may encompass as many as a trillion different kinds of proteins on earth, most structural biologists agree there are probably only about 10,000 distinctly different types of folds.

This is because proteins have evolved into the architectural structures that are most appropriate for their specific jobs. These folds are essentially identical for proteins from all life forms, even though the genes for a specific type of protein can vary greatly from the genome of one organism to another, and at times even within the same organism.

In the map created by Kim and his colleagues, UC Berkeley graduate students **Jingtong Hou** and **Gregory Sims** and research associate **Chao Zhang**, groups of folds corresponding to the four SCOP structural classifications are plotted. These classifications, based on secondary structural compositions and topology, are the "alpha" helices, "beta" sheets, and two mixes of helices and sheets, one called "alpha plus beta" and the other "alpha slash beta." (An alpha helix is one common structural element of protein motifs, consisting of a tightly coiled helical spiral of amino acids. A beta sheet has a fully stretched polypeptide chain and has a zig-zag appearance when viewed from the side.) The Kim map reveals that the first three groups share a common area of origin, possibly related to small ancient proteins, while the "alpha slash beta" class of proteins evolved much later.

"The map seems to have a loose evolutionary clock embedded in it," Kim said. "It shows the alpha helices and beta sheets developing early, then they started mixing, and finally, one of the mixes took off."

Kim is a member of UC Berkeley's Health Sciences Initiative, a campus-wide collaboration that brings the physical sciences together with the biological sciences to tackle health issues of the 21st century. He also is a Faculty Senior Scientist in the Physical Biosciences Division at LBNL and a member of the California Institute for Quantitative Biomedical Research (QB3), a cooperative effort among three UC campuses and private industry that harnesses the quantitative sciences to integrate our understanding of biological systems at all levels of complexity.

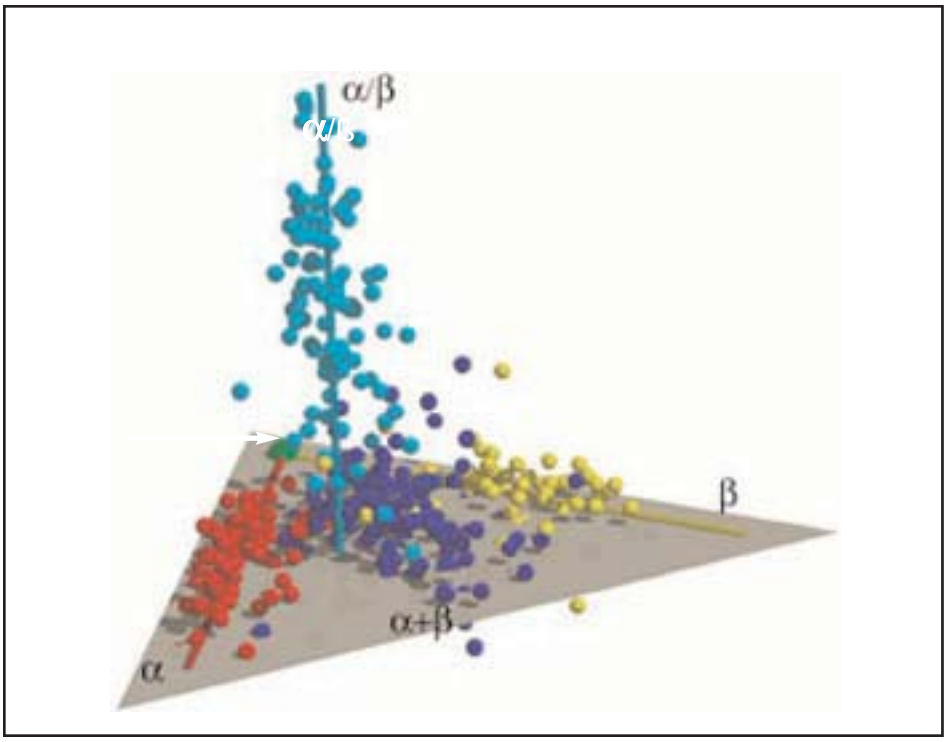


image courtesy Sung-Hou Kim

◀ A three-dimensional plot of nearly 500 building blocks or motifs found naturally in folded proteins, showing clustering that appears to be related to the evolution of complex folds. Each sphere represents a protein family exhibiting similar folds. Protein folds that belong to the alpha-helix, beta-sheet and alpha/beta class are mostly clustered around three separate axes.

