A renovation and seismic retrofit of Barker Hall is scheduled to begin in January, 2000. The retrofit will upgrade the building's predicted seismic performance, rated in a campus survey as "poor," to a rating of "good." The renovation of Barker, which was built in 1964, will include modernization of major building support systems.

Planned major building systems renovations and other improvements include piping, ventilation, elevators, constant temperature rooms, shared core equipment and facilities, and new flooring, ceilings, and conference rooms. A high-speed data network and an air conditioning system will also be installed.

The seismic retrofit will include new exterior shear walls and 50 steel-reinforced piers which will extend 60-feet deep to support the new foundation. Large sections of interior perimeter walls will be removed to install approximately 385 steel beams that will reinforce concrete support columns. A new covered walkway, lobby, and exterior landscaping are also included in the project.

Funding for the retrofit, approximately $14 million, was provided by Proposition 1A, the public education facilities bond that was passed by California voters in 1998. The remainder of the funding will be from various campus sources and the Howard Hughes Medical Institute. In total, about $20 million has been allocated to the project, and additional funds have been requested to complete the planned renovations.

The scope of the seismic and systems renovation will make it impossible for research, teaching, and administrative support programs to continue in Barker during construction. Laboratories are moving to other MCB buildings (LSA and Stanley Hall) and to other biology buildings on campus (Mulford, Valley Life Sciences, Wellman Court). Laboratories are also moving to off-campus sites (Lawrence Berkeley National Laboratory, Children's Hospital Oakland Research Institute). Laboratories hope to return to the building late in 2001.

The renovation of Barker continues the campus construction of state-of-the-art biology facilities that began in the mid-1980's and will continue well into the next decade as part of the Health Sciences Initiative. (For more on the Health Sciences Initiative, see page 4.)
In July of 1999, immunologist Mark Schlissel moved his laboratory from the Johns Hopkins University School of Medicine where he had been an associate professor in the Departments of Medicine, Molecular Biology and Genetics, and Oncology. He began his career at Johns Hopkins as an MD/PhD student, continued as a medical resident, and later joined the faculty as an assistant professor in 1991. He became an associate professor in 1995.

In fact, he left Johns Hopkins only for his postdoctoral research, which he conducted at the Whitehead Institute for Biological Research at the Massachusetts Institute of Technology. There, as a postdoctoral fellow in David Baltimore’s laboratory, Schlissel began the study of the basic immunological process of antigen receptor gene assembly which he continues today.

Please describe your research.

We are interested in understanding how the process of antigen receptor gene assembly is regulated during lymphocyte development. Lymphocytes can recognize an enormous array of foreign antigens. This recognition is mediated by antigen receptors called immunoglobulin (Ig) on the surface of B cells and T cell receptor (TCR) on the surface of T cells. Unlike any other metazoan genes, Ig and TCR genes are assembled from gene-segments during lymphocyte development via a series of site-specific DNA recombination reactions called V(D)J recombination. By this process, an enormous diversity of antigen receptor structures, each specific for a particular antigen, are created from a modest number of gene segments.

Currently, my lab is attempting to understand the biochemical and developmental regulation of V(D)J recombination. In particular, we have found that chromatin structure regulates the choice of gene segments which undergo recombination and that transcriptional activation of unarranged gene segments precedes their activation for recombination. We are currently studying the role of transcriptional enhancers in targeting the recombinase, the role of Ig protein as a regulator of B cell development, and the regulation of recombinase gene expression.

What is the significance of your research?

The significance of this work lies in the involvement of V(D)J recombination in several disease processes. Mutations that disrupt this process result in profound, inherited immunodeficiency—much more lethal than AIDS. Second, errors in the selection of genes for recombination can result in the activation of oncogenes by translocation to Ig or TCR loci—a very common cause of leukemias and lymphomas. Finally, the regulation of V(D)J recombination reaction plays a role in self-tolerance. If a randomly generated Ig gene produces an Ig with self-specificity, the recombination reaction resumes and gets rid of the offending gene. Failure of this process may contribute to autoimmune diseases such as lupus or rheumatoid arthritis.

What is the most rewarding achievement in your career so far?

