



FREE PUBLIC LECTURE

**Gene Therapy  
for Heart Failure**



Dr. Kirk Hammond  
*Department of Medicine*

Wednesday  
May 18, 2005, 7:00 P.M.  
Garren Auditorium  
Basic Science Building  
University of California, San Diego

**NEXT MONTH**

**Low Back Pain**

Dr. John Chardos  
*Department of Medicine, VA*

Wednesday  
June 15, 2005, 7:00 P.M.  
Garren Auditorium  
Basic Science Building  
University of California, San Diego

No reservations required

Free parking will be provided for SIRA contributing members. Please call (858) 534-6299 TWO WEEKS BEFORE THE LECTURE to receive your free parking permit. All other lecture attendees must buy a permit at the parking kiosk on Gilman Drive or park at the metered sites.

*Healthwise* is available online at [sira.ucsd.edu](http://sira.ucsd.edu).

**Thank You, Robert Silagi**

**An Example of a Legacy**

SIRA exists through the generosity of its members and contributors. Although part of the university, we are financially independent, and must be responsible for obtaining the necessary money to thrive and function. Thus we are dependent upon the community, and the largesse of our members and donors.

We would like to thank Robert Silagi who died on February 12 at 88 leaving a legacy of \$72,000 for SIRA's unrestricted use. Bob, a New York labor lawyer, was a past SIRA board member and generous friend to SIRA through the years. Prior to this gift, he established an operating fund rewarding \$1,000 to the best student researcher of our annual Student Investigator Program. This fund was named in honor of his adored wife, Selma Silagi, who had died many years ago.

SIRA under the direction of Dr. Dilip V. Jeste has taken a bold approach in augmenting longitudinal studies on "successful aging" bringing SIRA into the twenty-first century. The intent of these studies is to further understand the biopsychosocial factors that pertain to aging successfully—aging with longevity, health, and well-being. These projects are expensive and we are particularly grateful to Bob Silagi for his timely legacy.

So . . . thank you Bob, wherever you are. Your gift is much appreciated.

You, too, can leave a legacy and there are many interesting ways of doing this. Please think of SIRA in your estate planning. If you are interested and/or need information, call Adam Milgram, executive director, at (858) 534-4405.

<b>UC SD TV</b>	<b>PUBLIC LECTURE SERIES UCSD-TV SCHEDULE</b> Lectures air on Cox Communications San Diego, channel 66; Cox North County, channel 69; Time Warner Cable, channel 18; Del Mar TV 66, or UHF (without cable), channel 35.	<b>Selenium in Cancer Prevention and Human Health</b> Dr. Gerhard N. Schrauzer	5/12	8:00 P.M.
			5/13	10:00 P.M.
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		<b>Pop! Goes the Memory</b> Dr. Jody Corey Bloom	5/26	9:00 P.M.
			5/27	11:00 P.M.
			5/31	7:00 P.M.

**MORE OF SIRA ON UCSD-TV**

**Successful Aging Series**

<b>Images of Aging: Stereotypes and Ageism in Society</b> Dr. Joaquin Anguera	5/19	8:00 P.M.
	5/20	10:00 P.M.
	5/24	6:00 P.M.

For clinical trials at UCSD: <http://health.ucsd.edu/ntrials/>

## Transitioning into Retirement

By Community Board of Advisors member

Dr. Natasha Josefowitz

People who retire fall into three main categories: those who make things happen, those to whom things happen, and those who say: "What happened?"

Transitions are tough. Some people spend more time planning a one-week vacation than how they will spend the last third of their lives. Yes, if you live until you're in your 90s and you retire in your 60s, you have one-third more of your life to live. Better give it some thought. This is why the preparation is critical. You don't retire from something, you retire to something. Work has always been outer-directed with performance as the criteria for reward with other people being the judges. This is what you do eight hours a day! Retirement is inner-directed with a new need to define success as well as find happiness in personal life, in relationships, and in creative mental activities. Success means different things to different people. What is it for you? What is going to be important now? Is it your own feelings of self-worth or how others perceive you? What will that be predicated on? You are the only one being the judge.

