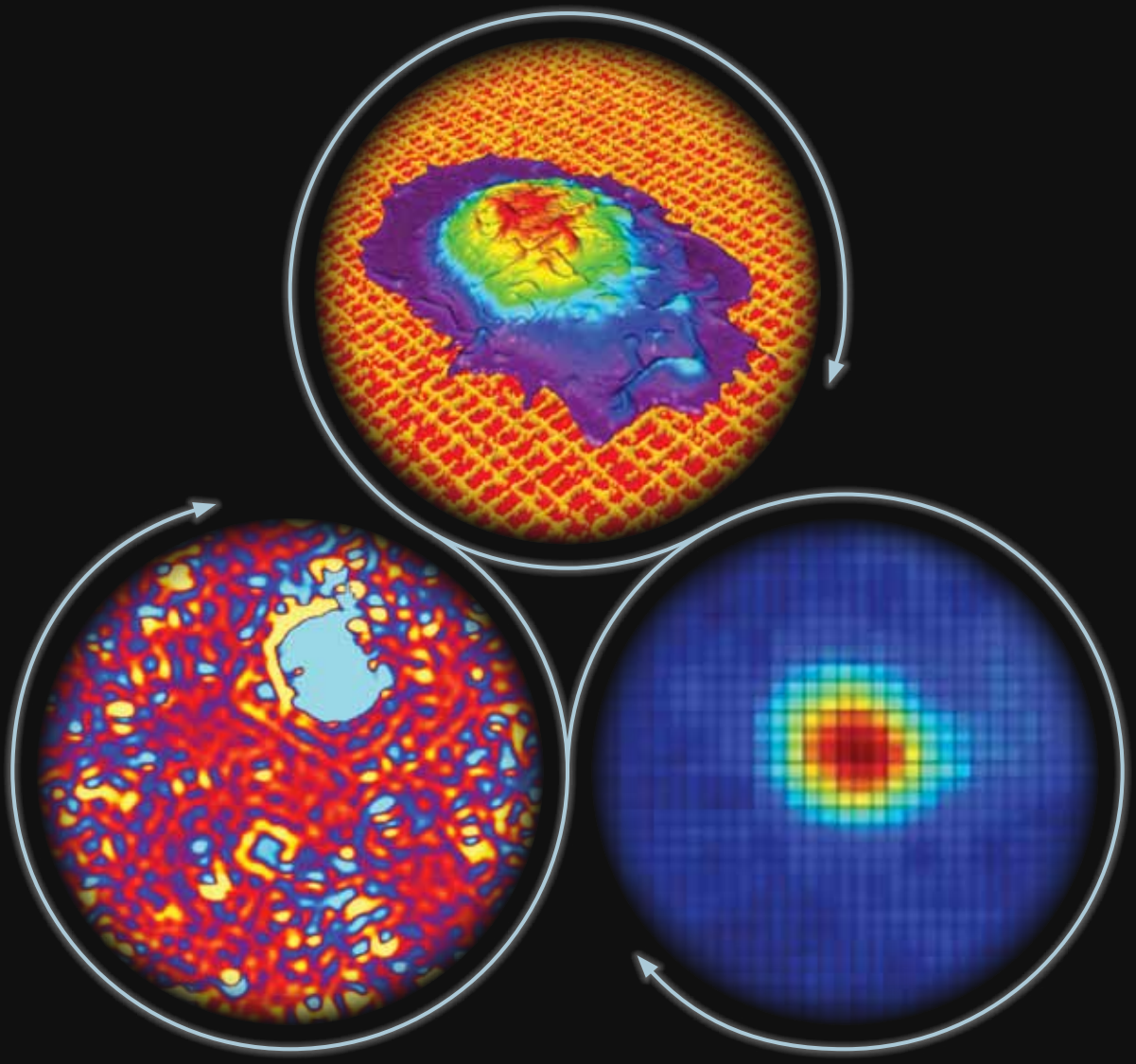
W. M. KECK FOUNDATION

2012 ANNUAL REPORT



DETECTION

New single molecule detection techniques are expanding our imaging and detection capabilities for applications in the medical, biological and physical sciences.

W. M. KECK FOUNDATION

2012 Annual Report

CHAIRMAN'S MESSAGE

Our ability to detect objects that are vanishingly small or incredibly distant continues to increase. These new capabilities are driven by technology: from van Leeuwenhoek's first magnifying lenses to today's atom-detecting electron microscopes, science has been driven by the instruments that make it possible to find, image, and measure that which has only been inferred, or perhaps not even theorized, in the past.

To stimulate thinking about new high-risk, high-impact innovations in instrumentation, the W. M. Keck Foundation was pleased this year to support a multi-disciplinary workshop on Single Molecule Detection and Imaging. Featuring 21 of our grantees, this symposium underscored the importance of developing new technologies and methodologies to enable scientific inquiry at scales not yet readily available to scientists. For example, the nucleus of a cell is at the micrometer scale; the DNA it contains is a mere 2.5 nm (a nanometer is a billionth of a meter) in diameter, which is beyond the reach of light microscopy. The work discussed by our grantees included investigations of phenomena occurring at the "meso" scale, which is loosely defined as spanning the scales between single atoms (0.1-0.5 nm) and classical systems. In materials science, mesoscale structures are between 100 nanometers and a few millimeters. This is a region where neither quantum theory nor classical laws governing bulk-material dynamics fully apply. At the mesoscale, assemblies of molecules create complexities that enable new functionalities yet to be explored.

I would like to take this opportunity to thank the distinguished experts who

chaired the panels for this meeting: John Hemminger, Scott Fraser, and Paul Weiss, and all the participants. While we cannot share all of the energy and excitement of these two days in the pages that follow, we are happy to share highlights of several of our grantees' presentations here.

I am pleased to report that the Foundation continues to prosper financially, with year-end total assets of $1.11 billion. We look forward to continued growth in 2013. In 2012 the directors approved 51 grants totaling $29.8 million, with nearly $45 million in distributions, including both prior commitments and new awards. These include a balanced portfolio of science research, undergraduate education and grants to benefit the Los Angeles community.

In our grantmaking, our primary focus remains on pioneering and potentially high-impact science that requires private philanthropic support so it can move forward. We also continue to be committed to promoting the arts, civic engagement and community services, early childhood and K-12 education, and health care programs in Los Angeles. Programs serving children, youth and families remain a special emphasis, as does support for innovative undergraduate education. Specifics about these programs can be found on our website.

Since we issued our last annual report, our board composition has changed. In April 2013, we sadly said good-by to Steve Ryan, who passed away after a brief illness. Steve, who was president of Doheny Eye Institute, joined the Foundation in 1996 and served as chair of the Medical Research Committee from 2006 until his death. Steve's wise counsel, exceptional scientific knowledge, and passion for innovative medical research have been an invaluable benefit to our board and staff. He was a good friend, and we will miss him.

At the end of 2012, two significant contributors to our board, Simon Ramo and Marsh Cooper, retired. Both have served the Foundation with distinction, wisdom and irreplaceable friendship. Their three-decade tenure saw the Foundation grow to over $1 billion from less than half that amount, during which time the board also approved charitable grants of nearly $1.5 billion. Si and Marsh's time at the Foundation will be remembered for their championing of cutting-edge science, engineering and

medical research and their service as valuable advisors. The members and directors of the Foundation join me in expressing their deep appreciation and thanks to Si and Marsh for their many years of service to the Foundation, to charity and to the public.

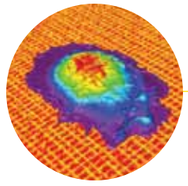
Even as we reluctantly accept the retirement of Si and Marsh, we are happy to welcome back to our board John Bryson, who most recently served as United States Secretary of Commerce and as the chairman, chief executive officer and president of Edison International. In addition, I am delighted to welcome three new directors: Jerry Carlton, the vice chairman of Oakmont Corporation and an attorney with the law firm of O'Melveny & Myers LLP for over 35 years; Maria Hummer-Tuttle, former co-managing partner of Manatt, Phelps & Phillips where she practiced law for over 25 years; and Sherry Lansing, current chairman of the Board of Regents of the University of California and former chairman and chief executive officer of Paramount Pictures Motion Picture Group.

There have been other constructive governance changes as well. I am happy to welcome Lucinda Day Fournier to our Executive Committee. I am very pleased that Jim Ukropina, chair of the Southern California and Liberal Arts Committee, agreed in June to become the President of the W. M. Keck Foundation. I have enjoyed working with Jim for many years in both the for-profit and not-for-profit arenas, and I will continue to rely on his extensive experience and good judgment as the Foundation moves forward.

W. M. Keck's success in part derived from his ability to drill for oil he inferred was beneath the ground from newly available seismograph data. His Foundation is proud to continue to fund innovators and inventors who design the instrumentation and methodologies to successfully extract new information from living and material systems. In this way, we hope to enable new explorations. You never know what you will find.

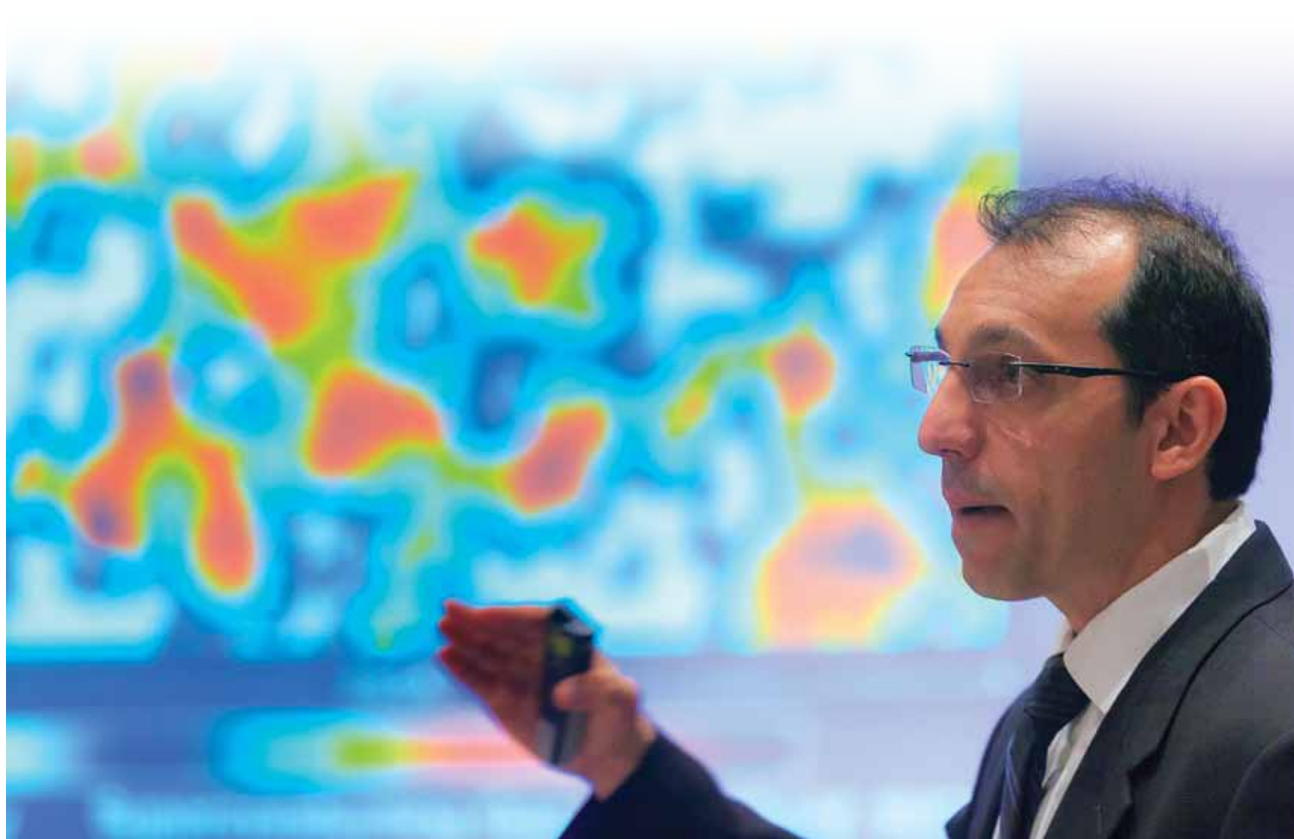
Sincerely,

ROBERT A. DAY
Chairman and Chief Executive Officer



DETECTION

On August 13-14, 2012, the W. M. Keck Foundation hosted its first workshop focused on a single interdisciplinary field: Imaging and Detection of Single Molecules. The workshop's overall goal was to assess the state of the art in instrumentation and technologies for detection and imaging of individual molecules in the physical, biological and medical sciences.



