

Gambhir
to head
Radiology



P 6

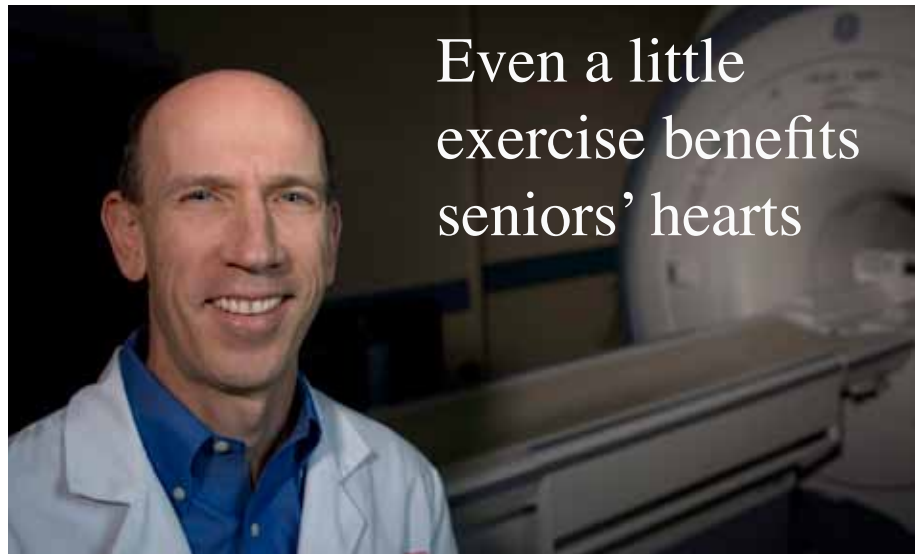


CVI scientists
at Maker Faire

P 8

In This Issue:

Exercise benefit to seniors	1
Accuracy of athletes' ECG	3
Advice for reading ECGs	4
Bioengineering gets \$20 mil	5
Gambhir head radiology	6
Kobilka elected to NAS	6
\$5.7 mil in CIRM grants	7
Maker Faire presentations	8



Even a little
exercise benefits
seniors' hearts

Michael McConnell, MD

Study presents new evidence of how physical activity benefits heart health in seniors

Scientists at the Stanford University School of Medicine have found the strongest evidence to date that staying physically active helps improve the functioning of heart arteries in older Americans. The findings, published online June 13 in the *Journal of the American College of Cardiology: Cardiovascular Imaging*, support the heart-health benefits of even moderate exercise, such as walking one hour per day.

In the study, scientists directly measured the improved ability of heart artery dilation — a measurement of artery health — in more-active older patients. Previous studies have shown the same benefits among male athletes, such as ultra-marathon runners, but this new study was unique in looking at both men and women between the ages of 60 and 72 doing typical physical activities. The benefits were found equally in both genders.

“My patients ask me, ‘How do we really know that exercise is benefiting my heart arteries?’” said senior author Michael

Exercise benefit to seniors

(Continued from Page 1)

McConnell, MD, associate professor of cardiovascular medicine and director of the Preventive Cardiology Clinic at Stanford. "Now we can say that we've looked directly at their arteries and shown that the more physically active subjects, even in their 60s, see measurable benefits." Scientists compared the healthiness of heart arteries in older adults with their physical activity levels in a group of 212 older patients with no history of heart disease. The patients had been part of the Stanford/Kaiser ADVANCE study of heart disease.

They found a significant positive correlation between coronary vasodilatation and physical activity. The subjects with moderate activity levels, equivalent to one hour of walking a day, dilated their coronary arteries almost 50 percent more than subjects with lower activity levels. These findings remained significant even after adjustment for cardiac risk factors, coronary calcium score and the use of heart medications such as statins.

"If you exercise more, your vessels dilate more," McConnell said. "The more a vessel dilates, the healthier the vessel. Those who don't do anything beyond light activity have by far the lowest dilation levels. Those who include high-level activities, like singles tennis or swimming, at least once a week dilated their heart arteries twice as much."