What are your fantasies as you contemplate retirement? Is it jubilation at the idea of sleeping without an alarm clock ticking by your bedside, time to leisurely read the morning paper, and do whatever your heart dictates for the rest of the day? Or, is it anxiety at the prospect of idle hours and empty days, with secret fears of physical or mental disabilities looming in a bleak future?

We pose ourselves new questions: What contributions could I still make, what do I still want to learn, what relationships do I want to improve, who am I? Although we may lose our identity as a worker, we don't lose the need for it. The need for status, satisfaction, collegiality, structure,

excitement, direction, goals—things usually found at work must be recognized and alternative sources found. Life needs to have meaning and reward as you pass from a life of necessary productivity to a life of personal accomplishment, leisure, and choice.

One of the hurdles to overcome after a lifetime of being an expert at work is the need to become a learner again—whether it's a new hobby or skill or just learning how to fill one's days meaningfully. This is especially true for people whose main relationships were with people at the work place. We need to learn to form new relationships and how to maintain old ones without the glue of job-related topics. One of the most difficult things to do is find a new passion, and if not a passion, at least something we really love to do and look forward to doing. We don't "grow" old, it's when we stop growing that we become "old."

Happiness in retirement is not a destination; it is a way of traveling, and the prepared person will have a smoother road. So go from being undirected to either becoming an outer-directed person who makes things happen by volunteering and being active in your community; or be the inner-directed person who can sit back confidently and let things happen, going to lectures, playing a round of golf, enjoying the grandchildren, reading. Both are reaping the rewards of that next journey, that next adventure.

For those of you who want to learn more, my new book, *Retirement, Wise and Witty Advice for Making It the Next Great Adventure* helps people to not only manage the transition into retirement but also includes strategies for living a full and happy life in retirement.



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*We would like to express our deep appreciation for all those listed, as well as the anonymous donors, who chose to support the research, education, and training at the Sam and Rose Stein Institute for Research on Aging.*

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## Center of Excellence in Geriatric Psychiatry Announced

*UCSD Health Science News, March 2005*

The United States faces a critical health-care problem as the number of mentally ill older Americans is steadily increasing, while the number of psychiatrists trained to care for them is too low to meet the demand.

With a \$450,000 grant from the John A. Hartford Foundation, the University of California, San Diego (UCSD) School of Medicine and the VA San Diego Healthcare System will train a new generation of geriatric psychiatrists and physician-researchers to meet the needs of older persons with illnesses ranging from depression to psychotic disorders such as schizophrenia.

The Hartford Foundation is a committed champion of training, research and service system innovations that promote the

health and independence of America's older adults. Through its grantmaking, the Foundation seeks to strengthen the nation's capacity to provide effective, affordable care to the rapidly increasing older population.

"The Hartford Foundation grant will greatly help UCSD recruit and train geriatric psychiatrists and researchers with an interest in mental health problems of the elderly," said Edward W. Holmes, UCSD Vice Chancellor for Health Sciences.

According to a Surgeon General's Report, "disability due to mental illness in individuals over 65 years old will become a major public health problem in the near future because of demographic changes." The number of psychiatrically ill elderly is expected to rise by 275 percent, from 4 million in 1970 to 15 million in 2030. Epidemiologic studies suggest that 18 to 28 percent of the elderly population has significant psychiatric symptoms. At the same time, of 39,000 psychiatrists in the United States, only 5,000 list "geriatric psychiatry" as one of their three primary interests.

"With the Hartford Foundation grant and establishment of the Center for Excellence in Geriatric Psychiatry, we will be able to provide positive role models for promising psychiatric researchers, develop award programs and affinity groups, share resources, make programs sensitive to trainees' practical needs, and assist individuals with the transition to an academic career," said the Center's director Dilip Jeste, M.D., Estelle and Edgar Levi Chair in Aging and professor of psychiatry and neurosciences, chief of the UCSD Division of Geriatric Psychiatry, director of the UCSD Sam and Rose Stein Institute for Research on Aging (SIRA), and a geriatric psychiatrist

with the VA San Diego Healthcare System.