Workshop participants left to right: Steve Ryan and Ed Stone, Nongjian Tao, Gary Friedman, Miyoung Chun and Mat Varma, Mark Sherwin.

The Imaging and Detection of Single Molecules workshop participants were charged with identifying challenges and opportunities for technology development in this arena. Panelists were asked to address the following questions:

- What are the limitations of current technologies?
- What kind of basic understandings can be gained from detecting and imaging single molecules?
- Does combining different detection and imaging modalities provide unique windows for research?
- What are the challenges for *in vivo* detection and imaging?
- What are the opportunities for overcoming limitations on data collection, mining and interpretation?

The workshop was organized into three panels. Each panel was chaired by a distinguished expert: John Hemminger of UC Irvine for Physical Sciences, Scott Fraser of Caltech for Biological Sciences, and Paul Weiss of UC Los Angeles for Medical Sciences. The Foundation's perspective for the meeting was provided by Ed Stone and Steve Ryan. Dr. Stone is chair of the Keck Foundation's Science and Engineering Committee; Dr. Ryan served as chair of the Medical Research Committee. A list of all of the presenters is included at the end of this report.

Both in individual presentations and group discussions, the participants examined many lines of inquiry. While each has his or her "molecule of choice," they seek many of the same pressing answers, ranging from mass and chemical composition to a molecule's structure and interaction partners. To begin to answer these questions, contributors dreamed of novel instrumentation that is multi-modal (different observational approaches within the same instrument), multi-scale in regard to size (from sub nanometer to tens of microns), and multi-scale in regard to time (observations that last from femtoseconds to days), all without the loss of sensitivity or selectivity. Success in building such next-generation data acquisition tools, however, will bring a second concern by making today's data analysis challenges even more daunting. Handling the large datasets such instruments could record will require new hardware, theory and computational analysis strategies, including compressed sensing (efficient use of smaller but relevant data sets), and new knowledge extraction capabilities.

Consensus emerged around the "meso" scale, which is loosely defined as spanning the scales between single atoms and classical systems, as one size scale that deserves greater attention. New technological developments are required to make it more amenable to study. The participants also agreed that combining modalities and scales will be challenging, as is the hurdle of adding the fourth dimension of time. Imaging at depth, particularly in biological samples, presents another opportunity.

We were privileged to have had the opportunity to organize this workshop. The stories that follow are some of the highlights of research directions, strategies and opportunities presented at the meeting. ■

Above, top to bottom: Jean-Claude Diels, John Hemminger, Ali Yazadani.

Microscopy at its limits:

Detecting QUANTUM COHERENCE of Electrons

— PRINCETON UNIVERSITY —

BY PROBING ELECTRONS WITH FINER ENERGY, SPATIAL AND TIME RESOLUTION, THE NEW GENERATION OF MICROSCOPES IS ENABLING SCIENTISTS TO DETECT AND MANIPULATE QUANTUM PROPERTIES OF ELECTRONS IN MATERIALS AT UNPRECEDENTED RESOLUTION. THESE SPECIALIZED INSTRUMENTS ARE NEEDED TO ADDRESS SUCH QUESTIONS AS: HOW DO EXOTIC QUANTUM STATES, SUCH AS SUPERCONDUCTIVITY AT HIGH TEMPERATURES, EMERGE FROM ELECTRONS INTERACTING AT THE ATOMIC SCALE? HOW CAN WE HARNESS THE QUANTUM PROPERTIES OF ELECTRONS IN MATERIALS TO CREATE A NEW GENERATION OF QUANTUM ELECTRONICS?

Microscopes have played a pivotal role in science since Antonie van Leeuwenhoek advanced optical microscopy to then unthinkable spatial resolutions in the late 1600s, helping to create the discipline of microbiology. The invention of the scanning tunneling microscope (STM) in the 1980s caused a similar revolution in the science of materials by providing a tool that could image and even manipulate individual atoms. The STM operates by spatially mapping the local quantum mechanical interaction between a sharp tip and a surface of the sample.

With funding from the W.M. Keck Foundation in 2008, researchers at Princeton University, led by Professor of Physics Ali Yazdani, have created a new generation of STMs that are pushing the limits of measuring quantum behavior of electrons in solids. With the development of this state-of-the-art microscope, they are poised to crack some of the most challenging problems in the physics of materials.

The team's STM required construction of a microscope that operates at temperatures down to just 10 millikelvin above absolute zero. The ultra-low temperatures prevent thermal excitations, which cause unwanted distortions that blur the measurements. The team has devised a specialized low-noise measurement facility to isolate the instrument from seismic and acoustic vibrations and electrical noise. Together these capabilities are making it possible to map electron waves with micro-electron-volt energy and at pico-meter spatial resolutions. Perhaps the most unique feature of the instrument is the integration of advanced methods of probing the temporal response of electronic states with nano-second resolution. This allows the team to probe the quantum dynamics of electrons at the nanoscale.

Above: Maintaining the STM's ultra-low temperatures: the cryogenics and microscope head before insertion into the cryostat.

Over the last few years, the Princeton team has made several major breakthroughs. In one study, the team was able to visualize electron entanglement in complex metals with multiple orbitals. These entangled electrons behave like particles that are hundreds of times heavier than typical electrons moving in metals and semiconductors. The team is now investigating the role of these heavy electrons in the development of superconductivity, a project that will offer clues to the phenomena of high temperature superconductivity in ceramic oxides.

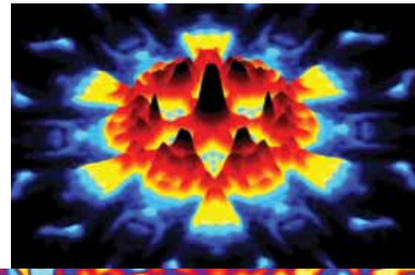
Scientists are poised to crack some of the most challenging problems in the physics of materials.

Yazdani's team is using their unique capability to examine how electrons move on the surface of a new class of compounds known as topological insulators. Unlike electrons in metals, or on the surface of ordinary insulators, topological surface electrons are not deflected when they encounter a defect. There have been a number of proposals for how this new class of topological quantum states can be used for quantum information processing.

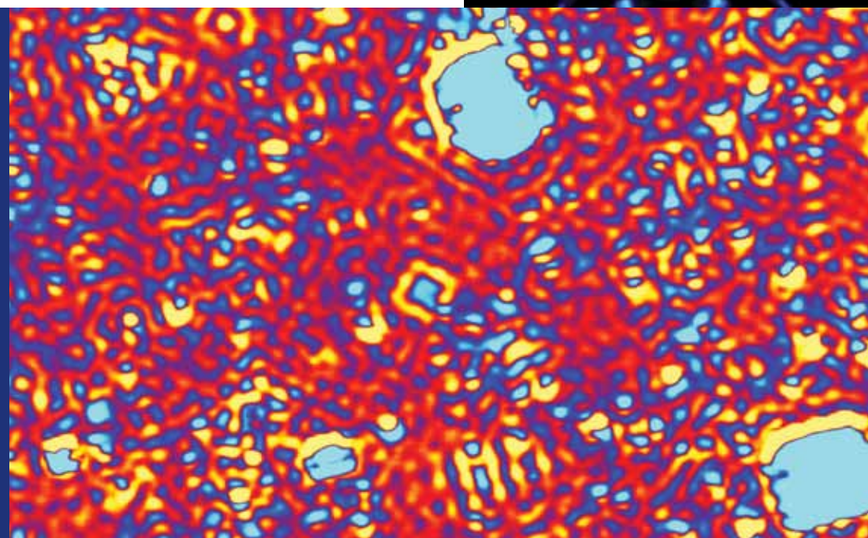
Looking to the future, the team is focusing on harnessing the time resolution of their STMs to assess how quantum coherence of single electron spins are influenced by their local environment in solid state systems. This is another step towards realizing a working quantum computer. That puts a new "spin" on an old idea. ■

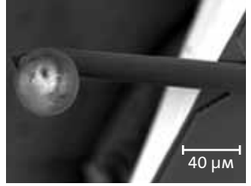
Below right: In topological insulators, Fourier analysis of STM data has demonstrated that electrons cannot make a U-turn when they scatter upon encountering defects in the material.

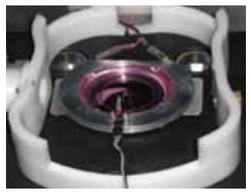
Bottom of page: Direct visualization of electron waves that behave as massive particles but superconduct at low temperatures.



→ Ultra high resolution imaging of electron waves is used to study how electrons can behave as heavy particles.







Above: View of the AFM cantilever with 40 micron glass sphere (top image). Cellular incubator for AFM single cell compression set up (bottom image).

Like squeezing a balloon:

CELL FORCE and MULTIMODAL IMAGING

— UNIVERSITY OF CALIFORNIA, DAVIS —

WHEN A CELL "LOOKS" WRONG AND "FEELS" WRONG, SOMETHING MAY BE WRONG. FOR THIS REASON, RESEARCHERS AT THE UNIVERSITY OF CALIFORNIA AT DAVIS ARE DEVELOPING NEW TECHNOLOGIES FOR PROBING CELLS' MECHANICAL PROPERTIES ASSOCIATED WITH ABNORMALITIES.

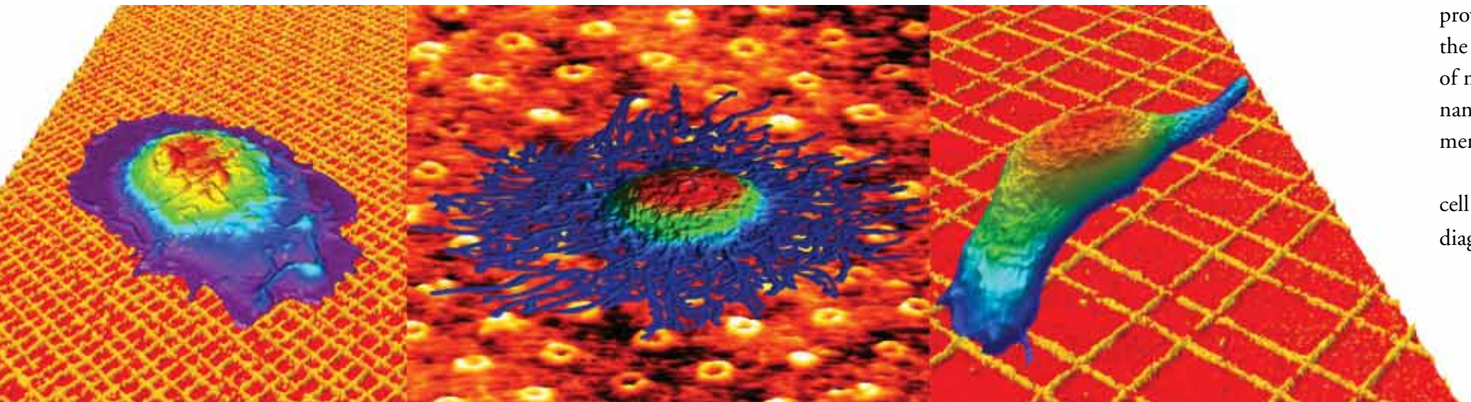
Cells' characteristic morphologies can be used to determine their biological state.

