



Jon Nalick

**GLAD GRADS**—The Keck School of Medicine, the School of Pharmacy and many other USC schools celebrated commencement in ceremonies on both the University Park and Health Sciences campuses on May 16 and 18. Above, a pharmacy graduate accepts her diploma from Ron Alkana, professor of molecular pharmacology and toxicology. See additional commencement-related photos, page 3.

## Asthma risk rises with exposure to chemicals, pollutants in infancy

Day-to-day exposure to certain chemicals, pollutants and other environmental factors during the first year of life appears to raise children's risk of developing asthma, according to a study released today from the Keck School of Medicine of USC.

Frank D. Gilliland, professor of preventive medicine at the Keck School, presented findings from the Children's Health Study at the 99th Annual International Conference of the American Thoracic Society.

Gilliland and colleagues found that exposures to cockroaches, weed killers, pesticides, fuel oil, soot, exhaust and farm crops, dust and animals beginning in the first year of life were all linked to early asthma, while babies who first attended daycare before 4 months of age also were more likely to be diagnosed with the respiratory disease later on.

"The first year of life seems uniquely important in terms of susceptibility to environmental triggers of asthma," Gilliland said.

The research team conducted the case-controlled study within a large subset of children participating in the ongoing Children's Health Study. Researchers with the USC-led Children's Health Study have monitored levels of major pollutants in a dozen Southern California communities since 1993, while carefully following the respiratory health of more than 3,000 students.

Researchers looked at 338 children who were diagnosed with asthma by a physician before they turned 5 years old. They then matched those children to 570 asthma-free children of the same age who lived in the same communities. They also matched them according to whether the children had been exposed to maternal smoking while still in the womb.

They found that the risk of developing asthma before age 5 rose significantly with these exposures (figures given in odds ratios):

Exposure	Risk increased by
Cockroaches in home before age 1	Over two times (2.03)
Around herbicides before age 1	Over four-and-a-half times (4.59)
Around pesticides before age 1	Nearly two-and-a-half times (2.40)
Farm crops, dust or animals before age 1	Nearly two times (1.81)
Daycare attendance before 4 months of age	Nearly two-and-a-half times (2.34)
Wood or oil smoke, soot or exhaust before birth and 5	More than 50 percent (1.57)

The study was not designed to find out specifically why risk increased. In general, Gilliland noted: "The first year of life is a critical time period of lung development—both for immunity and airway structure. Others have

Preventive medicine researchers and doctoral students presented a number of studies at the American Thoracic Society annual meeting in mid-May.

Among them, Tracy Bastain, science coordinator with the Children's Environmental Health Center and Southern California Environmental Health Sciences Center, tackled the topic of diesel exhaust particles and their ability to worsen allergy symptoms among those with rhinitis. She found that susceptibility to the effects of diesel exhaust particles was highly repeatable; allergy symptoms worsened every time the subject was exposed to the particles.

Yu-Fen Li, doctoral student in preventive medicine, presented a poster on the effects of smoking by pregnant women. Using data from the Children's Health Study, she and colleagues showed that maternal smoking while a child is still in the womb raises the risk of developing asthma, especially early onset asthma.

shown that certain early-life exposures are important for asthma development."

In the case of daycare attendance, Gilliland theorizes that early and frequent exposure to respiratory infections, such as respiratory syncytial virus, or RSV, in a daycare setting might raise early asthma risk.

The research team found that the more older brothers and sisters a child had at birth, the lower the child's risk of early asthma. But they found nothing to indicate that other early childhood experiences such as exclusive breast-feeding or exposure to cats, dogs or other pets protect against early asthma.

More research is needed to determine what levels of exposure may be important and whether reducing exposures reduces risk.

Asthma is the most common chronic disease of childhood, affecting about one in 14 children in the United States, according to the National Heart, Lung and Blood Institute, one of the groups sponsoring the research. The California Air Resources Board, National Institute of Environmental Health Sciences and the Environmental Protection Agency also sponsored the study.

