In Memoriam

Samuel Abraham, PhD
September 23rd, 1923 – March 16th, 2012

We are deeply saddened by the loss of Dr. Samuel (Sandy) Abraham, PhD, who after 88 ½ years of living, learning and teaching, passed away this spring. A preeminent scientist in the field of lipid and carbohydrate metabolism, Sandy was the director of the Bruce Lyon Memorial Research Laboratory (BLMRL) for nearly two decades. Under Sandy’s dedicated leadership, the BLMRL expanded and thrived, with the recruitment of new investigators and the construction of a second story to accommodate an ever-growing research enterprise, now called Children’s Hospital Oakland Research Institute (CHORI). Sandy will be missed by all those whose lives he touched here at CHORI, both through his contributions to lipid metabolism research and through his passionate and heartfelt leadership of this institute.
CHORI is an internationally renowned biomedical research institute with over 350 scientists and an annual budget of over $50 million. We have created the first and only not-for-profit sibling donor cord blood program in the world. We achieved the first cure of alpha thalassemia major in North America, and house the most comprehensive sickle cell disease and thalassemia centers worldwide. CHORI has the largest resource of recombinant DNA libraries across the globe, and provided 85 percent of the genes cloned for the Human Genome Project. Over 50 children have been cured of debilitating blood diseases or cancers through our innovative transplantation research program. We established the Children’s Global Health Initiative to provide a venue for the medical and scientific world to collaborate in alleviating the suffering of the world’s children.

While our success is global, our origins are humble. The premier research institute now known as CHORI began over 50 years ago, in 1959, with a generous gift from the Lyon Family in memory of Lt. Bruce Lyon. It seems fitting then, to dedicate our inaugural annual report to the Lyon Family, whose visionary gift provided the foundation of our institute.

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From the Executive Director

REFLECTIONS ON 2011

The research branch of Children's Hospital & Research Center Oakland, CHORI is a thriving organization with eight different research centers with robust basic, clinical and translational programs in both pediatric and adult research. The year 2011 brought many exciting developments: a successful clinical trial in the treatment of basal cell carcinomas, the most common skin cancer; the development of meningococcal vaccines and the groundwork for a second generation vaccine with even greater protection; and a novel proof of principle methodology for mismatched donor transplantation that has the potential to greatly increase the ability to provide cures for our most debilitating cancers and blood diseases. We've identified a previously unknown mechanism for iron absorption that could help in the eradication of global iron deficiency, demonstrated a novel use of statin therapy in the treatment of sickle cell disease pain crises and developed a new translational research and prevention program that identifies and works with children in our local community who are at risk for cardiovascular disease, diabetes and obesity.

Yet what has made our successes in the past year possible is our sustained commitment to the research that is at the core of all clinical and translational achievements. Cancer therapies, vaccines, and cures for fatal or debilitating conditions do not happen without the dedicated support of research that explores the fundamental basis of disease.

A sustained commitment to research is only possible, however, with the support of generous and visionary donors like the Lyon Family, to whom this inaugural annual report is dedicated, and institutions like the National Institutes of Health (NIH).

Garnering research grants is the lifeblood of any research organization, and we at CHORI are no different. Our annual operating budget is defined almost exclusively by how successful our investigators are at pulling together comprehensive and competitive grant applications—and being able to conduct the innovative research required to win them. We recognize the many challenges facing us as we move into a future in which federal research funding remains less and less certain. Yet our success in garnering NIH grants demonstrates our ability to remain fiscally strong and highly competitive, even in these challenging economic times.

As always, we strive to bring that strength back to you, with our continued commitment to the research that is the foundation for every new prevention, treatment or cure on the path to improving health.

Alexander H. Lucas, PhD
Executive Director, Children’s Hospital Oakland Research Institute
Senior Vice President, Children's Hospital & Research Center Oakland
A WORD FROM OUR PRESIDENT & CEO

Children's Hospital & Research Center Oakland (Children's) is Northern California’s only independent not-for-profit regional medical center for children. Our hospital leads the national field in a number of pediatric specialties and subspecialties, such as hematology/oncology, neonatology, cardiology and neurosurgery, while our research branch, Children's Hospital Oakland Research Institute (CHORI), is an internationally renowned biomedical research enterprise that is critical to our ability to understand disease and deliver the state-of-the-art treatment, care and cures for which our medical center is known.

We provided the first cure for alpha thalassemia major in North America, and have cured dozens of children who suffered from previously debilitating or fatal genetic blood diseases and cancers. We are worldwide leaders in establishing standards of care and developing novel treatments for sickle cell disease and thalassemia. Our pediatric and neonatal intensive care units participate in national and international trials to determine best practices in meeting the most urgent needs of this vulnerable population. We treat children every day from our local community who face conditions such as asthma, cystic fibrosis, obesity, and diabetes, and we do so armed with the most innovative and up-to-date practices. We are engaged in over 400 clinical trials and participate in the National Institutes of Health supported clinical translational research program.

We are able to do all this because of our commitment to the research from which clinical and translational innovation follow. CHORI is central to that commitment, and provides the basic and clinical investigators in our medical center with the ability to participate in the bench-to-bedside research that defines Children’s as a leader in pediatric treatment and care.

Bertram H. Lubin, MD
President & Chief Executive Officer
Children’s Hospital & Research Center Oakland
Curing Cancer: An Investment in Basic Research

A new study completed in 2011 by CHORI Senior Scientist Ervin H. Epstein Jr., MD, and University of Columbia’s David Bickers, MD, heralds a new day in the treatment of the most common cancer in the United States: basal cell carcinomas (BCCs). In the three-year, randomized, double-blind, placebo-controlled study conducted at three different clinics, patients suffering from basal cell nevus syndrome (BCNS), a genetic condition in which patients develop hundreds to thousands of BCCs throughout their lives, were treated with a revolutionary new drug developed by Genentech, called vismodegib.

“Patients in our study showed a dramatic reduction in the growth of existing tumors and the development of new tumors,” says Dr. Epstein. “Patients improved in just one month of treatment. Not only did all the BCC tumors respond to treatment, but some subjects achieved near complete clinical remission.”

The groundbreaking results mark an incredible chapter in a story that began over three decades ago, with the dedication of a handful of scientists and an investment in basic science.

“This all began with a pair of investigators in Germany doing fundamental basic research that focused on a very rare disease,” says Dr. Epstein, whose own involvement in the story began 25 years ago, when he began collecting blood from a huge family suffering from BCNS.

“It starts there, with a patient, with a tumor you can see on their skin, and goes to a vial of blood, and the DNA that gets amplified from that blood, and the genetic testing that is done on the DNA that came from that blood, from that tumor, from that patient. You don’t really know whether all these levels of abstraction are correct, even when you find a defective gene.”

In this case, the gene defect that Dr. Epstein and his collaborators found was a mutation in what is called the PTCH1 gene. Under normal conditions, the PTCH1 gene codes for a protein that acts as a tumor suppressor by inhibiting a very common signaling pathway, called the hedgehog (HH) signaling pathway. In patients with BCNS, however, a mutation in the PTCH1 gene causes the protein it codes to be defective. As a result, the HH signaling pathway is upregulated, and tumor growth is rampant.

Patients with BCNS, like those from whom Dr. Epstein took his original blood samples, have uncontrolled BCC tumor growth. Their quality of life is marked by frequent and repetitive tumor

Tumor in the intestines of an ApcMin/+ mouse, which has a mutation that leads to activation of the Wnt signaling pathway that underlies most human colon cancers. The brown staining is for the active form of beta-catenin, the central protein in the Wnt pathway.
“It’s often hard to understand that dramatic, groundbreaking treatments and cures don’t come about without committed and substantial investment in basic research, but this is an example of fundamental and translational science at its best.”

Ervin H. Epstein Jr., MD
The CCR & Swim Across America Team Up

A national organization with the mission of raising money for cancer research, prevention and treatment through swimming-related events, Swim Across America (SAA) hosts an annual swimming fundraiser in the Bay Area. Participants swim either a certain number of pool laps, or brave the sometimes frigid temperatures of the San Francisco Bay for a 0.5 or 1.5-mile swim. The amount of funding garnered through the annual SAA swim however, depends on how many volunteers wriggle into their suits in September and October, as swimmers collect pledges for reaching their individually determined swimming goals.

This year, 350 cancer research supporters, including five Olympic swimmers, dove into the deep end to collectively raise $110,000, which was presented to the CCR in a special award ceremony in March, 2012. The SAA funds will be used to expand existing programs and core facilities, as well as to support the career development of junior researchers through SAA fellowships.

“SAA recognizes that the genetic complexity of cancer and its ability to develop resistance requires us to strive for an ever greater understanding of the problem," says Dr. Saba. “We’re very grateful for the opportunity to work with the SAA in the fight against cancer.”

removal surgeries that leave significant scar tissue behind, along with a significantly diminished quality of life. Since the discovery of the PTCH1 mutation, researchers have been trying to develop a drug that replaces the function of the mutated protein.

Vismodegib is the first such inhibitor of HH signaling to be taken to trial.

As Dr. Epstein explains, “The protein the PTCH1 gene makes is still dysfunctional, but the drug provides a small molecule that inhibits the same target in the HH signaling pathway and substitutes for the defective protein.”

In this trial, vismodegib significantly reduced the per-patient rate of new surgically eligible BCCs when compared to the placebo, as well as reducing the size of existing clinically significant BCCs by 65 percent, with some patients experiencing the disappearance of all BCCs.

The first treatment available to restore quality of life for patients with BCNS, vismodegib also provides new possibilities for treating other cancers in which tumor growth is linked to similar HH signaling pathway dysfunctions. “There are currently three to four dozen trials of drugs produced by five other companies in patients with a variety of different cancers as well as other kinds of conditions, and none of this could have happened without the early support we all had in pursuing our basic research,” says Dr. Epstein.

A landmark example of bench to bedside research, the vismodegib study was selected from about 5,000 other studies for presentation in the opening plenary session of the American Association for Cancer’s 2011 Meeting in Orlando, Florida. Officially approved by the FDA as of January 30, 2012 for marketing by Genentech under the trade name Erivedge, vismodegib, and other drugs like it, have made treating a variety of different cancers not a hope, but a reality.

“Amazing moments like this are built on fundamental knowledge accumulated over years,” says Dr. Epstein. “It’s often hard to understand that dramatic, groundbreaking treatments and cures of this kind don’t come about without committed and substantial investment in basic research, but this is an example of fundamental and translational science at its best.”

Back row (left to right): Daniel Watters, Olympian; Dan Truesdale, longtime SAA volunteer and swimmer; Craig Beardsley, Olympian and director of SAA’s National Pool Swim; Katherine Starr, Olympian; Mark Henderson, Olympian; Kirk Stackle, Olympian; Susan Helmrich, SAA SF Bay Area Co-Event Director; and Janel Jorgensen McArdle, SAA President. Front row: Kay Foley, SAA Program Director.
Finding New Ways to Fight Cancer

Currently the most effective cancer therapies target all rapidly growing cells. This includes healthy cells in the gut, bone marrow and reproductive organs, as well as cancer cells.

New studies conducted by CHORI Senior Scientist and Center for Cancer Research Chair Julie Saba, MD, PhD, however, suggest that researchers could target an enzyme called sphingosine-1-phosphate lyase, or SPL, in order to reduce the amount of damage that radiation and chemotherapy cause in healthy cells, and to increase radiation-induced cancer cell death.

The primary role of the SPL enzyme is to break down sphingosine-1 phosphate, or SIP. Important studies have shown in the past that SIP protects cells from death, and that increasing or decreasing SPL directly regulates SIP levels. Dr. Saba’s 2011 publications however, take this knowledge a step further, by elucidating for the first time the mechanisms by which increasing or decreasing SPL impacts cell survival.

“What our studies show for the first time is that SIP has a direct role in regulating cell cycle response and DNA repair, the two ways in which cells try to repair radiation-induced damage,” says Dr. Saba. “By inhibiting SPL, we impact the cell cycle control and DNA repair pathways that keep cells alive.”

In addition, Dr. Saba’s studies also provide first-time evidence that when SPL breaks down SIP, it turns SIP into a toxic aldehyde, called trans-2-hexadecenal, which increases cell death. These combined results mean that using an SPL inhibitor increases protection against cell death by both increasing SIP levels and decreasing SIP degradation. Two compounds that function as SPL inhibitors already exist, and these could be approved for use in radiation therapy. Alternatively, Dr. Saba’s latest research looks to make cancer cells more sensitive to radiation by increasing their SPL expression.

“We hope to eventually be able to use SPL to help cancer patients in two ways,” says Dr. Saba. “We could use an inhibitor to decrease SPL levels and thereby protect the DNA of patients’ normal cells during cancer radiation, or we could find a way to make cancer cells express more SPL to increase tumor shrinkage after radiation.”

CHILDREN’S ONCOLOGY GROUP (COG) STUDIES IN 2011

The COG is the world’s largest cooperative research enterprise focused on childhood cancers. By combining research efforts on a global scale, the COG investigates novel cancer therapies much more efficiently than any group could do alone. Participation in the COG has helped the international effort to dramatically increase pediatric cancer survival rates to over 70 percent.

Children's participated in 21 different COG trials in 2011. This included 34 patients with diagnoses such as as leukemia, myelodysplastic syndrome, Wilms, rhabdomyosarcoma, hepatoblastoma, neuroblastoma, Ewings sarcoma, and soft tissue sarcoma. The survival of these patients to date is 97.1 percent.

Clinical oncology scientists designed a hepatoblastoma trial that helped to better define treatment strategies for the three different risk categories within hepatoblastoma patients, with completely different approaches for each category. In addition, discoveries in some of these studies have dramatically altered how we treat children with cancer, especially children with neuroblastoma, leukemia, hepatoblastoma and APL.

Laser scanning confocal micrograph of human melanoma SK-MEL-28 cells. The cells were treated with detergent to allow staining of intracellular neuraminic acid containing polysialic acid (NeuPSA) marked by anti-NeuPSA monoclonal antibody DA1 (Alexa Fluor® 546 red fluorescence). Nuclear DNA was stained with DAPI (blue fluorescence). NeuPSA is highly expressed in melanoma tumors were it appears to have a role in cell adhesion and migration, which are key elements of melanoma metastasis.
Huge inroads have been made in the care of premature babies. However, researchers are still presented with the fundamental challenge of these infants being born before their lungs have fully developed. As a result, many of the national and international clinical trials in which the neonatal group participate focus on high frequency ventilation, liquid ventilation, surfactant replacement, and inhaled nitric oxide. Clinical trials in the pediatric arena on the other hand, focus on such areas as asthma, cystic fibrosis, sepsis, and hospital- and community-acquired pneumonia.

In addition, the researchers in the CCCM realize that neonatal and pediatric care represent but a fraction of the total adult care going on in the United States. Therefore, the best opportunities to understand pediatric and neonatal illness and disease lie in collaboration.

“Most of the easy things you can study in a single center trial have already been done,” says David Durand, MD, director of the Neonatal Critical Care Department and chair of the CCCM. “The future of improving critical care is in multicenter collaborations.”

The CCCM participates in a variety of collaborations including those with the Pediatric Acute Lung Injury and Sepsis Investigators Network, the University of California, San Francisco Medical Center, the Cardiovascular Research Institute, San Francisco General Hospital, Cincinnati Children’s Hospital Medical Center, Children’s Hospital Boston, Stanford University and the Lucille Packard Children’s Hospital, the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and the California Department of Health.
“We have always focused our research on understanding the burden of critical illness as well as the mechanisms and pathophysiology of disease. As medicine advances, however, we are understanding that the individual patient’s response is as important to investigate as the virulence of the organisms that infect our children.”

Heidi Flori, MD
Establishing New Standards

Up to four percent of pediatric intensive care unit (PICU) admissions are due to acute lung injury (ALI) or its most severe form, acute respiratory distress syndrome (ARDS). As many as 20 percent of patients suffering from ALI will die. While the underlying causes of the lung injury can vary, from infections such as pneumonia to trauma, until those underlying causes can be resolved, the standard treatment to prevent mortality and provide consistent oxygen levels in the blood is the same—invasive and non-invasive forms of mechanical ventilation.

Although potentially life-saving, mechanical ventilation can also result in lung injury. Various approaches, called recruitment maneuvers (RMs), have been used, predominantly in adult studies, for its prevention. The use of RMs in a pediatric setting has yielded controversial results, however, with some studies showing significant benefit and others showing no benefit.

“Recruitment maneuvers seek to open collapsed lungs as uniformly as possible without causing any injury to the lungs,” explains CHORI Clinical Scientist and Pediatric Critical Care Medical Director at Children’s Hospital Oakland, Heidi Flori, MD. “While they have been used extensively in adult populations, there is a significant paucity of pediatric literature to define whether they could be of use in children.”

In 2011, however, Dr. Flori published a study in Pediatric Clinical Care Medicine with Juan Boriosi, MD, that assessed for the first time the safety and efficacy of a modified RM in mechanically ventilated pediatric patients with ALI and ARDS.

The study, which was conducted at the Children’s Hospital Oakland PICU between December 2007 and March 2009, evaluated the open lung tool (OLT) recruitment maneuver in 21 patients between the ages of 1 month to 18 years.

“Because the OLT was designed for adult studies, we used a modified version of it adjusted for pediatric populations,” Dr. Flori says. “Our results were overwhelmingly positive, with improved oxygenation resulting from the modified OLT for as long as 12 hours after the procedure, and with no adverse side effects.”

This study was conducted at a single site, and with a small number of patients, so longer-term outcomes past 12 hours, such as ventilator-free days and survival, could not be evaluated. Nevertheless, the early and lasting improvements in oxygenation without lung injury warrant larger, multicenter trials to fully explore whether or not this pediatric-specific OLT should become the new gold standard for recruitment maneuvers in pediatric ALI/ARDS patients.