Two of them come to mind. The first is that I devised several novel assays of gene rearrangement which have led to major breakthroughs in our understanding of the regulation of V(D)J recombination. These assays are used routinely in most every lab that studies this process. Second, I have gained great satisfaction from having run the basic immunology course for first year medical students at Hopkins. It is difficult to teach basic science to medical students because many of them do not realize how important it is for their understanding and treatment of disease. Two years after I took over the poorly organized and unpopular course, it was the highest rated course at Hopkins Medical School.

What special contribution do you hope to make to the department?

I hope to bring the perspectives I gained while studying medicine and disease biology to the intellectual community here. I also hope to contribute to communal progress on an area of interest to a significant subset of the faculty here—how the packaging of DNA into chromatin influences the activity of protein complexes which have to act upon DNA substrates. Finally, I want to offer undergraduate and graduate students good teaching and mentoring.

Education:

• A.B. in Biochemical Sciences, 1979, Princeton University.

Selected Awards and Honors:

• Cancer Research Institute Investigator Award, 1992.
• Culpere Foundation Scholar, 1993.
• Leukemia Society Scholar, 1996.
• American Society for Clinical Investigation, Elected to Membership, (1998).
• Graduate Student Teaching Award (1998).

Personal Information:

I am married and have four children. My wife, Monica Schwebs, is an environmental lawyer. Our children are 14, 12, 9, and 6 years old.
**OBITUARY**

MCB Professor emeritus Heinz Fraenkel-Conrat died on April 10, 1999. He was 88. Fraenkel-Conrat was a member of the National Academy of Sciences and a recipient of the Lasker Award, among other honors. With colleague Robley Williams in 1955, Fraenkel-Conrat demonstrated that infectious tobacco mosaic virus could be reconstituted from RNA and the protein coat, the first known example of self-assembly of an active biological structure. That same experiment proved that the genetic information was contained in the RNA and not in the protein.

**AWARDS AND HONORS**

RECEIVED FROM DECEMBER, 1998 THROUGH NOVEMBER, 1999

- Dan Kosshland was named to the Council on Bioscience by Governor Gray Davis.
- Edward Penhoet was named to the Council on Bioscience by Governor Gray Davis.
- Randy Schekman received the 1999 Apgen Lecture Award of the Protein Society.
- Jeremy T. Horner was elected a Fellow of the American Academy of Microbiology and was reappointed to the William V. Power Chair in Biology for another 5-year term.

**Cell and Developmental Biology Faculty**

- Beth Burnside received the Outstanding Alumna Award from the Graduate School of the University of Texas at Austin in May, 1999.
- John Forte was appointed the 1998 National Lecturer in Physiology by the Swedish Royal Academy of Sciences and was elected an Honorary Member of the British Society of Gastroenterology.
- Rebecca Hald received the Pew Scholars Award in Biomedical Sciences beginning July 1, 1999.
- Tito Serafini received the EJLB Foundation Scholar Research Award and a UC Berkeley Faculty Fund for the Biological Sciences Award for 1999.
- Richard Steinhardt gave the plenary address to the British Society Meeting for Cell Biology on September 20, 1999.
- Richard Strohman received the Harriss Award Lectureship for the year 2000 at the University of Nebraska.

**Immunology Faculty**

- David Raulet was appointed to the Choh-Hao Li Endowed Chair and was elected to the Program Committee of the American Association of Immunologists, both in July, 1999.

**Neurobiology Faculty**

- Corey Goodman was elected to the American Philosophical Society.
- Ehud Isacoff is part of a team of UCB researchers who received a 1999 D avid and Lucile Packard Foundation Interdisciplinary Science Research Award.
- Carla Shatz was elected to the Institute of Medicine of the National Academy of Sciences.

**PROMOTIONS AND APPOINTMENTS**

EFFECTIVE JULY 1, 1999

- Steve Martin was appointed Cell and Developmental Biology Division Head.
- Jeff Owen was appointed Neurobiology Division Head.
- Caroline Kane was promoted to Adjunct Professor of Biochemistry and Molecular Biology.
- Joshua Kaplan was promoted to Associate Professor of Cell and Developmental Biology.
- Astar Winoto was promoted to Professor of Immunology.
- David Presti was appointed MCB Professor emeritus of Employment (effective January 1, 2000).