F.D. Gilliland, M.T. Salam, Y. Li and B.M. Langholz, "Early Life Risk Factors for Asthma: Findings from the Children's Health Study," ATS 2003—International Conference of the American Thoracic Society, Mini-symposium D011, 9:15 a.m. May 21, 2003.

—Alicia Di Rado

## Protein snippet boosts cancer therapy

Keck researchers publish findings in *Journal of the National Cancer Institute*

Researchers from the Keck School of Medicine have isolated a protein fragment derived from the cancer immunotherapy drug interleukin 2 (IL-2) that seems to enhance the uptake of chemotherapeutic agents into tumors.

In fact, said Alan Epstein, professor of pathology, when this patented protein fragment is attached to a tumor-targeting antibody, it can prompt tumors to soak up more than 300 percent of the normal amount of chemotherapy drugs.

It does this, Epstein said, by making the tumor's blood vessel walls more "open" or permeable to the drugs. (Blood vessel walls are made of epithelial cells that are usually tightly joined together; when the junctions between those cells loosen up, it becomes easier for molecules to enter or leave the bloodstream.)

This work was described in a paper being published in the May 21 issue of the *Journal of the National Cancer Institute*.

The interleukins are part of a class of proteins called cytokines, which play a role in the human immune response. It has been hoped that IL-2 and its brethren might play a central role in cancer immunotherapy—battling cancer by revving up the immune system. Unfortunately, IL-2 can only be tolerated in small doses by the body. Taken at levels that would take advantage of its therapeutic value it causes wide-spread edema and other problems due to blood vessel leakiness.

While seeking the cause of this leakiness, Epstein and his Keck School colleagues isolated a stretch of 37 amino acids on the IL-2 protein; this sequence, he says, "is responsible for 100 percent of the vasopermeability." Dubbed PEP, for permeability-enhancing peptide, the molecule is now being commercially developed by Peregrine Pharmaceuticals of Tustin, Calif.

Having determined that PEP is indeed a per-  
See **PEP**, Page 2

# Microarray facility offers treasure trove of genetic research options

Ruty Mehrian-Shai is helping USC researchers harness the power of the microarray.

Mehrian-Shai directs the Custom Microarray Core Facility, a new, advanced resource for scientists at the Institute for Genetic Medicine. The facility aims to corral the vast world of gene expression.

As she explained, the fate of any cell is determined largely by the subset of genes it expresses. This governs the cell's behavioral characteristics, the type of tissue it constructs and whether it is normal or diseased.

Activation or expression of a specific combination of genes, in precise amounts and a timely manner, is crucial for a cell's normal activity. Fortunately, recent complementary advances in knowledge and technology are speeding progress in the study of this gene expression.

On the knowledge front, the Human Genome Project has resulted in an exponential growth in the amount of information available about the DNA sequence of the human genome. Consequently, researchers have identified a large number of novel genes within these previously unknown sequences.

The second advance is the emergence of DNA microarray technology. DNA microarrays are small, solid sup-



Ruty Mehrian-Shai, director of the Custom Microarray Core Facility, says it opens a wide range of genetic research options for scientists.

ports onto which the sequences from thousands of different genes are immobilized, or attached, at fixed locations. The support surfaces are usually glass microscope slides.

The power of microarray analysis lies in its miniature platform features: researchers can determine the expression level of hundreds of thousands of genes at the same time, allowing them to compare large sets of genes in different tissues or conditions to identify pathways and regulatory networks.

Mehrian-Shai did her postdoctoral work at UCLA in the lab of a leading microarray researcher, Stan Nelson, assistant professor in psychiatry and

biobehavioral sciences and human genetics, focusing on gene expression of glial brain tumors, or gliomas.

Gliomas are the most common form of brain tumors. Accurate diagnosis of glioma type is fundamental for proper patient management. Today, physicians assess the tumors and group them into types based on histopathology—their cellular structure and characteristics as seen under a microscope.

While generally accurate and reproducible, the interpretation can be subjective, with gray borders between groups.