To measure the dilating capacity of heart vessels, scientists used noninvasive, high-resolution magnetic resonance imaging of the coronary arteries, a technique developed at Stanford. An MRI coronary angiogram was conducted both before and after administering a nitroglycerin pill under the tongue with a five-minute wait between the two angiograms. The change in size of the coronary artery was then measured.

The physical activity levels of the subjects were measured using the Stanford Seven-Day Physical Activity Recall Questionnaire, which was developed at Stanford in the 1980s and has been used in many

epidemiologic studies. The interview-administered survey asked subjects to estimate energy levels recalling typical weekly activities: mopping or a brisk walk equaled moderate activity levels; construction work or doubles tennis equaled intense levels; chopping wood or running equaled very intense levels.

Previous studies have shown that athletes have a greater coronary vasodilatory response to nitroglycerin, which gets converted to nitric oxide, compared with people who are not physically active. Nitric oxide is the main chemical that the walls of the heart arteries produce to tell the vessels to dilate.

"By imaging after giving nitroglycerin, we could measure the coronary artery response to nitric oxide, and found that inactive people are less responsive than active people," said Patricia Nguyen, MD, an instructor in cardiovascular medicine and first author of the study.

According to the American Heart Association, nearly 70 percent of Americans don't get enough physical activity. It recommends at least 30 minutes of moderate physical activity, like brisk walking, at least five times a week to lower the risks of heart disease, stroke and diabetes. Children need 60 minutes every day.

The study's co-authors at the Stanford Prevention Research Center include: Ruth Taylor-Piliae, PhD, RN, a former research fellow; William Haskell, PhD, professor emeritus of medicine; Stephen Fortmann, MD, former professor of medicine; Joan Fair, PhD, a former consulting assistant professor; and former staff member Ann Varady. Co-authors from the Stanford cardiovascular medicine division are Masahiro Terashima, MD, PhD, a former research fellow; and Mark Hlatky, MD, professor of medicine and of health research and policy.

Pediatric cardiologists are prone to misinterpreting electrocardiograms when using the results to determine whether young athletes have heart defects

Pediatric cardiologists not always accurate in interpreting ECG results for young athletes



Allison Hill, MD



Anne Dubin, MD

Pediatric cardiologists are prone to misinterpreting electrocardiograms when using the results to determine whether young athletes have heart defects that could make exercising perilous, according to a new study from the Stanford University School of Medicine and Lucile Packard Children's Hospital. This is the first research to examine the acumen of pediatric cardiologists from several health-care institutions in using ECGs to detect rare heart conditions associated with sudden cardiac death.

Public outcries about sudden cardiac deaths among athletes have already prompted some European countries to require that young athletes undergo heart exams via ECG before they participate in sports. Even though the number of sudden cardiac deaths among young U.S. athletes is low — an estimated 76 per year — some people have suggested that athletes here should also receive mandatory ECGs so that those vulnerable to sudden cardiac death could be warned not to play sports.

Not so fast, say the authors of the new research. “An ECG doesn't always pick up the abnormalities that may predispose someone to sudden cardiac death,” said Allison Hill, MD, the study's first author. “And this exam can be difficult to interpret, even if the person reading the scan is a pediatric cardiologist.” Hill recently finished her pediatric residency at Packard Children's Hospital and is now a pediatric cardiology fellow at Children's Hospital Boston. In the new study, published online July 14 in the

Journal of Pediatrics, 53 members of the Western Society of Pediatric Cardiology were asked to interpret a set of 18 ECG exams, some from healthy athletes and some from those with heart defects. The physicians, who had an average of five to 15 years of experience in their field, accurately diagnosed the heart conditions only 67 percent of the time. They correctly permitted sport participation for healthy individuals 74 percent of the time, and correctly restricted sport participation for those with cardiac defects 81 percent of the time.

“As athletes' hearts grow stronger, they undergo some changes that make it very difficult to tell: Is this a well-trained athlete or does this person have some underlying disorder that may predispose them to sudden cardiac death?” Hill said. A fit heart tends to grow somewhat larger and beat more slowly, which can make it look similar on an ECG to a defective heart vulnerable to sudden cardiac death. This similarity could lead to unnecessary exclusion of healthy young people from sport participation. Conversely, some young athletes who are predisposed to sudden cardiac death may be given a clean bill of health based on a flawed ECG interpretation.

