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Weekly Research Seminar invites emerging talents to Rockefeller

Several dozen researchers from around the country will be visiting Rockefeller this year to speak at the Weekly Research Seminar, the scientific lecture series previously known as the Junior Faculty-Student Seminar Series.

"The series is really not just for junior members of the community, it's of interest to everyone," said Associate Professor Claude Desplan, who retitled the series this year. "It's useful only if we invite the best emerging talents, and we need people who know what the newest research is in their respec-

tive fields to make recommendations," he said.

Desplan solicits suggestions for speakers from the university at large. About a dozen spring dates are still open, and he is still seeking recommendations, though he pleaded: "Please, argue for your speaker in two lines!"

Desplan and the seminar selection committee then choose speakers according to three criteria: the science should be of high quality, the topic should be of interest to a large portion of the campus community, and the speaker should be able to convey enthusiasm. Desplan also invites members of the Rockefeller community to present their work. Speakers lecture in a classroom (usually Tower Building 301), an informal setting that facilitates discussion. The hour-long seminar is held on Wednesdays at 11:00 A.M.

This lecture series is not just less formal than the one on Friday afternoons. "Its focus differs," said Steve DiNardo, an associate professor who attends the seminar regularly. "The Friday series features well-known people who give a broad synthesis of the state of the field in their area. The Wednesday series,

See *Series*, page 2

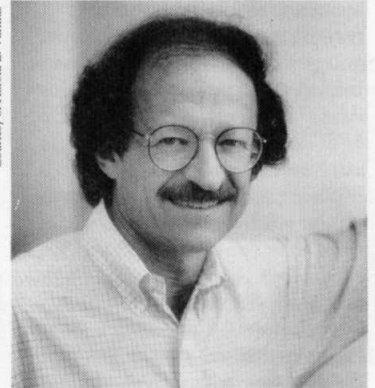
Nobelist and N.I.H. director Varmus lectures today on genetics of breast cancer

Harold E. Varmus, the Nobel Prize-winning director of the National Institutes of Health, will speak on "Wnt Genes in Development and in a Multistep Model for Mammary Carcinogenesis" at the Friday lecture today (Oct. 7).

Varmus will discuss his work on the Wnt gene family. The first Wnt gene was discovered in his lab as the main target of virally induced breast cancer in mice.

"The Wnt genes are now known to be important players in the early development of highly diverged animals such as flies, worms, birds, and mammals," said Assistant Professor Titia de Lange, who will introduce Varmus today. "Harold and his coworkers are currently investigating the role of Wnt genes in development and tumorigenesis in mice using transgenics, gene targeting, and retroviral infection."

Varmus shared the 1989 Nobel Prize in Physiology or Medicine with J. Michael Bishop for their demonstration that oncogenes can arise from normal cellular genes, called protooncogenes. In 1993, Varmus was appointed director of



Courtesy of Harold E. Varmus

Harold E. Varmus, who shared a Nobel Prize with J. Michael Bishop for work on oncogenes, lectures today (Oct. 7).

N.I.H. by President Bill Clinton.

A graduate of Amherst College (B.A., 1961) and Harvard University (M.A., 1962), Varmus received an M.D. degree from Columbia University in 1966. After an internship and residency in internal medicine at Presbyterian Hospital in New York, he served as a clinical associate for two years at N.I.H. investigating

See *Varmus*, page 2

Save the date: Oct. 20

Physics and Biology Center to open

A lecture by Albert Libchaber inaugurates Rockefeller's new Center for Studies in Physics and Biology on Thurs., Oct. 20.

Libchaber joined Rockefeller as professor last year. He shared the 1986 Wolf Prize in physics with Toyota Professor Mitchell Feigenbaum, director of the new center. Libchaber's lecture, entitled "Physics and Biology: The Universal and the Specific," will be given in Caspary Auditorium on Thurs., Oct. 20 at 5:00 P.M. It will be followed by a reception in Smith Hall Annex.

Look for more on the center in next week's *News&Notes*.

2 Pose for posterity

3 Gene shuttles to brain

4 New beer on tap



McCarty's moment

Professor Emeritus Maclyn McCarty (*center*) received the Albert Lasker Special Public Health Award in honor of experiments he did half a century ago with Oswald Avery and Colin Macleod proving that DNA was the genetic substance. Here, he celebrates with the Honorable Donna Shalala (*right*), keynote speaker at the awards ceremony, held Fri., Sept. 30 at New York's Pierre Hotel. Stanley Prusiner (*left*) won the Albert Lasker Basic Medical Research Award.