Infant in Neonatal Intensive Care Unit.
First-Time Comparison of Pediatric Transcriptomes

Septic shock—caused by a bacterial infection in the blood—is one of the most common conditions resulting in intensive care treatment. Even in pediatric populations, septic shock is particularly deadly, and neonates—infants less than a month old—are the most vulnerable group. Neonatal sepsis is the seventh leading cause of infant death in the United States, and kills over one million newborns worldwide every year. Yet in spite of the many different approaches investigators have tried to improve immune responses in neonates, successful interventions have remained elusive.

Since 2004, CHORI Clinical Scientist Natalie Z. Cvijanovich, MD, and her colleagues in the Genomics in Pediatric Sepsis Study Group, led by Hector R. Wong, MD, of Cincinnati Children’s Hospital and Medical Center, have been investigating gene expression patterns in pediatric systemic inflammatory response. A 2011 study undertaking the first development-age group comparison of the transcriptomic response of children with septic shock may have identified the underpinnings of why standard interventions for sepsis have been less successful in neonates.

“Transcriptomes are like genomes, except that instead of categorizing the whole set of genes a given child has, transcriptomes tell us which messenger RNAs are being transcribed at a given time,” Dr. Cvijanovich explains. “This provides us with a very specific snapshot of only those genes that are currently being expressed.”

The study looked at transcriptomes in children at four different developmental ages—neonatal, infants aged one month to a year, toddlers aged two to five years, and school-aged children six years or older—with striking results.

“The infant, toddler and school-age groups had very few differences in which genes were being expressed during septic shock,” says Dr. Cvijanovich. “But the neonatal group was profoundly different, and showed significantly reduced expression of genes that correspond with inflammatory and immune system responses.”

In some ways, the data aren’t surprising at all, as they correspond with what doctors see in the clinic on a regular basis: that infants less than a month old have a much harder time launching an immune response against infection than older infants and children. What is most compelling about the transcriptome data, however, relates to how sepsis in neonates is currently treated.

“Our study suggests that certain therapies that have significantly reduced mortality in adults and adult animals with sepsis may not work in infants less than a month old because the immune pathways those therapies target aren’t functioning in the same ways in infants at that age,” says Dr. Cvijanovich.

The results also provide an explanation for the failure of so many interventions that have tried to improve neonate immune responses: it isn’t possible to improve a function that doesn’t yet exist.

“We know that children are not small adults, but what our study reflects is that days-old infants are not small children either, at least in terms of their ability to respond to sepsis,” says Dr. Cvijanovich.

“This means that the only way we are ever going to be able to come up with new treatments that lead to improved sepsis outcomes is if we undertake age-specific studies of immune responses to septic shock.”

Intracellular pH in a living cystic fibrosis cell measured by dual-excitation, dual-emission ratioing of a pH reporter dye. pH is rainbow color-coded with blue colors coding for acidic and red colors for alkaline values. Local pH values are alkaline in the nucleus and acidic in the periphery. Line drawing shows actual pH values.
How Finding Causes Leads to Prevention: Connecting the Folate Pathway to Spina Bifida

Neural tube defects (NTDs), of which spina bifida is one, are some of the most common forms of birth defects, occurring in approximately 1/1000 births in the United States alone. While maternal supplementation with folic acid significantly reduces the risk of NTDs like spina bifida, over two decades of research have yet to identify which genes that encode folate-related enzymes, if any, might actually cause NTDs.

By taking a step back to look at the bigger picture, however, and sequencing 31 folate-related genes in order to analyze the total amount of genetic variation (rare plus common) that occurs in spina bifida cases, CHORI Scientist Edward Lammer, MD, and his colleague, California Institute for Quantitative Biosciences Scientist Nicholas J. Marini, PhD, for the first time found a correlation between folic acid pathways and spina bifida. In 2011, Drs. Lammer and Marini undertook the most comprehensive DNA sequencing study ever performed to identify genetic factors that might explain the risk factors for spina bifida and why maternal folic acid supplementation can prevent it. In collaboration with the University of California, Berkeley, the University of California, San Francisco, Stanford University, and the Department of Energy’s Joint Genome Institute, the study was the first to analyze genetic risk factors for spina bifida from a pathway approach, rather than looking for associations based on individual genes.

Utilizing data from 250 children born with spina bifida and 250 controls, the massive
“What this study tells us is that genetic variation of folate biology pathways, rather than of individual genes, is conferring the increased risk for NTDs. The future of research on folate and NTDs lies in this kind of big-picture pathway analysis.”

Edward Lammer, MD
Global Solutions to Solving the Genetics of Type 1 Diabetes

Researchers have been searching for decades for the keys to unraveling the complex puzzle of what causes type 1 diabetes (T1D), a disease in which the immune system attacks insulin-producing cells in the pancreas. While genes in the Human Leukocyte Antigen (HLA) region of chromosome six have long been identified as the major players in T1D susceptibility, no studies have been large enough to reveal the complexity of classical HLA gene associations or to capture other genes in the HLA region that could contribute to disease susceptibility.

CHORI Scientists Janelle Noble, PhD, principal investigator of the North American HLA genotyping core for the Type 1 Diabetes Genetics Consortium (T1DGC), and Henry Erlich, PhD, are working to change that. The T1DGC is a worldwide group of researchers who, over the course of more than five years, pooled their resources to create the largest T1D disease susceptibility study ever undertaken.

“Although we’ve had genome scanning technology available since the ‘90’s, our studies were simply too small to accurately identify all of the genetic players that might be impacting T1D susceptibility,” explains Dr. Noble. “With the data from the Consortium, we are finally able to undertake analyses that have good enough statistical power to show independent contributions to T1D disease susceptibility.”

The data collection of thousands of samples from individual diabetes patients, their families, and non-diabetic controls, was completed in 2008, but the analysis of those data is still underway, with over 40 T1DGC publications in the last three years, and five in 2011 alone.

Next-Generation Sequencing: Leading the Field

Human Leukocyte Antigen (HLA) genes are part of a complex cluster of genes along chromosome six. These genes play a key role in stem cell transplantation and autoimmune diseases like diabetes, celiac disease, inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis.

CHORI’s Center for Genetics is home to the Applied Genomics Laboratory, directed by CHORI Scientist Elizabeth A. Trachtenberg, PhD, and one of only four research labs worldwide participating in an alpha trial of HLA sequencing using the Roche GS FLX 454, the next generation in high through-put sequencing of genes.

Utilizing the next-generation sequencing exponentially increases the ability to investigate these key genes, and allows researchers to produce data four to five times faster than ever before.

Now a world leader in next-generation HLA sequencing, the Applied Genomics Laboratory has analyzed over 5,000 genotypes in 2011 alone.

Portion of a “flowgram” of a DNA sequence from a patient with autoimmune disease generated with next-generation sequencing technology. Peak height represents the number of DNA bases.
A DIFFERENT KIND OF LIBRARY

Through the laboratory of CHORI Scientist Pieter de Jong, PhD, CHORI currently maintains in a deep-frozen state over 40 million Bacterial Artificial Chromosomes (BACs) and P1-derived Artificial Chromosomes (PACs), representing more than 150 species. Two of these collections provided the source material for the decoding of 85 percent of the Human Genome Project. Over the last decade since the human reference genome was completed, the de Jong lab has distributed over 240,000 distinct clones to the worldwide scientific community for the support of genome projects for multiple species, for diagnostics and as a starting point for functional gene studies. The largest genome library in the world, Dr. de Jong’s BACPACs provide the necessary building blocks to decode the genetic sources of disease, which could lead to their eventual treatment or prevention.

In 2011 alone, the de Jong lab distributed approximately 15,210 clones to 2,395 scientists, and created 7,000 conditional knock-out vectors for analyzing over 5,000 mouse genes as proxies for human gene research. Used in the genetic engineering of mouse stem cells, knock-out vectors eliminate the functional capacity of specific genes. The functional consequences resulting from the disrupted genes can help unravel the mystery of human health and disease.

A Genetic Alternative for Cholesterol Research & Management?

A new 2011 study by CHORI Assistant Scientist Marisa W. Medina, PhD, establishes for the first time that alternative splicing is an important player in the maintenance of cellular cholesterol levels, or homeostasis. Alternative splicing could play a significant role in regulating blood cholesterol levels that impact heart disease, the number one cause of death in the United States.

Dr. Medina’s study shows that exposing cells to conditions of extreme cholesterol depletion results in a reduction in alternative splicing in the genes that code for two key players in cholesterol homeostasis: 3-hydroxy-3-methylglutaryl coenzyme A reductase, or HMGCR, and the low density lipoprotein receptor, or LDLR.

“Alternative splicing is a process by which certain portions of a gene’s coding regions, known as exons, are cut from the gene in a way that affects the function of the resulting protein or enzyme,” explains Dr. Medina.

In the case of HMGCR and LDLR, the reduction in alternative splicing results in an increase in the activity of the proteins and enzymes responsible for stimulating cholesterol biosynthesis and uptake. When cholesterol is added back into these depleted environments, alternative splicing increases, thereby decreasing cholesterol biosynthesis and uptake.

“Alternative splicing has long been thought of as simply a way of increasing protein diversity,” says Dr. Medina. “Overall, what our results suggest is that it may be possible to harness alternative splicing as a way to regulate the cholesterol biosynthesis and uptake pathways.”

In addition to shedding light on spina bifida genetics, the study also serves as a paradigm for investigating other diseases with complex genetic components.

As Dr. Marini explains, “The incorporation of meaningful biological relationships into genetic association studies may reveal more relevant risk determinants from such studies, which have often been equivocal or inconsistent.”

While the study results need to be replicated, they lay the foundation for using pathway analysis to identify the genetic factors that influence NTD risk. By identifying higher risk groups, clinicians may finally be able to prevent NTDs using targeted folate treatments that are specific to each individual.
“It’s really quite gratifying to have a study like this that has direct translation into making better vaccines against infections, especially the meningococcal disease. Almost no other infection can kill a previously healthy child as fast as the meningococcus.”

Dan Granoff, MD
Neisseria meningitidis are meningococci bacteria that invade the body and produce meningitis and sepsis—a serious whole-body inflammatory state that is especially virulent and can be fatal. Young children and teenagers are particularly vulnerable. Even with the best of treatment, 10 percent of those infected will not survive. About 20 percent of those who do survive are left with long-term medical problems including deafness, seizures or limb amputation. While there are vaccines available for prevention of certain strains of the bacteria, there is no vaccine against “group B” strains, which account for approximately 40 percent of cases in the United States.

CHORI Senior Scientist Dan Granoff, MD, however, has been utilizing careful and methodical basic research over the last decade to lay the groundwork for completely eradicating meningococcal disease in our lifetime. Two drug companies have already developed a first generation vaccine that utilizes a novel antigen called factor H-binding protein (fHbp), which is effective against all meningococcal strains—including the B strain.

In 2011, however, Dr. Granoff and CHORI Assistant Scientist Peter Beernink, PhD, identified a new mutant vaccine antigen for Neisseria meningitidis that significantly improves the first generation meningitis vaccines, and provides proof of principle for vaccine development against other bacterial infections as well.

“It’s really quite gratifying to have a study like this that has direct translation into making better vaccines against infections, especially the meningococcal disease,” says Dr. Granoff. “Almost no other infection can kill a previously healthy child as fast as the meningococcus.”

The new vaccines are already in advanced clinical development and one has been submitted for regulatory approval in Europe. However, the 2011 discovery by Dr. Granoff and his colleagues shows how a relatively simple change in the proteins that make up the vaccines can greatly improve their efficacy.

At issue is the fact that the fHbp antigen in the vaccines binds with human factor H (fH), which is a protein normally present in the bloodstream. Animal studies would not be able to capture the effects of this, because fH in animals is slightly different than it is in humans, and the fHbp vaccine only binds with human fH, not non-human fH.

“To investigate the effect of fH binding on the fHbp vaccine, our colleagues, Sanjay Ram, MD, and Peter Rice, MD, at the University of Massachusetts, Worcester, developed a mouse with human fH,” explains Dr. Granoff.
The fHbp antigen vaccines worked exceptionally well in normal mice whose mouse fH didn’t bind to the vaccine. But in the mice with human fH, the protective ability of the vaccine dropped four- to eight-fold. In addition, the drop in protection was dose dependant, in that the more human fH a mouse had, the worse the level of protection the vaccine provided.

The good news, however, is that in the same study, Dr. Granoff and his colleagues also showed that using an fHbp antigen with a slight mutation in it resulted in significant increases in protection. “This mutant antigen has just one amino acid difference between it and the fHbp in the current vaccines, but that difference means that it no longer binds to human fH. That change resulted in much higher protective responses,” says Dr. Granoff.

“What this tells us is that a vaccine that actually targets fH binding proteins offers the unique opportunity to prevent disease, but that you probably don’t want forms of the vaccine that bind to the host protein. Instead, we need to look at mutants like the ones we’ve created that make the antigen look like the fH binding proteins, but that remove the function.”

Although the results still need to be replicated by other labs, the 2011 and 2012 studies provide a solid foundation for the development of second-generation meningococcal vaccines. In addition, a variety of other infectious bacteria also utilize fH binding. This means that the same methodology Dr. Granoff has developed to eradicate meningitis can be used to create highly effective vaccines against other debilitating infections as well.

A Vaccine For Cancer?

In 2011, CHORI Scientist Gregory R. Moe, PhD, and his colleagues made a landmark discovery that may provide a critical new approach to the possibility of preventing cancer—with a vaccine. That discovery is a sugar molecule Dr. Moe named neuraminic acid containing polysialic acid (NeuPSA). A derivative of polysialic acid (PSA), NeuPSA is expressed in every single type of human tissue Dr. Moe has tested, spanning all the major organs. Dr. Moe has also found NeuPSA in much higher amounts in tumors and cancer cell lines compared to normal tissues, opening a whole new area of research in the treatment of cancers.

Dr. Moe’s most recent studies published in 2011 demonstrate that antibodies directed against NeuPSA cause programmed cell death in all of the cancer lines tested, suggesting that NeuPSA may be an incredibly useful target for developing a cancer vaccine. While larger questions regarding the function of NeuPSA still need to be explored, the Moe lab is already working on ways to use NeuPSA as a potential target in cancer-fighting vaccines and drugs, both in the ongoing development of a vaccine to elicit the same anti-cancer antibodies they used in their studies, as well as in the development of designer molecules to inhibit NeuPSA in cancer cells. While a novel treatment available to patients is far in the future, Dr. Moe’s latest research provides a glimmer of hope for turning a new corner in current cancer treatment approaches. “NeuPSA appears to have a much broader role in human biology than previously recognized,” says Dr. Moe. “Targeting the NeuPSA pathway with vaccines, antibodies, and drugs offers many possible new approaches to preventing and treating cancer in humans.”

*Chlamydia trachomatis* (pink) infected human cell that formed an inclusion body or intracytoplasmic vacuole surrounded by the green staining of the cytoplasm. The blue stain denotes DNA in the cell nucleus and also in the inclusion.
The Basic Research Backbone

Chlamydia trachomatis is a scourge of humankind: an infectious bacterium that is the leading cause of preventable blindness in the developing world and the leading cause of bacterial sexually transmitted diseases (STDs) across the globe. Millions of STDs each year are caused by various strains of C. trachomatis. Lymphogranuloma venereum (LGV) is one of these STDs and is caused by biological variants of C. trachomatis. LGV is particularly prevalent in the developing world, but recently, there have been recurring outbreaks reported in Australia, Europe and the United States.

In 2011, CHORI Senior Scientist Deborah Dean, MD, MPH, a leading expert in C. trachomatis research, demonstrated for the first time whole-genome evidence of genetic recombination in an LGV strain of C. trachomatis.

“Recombination is the mixing of DNA between different strains of an organism. It is the way an organism evolves, for better or worse, and may result in a bacterial strain becoming more persistent and virulent, or less so,” says Dr. Dean. “Understanding when, how, and how often, different strains of a bacterium undergo recombination will be key to eventually developing an effective vaccine against that bacteria, as well as new therapeutics.”

The 2011 study utilized genome sequencing and bioinformatic and statistical analyses to assess an LGV strain that was isolated from a patient who had particularly severe clinical symptoms associated with LGV.

“This particular LGV strain demonstrated a uniquely different size and shape when we cultured it than any other LGV strains we had observed. That, combined with the severe clinical presentation of the patient, led us to take a deeper look,” says Dr. Dean.

Previous indications of C. trachomatis recombination have been based on comparing multiple genes from clinical strains of the bacteria with genes from reference strains created in the lab. This study, however, is both unique and particularly sound in that the results provide the first analytically confirmed whole-genome evidence for recombination in the organism.

“What was particularly unexpected was that the unique LGV strain was actually a recombinant of an invasive strain LGV and a non-invasive strain. The resulting clinical presentation is one of the most aggressive we’ve seen, and tells us that we need to rethink our assumptions about C. trachomatis infections and how they evolve in the clinical setting,” says Dr. Dean.

“Our findings suggest that recombination is a key process for bacterial evolution and, in the case of ongoing LGV outbreaks, they suggest that recombination is a primary mechanism by which new disease strains emerge that cause significant disease pathology.”

Through whole genome analyses such as these, researchers like Dr. Dean will be able to clarify which genes are the key players in chlamydial recombination. That information will eventually provide the basic research backbone from which the first vaccine against chlamydial infections can be developed.

CLOROX ENDOWED CHAIR AT CHORI

In 2011, The Clorox Company provided CHORI with a generous $1 million gift to establish The Clorox Endowed Chair for Immunobiology & Vaccine Development at CHORI, which will support CHORI Senior Scientist Dan Granoff, MD. Dr. Granoff played a major role in the development and evaluation of vaccines against Haemophilus influenzae type b (Hib) in children and is also the author or co-author of more than 184 peer-reviewed articles in microbiology and vaccine research.

