USC receives $3.2 million for drug-delivery research

A better and easier way to deliver biotechnology's best and safest drugs may soon be just a deep breath away, thanks to a $3.2 million grant awarded to Edward C. Crandall and an interdisciplinary team of researchers from the Keck School of Medicine and the USC School of Pharmacy by the National Heart, Lung, and Blood Institute of the National Institutes of Health.

Led by Crandall, Hastings Professor and Chair of the Department of Medicine, the team will explore the means by which large molecules make their way across the alveolar epithelium, the single layer of cells that separates the lung's air spaces from the bloodstream and the rest of the body.

Lined with enough cells to more than cover a tennis court, the human lung offers an untapped potential for enhancing and improving the delivery of biotechnology drugs from insulin to human growth hormone—larger pharmaceuticals that currently have to be delivered through the sharp end of a needle, directly into the body.

“The pharmaceutical industry is interested in unique routes of drug delivery for newly developed products,” noted Crandall. “Many of them are peptides or protein molecules, which tend to be digested in the gastrointestinal tract if given in pill form.” It is for this reason that drugs like insulin have long had to be injected into the body in order to avoid being chewed up by the digestive juices.

“The idea of being able to inhale a drug such as insulin has recently become hotly pursued by industry, but industry is primarily interested in safety and reproducibility—not mechanisms. That’s where this grant comes in. We’re studying at the molecular and cellular levels the mechanisms by which peptide and protein drugs can get across the lung,” said Crandall.

If they can successfully understand these mechanisms, Crandall added, it will “clearly be of tremendous help in designing ways to deliver drugs via the lungs and possibly even to target drugs for that particular delivery route.”

Joining the interdisciplinary research effort are, from left: Edward Crandall, chair of medicine; Kwang-Jin Kim, associate professor of medicine; Wei-Chiang Shen, professor of pharmaceutical sciences; and Vincent Lee, chair of the Department of Pharmaceutical Sciences in the School of Pharmacy.

Together with Kwang-Jin Kim, associate professor of medicine, Vincent Lee, Gavin S. Herbert Professor and chair of the Department of Pharmaceutical Sciences in the School of Pharmacy, and Wei-Chiang Shen, professor of pharmaceutical sciences, that is precisely what Crandall is attempting to do. “Each of us comes at the problem from a different perspective,” said Crandall. “It makes for a perfect collaboration.”

This quartet of top-notch researchers already knows that most proteins and peptides are too large to just diffuse over a cell’s membrane—instead, they must somehow physically traverse it, often times being engulfed and carried through the cell in little membrane-bound bubbles known as vesicles. “We think the vesicles are functioning as a shuttle to take the molecules across the membrane,” explained Crandall. This process, called transcytosis, is at the heart of the team’s investigations.

What happens next to those packages and the molecules in them is less clear. They may be degraded by cellular enzymes, or they may enter what Crandall calls the transcytotic pathway, which results in their ultimately being delivered, unscathed, to the bloodstream.

But getting the lung to take up a protein or peptide molecule in the first place may take some convincing.

See LUNG, Page 3

Nobel Laureate lectures at HSC

Günter Blobel, Howard Hughes Medical Institute Investigator and Professor at The Rockefeller University in New York, presented the 1999 Mesry Prize Seminar last week.

Blobel was chosen for the award because of his research into how proteins are transported and find their proper location within the cell. His work opened the door to the understanding of how proteins are directed to the nucleus of a cell and to the mitochondria, said Shaal Mesry, the Barnard J. Hanley Professor of Medicine and chief of nephrology at the Keck School of Medicine.

The Mesry Prize is an international award that honors individual scientists who have made outstanding contributions to biomedical sciences and to the advancement of health. It is given each year by the Mesry and Shaal Mesry Foundation. Blobel was also the recipient of the 1999 Nobel Prize in Physiology or Medicine, “for the discovery that proteins have intrinsic signals that govern their transport and localization in the cell.”

Before a standing-room only audience of more than 500 faculty, postdocs and students at the Mayer Auditorium, Blobel gave a brief account of his travels on the otherwise bumpy road to scientific success. His initial idea that the proteins might be making their way across intracellular membranes through some sort of protein channel, he said, “acted as a lightning rod for people criticizing me for proposing such an outlandish idea.” It took 20 years for him to get the proof he needed to quiet the critics, he added, but he did it.

Mixed in with the technical details of his discoveries were invaluable nuggets of advice to those just beginning the journey. Recounting how colleagues of his had called him “temperamental” and “opinionated” in the press after the Nobel announcement, he laughed loudly. “Don’t be afraid to go against the grain,” he said. And, later, he advised, “When you work, you must not be afraid of anything.”