"The story shows how some researchers' doggedness, faith, and insight can disturb the universe of scientific inquiry, with vast consequences for the uncomprehending public, with scarcely any public notice or recognition."

—The Boston Globe, Oct. 3, 1994

Two thousand smiles: The making of the RU phone book

Denizens of the Rockefeller campus showed up in Founder's Hall at a rate of 300 a day to be photographed for the new phone book. Poised on a tiny stool, people posed for one brief shining moment for an image that will endure in the new directory for years.

John Sholtis and Shari Diamond of the university's Media Resource Center presided over the process—Diamond amid a mountain of equipment, clicking the shutter again and again, and Sholtis recording each person with paper and pencil. The two volleyed vital information back and forth for five days. "That person was number 70-18." "Wasn't it 70-19?" "Yes, 70-19, sorry."

Sheer logistics aside, the new phone book is a high-tech production, with contributions by a Macintosh Powerbook, CD-ROMs, and Media's state-of-the-art Compugraphic Imagesetter. "It's a big, complicated project, but by doing it mostly ourselves, we are saving quite a bit," said Frank Lees, chief information officer. "There is also a tremendous savings in cost by doing it electronically."

Last spring, the Academic Council recommended a new photo directory, and the university decided to combine this with the phone book. Along with the photo portraits, the phone book will list names, titles, campus addresses, phone numbers, boxes, and e-mail addresses. But who knows *who* to list? "Portia Goodman and her staff knock themselves out to keep an accurate database of people on

campus, in conjunction with Personnel and other offices," said Lees. The directory will debut in mid-November.

The data have a long journey from film to final page. Media's staff will first transfer the 2,000 or so photographs to CD-ROM disks, which reduce the pictures to a matrix of tiny dots, called pixels. A software program designed by Computing Services will match the images and their assigned numbers with the master list of numbers and names made by Sholtis and Diamond on a Macintosh PowerBook. The resulting image database will be linked to a page layout program containing the phone book text, and this file will be used by Media's Compugraphic Imagesetter to generate a negative page layout, which will then be

sent to a traditional offset printer.

"It's a hybrid, high-tech process," Sholtis said. "It required a lot of planning. We built many safeguards into the process. We had weeks of discussion about how to do this." One consideration was possible future uses of the information. "The database used to compile the phone book may also serve Security in some way, or it can be integrated into the on-line directory," explained Ray Aldrete, director of the Media Resource Center. Users of the recently announced RU World Wide Web will soon be able to access the phone book and click onto their screens an image of the person whose telephone number they are requesting. "Other uses may develop. The more we employ this database, the more options we will discover," Aldrete said.

But that is the future. The first stage of the current production is not complete: Not everyone on campus has taken a turn in Founder's Hall. Make-up days are Tues. Oct. 11 and Wed., Oct. 12. Those who missed their appointments are now being notified.

One issue that remains to be resolved is: When will pictures need updating? In five years? Ten? Aldrete pondered the question. "Maybe when people go gray, they can request a new photo. Or maybe they won't want to. We'll see."

Varmus

(continued from page 1)

transcription in *E. coli*. In 1970 he went to the University of California in San Francisco (U.C.S.F.) to study tumor viruses with Bishop, and was appointed assistant professor at U.C.S.F. in 1972. He became a full professor in 1979, and was named American Cancer Society Professor of Molecular Virology in 1984.

In addition to the Nobel Prize, Varmus has received an Albert Lasker Basic Medical Research Award and the Alfred P. Sloan Prize. He is a member of the National Academy of Sciences, and is the author or editor of four books and nearly 300 scientific papers.

The lecture will be held in Caspary Auditorium at 3:45 P.M. and preceded by tea at 3:15 P.M. in Abby Aldrich Rockefeller lounge. Admission is free and all are welcome to attend.



Say "cheese." Matthew Zschack poses for posterity—aka the forthcoming RU phonebook—in Founder's Hall, as Shari Diamond enters his name in a PowerBook. Zschack is a new member of Media who will be doing computer graphics.

New courses for students

Three new courses have been added to the more than two dozen available this academic year.