“Establishing this chair and the research it will foster aligns strategically with our company’s global platform to safeguard family wellbeing with a focus on infection prevention,” said Donald R. Knauss, Chairman and CEO of The Clorox Company. “Clorox is thrilled to partner with CHORI in the fight against devastating infectious diseases.”

The Clorox Endowment will help develop a vaccine against meningococcal disease—a potentially deadly bacterial infection that affects hundreds of thousands of children and young adults throughout the world.

“I am confident that a successful vaccine can be made to control meningococcal disease,” said Dr. Dan Granoff. “This generous gift from The Clorox Company brings us closer than ever to finding a means for eradicating this devastating bacterial infection.”
Placental chorionic mesenchymal stem cells express markers of embryonic stem cells. Fluorescent confocal microscopy merged image.

“Our goal is to bring groundbreaking discoveries from the laboratory directly to the clinic in order to translate the great promise of stem cell transplantation into novel therapies, innovative treatments, and life-sustaining cures.”

Mark Walters, MD
Pre-Clinical Mismatched Donor Transplantation Model Wins 2011 Best Paper Award

The standard procedure in stem cell transplantation, whether using bone marrow or cord blood, is to select a donor who is as closely matched as possible to the Human Leukocyte Antigen (HLA) type of the recipient. Although there are now 14 million volunteers worldwide who have joined the donor registry, finding a perfect, or near-perfect HLA match is incredibly difficult. Thousands and thousands of patients are unable to find that near perfection and never have the opportunity to receive the potentially disease-curing transplantations.

In 2011, however, CHORI Scientists Bindu Kanathezhath, MD, Frans Kuypers, PhD, and Mark Walters, MD, and their colleagues provided first-time proof of principle data to show that a new method of treating donor cord blood might make mismatched transplantation possible. The study demonstrated successful transplantation using mismatched umbilical cord stem cells in a mouse model for the first time, and garnered the authors the Experimental Biology and Medicine Best paper Award for 2011 in the Clinical/preclinical and translational category.

“We have shown that we can use completely unrelated donor sources in mice and still have successful cord blood transplantation,” says Dr. Kuypers. “While that kind of risk is something we would never undertake in people, if you can stretch it that far in mice, there is a good reason to think that this approach could be used successfully in transplants in humans with a less than perfect match.”

Our immune system relies on HLA genes to tell the difference between self tissue and foreign matter, such as bacteria or viruses. When the HLA genes recognize foreign matter, they trigger the immune system’s T cells to destroy the harmful germs without harming healthy tissues.

“Obviously this is a good system for infections,
but it’s not such a good system for transplantation,” says Dr. Kuypers. “When the donor stem cells are incorporated into the recipient and begin to reproduce—which is what we call engraftment—those new stem cells create their own T cells. These T cells recognize the recipient’s cells as not-self and launch an immune attack against them.”

The result is graft versus host disease, which can be life-threatening. But simply removing T cells from the equation isn’t an option: the donor T cells also help clear recipient cells out of the way for engraftment of the new stem cells to occur, a role that is integral to the success of stem cell transplantation.

“On the one hand, you want the T cells so that the new donor stem cells take root and grow, but on the other hand, you don’t want them, because they could result in graft versus host disease,” says Dr. Kanathezhath.

Utilizing a unique approach in which donor T cells were pre-treated with a synthetic psoralen to make them susceptible to ultraviolet light, Dr. Kanathezhath and her colleagues were able to photochemically expose the T cells prior to transplantation. Combining the photochemically modified T cells with cord blood stem cells resulted in superior engraftment and increased survival of the donor cord blood stem cells, but without graft versus host disease.

“We don’t kill the donor’s T cells, we simply modify the response, allowing the donor T cells to clear space to facilitate engraftment of stem cells, but preventing the same T cells from proliferating and attacking the host cells,” Dr. Kanathezhath explains.

While the key to translating this revolutionary new process from mice to people is still in the future, these preliminary results offer hope that using mismatched donor-recipient pairs in cord blood stem cell transplantation might one day be both safe and feasible.

“Transplantation technology has improved tremendously over the last couple of decades, but no matter what, you still need a stem cell resource to have a successful transplant,” says Dr. Kuypers.

“Being able to lower the need for a perfect match and at the same time provide modern medicine with a larger resource is very important, and ultimately, our long term goal.”

Frans Kuypers, PhD

“Being able to lower the need for a perfect match and at the same time provide modern medicine with a larger resource is very important, and ultimately, our long term goal.”

JORDAN FAMILY CENTER HIGHLIGHTS
• Children’s achieved the first cure of alpha thalassemia major in North America in 2000 through the innovative transplantation procedures developed by CHORI Scientist Mark Walters, MD
• Since then, dozens of children at the hospital have received cures for various cancers and deadly blood disorders under Dr. Walter’s direction
• Our ability to provide cures is uniquely enhanced by our Sibling Donor Cord Blood Program, the first and only not-for-profit program of its kind
BLOOD AND MARROW TRANSPLANT (BMT) PROGRAM

Children’s Hospital Oakland’s BMT program, directed by CHORI Scientist Mark Walters, MD, conducts interdisciplinary translational research with CHORI’s Jordan Family Center and the Center for Sickle Cell Disease & Thalassemia. The BMT program:

- has accreditation through the Foundation for the Accreditation of Cellular Therapy
- is a member in the Pediatric Blood and Marrow Transplantation Consortium
- is an affiliate member of the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN), which is supported by the National Heart Lung and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- is a research transplant team in the Center of International Blood and Marrow Transplantation Research (CIBMTR)
- is a transplantation center in the Children’s Oncology Group (COG)

In 2011, the BMT program took the lead in an unrelated donor transplantation trial in sickle cell disease (SCD) and thalassemia major, developed an unrelated donor bone marrow transplant trial for young adults with SCD, which led to a NHLBI-approved plan to initiate a multicenter pilot clinical trial, and was a leading center in the recruitment of patients for a phase III prospective trial of dual versus single umbilical cord blood transplantation for blood diseases in children.

Scientist Profile: Wen-Shu Wu, PhD

An expert in hematopoietic stem cell renewal and cell-fate determinations, Wen-Shu Wu, PhD, was recruited from the Maine Medical Research Institute to expand his research in the areas of pluripotent stem cells and genetic reprogramming.

“My broad area of research is on stem cell biology and the development of new tools for use in the application of stem cell therapies for some of the most debilitating conditions, such as cancer, sickle cell disease or thalassemia,” says Dr. Wu.

Dr. Wu has two ongoing National Institutes of Health (NIH) grants to investigate ways to enhance stem cell regeneration following stem cell transplantation. Currently, Dr. Wu has plans to develop novel stem cell therapy for curing blood cell diseases by combining somatic cell reprogramming and genome editing approaches.

While much of Dr. Wu’s work has been in the basic laboratory, stem cell research at its heart is about improving the odds for patients whose only recourse for a cure lies in stem cell transplantation. As a result, Dr. Wu was drawn to the Jordan Family Center in particular for its signature translational research approach.

“I am really excited about the opportunity to work in an environment that fosters such wonderful collaborations between basic science and the clinic. While I work in the lab, I want my research to contribute to the development of novel therapies for conditions like sickle cell disease. Here at CHORI, there is the opportunity to truly bring my work directly to the clinic and the patients who need it.”

Prior to joining CHORI, Dr. Wu was a principal investigator at the Center of Biomedical Research Excellence in Stem Cell and Progenitor Cell Biology, Center for Molecular Medicine, Main Medical Center Research Institute, and an assistant professor of the Program in Cell, Molecular and Developmental Biology, the Sackler School of Graduate Biomedical Sciences at Tufts University School of Medicine. Dr. Wu received his PhD degree in cancer biology from the University of Texas MD, Anderson Cancer Center, Houston, TX in 2001 and pursued his postdoctoral training at Dana-Farber Cancer Institute/Harvard Medical School.
“Our study shows a different mechanism of absorption of iron from plant ferritin than from typical chemical supplements or from heme, which is more efficient, likely to be more gentle and could be a key, new contributing factor to solving global iron deficiency.”

Elizabeth Theil, PhD
Iron deficiency is the most common nutrient deficiency known to man, and affects about 2 billion people worldwide from both developing and non-developing nations. Traditional approaches to treating iron deficiency include providing iron supplements and trying to increase meat consumption. Both of these approaches have proven to have significant limitations in reducing global iron deficiency. A 2011 study by CHORI Senior Scientist Elizabeth Theil, PhD, and her international colleagues, however, identifies for the first time an alternative and highly efficient mechanism for iron absorption from legumes, which could provide the key to solving worldwide iron deficiency by providing an alternative, affordable and readily available source of iron.

“Our study is the first to show that there are at least two independent mechanisms for iron absorption from non-meat sources,” says Dr. Theil. “One is for the absorption of ferritin, the large, protein-coated iron mineral found in vegetables and legumes, while the other, more well-known mechanism, is for iron absorption of small iron complexes like those found in iron supplements.”

The paradigm-shifting study combines the results of two different experiments, one in a rat model, and one in humans. In the rat model experiment, portions of rat intestines were bathed with solutions of traceable iron, either as a typical type of iron supplement, or as ferritin. Dr. Theil was able to measure how much of each type of iron crossed the intestinal barrier, and at what rates, demonstrating that both the ferritin mineral and the smaller iron atoms associated with typical iron supplements were absorbed through the intestines. In the second experiment, traceable iron in ferritin was consumed by volunteers with a 9:1 ratio of unlabelled, non-meat iron dietary supplement, or with hemoglobin, the type of iron in meat, to see if the two types of iron competed with ferritin iron for the same absorption mechanism. In each case, the iron competitor had no effect on the individual’s iron levels.

“What these studies show together is that during digestion, ferritin is not converted from its large, mineral complex, which contains a thousand iron atoms, to individual iron atoms like those found in many iron supplements,” explains Dr. Theil. “Instead, ferritin iron is absorbed in its mineral form by a different, independent
$6 Million NIH Grant to Study Impact of Protein Sources on Heart Disease Risk

A 2011 study by CHORI Senior Scientist Ronald Krauss, MD, and his colleagues showed for the first time that decreasing carbohydrate intake and increasing saturated fat intake may only have a negative effect on lipid profiles when the diet is high in beef protein.

“The common wisdom is that saturated fat in isolation is something that raises cholesterol and may increase the risk of heart disease,” says Dr. Krauss. “But our study suggests there is a much greater need to look at saturated fat intake in the context of the rest of the diet, in particular, in combination with the source of dietary protein.”

Previous studies by Dr. Krauss and his colleagues showed that decreasing dietary carbohydrates and increasing saturated fat in a diet with mixed sources of protein increased only large low density lipoproteins (LDL), which don’t pose the same risks for heart disease as small dense LDL. The Krauss lab expected to find the same was true of a diet with similar levels of carbohydrates and saturated fat, but that was high in beef protein. The results, however, were dramatically different.

“The diet high in beef as well as saturated fat significantly increased all LDL particles, including small dense LDL, creating a lipid profile associated with a much higher risk of heart disease,” says Dr. Krauss.

The provocative new results raise more questions than they answer, however. As a result, Dr. Krauss and his colleagues garnered a $6 million, five-year National Institutes of Health grant to compare diets with three different sources of protein—red meat, white meat, and vegetarian sources. Under each of these three dietary conditions, the investigators will then examine how the source of saturated fat affects study participants’ lipid profiles. This will allow the Krauss group to determine whether there is a specific interaction between saturated fat and the protein source that might influence heart disease risk.

“Ultimately, we must move toward a much broader approach to nutritional studies in which the overall food intake and dietary patterns are looked at as influencing heart disease risk, rather than looking at an individual nutrient, such as saturated fat, in isolation,” says Dr. Krauss.

While further studies are needed to elucidate the exact mechanism of ferritin absorption, in the mean time, the results demonstrate that ferritin-rich foods such as legumes can provide a significant source of dietary iron, and provide new hope in the decades-long struggle to reduce global iron deficiency.

Ferritin, a food (legume) source of iron and an intracellular metabolic iron concentrate is a natural combination of iron and protein. It has a complex structure and function that concentrates iron as a mineral (rust) inside the protein. Pores and channels are part of the ferritin structure that control iron entry through the ferritin protein into the ferritin iron mineral and from the iron mineral to provide iron for cellular use. The ferritin protein is shown from the outside (yellow) with one of the iron entry/exit pores colored red. (This figure is part of a larger figure published in Theil, EC, Current Opinions in Chemical Biology 15:304-311(2011).)
Revolutionizing Maternal Health

As many as a third of the world’s population of expecting mothers is micronutrient deficient. In Southeast Asia in particular, researchers estimate that 25 percent of newborns suffer from the malnutrition of their mothers. The result is lower birth weights, greater susceptibility to infection, and significantly increased morbidity and mortality.

While researchers have understood the impact that malnutrition can have on the health of the newborn for decades, nutritional interventions have failed to show significant positive results. CHORI Senior Scientist Janet King, PhD, has long believed the lackluster interventions have failed to show significant positive results. CHORI Senior Scientist Janet King, PhD, has long believed the lackluster results are due to the fact that nutritional supplementation alone cannot make up for inadequate diets, and that one of the most important factors influencing the course of pregnancy is the mother’s health before conception.

“A key factor influencing the course of pregnancy is the nutritional state of the mother at conception,” says Dr. King. “We don’t have a lot of human data to support this, but we have a huge amount of animal data. The backbone of animal husbandry throughout the world is that before you breed an animal you want to make sure that animal is well nourished. Somehow this knowledge hasn’t been translated to people.”

As part of the Children’s Global Health Initiative (CGHI) highlighted on page 40, Dr. King, along with CHORI Senior Scientist and CGHI Director Deborah Dean, MD, MPH, and their international colleagues, is undertaking an innovative first-time study to determine if providing increased nutrition to women before conception can impact fetal health and improve birth weight.

The study, which partners with the Vietnamese government and utilizes the existing Vietnamese VAC program—translated as vegetables, aquaculture (or fish), and caged animals (chicken and pork)—has the potential to revolutionize maternal and newborn health in Vietnam.

“If we are able to show that providing even just a small intake of animal source foods has a positive impact on pregnancy outcomes, the Vietnamese government will then make sure that all pregnant women have access to animal source foods every day,” says Dr. King.

The results of the three-year study, funded by the Thrasher Research Fund and the Nestle Foundation, will hopefully provide not only a foundation for increasing maternal health in Vietnam, but also a framework for how to combat maternal malnutrition and low birth weights on a global scale.

GETTING AN EARLY START ON HEART DISEASE PREVENTION

Heart disease is the number one cause of death in the United States, and may eventually become the number one cause of death worldwide. A 2011 presentation by CHORI Scientists Ashutosh Lal, MD, Michele Mietus-Snyder, MD, Bruce Ames, PhD, and their colleagues at the Annual Preventative Cardiology Meeting of the American Heart Association provided fresh evidence of the need for targeted interventions in children to reduce the incidence of cardiovascular disease in adults. Their presentation, Metabolic Burden of Nutritional Deficiency in Obese Children and Adolescents, demonstrated that obese children with poor diets presented with an alarmingly high number of precursors for heart disease later in life.

“When we compared the metabolism of children with and without obesity, we found that many of the processes that eventually lead to heart disease are already visible in obese children,” says Dr. Lal.

The highly sensitive measurements showed that C-reactive protein levels, which are a marker of increased inflammation, were almost ten times higher in obese children than in healthy-weight children. In addition, insulin levels were off the charts, indicating a predisposition for type 2 diabetes, and the levels of oxidative stress were 125 percent higher.

Significantly, diets of the children in the obese group were low in potassium, and vitamins C, D, and A—all nutrients found in fortified dairy products and fresh produce. Clinicians who deal with obese children shouldn’t just be focused on reducing the amount a child eats, points out Dr. Lal. Instead, they should focus on the quality of what the child eats, making sure that the diet is sufficient in micronutrients.

“It’s not just the quantity of the diet that is important, but the quality. You can get calories from almost anything, but you can’t get micronutrients from just anything.”

As Dr. Lal explains, “There was a clear association between lower quality diets and increased markers of inflammation and other metabolic abnormalities associated with heart disease in adulthood.”

While the process by which a poor diet lacking in micronutrients might produce the biochemical changes seen in the study requires further exploration, the results couldn’t be clearer in terms of the need to provide earlier interventions for obese children.
“Understanding the mechanism of disease ultimately provides an opportunity to develop new strategies to diagnose, prevent and treat these debilitating diseases that have such an impact in our society today.”

Robert O. Ryan, PhD
CHORI Launches New Community-Based Translational Research & Prevention Program

While healthcare professionals are looking for any and every means possible to combat the skyrocketing childhood obesity rates in the United States, CHORI Senior Scientist Ronald Krauss, MD, is falling back on what he knows best: translational research. With an innovative plan to create a synergistic flow of information between researchers, study participants, and the families of those participants, Dr. Krauss hopes to tackle heart disease before it even starts.

The Family Heart and Nutrition Center, led by Dr. Krauss and launched in 2011 in part through a generous donation by The Branches, is a collaborative effort between the Cardiology Department and the Healthy Hearts program at the hospital, and Dr. Krauss's own research lab.

“There is an incredibly important need to identify children who may be at risk for heart disease and diabetes, who are becoming obese and don’t have good nutritional practices, and to work with them and their families on preventative interventions,” says Dr. Krauss.

An international expert in cardiovascular disease research, Dr. Krauss has been studying the confluence of genetics, diet, lipoprotein profiles and heart disease risk in adults for decades. Now, he plans to take that same information and apply it to the children and families of study participants.

“It has been my vision to integrate the kind of clinical work and research we’ve been carrying out, primarily in adults, related to lipid profiles and heart disease risk, and diet in particular, and to integrate that with working with younger individuals, including children of the families with whom I’ve worked,” says Dr. Krauss.