**OBITUARY**

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The Center for Neuroscience has a new name and a new director. It has been re-named the Helen Wills Neuroscience Center in honor of the tennis star and Cal alumna who donated her entire estate to the Center. The Center’s new director is MCB Neurobiology Professor Corey Goodman who has taken over for Carla Shatz. Shatz, MCB professor of neurobiology, is leaving UC Berkeley in June, 2000. For more on the Center, see the Spring, 1998 issue of the MCB Newsletter (mcb.berkeley.edu/news/spring98.html).

On October 6, 1999, UC Berkeley formally announced the plans for the Health Sciences Initiative, a multidisciplinary research and teaching program which was described in detail in the Spring, 1999 issue (mcb.berkeley.edu/news/newsletter.html).

Berdahl estimated the total investment in the initiative at $500 million. Of that amount, $300 million will be for new facilities that will replace Stanley Hall and Warren Hall, both seismically poor buildings.

The two new buildings will house as many as 400 UC Berkeley researchers brought from various disciplines including biology, public health, chemistry, physics, engineering, and psychology. About a dozen new faculty hires will join them, said Provost and Executive Vice Chancellor Carol Christ.

Funding will be from a combination of public and private support. Along with $24 million in state support, $100 million in private gifts has been collected. This includes $50 million from an anonymous donor, which is the largest single gift ever to the UC Berkeley campus.

Playing an important part in the Health Sciences Initiative will be MCB researchers, whose work has already had a “very high impact on the field of biomedicine,” according to MCB Co-Chair Jim Allison. Allison, who was one of three UC Berkeley faculty to speak at the press conference, said, “I think it is fair to say that Berkeley has a superb reputation for the quality of basic research in biology, but overall the contributions that work has made to health issues is perhaps underrecognized.” He went on to describe recent work from his lab as an example of basic research with medical applications. An account of his research follows on this page.

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A promising cancer treatment headed for human trials was developed in the laboratory of MCB Professor of Immunology James Allison. Their research on the basic mechanisms of T cell activation led directly to an immune therapy called CTLA-4 blockade. This therapy generally enhances immune responses so that they are effective against tumors.

“I consider myself a basic scientist . . . I do not necessarily look for ways to do tumor immunology,” said Allison. “But once we find something that looks like it might be a fundamental way of regulating immune responses, then I immediately start thinking of some way to manipulate that . . . The translation can be pretty direct from basic work to the clinic.”

Over many years, Allison's lab and others have elucidated the interaction of signaling pathways involved in T cell activation, which Allison explains using an analogy. He likens the antigen receptor on T cells to the ignition switch in a car and the antigen to the ignition key. “Each of the about 10 billion different ones circulating in your body fit a different antigen exactly,” explained Allison. “But there are two additional types of signals. The co-stimulatory signal, which is given by the receptor called CD28, is like the gas pedal in your car. Just as turning the ignition on is not going to make the car move, the T cell is not activated without this second signal.” He continued, “And then a couple of years ago, we demonstrated there is another signal which is inhibitory, mediated by the receptor called CTLA-4, which is sort of like the brakes on a car. It down-regulates the immune system.”

Allison thinks that the inhibition of T cell activation mediated by CTLA-4 is one way our bodies keep autoimmune reactions in check. But by protecting normal cells from attack by T cells, it also protects tumor cells. “In general we can't launch an immune response against cancer, the cancer is ourselves,” said Eric Small, an associate professor of urology at UC San Francisco, in a UC Berkeley press release. “But Allison's work shows that the
body does have the capacity to do so, and his therapy makes this more robust. Small plans to direct the first clinical trials of the drug in patients with prostate cancer.

The drug is an antibody to the CTLA-4 receptor which blocks the receptor’s inhibitory effects. “Blocking the CTLA-4 signal essentially takes the brakes off the immune system at least temporarily, augmenting significantly the immune responses,” said Allison. “We found that after merely injecting mice with this antibody, T cells begin to come out of blood vessels, move into the tumor and begin to kill tumor cells.”

Simple administration of the antibody resulted in rejection of tumors in a variety of mouse tumor systems including colon and prostate carcinomas. It was also effective against metastases, the secondary growths that have spread from the primary tumor to other parts of the body.