An internationally known expert in geriatric psychiatry, Jeste and his team are uniquely qualified to train geriatric psychiatrists and researchers. The UCSD Division of Geriatric Psychiatry includes National Institute of Mental Health (NIMH)-supported programs such as an Advanced Center for Interventions and Services Research in Geriatric Psychiatry, a T-32 Research Fellowship program, and a Summer Research Institute in Geriatric Psychiatry.

The mentally ill elderly present a unique challenge to healthcare providers and geriatric researchers, Jeste noted. "These include, but are not limited to normal age-related changes in brain structure and function, co-existing diseases in one individual, multiple medications, cognitive impairment, issues of classification and measurement of symptoms and diagnosis, and difficulties in long-term follow-up."

Noting that new researchers constitute the lifeblood of scientific infrastructure, Jeste said the need to attract and train new investigators is a critical priority for geriatric mental health. Unfortunately, the current healthcare environment contributes to the difficulty of training new investigators. Post-residency psychiatrists are under increasing pressure to generate their salaries and be clinically productive, with very little time devoted to research. It has also become increasingly difficult to obtain independent federal grant support for young investigators, thus forcing them to maintain and increase their clinical responsibilities. Even among individuals who participate in fellowships, 68 percent spend less than 10 percent of their time in research.

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### BROCHURES

*Arthritis Magazine*, March-April 2005

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## Gene Therapy for Heart Failure

Dr. Kirk Hammond, Professor of Medicine, VA San Diego Healthcare System

**Editor:** Could you tell us how you came to study cardiology and how you became involved with gene therapy for the heart?

**Dr. Hammond:** The initial part of my career was at Indiana University where I did both pre-medicine and medicine (M.D., 1980). In Portland, Oregon I completed an internal medicine residency. My favorite patients were those with pulmonary edema, acute myocardial infarction, and severe heart failure. Cognizant of my need to be involved in research, I completed a two-year fellowship in cardiovascular research at UCSD, and explored basic scientific inquiry into the function of the heart. I was mainly interested in how one could modify heart function without medicines. I then did my clinical cardiology training at UCSD and joined the faculty in 1987. That was also the year my first daughter was born. I mention this because it changed my goals in science. I became much more goal-directed and obsessed. The questions that I was interested in had to have relevance to human disease or I was no longer that interested in them. Although I used basic approaches, my work had to be translatable into something that would help patients. The first breakthrough was in 1993 during the study of myocardial ischemia (angina).

**Editor:** Angina is related to the lack of blood flowing into the heart?

**Dr. Hammond:** Yes, inadequate blood flow to the heart muscle. If the arteries that provide blood flow to the heart are narrowed by atherosclerosis and plaque and so forth, myocardial infarction can result. Even without myocardial infarction, inadequate blood flow can cause chest pain—what we call angina. I was performing cardiac catheterizations on patients at the VA Hospital. It was very surprising to me that some patients would have no collateral blood vessels in their heart and other patients would be blessed with a rich network of collateral blood vessels. A collateral vessel is a vessel that is not usually there and connects two previously unconnected vascular beds, providing increased blood flow to oxygen starved regions of the heart.

**Editor:** Is it a compensatory kind of response?

**Dr. Hammond:** Yes. If you have poor blood flow to a section of heart, collateral vessels which did not previously exist would provide an alternative blood flow to that area. I thought if

there is so much variability in a person's ability to generate collateral vessels, then if you could get an angiogenic gene into the heart, it would promote new blood vessels to form. So we started thinking about how to get an angiogenic gene into the heart of patients with myocardial ischemia. This idea was sort of a way to have bypass surgery without the surgery. You would just inject the gene into the coronary arteries, ideally, and the gene would enter into the cells of the heart and make new blood vessels grow. And that idea actually turned out to work, at least in pigs.