By using the data from his adult studies that identify individuals with genetic markers and lipid profiles that are particularly risky, Dr. Krauss has a unique pool from which to identify children now who may be at risk later for heart disease, diabetes or obesity because of their parents’ profiles. In particular, the data regarding the interactions of different kinds of diets with specific genetic and lipid profiles can guide Dr. Krauss in which dietary approaches to take with kids, and indeed, the whole
**Creative Solutions to Childhood Obesity: The Built Environment**

CHORI Associate Clinical Scientist June Tester, MD, MPH, is co-director of Healthy Hearts at Children’s Hospital Oakland, a hands-on weight-management clinic for obese and morbidly obese children and teens. Half of Dr. Tester’s time, however, is spent conducting research on the connection between children’s health and the environment around them.

“What this basically translates to is the idea that our neighborhoods, our playgrounds, the traffic on our streets—our physical environment—impact children’s health,” says Dr. Tester.

Too often people think of urban design and public health as having no relationship to one another. But a century ago, during cholera or tuberculosis outbreaks, public health efforts were very effective at separating people from toxins and “bad air” in the environment. As a result, Dr. Tester is focusing on research that can have a larger impact on public health policy, and thereby translate directly from the bench to the environments in which kids live and play.

“It would be wonderful if pediatricians could simply say that walking to school is part of a healthy lifestyle. However, a host of factors related to the built environment, like whether there are sidewalks, how far away the school is from their homes, and how much traffic congestion there is—makes it prohibitive to do so,” says Dr. Tester.

Recent studies by Dr. Tester have focused on evaluating how better access to healthy foods could impact children’s eating habits, whether through making fruits and vegetables available from street vendors, or examining the availability of healthy foods in local food stores by income status.

In addition, Dr. Tester is evaluating how playlot design can influence physical activity and the overall health of a neighborhood, with a focus on policy-relevant research that can inform decision-makers about what community-level solutions exist to make children’s lives both more active and healthier.

“The built environment is not shaped by chance, but by policies. Years ago public health and design came together to help people out, and it’s the same opportunity for intersection now,” says Dr. Tester.

With evidence-based information generated from the kinds of studies Dr. Tester is pioneering, however, researchers can have a greater impact on shaping public policy that directly improves children’s health.

“We envision a two-way street that involves integrating the results of the research studies with treatment protocols for the whole family.”

**Ronald Krauss, MD**

“We envision a two-way street that involves integrating the results of the research studies with treatment protocols for the whole family. It’s just as important to give back to the families in the community the information we’ve learned from these studies as it is to get that information from the studies to begin with.”

Aptly named to encompass the importance of the family approach and nutrition’s role in heart disease, the new translational program brings together a broad mix of participants from many different ethnic and socioeconomic backgrounds to conduct more meaningful research with direct application to the local community.

“We hope to take this to a much broader level, to do outreach in the Hispanic community, and San Francisco General Hospital, to make some of these connections...
with underserved communities where the risk for obesity and its complications is quite a bit larger than in the general community,” says Dr. Krauss.

“In this way we take a much more comprehensive look at the influence of genetic variation both on health and response to drug and dietary interventions that helps individualize and eventually personalize the evaluation and management of heart disease, diabetes and obesity so that it all comes together.”

ASSESSING CARDIOVASCULAR DISEASE RISK: A NOVEL APPROACH
Measuring the amount of high density lipoprotein (HDL) cholesterol in the blood has been a standard parameter used to assess heart disease risk for decades, but recent drug trials suggest that it is the quality of a patient’s HDL—or its functional capacity—rather than the amount of HDL cholesterol that may be the key. In 2011, CHORI Associate Scientist Michael Oda, PhD, developed an innovative new assay that evaluates how well a person’s HDL is functioning by measuring the ability of the HDL to effectively withdraw cholesterol from the cell. The assay takes 10 minutes and requires less than a drop of blood. Dr. Oda’s assay uses paramagnetically labeled apolipoprotein A-I (apoA-I)—the primary protein component of HDL.

“ApoA-I specifically binds only to the form of HDL that is responsible for withdrawing cholesterol from the cells,” explains Dr. Oda. “Measuring the binding capacity of HDL to the paramagnetically-labeled apoA-I provides a relative measure of HDL functional capacity.”

While additional validation studies are still needed for FDA approval, Dr. Oda’s assay has the potential to revolutionize heart disease risk assessment.

MERIT Award Supports Critical Cholesterol Metabolism Research
Apolipoprotein E (apo E) is the protein responsible for transporting lipids through the bloodstream. Understanding the structural and functional mechanisms of apo E is critically important basic research required to develop novel treatments and preventative strategies for diseases related to cholesterol metabolism, such as heart disease and Alzheimer’s disease. CHORI Senior Scientist Robert O. Ryan, PhD, is currently investigating apo E’s binding mechanisms with the support of a coveted National Institutes of Health (NIH) Method to Extend Research in Time (MERIT) Award, which began in 2010. Given to less than five percent of all investigators nationwide, the MERIT Award supports Dr. Ryan’s research for a 10-year period.

“Receiving the MERIT award demonstrates that Dr. Ryan is a leader in his field and that his research is recognized as having made major contributions to his area of study,” says CHORI Executive Director Alexander H. Lucas, PhD. “To be recognized by the MERIT program is to be exceptional.”

Throughout the course of the grant, Dr. Ryan’s team will use a novel technique to evaluate apo E, called expressed protein ligation, which allows researchers for the first time to study apo E at high resolution while it is actually bound to lipids.

Apolipoprotein E isoform specific structural differences correlate with altered function and predispose to disease, including cardiovascular disease and neurodegeneration. See Hauser et al., 2011 Progress Lipid Res for details. Figure create by Paul Hauser.
Statins Provide New Hope for Sickle Cell Disease Treatment

Patients with sickle cell disease (SCD) have a variety of complications, including what are known as vaso-occlusive crises, in which restricted blood flow causes episodes of extreme pain. Patients miss school, appointments, work, and often end up hospitalized until the pain subsides. While researchers have been working to identify certain biomarkers that indicate when SCD patients are going to have pain crises, no treatments have yet been discovered to prevent or alleviate the vaso-occlusive crises when they strike.

In the last decade or so, new research suggests that injury to the endothelial cells that line the walls of the blood vessels is a key culprit in causing these pain crises, and that such injury is actually due to a chain reaction in which nitric oxide (NO) deficiency causes increased inflammation, which in turn causes endothelial injury.

A new study by CHORI Associate Scientist Carolyn Hoppe, MD, however, indicates that statins—a family of drugs used to prevent heart disease—may provide new hope for preventing or treating these debilitating SCD pain crises.

“We know that SCD is characterized by chronic inflammation and sustained endothelial activation, but what is intriguing is that patients with atherosclerotic heart disease have similarly high levels of inflammation and endothelial injury,” says Dr. Hoppe. “Recent studies have also shown that many of the clinical benefits of statins may actually be due to their ability to increase NO...
“In the hospital we help many children, one child at a time. In the research institute, we benefit countless children around the world.”

Elliott Vichinsky, MD
Study May Help Expand National Newborn Thalassemia Screenings

Thalassemia is a blood disorder characterized by genetic mutations that impact the creation, size, or shape of hemoglobin in the red blood cell—the part of the red blood cell that transports oxygen throughout the body’s tissues and organs. There are a variety of different types of thalassemia mutations, with variations in disease symptoms and severity. Hemoglobin H disease (HbH) is a subtype of alpha-thalassemia in which the genetic mutation causes the body to produce insufficient amounts of hemoglobin.

In a landmark 2011 study published in the *New England Journal of Medicine*, CHORI Scientists Ashutosh Lal, MD, Elliott Vichinsky, MD, and their colleagues conducted a first-time longitudinal study analyzing the clinical data of HbH patients over the course of 15 years. The study revealed remarkable and significant differences between the regular HbH disease and that found in a subset of HbH patients caused by what is referred to as the hemoglobin Constant Spring (HCS) mutation.

“Our study demonstrated a clear difference between HbH and HCS,” explains Dr. Lal. “Patients with HbH have a mild disease course that is fairly predictable and treatable, while patients with HCS have a much more severe disease course, beginning in infancy.”

When children with HCS become sick with infection and fever, their already low hemoglobin levels can drop even further, to life-threatening ranges that require blood transfusions. As a result, almost 80 percent of HCS patients had at least one transfusion before 20 years of age. Even more significantly, the first transfusion was often before six years of age, if not in infancy.

While differences between HbH and HCS were always suspected, this is the first longitudinal study in which patients were followed over time at a single medical center using uniform guidelines for management. The results underscore the need for newborn screenings that flag children with HCS for early intervention and treatment.

“These data really do have an implication on whether you diagnose HCS by newborn screening, or whether you do it during an episode of significant illness when a clinician is trying to make a diagnosis in an emergency situation,” says Dr. Lal.

As a result, Dr. Lal and his colleagues are strongly recommending that HCS be added to national newborn screening programs. The test itself is relatively inexpensive and nearly 100 percent accurate. Previous proposals by Dr. Vichinsky, Director of Children’s Hospital Oakland’s Hematology/Oncology Department, to expand national newborn screenings to include hemoglobin H disease have not been supported. However, preliminary feedback from leadership in the United States Secretary of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children in 2011 suggests that in light of the critical evidence demonstrating the clinical benefits of newborn screening provided by Dr. Lal and his colleagues, the proposal may be reconsidered.

“Using early diagnosis, we can predict the course of the disease and develop proper interventions to ensure that patients with all forms of hemoglobin H disease get the best treatment possible.”
levels and thus stop the chain reaction that causes endothelial cell injury. We wanted to see if statins could provide similar endothelial protection in patients with SCD."

In the first-time pilot study, Dr. Hoppe and her colleagues examined the effect of statin treatment on plasma NO levels and selected biomarkers of endothelial dysfunction in 26 SCD patients, with 14 of the patients on a low statin dose, and 12 of the patients the patients on a moderate statin dose.

Plasma NO levels increased by 23 percent in the low dose group, and by 106 percent in the moderate dose group, while biomarkers of inflammation significantly decreased in both groups in an equally dose-dependent fashion.

"Biomarkers of NO deficiency and inflammation were measured prior to treatment with statins and indicated that SCD patients in general have a steady low-grade inflammation. In addition, the four patients who experienced mild pain crises during the study showed sharp declines in NO levels and a simultaneous increase in inflammatory biomarkers," Dr. Hoppe says.

The fact that statin treatment was so effective in increasing NO levels and decreasing inflammation indicates that Dr. Hoppe and her colleagues may have just found a new approach to treating SCD pain crises. Confirmation in larger studies is needed, but the overwhelmingly positive results of the pilot study, in combination with a sound safety profile, should lead to large, randomized, placebo-controlled trials to assess whether or not statins can provide a preventative treatment for SCD pain crises. Dr. Hoppe has already procured a Doris Duke Charitable Foundation Award to determine whether treatment with statins reduces the frequency and intensity of pain crises in patients with SCD. "Our pilot study showed conclusive improvements in NO levels and downstream inflammatory markers associated with endothelial dysfunction," says Dr. Hoppe.

“Our hope is that these biomarker data will translate in our next study into the prevention of endothelial injury and the chain of events that causes sickle cell pain crises.”

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**THE RED BLOOD CELL LABORATORY**

In 2011, the CST's Red Cell Research Laboratory and Children’s Hospital Oakland’s Hemoglobinopathy Reference Laboratory joined forces to become The Red Blood Cell Laboratory (RBCL). Functioning both as a clinical and diagnostic support lab as well as a research laboratory, the RBCL (www.rbclab.com) provides integrated resources to support hemoglobinopathy diagnosis and clinical and translational hemoglobinopathy research studies.

The CST’s RBCL supports the California State Newborn Screening program, the Hemoglobinopathy Follow-Up Program, and the National Marrow Donor Program through providing hemoglobin analysis, using both protein and DNA-based assays. The RBCL also serves a key role in translational research to improve the quality of life of patients with hemoglobinopathies by providing diagnostic support for red cell disorders, as well as a large variety of assays used in translational research studies. In addition, the RBCL provides many years of experience in the design and execution of clinical and translational studies. The RBCL and its ability to translate knowledge in a reciprocal flow between scientist and clinician is at the heart of the CST’s national and international reputation in translational research.
CHILDREN’S GLOBAL HEALTH INITIATIVE

Children are the most vulnerable population on the planet and represent the greatest challenge to improving health and decreasing mortality on global scale. In 2008, CHORI launched the Children’s Global Health Initiative (CGHI). The CGHI believes the key to achieving global health for children and their communities is through creating a sustainable infrastructure for clinical service, education, training, and translational research.

Through the CGHI, CHORI researchers and clinicians can translate their wealth of skills and knowledge to developing countries through international partnerships, in-country training programs, technology transfer and research program development.
The CGHI focuses specifically on creating bi-lateral relationships in which training, resources and research results are shared. By collaborating with local communities, in-country clinics and institutions, and government agencies, the knowledge, training and education we provide persists within local resources long after we have left.

Throughout 2011, the CGHI has been actively increasing the efforts of its three Focused Country programs in Ecuador, Uganda and Vietnam. These programs focus on the cornerstones of sustainability: Capacity Building—improving infrastructure such as clinical labs and associated training to advance our understanding of in-country diseases; Clinical Service—identifying areas of clinical need and providing hands on training and education; and Translational Research—identifying areas of research that will advance our understanding of in-country diseases and help direct interventions and policy. In addition to these signature country programs, the CGHI has a variety of other clinical and translational research projects in over 30 different countries, as shown on our global outreach map above. In 2010, the CGHI garnered a United Nations Global Citizen Award for its dedicated efforts to help reduce child mortality, one of the eight different United Nations Millennium Development Goals.

“We have something we can translate to the third world, whether it’s a technology or a medical treatment regimen or a protocol that can be incorporated into their own clinical work. We help provide stability by educating and training people on the ground to carry on with the work after we leave.”

Deborah Dean, MD, MPH

Tackling Mosquito-Borne Viruses Across the Globe

Mosquito-borne viruses, called arboviruses, affect millions of people across the globe, with over 50 million cases of Dengue fever alone each year. Resources are often limited to conduct the research required to adequately fight and prevent arbovirus outbreaks. A new study by CHORI Assistant Scientist and CGHI Country Projects Director A. Desiree LaBeaud, MD, MS, and her colleagues, published in 2011, provides key data in the effort to help improve prevention and treatment strategies to
reduce worldwide infection and mortality rates.

Dr. LaBeaud’s study focused on identifying viral prevalence in mosquitoes during an outbreak of Rift Valley fever virus (RVFV) in Kenya, and represents one of the first studies of its kind in this arbovirus-rife region.

Although conducted during a RVFV outbreak, the study demonstrated significantly higher than expected prevalence numbers, with 22 percent of tested mosquito pools positive for RVFV, 18 percent positive for West Nile virus (WNV), and 3 percent positive for both. In addition, the minimum infection rates (MIRs), which are an estimation of the lowest proportion of the mosquito population that is carrying a particular virus, were also higher than expected for both RVFV and WNV.

“One of our biggest findings is that the clinical signs and symptoms of different arbovirus infections overlap,” says Dr. LaBeaud. “When an outbreak of a specific arbovirus occurs, everyone is focused on treating just that one infection, but in fact, what our study highlights is real-life simultaneous arbovirus circulation. This means that all patients with typical symptoms may not be infected by the outbreak virus. They may have a different infection, or an infection with a second virus.”

Recognizing the possibility of multiple infections or varying infections is critical for clinicians to know in order to treat patients during an outbreak, as well as to prevent further disease in the community. The other significant finding was a disparity between human and mosquito infection rates, which suggests that even though infected mosquitoes are everywhere during an outbreak, infected humans aren’t.

“This tells us that there is another component—probably infected animals—that makes a significant contribution to transmission to humans, but we have yet to identify the specific animal exposures that put humans at the most risk,” says Dr. LaBeaud.

The results of the study underscore the need for far greater resources to be applied to arbovirus prevention and treatment, and provide researchers with essential information in the effort to develop appropriate arbovirus strategies to reduce the global burden of disease.

2011 CGHI Successes

Already, the CGHI has made incredible strides for children worldwide, including:

• Helping launch the Holy Innocents Children’s Hospital, the first-ever children’s hospital in Uganda

• Joining forces with Collaborate for Africa for a full-day research symposium on Africa projects that brought together like-minded individuals with a passion for improving lives in Africa

• Implementing novel studies to improve maternal and infant health through preconception supplementation—the first of its kind in the world

• Adding four new organizations to its roster of 20 different global partnerships

Left to right: Somali girls on their way home from school, Masalani, Kenya; Vietnamese school children in a rural province awaiting screening for trachoma; Vietnamese girl getting ready to be screened for trachoma.
GLOBAL OUTREACH: CGHI FEATURED IN SHORT FILM BY GLOBAL HEALTH TV

In 2011, Children’s Global Health Initiative (CGHI) was on a very short list of global health initiatives to be selected by Global Health TV for a short film. Produced by WebsEdge, Global Health TV brings the global health community together by sharing through online films inspiring stories on the work being done around the world.

Each year, Global Health TV screens a variety of global health initiatives looking for just the right kind of project from which to create a short film. The films are posted on YouTube, Global Health TV, and are shown on continuous feed throughout the annual Joint Global Health Conference in Montreal, Canada, which brings together all the major players on the international global health stage, such as the Gates and Rockefeller Foundations, Fogherty International, and the National Institutes of Health.

“Being selected by Global Health TV is such an honor,” says CGHI Director and CHORI Senior Scientist Deborah Dean, MD, MPH. “Not only does it make us feel great about the work we are doing, but by broadcasting our project at the Joint Global Health Conference, Global TV gave us an incredible opportunity to network with key individuals and organizations in global health.”

The short film, which can be found on YouTube at www.youtube.com/watch?v=zcubAnCgy_k, showcased one of the CGHI’s many global initiatives, this one in Phu Tho Provence in Northern Vietnam. The project, highlighted in CHORI’s Center for Nutrition on page 31, involves utilizing the Vietnamese government’s agricultural infrastructure to provide—preconception—a micronutrient food supplement to boost maternal health and improve newborn outcomes.