One new course, which began this week (Wed., Oct. 5), is Grand Tour of Mathematics, taught by Toyota Professor Mitchell Feigenbaum. It will cover a variety of mathematical topics, including linear algebra, complex analysis, and statistics and their distributions. "This course is designed to extend the student's mathematical tools," said Feigenbaum. "This course is an experiment. It will proceed at a pace dictated by comprehension."

A second new course, Neural Systems, began last month. Taught by Professor Charles Gilbert, it gives students broader training in the neurosciences. "This course focuses on the integrative action of the neurosystem," said Gilbert. "We will examine how neurons

interact to perform complex tasks, such as visual recognition, interaction with extrapersonal space, and higher-order cognitive functions." Discussions of neurosciences texts will be supplemented by guest lectures.

In the spring, Vincent Astor Professor Paul Greengard will offer another neuroscience course, Signal Transduction in the Brain. This course will examine the mechanisms by which neurotransmitters and other intracellular messengers produce their effects on target neurons. Topics will include receptors, ion channels, and the biology of Alzheimer's disease.

Postdoctoral fellows and other members of the university community are often allowed to attend courses, although attendance of a single lecture in a series is discouraged. Further information can be obtained from course administrators or the Dean's Office, x8086.

Series

(continued from page 1)

which has been excellent for the past few years, brings in a wide spectrum of first class researchers who give very detailed descriptions of their own work."

Some researchers speaking this fall are: Ulrike Gaul, of Rockefeller, Nov. 16; Hans-Ulrich Hartle, from Memorial Sloan-Kettering Cancer Center, Dec. 7; and Lloyd Green, from Columbia University College of Physicians and Surgeons, Jan. 7.

Desplan, who has run the series for four years, is pleased with the line-up of speakers for the fall and the way the series is coming together. "We owe thanks to the Dean's Office and to Norton Zinder in particular for the increased budget," he said.

Desplan may be reached at e-mail desplan, x7965, box 151, or fax x8370.

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Rockefeller researchers transfer genes into brain

by Susan Blum

People with Parkinson's disease live in a nightmarish prison: their mental capacities are fully intact, but their bodies constrain them. Incapable of smooth movements, they suffer rigidity, tremors, and frustrating failures of momentum that make it difficult to move and, once moving, to stop.

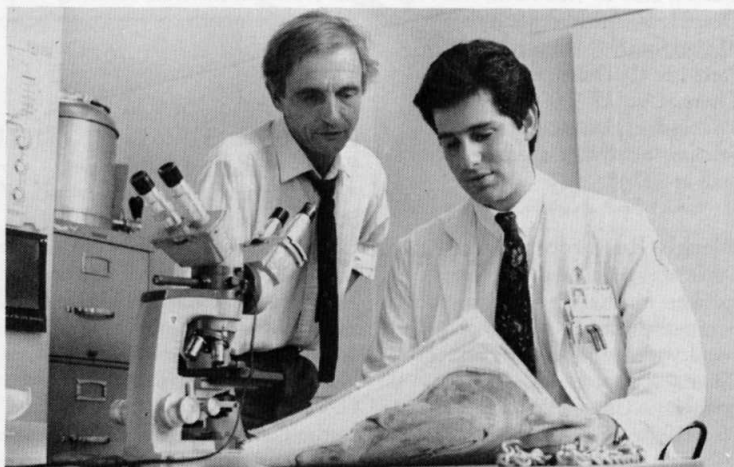
The problem results from the degeneration of cells in the brain region called the substantia nigra. These cells, which produce the neurotransmitter dopamine, project their axons into another brain region, the basal ganglia, which controls fluid movements of the body and limbs. Dopamine helps regulate a complex balance of inhibitory and activating signals originating in the basal ganglia. Without the neurotransmitter, parkinsonian movements develop.

Current treatments for Parkinson's leave much to be desired. Various drugs help alleviate the symptoms, but their benefits are inconsistent and they cause side effects. Transplants of dopamine-producing fetal brain cells have been attempted, but so far these experiments have engendered both scientific and political controversy. Many researchers believe that a more successful approach might eventually be to treat Parkinson's through gene therapy. Such therapy would fix the problem on a molecular level, by providing the genes necessary for the cells in the basal ganglia to get the dopamine they need.