The lecture was sponsored by the Institute of Genetic Medicine—whose director, Laurence Kedes, was also chair of the Mesry Prize jury—and the Department of Medicine, Division of Nephrology.

—Lori Oliwenstein

Keck School bucks recent statewide trend

Minority enrollment jumps 71% at School of Medicine this fall

While California medical schools grapple with declining admission and enrollment of underrepresented minority students, enrollment figures show numbers of new minority students at the Keck School grew significantly this fall.

Young men and women considered underrepresented minorities in the medical student population—African Americans, mainland Puerto Ricans, Mexican Americans and Native Americans—were admitted and matriculated at USC in greater numbers in 1999 than 1998, after a decreasing trend in matriculation in recent years.

“We actively recruited students, kept in touch and encouraged them to choose USC,” said Erin Quinn, associate dean of admissions.

Quinn and other school leaders are excited about the increasing numbers of minority students, as well as the diversity of life experience and backgrounds that the 1999 class as a whole has brought to campus.

“The school leadership has been totally supportive,” Quinn said. “The admissions committee is very committed to a diverse class, and we worked together to admit an excellent class.”

The number of underrepresented minorities admitted to USC jumped from 46 in 1998 to 59 in 1999, a 28 percent increase. The number of underrepresented minority students who enrolled at USC grew from 14 to 24, a 71 percent increase, in the same time span.

At the same time, the science grade point average of the entering class rose from 3.48 to 3.60.

Earlier this year, newspapers and other media publicized reports that California’s nine medical schools have seen declining applications and admissions of underrepresented minority students.

Researchers at the Center for California Health Workforce Studies at UC San Francisco, who compiled the numbers, concluded that Proposition 209 and changes in admissions policies at the University of California have contributed to a less hospitable environment for underrepresented minorities in the state’s medical schools.

Many such students choose to leave the state, they concluded.

At USC, admissions officials have kept entrance requirements consistent while increasing recruitment.
Depressed patients less likely to finish treatment when drug choices restricted by HMOs

When health insurance companies limit coverage on antidepressant drug therapy to a single medication, it may have unintended results on how patients follow their course of treatment, according to a study by USC pharmacy researcher Jeffrey S. McCombs. Patients in an HMO that limited coverage to one antidepressant (paroxetine) in a class of drugs called selective serotonin reuptake inhibitors (SSRIs) were 80 percent less likely to complete therapy for depression than patients in an HMO that listed two such antidepressants: fluoxetine and paroxetine among its covered drugs, or formulary. McCombs, associate professor of pharmaceutical economics and policy, and colleagues from a California medical group reported their findings in the October issue of the American Journal of Managed Care.

The brand name for paroxetine is Paxil. Fluoxetine goes by the brand name Prozac.

The type of drug chosen for therapy was also found to affect the proportion of patients who completed their treatment (taking the minimum required dosage for 180 straight days). The study indicates that patients treated with paroxetine were 64 percent less likely to complete treatment than patients treated with fluoxetine. Similarly, patients treated with the common antidepressant sertraline, known by the brand name Zoloft, were 68 percent less likely to complete therapy than those on fluoxetine. Several other studies also have found that fluoxetine patients achieve longer duration of therapy compared to both paroxetine and sertraline. The exact cause for the higher completion rates with fluoxetine is unclear.

Researchers are unsure why patients with access to two antidepressants have higher completion rates than patients subjected to a more restrictive formulation. Further research using a larger sample drawn from additional HMOs is needed to confirm the findings, McCombs said.

Previous research also has found a significant association between antidepressant completion rates and both post-treatment costs for ambulatory services and recurrence of depressive episodes.

“These findings are important because limiting antidepressant options to a single agent appears to hinder completion rates,” McCombs said. “However, important clinical factors are often overlooked in the formulary decision process. Some HMOs capitalize physician groups for the cost of ambulatory care, so patients’ increased use of office visits due to their premature termination of antidepressant therapy does not directly increase HMOs’ costs. This leads to formulary decisions being made solely on the basis of the cost of a drug or the size of the rebate that drug manufacturers pay directly to the HMO.”

“Historically, the treatment of depression in the primary care setting has been shown to be less than optimal, due either to missed diagnosis or patients’ failure to achieve an adequate course of drug therapy,” McCombs said. “While unrecognized depression may still be a problem, the newer SSRIs antidepressants have significantly improved the ability of the primary care physician to treat depressed patients effectively assuming that a range of treatment alternatives is available.”

Nearly three of every four Americans who seek help for depression or symptoms of depression go to a primary care physician rather than a mental health professional, such as a psychiatrist.