Pricilla Joe, MD, with nurses at Holy Innocents Hospital in Mbarra, Uganda.
CHORI Noteable News 2011

Coming Home

CHORI was pleased this year to welcome to its ranks Rajnesh (Raj) Prasad, MBA, as the vice president of Research Operations (VPRO). No stranger to CHORI, Mr. Prasad has 10 years experience in various roles at Children’s Hospital & Research Center Oakland, both at the hospital and at the research institute.

“Children’s has always been my home, whether at the hospital or at CHORI. It’s where I am comfortable, and I look forward to the opportunity to return with more of a leadership role,” says Mr. Prasad, who most recently worked for California State University, East Bay, as the director for the Office of Research & Sponsored Programs.

Holding a masters degree in business administration and specializing in accounting and financial management, Mr. Prasad brings 15 years of financial management and 10 years of grants management experience to the table, including overseeing $36 million in grant funding.

“Raj has extensive experience and deep knowledge of how the research enterprise is conducted,” says Alexander H. Lucas, PhD, CHORI executive director. “With his strong background in grants management and his sharp business perspective, Raj will be an incredible asset to our organization. I couldn’t be more pleased he accepted the position.”

The VPRO will be responsible for overseeing critical research operations such as finance, laboratory and core facilities, and will serve as a key partner to senior leadership as the institute continues to align its research programs and activities with its strategic initiatives.

A Special Place

Mary Dugbartey has held human resource leadership roles in healthcare for over 20 years before joining CHORI this year as the director of Human Capital. Although Ms. Dugbartey worked at such institutions as the Alameda County Medical Center and San Pablo’s Doctor’s Medical Center, Ms. Dugbartey has always had an eye on Children’s Hospital & Research Center Oakland.

“Children’s has always had a special place in my heart on a personal level,” says Ms. Dugbartey, who was diagnosed with sickle cell disease (SCD) as an adult and referred to the hospital’s internationally renowned SCD center for treatment.

“When I heard of the opportunity to work for CHORI, I knew I had to jump on it.”

As the director of Human Capital, Ms. Dugbartey serves as a key partner to senior leadership in the planning, implementing and coordinating of a wide variety of strategic and operational initiatives.

“I really love working with people, and I pride myself on being able to speak with people in a way that makes them feel heard and respected,” says Ms. Dugbartey. “It’s not always easy to balance the organization’s bottom line with employee needs, but that’s exactly the skill that someone in my position needs to have and that is where my talent lies.”

Long-Term Vice President Retires

Kathleen Hogue Gonzalez has been with CHORI since its inception, when the organization was comprised of just a handful of researchers with a vision of what CHORI could eventually become. Then, Ms. Gonzalez managed all of the research institute’s funds in paper ledgers that were edited by hand. More than 40 years and millions of dollars later, Ms. Gonzalez leaves behind a robust and thriving research organization that she helped grow to become 8th in the nation for NIH funding of children’s research hospitals.

In her decades-long career at CHORI, Ms. Gonzalez was a mainstay of the organization, helping manage its numerous grants and providing invaluable resources to the management of the institution.

“Kathleen was a dedicated employee of CHORI, and a core member of our leadership team. We wish her well as she transitions into retirement, and will miss her and her wonderful contributions to this institute,” says CHORI Executive Director, Alexander H. Lucas, PhD.
LITTLE KERNELS OF TRUTH
After 48 years of scientific research and over 40 years of research at CHORI, Senior Scientist Stuart Smith, PhD, officially retired this year.

"Stuart will be greatly missed both as a major contributor of scientific achievement to his field and as a faculty member here at CHORI who has been a solid leader in our own community," says CHORI Executive Director, Alexander H. Lucas, PhD.

The quintessential lab scientist, Dr. Smith was driven by his passion for discovery, a passion that sustained him for nearly a half-century of groundbreaking research.

"While clinicians try to understand the human biology of disease," says Dr. Smith, "I guess you could say that what I’ve been trying to do throughout my career is to discover little kernels of truth about how one small part of the universe works."

Dr. Smith began his scientific career in the study of lipid metabolism using classic biochemical approaches, eventually integrating the tools of molecular biology and structural biology into his program that focused increasingly on the structure and mechanism of the megasynthase responsible for making fat, the fatty acid synthase (FAS). Dr. Smith’s studies over more than two decades were integral in finally confirming the particularly elusive structure of FAS. In contrast to the structural model that had long been widely accepted, Dr. Smith and his colleague, Francisco Asturias, PhD, at The Scripps Research Institute, utilized state-of-the-art electron microscopy tools to finally reveal the array of different conformations FAS adopts throughout a series of reactions in the biosynthetic pathway.

In a fitting finale for Dr. Smith’s decades long research, the landmark study was featured on the cover of the February, 2009 issue of Nature Structural and Molecular Biology and has the potential to revolutionize drug development for treating obesity, cancer and other diseases.

“There is still more work to be done of course, but there will always be more work to do,” says Dr. Smith. “I’m really pleased with having been a part of solving the conformational structure of FAS. It’s incredibly gratifying to have had the opportunity to make that kind of contribution.”

The FAS Dance. Structural and biochemical evidence revealed that the upper and lower sections of the FAS molecule undergo dramatic swinging and swiveling motions relative to each other that facilitate functional interactions between constituent catalytic domains.

$13 Million Pharmacogenetics Research Network Grant
Statins are a family of drugs that have been shown to lower cholesterol and reduce heart disease risk. They have shown a consistent reduction in heart disease in various populations of 30 to 40 percent, and are among the largest selling class of drugs in the world. Seventy percent or more of individuals who are taking statins, however, are still at risk for heart disease, suggesting a genetic basis for individual variation in treatment response.

CHORI Senior Scientist Ronald Krauss, MD, is currently supported by a five-year $13.2 million National Institutes of Health (NIH) Pharmacogenetics Research Network (PGRN) award. Dr. Krauss’s Pharmacogenomics and Risk of Cardiovascular Disease (PARC) grant focuses on identifying the genetic basis for the wide variation in effectiveness of statin treatment for reducing the risk of coronary heart disease. Composed of an interdisciplinary consortium of expert researchers from different institutions, the PARC group utilizes a variety of genomic tools to identify which genes are most strongly identified with statin’s beneficial effects. Dr. Krauss will then test whether these results can predict heart disease risk in a clinical population receiving statin treatment.
Paradigm-Shifting Publication on Alzheimer’s Disease Wins 2011 Paper of the Year Award

Millions of individuals suffer worldwide from Alzheimer’s disease (AD), a debilitating neurodegenerative disease that causes dementia. In 2011, CHORI Associate Scientist Vasanthy Narayanaswami, PhD, was involved in a paradigm-shifting discovery, however, that has the potential to significantly help unravel the mystery of AD progression.

The study consisted of an international collaboration with Vincent Raussens, PhD, who leads one of the most premier labs worldwide in the use of infrared spectrometry to probe protein structures, and his graduate students, Emilie Cerf, PhD, and Rabia Sarroukh, PhD.

Utilizing state-of-the-art attenuated total reflection-Fourier-transform infrared (ATR-FTIR) spectroscopy, the study analyzed two different structural states of the dense clustering, or aggregation, of amyloid proteins that are the physiological hallmark of AD.

“Proteins are long chains of amino acids, and how they fold together is critically important for their proper function,” explains Dr. Narayanaswami. “In AD, mis-folded amyloid proteins aggregate outside the nerve cells, causing problems in the communication between the neurons in the brain.”

The amyloid aggregates are primarily composed of amyloid beta-peptide, or Aβ, but several different stages have been identified for Aβ, which can exist as a single molecule, as larger, soluble entities called oligomers, or as insoluble fibrils. The structure of the fibril stage has long been identified as being composed of parallel β-sheets.

Researchers always assumed that the oligomer state was similarly composed of parallel β-sheets. The new study by Drs. Raussen, Cerf and Narayanaswami, however, conclusively demonstrated for the first time that oligomers are actually composed of anti-parallel Aβ-sheets.

“This important finding has implications in different areas,” says Dr. Raussen. “It explains how it would be physically possible for oligomers to interact with lipid membranes, which would allow the oligomer to be part of the toxic mechanism involved in AD, and it has a direct implication on other diseases involving mis-folded proteins that share common structural features.”

As a result, the study is a game-changer in both AD research and the study of other neurodegenerative diseases that are similarly caused by protein mis-folding. The study even garnered a 2011 Paper of the Year Award for Structure, a subset of Biochemical Journal. One of the most cited publications of the year in Structure’s online Knowledge Environment, the study significantly contributed to increasing Structure’s impact factor for the year.

Schematic representation Aβ oligomers in a putative pore-forming conformation resembling a “barrel” as proposed by Cerf et al. (Biochemical Journal (2009) 421, 415-423). The anti-parallel beta strands constitute the “staves” of the barrel (Center). The monomeric (Left) and fibrillar (Right) structures of Aβ were derived from the Protein Data Bank (ID # 1Z0Q and 2BEG, respectively). The barrel conformation is considered toxic to cells as it is ideally suited to insert into a cell membrane, potentially causing the cells to be leaky. The size of the pore and the number of strands involved in pore formation are hypothetical.
Mitochondria are about 1 to 2 micrometers long and are the power houses of living cells. But not all work equally hard. Mitochondria stained green are active and maintain their membrane potential, while those stained red sit idly. Mitochondria stained with the membrane potential-sensitive, fluorescent dye JCI in airway epithelium.
An institution is only as innovative as the researchers and clinicians that drive its inquiries. Without the influx of younger generations of practicing researchers, the promise of science is an empty one. Although CHORI is a stand-alone research institute unaffiliated with any university, fostering the next generation of scientists and clinicians is one of CHORI’s core values. CHORI provides educational opportunities in biological science at all levels of schooling, from K-12 to the postdoctoral level.

Opening the Doors of Clinical Research: CHORI Receives Doris Duke Charitable Foundation Award

In 2011, CHORI’s Summer Student Research Program was chosen to receive a highly coveted Doris Duke Charitable Foundation (DDCF) Grant to support Clinical Research Experiences for High School Students (CREHSS). Only nine institutions were selected from a pool of 63 applicants across the nation to receive three years of funding to provide high school students from underrepresented groups in medicine the opportunity to participate in mentored clinical research activities.

“The Summer Student Research Program is a central element of CHORI’s commitment to educating the next generation of scientists, and we are thrilled to join with the Doris Duke Charitable Foundation. Together we are making funded clinical research experiences a reality for high school students who would otherwise not be at liberty...
to experience the excitement of basic, translational, clinical or community-based research," says CHORI Executive Director, Alexander H. Lucas, PhD.

CHORI’s Summer Student Research Program pairs students from high school through postgraduate school with CHORI clinical, basic and translational researchers who serve as their mentors over the course of nine summer weeks. Students work with their mentors to identify a hypothesis, develop a research proposal, conduct research, and present that research in a public and professional format at the annual CHORI Research Symposium.

“We have had an excellent educational research training program in place for 30 years at CHORI, and we’ve had high school students participating in our programs for a long time,” says CHORI scientist Vasanthy Narayanaswami, PhD, who, along with Children’s Hospital & Research Center Oakland CEO, Bertram Lubin, MD, serves as a co-principal investigator for the new DDCF award.

“We have all the elements in place for training students, and a very good track record of success, with students who have participated in our program going on to follow research careers. I believe these were key factors in CHORI’s proposal being so competitive for the DDCF award.”

According to the DDCF, the ultimate goal of the CREHSS program is to increase the diversity of the biomedical research workforce by providing the motivation for students to pursue a career in clinical research or a related field. While minorities are the fastest growing segment of the US population, they remain underrepresented in medical research careers. Almost 13 percent of the population is black and about 16 percent is Hispanic, yet among medical students, only seven percent and eight percent are black and Hispanic, respectively.

“The mission of the Doris Duke Foundation is very much aligned with that of CHORI’s,” says Dr. Narayanaswami. “Oakland and the surrounding areas are some of the most diverse communities in the country, so CHORI is well-positioned to open the doors of clinical research to underrepresented populations and the local community at the same time.”

“I have witnessed medicine going from the lab bench to the patient’s bedside, and the amazing impact that can have on a patient’s quality of life.”

Anita Chanana, 2011 Summer Student Research Program Participant
Educating the Next Generation of Scientists & Clinicians

**Education Opportunities at CHORI**

**K-12 Training**
The Health Professions Internship Partnership, known as FACES (Forum, Adolescent Advocacy, Community Outreach, Education and Support) for the Future, introduces underrepresented minority teenagers to—and prepares them for—careers in healthcare. More than 50 minority students from Berkeley and Oakland high schools interact with both health professionals at the hospital and researchers at CHORI, who serve as internship supervisors and mentors.

**High School, Undergraduate & Graduate Training**
CHORI's Summer Student Research Program has become a standout in NIH-supported training programs for high school, college, and graduate students. This year marked the 30th Anniversary of the program, which was initiated in 1981 with just a handful of trainees, and now provides opportunities to at least 45 students every year. CHORI was joined in the celebration of this 30-year anniversary by California Assemblywoman, Nancy Skinner, who recognized the hard work of this year’s students by providing them with a certificate of achievement, stamped with a golden state seal.

**Postgraduate Training**
CHORI provides rich opportunities for postdoctoral fellowships through a variety of funding avenues from The Elizabeth Nash Foundation, which supports doctoral fellows interested in pursuing cystic fibrosis research, to four different National Institutes of Health funded T32 training grants, which focus on a variety of topics, such as genetics in cardiovascular research, cancer, hematology and immunology, and stem cell biology. Some of these training programs are offered in partnership with other institutions, such as the Lawrence Berkeley National Laboratory/Joint Genome Institute, the University of California, Berkeley, the University of California, San Francisco, and the California Institute for Regenerative Medicine (CIRM).

**Clinical Fellowship Training**
CHORI is a diverse resource for fellowship training programs in collaboration with the University of California, San Francisco, and a critical resource for young clinical investigators. CHORI also provides training for local community based clinics including: Highland Hospital, Eastmont Wellness Center, Asian Health Services, La Clinica de la Raza, and Juvenile Justice Center. These established relationships and training commitments with local community agencies and care providers help educate the next generation of clinical researchers while providing unique opportunities for the local community to participate in clinical studies.

**Pediatric Subspecialty Fellowships**
Accredited pediatric subspecialty fellowships offer outstanding postgraduate training in five different areas: Critical Care Medicine; Emergency Medicine; Hematology/Oncology; Infectious Diseases; and Pulmonary Medicine. All these fellowships utilize CHORI as a touchstone for clinical training research, with fellows working directly with CHORI scientists in CHORI labs to learn to bring translational research from bench to bedside.

“If we want excellence in scientific inquiry to continue on after us, we have to make sure that we train the next generation of scientists. It may be clichéd, but it is true.”

Vasanthy Narayanaswami, PhD

**CHORI WEEKLY SEMINARS**
CHORI conducts weekly seminars to provide the opportunity for educational enrichment to the local community, including CHORI researchers, the surrounding scientific and clinical community, and the public at large. This year’s roster included a variety of notable speakers, from postdoctoral fellows to scholars from the National Institutes of Health, to internationally renowned researchers. Please take a look at this year’s participants on page 109.

Summer Student Research Program Participant, Hanna Kim, during the Annual Summer Research Symposium poster presentations.
Clinical & Translational Science Institute—Clinical Research Services

Children’s Hospital & Research Center Oakland’s Clinical Research Services (CRS) is part of the University of California, San Francisco’s Clinical and Translational Science Institute (CTSI) program. Funded through the National Institutes of Health (NIH), the CTSI program at Children’s is led by Associate Program Director Laurie Schumacher, MPH, PhD. The key resource and central site for adult and pediatric clinical research at CHORI and in the East Bay, the CTSI-CRS provides vital research infrastructure for 40 percent of clinical research at Children’s, and allows clinician scientists to initiate pilot studies, implement programs and collaborate with other institutions or industry partners.

Clinical investigators use the CTSI-CRS as the basis for participating in NIH-funded network studies, such as AsthmaNet, Diabetes Trialnet, Immune Tolerance Network, Thalassemia Clinical Research Network, Sickle Cell Research, Children’s Oncology Group (COG), Rare Diseases Clinical Research Network, Therapeutic Advances in Childhood Leukemia (TACL), the Pharmacogenetics Research Network, and the Vaccine Trial and Evaluation Unit.

Utilizing CTSI-CRS resources also allows investigators both from CHORI and from the local area the unique opportunity to conduct research that focuses directly on problems facing the local community, such as unusually high rates of asthma, obesity, diabetes and other poor health outcomes. As a result the CTSI-CRS provides local community members access to research studies most relevant to their health issues.

The success we have as an affiliate of the UCSF CTSI is the result of a dynamic interchange between the CHORI research arm and the hospital’s clinical arm. The CTSI-CRS is the living representative of this bench to bedside collaboration, providing the essential resources and central hub that makes this collaboration possible.”

Laurie Schumacher, MPH, PhD

“...the success we have as an affiliate of the UCSF CTSI is the result of a dynamic interchange between the CHORI research arm and the hospital’s clinical arm. The CTSI-CRS is the living representative of this bench to bedside collaboration, providing the essential resources and central hub that makes this collaboration possible.”

Laurie Schumacher, MPH, PhD
A Closer Look: AsthmaNet

The CTsi-CRS has been expanding its research opportunities to low income populations through the Primary Care Clinic (PCC), a Federally Qualified Health Center for the underserved and poor. In addition to meeting the primary care needs of the local community, the PCC is also dedicated to participating in clinical and translational research studies that both have broad public health importance and investigate those health issues most relevant to low income populations.