Most protein folds of the alpha+beta class (lower center), which are a random mixture of alpha-helices and beta-sheets, fall within a plane between the alpha and beta axes. The alpha- and beta-axes approximately intersect at a single point indicated by the arrow.

Center for Biophotonics Science and Technology

Jay Groves is part of the new Center for Biophotonics Science and Technology. Funded with $52 million over 10 years from the NSF and matching funds from federal and state grants and private sources, the center includes researchers from across the country with headquarters at UC Davis. The new center will sponsor R&D of applications of biophotonics—the science of generating and harnessing light (photons) to understand the inner workings of cells and tissues.

"There is a need for imaging methods that resolve biochemical reactions at the membrane," said Groves. "A membrane bilayer structure is common to all metabolically active life, and 80 percent of drugs target membranes or molecules embedded within the membranes."

Groves, an assistant professor of chemistry, and his colleagues are using light to distinguish signaling events at the membrane in his quest to understand cell-cell communication.

Cells recognize physical patterns

"We have evidence that cells recognize each other by physical interactions as well as chemical signals," explained Groves. His group has shown that when two membranes interact, for example, when two cells touch each other, proteins embedded in the cell membrane surface rearrange into a pattern that the cell can interpret from within. "As two cells come into contact, a pattern of proteins emerges on the cell surface. This change in spatial configuration likely sets off a signaling cascade that affects the entire cell."

"We are developing new optical techniques to study the real-time interactions at the interface between two cell membranes," he continued.

A technique known as optical standing wave interferometry allows Groves to map the topography of the region where two membranes interact and watch the dynamics of the proteins within the membrane interface. With this "molecular sonar," he can see molecular elements on the nanometer level, which is hundreds of times smaller than what traditional optical microscopes can distinguish.

Membranes on a slide support

"We can also uniquely reconstruct the membrane on a slide support for imaging reactions," Groves added. Research using supported membranes holds the promise of capturing the functionality of live cell membranes while maintaining the simplicity and controllability of reconstituted assay systems, he noted. It is simpler than a living cell membrane yet still capable of performing certain acts of life.

Supported membranes are assembled on a solid substrate by a vesicle fusion process, which allows the membrane to be freely supported in a plane, separated from the solid surface by a nanometer layer of water. This water layer allows the membrane to retain its lateral fluidity such that the molecules within the membrane interact and rearrange as they would in natural membranes.

"Our goal is to use the tools we are developing to learn more about how molecules organize together and perform biological functions," said Groves. ▲

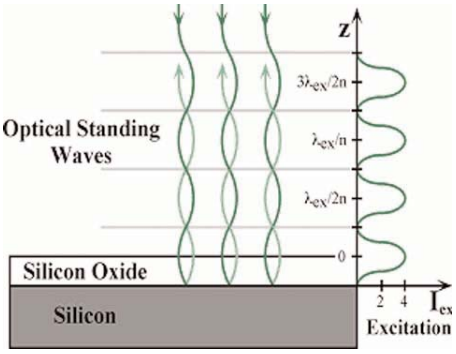


image courtesy Jay Groves

◀ The technique of optical standing wave interferometry can map the membrane surface with nanometer precision.

Jay Groves holds a membrane on a slide support.

Fréchet and Klinman Appointed to Endowed Positions

Chemistry professor **Jean Fréchet** has been appointed the first holder of the Henry Rapoport Chair in Organic Chemistry, effective January 1, 2003. Internationally recognized in both chemistry and engineering circles for his work relating structure to function of molecules, Fréchet studies organic chemistry on the nanometer scale, using macromolecules to investigate a range of topics, from catalysis and chiral recognition to targeted drug delivery.

Additionally, chemistry chair **Judith Klinman** has been appointed to the recently approved Joel H. Hildebrand Distinguished Professorship in Chemistry, an administrative position designed to give the chair funds for the support of young faculty and other top priorities of the department. ▲

Alivisatos to Head LBNL Materials Sciences

Paul Alivisatos, a physical chemist and pioneer in the burgeoning field of nanoscience, has been named director of Lawrence Berkeley National Laboratory's Materials Sciences Division (MSD).