With this therapy, tumors are destroyed by the unleashing of an autoimmune attack, so it follows that normal tissue might also be affected. For example, in melanoma model systems, the mice developed an autoimmune condition called vitiligo. Vitiligo is characterized by areas of depigmentation of skin and hair caused by destruction of melanocytes, the pigment-producing cells from which melanoma arises. The depigmentation is evident as white spots on dark-colored mice, as shown in the photo above. Similarly, people who recover from melanoma often develop vitiligo.

“But those are the only ill effects that we have seen, tissue-specific immunity to the tissue from which the tumor derived, which is certainly acceptable for many kinds of cancer,” said Allison, referring to cancers of the prostate, breast, and other non-vital tissues. “At this point we would not even propose this as therapy in humans for (cancers of) tissues that are not dispensable, such as lung cancer.”

The cost of treatment with CTLA-4 blockade may be an autoimmune condition, but its benefits are considerable. “The beauty of eliminating a tumor this way is that then the T cells ought to be able to go out and find metastases, and it provides immunity which, by definition, means it should be a long-term cure and protection against recurrence,” said Allison.

In the last year, human antibodies to human CTLA-4 were produced by the biopharmaceutical company GenPharm, in Palo Alto, CA. GenPharm has developed a technology for making completely human antibodies by immunizing genetically modified mice whose immunoglobulin genes have been replaced with human immunoglobulin genes. GenPharm is a subsidiary of Medarex, Inc., of Annandale, N.J., which has sublicensed the patents for CTLA-4 blockade obtained by Allison and U.C. Berkeley.

“Our target is to get this drug into patients in the year 2000,” said Nils Lonberg, vice-president and director of research at GenPharm. “With a cancer treatment, you never know until you put it into clinical trials, but the animal studies done by Allison’s lab are extraordinary. A lot of people have cured cancers in mice, but these studies really stand out amongst all the drugs that have looked promising in mice. I think this may be an unusual opportunity to develop a drug that is also going to be spectacular in humans, but we have to wait and see.”

The initial trials will be designed to assess safety, but clinical effects may be seen because the trials will involve prostate cancer patients and not healthy volunteers. Subsequent trials will prove whether CTLA-4 blockade is an effective cancer treatment by itself or in combination with other therapies. Allison suggests it could be useful in combination with conventional chemotherapy (at reduced dosages to limit side effects) or with surgery or radiation, especially for large or resistant tumors.

“I don’t really have any hope that this is a magic bullet, that CTLA-4 blockade is going to take care of huge tumors,” said Allison. “But if the tumor’s size can be reduced to something that the immune system can handle, hopefully, it can mop up and also provide long-lasting immunity to recurrence . . . Metastasis is usually what kills patients, and it ought to be able to take care of that.”

In mice, Allison’s lab combined CTLA-4 blockade with another immune therapy, a tumor cell vaccine producing the cytokine GM-CSF. Neither treatment works alone, but together they synergize and cure a “nasty” type of melanoma that, Allison said, “no one has been able to cure before.”

Because CTLA-4 blockade therapy exploits such a basic mechanism of the immune system, it may be useful not only for treating cancer, but for other diseases as well. “If it works it could be generally applicable to a lot of different things where you want a stronger immune response,” said Allison. For instance, CTLA-4 blockade enhances the effectiveness of vaccines. Allison believes it could accelerate the development of infectious disease vaccines needed for antibiotic-resistant strains of bacteria such as those that cause tuberculosis and for viruses such as H.I.V. He has experiments underway to apply CTLA-4 blockade to an HIV vaccine model.

But taking on H.I.V. and cancer is not enough for Allison, he also plans to tackle autoimmune disease. “Now the trick is to get back to lab and figure out how to make it work in reverse. What we’re doing now is blocking the (inhibitory) signal, and what we have got to figure out is how to give the signal. Then we can presumably turn immune responses off,” said Allison. “That has implications for diabetes, multiple sclerosis, and other autoimmune diseases.”