Currently, the PCC is a key site for the National Institutes of Health (NIH) AsthmaNet studies. One of only eight asthma centers in the country to receive NIH funding, the PCC’s AsthmaNet, renewed in 2011, participates in national research protocols that have greater statistical power due to increased numbers, while still meeting community health needs.

“Asthma is a chronic condition in which inflammation and bronchoconstriction compromise the airways,” says Mindy Benson, a nurse practitioner and manger of both the PCC and AsthmaNet. “It’s a huge problem in the United States, but in the local community of Oakland, we have an asthma epicenter, with asthma numbers triple or quadruple those found nationally.”

The causes of asthma are multi-factorial, but include conditions particular to the Bay Area—mold because of moist conditions, housing along the 880 highway corridor, which runs through low-income housing in Oakland, and the exponential growth of the port of Oakland—which results in large trucks driving through neighborhoods and idling for as long as 10 or 12 hours while waiting for barges to come in.

While the gold standard for treating asthma is inhaled corticosteroids, which reduce inflammation globally, the studies conducted through AsthmaNet specifically look to alternative methods of treatment that can decrease inflammation on a more individualized basis.

“Each person has a different make-up of inflammation,” explains Ms. Benson. “In some patients, an antihistamine can reduce asthma symptoms, while in other patients different treatments are required. It really depends on the cause of the inflammation as to which treatment might work best.”

While we are still a long way from being able to provide treatments tailored to each individual’s own source of inflammation, AsthmaNet provides the resources to move such an ideal forward. Through AsthmaNet, CHORI clinical researchers can develop a better understanding of best practices and treatment responses, and create interventions geared toward establishing new and better treatment and prevention protocols for the future.

pulmonary hypertension in sickle cell disease, arginine and nitric oxide bioavailability, lysosomal storage diseases, iron overload, and acute lung injury.

Yet across all these disciplines served by the CTsi-CRS, CHORI clinical studies have the common goals of investigating potential contributions to disease risks; providing novel therapies and promising treatments for debilitating or life-threatening conditions; and improving patient outcomes and quality of life—one treatment, one study, one patient at a time.
CTSI-CRS Research at CHORI in 2011

• Children’s Primary Care Clinic is a Federally Qualified Health Clinic with ongoing studies in asthma, immunology, and VTEU, including: NIH AsthmaNet; UCSF’s Sandler Center for Asthma Research—conducting a cross sectional case-control gene-environment study of asthma among African American populations; and an NIH Vaccine Trial and Evaluation Unit site for HPV (rotavirus) in adolescents.

• The Cholesterol Research Center, led by Director and Senior Scientist Ronald Krauss, MD, conducts basic and clinical research on cardiovascular disease risk and prevention spanning childhood through adulthood, including: a collaboration with the hospital’s Healthy Hearts program and pediatric cardiologists that links research and the medical management of patients with obesity and cardiovascular issues; a study in African Americans on genetic susceptibility to obesity-related dyslipidemia; a pilot study to evaluate dietary choline and its relationship to increased risk of cardiovascular disease; and studies through the Family Heart and Nutrition Center, launched in 2011 and highlighted on page 33, which takes an integrated approach to basic and clinical research to prevent cardiovascular disease in all ages.

• Pediatric Surgery Research Group, a new collaboration in 2011 that joins CHORI researchers Frans Kuypers, PhD, and Jung Suh, PhD, and Children’s Hospital Oakland pediatric surgeons Wolfgang Stehr, MD, Robert Bell, MD, and Jim Betts, MD, in conducting research on metabolic and inflammatory mediators in newborns.

• Rare Diseases Clinical Research Network has 17 new and continuing studies in enzyme storage diseases for 2011-2012 that address issues of therapies, surveillance, and long term consequences of improved life spans. Paul Harmatz, MD, is leading a number of these studies, including a longitudinal, multicenter, multinational natural history study of patients with enzyme storage diseases, a phase 3 randomized, placebo controlled trial of enzyme replacement therapy, and a longitudinal study of brain disease through the NIH-sponsored Lysosomal Disease Network.

• The Hematology/Oncology Department has researchers who received funding in 2011 to conduct an international project on neurodegeneration with brain iron accumulation.

• In the area of Endocrinology, there are two ongoing NIH networks in the East Bay in collaboration with UCSF in addition to Diabetes TrialNet: the Immune Tolerance Network, a clinical trial of the drug saxagliptin in patients with type 2 diabetes funded by Bristol Myers Squibb, and a collaboration between CHORI and the University of California, Berkeley, to assess whether children with metabolic syndrome exhibit different HDL functions.

• In the area of Neurology, a variety of studies were funded in 2011, including a collaborative study with investigators at the University of California, San Diego, on therapies for neonatal seizures, and two industry-supported studies investigating therapies for tuberous sclerosis.

CTSI-CRC Research & Support Staff

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Study Coordinators
Jo Ann Johnson
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Vivian Ng
Olivia Oliveros
Rona Osmani

Study Coordinator
Melinee Stewart
"The research undertaken at this institute is only as strong as the scientists behind that research. When we celebrate CHORI’s successes, we are truly celebrating the hard work, passion and dedication of CHORI’s scientists. CHORI has become what it is thanks to them."

*Alexander H. Lucas, PhD, Executive Director, CHORI*
Most of the world’s population, even in developed countries, have modestly inadequate intake of one or more of the approximately 30 essential vitamins or minerals (V/Ms). Concern is limited because there is no generally recognized pathology. Dr. Ames has postulated what he refers to as the Triage Theory: that during evolution animals were intermittently running out of one or more V/Ms. In order to adapt, organisms developed a triage mechanism, trading long-term damage for short-term survival. Thus, during V/M shortages, proteins essential for immediate survival and reproduction retain V/Ms, while other proteins, only essential for long-term health, lose V/Ms and become dysfunctional. The theory proposes that the resulting adaptive dysfunction causes insidious damage leading to diseases associated with aging.

Dr. Ames and his colleague, Associate Staff Scientist Joyce McCann, PhD, have provided strong support for the triage theory with their landmark analyses of vitamin K and selenium. For vitamin K, all essential vitamin K-dependent proteins (required for coagulation) are activated in the liver, the organ that receives the bulk of the major dietary form of vitamin K. In contrast, all nonessential vitamin K-dependent proteins are activated in tissues outside the liver, and have functions that are disabled causing age-related conditions such as arterial calcification and bone fragility. Selenium is incorporated into 25 “selenoproteins” as selenocysteine. Several mechanisms have been developed by the body to ensure that essential selenoproteins continue to be synthesized when there is modest selenium deficiency—but at the expense of those that are nonessential. Systematic application of the triage paradigm to study the exceedingly complex biology of additional micronutrient-dependent processes will lead to a firmer theoretical foundation for nutrition and a better understanding of disease mechanisms linked to poor nutrition. Furthermore, the triage paradigm will aid in the development of biomarkers detecting biochemical changes preceding clinical symptoms of disease, and clear guidelines for appropriate use of micronutrient supplementation to minimize mutation, cancer, cardiovascular disease, cognitive decline, and immune dysfunction.

**Selected Publications 2011**


**Scientists & Staff**

Patrick Grant, PhD, Associate Staff Scientist

Jung-Hyuk Suh, MPH, PhD, Associate Staff Scientist

David Killilea, PhD, Associate Staff Scientist

Joyce McCann, PhD, Associate Staff Scientist

Ashutosh Lal, MD, Staff Scientist

Harold Helbock, MD, Visiting Scientist

Michele Mietus-Snyder, MD, Visiting Scientist

Nisha Narayanan, Study Coordinator I

Tai Holland, Staff Research Associate II

Jay Kim, Staff Research Associate I

Alicia Zhou, PhD, Postdoctoral Fellow I

Swapan Shenvi, PhD, Postdoctoral Fellow II

Teresa Klasik, Project Coordinator

Kirsten Graves, Registered Dietitian II
Infectious diseases are of particular importance for children, whose immune systems are the least developed. As a result, children remain highly vulnerable to potentially life-threatening bacteria, fungi, and viruses. All of Dr. Azimi’s clinical research studies are geared toward helping children fight infections through investigating novel antibacterial, antifungal and antiviral agents, or through studying the safety and efficacy of novel childhood vaccines. Dr. Azimi’s lab competes nationally with other children’s research institutes in order to participate in these multi-center, pharmaceutical company or NIH-sponsored studies. In addition, Dr. Azimi’s team participates in competitive epidemiological studies sponsored by the Center for Disease Control (CDC), in which they help in quantifying disease prevalence, vaccine use among certain populations, and other relevant statistics that can help guide public policies. Recent studies include a multicenter trial, coordinated by Dr. Azimi, which investigates the effects of maternal colonization with group B Streptococcus (GBS) on morbidity in newborns. The primary goal of this study was to evaluate the effect of maternal GBS colonization in causation of early onset respiratory distress of the newborns. The study showed that nearly 10 percent of prenatally GBS-negative women were positive during labor and missed intrapartum antibiotic treatment, while approximately 50 percent of prenatally GBS-positive women were GBS-negative during labor and treated unnecessarily. These findings urge the need for rapid diagnostics during labor. Maternal immunization with a GBS vaccine is a logical choice for future prevention of GBS disease in newborns. Dr. Azimi is also working on a study that describes the burden and epidemiology of rotavirus infection, a common virus that is the leading cause of diarrhea in children. The study will help determine the effectiveness of available rotavirus vaccines. By participating in studies such as these, Dr. Azimi and her colleagues in the Pediatric Infectious Diseases Department continue to make inroads in establishing best practices for childhood infectious diseases and are helping to drive new treatments and vaccine development for our most vulnerable populations.

Selected Publications 2011

Scientists & Staff
Ann M. Petru, MD, Medical Director, Infectious Disease
Charlotte J. Hsieh, MD, Associate, Infectious Disease
Samantha Johnston, MD, Associate physician, Infectious Disease
Julie A. Kulhanjian, MD, Associate, Infectious Disease
Brian P. Lee, MD, Associate, Infectious Disease

“The goal of our research program is to investigate the safety and efficacy of various agents used to treat or prevent childhood infections through participation in clinical trials that help to identify optimal and novel treatments and vaccines.”
Investigators

“Our lab investigates genetic, biochemical and immunological aspects of surface antigens of the encapsulated bacterial pathogen, Neisseria meningitidis, which causes severe cases of septic shock and meningitis. We are particularly interested in developing vaccines based on a surface protein known as factor H-binding protein.”

Peter T. Beernink, PhD
Assistant Scientist, CHORI

Dr. Beernink focuses his research on the development of broadly protective vaccines against Neisseria meningitidis, including group B strain, against which there is no licensed vaccine. One project is to identify novel meningococcal antigens (any substances that elicit an immune response) when the N. meningitidis bacteria are grown in human blood. For these studies, Dr. Beernink is using DNA microarrays, which enable him to examine all the bacterial genes in a single experiment. These studies may be useful in identifying protein antigens whose expression is increased during infection, and therefore could be potential novel targets for vaccine development.

A second area of investigation is the promising vaccine candidate known as factor H-binding protein, or fHbp. The Beernink lab is interested in understanding the sequence diversity of fHbp and its effect on function and on the cross-reactivity of the protective immune responses. Meningococci use fHbp to evade the immune system of the host by binding human complement factor H to meningococcal surfaces. Consequently, antibodies against fHbp can block the binding of human factor H, which renders the bacteria more susceptible to killing.

Dr. Beernink and his colleagues were able to exploit this susceptibility by engineering a mutant fHbp that does not bind human factor H. When transgenic mice that express human factor H are immunized with the mutant fHbp, the antibodies elicited have greater ability to block binding of factor H and higher protective antibody responses. These recent and ongoing studies have the potential to increase the efficacy of fHbp-based meningococcal vaccines.

Selected Publications 2011


Scientists & Staff

Monica Konar, Postdoctoral Fellow I
Helen Walter, Volunteer
Understanding the role that DNA sequence variation plays in human disease requires the ability to predict the functional impact of individual variations in DNA sequences (sequence variants). Not all changes in genetic expression occur from changes in DNA sequence. Epigenetic factors can influence gene expression without impacting the DNA code itself. Dr. Boffelli and his colleagues compare genomes of multiple sets of related vertebrate species in order to identify sequences that do not encode proteins but that may nevertheless play a functional role within these species.

Dr. Boffelli also leverages the deep datasets of human sequence variation generated by the 1,000 Genomes Project by using the patterns of rare and common sequence variants to tease out regions of the genome with higher likelihood of being functional. The results of these analyses, when combined with public epigenomic datasets, provides Dr. Boffelli and his colleagues with a functional annotation of the non-coding portion of the genome.

Dr. Boffelli is also exploring differences in methylation states between humans, chimpanzees and orangutans. Methylation is one of the ways in which genes are regulated without changes in the DNA sequence, and differences in methylation between species provide evidence for epigenetic changes occurring in the germline that distinguish closely related species. As part of this research, Dr. Boffelli has collaborated with Scientist David Martin, MD, to develop a high throughput second generation sequencing method to survey DNA methylation states on a genomewide scale. The method is sufficiently inexpensive to be applied to a large number of samples and used in comparative studies. Dr. Boffelli is also expanding this approach to study variation in DNA methylation states among humans and its possible correlation to disease risk.

“**We investigate the evolutionary biology and function of multiple components of the epigenome, and pursue the annotation of non-protein coding functional elements in the human genome by using computational strategies.**”
“Our research focuses on unraveling the mechanisms of infection due to Chlamydia trachomatis, an obligate intracellular bacterium implicated in hundreds of millions of infections worldwide. Our long term goal is to develop a Chlamydia vaccine.”

Deborah Dean, MD, MPH
Senior Scientist, CHORI; Director, Children’s Global Health Initiative

Chlamydia trachomatis is the leading cause of preventable blindness and the most common bacterial cause of sexually transmitted diseases in the world. Dr. Dean’s goal is to understand the pathogenesis of chlamydial diseases, the structure and evolution of the organism and essential microbial elements to develop an efficacious vaccine to prevent and ameliorate these infections.

A pioneer of C. trachomatis genotyping based on the genes that encode the major outer membrane protein of the organism, Dr. Dean and her lab have recently developed a multi-locus sequence typing scheme that significantly enhances strain identification and the association of strain types with disease phenotype. Dr. Dean was the first to identify recombination in this obligate intracellular pathogen as a critical strategy for the evolution of Chlamydia trachomatis in the human host. She has also developed a database for chlamydial genes and genomes of functional significance.

Conducting worldwide research with broad international reach, Dr. Dean’s various projects focus on molecular epidemiology and the role of host/pathogen interactions on the pathogenesis of chlamydial ocular and sexually transmitted diseases; the association of persistent organisms with disease pathology; host genetic susceptibility to chlamydial infection, inflammation, and disease among diverse global populations; and the structure and evolution of the organism at the comparative and function genomic level to understand emergence of virulent strain types. Dr. Dean is also collaborating with biotech to develop a vaccine to prevent and ameliorate chlamydial related infections among all age groups, a topical microbicde for chlamydiae using state-of-the-art nanotechnology, and a readily deployable, cost effective and rapid-point-of-care test that can be used to screen for chlamydial infections not just in hospitals and clinical labs in developed countries but globally in inner city and rural clinics, and field sites worldwide.

Selected Publications 2011

Scientists & Staff
Raymond Wan, MS, Scientist
Randy Mrsny, PhD, Adjunct Visiting Scientist
David Ojcius, PhD, Adjunct Visiting Scientist
Shireen Vaii, PhD, Adjunct Visiting Scientist
Thomas Pham, BA, Staff Research Associate I
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Brooke Liang
Elora Majumder
Van Nguyen
Lisa Patel
Tara Srinivasan
Ryan Wang

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Prior to the start of the Human Genome Project in the late 80’s, Dr. de Jong helped develop specialized technologies to stabilize and amplify large genomic DNA fragments in laboratory bacterial strains of Escherichia coli. During the early 90’s, Dr. de Jong co-developed an E. coli recombinant DNA approach to propagate very large “foreign” genome fragments in the form of Bacterial Artificial Chromosomes (BACs) and PI-derived Artificial Chromosomes (PACs). These clone resources, called “libraries,” filled a void in the strategy to decode the human blueprint. Two collections of E. coli BAC & PAC clones generated in the de Jong lab provided the source material for decoding about 85 percent of the human reference genome.

The de Jong lab has continued to create similar resources to support genome projects for other species, for diagnostics, and as a starting point for functional gene studies. The BACs from other species permit comparisons with human DNA, leading to gene-function hypotheses and to the identification of DNA elements conserved over evolutionary time.

CHORI currently maintains in deep-frozen state (-80 degrees Celsius, in 120 freezers) over 40 million E. coli clones representing more than 150 species, and has distributed over 240,000 distinct clones to the worldwide scientific community. This distribution is organized through the CHORI BACPAC Resources Center (BPRC, http://bacpac.chori.org). There are currently over 8 million data records in the NCBI public databases using the “CHORI & BAC” label; many more records beyond those exist but use abbreviations & labels other than CHORI. In 2011, the de Jong lab distributed approximately 15,210 E. coli clones to 2,355 scientists, and completed a NIH-funded project to create 7,000 “conditional knock-out vectors” for analyzing more than 5,000 mouse genes as proxies for human gene analysis. Current research in the de Jong lab focuses heavily on the development of resources for stem cell biology and tools for analyzing (human-) genome diversity. Dr. de Jong recently demonstrated efficient techniques to insert large fluorescent reporter genes (entire BACs) into human pluripotent stem cells as transposable elements. Such reporters allow tracking differentiation into a large variety of specialized cell types.

“Our goal for more than 25 years has been to understand the structure and function of the human genome; to develop unique resources and technologies that increase that understanding; and to disseminate them worldwide to the scientific community, which we accomplish through our BACPAC Resources Center.”