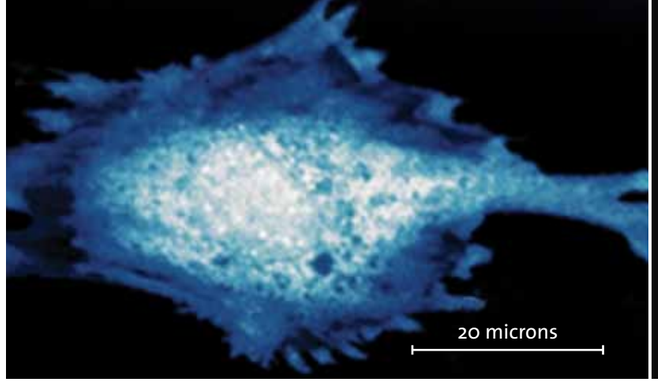
Humans have bones; cells have cytoskeletons. These protein filaments form a scaffold for intracellular transport and determine a cell's mechanical properties. These properties affect cell function, and are often altered in disease or aging. With help from the Keck Foundation in 2011, researchers at UC Davis are developing an instrument for simultaneously testing a cell's mechanical responses and obtaining a high resolution image of the cell membrane's local properties, such as height and friction.

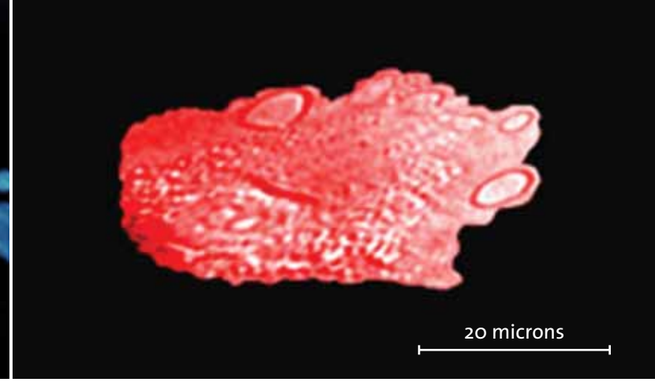
To achieve this goal, Gang-yu Liu and Ian Kennedy at UC Davis led their teams to develop a new method of multimodal imaging that integrates atomic force microscopy (AFM) and optical microscopy. They have modified an AFM probe tip with a 40-micron glass microsphere, which is about the diameter of a slender human hair. This new probe allows the team to apply a precise amount of pressure on a cell. As Dr. Liu explains, it is "like squeezing a balloon."

During compression of the cell, a force curve is recorded, creating the cell's compression profile. Confocal images monitor the cell's deformation,

Below: Bone marrow-derived mast cells interact with differentially patterned nanogrids.







Above left: Uncompressed control cell. Above right: Compressed cell treated with zinc oxide nanoparticles.

which can include blistering, bubbling or bursting of the cell membrane. In comparison to existing cell mechanics measurements, this method provides direct and independent measurements of force and elasticity. The team has demonstrated that different types of cells have distinct compression profiles.

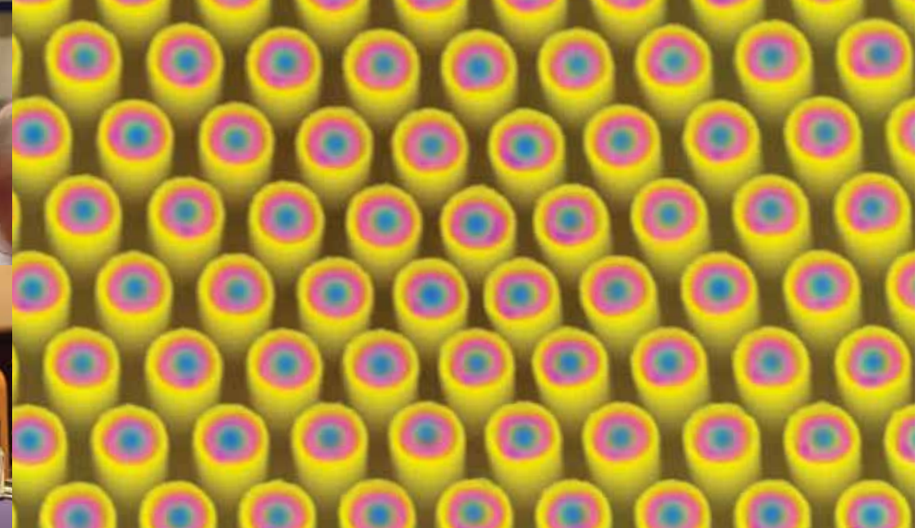
Liu and Kennedy use confocal microscopy to guide the position of the probe and monitor the cell response to compression. The multi-modal data available from this platform includes nanometer scale high resolution imaging of membrane structures (via AFM), 3D cellular imaging (via confocal microscopy), and cellular mechanics (from the force-deformation profile).

Establishing the parameters of "right" or "wrong" for a cell requires extensive studies to profile healthy and unhealthy cells during various cellular activities, such as signaling or responding to insult. For example, the team has studied bone marrow derived mast cells, which are involved in inflammation during allergic reactions. They showed that the cell membrane exhibits different morphologies depending on whether the cell is resting or activated. The activated mast cell's membrane has a very distinctive ridge-like structure, in contrast to the relatively smooth surface of resting cells. These preliminary investigations indicate that cells' characteristic morphologies can be used to determine their biological status. Importantly, by incorporating a microculture platform into the microscope design, these imaging and compression measurements can be performed in a near-physiological environment, helping to ensure the resulting data is biologically relevant.

The cell compression profiles generated by the new microscope provide a sensitive, reproducible measure of cell robustness. For example, the preliminary results indicate that cells become much stiffer upon uptake of nanomaterials. Calculations based on these measurements indicate that nanoparticles of zinc oxide are absorbed by cells, and are clustered in the membrane as well as the cytoskeleton.

In future studies, the team will explore using this approach to control cell signaling, to facilitate tissue engineering and development of new cancer diagnosis, and to develop an animal-free test of nanomaterial toxicity. ■

Below, top to bottom: Gang-yu Liu, Hrovje Petek, Michelle Digman and Norbert Scherer.



Above, top to bottom:
Mike Naughton, Akos Vertes, Aaron Dinner.

Top right: SEM image of a nanocoax array with Au cores (blue), Al_20_3 annuli (pink) and Cr shields (yellow). Magnified 10,000x, each coax is less than 1 micron in diameter.

A nanoscale coaxial optical microscope:

Beating the DIFFRACTION LIMIT

— BOSTON COLLEGE —

IN OPTICAL IMAGING, MICHAEL J. NAUGHTON AND KRIS KEMPA ARE DEVELOPING AN APPROACH TO NANOSCALE OPTICS THAT BRIDGES NEAR- AND FAR-FIELD OPTICS WITH SUB-DIFFRACTION-LIMITED RESOLUTION. THE BASIC CONCEPT IS A TYPE OF SUPER-LENSING – GOING BEYOND THE DIFFRACTION LIMIT – USING METAMATERIALS WITH SPECIFICALLY ENGINEERED PROPERTIES TO BUILD AN ARRAY OF NANOSCALE COAXIAL WAVEGUIDES.

The diffraction limit defines the minimum size of objects that can be resolved in microscopy, photography and telescopy. With visible light having wavelengths in the range of 400 to 700 nm, spatial resolution of conventional optical microscopy is limited to about 200-350 nm. Electron microscopes use beams of accelerated electrons of much smaller (deBroglie) wavelengths than those in light, and so can attain sub-nanometer resolution. Samples imaged by electron microscopes, however, are generally in a vacuum. As a result, there is an imaging gap for biological samples of cells, proteins and viruses that are too small to be seen by conventional optical microscopy, and too fragile to withstand a vacuum.

This gap is now being filled with a growing number of sophisticated schemes that abide by, yet effectively overcome, the diffraction limit. One such technology is Naughton's and Kempa's nanoscale coaxial optical microscope (NCOM), based on the ubiquitous coaxial cable and supported by Keck in 2010.

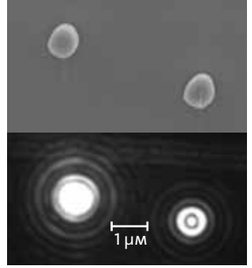
The basic scheme of the NCOM consists of a converging array of nanocoaxial cables that functions as a type of discrete objective lens, with each coax collecting light and delivering it to the distal end. As the inter-coax spacing is microscale (non-diffraction-limited), these distal "points of light" can be imaged by conventional optical microscopy. As long as the diameters of the coaxial cables are smaller than the length of the light wave, electromagnetic waves will, in principle, propagate with no cutoff. The team is also pursuing a plan to couple these distal ends directly to digital photodetectors, like those found in most of today's digital cameras.

There are, of course, many challenges to overcome. Fabricating the nanocoaxes is not trivial, and the team is pursuing several fabrication schemes in parallel, including coax core formation via direct-write focused ion beam deposition, electrochemical deposition in nanopores, metallization of nanoimprinted nanopillars, and electron beam nanolithography. The Boston College group will optimize techniques for assembling the arrays and must prove that the coaxes are capable of receiving, propagating, and broadcasting visible light. Here the team is again borrowing from radio technology, adopting the use of nano-antennae, to couple radiation to the coaxes.

There are many challenges that must be overcome to build such a device.

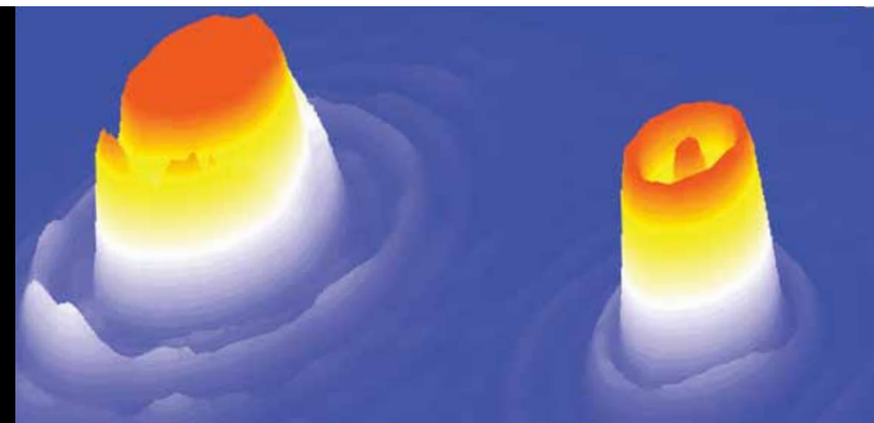
One of the modes in which a nanocoax can facilitate high spatial-resolution optical imaging is as an advanced near-field probe in a scanning mode environment, basically a nanocoax-enhanced near field scanning-optical microscope (NSOM). This could allow the NSOM technique to overcome the problem of low optical throughput, which translates to requiring high optical intensities and/or slow scan rates. Both are important considerations when imaging biological systems.