“We need to be careful about giving a false sense of security to families, parents or an entire community if we have an ECG that's normal,” Hill said. “It's important to know that it's not a perfect test.” The physicians' accuracy at interpreting ECGs varied depending on what heart defect they were looking at. They were most accurate at picking up long QT syndrome and myocarditis, showing 98 percent and 90 percent accuracy at restricting sport participation for these two conditions. In contrast, they correctly restricted sport participation for patients with hypertrophic cardiomyopathy, Wolff-Parkinson-White syndrome and pulmonary arterial hypertension 80 percent, 64 percent and 38 percent of the time, respectively. Anne Dubin MD, associate professor of pediatric cardiology, and Christina Miyake, MD, instructor in pediatric cardiology, are also co-authors.

New recommendations on interpreting athletes' ECG results prepared by Stanford team

In an effort to improve the accuracy of interpreting the electrocardiogram results of the extremely fit, researchers from the Stanford University School of Medicine have prepared a how-to guide for doctors who may be screening young athletes for heart defects. The new recommendations, published Aug. 9 in *Circulation*, are based on the consensus of experts from five countries with the aim of helping to reduce the high percentage of false positives in heart screenings for athletes that lead to unnecessary follow-up tests and emotional trauma. Athletes' electrocardiograms — which measure the electrical activity of the heart by attaching electrodes to the chest — have proven notoriously difficult to interpret. A recent Stanford study found that even highly trained pediatric cardiologists are prone to misinterpreting these results.

The reason for this, researchers say, is that athletes' ECGs are often dramatically different from those of people with more sedentary lifestyles and don't follow the same set of rules of interpretation. What may be interpreted as a heart attack in your average couch potato may be a perfectly normal ECG in an athlete. "Currently there are no clear-cut guidelines for reading ECGs for athletes," said Vic Froelicher, MD, a Stanford professor of cardiovascular medicine and one of two senior authors of the paper. He has been interpreting the ECG results of athletes going back 20 years in his work with astronauts and military pilots. "This recommendation paper we've put together reflects years of experience and helps to provide a consensus among experts worldwide."

"Although physicians understand that athletes have ECGs that are different, this has never really been formalized in a detailed way," said co-senior author Euan Ashley, MD, PhD. "So it's hardly surprising that without good guidelines, you can get inaccurate readings."

The recommendations are also designed to help practitioners determine what follow-up tests they

need to do when they determine an ECG reading is abnormal, Ashley said.

An ongoing debate over how best to screen young athletes for heart defects that could lead to sudden death has heated up in recent years.

Some European countries require that athletes undergo heart exams via ECG before they participate in



Euan Ashley, MD, PhD

sports. The American Heart Association recommends against mandatory ECG testing, citing high costs, frequent false positives and the low rate of sudden cardiac death among young athletes — an estimated 76 per year. But these numbers are based primarily on newspaper reports and could be significantly higher, according to a recent study in *Circulation* by Jonathan Drezner, MD, at the University of Washington, also a co-author of this paper, whose previous study found surprisingly high rates among collegiate basketball players.

The paper provides a chart with straightforward guidelines designed to unify physician interpretations when searching for signs of possible heart defects. "We provided more detailed criteria with explicit number cutoffs and descriptors for how an untrained evaluator could analyze the ECG tracing," said Uberoi. "We did our best to accrue the most universally accepted definitions and pieced them together in a way that our expert panel agreed with."

Coulter and Stanford establish \$20 million endowment for bioengineering projects to fill medical needs

A \$20 million endowment to support the translation of ideas that address unmet medical needs into treatments and devices that improve human health has been established in the Stanford University Department of Bioengineering, with support from the Wallace H. Coulter Foundation and the university.

The foundation provided a \$10 million grant to create the endowment, with matching funds coming from the office of University President John Hennessy, PhD. The money will enable the Wallace H. Coulter Translational Research Grant Program at Stanford to continue in perpetuity.