The new study examines prescription drug and medical record data for 187 patients taking SSRIs in a single group practice of primary care physicians. The group practice contracted with two HMOs that had different SSRIs formulary restrictions.

The study was funded through an unrestricted grant to the medical group and USC from Eli Lilly and Company, the maker of fluoxetine.

According to the National Institute of Mental Health, more than 80 percent of people with depression can be treated successfully.

About 18 million adults in the United States suffer from depression, according to national patient advocacy groups.

— Alicia Di Rado

Student scholar chosen to join prestigious NIH research program

Just a few months ago, Wade Chien was plugging away in labs and classrooms with a fervor familiar to any Keck School second-year medical student. Today, he’s doing research with the director of the National Institute of Neurological Disorders and Stroke (NINDS).

Chien, 23, is participating in the Howard Hughes Medical Institute-National Institutes of Health Research Scholars Program in Bethesda, Md., and is one of only 42 students from 24 medical and dental schools across the nation chosen to join the Howard Hughes Medical Institute-National Institutes of Health Research Scholars Program.

Chien has seen advantages to slowing down and focusing on one area of study for a while. “I’ve found that doing research there is slower paced than being in medical school,” said Chien, a Taiwan native. “It’s a different kind of experience.”

As a program participant, he lives in The Cloister, a residential facility with amenities provided by the sciences. Medicine combines his interest in people with his strengths in science.

“I think I’d like to be involved in research, as well as treating patients,” Chien said, looking forward to his future work. “The whole discovery process in research is amazing. As an undergraduate researcher, even the little things I found were such a great feeling.”

For more information about the program, see http://www.hhmi.org/science/cloister.htm.

— Alicia Di Rado

Reminder:

Open Enrollment for benefits eligible faculty and staff runs from November 1 through December 3 Changes effective Jan. 1, 2000

USC: Time Magazine’s College of the Year 2000

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School of Pharmacy to host herbal medicine expert

As a nation, America seems to be embracing alternative or "complementary" medicine at a growing rate. American adults now spend more than $3.5 billion a year on herbal supplements. Faced with thousands of choices in the herbal medicine stores, it is easy for the consumer to be confused. That is why best-selling author and herbal medicine expert Varro Tyler has become successful by helping consumers sort through which herbs are used for which conditions. And to this end, he will discuss "The Future of Herbal and Nutritional Products: Public Health and Scientific Issues" at 3 p.m. on Thursday, Nov. 11 in the Mayer Auditorium.

The public may just be coming to grips with herbs and plants used for their purported restorative powers, such as echinacea and St. John’s Wort, but Tyler has been analyzing their medicinal qualities for decades. He has long been outspoken about the appropriate use of herbs and their safety and effectiveness. Now retired, Tyler was the dean of pharmacy at Purdue University for 20 years. He has written numerous books and scientific and educational articles on medicinal plants. His book The Honest Herbal is considered a definitive volume on so-called botanical medicine.

Young patients share their ‘Dream’

Young patients at Children’s Hospital (CHLA) are the stars and co-creators of a new 30 minute documentary that had its first screening Oct. 23 at the American Film Institute.

Directed by Sarah Elgart, "The Dream Project" takes as its raw material dreams recounted by six critically ill young people being treated at the USC-affiliated hospital.

The project fused interviews with the patients and documentation of their lives, in the hospital and in their homes with realizations — using animation and special effects where indicated — of the dreams, which are told in the patients' own words.

The patients ranged in age during the filming from 13 to 20, suffering from a variety of life-threatening illnesses. All are Latino, either children of recent immigrants or themselves born in Mexico or El Salvador.

Director Elgart worked closely with staff at CHLA, including social worker Tracy Mitchell and Jennifer Armstrong, arts facilitator of the Mark Taper-John Mercers Artist Program.

Armstrong helped Elgart find patients to participate in the project — those undergoing dialysis, who had to return to the hospital on a regular basis over a long period of time fit best.

The film presents the young people’s words and their simple, often eloquently phrased wishes supported by music, with the hospital setting where their dreams begin to merge with the scenes of their fantasies.

Filmmaker Elgart has worked as a choreographer and stage director as well as film, and has received grants from the National Endowment for the Arts and the City of Los Angeles Cultural Affairs department. She has worked at CHLA for more than a year on this project.

— Erik Mankin

Reception for new women faculty slated for Nov. 10

The Medical Faculty Women’s Association (MFWA) will host a reception for new women faculty members on Nov. 10 at the Edmondson Faculty Center.