The first steps toward that goal have just been achieved through research conducted by Michael Kaplitt in the laboratory of Professor Donald Pfaff, in collaboration with researchers at Yale. In the Oct. 1 issue of *Nature Genetics*, the Rockefeller researchers report the safe and stable transfer of a gene into the brains of rats with the rodent version of Parkinson's. The animals who received this gene therapy showed significant lasting improvement in motor function.

The work is a milestone in two respects. For one thing, it is the first time that a particular kind of gene shuttle (called an adeno-associated viral vector) was used to directly transfer genes into brains—not merely into cells in culture. It is also the first time that gene transfer has been shown to produce a therapeutic effect on behavior.

The research was initiated by Kaplitt, a postdoc in the Pfaff lab,



Professor Donald Pfaff and postdoctoral fellow Michael Kaplitt have used gene transfer to produce a therapeutic change in the behavior of rats with the rodent version of Parkinson's disease.

where he earned his Ph.D. in 1993. A member of Rockefeller's M.D.-Ph.D. program, Kaplitt is now completing his final year of medical school at Cornell University Medical College. His aim is to become a neurosurgeon, partly in the hope that should his work prove applicable to humans, he will be able to implement it himself.

Gene therapy

There are two basic gene therapy strategies, Kaplitt explains. With the *ex vivo* approach, the therapeutic genes are introduced into cells that have been taken from the patient and grown up in culture; the genetically engineered cells are then reintroduced into the patient. With the *in vivo* approach, the cells receive their cargo of therapeutic genes without being taken out of the body. Kaplitt prefers the *in vivo* approach, particularly for therapy in the brain. "There is little you can do *ex vivo* that you can't do *in vivo*, and some things you can do *in vivo* that you can't do *ex vivo*," he says.

Just as scientists contemplating gene therapy must choose between the *ex* and *in vivo* approaches, they must also decide on a way to shuttle the new genes into the cells. The most common way is to exploit viruses, which Kaplitt calls "nature's own gene transfer mechanism." Consisting only of viral genetic material wrapped in a fat-and-protein coat, viruses use the machinery of the cells they infect to make all the proteins they need to survive and propagate. Viral vectors are viruses that have been engineered to transfer therapeutic genes into the cells they infect, where the instructions can be read out to produce effective proteins.

A number of viral vectors have

been explored for use in gene therapy. For various reasons, only those viruses whose genes are made of DNA can efficiently infect cells that do not divide, such as mature brain cells. Both the adenovirus and the herpes simplex virus have been made into recombinant DNA viral vectors—that is, vectors that contain some viral genes and some new, potentially therapeutic ones.

These recombinant vectors have been designed to maximize their efficiency as gene transfer machines and minimize their ability to cause unwanted side effects. But many questions remain, among them: Might some of the viral proteins turn out to be toxic? Might those proteins induce an immune-system attack? Could the genetically engineered vectors recombine with normal versions of the virus that might already be present within in the body?

The extent of the risks posed by various recombinant vectors is still unknown. But, said Kaplitt, recombinant viral vectors carry "enough baggage" that, when he started his Ph.D. project six years ago, he decided to work with a type of vector that might travel a little lighter. This was the *defective* herpes simplex virus—a vector denuded of all its viral genes, and left with only two signals needed for packaging into a viral coat. Such vectors are completely dependent on "helper" herpes virus (those with more of their genome intact) to package themselves for therapeutic use.

Search for ideal solution

In 1991 Kaplitt and Pfaff published a paper showing for the first time that the defective herpes simplex vector could transfer a functional gene into animal brains. But Kaplitt was always bothered by one

aspect of this vector: For technical reasons, it is impossible to eliminate every single helper virus from the system, thus raising potential problems of recombination. "The ideal solution would be to make a vector that, like the defective herpes simplex vector, had no viral genes, but that, unlike the herpes simplex vector, had no associated helper virus," he says.

This he and his colleagues accomplished through the use of another vector, the adeno-associated viral (AAV) vector. As its name implies, the AAV vector uses the adenovirus as a helper virus. With the AAV vector, various tricks of molecular biology make it possible to remove not only all the viral genome but all the helper virus as well, so that "in theory, you've eliminated anything that could cause disease," Kaplitt says.