The team now has proof of principle for the NCOM, having demonstrated the transmission of light out of individual nanocoaxes. Above, a scanning electron microscope image reveals the top ends of the two coaxes, while the corresponding optical image reveals the light propagating from the bottom and out the top. These images demonstrate that it is possible to couple visible radiation to nanoscale coaxial cables. The world of nanoscale imaging of biological systems is not too far in the future. ■

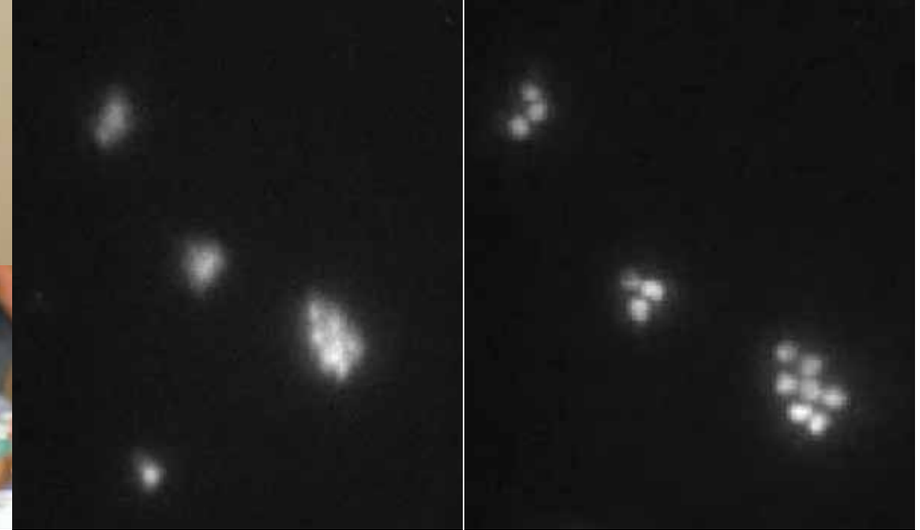


Above: SEM image of two nanocoaxes (top image). Optical micrograph of light projected out of the coaxes (bottom image).

→ **These images demonstrate that it is possible to couple visible radiation to nanoscale coaxial cables.**



Below: Intensity contour of projected light from the nanocoaxes.



Above, top to bottom: Natalie Ahn, Joel Kubby, Scott Fraser.

Above right: One micron beads imaged through 20 microns of *Drosophila* tissue without AO (left) and with AO (right).

From far to near:

ADAPTIVE OPTICS in Biology

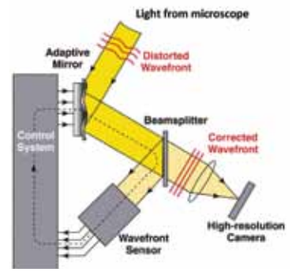
— UNIVERSITY OF CALIFORNIA, SANTA CRUZ —

ADAPTIVE OPTICS (AO), TECHNOLOGY THAT WAS ORIGINALLY DEVELOPED TO AID TELESCOPIC OBSERVATION OF DEEP SPACE BY CANCELING OUT ATMOSPHERIC DISTORTION OF STARLIGHT, IS NOW BEING USED BY RESEARCHERS AT THE UNIVERSITY OF CALIFORNIA AT SANTA CRUZ TO DRAMATICALLY IMPROVE REAL-TIME IMAGING AT DEPTH IN LIVING TISSUES AND ORGANS.

UC Santa Cruz has had a successful history pioneering adaptive optics for astronomy, including technology for the AO instrumentation for the Keck Telescopes on Mauna Kea. A team of engineers and physicists led by Joel Kubby has begun working with biologists to use the same principles to dramatically improve the resolution and signal-to-noise ratios that are barriers to deep-tissue, high-resolution optical microscopy. The team's innovative application of adaptive optics may enable biologists to study crucial processes at depth in living tissue. This has the potential to revolutionize our ability to understand, diagnose, and treat disease.

The challenges presented by deep-tissue biological imaging are similar to those faced by astronomers attempting to view objects in space from ground-based telescopes. In astronomy, light from space becomes severely distorted once it enters the Earth's turbulent atmosphere. In microscopy, light is similarly distorted as it traverses the opaque, turbulent cytoplasm of living tissues. Even with two-photon microscopy and cells labeled with bright fluorescent dyes, the image quality rapidly deteriorates at depths greater than 200 microns. With the new technology, the team hopes to increase high resolution imaging to depths of 1,000 microns, deep enough to study synaptic organization in the cortex of a mouse brain.

How does adaptive optics work? AO systems for telescopes use a point source of light – either a bright star or an artificial guide-star created by a laser – as a reference beacon for measuring atmospheric blurring. The adaptive optics system calculates the corrections needed to counteract the image distortion hundreds of times per second, then uses those calculations to configure a deformable mirror. When the guide star's light bounces off the properly deformed mirror, atmospheric distortion is removed from the signal, sharpening the signal from stars near the guide star. Likewise, biological AO attempts to correct the wavefront aberrations caused by light propagation through turbid biological samples.



Above, Adaptive optics for microscopy.

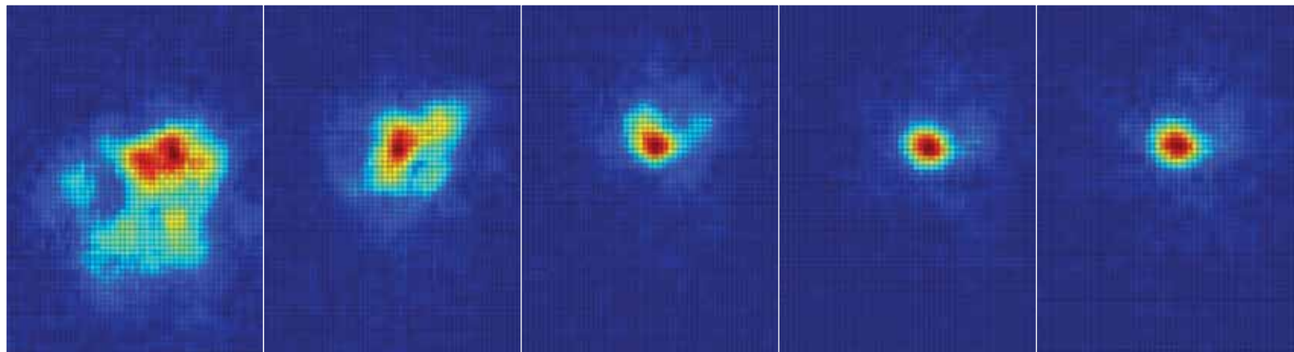
Some systems for biological AO have been developed, but to be most effective, they will need their own guide star. The team's biological guide stars are created using genetically modified, fluorescently tagged proteins. At the same time, they have developed an adaptive optics microscope with the sensing systems and deformable mirrors needed to take advantage of the guide stars. The group will first test this technology in model tissue systems, including fruit fly embryos.

> Adaptive optics microscopy will allow us to explore the structural and functional plasticity of synapses in the deeper cortex.

The deep imaging technologies being developed by Kubby and his colleagues could have broad applications, including the advancement of stem cell and brain function research, as well as clinically useful applications like the possible early diagnosis and treatment of cancer.

Among those planning to be an early adaptor of this technology is Kubby's collaborator Yi Zuo. Zuo will use adaptive optics microscopy to extend her research on synaptic reorganization in the brain during development and learning. "So far, most of our understanding of synaptic remodeling in living brains has been limited to the superficial cortical layers," Zuo said. "Adaptive optics microscopy will allow us to explore the structural and functional plasticity of synapses in the deeper cortex." ■

Below, left to right: Adaptive optics microscope corrections of a one micron bead located 20 microns beneath the surface of a *Drosophila* embryo.



As rare as a day in June:

FINDING Elusive Cells

— UNIVERSITY OF CALIFORNIA, BERKELEY —

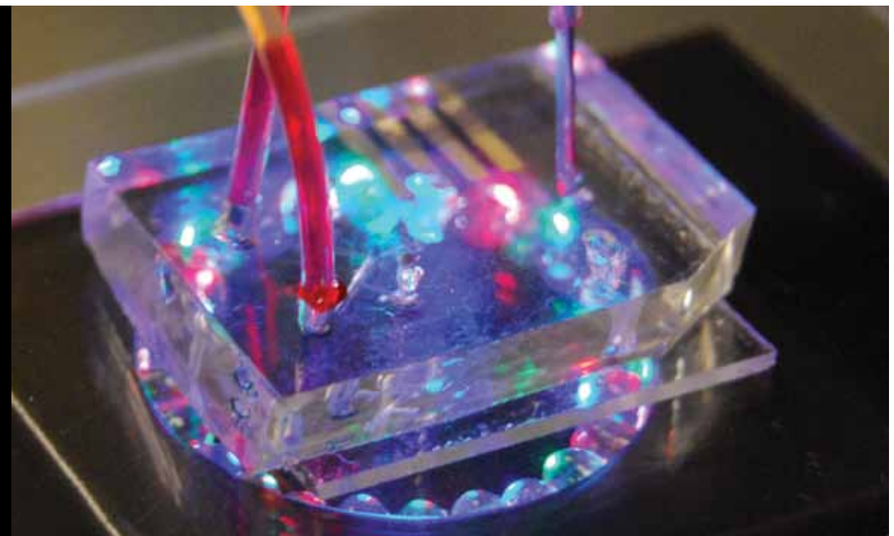
HOW DO YOU DETECT ONE RARE CELL IN A BILLION? IT IS AN IMPORTANT QUESTION FOR RESEARCH BIOLOGISTS AND CLINICIANS ALIKE. BIOLOGISTS MAY BE SEEKING THE ONE CELL THAT CAN REGENERATE TISSUE, WHILE CLINICIANS MAY SEEK THE ATYPICAL CELL THAT DETERMINES A DIAGNOSIS.

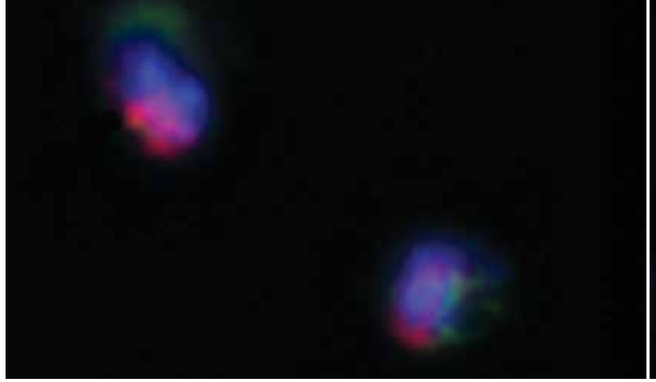
They were astonished that muscle stem cell functionality correlated with marker expression.

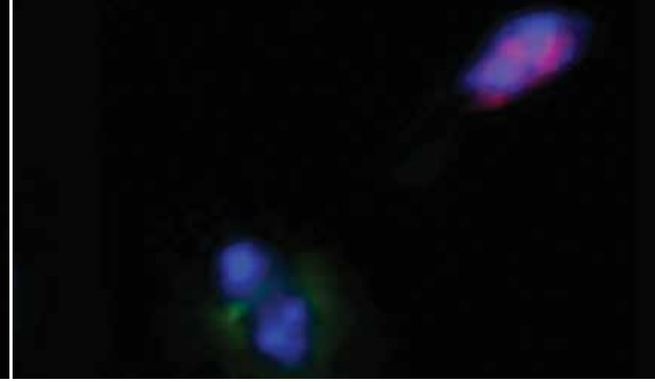
Traditional screening and detection methods rely on labeling cells with fluorescent molecules or quantum dot nanoparticles. These tags attach to specific protein markers on the surface of cells. Microscopy techniques are then used to image these fluorophores and hence the attached cells. This powerful technology is not without its limitations, however. For example, the process of labeling cells can result in losses, including rare cells, and the probes themselves can alter the very cellular properties researchers wish to study.