“The Coulter Endowment fits perfectly at Stanford, with our shared commitments to innovation, entrepreneurship and the translation of scientific discoveries into treatments that prevent illness, relieve suffering and save lives,” said Hennessy. “With this endowment, we will vastly expand our ability to launch groundbreaking bioengineering research projects that could transform medical care around the world. We thank the Coulter Foundation for the generous support it has provided to establish this program.”

With its unique position in Silicon Valley, Stanford has a rich history of supporting the process of doing basic research, developing its commercial applications and then helping to launch start-ups or collaborate with existing companies that produce and distribute the new technologies. The Coulter Process helped to advance Stanford’s translational efforts by providing a template for how to quickly and efficiently turn bioengineering research into medical products and clinical practices. The Coulter grants work differently than grants from the National Institutes of Health and other federal research agencies. “This is more like business,” said Russ Altman, MD, PhD, chair of bioengineering. “The projects have quarterly milestones and can be killed by the oversight committee if the milestones are not met — this is not how academic grants usually go. There is

a very strong emphasis on keeping focused on what is needed for successful transfer to professional management via a start-up or a license to an existing company.



Paul Yock, MD

“Funding for this sort of work is hard to get from the NIH, so the existence of a fund in perpetuity to support this kind of work is incredibly valuable,” said Altman, who holds the Guidant Professorship for Applied Biomedical Engineering.

Paul Yock, MD, director of the Stanford Biodesign Program and associate chair for translational research in the bioengineering department, noted that bioengineering faculty do a range of research from basic to translational and that the translational work is not only in medicine but also in environmental and energy technologies. “The Coulter program focuses on the portion of a faculty member’s research that is directed toward the development of clinical technologies and is designed to help reduce the barriers of getting these discoveries moved into patient care,” said Yock.

Molecular-imaging expert Gambhir heads Stanford radiology department

Sanjiv “Sam” Gambhir, MD, PhD, a professor of radiology at the Stanford University School of Medicine and well-known leader in the field of molecular imaging, is the new chair of the school’s Department of Radiology.

In announcing the selection, medical school Dean Philip Pizzo, MD, said Gambhir is “internationally recognized for his incredible scientific contributions, and for training and educating the new generation of physicians and scientists focusing on molecular imaging. While there is also no doubt that the field of radiology and imaging will change dramatically in the years ahead, Stanford is clearly fortunate to have Dr. Gambhir carrying on the tradition of excellence in radiology and imaging science already established at Stanford.”

Gambhir, who is also the Virginia and D.K. Ludwig Professor in Cancer Research, has a diverse background, having trained in physics, applied mathematics, cell and molecular biology, medicine, nuclear medicine and molecular imaging — a field that focuses on the way organs and tissue operate at the cellular and sub-cellular levels. His research seeks to identify and manipulate molecules that can be used to image *in vivo* biological processes, such as cancer and cardiovascular disease.

Gambhir said he considers radiology to be one of

the most multidisciplinary fields in the realm of medicine, adding that he plans to continue encouraging collaborative projects in his new position, which he will take over on Sept. 1.

“My vision is to foster science without borders,” Gambhir said. “We need to break down traditional boundaries between disciplines and really take advantage of the excellent science ongoing in the schools of Medicine, Engineering, and Humanities and Sciences. I also want to build bridges to SLAC



Sam Gambhir, MD, PhD

by bringing fundamentally new ways to interrogate matter, including living matter, to clinical reality.” Gambhir said his other equally important goals as chair will be to significantly enhance patient care at Stanford Hospital & Clinics and Lucile Packard Children’s Hospital, and to train a new generation of physician-scientists who will continue to broaden the field of biomedical imaging. “This would be our greatest accomplishment – even over any major individual scientific discoveries,” he said.

The search process for the new chair was led by Robert Robbins, MD, professor and chair of cardiothoracic surgery and director of the Stanford Cardiovascular Institute.