Standard treatment for these tumors is typically surgery, followed

## A Resource for Scientists

The IGM's Custom Microarray Core Facility is equipped with the most advanced instrumentation of this field. It gives USC-affiliated researchers access to cutting-edge genetic research through microarray technology. The Microarray Core supports all aspects of expression studies by microarrays: RNA extraction from tissue and cell culture, cDNA synthesis, cRNA amplification, probe labeling, hybridization to the microarray slides (which are printed in the core), scanning of the slides and analysis of the results. This sensitive, large-scale technology will facilitate gene-expression, genomic-alteration and signaling-pathways profiling for a wide variety of organisms.

Identification of genes involved in pathogenesis and molecular fingerprinting of patients, especially in such complex diseases as cancer, will assist in diagnosis, prevention and specific and thus efficient patient management.

Microarray is a technique that can be applied to many other fields of research beyond gene expression:

- Genotyping, or detecting differences in the genetic code;
- Resequencing, or detecting the exact coding of a gene; and
- Comparative genome analysis, or detecting differences in copies of genes on the chromosomes of different species.

As scientists accumulate information, they will be able to use microarrays to ask increasingly complex questions and perform more intricate experiments.

by radiation and chemotherapy. No independent method exists, though, to predict which patient will benefit from those treatments.

Mehrian-Shai has made inroads in changing that.

To find the molecular fingerprint of the different types of brain tumors, Mehrian-Shai analyzed microarray experiments and constructed gene lists with specific differentiating

genes. These lists of genes can serve to classify samples taken from patients' tumors, predict patient survival time and explore novel personalized molecular targets for chemotherapy.

The idea is to better understand and characterize the tumor and customize treatment to each patient's specific cancer, while sparing the patient unnecessary treatment that is unlikely to help.

## USC pharmacists examine genetic differences that alter drugs' effectiveness

The completion of the Human Genome Project is the first step in determining how a person's genetic makeup—their genotype—affects their heredity, health and how well they will ward off disease.

Scientists in the USC School of Pharmacy who say this observe that by determining genetic differences among patients, they can predict how those patients will respond to medications.

With this understanding, new and existing drugs can be evaluated for patient safety, minimizing side effects and maximizing therapeutic effectiveness.

Paul Beringer, associate professor of clinical pharmacy at the USC School of Pharmacy, is contributing to this research by studying how a protein transporter—called P-glycoprotein (P-

gp) affects how specific drugs are eliminated from the body.

Located in the gastrointestinal tract, kidneys, liver and central nervous system, P-gp acts as a membrane pump that moves drugs from inside to outside the cell.

"Every person has these pumps to keep the inside of the cell free from foreign substances," said Beringer.

After a drug is absorbed into the bloodstream, it is eliminated through liver metabolism or kidney filtration. Kidney filtration—or renal clearance—allows the body to excrete toxins through the urine.

"Due to genetic differences, some individuals are born with more efficient P-gp, which is associated with faster renal clearance," said Beringer. "A patient with enhanced renal clear-

ance eliminates drugs into the urine at an increased rate. If an individual makes more P-gp, then they will require more of specific drugs to receive a therapeutic effect."

Ninety-five percent of an individual's genotype is identical to any other human, yet there are approximately 1.4 million genetic variations that make people different.

These differences are referred to as genetic polymorphisms.

Over the last decade, scientists have linked one gene called MDR1 to the production of P-gp, said Beringer. "Within MDR1, there are some polymorphisms that can cause over-production of P-gp, while others can cause under-production," he said.

Collaborative research is currently underway  
See **BERINGER**, Page 3

## PEP: Protein fragment can increase potency of cancer drugs

Continued from Page 1

meability enhancer, Epstein and his colleagues took their exploration a step further: They transplanted mice with human tumor cells and pretreated them with monoclonal antibodies coupled with PEP.

When these mice and control mice were later injected with a radiolabeled tracer antibody or drug, there was a three- to four-fold increase in the amount of the antibody taken up by the

tumors of the pretreated mice as compared to those of the control mice.