**Scientists & Staff**

Barbara Swiatkiewicz, Senior Staff Research Associate

Yuko Yoshinaga, PhD, Assistant Staff Scientist

Maxim Koriabine, PhD, Assistant Staff Scientist

Ann Holtz-Morris, Staff Research Associate II

Maria Kimwell, Staff Research Associate III

Ann Holtz-Morris, Staff Research Associate III

Christine Jung, PhD, Visiting Scholar

Cleo Eng, Volunteer

Hee-Yun (Helen) Park, Volunteer
While huge inroads have been made in the care of premature babies, researchers are still presented with the fundamental challenge of these infants being born before their lungs have fully developed. As a result, much of Dr. Durand and his research group’s focus is on the participation in national and international clinical trials that investigate currently available medications or techniques to help premature infants breathe, including: high frequency ventilation, liquid ventilation, surfactant replacement, and inhaled nitric oxide. In addition, Dr. Durand’s Neonatal Critical Care Research Group has also participated in, or taken the lead on, pilot clinical trials of novel therapies to reduce the risks of long-term brain damage in full term pregnancies, with the goal of improving neonate survival without negative neurological impacts.

Selected 2011 Publications
Ervin H. Epstein Jr., MD  
Senior Scientist, CHORI  

The hedgehog (HH) signaling pathway is well known and is implicated in a variety of different cancers. Dr. Epstein’s program currently encompasses both molecular and cell based studies, as well as clinical studies. The basic research utilizes murine basal cell carcinoma (BCC) cell lines and mice genetically predisposed to develop BCCs due to their Ptch1+/− genotype, while the clinical trials in humans focus on individuals who are genetically predisposed to develop BCC tumors—patients with the basal cell nevus (Gorlin) syndrome, or BCNS, who also have the PTCH1+/− genotype.

Dr. Epstein’s lab also participated in the identification of the PTCH1 gene defect in BCNS patients that led to the understanding of the pivotal role of HH signaling in BCCs and is currently testing the anti-BCC effects of the first-in-man HH inhibitor, GDC-0449/vismodegib, in BCNS patients. A Data Safety Monitoring Board analysis of the interim data from the study indicated a highly statistically significant difference between placebo and drug groups, in particular, in reduced development of new BCCs of clinically significant size, reduced size of those BCCs existing at the start of the trial, and the acceptable adverse events, none of which appeared to differ from those observed in previous trials of this agent. As a result, the Board recommended that the trial be unblinded so that patients who were taking placebo could be offered the active drug.

**Selected Publications 2011**


**Scientists & Staff**

Ying Grace Wang PhD, Assistant Staff Scientist
Yefim Khaimskiy, Staff Research Associate
Joy Wang, Staff Research Associate
Lynn Wang, Staff Research Associate
Joselyn Lindgren, Project Coordinator
Maria Acosta-Raphael, Study Coordinator I
Anastasia Makarova, Postdoctoral Fellow
Anita Chanana, Student Intern
Jane Cheong, Student Intern
Eileen Libove, Student Intern
Serena Sam, Student Intern
Christiania Yuan, Student Intern
Alexander Lee, Volunteer
Jean Tang MD, PhD, Consultant

“Our research focuses on hedgehog signaling and cancer, in particular on the activation of this signaling pathway due to genetic mutations in basal cell carcinomas, the most common human cancer.”
Dr. Erlich investigates the highly polymorphic human leukocyte antigen (HLA) genes and mitochondrial DNA (mtDNA) variation, and the mechanisms that generate this variation. These genetic systems are well known for their applications in the histocompatibility and forensics fields, but are also pertinent to studies of human disease, history, and evolution. Dr. Erlich’s immunogenetics research focuses on genetic associations with complex diseases, on autoimmunity, and on type 1 diabetes (T1D) and demonstrated that multiple HLA class I and class II alleles and haplotypes contribute to susceptibility and resistance to type T1D, as well as to other autoimmune diseases. The prediction and, ultimately, the prevention, of T1D is a major research goal.

Dr. Erlich investigates the mechanisms by which HLA polymorphism results in susceptibility and resistance to both cancer and to infectious and autoimmune diseases. Dr. Erlich also seeks to make inferences about human history by relating the distribution of HLA polymorphism to global patterns of disease prevalence.

For the past several years, Dr. Erlich’s lab has developed and applied next-generation sequencing methods for analyzing the variation at the HLA genes and of mtDNA. These methods, characterized by massively parallel clonal sequencing, allow very high resolution and very high throughput HLA sequencing as well as the ability to use mtDNA sequence analysis to identify the contributors in forensics mixed specimens, a very challenging area in forensic DNA analysis.

Selected Publications 2011


Investigators

Dr. Feusner and his team of researchers and clinicians focus their research mainly in participating in the Children’s Oncology Group (COG), the world’s largest cooperative research enterprise focused on childhood cancers. By combining the efforts of researchers on a global scale, the COG is able to investigate novel cancer therapies on a large-scale basis much more efficiently than any group could do alone. By participating in the COG, Dr. Feusner’s group has helped in the international effort to dramatically increase pediatric cancer survival rates to over 70 percent.

In addition to the COG, the Feusner team also participates with the UC Berkeley Department of Public Health in a large study of acute leukemia in California (now in its 11th year) and with two smaller organizations targeting special pediatric cancer subgroups: one for treatment of relapsed leukemia or lymphoma (TACL) and another investigating innovative means of treating children with high risk brain tumors (Head Start). The Feusner group currently has 42 different open studies investigating the etiology, biology, and treatment of 10 different types of childhood cancers.

Dr. Feusner has also been very active in acute myeloid leukemia (AML) research, chairing two studies of acute promyelocytic leukemia [Apl] locally, Dr. Feusner is investigating: hyperleukocytic leukemia in a joint study with Emory, and the Hospital for Sick Children in Toronto, Canada; the proper duration of antibiotic therapy for children with neutropenia and sepsis; and the incidence of and treatment for meningeal leukemia of APL, with Stanford and Memorial Sloan Kettering.

Selected Publications 2011


Marsh A, Lo L, Cohen R, et al. Sorafenib (Soraf) and bevacizumab (Beva) for recurrent metastatic hepatoblastoma (HB). Ibid. abstr 9575, pg 603S. 2011 ASCO meeting.


Scientists & Staff

Caroline Hastings, MD, Director, Hematology/Oncology Fellowship Program

Hematology/Oncology Associates

Barbara Beach, MD
Carla Golden, MD
Jacob Garcia, MD
Jennifer Michlitsch, MD
Robert Raphael, MD
Joe Torkildson, MD

Hematology/Oncology Fellows

Ana Aguilar, MD
Jo Chung, MD
Jamie Jacobs, MD
Anne Marsh, MD

“Cancer is the leading cause of pediatric disease-related deaths, with thousands of children diagnosed with cancer each year. We investigate why children develop these potentially fatal cancers, and how best to treat them. Our goal is to contribute to investigations of the etiology and treatment of childhood cancers.”
Despite the continuous microbial challenge to the airways, the healthy, uninflamed airway epithelium is able to efficiently inactivate microbes and remain uninfected owing to constitutively active defense mechanisms expressed by the airway epithelium. In contrast, cystic fibrosis airways are prone to bacterial infections, and CF lung disease is difficult to treat. The major reason for CF complications is persistent bacterial lung infection. The reason for the dysfunction of airway defenses in CF is not well understood but represents a major area of intervention.

CF is caused by a mutation in an epithelial chloride channel, called CFTR. CFTR is responsible for epithelial salt and water secretion and it maintains the fluid composition of the airway surface liquid, which is the thin film of fluid that lines the airway mucosa. The impact of CFTR mutations on the airway defense function is unclear but it has been noted that CFTR is also responsible for bicarbonate secretion and thus, it affects the pH of the airways. CF airways are too acidic. Recently, Dr. Fischer identified a novel defense mechanism in the airway epithelium that is inhibited by an acidic pH. It is based on the NADPH oxidase isoform DUOX1 that is expressed in the apical membrane of ciliated cells. Dr. Fischer is researching a mechanism of airway epithelial defense by which DUOX1 activity is regulated by the pH of the airways. Focusing on epithelial acid and bicarbonate secretion that together determine the pH of the airways, Dr. Fischer measures intracellular pH, transport pathways of acid and bicarbonate across the plasma membrane and the pH of the airway surface liquid using bioelectrical techniques and fluorescence microscopy. Dr. Fischer’s long term goal is to identify the role of airway pH on bacterial killing and strategies to adjust the pH and reinstate normal antibacterial airway activity.

**Selected Publications 2011**


Investigators

Dr. Flori and the Pediatric Critical Care Clinical Research Group (PCCCR) investigate genetic predispositions to, and biomarkers of, worse outcomes after lung injury and sepsis, and ways to improve the diagnosis and prediction of disease severity in pneumonia. The PCCCR group is currently involved in 14 active clinical research projects, of which 9 are federally funded. The research in pediatric intensive care has always centered on understanding the burden of critical illness as well as the mechanisms and pathophysiology of disease while also testing new strategies to improve morbidity and mortality. Additional research includes independent investigations in clinical decision support tools for use in a hospital electronic medical record and in the transport of critically ill children, in identifying risk factors for brain edema in pediatric diabetic ketoacidosis and in pediatric neurocritical care.

The PCCCR group also offers subspecialty training in pediatric critical care; part of such training involves fostering the independent interests of research fellows. In support of such educational research, the PCCCR group has explored many new worlds such as medical ethics, transport and telemedicine, acupuncture, diabetes and racial disparities in pediatric critical care.

Finally, as there are fewer than 5,000 pediatric critical care beds in the US compared to approximately 90,000 adult critical care beds, Dr. Flori realizes that the best opportunities to understand pediatric critical illnesses are in collaboration. The PCCCR group participates in national and international collaborations with the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, UCSF Medical Center and the Cardiovascular Research Institute, San Francisco General Hospital, Cincinnati Children’s Hospital Medical Center, Children’s Hospital Boston, Stanford University and the Lucille Packard Children’s Hospital, NIH, Centers for Disease Control and Prevention (CDC), and the California Department of Health.

Selected Publications 2011


Scientists & Staff

Natalie Cvijanovich, MD, Intensivist, Pediatric Critical Care
R. Scott Heidersbach, MD, Intensivist
Mary McIlroy, RN, Clinical Nurse Specialist
Julie Simon, RN, Research Nurse, Intensive Care Unit
Jenny Tan, RN, PNP, Transport Coordinator

“As most pediatric illness involves respiratory disease and infection, we focus on the epidemiology, diagnosis and treatment of neonatal and pediatric respiratory failure and the diagnosis, pathophysiology and treatment of overwhelming shock and infection (sepsis).”
Osteoporosis, a condition of skeletal fragility, significant morbidity and decreased quality of life, is rapidly becoming one of the most prevalent and costly health care concerns in the United States. Currently, 30 million Americans are diagnosed with osteoporosis, an estimate projected to triple in 60 years because of increasing longevity and unhealthy lifestyle trends. Contrary to popular belief, osteoporosis is not simply a health problem of the elderly; it is present in many children with chronic disease. Because there is no established “cure” for osteoporosis, prevention is vital and must begin in childhood. Optimizing gains in bone strength during childhood is critical to achieving a robust peak bone mass, which serves as the individual’s bone bank for life. There are inevitable withdrawals of bone mineral with aging, menopause, and exposure to illness or medications. The greater the peak bone mass, the more bone losses an individual can tolerate without becoming vulnerable to fractures and subsequent pain and disability.

Dr. Fung is currently working to elucidate the etiology of bone deficits in many pediatric patients with chronic disease, such as those with sickle cell disease, thalassemia, mucopolysaccaridosis, vitamin D deficiency rickets and cerebral palsy. Dr. Fung’s research shows that for many disorders, bone formation is reduced, which is related to poor nutritional status and reduced physical activity. To explore this further, the Fung lab has three randomized clinical trials that are in progress. The first trial, funded by the NIH, will assess the effect of zinc supplementation on bone health in patients with thalassemia. The second is a pilot trial focused on the feasibility of vibration therapy to improve bone health in thalassemia. The most recent is a USDA funded trial to explore if calcium supplementation may curtail bone losses observed in healthy pregnant women.

Selected Publications 2011


**Neisseria meningitidis** is a major cause of bacterial meningitis (an infection of the membranes covering the brain) and sepsis. Six strains defined by different sugar capsules are responsible for nearly all cases of this disease. Dr. Granoff and his colleagues are investigating the vaccine-potential of protein antigens for inclusion in a universal vaccine against all meningococcal strains.

One of the most promising antigens is called factor H binding protein (fHbp). This protein is present in nearly all meningococcal strains and binds the complement-down-regulator, factor H (fH). Binding is specific for human fH and is an important mechanism by which the organism evades host defenses. Dr. Granoff is investigating mechanisms by which anti-fHbp antibodies bind to the bacterial surface, activate, complement, and confer protection against disease.

In human fH transgenic mice, binding of fH to a fHbp vaccine antigen impaired protective in human fH transgenic mice, binding of fH to a fHbp vaccine antigen impaired protective serum antibody responses. To improve protection, Dr. Granoff’s lab prepared mutant recombinant fHbp molecules that did not bind fH; these recombinant fHbp molecules appear to be superior vaccines. The lab also prepared outer membrane vesicle (OMV) vaccines from mutant meningococcal strains engineered to delete unwanted (toxic) molecules and to over-express fHbp. In mice and infant non-human primate models, the mutant OMV vaccines elicited broadly protective serum antibody responses.

**Selected Publications 2011**


**Scientists & Staff**

Rolando Pajon, PhD, Associate Staff Scientist
David Vu, MD, Assistant Staff Scientist
Helen Walter, PhD, Visiting Scientist
Andrew Fergus, Staff Research Associate II
Emily Braga, Staff Research Associate I
Mike Kai Wick Cheng, Staff Research Associate I
Denise Playdie Green, Staff Research Associate I
Kathleen Dunphy, PhD, Postdoctoral Fellow
Serena Giuntini, PhD, Graduate Student

“The goal of our research is to increase our understanding of how the bacterial pathogen, Neisseria meningitidis, causes disease in humans. With this greater understanding, we can develop new vaccine approaches for disease, particularly of group B strains, for which there are no currently licensed vaccines, and group A, W-135 and X strains, which cause epidemics in Africa.”

**Dan M. Granoff, MD**
Senior Scientist, Clorox Endowed Chair, Center for Immunobiology & Vaccine Development, CHORI
Investigators

“The goal of our research is to explore a variety of current problems in our field via national and international collaborative studies on cystic fibrosis and asthma; state studies specifically on our infants screened and positive for cystic fibrosis; and individual studies devised for individual patients by our fellows training in pediatric pulmonology.”

Karen Hardy, MD
Clinical Scientist, CHORI; Pediatric Pulmonary Department, Children’s Hospital Oakland

Dr. Hardy and her team of pediatric pulmonologists work together to undertake clinical trials in addition to daily clinical practice that span state, national and international boundaries. Current studies include participation in an international project to evaluate the safety and efficacy of long acting beta agonists (LABA) in combination with inhaled steroids for young children with asthma, and nearly half a dozen national studies that explore a variety of different issues from the genotypic and phenotypic differences or similarities of cystic fibrosis (CF) disease progression between twins and siblings, to pulmonary changes in patients receiving bone marrow transplant for sickle cell disease or therapeutic enzyme replacement for a condition called mucopolysaccardosis. In addition, Dr. Hardy and her colleagues are participating in California state studies that investigate the benefit of using sweat studies for CF diagnosis in newborns through two years of age, and the proficiency of genetic CF testing that will help serve as a pilot program for the Center for Disease Control to develop a national proficiency testing protocol.

In addition, a variety of fellows have been undertaking individual research projects as part of their successful graduation from the pediatric pulmonary fellowship. Dr. Villa is evaluating the effect of surgery to remove tonsils and adenoids on children with obstructive sleep apnea and asthma, while Dr. Bseikri is working with Senior Scientist Bruce Ames, PhD, to develop a translational project focusing on the effect of repleting micronutrient deficiencies in urban obese asthmatic teens in the Bay Area. This will be achieved by administering a specially developed nutrient bar twice daily along with exercise, nutritional and lifestyle education. While the research undertaken by Dr. Hardy and her colleagues can be as varied as the patients they see in the pediatric intensive care unit, the common theme among all the research is to improve the pulmonary health and wellbeing of children, both those they see in daily practice and those they will never meet.

Selected Publications 2011


Scientists & Staff
Edward Fong, MD, Pulmonologist
Manisha Newaskar, MD, Pulmonologist
Hazel Villa, MD, Pulmonary Fellow
Eric Zee, MD, Pulmonologist
Renee Benson, MD, Pulmonologist
Mustafa Bseikri, MD, Pulmonary Fellow
DJ Kaley RN, MSN, Registered Nurse, Case Manager
Alex Wulff, Research Coordinator
Linda Olson, Office Manager
The mucopolysaccharidoses (MPS) are a group of 11 rare genetic disorders in the lysosomal storage disease (LSD) family, each caused by the absence or reduced function of lysosomal enzymes needed to break down glycosaminoglycans (GAGs). GAGs are long chains of carbohydrate constituents of bone, cartilage, and connective tissue. In the absence of lysosomal enzyme function, these GAGs collect in the cells and connective tissues and result in progressive cellular damage and organ system dysfunction. The mucopolysaccharidoses share many clinical features but have varying degrees of severity.

Treating these patients has depended on medical and surgical care, with hematopoietic stem cell transplantation as the only cure. Since 2003, enzyme replacement therapy (ERT) has been approved for MPS I (Aldurazyme®, Genzyme/BioMarin), II (Elaprase, Shire) and VI (Naglazyme®, BioMarin) to provide specific therapy administered intravenously. Dr. Harmatz participated in the clinical trials for MPS II and VI that led to FDA approval. At present, Dr. Harmatz is leading one of only two US sites participating in a longitudinal, multicenter, multinational natural history study for MPS IVA or Morquio A. He is also PI of one the US sites for the phase 3, randomized, placebo controlled trial of enzyme replacement therapy and is presently enrolling patients for this study. In addition to these trials, Dr. Harmatz and his colleagues have been participating in the NIH-sponsored Lysosomal Disease Network studies and have been enrolling patients into a longitudinal study of brain disease in MPS I and II. The research group will also be participating as one of the sites evaluating spinal fluid enzyme therapy to prevent or treat MPS-related brain disease. These studies require close collaboration with radiology (Kenneth Martin, MD) and neurosurgery (Peter Sun, MD).