The Keck Foundation supported Lydia Sohn and her University of California at Berkeley lab in 2009 to develop an innovative, microfluidics-based technology for screening and sorting rare cells. This system sorts living cells from small sample sizes without the need for labels or complex sample processing. The team's platform records the current pulses caused when cells transit a microfluidic channel. The magnitude of each current pulse corresponds to the size of the cell, and the duration of the pulse corresponds to the time it takes the cell to transit the channel. This technique is called resistive-pulse sensing. These spatial and temporal measurements can be used to find cells with specific surface protein markers. When Sohn's team lines the microchannel with antibodies specific to the protein marker of interest, transient interactions between the cell-surface markers and the antibodies can be detected by how long the cell "lingers" in the channel.

→ Microfluidic resistive-pulse sensing platforms record current pulses as cells transit a channel.





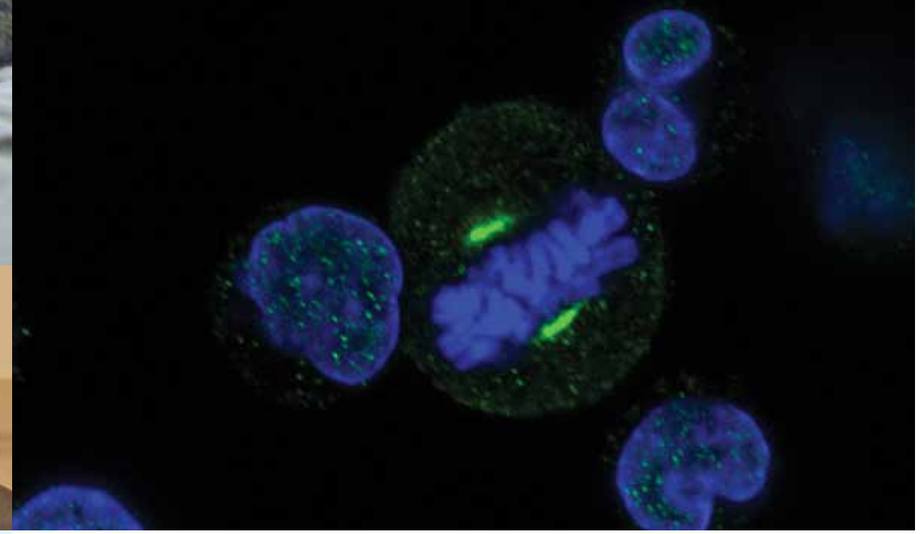


Above left: Sohn's microfluidic platform identified Sca1+/Pax7+ cells as muscle stem cells, contrary to expectations. Above right: Non-myogenic phenotypes. Colors indicate Sca1 (green), Pax7 (red), nucleus (blue).

With this technology in hand, Sohn has begun working with muscle tissue regeneration expert Irina Conboy to isolate muscle satellite cells – muscle stem cells – from single muscle fibers. These satellite cells are quiescent until the muscle is injured, after which they proliferate and become new muscle. Controversy surrounds the question of which surface protein markers scientists should use to identify these cells. Sohn and Conboy used the label-free detection method to examine cells directly from single muscle fibers rather than from bulk muscle, the traditional method. Their results surprised even them, revealing not only that muscle stem cells were not homogeneous, but that different muscle stem cells display different markers with a wide range of expression levels. They did not find some markers that were considered by the regeneration community to denote muscle stem cells. Other markers, thought to be uninformative, actually identified a very small population of cells that regenerated into muscle.

Since Sohn's label-free sorting does not alter the biology of the cells, she and Conboy could assay what the range of expression levels and markers meant. Again, they were astonished (and delighted) that they could correlate the functionality of the muscle stem cell with marker expression. Sohn's lab is now investigating the use of label-free detection for the identification, characterization, and isolation of rare circulating tumor cells and also fetal cells in maternal blood. They are also developing a method to screen for several surface markers simultaneously, and are introducing high resolution imaging to their platform. This will help them confront a complex question: what does the distribution pattern of receptors tell us about cell functionality? Each cell has its own story to tell. ■

Below, top to bottom: Enrico Gratton, Lydia Sohn, Paul Weiss.



Above, top to bottom: Deirdre Meldrum, Andrew Hillier, Joseph Ecker.

Top right: Live-cell CT will enable researchers to map spatial relationships between proteins (here, a 2D image of nuclear mitotic apparatus protein in green) and cellular compartments and structures in 3D and real time.

Cells in 3D:

Live Cell CT IMAGING

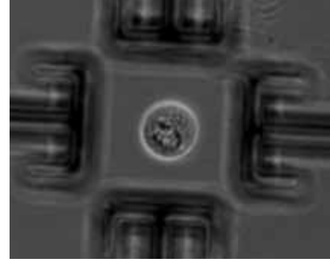
— ARIZONA STATE UNIVERSITY —

AS ANYONE WHO HAS HAD A RADIOLOGICAL CT SCAN KNOWS, COMPUTED TOMOGRAPHY (CT) SCANNING PROVIDES HIGH RESOLUTION THREE-DIMENSIONAL IMAGES OF TISSUE STRUCTURES. THESE ARE RECONSTRUCTED FROM HUNDREDS OF TWO-DIMENSIONAL IMAGES TAKEN AS THE IMAGER IS ROTATED AROUND THE PATIENT. IMAGINE IF THE LIVE CELLS THAT COMPOSE THESE TISSUES COULD SIMILARLY BE IMAGED IN THREE DIMENSIONS.

Current quasi-3D cell imaging methods require that the cells be grown or deposited on flat surfaces like microscope slides or glass-bottomed Petri dishes. Images are acquired as slices through the cell and assembled by a computer as a stack like a loaf of bread.

Deirdre Meldrum, with Roger Johnson and Laimonas Kelbauskas in the Center for Biosignatures Discovery Automation, are working to build an instrument that will instead image living cells suspended in a natural aqueous solution. This live-cell CT will be the next generation of the Cell-CT™ developed by VisionGate, Inc., that generates 3D images of cells fixed in a preservative medium. For true 3D live-cell CT, rare and interesting cells in solution can be selected, positioned and rotated with minute precision while being scanned by the Cell-CT. The cells can then be subjected to experimental treatments and imaged again, or harvested to be analyzed by genetic and proteomic studies.

It sounds straightforward, but precision rotation of the living cells is not trivial. The Meldrum team is investigating which of three strategies is best suited to their live-cell requirements. All strategies combine optical systems married with microfluidic and microelectronic components. One method spins cells in a microfluidic vortex, another propels the cells using dielectrophoretic forces (electrical fields), and the third uses asymmetric light traps to manipulate the cells.



Above: Time-sequenced high-frequency voltage applied to the eight microelectrodes exerts dielectrophoretic forces, rotating the cell they surround.

Careful attention is being given at each step to the effect of these manipulations on the cells themselves. This should ensure the images are free of artifacts of the tumbling and stress imposed on the cells, and true representations of the cell as it was in its original environment. Calculations estimating the stresses imposed on the cells by the device suggest that the researchers can expect to manipulate cells without compromising their data.

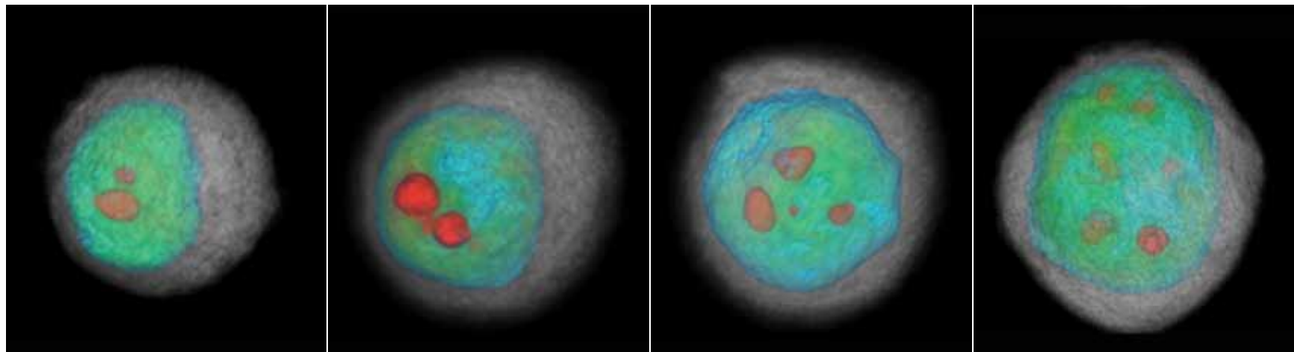
These 3D images promise to reveal the spatial and temporal relationships and interactions among differentially labeled proteins and cell structures (organelles). Early results in fixed cells have already revealed new diagnostic morphological features. The team believes their technology could reveal the molecular mechanisms underlying metabolic and disease processes, including cancer, making it a powerful tool for cell biology, clinical research and automated diagnostics.

These 3D images promise to reveal the spatial and temporal relationships and interactions among differentially labeled proteins and cell structures.

The targets for imaging – proteins and transcriptionally active chromatin regions – can be labeled fluorescently. Meldrum's team will validate their technology by studying cells from immortalized epithelial cell lines representative of various stages of esophageal cancer, and cells disaggregated from human biopsies spanning the same disease spectrum.

Early images will be similar in resolution to those available through confocal light microscopy, but with the significant analytical advantage of having uniform resolution in all directions. Meldrum has plans to extend the instrument's resolving power using light microscopy super-resolution techniques, including Stimulated Emission Depletion mode for data acquisition.

The ability to visualize and decipher 3D spatial plus temporal relationships among proteins, nucleic acids and cell structures will provide insights into many of today's challenging questions. Integrating statistics will yield biosignatures that could predict a person's disease status. The third dimension will add a new dimension to research and diagnostics. ■



Below: Cell-CT images of fixed cells progressing from normal cell (left) to invasive cancer cell (right). Live cell-CT will permit 3D images of live cells over time.

2012
GRANTS

MEDICAL RESEARCH

Broad Institute
Cambridge, MA
Feng Zhang
$1,000,000
To engineer a novel set of molecular tools – custom RNA binding proteins – that would enable researchers to manipulate gene expression levels in any animal model of choice.

J. David Gladstone Institutes
San Francisco, CA
Sheng Ding, Steven Finkbeiner, Shinya Yamanaka
$1,000,000
To develop a new methodology using small molecules to induce adult cells to become pluripotent and differentiate into various neuronal cell types.

Memorial Sloan-Kettering Cancer Center
New York, NY
Viviane Tabar
$500,000
To study the ability of tumor stem cells to develop into specific cell lineages, such as blood vessels, that aid the survival of the tumor.

Oregon Health & Science University
Portland, OR
Joe Gray
$1,000,000
To develop methodology for integrated fluorescence and electron microscopy to enable imaging of molecular assemblies with spatial resolution.

University of California, Berkeley
Berkeley, CA
David Schaffer, Mikhail Shapiro, Arash Komeili, Steven Conolly
$1,000,000
To develop genetically encoded magnetic reporters for magnetic resonance imaging in mammalian model systems.

University of California, San Diego
La Jolla, CA
Steven Dowdy, Yitzhak Tor
$1,000,000
To develop a unique class of small interfering RNA molecules that can self-deliver and thus allow researchers to knockdown gene expression inside cells.

University of Michigan
Ann Arbor, MI
Yukiko Yamashita
$500,000
To study non-random asymmetric chromosome segregation and its role in stem cell division and cell differentiation.

University of North Carolina at Chapel Hill
Chapel Hill, NC
Marcey Waters, Brian Strahl
$1,000,000
To generate new tools to characterize the methylation states of proteins especially those involved in the epigenetic control of gene expression.

University of Wisconsin, Madison
Madison, WI
Aseem Z. Ansari, Parameswaran Ramanathan, Jennifer Reed, David C. Schwarz
$1,000,000
To develop an integrated set of tools to design, fabricate, and assemble custom-made synthetic genomes for the production of novel materials in bacteria.