"We've showed that you can use PEP to induce selective and reversible blood vessel permeability at the tumor site to get better drug uptake," says Epstein. "This may turn out to be a hugely important tool in cancer therapy."

The next step, he says, "is to try to get this product ready to test in human patients."

This work was supported by grants from the

National Cancer Institute, Peregrine Pharmaceuticals, Inc. and Cancer Therapeutics Laboratories.

Alan L. Epstein, Myra Mizokami, Jiali Li, Peisheng Hu, Leslie A. Khawli, "Identification of a Protein Fragment of Interleukin 2 Responsible for Vasopermeability." *Journal of the National Cancer Institute*, Vol. 95, No. 10, May 21, 2003, pp. 741-749.

—Lori Oliwenstein

## HSC Weekly

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Clockwise from top left: Arlette Nazarians and Farnaz Nejad cheer fellow graduates during the School of Pharmacy commencement ceremony; Stephanie Zia, recipient of the Dr. George Herron Memorial Award, displays her certificate following a Keck School of Medicine honors ceremony in the HSC Quad May 17; Sajjad Yacoob, assistant professor of clinical medicine, accepts the AAMC/Pfizer Medical Humanities Initiative - Humanism in Medicine Award from Keck School Dean Stephen J. Ryan; Keck School graduate Karim Chamie and family celebrate after the ceremony; TV writer-producer and "Scrubs" creator Bill Lawrence serves as the Keck School's keynote speaker.

## BERINGER: Focuses on improving care for cystic fibrosis patients

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at the USC School of Pharmacy and Keck School of Medicine of USC to evaluate the relationship between MDR1 genotypes and the renal clearance of drugs that involve P-gp.

Beringer is focusing on improving therapies for patients with cystic fibrosis (CF), a life-threatening genetic disease that affects one in 30,000 children and adults living in the U.S.

"CF is caused by a defect of the CFTR gene that causes the faulty transport of sodium and chloride (salt)," said Beringer. "These patients develop an abundance of thick mucus secretions in the lungs, pancreas and sweat glands, which results in chronic pneumonia."

An individual must inherit a defective copy of the CFTR gene from both parents to develop CF, yet one in thirty-one Americans is an unknown carrier.

Over the past 25 years, there have been major strides in optimizing antibiotics for lung infections, said Beringer. Since 1950, the average life expectancy has increased from five to thirty-three years.

Beringer received the prestigious 2003 Career Development Research Award from the American College of Clinical Pharmacy, which will fund a two-year clinical trial at USC University Hospital.

Along with Bertrand Shapiro, professor of clinical medicine at the Keck School, he will study how 24 adults – 12 healthy and 12 with CF – eliminate drugs in relation to their P-gp production.

Project collaborators include School of Pharmacy faculty Gilbert Burckart, professor and chair, Department of Pharmacy; Mark Gill, professor of clinical pharmacy; Stan Louie, associate professor of clinical pharmacy, and Adupa Rao, visiting

assistant professor of clinical medicine.

The clinical trial will consist of three outpatient visits, where patients will be given a combination of drugs that are transported by P-gp, as well as drugs that stop how the transporter works. Renal clearance will be measured in both patient populations.

Past research has shown that CF patients have exhibited enhanced renal clearance with certain antibiotics, but no explanation for this difference had been confirmed, said Beringer.

"P-gp enhances chloride transport, which may be why CF patients produce more to compensate for their genetic defect," said Beringer. "It is also possible for CF patients to have a MDR1 polymorphism that increases P-gp production."

"If proven, this would allow clinicians to appropriately dose antibiotics that involve P-gp, allowing for greater

efficacy," said Shapiro. "By pinpointing the mechanism involved, it is also possible to develop more effective antibiotics."

Beringer added that a likely next

step would be the development of new therapies to boost the chloride transport defect in CF patients, eliminating some life-threatening anomalies.

—Alexis Bergen

### Free stroke screenings offered May 28, June 11

In honor of National Stroke Awareness month, the USC Executive Health Center is offering stroke screening on Wednesday May 28 and Wednesday, June 11.