**Editor:** How did you know that there was a gene that created that?

**Dr. Hammond:** The biological power of these proteins is amazing. If you put these angiogenic proteins together with endothelial cells in a petri dish, the endothelial cells will form tubes. If you soak a matrix of collagen with an angiogenic protein and put it in the peritoneal cavity of a rat it will form a vascular structure which is connected to the circulatory system. The question of how to get the genes easily and effectively into the heart and not elsewhere was critical. The solution to this turned out to be intracoronary injection of an adenovirus carrying the angiogenic gene. We remove the portion of the adenovirus genome that allows it to replicate and instead put in our gene—an angiogenic gene. We then injected this vector into the coronary arteries of pigs with myocardial ischemia, and the deficit in blood flow and heart function was resolved by the treatment. We then performed clinical studies in patients with angina. The first two of those trials worked pretty well, but they were both small trials. The third trial, a worldwide trial, failed to show a significant effect, although it was safe. The failure of this trial was an enormous disappointment to me. However, being the first large scale trial of gene transfer for cardiovascular disease, extra caution was applied. We used 30-fold less of the adenovirus than I had used in pigs, and that was probably the reason the trial failed.

**Editor:** There was not sufficient gene material?

**Dr. Hammond:** Yes, because there are some potential side effects, the sponsors of the trial were afraid that they would cause if higher levels were used.

**Editor:** Did you actually inject the adenovirus with the gene into the heart muscle itself?

**Dr. Hammond:** We take patients to the cardiac catheterization laboratory and they undergo a routine diagnostic coronary angiogram. Through a similar catheter we take about 5 cc of the adenovirus carrying the gene and slowly inject it into each of the two main coronary arteries. This can be performed as an outpatient procedure.

**Editor:** Wow.

**Dr. Hammond:** It is a serious procedure, but much safer than bypass surgery (CABG), which is a major surgical procedure that requires thoracotomy and cardio-pulmonary bypass.

**Editor:** So, what did you do because of this failure?

**Dr. Hammond:** We are focused on a new strategy that we have worked on for over twelve years. I've always been a heart failure researcher and we have animal models of heart failure in the laboratory. A failing heart simply cannot develop enough power to pump blood to the body. Those hearts get big and floppy and barely contract. A normal heart is about the size of your fist and it beats vigorously and provides all the blood flow that your body needs. Failing hearts can be two or three times normal in size but do not function well. Heart failure is a major problem in this country, with 6 million patients with congestive heart failure. Once severe symptoms are present, the chances of being alive in three years are about 50 percent, despite optimal therapy. This prognosis is worse than most cancers. There is a therapeutic vacuum in the area of treatment options for patients with heart failure.

**Editor:** Is this basically because of the narrowing of the wall?

**Dr. Hammond:** The major cause of heart failure in our country is previous myocardial infarction (heart attack) from coronary artery disease. Other contributing factors include high blood pressure, diabetes, and virus infection. If we could find a protein that increased the function of the failing heart, then we could use a gene transfer approach and start to treat patients. A hallmark of a failing heart is the inability to generate cyclic AMP, a second messenger. When hormones like the "flight and fight" hormones (epinephrine and norepinephrine) are released, the force and rate of heart contraction increases. This leads to an increase in blood flow to our bodies. Epinephrine and norepinephrine operate by interacting with protein receptors on the surface of heart muscle cells (cardiac myocytes). This causes an increase of cyclic AMP inside the cell.

This ultimately increases the force and rate of contraction of the heart. In a failing heart, that system functions poorly. We pinpointed the deficit to an effector molecule called adenylate cyclase (AC) which is an enzyme that converts ATP to a cyclic AMP. We made an adenovirus carrying the AC gene, did gene transfer in cell culture experiments, and found a robust increase in cyclic AMP. When we put the gene into transgenic mice, they had long normal lives with normal cardiac function at rest. But these mice showed supranormal heart function during stress. We next treated mice with heart failure. Their hearts functioned better and they lived longer. We then injected an adenovirus carrying the AC gene into pigs with heart failure—in the same way that we will conduct the trial in humans. AC gene transfer was associated with improvements in heart structure and function and cyclic AMP generation in these failing pigs.

**Editor:** Was this similar to what you had done before in terms of the compensatory pathways that would develop by expressing adenylate cyclase in the pigs and in the mice?

**Dr. Hammond:** In the previous trials we used an angiogenic gene to treat angina. Here we are using AC to treat heart failure—no angiogenesis is involved. The delivery methods are the same.