REFERENCES:
Two MCB graduate student volunteers, Jill Fuss and Jonghui Lee, created a career seminar series entitled Life After Grad School: Careers for Bioscience PhDs, which was offered last Spring semester as MCB 294. They each came up with the idea for such a course independently and worked together to organize it. Fuss obtained department approval for the course with the help of faculty sponsor Caroline Kane. Fuss also received a course development grant from campus. Lee almost single-handedly enlisted the approximately 40 speakers, although she credits others for suggesting the speakers, especially Ed Penhoet, dean of the School of Public Health and co-founder of Chiron Corporation, and Louise Rosenbaum, former associate director of the UC Systemwide Biotechnology Research and Education Program. Lee and Fuss also got assistance from the MCB Graduate Affairs Office. The funding for the series was provided by the MCB Department along with a contribution from the UC Berkeley Career Center. Fuss’s description of the course and Lee’s advice for fellow graduate students follow.

“In the same way that the weekly research seminars make students aware of exciting new fields of research, I felt that the department needed a career seminar series to ensure that students know about different career options.”

Life After Grad School: Careers for Bioscience PhDs by Jill Fuss, MCB Graduate Student

MCB 294 was organized as a weekly seminar series, and, over the course of the semester, there were presentations on sixteen different career options for bioscience PhDs. The topics ranged from more traditional careers, such as those in academia and the biotechnology and pharmaceutical industries, to careers in forensic science, patent law, finance, and science journalism. Every week, three or four speakers from a particular field were each given fifteen minutes to discuss their careers, with plenty of time for questions afterward. The speakers were also available for informal questions and discussion at a reception following the presentations. Each class was organized by a student host who also arranged a dinner with the speakers and interested students. The final presentation of the semester was by Andrew Green, PhD Counselor at the Career Center, who gave an overview of career resources for graduate students, as well as advice on resumes, interviewing, and networking.

The response to the course was overwhelmingly positive. Every seminar was well attended, drawing between 40 and 110 people, mostly graduate students. One student said that the course “opened up my eyes and mind in terms of job opportunity.” Another commented, “Prior to this, I had very limited exposure to non-academic job options and no idea where to look (for more information).” The popularity of the series sent a clear message that there is a real need for this type of information. In response to this need, the department will offer this course every Spring semester as MCB 295: Careers for Life Sciences PhDs.

“I was familiar with only two career paths, one was working as a postdoc until landing on the academic tenure track and the other was becoming a researcher in a biotech company.”

Advice for Graduate Students by Jonghui Lee, MCB Graduate Student

I urge fellow graduate students to find out what they can and want to do with their scientific training and to become active in developing skills for their desired careers, whatever those may be. On campus, both the Career Center (career.berkeley.edu) and the Postdoctoral Association (www.berkeley.edu:5060) offer several workshops to help young scientists with career planning and development for both academic and non-academic careers. For those who want to meet professionals with science backgrounds who are working in diverse fields, attending national meetings such as those organized by the American Association for the Advancement of Science (www.aaas.org) and the Biotechnology Industry Organization (www.bio.org) provide excellent opportunities. Various local professional groups such as the East Bay Chapter of the Association for Women in Science (www.ewas.org) and the Northern California Pharmaceutical Discussion Group (www.ncpdg.org) also offer useful workshops and seminars throughout the year.

From my involvement in MCB 294, I developed important organizational and personal skills and interacted with professionals in many fields. I encourage others to take advantage of this valuable opportunity by getting involved in the organization of future MCB 295 series. (Contact Eileen Bell in the MCB Graduate Affairs Office.)

EDITOR’S NOTE: Many of the speakers in this course, including myself, were former MCB graduate students. If you would like to participate, please contact Eileen Bell (510-642-0944, dbell@ucrlink4.berkeley.edu).
M CB is tracking the employment status of its former graduate students and those from its predecessor departments. During last spring and summer, Peggy McCutcheon-Smith, administrative assistant to M CB Co-Chair Randy Schekman, verified the employment status of most of 415 graduates who received their degrees from 1989, the year M CB was formed, to 1998, inclusive. For analysis, the graduates were divided into the following five job categories: post-doc; academic (includes university and college professors, research institute scientists, community college instructors, and high school teachers); biotech (those employed in the biotechnology industry); other employment (e.g., medicine, patent law, science writing, and computer analysis/bioinformatics); and uncertain (those we were unable to contact, those between jobs). For graphing, the degree years were combined into two-year periods.