The screening is recommended for anyone age 50 and over, especially those with a family history of high blood pressure, stroke, heart disease or diabetes.

The baseline stroke screening will include laboratory blood work for total cholesterol and glucose, blood pressure and pulse, height and weight and a short medical history questionnaire.

You will receive a report outlining your risk for stroke and referral to a physician if needed.

The fee is \$25.00, and appointments are required as space is limited. Call 213-437-1000 to reserve a time.

The USC Executive Health and Imaging Center is at 333 Hope Street, Concourse level C-145 in downtown Los Angeles. A free shuttle transports USC employees from campus.



Candy Chan (left) and PEO representative Grace Verburg.

## Student receives prestigious PEO scholarship

Candy Chan, an MD/PhD student in the Keck School of Medicine, has received an \$8,000 Philanthropic Education Organization (PEO) Sisterhood Scholar Award—the organization's highest honor—for the academic year 2003-2004.

Chan's research, conducted in the lab of Keck School Dean Stephen J. Ryan and David Hinton, the Gavin S. Herbert Chair in Vision Research and

professor of pathology, neurological surgery and ophthalmology, focuses on the genetic determinants of angiogenesis—the process by which new blood vessels grow from pre-existing ones.

Chan said she was honored to receive the award, adding that it would be used for her research in angiogenesis throughout her clinical training: "I am optimistic about

applying basic science discoveries in vascular biology to the clinical setting."

Chan was recognized for her outstanding research, Hinton said, as well as for "her mentoring of other young women who are interested in careers in medicine or medical research."

Ryan said that the Keck School "takes great pride in Candy as a stu-

dent and is pleased that the PEO Sisterhood shares our high regard of Candy. I congratulate the PEO Sisterhood on their selection of Candy for this prestigious award.

The PEO Sisterhood is a national philanthropic organization that has provided grants, loans and awards to more than 54,000 women since its inception in 1869.

—Sanny Chan

## Tennis-and-golf tourney slated for June 9

Salerni Collegium and the Keck School of Medicine will host their 2nd Annual Tennis Tournament and 20th Annual Golf Tournament on June 9, to fund scholarships for USC medical students.

The tennis tournament will be at the historic Los Angeles Tennis Club starting at 12:30 p.m. and will include a pro-am exhibition, featuring Peter Smith, head coach of the USC Men's Tennis Team, and Andrew Park, USC's number-one singles player in 2002 and now a first-year medical student.

The golf tournament will take place at the Wilshire Country Club at 11 a.m. and will include lunch, warm-up and a shotgun start (scramble format).

For information on participating or donating, call (323) 442-3292 or email elaw@usc.edu.

## Calendar

### Tuesday, May 27

11 a.m. Endocrinology and Diabetes Grand Rounds. "Diabetic Neuropathies and the Treatment of Neuropathic Pain," Said Beydoun, USC. AHC Aud., Room 102. Info: 442-2806

12:15 p.m. Psychiatry Grand Rounds. "Take Me Out to the Ball Game: A Clinical Case Conference with a Schizophrenic Patient," Joseph Mirkovich; Elaine Eaton, and Steven Kingsbury, USC. Hoffman Hall, Hastings Aud. Info: 226-5572

### Wednesday, May 28

7 a.m. Medicine Grand Rounds. "TTP," Ilene Weitz, USC. GNH 1645. Info: 226-7591

Noon. Medicine Master Grand Rounds. "Providing Perfect Care: Is it Possible?" Robert Brook, RAND Corp. GNH 1645. Info: 226-7644

### Thursday, May 29

3:15 p.m. Robert and Ray Kroc Lecture Series. "The Nexus of Inflammation, Nutrition and Aging," Caleb Finch, USC. McKibben Hall, Room 256. Info: 442-1039

### Tuesday, June 3

Noon. CHLA Research Seminar. "Paradigm Shift in Neuroprotection: How to Make Bad Drugs Do Good Things," Stuart Lipton, UCSD. Page Conf. Room, CHLA. Info: 669-4110