Using this system, Kaplitt collaborated with Matt During, a Yale researcher with a longstanding interest in Parkinson's. Into the AAV vector they put the gene for thymidine kinase (TH), an enzyme essential for the biochemical reactions leading up to the production of dopamine. Using stereotactic injection (the method used for precise brain surgery) they injected the AAV vector into the basal ganglia of rats with rodent Parkinson's. The gene remained active for four months, and the rats showed a 40 percent improvement in their motor function. TH catalyzes the production of dopamine's precursor, L-dopa, and the researchers believe they may get even better results if they also add the gene for the enzyme that catalyzes the conversion of L-dopa to dopamine. They are constructing such vectors now.

According to Kaplitt, *in vivo* gene therapy for Parkinson's may eventually make it possible not only to restore enzymes needed for dopamine production, but also to provide proteins that protect against neural degeneration in the first place. Such therapies might also be possible for other neurodegenerative diseases.

The therapeutic potential doesn't stop at the head. It also goes straight to the heart, where, Kaplitt says, AAV vector therapy might shuttle in genes to failing cardiac muscle cells, which, like brain cells, do not divide. "Much work remains to be done, but our studies have already shown that well-engineered viral vectors present exciting new therapeutic opportunities, and can also be used to address basic neurobiological questions," he says.

Potpourri

Tri-Institutional Noon Recital
Classical guitarist Ignacio Rodes will perform the works of Dowland, Bach, Sor, Granados, Turina, and Rodrigo at the Tri-Institutional Noon Recital today (Oct. 7). The concert, to be held in Caspary Auditorium at noon, is free. All are welcome.

Marta Sanchez-Vives



Ignacio Rodes plays classical guitar at today's Tri-Institutional Noon Recital.

Clinical Research Seminar

Associate Professor Samuel D. Wright will speak on "Recognition of Bacterial Lipopolysaccharide (LPS) by Mammalian Cells" at the Clinical Research Seminar, Wed., Oct. 12, at noon in Nurses Residence 110B.

Computer workshops

Space is still available in the following Computing Services workshops:

- Word for the Macintosh, Parts I & II: Wed., Oct. 12 and Fri., Oct. 21, 2:00 to 4:00 P.M.;

- Introduction to Windows: Fri., Oct. 14, 2:00 to 4:00 P.M., and Fri., Oct. 21, 10 A.M. to noon;
- Excel for the Macintosh and PC, Parts I & II: Thurs., Oct. 20, and Thurs., Oct. 27, 2:00 to 4:00 P.M. To register, please contact Joan Falciano at x8925 or leave voice mail at x7768.

Weekly Research Seminar

Dates are still available to invite speakers for the Weekly Research Seminar (formerly the Junior Faculty-Student Seminar Series). Submit your proposals as soon as possible to Claude Desplan, fax x8370, box 151, or phone x7965.

October feast

Members of the Rockefeller community can bring a guest from one of the neighboring institutions (MSKCC/NYH/CUMC) and receive a 25 percent discount on lunch in the Abby Aldrich Rockefeller dining room during October. This offer is extended to groups of four or less. Reservations are recommended. Contact Alzatta Fogg, x8894.

Choral rehearsal

The Choral Symphony Society rehearses the Bach Christmas Oratorio Tuesdays from 7:20 P.M. to 9:30 P.M. in the Caspary music room. For more information on joining the group, contact David Labovitz, 864-7541.

Presentation

Professor Mary Jeanne Kreek delivered a presentation entitled "Pharmacotherapy for Addictions: Insights from Laboratory and Clinical Research" at a symposium

marking the 20th anniversary of the National Institute on Drug Abuse last month.

Arrivals

Adjunct Faculty: Robert Auerbach, Carter lab.

Postdoctoral Associates: Janet Alder, Hatten lab; David Avigan, Steinman lab; Tie Chen, Gotschlich-Fischetti lab; Yang Dan, Wiesel lab; Shawn Erickson, Manning lab; Ketan Gajiwala, Burley lab; Ming Guo, Nussenzweig lab; Celia Harrison, Kuriyan; Pilar Nosti, Breslow lab; Elizabeth Wirtz, G. Cross lab; Jillian Jue Zhang, J. Darnell lab.

Postdoctoral Fellows: Dominique Broccoli, de Lange lab; Tyler Cutforth, Gaul lab; Liisa Galea, McEwen lab; Eric Marechal, Chua lab; Gustavo Stolovitsky, Magnasco lab.