SCIENCE AND ENGINEERING RESEARCH

California Association for Research in Astronomy
Kamuela, HI
Peter Wizinowich
$1,500,000
To procure and install a new laser for the laser guide star Adaptive Optics system at the Keck Observatory.

Northwestern University
Evanston, IL
Neil Kelleher
$1,000,000
To develop a hybrid mass spectrometer to accelerate the Human Proteome Project.

Purdue University
West Lafayette, IN
Michael Manfra, Gabor Csathy
$1,000,000
To increase by tenfold the electron mobility in materials for research with two-dimensional electron gases.

University of California, Berkeley
Berkeley, CA
Geoff Marcy
$1,000,000
To develop a new instrument for discovering Earth-size planets around nearby stars.

University of California, Irvine
Irvine, CA
Derek Dunn-Ranking, Peter Taborek
$1,000,000
To build an experimental facility for the study of methane clathrate combustion and carbon dioxide sequestration under oceanic conditions of temperature and pressure.

University of California, Los Angeles
Los Angeles, CA
Paul Weiss
$1,000,000
To establish the field of imaging science by developing novel approaches based on data sparsity.

University of Houston
Houston, TX
Steven Baldelli, Kevin Kelly
$1,000,000
To develop a new instrument for the super resolution chemical imaging of surfaces.

University of Illinois at Urbana-Champaign
Champaign, IL
Scott Denmark
$1,000,000
To develop a new methodology for designing asymmetric catalysts guided by chemoinformatics.

University of Massachusetts at Amherst
Amherst, MA
Narayanan Menon
$1,000,000
To study the dynamics of newly discovered solid surfactant thin films.

University of Utah
Salt Lake City, UT
John Belz
$1,000,000
To develop a low-cost bistatic radar detector for studying ultra-high energy cosmic rays.

Special Grant

National Academy of Engineering Fund
Washington, DC
$500,000
To endow the Si Ramo Founders Award.

UNDERGRADUATE EDUCATION

California State University, Dominguez Hills
Carson, CA
H. Leonard Martinez
$200,000
To acquire a mass spectrometer for use by remote access in the chemistry program.

California State University, East Bay
Hayward, CA
James Murray
$250,000
To acquire a confocal microscope for teaching and research.

California State University, Stanislaus
Turlock, CA
S. Steve Arounsack
$250,000
To implement a new program incorporating research and coursework in visual anthropology.

Loyola Marymount University
Los Angeles, CA
Eric Strauss, Curtis Bennett
$250,000
To develop a program of training and mentoring for postdoctoral fellows.

Reed College
Portland, OR
Dena Hutto, Martin Ringle
$150,000
To develop resources and curricular approaches for developing scholarly research skills in mid-level students.

St. Edward's University
Austin, TX
Thomas Mitzel
$200,000
To develop a digital database of species relationships in a nearby wilderness preserve.

St. Mary's University
San Antonio, TX
Winston Erevelles
$250,000
To improve undergraduate engineering education and research by upgrading the Automated Manufacturing and Robotics Laboratory.

Trinity University
San Antonio, TX
Jennifer Steele
$250,000
To acquire a suite of microscopes for imaging and analyzing materials at the nanoscale.

University of San Francisco
San Francisco, CA
David Wolber
$200,000
To engage students in computer science by expanding and enhancing instruction on the creation of applications for mobile devices.

University of Utah
Salt Lake City, UT
Ian Harvey
$200,000
To expand a new undergraduate program that uses micro- and nano-chip fabrication to engage students and teach the science and engineering of scaling.

SOUTHERN CALIFORNIA

Arts and Culture

P. S. ARTS
Venice, CA
$250,000
To expand and sustain visual arts education in three Centinela Valley school districts by supporting the Take Part Initiative.

Venice Arts
Venice, CA
$150,000
To enhance and expand the Art Mentoring program serving low-income youth.

Civic and Community

Advancement Project
Los Angeles, CA
$250,000
To intervene earlier and improve outcomes for probation youth and their families by providing research-based recommendations to the Los Angeles County Probation Department.

Chrysalis Center
Santa Monica, CA
$200,000
To expand job preparation, placement and retention services by enlarging their Skid Row service center.

Enterprise Community Partners
Los Angeles, CA
$200,000
To create between 200 and 300 units of permanent supportive housing for homeless people through a capacity building initiative.

First Place for Youth
Oakland, CA
$200,000
To replicate a scattered-site supportive housing program for youth exiting Los Angeles County's foster care system.

Inner City Law Center
Los Angeles, CA
$150,000
To provide legal services for homeless veterans with a focus on female veterans.

LAMP Community
Los Angeles, CA
$150,000
To reduce service duplication and increase supportive housing placements for the most vulnerable homeless individuals on Skid Row.

Public Counsel Law Center
Los Angeles, CA
$250,000
To improve outcomes for probation youth with developmental disabilities by monitoring implementation of a legal settlement.

St. John's Well Child & Family Center
Los Angeles, CA
$250,000
To support a multi-agency collaboration to improve developmental outcomes for children age 0-5 in South Los Angeles at high risk of entering the foster care system.

Health Care

Direct Relief International
Santa Barbara, CA
$100,000
To expand the Replenishment Program that provides donated prescription medications to community clinics.

East Valley Community Health Center, Inc.
West Covina, CA
$250,000
To expand access to primary health care by renovating a larger facility to house the Pomona clinic.

UMMA Community Clinic
Los Angeles, CA
$250,000
To support a new school-based health and wellness center at Fremont High School in South Los Angeles.

Precollegiate Education

Alliance for College Ready Public Schools
Los Angeles, CA
$250,000
To improve student academic performance by supporting a blended learning high school program in Lincoln Heights.

College Bound - Dollars for Achievers
Cerritos, CA
$150,000
To support and enhance the middle-school STEM component of the college-access Saturday School Program serving under-represented students.

Level Playing Field Institute
Oakland, CA
$200,000
To expand the Summer Math and Science Honors Academy for low-income under-represented high school students at two local university campuses.

New Teacher Center
Santa Cruz, CA
$200,000
To facilitate the growth and retention of beginning teachers in Los Angeles Unified School District's most challenging schools through a teacher development program.

Pueblo Nuevo Development
Los Angeles, CA
$200,000
To complete a K-12 pathway for the Camino Nuevo Charter Academy by constructing a new middle school campus.

Spark Los Angeles
Los Angeles, CA
$150,000
To expand an apprenticeship program for middle school students to motivate them to stay in school and go to college.

University of California System
Oakland, CA
$100,000
To support the California State Summer School for Mathematics and Science (COSMOS), particularly for local, low-income, high-achieving high school students.

Special Grant

Southern California Public Radio
Pasadena, CA
$1,000,000
To support the digital component of an initiative to expand local news coverage.

2012

FINANCIAL STATEMENTS

December 31 (in thousands)	2012	2011
ASSETS		
Cash and cash equivalents	$ 54,209	$ 33,374
Receivable from brokers	1,852	399
Interest and dividends receivable	1,906	2,249
Prepaid federal excise taxes	–	925
Investments	1,045,645	985,321
Other assets	2,121	532
Total assets	$ 1,105,733	$ 1,022,800
LIABILITIES AND NET ASSETS		
Payable to brokers	$ 3,781	$ 899
Accounts payable and accrued expenses	1,930	1,664
Grants payable, net (*Note 5*)	15,476	16,939
Federal excise tax payable	45	–
Deferred federal excise taxes payable	2,616	1,070
Total liabilities	23,848	20,572
Unrestricted net assets	1,081,885	1,002,228
Total liabilities and unrestricted net assets	$ 1,105,733	$ 1,022,800

See accompanying notes.

Year Ended December 31 (in thousands)	2012	2011
REVENUE		
Interest	$ 8,662	$ 8,905
Dividends	6,548	6,883
Other income	673	288
	15,883	16,076
Realized and unrealized gains and losses on investments:		
Net realized gains	42,412	22,379
Change in net unrealized gains	77,307	(120,953)
	$ 119,719	$ (98,574)
Total revenues and net realized and unrealized gains and (losses) on investments	135,602	(82,498)
EXPENSES		
Grants	$ 43,490	$ 48,453
Management and general services	5,758	5,847
Investment management fees	3,964	4,019
Federal excise tax provision (benefit)	2,666	(2,002)
Foreign tax withheld	67	64
Total expenses	$ 55,945	$ 56,381
Change in unrestricted net assets	79,657	(138,879)
Unrestricted net assets, beginning of year	1,002,228	1,141,107
Unrestricted net assets, end of year	$ 1,081,885	$ 1,002,228

See accompanying notes.

Year Ended December 31 (in thousands)	2012	2011
OPERATING ACTIVITIES		
Change in unrestricted net assets	$ 79,657	$ (138,879)
Adjustments to reconcile change in unrestricted net assets to net cash used in operating activities:		
Depreciation and amortization	123	146
Accretion of bond discounts	(206)	(209)
Net realized gains on investments	(42,412)	(22,379)
Change in net unrealized gain on investments	(77,307)	120,953
Changes in operating assets and liabilities:		
Receivable from brokers	(1,453)	(380)
Interest and dividends receivable	343	(65)
Other assets	(1,663)	145
Prepaid federal excise taxes	970	417
Payable to brokers	2,883	882
Accounts payable and accrued expenses	266	(488)
Deferred federal excise taxes payable	1,546	(2,419)
Grants payable	(1,463)	(3,725)
Net cash used in operating activities	(38,716)	(46,001)
INVESTING ACTIVITIES		
Purchases of investments	(340,102)	(210,240)
Proceeds on disposition of investments and return of capital	399,702	269,296
Acquisition of fixed assets	(56)	–
Proceeds on disposition of fixed assets	7	–
Net cash provided by investing activities	59,551	59,056
Net increase in cash and cash equivalents	20,835	13,055
Cash and cash equivalents, beginning of year	33,374	20,319
Cash and cash equivalents, end of year	$ 54,209	$ 33,374
SUPPLEMENTAL DISCLOSURE		
Taxes paid during the year	$ 150	$ –

See accompanying notes.

1. ORGANIZATION

Formation and Goals of the Foundation

The W. M. Keck Foundation (the Foundation) was incorporated in the state of Delaware on January 20, 1959, as a not-for-profit charitable corporation. The Foundation's goals are principally to identify and support university and college research and education programs in the areas of science, engineering and medicine. In addition, the Foundation gives some consideration to promoting liberal arts education and, in Southern California only, to supporting community services, health care, precollegiate education, and the arts. Operations are funded by the Foundation's returns on its investment portfolio.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Grant Payments Made

In accordance with accounting standards for not-for-profit entities, unconditional grant payments are recognized as an expense in the period in which they are approved. If these grants are to be paid over a period exceeding one year, they are recorded at the net present value of the future cash payments, using an applicable Treasury Bill rate. Grants that are conditioned upon a future and uncertain event are expensed when these conditions are met or expected to be met in the subsequent year. A conditional promise to give is considered unconditional if the possibility that the condition will not be met is remote.

Cash and Cash Equivalents

Cash and cash equivalents are defined as liquid investments with remaining maturities of three months or less at time of purchase.

Investments

Investments in equity securities with readily determinable fair values and all investments in debt securities are measured at fair value in the statements of financial position. Fair value is established based on quoted prices from recognized securities exchanges.

Investments in private equity funds, commingled funds and hedge funds are measured at fair value, using the net asset value as a practical expedient, which is based on net asset values reported by the fund managers. Pursuant to provisions of ASU 2009-12, *Investments in Certain Entities that Calculate Net Assets Value per share (or its Equivalent),* the Foundation believes that the net asset value of these investments as of December, 2012 and 2011 approximates their fair value as of that date. However, because of the inherent uncertainty of valuation, the estimated fair values for the aforementioned securities and interests may differ from the values that would have been used had a ready market for the investments existed, and the differences could be material.