12:15 p.m. Psychiatry Grand Rounds. "Bipolar Depression," Lori Altshuler, UCLA. Hoffman Hall, Hastings Aud. Info: 226-5572

### Wednesday, June 4

7 a.m. Medicine Grand Rounds. "Obesity," Jonathan LoPresti, USC. GNH 1645. Info: 226-7591

Noon. "Signaling at the Crossroads of Cell Aging and Cancer," Stuart Aaronson, Mt. Sinai School of Medicine. CSC, IGM Aud. Info: 442-1144

### Thursday, June 5

3:15 p.m. Robert and Ray Kroc Lecture Series. "Exocytosis, Glutamate Release and Reuptake at a Ribbon-Type Synapse," Henrike vonGersdorff, Oregon Health and Science Univ. McKibben Hall, Room 256. Info: 442-1039

### Saturday, June 7

9:30 a.m. – 1 p.m. Arthritis Seminar. "Rheumatoid Arthritis," Daniel Arkfeld and Glenn Ehresmann, USC, and Andreas Reiff, CHLA. Mayer Aud. Info: 442-1946

### Monday, June 9

Noon. Health Research Assoc. Seminar. "Genetic Analysis of Mammalian Hearing," Jian Zuo, St. Jude's Children's Research Hospital. Norris Tower 7th Floor Conf. Ctr. Info: 442-1145

### Wednesday, June 11

7 a.m. Medicine Grand Rounds. "CML," Aziz Khan, USC. GNH 1645. Info: 226-7591

Noon. Cell & Neurobiology Seminar. "The Hypocretin (Orexin) Peptides: Roles in Sleep, Feeding & Motor Control," Jerry Siegel, UCLA. AHC Aud., Room 102. Info: 442-1881

Notice: Deadline for calendar submission is 4 p.m. Tuesday to be considered for that week's issue—although three weeks advance notice of events is recommended. Please note that timely submission does not guarantee an item will be printed. Send calendar items to HSC Weekly, DEI 2510 or fax to 442-2832, or e-mail to lpratt@usc.edu. Entries must include day, date, time, title of talk, first and last name of speaker, affiliation of speaker, location, and a phone number for information.

The HSC Calendar is online at <http://www.usc.edu/hscalendar>

## Newsmakers

The June issue of *Shape* magazine contains a story on the link between exercise and breast cancer. The story quotes cancer researcher **Leslie Bernstein**.

On May 21, *Wired News* looked at so-called "superspreaders" of the SARS virus. The story quoted microbiologist **Michael Lai**. Lai was also quoted in two articles on SARS in the *Taipei Times* May 17 and 19th, one of which described him as the "father of the coronavirus." Lai appeared in a similar story in the May 16 *Washington Post*.

A May 21 *Riverside Press-Enterprise* story examined the link between environmental exposures and children's asthma. The story quoted study author **Frank Gilliland**. Similar stories appeared on the Reuters news service, HealthScout News, ABC News.com, the *Atlanta Journal-Constitution* and Healthfinder.gov.

The May issue of the *NCRN Reporter* highlighted the Women's Ischemia Syndrome Evaluation (WISE) and quoted investigator **Gerald Pohost**.

On May 19, environmental health researcher **Ed Avol** appeared on KFVB-AM news radio in a story about freeway expansion.

On May 19, CNN television interviewed obesity expert **Peter Pressman** for an upcoming story on liquid fasting.

The May 19 *Pasadena Star News* reported on results from the Latino Eye Study led by Doheny ophthalmologist **Rohit Varma**. The story also appeared in the *San Gabriel Valley News*, *Long Beach Press Telegram* and the *Los Angeles Daily News*.

A May 19 *People* magazine story on actress Suzanne Somers' return to the stage quoted her USC/Norris cancer surgeon, **Melvin J. Silverstein**.

A story on a May 16 KABC-TV Channel 7 newscast focused on the importance of vascular screening. The story included USC UH vascular surgeon **Doug Hood**.

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