Alumni Survey

We plan to include a regular feature on alumni news, and we would like to hear from you. Please complete the following for inclusion in an upcoming issue and mail to:

University of California at Berkeley
Department of Molecular and Cell Biology
597 Life Sciences Addition #3200
Berkeley, CA 94720-3200

You may also submit the information via e-mail to:
william5@udlink4.berkeley.edu

Name __________________________________________________________
Degree(s) conferred and year _________________________________

Address ______________________________________________________  City/State/Zip__________________________________________

E-mail address _______________________________________________________________________________________________________

BRIEF CAREER HISTORY:

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Any additional professional information or news about yourself or other alumni: ________________________________________________
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PhD GRADUATES

Fall, 1998

- So-ching Wong Brazer (Cande) Kinesin Motor Proteins in Schizosaccharomyces pombe.
- Daniel Campbell (Shatz) Bacterial T Cell Antigens: Identification and Processing Pathways.
- Ilil Carmi (Mayer) The Primary Sex Determination Signal of Caenorhabditis elegans.
- Mark Coles (Raitt) Role of the Major Histocompatibility Complex and T Histamines in the Development of T Cells that Express Natural Killer Cell Markers.
- José De Jesús-Escobar (Shatz) The Role of Neurotrophins in the Activity-Dependent Formation of Patterned Neuronal Connections in the Avian Brain.
- Heather Corbett Etchevers (Bentley) Neural Crest-Related Differentiation of the Embryonic Avian Brain.
- Kathi Glauner (Isacoff) Structural and Conformational Mapping of the Shaker Potassium Channel.
- Chau Huynh (Thorner) Molecular Genetic Analysis of a Phosphoinositide-Specific Phospholipase C (PLC1 Gene Product) in the Yeast Saccharomyces cerevisiae.
- Adam Jacobs (Werbin) Patterns of Activity in the Vertebrate Retina: Prediction by a Computational Model and Subsequent Physiological Confirmation of a Neuronal Mechanism for Edge Extraction in the Retina.
- Beatriz Quiroga (Bentley) Expression Patterns, Biochemical Properties, and Intracellular Localizations of the Syntaxin 2 Variants.

Spring, 1999

- Joanne Adamkewicz (Thorner) Biochemical and Genetic Analysis of MGT1, a Regulator of Basal Transcription in Saccharomyces cerevisiae.
- Giselle Giorgi (Machin) Wound Healing and Genetic Analysis of Mot1, a Regulator of Chromosome Segregation in Schizosaccharomyces pombe.
- Frederick Wolf (Garraway) Posterior Migrating Guidance in Caenorhabditis elegans.
- Francesco Mariani (Harland) Identification of New Molecules With Neuroregulating Activities: XBF-2, Xenopus Brain Factor 2.
- Monique Nicoll (Mayer) Transcriptional and Post-Transcriptional Regulation of xol-1 by the Primary Sex Determination Signal in C. elegans.
- Sara M le ko O kamura (Rine) Genes Required in the α Cell Type of Saccharomyces cerevisiae.
- Sophie Petersen (Goodman) A Genetic Analysis of Synaptic Plasticity at the Neuronal Synaptic Function in Drosophila.
- Michelle Poitier (Bennett) Biochemical Characterization and Structural Analysis of the Synaptic SNARE Complex.
- Erica Roulier (Bekendorn) Tec9 Tyrosine Kinase: Multiple Function in the Development of Drosophila melanogaster.
- Nam Vo (Chamberlin) In vitro studies of the Transcription Initiation Process by E. coli RNA Polymerase.
- Frederic Pikler (Linn) Identification, Cloning and Characterization of three Associated Subunits of the Escherichia coli H2O2 Challenge in E. coli.
- Francesca Mariani (Harland) Identification of New Molecules With Neuroregulating Activities: XBF-2, Xenopus Brain Factor 2.
- Pakming Lau (Bentley) Induction of Filopodia by Direct Local Elevation of Intracellular Calcium Ion Concentration.
- Greg Lazar (Handel) Hydrophobic Core Packing and Protein Design.

Please note that Judith Dave, Jason Dugas, Andrew Kasarskis, and Nell Shimasaki are 1998-99 graduates who were mistakenly included in the previous year’s list.