Kobilka one of three medical school faculty elected as a member of the National Academy of Sciences

CVI researcher Brian Kobilka, MD, professor and chair of molecular and cellular physiology, was one of three medical school faculty who were recently elected to the NAS. Kobilka, who is also a professor of medicine, studies several aspects of the biology of adrenergic receptors. Adrenergic receptors form the interface between the sympathetic nervous system and the cardiovascular system and play a critical role in the regulation of cardiovascular function. Also elected were David Kingsley, PhD, professor of developmental biology and a Howard Hughes Medical Institute investigator; and Robert Malenka, MD, PhD, the Nancy Friend Pritzker Professor in Psychiatry and Behavioral Sciences, and director of the Nancy Friend Pritzker Laboratory.



Scientists receive \$5.7 million in new CIRM funding

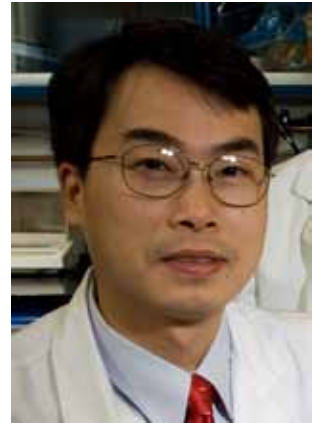
Four scientists at the Stanford University School of Medicine have been awarded a total of \$5.7 million by the state stem cell agency to investigate the basic mechanisms of stem cell biology, cellular plasticity and differentiation.

The awards were part of \$37.7 million distributed to 27 investigators from nine institutions by the California Institute for Regenerative Medicine in the third round of the agency's Basic Biology Awards. In addition, the organization's governing board also voted to award \$25 million to Geron Corp., based in Menlo Park, Calif., to fund the company's ongoing FDA-approved clinical trial of the use of neural support cells derived from human embryonic stem cells to repair damage from spinal cord injury. This is the first human clinical trial of a stem cell-derived therapy funded by the agency.

In January, Stanford and Santa Clara Valley Medical Center became the third site approved to participate in Geron's phase-1 clinical trial of the cells. The first patient was treated in October 2010 at the Shepherd Center in Atlanta; Stanford has not yet treated a patient. Up to 10 patients will be enrolled during the first phase of the trial at seven sites nationwide. "Supporting the Geron trial is a landmark step for CIRM," said board chair Robert Klein in a statement issued by the institute. "However, we must remember that there will be successes and interim failures as human trials proceed through the refinements necessary to achieve a successful human therapy. ... When the people of California voted for Proposition 71, they did so with the hope of seeing new therapies for disabling diseases like Alzheimer's disease, Parkinson's disease, diabetes and other chronic diseases and injuries. By funding this trial, CIRM is taking a major step toward making that hope a reality." Stanford scientists who each received \$1.42 million

Basic Biology Awards include:

- Michael Clarke, MD, the Karel H. and Avice N. Beekhuis Professor in Cancer Biology, to study the role of a gene involved in the self-renewal of stem cells in Down syndrome and cancer.
- Renee Reijo Pera, PhD, professor of obstetrics and gynecology and the director of Stanford's Center for Human Embryonic Stem Cell Research and Education, to correlate time-lapse studies and single-cell molecular analysis to better understand human embryo development.
- Joseph Wu, MD, PhD, associate professor of cardiovascular medicine and of radiology, to use induced pluripotent stem cells to study the molecular basis of familial hypertrophic cardiomyopathy, a leading cause of cardiac death in young people.
- Joanna Wysocka, PhD, assistant professor of developmental biology and of chemical and systems biology, to study how non-coding genetic regulatory regions called enhancers rapidly switch on the expression of genes to induce stem cell differentiation.



Joseph Wu, MD, PhD

With these grants, Stanford has now received a total of about \$192 million from CIRM — more than any other institution.

CIRM was established in November 2004 with the passage of Prop. 71, the California Stem Cell Research and Cures Act. The statewide ballot measure provided \$3 billion in funding for stem cell research at California universities and research institutions and required setting up the agency, CIRM, to oversee allocation of the money.

CVI students present displays at the Maker Faire

Students from the labs of CVI investigators Alex Dunn and Beth Pruitt presented hands-on displays at this year's Maker Faire to investigate manipulation of signal molecules of DNA and force sensors to probe the mechanobiology of touch sensation. Hundreds of children, adults, teachers, and inventors visited the displays to learn how mechanics influences basic life processes.