"This is an extremely propitious time for Paul Alivisatos to lead MSD, as we begin to establish the Molecular Foundry project at Berkeley Lab," said chemistry professor and LBNL director **Charles Shank** in announcing the appointment.

Alivisatos is currently the director of LBNL's Molecular Foundary, a new facility for nanoscale materials. The Foundary incorporates various aspects of research, including nanofabrication and synthesis, imaging and manipulation, and biological nanostructures.

"He is recognized internationally as one of the fathers of nanoscience, having led the way in the synthesis, characterization, and understanding of semiconductor and metal nanocrystals, and having been among the first to publish results in this field more than a decade ago," said Shank.

Moving into the new millennium, the research group that Alivisatos heads has scored a number of landmark successes in nanoscience. For example, in 2000 they created the first semiconductor nanocrystals to be shaped like rods rather than spheres. This breakthrough led to a variety of even more exotic shapes, including teardrops, tetrapods and even arrowheads, all of which demonstrated the group's ability to control nanocrystal shapes and sizes. Most recently, Alivisatos and his group produced a hybrid solar cell that advantageously combines nanotechnology with plastic electronics. ▲

Keasling Engineers *E. coli*

Chemical engineering professor **Jay Keasling** is once again stretching the limits of metabolic engineering. His lab has developed a strain of bacteria that, under the right growing conditions, produces a large amount of the five-carbon compounds known as isoprenes, which join

photo by Peg Skorpinski

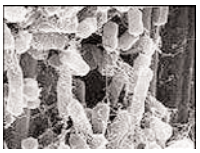
together in thousands of unique ways to form terpenes. Terpenes are natural products with medicinal applications and are used in the synthesis of some very potent cancer drugs, including taxol.

"Recently, many of the genes responsible for isoprenoid synthesis have been cloned from plants and microorganisms," said Professor Keasling. "Surprisingly, many of these genes can be expressed in functional form in *Escherichia coli* and other microorganisms. From the basic prenyl diphosphate precursors, the terpene synthases are able to produce a very diverse group of compounds. The use of these enzymes to produce these natural products at high levels in a simple way could significantly reduce their costs," he added.

All terpenes use one of three precursors, all of which are derived from the same molecule. Each terpene molecule can be made into a different drug depending upon what is stuck into the side of it. More than 30,000 different compounds can be produced from one terpene precursor.

Environmentally Friendly

In many cases, the desired isoprene compound must be extracted from its native source, usually a tree, and purified before use; hence, these compounds can be extremely expensive. "With our method, we can take a gene out of anywhere, put it in our bacteria, and generate a product that is economically useful and do this in an environmentally friendly manner. We take the gene out of the tree and put it into the bacteria," said **Jack Newman**, a postdoctoral fellow in Keasling's lab. ▲



▶The bacteria *E. coli* can be engineered to produce drug precursors.

The *NEWSLETTER OF THE COLLEGE OF CHEMISTRY* at UC Berkeley is published several times each year to support the college's mission of providing excellent teaching, research and public service in the fields of chemistry and chemical engineering.

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Noteworthy News

Armando J. Durazo, an undergraduate student in chemical engineering, was selected as an American Chemical Society Scholar, chosen on the basis of both academic scholarship and extracurricular activities.

photo courtesy Aileen Harris

◀The Merck Outstanding Teaching Assistant prize of $1,000 was awarded to chemical engineering graduate student **David Durkee**, who is advised by Professors Nitash Balsara and Alex Bell. Comments from his class (chemical engineering 150A Transport Processes with Alex Bell) include: "He's dedicated, knowledgeable, patient, understanding, approachable, and has a good sense of humor"; and "He clearly explained concepts and these 'discussion problems' he made really helped with understanding course material."

Chemistry professor **Graham Fleming** will be giving the E. U. Condon Lecture at the University of Colorado, the Phi Beta Kappa Visiting Scholar lectures at eight undergraduate institutions, and a lecture as the ACS Sierra Nevada Section Distinguished Chemist at the University of Nevada, Reno in the fall.

◀**Catherine Liang** is a 2002-2003 Eastman Kodak Fellow in Chemistry with chemistry professor Jean Fréchet.

Assistant Professor of Chemistry **Jeff Long** has been approved for tenure and promotion to associate professor, effective July 1. Congratulations!