Guest Investigators: Ivan Cohen, Libchaber lab; Gerhard Heilig, J. Cohen lab; Marie Larsson, Steinman lab; Seiichiro Morisako, Carter lab; Mirjana Nesin, and Adam Stracher, Tomasz lab.

Departures

Associate Professor: Timothy Marinetti, Mauzerall lab.

Assistant Professor: Robert Soodak, Wilson lab.

Adjunct Faculty: John J. Burns, unaffiliated; Mimi Halpern, Pfaff lab; James Tam, Merrifield lab.

Visiting Professor: Robert Olby, Wiesel lab.

Visiting Assistant Professor: Toshiharu Suzuki, Greengard lab.

Research Associates: Margaret Burroughs and Joan Muller, Steinman lab; Chihong Chou, Khuri lab; David Cooper, Hatten lab; Ken-ichi Mitsui, Greengard

Repairs on Tower elevators to begin

The modernization of the Tower Building elevators is scheduled to begin Sat., Oct. 15.

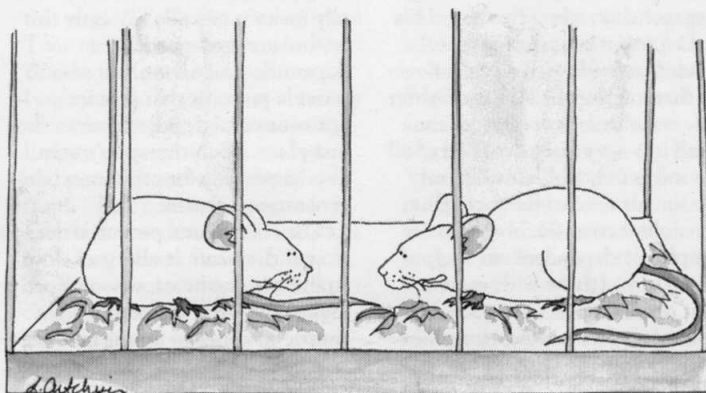
"We know elevator service has been frustrating and frightening to some people, but the poor performance is due to outdated motion equipment and inadequate door operators. There is no safety hazard," said Bob Francis, director of plant operations. "Tower elevators just passed both city inspection and our own private inspection. But the system is old, so we are updating every component that affects travel."

The \$400,000 project will bring the 25-year-old system to state-of-the-art functioning. Renovation will proceed car by car, and every door operator, control panel, motor, and motion controller will be replaced by next summer. For more information, contact Francis or Larry Yuan, both at x8001.

lab; Susan Szapiel, Wiesel lab.
Postdoctoral Fellows: Luz Hermida-Matsumoto, Roeder lab; C. Thais Zaia, Greengard lab.

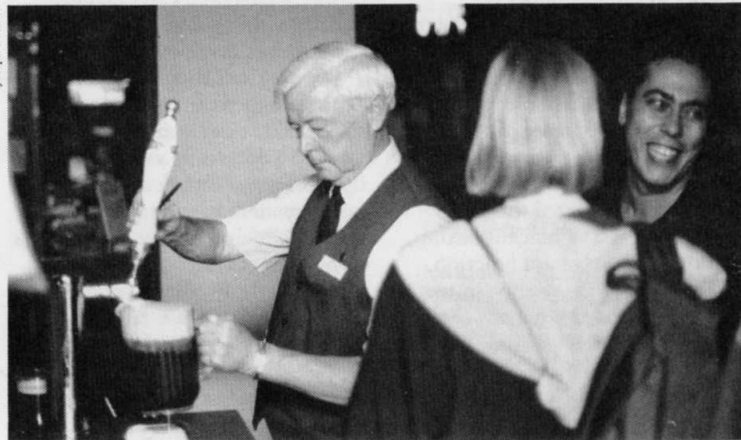
Guest Investigators: Catherine Coffinier, and Katherine Neal, Desplan lab; Rong-Xiang Fang, Chua lab; Michiel van der Flier, Tuomanen lab; Manuel Gonzalez de la Pena, King lab; Ricardo Gurtler, J. Cohen lab; Mitesh Kapadia, Gilbert lab; Dimas Zaia, Merrifield lab.

Lelle Aitchison



"The amazing thing is, when I first got here, I was a fruit fly."

Joseph Benner



Patrick Griffin, manager of the Faculty and Students Club, fills one of the many pitchers quaffed on Sept. 16 when a new beer, Fuller's ESB, was inaugurated.