**Editor:** And the cyclic AMP does what?

**Dr. Hammond:** Cyclic AMP is the second messenger that is required for an increase in force of contraction of the heart and an increase in heart rate.

**Editor:** And so, where are you with this now?

**Dr. Hammond:** We have had initial meetings with the FDA, and have obtained approval from the internal review boards at the participating hospitals (UCSD Medical Center in Hillcrest and VA San Diego). The National Institutes of Health's Recombinant DNA Advisory Committee (RAC) and the National Heart, Lung and Blood Institute's Data and Safety Monitoring Board have approved the human trials. The final decision will be made by the FDA. We hope to start the clinical trial soon, perhaps in 6 to 12 months.

Cardiovascular gene transfer is a marathon, not a sprint. If you would have told me in 1993 that I would not be starting a clinical gene transfer trial for heart failure until 2005, I probably would have given up...

**Editor:** Thank you.

## Noninvasive Method to Evaluate Status of Vascular System

Dr. A. Fronck has developed a noninvasive method to evaluate the status of the vascular system especially in patients with coronary or peripheral artery disease, hypertension, hypercholesterolemia, diabetes. The procedure is completely painless, takes about 40 minutes, and is approved by the UCSD Human Research Protection Program. Also, persons without known disease above the age of 50 years are encouraged to participate. Volunteers are invited to call (858) 534-4270 for additional information.

## Controlling Anxiety in Later-life Medical Patients (CALM Study)

Dr. Julie Wetherell and her colleagues are conducting a study to see whether anxiety management training helps older adults. You may be eligible if you are at least 60 years old, have a health care provider, and often feel tense, worried, or anxious.

If you participate, you will either receive:

- 12 sessions of anxiety management training from the CALM study team
- Or treatment as usual from your regular health care provider.

Anxiety management will help you learn relaxation techniques, problem-solving skills, and how to let go of past and present experiences that make you anxious.

Possible benefits include:

- \$80 for four assessments over a 16-month period
- You and your health care provider will receive information about your symptoms, which may lead to better care for you
- You may receive anxiety management training at no cost to you
- You may experience relief of your anxiety symptoms

For more information, please call Georgia Birchler at (858) 552-8585 ext. 2390 or Dr. Wetherell at (858) 552-8585 ext. 2752.

## Biomarkers in Aging, MCI, and Alzheimer's Disease

Dr. Galasko at the UCSD Alzheimer's Disease Research Center is conducting a study to measure the levels of a number of different proteins (called biomarkers) in cerebrospinal fluid (CSF) and in blood. The purpose of the study is to find out whether levels of these proteins are altered in people who have normal cognitive ability, mild memory problems, or early Alzheimer's Disease (AD). We aim to study these markers in detail to determine which combination of biomarkers is most helpful to indicate whether people with mild memory problems are at high risk of worsening over time, or progressing to AD. We will also test blood to find which form of a gene called Apolipoprotein E (APOE) an individual may have. Studies suggest that this gene may influence the risk of developing AD.

Recruitment is now underway to enroll subjects in one of the following categories:

- 1) healthy adults without memory problems, between ages 40–90
- 2) individuals with Mild Cognitive Impairment (MCI), between ages 60–90
- 3) individuals with early AD, between ages 60–90

The study will last five years and each year will involve a two-day (non-consecutive) visit.

### Brain Imaging Study

Sean Drummond, Ph.D., is conducting a brain imaging (MRI) study to determine how the brain reacts to lack of sleep. Participants must be 60 to 80 years of age and in good health. This study involves an overnight hospital stay at the VA Hospital in La Jolla and several brain imaging sessions. Participants will be given a physical exam, lab and ECG, a thorough sleep study, and are paid for their time and travel. If interested, please call Jen at (858) 642-1259.

During the first visit, participants will undergo brief physical and neurological examinations and will be asked a series of questions that are designed to evaluate memory, thinking capacity, and mood. They will also undergo laboratory (blood and urine) tests. The second visit will consist of further blood work and undergoing a spinal tap. Spinal taps, or lumbar punctures, are routine neurological outpatient tests in which a small amount of fluid is removed from the lower part of the back. The spinal taps are done to measure the biomarker proteins. Subjects will receive up to \$200 compensation per year of the study for undergoing the spinal taps. Subjects are not required to have a spinal tap each year if they choose not to do so. If you are interested in participating, call Helen Vanderswag, RN, at (858) 622-5805.