Scott T. Phillips received the Lilly Discovery Chemistry Research & Technologies graduate fellowship for 2002-2003. Phillips is a graduate student in Paul Bartlett's group.

Matthew D. Simon, a graduate student studying with Professor Kevan Shokat, and **Kian L. Tan**, who studies in the laboratories of Professors Jonathan Ellman and Robert Bergman, have been awarded 2002-2003 Graduate Fellowships from the ACS Division of Organic Chemistry. In his graduate studies, Simon has been involved in the development of a small-molecule switch approach for controlling transcription factors. Tan has developed methodology toward selective C-H activation of heterocycles and currently studies the mechanism and intermolecular variants of this reaction.

F. Dean Toste, assistant professor of chemistry, received a Research Innovation Award from the Research Corporation in support of his project "Development of new methods and transition metal catalysts for enantioselective synthesis."

Postdoctoral fellow **Lei Wang** was a winner in the the Collegiate Inventors Competition for his "Genetically Encoded Amino Acid," a new technique for modifying bacteria so that they produce amino acids never before found in nature. "The approach," said the Hall of Fame in announcing the winners, "may open up broad avenues of research and enable the manufacture of new, useful proteins for research and pharmaceutical applications." Wang received his Ph.D. this year in bio-organic chemistry with Professor Peter Schultz.

Matthew Young, a postdoctoral fellow with Professor John Kuriyan, has won a prestigious "Career Award at the Scientific Interface" from the Burroughs Wellcome Fund.

Bell is the 2003 Burwell Lecturer

Alex Bell

Chemical engineering professor and former dean **Alexis T. Bell** has been awarded the 2003 Robert Burwell Lectureship in Catalysis by the North American Catalysis Society (NACS). The Lectureship is sponsored by Johnson Matthey PLC's Catalysts and Chemicals Division and is given in recognition of substantial contributions to one or more areas in the field of catalysis with emphasis on discovery and understanding of catalytic phenomena, catalytic reaction mechanisms and identification and description of catalytic sites and species. Bell's research activities have led to more than 400 publications in the most prestigious journals in catalysis, chemistry and chemical engineering. Over many years he has applied cutting-edge spectroscopy and theory to study surfaces before and after catalytic reactions. ▲

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Caveat Pensionarius *by Wendy Zukas*

photo by Jane Scheiber

In late fall of 2001, as the news of **Paul Bartlett**'s early retirement made its way along the former-member grapevine, a group of his alumnae/alumni began to discuss ideas for an event to honor him for his many contributions to bioorganic chemistry, including CAVEAT, a computer program used to facilitate design of organic molecules.

A small planning committee was formed, and the result is a one-day scientific symposium that will take place in Pitzer Auditorium on Saturday, June 7, 2003. This special event will include a day full of scientific presentations from former Bartlett group members, in both industry and academia, from all over the world. The symposium is open to the public. More details will be posted on the Bartlett group research website in mid-May: http://www.cchem.berkeley.edu/pabgrp/index.html.

For information, please contact **Wendy Zukas** at 510/642-8066 or wendy@fire.cchem.berkeley.edu. ▲

E-mail Newsletters

Do we have your current contact information? The College of Chemistry is now sending out regular newsletters by e-mail. Keep up with news and events in the college and help save some trees. To be included on this list, please send an e-mail to editor@cchem.berkeley.edu or fill out the alumni questionnaire form at http://chemistry.berkeley.edu/alumni/index.htm. Hurry, you don't want to miss a thing! ▲

Attention all CHEMillenniums!

The CHEMillenniums alumni group will hold its inaugural event on May 21, so if you were part of the college between 1980 and 1999, look for an invitation in your mail soon. The event will feature an informal reception, following which a panel of distinguished alumni- Berkeley chemistry professor **Carolyn Bertozzi** (Ph.D. '93), **Steve Fodor** (Post-doc '91), CEO and Chairman of gene chip pioneer Affymetrix, and **David Soane** (M.S. '77, Ph.D. '78), Chairman of Alnis Biosciences and Founder of Nano-Tex- will discuss some of the exciting developments in their fields. The evening promises to be both informative and fun, so mark your calendar! For more information, please contact **Camille Olufson** at 510/643-7379 or colufson@cchem.berkeley.edu. ▲