Purchases and sales of securities are recorded on the trade date. Dividend income is recorded based upon the ex-dividend date. Interest income is recorded as earned on an accrual basis. Realized gains and losses are recorded upon disposition of securities based on the specific identification method. Unrealized gains and losses are included in the statements of activities and represent the net change in fair value for investments held at the end of the year.

Fair Value of Financial Instruments

The Foundation's statements of financial position include but are not limited to the following financial instruments: cash and cash equivalents, accounts payable and accrued liabilities. The Foundation considers the carrying amounts of these assets and liabilities in the statements of financial position to approximate the fair value of these financial instruments because of the relatively short period of time between origination of the instruments and their expected realization.

Concentrations of Credit Risk

Financial instruments that potentially subject the Foundation to concentrations of credit risk consist of cash and cash equivalents and investments. The investment portfolio is managed within the investment guidelines established by the Board of Directors.

Fixed Assets

Fixed assets are carried at cost, less accumulated depreciation and are included in other assets in the statements of financial position. Depreciation is computed on the straight-line method over the estimated useful life of each type of asset or the term of the related lease, whichever is shorter. The depreciable lives for leasehold improvements are ten years and for furniture and equipment are five years.

Fair Value Measurement

The Foundation applies the principles of the accounting standard, *Fair Value Measurements and Disclosures*, for all financial assets and liabilities that are recognized or disclosed at fair value in the financial statements. This standard defines fair value, establishes a consistent framework for measuring fair value, and expands disclosure for each major asset and liability category measured at fair value on either a recurring or nonrecurring basis. The standard clarifies that fair value is an exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. As a basis for considering such assumptions, the Foundation establishes a three-level fair value hierarchy, which prioritizes the inputs used in measuring fair value as follows:

Level 1 – Assets that have readily observable prices (quoted prices in active markets accessible at the measurement date for assets). The fair value hierarchy gives the highest priority to Level 1 inputs.

Level 2 – Assets that are based on quoted prices for similar instruments in active markets, quoted prices for identical or similar instruments in markets that are not active, and model based valuation techniques for which all significant assumptions are observable in the market or can be corroborated by observable market data for substantially the full term of the assets or liabilities. Financial assets and liabilities in this category generally include asset-backed securities, corporate bonds and loans, municipal bonds, forward contracts, future contracts, interest and credit swap agreements, options and interest rate swaps.

Level 3 – Assets whose fair value cannot be determined by using observable measures, and can only be calculated using estimates or risk-adjusted value ranges, when little or no market data is available. The inputs into the determination of fair value require management's judgment or estimation of assumptions that market participants would use in pricing the assets or liabilities. The fair values are therefore determined using factors that involve considerable judgment and interpretations, including, but not limited to, private and public comparables, third-party appraisals, discounted cash flow models, and fund manager estimates. The fair value hierarchy gives lowest priority to Level 3 inputs.

Assets and liabilities measured at fair value are based on one or more of three valuation techniques noted in the tables below:

(a) *Market approach.* Prices and other relevant information generated by market transactions involving identical or comparable assets or liabilities.

(b) *Cost approach.* Amount that would be required to replace the service capacity of an asset (replacement cost).

(c) *Income approach.* Techniques to convert future amounts to a single present amount based on market expectations (including present value techniques, option-pricing and excess earnings models).

The Foundation's assets measured at fair value on a recurring basis at December 31, 2012, were as follows (in thousands):

	December 31, 2012			Valuation Technique
	Level 1	Level 2	Level 3	(a, b, c)
Assets:				
Common and Preferred Stock	$ 274,481	$ –	$ –	a
Corporate Bonds	–	65,624	–	a
Municipal Bonds	–	6,062	–	a
Government Bonds	16,759	900	–	a
Foreign Investments	10,849	11,254	–	a
Mortgage and Asset-backed Securities	–	29,708	–	a
Bank Loans	–	15,249	–	a
Mutual Funds	187,498	–	–	a
Private Equity Funds	–	–	85,210	c
Commingled Funds	–	183,095	–	a
Hedge Funds	–	158,956	–	a
Total	$ 489,587	$470,848	$ 85,210	

The Foundation's assets measured at fair value on a recurring basis at December 31, 2011, were as follows (in thousands):

	December 31, 2011			Valuation Technique
	Level 1	Level 2	Level 3	(a, b, c)
Assets:				
Common and Preferred Stock	$ 267,530	$ –	$ –	a
Corporate Bonds	–	63,681	–	a
Municipal Bonds	–	5,264	–	a
Government Bonds	5,933	1,140	–	a
Foreign Investments	30,234	13,329	–	a
Mortgage and Asset-backed Securities	–	36,132	–	a
Bank Loans	–	6,426	–	a
Mutual Funds	122,685	–	–	a
Private Equity Funds	–	–	77,350	c
Commingled Funds	–	153,444	–	a
Hedge Funds	–	202,173	–	a
Total	$ 426,382	$ 481,589	$ 77,350	

The Foundation has classified its mutual funds, equity securities, preferred stock and certain of its government bonds and foreign investments which have quoted prices in active markets as Level 1 within the fair value hierarchy. These securities are valued under the market approach using inputs observable in active markets for identical securities. The Foundation has classified its government bonds, corporate bonds, municipal bonds, mortgage and asset-backed securities, bank loans, commingled funds and hedge funds as Level 2 investments. The fair value of these assets is valued under the market approach using inputs observable in active markets for similar assets. The Foundation has classified its private equity funds as Level 3 investments. The fair value of the underlying assets in private equity funds are valued under the income approach using discounted cash flows and other inputs not observable in active markets.

The table below sets forth a summary of changes in fair value of the Level 3 assets for the years ended December 31, 2012 and 2011 (in thousands):

Year Ended December 31	2012	2011
Balance – beginning of year	$ 77,350	$ 67,687
Additions	$ 11,186	$ 23,604
Distributions	$ (4,625)	$ (7,302)
Change in fair value	$ 1,299	$ (6,639)
Balance – end of year	$ 85,210	$ 77,350

The cumulative unrealized losses in Level 3 assets held at December 31, 2012 and 2011 (as reported in the summary of changes in fair values above) were $18,720,000 and $20,019,000, respectively.

Subsequent Events

The Foundation's management has evaluated subsequent events through May 15, 2013, which is the date these financial statements were available to be issued. Management has determined that no material subsequent events have occurred during that period that would require the Foundation to either recognize the financial impact of such events in the accompanying financial statements or disclose any such events to ensure the financial statements are not misleading.

New Accounting Standards

In May 2011, the FASB issued ASU No. 2011-04, *Fair Value Measurements (Topic 820), Amendments to Achieve Common Fair Value Measurement and Disclosures Requirements in U.S. GAAP and IFRSs.* The amendments in ASU 2011-04 changed the wording used to describe many of the requirements in U.S. generally accepted accounting principles for measuring fair value and for disclosing information about fair value measurements. The ASU is effective for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2011. The Foundation adopted this guidance effective January 1, 2012 and the adoption of the standard did not have a material impact on the Foundation's financial statements.

3. INVESTMENTS

The cost and fair value of investments are as follows (in thousands):

	December 31, 2012		December 31, 2011	
	Cost	Fair Value	Cost	Fair Value
Common and Preferred Stock	$ 207,860	$ 274,481	$ 209,238	$ 267,530
Corporate Bonds	59,643	65,624	61,216	63,681
Municipal Bonds	4,707	6,062	4,489	5,264
Government Bonds	17,586	17,659	7,009	7,073
Foreign Investments	20,548	22,103	48,259	43,563
Mortgage and Asset-backed Securities	28,754	29,708	34,822	36,132
Bank Loans	14,979	15,249	6,460	6,426
Mutual Funds	204,017	187,498	152,635	122,685
Private Equity Funds	103,930	85,210	97,369	77,350
Commingled Funds	156,677	183,095	156,677	153,444
Hedge Funds	96,183	158,956	153,693	202,173
	$ 914,884	$ 1,045,645	$ 931,867	$ 985,321

The change in net unrealized gains (losses) on investments is reflected in the statements of activities and is summarized as follows (in thousands):

Year Ended December 31	2012	2011
Net unrealized gains, beginning of year	$ 53,454	$ 174,407
Add net unrealized gains (losses) on investments for the year	$ 77,307	$ (120,953)
Net unrealized gains, end of year	$ 130,761	$ 53,454

The Foundation has made total capital contributions (net of distributions/return of capital) of $356,790,000 to five private equity funds, three commingled funds and two hedge funds it holds as of December 31, 2012. The commingled funds can be redeemed on a monthly basis and are primarily invested in Level 1 equity securities in the international and emerging markets. The hedge funds can be redeemed on a quarterly or annual basis and are primarily invested in Level 1 equity securities (U.S. and international) and some corporate bonds and various other Level 2 investments. The private equity funds are primarily invested in life sciences, biotechnology and energy companies which are valued using Level 3 inputs and are subject to lock up provisions ranging from 0 to 7 years subject to certain further extension adjustments. The Foundation has a total future capital commitment related to five private equity funds of $33,015,000 as of December 31, 2012.

4. TAXES

The Foundation qualifies as a tax-exempt organization under Section 501(c)(3) of the Internal Revenue Code and, accordingly, is not subject to federal income taxes. However, the Foundation is classified under the Internal Revenue Code (IRC) as a private foundation and, as such, is subject to a federal excise tax.

During 2012, the Foundation accrued a 2% excise tax on net investment income. Private foundations are required to distribute annually, in qualifying charitable distributions, an amount equal to approximately 5% of the average fair market value of the Foundation's assets (the minimum distribution). If the Foundation does not distribute the required minimum distribution, a one-year grace period is granted to distribute the undistributed income. Under IRC §4942(a), if undistributed income is not distributed by the close of the following year, a minimum penalty of 30% of such undistributed income will apply. The Foundation's annual distributions were in excess of the required minimum for 2012 and 2011 to avoid the 30% penalty. Although the Foundation does have cumulative undistributed income at December 31, 2012, based on the Foundation's distribution history, the Foundation will be able to and intends to distribute the cumulative undistributed income from December 31, 2012, in 2013. Accordingly, the Foundation has not accrued a liability for the penalty on undistributed income. The Foundation uses the liability method for accounting for excise taxes. The federal excise tax provision (benefit) consists of the following (in thousands):

Year Ended December 31	2012	2011
Current	$ 1,120	$ 417
Deferred	$ 1,546	$ (2,419)
	$ 2,666	$ (2,002)

Deferred federal excise taxes have been recorded at a tax rate of 2% of the unrealized appreciation in the fair value of investments in 2012 and 2011.

The Foundation completed an analysis of its tax positions, in accordance with FASB ASC 740, *Income Taxes*, and determined that there are no uncertain tax positions taken or expected to be taken. The Foundation has recognized no interest or penalties related to uncertain tax positions. The Foundation is subject to routine audits by the taxing jurisdictions; however, there are currently no audits in progress for any tax periods (tax year 2010 through 2012 remain open and subject to selection for such routine audits).

5. GRANTS PAYABLE AND CONDITIONAL GRANT COMMITMENTS

Grants payable and conditional grant commitments as of December 31, 2012, are as follows (in thousands):

	Unconditional	Conditional
2013	$ 15,476	$ 450
2014–2017	–	41,982
2018 and thereafter	–	105,000
	15,476	$ 147,432
Less present value discount	–	
	$ 15,476	

Projected timetable and payment amounts shown above for conditional grants are estimated. Conditional grants will be recorded as an expense in the period when the conditions to the grant are met. These grants are conditioned upon other donors matching the amounts contributed by the Foundation, receipt of building permits and other regulations, and compliance with budget, timetable, and grant agreements' requirements.