## Are You at Risk for Developing Type 2 Diabetes?

- Are you concerned about developing Type 2 Diabetes due to a family history, high blood sugar, or being overweight?
- Have you ever been told that you are at an increased risk for developing Type 2 Diabetes?

Dr. Mudaliar at the VA Medical Center in La Jolla is currently screening volunteers (Vets and Non-Vets) for the ACTOS NOW study. This study looks at an investigational use of the drug Pioglitazone to determine if the drug can prevent or delay the development of Type 2 Diabetes.

Subjects who qualify will receive:

- study related medical care by board certified physicians
- counseling with a certified diabetes educator
- compensation up to \$600

If interested, please call Alana Clark at (858) 552-8585 ext. 2884.

## UCSD Clinical Trials Center is Recruiting!

- Do you have COPD?
- Have you had a COPD exacerbation in the last 12 months . . . such as increase shortness of breath, increased sputum production, or change in the color of the sputum?
- Did you require either oral corticosteroids, antibiotics, and/or hospitalization to treat these symptoms?

UCSD Clinical Trials Center is conducting a national research study for COPD.

If you answered yes to the above questions, call Arlene at (619) 294-6239 or toll free at (888) UCSD-Air to learn about the study.

### Colorectal Cancer Screening among Adults Aged 50 or Older: Implementation of Fecal Occult Blood Testing in Clinical Practice

*CDC, Fact Sheet, January 2005*

#### Colorectal Cancer Facts

- Colorectal cancer (CRC) is second only to lung cancer as the leading cause of cancer-related death in the United States. In 2004, it's estimated that CRC caused nearly 57,000 deaths.
- In 2004, an estimated 147,000 new cases of CRC were diagnosed. Approximately 93 percent of colorectal cancers are diagnosed in men and women aged 50 years or older.
- Screening tests can find colorectal cancer in its earliest stages when it can be treated more successfully. Screening also can identify pre-cancerous polyps so they can be removed before they turn into cancer.

The fecal occult blood test (FOBT) is one type of CRC screening test. FOBT can be conducted in the doctor's office or at home. In the home test, the person collects several stool samples and places the samples on special cards, and then sends the cards back to the physician or a lab to be tested. During the in-office FOBT, the physician collects a single sample from a patient during a digital rectal exam. The home test is recommended for CRC screening. The in-office FOBT is **not** recommended for CRC screening.

## The Positive Side of Caregiving

*Positive Aging Newsletter*  
January-February, 2005

Research on care giving for the elderly typically emphasizes the negatives: stress, frustration, sadness, and the like. However, such results largely derive from the fact that care givers are asked about the costs. What happens, in contrast, if we ask about the benefits of care giving. Recent research gives us an answer. In this study a sample of 217 people who were responsible for giving care to Alzheimer's sufferers were queried. The caregivers were on the average 64 years old, mostly women, about half of whom were providing care for their spouses. The care recipients, who were deceased at the time of the research, were on the average 81 years old.

The caregivers were asked whether the extent to which they agreed or disagreed that providing help had:

- 1) Made me feel more useful
- 2) Made me feel good about myself
- 3) Made me feel needed
- 4) Made me feel appreciated
- 5) Made me feel important
- 6) Made me feel strong and confident
- 7) Given more meaning to my life
- 8) Enabled me to learn new skill
- 9) Enabled me to appreciate life more
- 10) Enabled me to develop a more positive attitude toward life
- 11) Strengthened my relationship with others

As the results showed, on virtually every dimension the respondents tended to agree with the benefits. Their feelings were associated with an increased sense of companionship, personal fulfillment, and the satisfaction of having done the right thing for a loved one. Caregivers who were gratified by their experience were especially likely to feel grief at the loss of their recipient, and this emotion was more frequent than depression. The researchers point out that the ratings of grief occurred soon after the death of the recipient, and seemed highly appropriate given the pleasure the caregiver took in his or her efforts.



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