The event, which will run from 4 p.m. to 6 p.m., will offer newcomers the opportunity to meet colleagues from other departments in an informal setting and learn about the MFWA. At 5 p.m., Nancy Warner, chair emeritus of pathology, will give a presentation on "Negotiation Skills". The event is open to everyone although reservations are encouraged. Those interested in attending should contact Maria Ramirez at the Office for Women at 442-2554.

Home-buying seminar at UPC to be held Nov. 13

The USC Federal Credit Union will host a home buying seminar at its University Park Campus offices on Nov. 13.

The seminar will include presentations by real estate brokers, home inspectors, escrow officers, appraisers and lending officers. It will also cover ways to select an agent, save money on closing costs and fees and a discussion of loan programs that require no money down.

The event will be held from 9 a.m. to noon at 1025 W. 34th St., King Hall, second floor. Registration, which is required due to space limitations, starts at 8:30 a.m. For more information, call (213) 821-7115.
ENROLL: ‘It’s about creating a pipeline of interesting students’

Continued from Page 1

ment to interest more students in the advantages of the campus.

Quinn, who teaches the Baccalaureate MD program on the University Park Campus, takes a personal interest in increasing representation for minority students at the Keck School. (Her own doctoral dissertation addressed Latinos in medicine.) She is involved in Francisco Bravo Medical Magnet High School and the Multicultural Area Health Education Center in East Los Angeles, which has programs for students from Roosevelt and Garfield high schools who are interested in medicine. A network of educators call her to let her know about bright minority students who may be interested in health careers.

Programs run through the office of Alton Alexander, assistant dean of minority student affairs, help bring in motivated students from a variety of backgrounds to USC for summer programs and other educational opportunities and identifying potential applicants.

“It’s about creating a pipeline of interesting students when they’re in junior high and high school,” Quinn said.

That means attracting students who not only bring their own unique background in terms of ethnicity, for example, but also those who are in their late 20s and have children, who have served in the Peace Corps, who come from other nations or bring other life experiences to their medical school class.

Clive Taylor, senior associate dean for academic affairs and professor and chair of pathology, said that once applicants meet a standard academic level of eligibility, members of the Keck School admission committee can look for other characteristics in an applicant. “Once they’ve gone over the hurdle, you look to bring richness to the class,” Taylor said.

Admissions staff members organized tours for students, introduced them to current USC students, invited them back to special events, “Accepted Students Day” and called them to encourage them to come to campus regardless of their race or ethnicity. Quinn also researched opportunities for student loans, so students who felt they could not afford the school costs could still pay for their education.

“We wanted to make sure they felt wanted here,” Quinn said.

It seemed to have worked: all students who enrolled had listed USC as their top choice. For minority students, as for the class as a whole, the opportunity to learn medicine in a hands-on atmosphere at LAC+USC Medical Center may have played a part, as well as the campus’s location in a multicultural urban environment.

When recruiting the next year’s class, admissions staff members will continue to reach out to prospective applicants to attract a qualified class of interesting first-year students.

“Part of the secret is our admissions committee,” Taylor said. “They’re diverse, and help us focus on getting a diverse class.”

— Alicia Di Rado

Calendar

Friday, Nov. 5
3:30 p.m. School of Pharmacy. “Regulation of Fluid Transport in the Pigmented Rabbit Conjunctiva,” Michael Shin, USC. Norris Tower 7th Floor Conf. Ch.: Info: 442-1451

Monday, Nov. 8

Tuesday, Nov. 9
8:30 a.m. - 5 p.m. Hekto Neuroscience 10th Anniversary Celebration. In Genesee Trust – or Do We?, Floyd Bloom, Scripps Inst. Alfred Newman Auditorium. Info: 749-5991

8:45 a.m. New Staff Orientation Part 1, KAM 308. Info: 442-2579

9 a.m. School of Pharmacy. “Neural Regulation of Goblet Cell Secretion,” Darlene Dartt, Schepens Eye Research Inst. PSC 104. Info: 442-1431

Noon. Cancer Center General Rounds. “Etiology of Malignant Melanoma... What we Do and Do Not Know.” Thomas Mack, Myes Cockburn, Norris Tower 7th Floor Conf. Ch.: Info: 605-8900

Wednesday, Nov. 10
7 a.m. Medical Grand Rounds. “Spondylo,” DePino DeQuattro, USC. GNH 1645. Info: 226-7591


4 p.m. The Medical Faculty Women’s Assoc. Welcome Reception for New Women Faculty. “Negotiation Skills,” Nancy Werner, USC. Edmondson Faculty Center. Info: 442-2574

Thursday, Nov. 11
9 a.m. New Staff Orientation Part 2, KAM 308. Info: 442-2579


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