Conditional grants outstanding as of December 31, 2012, consist of the following (in thousands):

Grantee	Date of Original Commitment	Original Commitment	Amount Outstanding*
National Academy of Sciences	2002	$ 40,345	$ 8,882
California Institute of Technology	2007	24,000	3,000
University of Southern California	2011	150,000	135,000
Other	Various	650	550
		$ 215,195	$ 147,432

* Only reflects the portion of the grant that remains conditional.

6. LEASE COMMITMENTS

The Foundation leases its main office space. Annual base rent is $435,000, which is payable through 2014. The term of the Foundation's lease expires in 2019, unless the Foundation accelerates termination. Rent expense is recognized on a straight-line basis over the lease term. As of December 31, 2012, the approximate future minimum scheduled lease obligation for the lease is as follows:

Year Ended December 31	
2013	$ 435,000
2014	444,000
2015	544,000
2016	544,000
2017	544,000
Thereafter	1,041000
	$ 3,552,000

Total rental expense for each of the years ended December 31, 2012 and 2011, was approximately $413,500 and $413,500, respectively. Deferred rent was approximately $692,000 and $713,000 at December 31, 2012 and 2011, respectively.

7. EMPLOYEE RETIREMENT PLAN

The Foundation maintains a qualified 401(k) Profit Sharing Plan (the Plan) for eligible employees. Employees can contribute a percentage of their pretax compensation subject to IRS limitations. The Foundation matches 200% of the employee's deferral, but not more than 6% of the employee's compensation in total. The Foundation's matching contributions to the Plan were approximately $242,000 and $242,000 for the years ended December 31, 2012 and 2011, respectively.

8. RELATED-PARTY TRANSACTIONS

A director and an officer of the Foundation are partners of a law firm that provided legal services to the Foundation. The Foundation incurred legal fees for services provided by the law firm totaling $450,000 and $450,000 for the years ended December 31, 2012 and 2011.

The Board of Directors of
the W. M. Keck Foundation

We have audited the accompanying financial statements of the W. M. Keck Foundation, which comprise the statements of financial position as of December 31, 2012 and 2011, and the related statements of activities, and cash flows for the years then ended, and the related notes to the financial statements.

MANAGEMENT'S RESPONSIBILITY FOR THE FINANCIAL STATEMENTS

Management is responsible for the preparation and fair presentation of these financial statements in conformity with U.S. generally accepted accounting principles; this includes the design, implementation, and maintenance of internal control relevant to the preparation and fair presentation of financial statements that are free of material misstatement, whether due to fraud or error.

AUDITOR'S RESPONSIBILITY

Our responsibility is to express an opinion on these financial statements based on our audits. We conducted our audits in accordance with auditing standards generally accepted in the United States. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statements. The procedures selected depend on the auditor's judgment, including the assessment of the risks of material misstatement of the financial statements, whether due to fraud or error. In making those risk assessments, the auditor considers internal control relevant to the entity's preparation and fair presentation of the financial statements in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control. Accordingly, we express no such opinion. An audit also includes evaluating the appropriateness of accounting policies used and the reasonableness of significant accounting estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

OPINION

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of the W. M. Keck Foundation as of December 31, 2012 and 2011, and the changes in its net assets and its cash flows for the years then ended in conformity with U.S. generally accepted accounting principles.

Ernst & Young LLP

May 15, 2013

2013

DIRECTORS, OFFICERS AND COMMITTEES

W. M. KECK FOUNDATION DIRECTORS, OFFICERS AND COMMITTEES, 2013**

FOUNDING MEMBERS

W. M. Keck, Sr.
Chairman, 1954 – 1964

Howard B. Keck
Chairman, 1964 – 1995

Naurice G. Cummings
Willametta Keck Day
Dr. Benjamin Hager
W. M. Keck, Jr.
Harold C. Morton

OFFICERS

Robert A. Day
Chairman and
Chief Executive Officer

Matt Day, Sr.
Vice Chairman

James R. Ukropina
President

Howard B. Keck, Jr.
Vice President

Allison M. Keller
Vice President, Executive Director and Chief Financial Officer

Dr. Maria Pellegrini
Executive Director of Programs

Stephanie L. Pulc
Secretary

MEMBERS AND DIRECTORS

James A. Baker, III
Peter K. Barker
John E. Bryson
Jerry Carlton
Dorothy W. Day*
Matt Day, Sr.
Matt Day, Jr.*
Robert A. Day
Tammis A. Day*
Theodore J. Day
Joseph Deegan-Day
Dr. Thomas E. Everhart
Brian A. Finch*
Dr. Richard N. Foster
Lucinda Day Fournier
Bradford Freeman
Maria Hummer-Tuttle
Brighton Keck*
Charisse Keck*
Erin A. Keck*
Howard B. Keck, Jr.
Stephen M. Keck
Theodore J. Keck
W. M. Keck II
W. M. Keck III
John E. Kolb
Kent Kresa
Sherry Lansing
James Paul Lower
Kerry K. Mott
Nelson Rising
Dr. Stephen J. Ryan
Dr. Edward C. Stone, Jr.
The Hon. David A. Thomas
James R. Ukropina
Sean Vaughan*

*Member only
**as of 1/1/2013

EXECUTIVE COMMITTEE

Robert A. Day
Chairman

James A. Baker, III
Peter K. Barker
John E. Bryson
Jerry Carlton
Matt Day, Sr.
Dr. Richard N. Foster
Joseph Deegan-Day
Lucinda Day Fournier
Bradford Freeman
Maria Hummer-Tuttle
Howard B. Keck, Jr.
Stephen M. Keck
W. M. Keck II
Kent Kresa
Sherry Lansing
Nelson Rising
Dr. Stephen J. Ryan
Dr. Edward C. Stone, Jr.
James R. Ukropina

AUDIT COMMITTEE

Peter K. Barker
Chairman

Jerry Carlton
Matt Day, Sr.
Theodore J. Day
Bradford Freeman
Maria Hummer-Tuttle
Howard B. Keck, Jr.
W. M. Keck II
Nelson Rising

LEGAL AND GOVERNANCE COMMITTEE

James R. Ukropina
Chairman

Brian A. Finch
John E. Kolb
James Paul Lower
The Hon. David A. Thomas

COMPENSATION COMMITTEE

Peter K. Barker
Chairman

Matt Day, Sr.
Robert A. Day
Dr. Stephen J. Ryan
Dr. Edward C. Stone, Jr.
James R. Ukropina (Ex Officio)

INVESTMENT COMMITTEE

Robert A. Day
Chairman

Peter K. Barker
Jerry Carlton
Matt Day, Sr.
Bradford Freeman
Stephen M. Keck
James Paul Lower
James R. Ukropina

GRANT COMMITTEES

Medical Research

Dr. Stephen J. Ryan
Chairman

Peter K. Barker
Matt Day, Sr.
Robert A. Day
Theodore J. Day
Dr. Richard N. Foster
Stephen M. Keck
W. M. Keck III
John E. Kolb
Kent Kresa
Sherry Lansing

Science and Engineering

Dr. Edward C. Stone, Jr.
Chairman

John E. Bryson
Jerry Carlton
Matt Day, Sr. (Ex Officio)
Robert A. Day
Joseph Deegan-Day
Dr. Richard N. Foster
Howard B. Keck, Jr.
Theodore J. Keck
Kent Kresa

Southern California and Liberal Arts

James R. Ukropina
Chairman

Peter K. Barker
John E. Bryson
Matt Day, Sr. (Ex Officio)
Robert A. Day
Joseph Deegan-Day
Lucinda Day Fournier
Maria Hummer-Tuttle
The Hon. David A. Thomas

GRANT PROGRAMS

Dr. Maria Pellegrini
Executive Director of Programs

Dr. Matesh Varma
Senior Program Director

Dr. Dorothy Fleisher
Program Director

Roxanne Ford
Program Director

Mercedes V. Talley
Program Director

SENIOR SCIENTIFIC ADVISOR

Dr. Thomas E. Everhart

LEGAL COUNSEL

Hanna and Morton LLP
Los Angeles, California

INDEPENDENT PUBLIC ACCOUNTANTS

Ernst & Young
Los Angeles, California

PUBLIC RELATIONS

Longview Communications Inc.
Vancouver, BC

THE W. M. KECK FOUNDATION

550 SOUTH HOPE STREET, SUITE 2500, LOS ANGELES, CALIFORNIA 90071

TEL: 213.680.3833

www.wmkeck.org

ACKNOWLEDGEMENTS

Thank you to the many people who graciously offered their time and expertise to tell these stories,
and who allowed their work and scientific images to be used:
Joel Kubby, Gang-yu Liu, Deirdre Meldrum, Michael J. Naughton, Lydia Sohn, and Ali Yazdani

IMAGE CREDITS

PAGES 8 AND 9 AND COVER:
Yazdani Lab

PAGES 10 AND COVER:
Jie-ren Li, Naining Yin, Zhao Deng, Kang-hsin Wang,
Shawn Riechers, Futong Liu and Gang-yu Liu

PAGE 11:
Ying X. Liu, Guohua Yang, Christopher C. Zimmer,
Joshua T. Morgan, Kanghsin Wang, Abdul I. Barakat,
Ian M. Kennedy, and Gang-yu Liu

PAGE 12 AND 13:
Naughton Lab

PAGE 14:
Oscar Azucena, UCSC

PAGE 15:
TOP: Lawrence Livermore National Lab and
NSF Center for Adaptive Optics
BOTTOM AND COVER: Oscar Azucena, Justin Crest,
Jian Cao, William Sullivan, Peter Kner, Donald Gavel,
Daren Dillon, Scot Olivier, Joel Kubby

PAGE 16:
Karthik Balakrishnan and Trongtuong Ngyuen, Sohn Laboratory

PAGE 17:
Ju Li, Conboy Laboratory

PAGE 18:
Honor Glenn in the Meldrum Lab

PAGE 19:
TOP: Iniyan Soundappa Elango, Matthew Stanley,
Roger Johnson, Deirdre Meldrum

BOTTOM: Vivek Nandakumar, Roger Johnson, Deirdre Meldrum
Images taken on the Cell-CT™
(VisionGate, Inc., Phoenix, AZ)

SINGLE MOLECULE DETECTION AND
IMAGING WORKSHOP PRESENTERS

Physical Sciences
John Hemminger, Chair | University of California, Irvine
Andrew Hillier | Iowa State University of Science & Technology
Ali Yazdani | Princeton University
Michael J. Naughton | Boston College
Nongjian Tao | Arizona State University
Hrvoje Petek | University of Pittsburgh

Biological Sciences
Scott Fraser, Chair | California Institute of Technology
Mark Sherwin | University of California, Santa Barbara
Gary Friedman | Drexel University
Jean-Claude Diels | University of New Mexico
Norbert Scherer and Aaron Dinner | University of Chicago
Enrico Gratton | University of California, Irvine
Deirdre Meldrum | Arizona State University
Joel Kubby | University of California, Santa Cruz

Medical Sciences
Paul Weiss, Chair | University of California, Los Angeles
Akos Vertes | George Washington University
Natalie Ahn | University of Colorado at Boulder
Lydia Sohn | University of California, Berkeley
Gang-yu Liu | University of California, Davis
Joseph Ecker | Salk Institute of Biological Sciences

For the W. M. Keck Foundation:
Steven J. Ryan
Edward C. Stone
Allison Keller
Maria Pellegrini
Mat Varma

Printed on Recycled Paper

Printing: COLORGRAPHICS

Photography: PAUL KENNEDY

Design: THE JEFFERIES ASSOCIATION