In addition, the Harmatz group is also focused on iron overload in hemoglobinopathies. Together with CHORI Senior Scientist Elliott Vichinksy, MD, and the Department of Hematology, Dr. Harmatz and his colleagues are evaluating mechanisms of iron trafficking and development of monitoring and treatment strategies.

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**Scientists & Staff**

- Patrick Walter, PhD, Staff Scientist
- Marcela Weyhmiller, PhD, Staff Research Associate II
- Jo Ann Johnson, MPH, Study Coordinator II
- Jacqueline Madden, MSN, Pediatric Nurse Practitioner
- Debra Citron, Nurse Clinician
- Jane Katsura, Nurse Clinician
- Adijat To La Asuni, BA, Case Assistant I
- Elena Yu, BS, Case Assistant I

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**Selected Publications 2011**


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“Our gastroenterology research group is focused on translational clinical research on the treatment of lysosomal storage diseases focused primarily on the mucopolysaccharidoses.”
Human cytomegalovirus (CMV) is a virus often acquired during childhood. Although infections with CMV do not produce any outward symptoms in healthy people, they can be the source of substantial morbidity and mortality in transplant recipients, whose immune systems are significantly depleted as part of standard preparations for accepting donor organs. CMV is also a major cause of long-term disability in children who acquire this virus from their mother during pregnancy. Because of this, the development of new antiviral therapies and of an anti-CMV vaccine is urgently needed.

Once acquired, CMV remains within infected people for the rest of their life in a dormant form, called latency. Periodically, this virus re-emerges from latency in a process called reactivation, and can spread to new individuals. The ability of this virus to remain latent for long periods of time without ever being eliminated by the immune system renders the development of novel treatment and prevention therapies particularly difficult.

The focus of Dr. Hertel’s current research is to identify the key viral and cellular factors controlling CMV infection of dendritic cells (DC), a crucial cell type for the generation of immune responses against pathogens and vaccines. Understanding how CMV gains access to DC, and how DC defend themselves from infection is vital for the development of new antiviral therapies and of an effective anti-CMV vaccine.

Another goal of Dr. Hertel’s research is to determine the mechanisms enabling lifelong maintenance of latent viral genomes in multiplying bone marrow stem cells. In particular, Dr. Hertel seeks to establish whether viral genomes are replicated during latency and whether they are subsequently partitioned into daughter cells. These studies will provide some urgently needed insights into poorly understood aspects of CMV latency and may become the foundation for the development of innovative therapies to eradicate CMV from the human population.
Dr. Hoppe studies genetic modifiers of sickle cell disease (SCD), and in particular, of stroke in SCD, which has led to the research and development of novel genotyping assays to identify potential risk-conferring genes in SCD. Being able to predict which SCD patients are at greater risk for stroke allows clinicians to intervene sooner with targeted prevention strategies. More recent research in the Hoppe lab has been on investigating the use of the statin drug, simvastatin, in SCD treatment. A recent FDA-sponsored phase I/II trial investigating the safety and preliminary efficacy of simvastatin treatment in SCD demonstrated significant changes in plasma biomarkers of inflammation and endothelial activation, which are now being extended to a phase II study to determine whether simvastatin translates into clinical benefit. As part of this research effort, Dr. Hoppe was awarded in 2011 a Doris Duke Charitable Foundation Innovations in Clinical Research grant to conduct a pilot clinical trial investigating whether treatment with simvastatin reduces vaso-occlusive pain episodes in patients with SCD. This trial incorporates the use of a novel smartphone application to monitor daily pain ratings.

In addition to the clinical studies in SCD, Dr. Hoppe also leads, along with CHORI Senior Scientist Frans Kuypers, PhD, the Red Blood Cell Laboratory (RBCL), which serves as a clinical and diagnostic support laboratory and as a core resource for clinical and translational research studies pertaining to hemoglobinopathies. The RBCL serves several different programs, including the Children’s Hospital Oakland’s comprehensive Sickle Cell and Thalassemia centers, the California State Newborn Screening (NBS) Hemoglobinopathy Follow-up Program, the National Marrow Donor Program and several other cord blood banks, as well as clinical referrals from other state newborn screening programs and health care providers.

Several novel molecular assays have been developed and validated in the RBCL, including a multiplex linear array assay capable of detecting more than 95 percent of the most common beta-thalassemia mutations; gap-PCR assays to identify the most common alpha-thalassemia and HPFH deletional mutations; and a multiplex ligation-dependent probe amplification (MLPA) assay to screen for large globin gene deletions.

"The focus of my work is on translational research in sickle cell disease, in particular on looking at genetic modifiers of sickle cell disease. My research interests have more recently extended to clinical investigations of statins as a potential therapy for sickle cell disease."
 Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects approximately one percent of the adult world population in a 3:1 female to male ratio, and results in inflammation and progressive destruction of “synovial joints.” It is one of the leading causes of chronic disablement worldwide. Recent genetic studies have identified several regions in the genome that are associated with RA, although it is not clear yet which genes actually cause the disease. Despite RA being more common among women, gender-specific factors have not been thoroughly investigated. Further, among women, some as yet unknown factors related to pregnancy appear to influence RA disease activity. A natural improvement of RA symptoms occurs during pregnancy in approximately 48 to 75 percent of women with RA, a phenomenon that is yet to be explained. This is followed by a flare, usually by three to four months post-partum. Hence, Dr. Jawaheer’s research, which involves a variety of different international collaborations, is focused on identifying risk factors, including genetic factors, which may account for the increased occurrence of RA among women. In addition, Dr. Jawaheer is examining responses to treatment among men and women with RA in several large datasets. Dr. Jawaheer and her colleagues have shown that although men appear to have a worse prognosis, they respond better to treatment than women. Further investigations focus on possible factors that may contribute to gender disparities in treatment responses. Finally, Dr. Jawaheer is also following up a pregnancy cohort of women with RA, to identify what gene or genes may be involved in controlling disease activity in RA, leading to the natural amelioration then relapse. An understanding of these natural phenomena may help uncover novel biomarkers and drug targets, which may have a huge impact on RA prognosis and treatment.

Selected Publications 2011

“Our primary goal is to provide a better understanding of the genetic and environmental factors that influence the onset of rheumatoid arthritis (RA), fluctuations in RA disease activity and patient responses to treatment, with a focus on gender-specific aspects.”

Damini Jawaheer, PhD
Assistant Scientist, CHORI

Damini Jawaheer, PhD
Assistant Scientist, CHORI
Although the importance of maternal nutrition on pregnancy outcome was identified nearly 100 years ago, few pregnant women receive dietary advice. Currently, over half of pregnant women in the United States are obese. Obesity shifts maternal metabolism, which increases the fetal fuel supply, causing excessive fetal fat gain. Preliminary data show that babies overweight at birth continue to gain and retain excess fat after birth, possibly because they were 'programmed' to do so in utero. Dr. King and her colleagues led a dietary intervention study in obese women demonstrating that simple dietary adjustments made during the last half of gestation reduced maternal fat gain, improved carbohydrate and lipid metabolism, and limited fetal overgrowth.

In contrast, women in developing countries usually enter pregnancy in an undernourished state. Attempts to improve maternal nutrition and fetal growth with vitamin-mineral supplements have been unsuccessful. Dr. King is currently investigating the impact on fetal growth of daily consumption, pre-conception, of a small, nutrient-dense meal among undernourished Vietnamese women to determine if maternal nutrient stores at conception are the primary determinants of pregnancy outcome. Shifting nutritional focus from post- to pre-conception would be a novel nutritional approach that could provide the answer to improving overall maternal health and nutritional status.

Dr. King also conducts research on zinc, an essential nutrient that is key to reducing childhood diarrhea and pneumonia, improving growth, and decreasing infant and child mortality in developing countries. Despite the proven impact of zinc nutrition, two billion people worldwide are at risk for zinc deficiency. Solutions to zinc deficiency have been hampered by the inability to measure an individual’s zinc nutrition, a problem Dr. King’s current research hopes to resolve. Recent in vitro cellular studies in Dr. King’s lab demonstrate that cellular markers of zinc nutrition are more sensitive to changes in zinc status than plasma/serum zinc. A human zinc depletion/repletion study is underway to validate these cellular findings and could provide the key to accurate measurements of nutritional zinc status.

Selected Publications 2011


Scientists & Staff
Barbara Sutherland, PhD, Associate Staff Scientist
June Tester, MD, Clinical Scientist and Co-Director of HEALTHy Hearts, Children’s Hospital Oakland
Sarah Burke, BS, Staff Research Associate II
Tai Holland, BS, Staff Research Associate II
Lisa Sawrey-Kubicek, MS, Research Dietitian II
Andrew G. Hall, PhD, Postdoctoral Fellow I, and UCD
Kasuen Mauldin, PhD, Postdoctoral Fellow I
Francis Chen, BS, Predoctoral Fellow, UCD
Andrea Hacker-Thompson, MS, Predoctoral Fellow, UCD

“The goal of our research is to understand the metabolic and health effects of dietary interventions in pregnant women and children. We aim to identify diets that reduce the risk of maternal insulin resistance, infection, and undernourishment, all of which influence the long-term health of the mother and child, while developing new biomarkers of nutrient status, particularly zinc.”

Janet C. King, PhD
Senior Scientist, CHORI
Despite recent advances in treatment, cardiovascular disease (CVD) remains the leading cause of death in the US and will soon achieve this status globally. The Krauss research group aims to reduce this enormous disease burden by focusing on three research areas.

First, the Krauss group has developed a sophisticated new procedure for lipoprotein analysis that provides more specific information than ordinary testing and improves the assessment and management of CVD risk. Second, recent studies by Dr. Krauss demonstrate that dietary carbohydrate restriction can reverse the atherogenic dyslipidemia found in a high proportion of overweight and obese individuals, even in the absence of weight loss and independent of saturated fat intake. These findings contributed to new national dietary guidelines that place a greater emphasis on limiting refined carbohydrates rather than fats. In addition, the Krauss group recently demonstrated that individuals with atherogenic dyslipidemia have a reduced capacity to oxidize fat, suggesting a common metabolic defect contributing to both adiposity and dyslipidemia.

Finally, in collaboration with CHORI Assistant Scientist Marisa Medina, PhD, Dr. Krauss and his colleagues investigate the application and development of genomic methodology for dissecting genetic influences on therapeutic responses to statins, the most widely prescribed class of drugs for reducing CVD risk. This research is supported by a large, nationwide, multi-investigator NIH PARC grant. Dr. Krauss provided the first genome-wide study of genetic variants associated with cholesterol response to statins. Using a unique repository of lymphocyte cell lines derived from their clinical trials, the Krauss group links statin response to variations in cholesterol metabolic pathways. This “systems” approach integrates genomic sequence variation and gene expression data, and promises to provide comprehensive molecular assessment of the full range of statin treatment effects.

Selected Publications 2011


Cholesterol Research Center
Kathryn Hoffman, Study Coordinator
Deborah Bruimley, Study Coordinator
Daniela Molien, Study Coordinator
Robin Rawlings, RN, Manager, Nursing
Megan Bennett, Management Coordinator
Caryn Goldman, Nurse Clinician

Postdoctoral Fellows
Fred Bauzon, PhD
Eugene Bolotin, PhD
Feng Gao, PhD
Beth Theusch, PhD
Yu-Lin Kuang, PhD

Scientists & Staff
Nastaran Faghihnia, PhD, Assistant Staff Scientist
Nathalie Bergeron, PhD, Associate Staff Scientist
Sally Chiu, PhD, Associate Staff Scientist
Barbara Sutherland, PhD, RD, Associate Staff Scientist
Katie Wojnoonski, Laboratory Manager Coordinator
Joseph Orr, Staff Research Associate
Larry Wong, Staff Research Associate
Bahareh Sahami, Staff Research Associate
Over the last 25 years, the Kuypers lab defined several factors and proteins involved in the lipid bilayer organization of red blood cell membranes, and defined how alterations, in part induced by oxidant stress, lead to pathology in sickle cell disease and thalassemia. In 2011, Dr. Kuypers and CHORI Associate Staff Scientist Eric Soupene, PhD, expanded their lipid biology studies to malaria, a mosquito-born infection, and, with CHORI Senior Scientist Deborah Dean, MD, MPH, to Chlamydia trachomatis, an intracellular parasite that causes a variety of infections worldwide.

The Kuypers lab serves as a central site for the analysis of blood components in translational research studies in hemoglobinopathies, while Dr. Kuypers directs the CHORI Red Blood Cell Laboratory (www.rbclab.com). As part of the translational research support, Dr. Kuypers has developed different strategies to improve stem cell transplant protocols, as transplantation is the only cure for hemoglobinopathies. Dr. Kuypers, in conjunction with CHORI Scientist Vladimir Serikov, MD, PhD, has also shown that the human term placenta is an important source of hematopoietic stem cells. Working with CHORI Scientist Bindu Kanathezhath, MD, the Kuypers lab has developed ways to modulate T-cell behavior to improve stem cell engraftment and drastically reduce graft versus host disease. In 2011 Dr. Kuypers and Serikov provided first-time proof that the chorion of the human term placenta contains cells that can be grown in cell culture as multipotent cells, which have a high therapeutic potential.

Finally, the Kuypers lab is working with the Mechanical Engineering Department at UC Berkeley to develop novel ways to apply nanotechnology for the analysis of heterogeneous pathologic cell populations, including circulating tumor cells, and Dr. Kuypers has started a collaborative project with the Surgery Department at Children’s Hospital Oakland to better define the biology of Necrotizing Endocolitits, a devastating condition in pediatric patients.

Selected Publications 2011


Rift Valley fever (RVF) is a life threatening, mosquito-borne zoonotic disease found in many areas of sub-Saharan Africa and the Middle East. Because Rift Valley fever virus (RVFV) readily infects both humans and their livestock, RVF poses a severe, dual threat to public health and to livestock food production in endemic regions. Humans infected with RVFV can suffer a wide spectrum of disease, from mild febrile illness to fatal hemorrhagic fever. The United States has all of the necessary components (mosquitoes, livestock, and humans) to allow RVFV to embed in our local ecosystems; therefore RVFV remains a high priority threat for both the Centers for Disease Control and Prevention (CDC) and the United States Department of Agriculture (USDA).

Currently Dr. LaBeaud and her colleagues are working to understand the broad spectrum of human RVF disease by identifying the environmental, genetic and immunologic risk factors that determine RVFV-related disease syndromes. The LaBeaud lab is also trying to improve field diagnostics for RVFV and other arthropod-borne viral infections, so that early diagnosis can prevent disease spread and optimize control.

In addition, Dr. LaBeaud also investigates maternal parasitic infections, such as malaria, schistosomiasis, and soil-transmitted helminths, and infant vaccine response. Maternal parasitic infections can affect fetal immunity, but it is unknown whether treating these infections improves vaccine efficacy in the developing world. Current NIH-funded research in the LaBeaud lab may help identify the importance of treating maternal parasitic infections as part of any vaccine campaign or future vaccine trials.

**Selected Publications 2011**


“The goal of our research is to understand the risk factors and long-term consequences of arthropod-borne viral diseases, particularly Rift Valley fever virus, in order to predict, prevent and control these emerging global threats.”

**A. Desiree LaBeaud, MD, MS**

Assistant Scientist, CHORI
With improvements in treating premature babies, birth defects have become the number one cause of death in the first year of life and occur in two to three percent of all pregnancies in the United States. Preventing birth defects has become more and more important as a result. Prevention can only be achieved when we fully understand what causes birth defects. With that in mind, Dr. Lammer focuses his research on determining both environmental and genetic causes of birth defects.

In order to identify environmental factors causing common major birth defects, the Lammer lab examines mothers’ diets and their use of vitamins before conception and during pregnancy and has found some dietary factors that prevent birth defects, as well as some dietary deficiencies among some mothers who have delivered babies with birth defects. In general, the research has shown that women who have higher dietary intakes of folates and vitamin B12 have lower risks to deliver babies with many birth defects.

To investigate genetic causes of birth defects, Dr. Lammer and his colleagues use tools like DNA sequencing to locate mutations in genes important to developing fetuses, as well as a genetic technique called microarray comparative genomic hybridization. This technique can identify children born with chromosome abnormalities that are too small to be seen with a microscope, by looking for small deleted or duplicated segments of a chromosome. These deleted segments provide clues that a gene important to that birth defect may be located within the deleted piece of the chromosome.

In addition, Dr. Lammer and his collaborators also conduct epidemiological and genetic investigations of California infants born with spina bifida or anencephaly, conotruncal heart defects, craniosynostosis, cleft lip and cleft palate, hypospadias and gastroschisis. The goal of our research is to identify environmental and genetic contributions to risks of common major birth defects, including investigations of California infants born with spina bifida or anencephaly, conotruncal heart defects, craniosynostosis, cleft lip and cleft palate, hypospadias and gastroschisis.

Selected Publications

2011


Scientists & Staff

David Iovannisci, MS, PhD, Assistant Staff Scientist
Kazu Osoegawa, PhD, Staff Scientist
Kathy Schultz, MS, Staff Research Associate II
Nebil Mohammed, Staff Research Associate I
Christina Parodi, Staff Research Associate I

Edward Lammer, MD
Scientist, CHORI
The accelerating scope, scale, and consequences associated with infectious disease outbreaks are unprecedented. The lack of a coherent global system for facile detection, characterization, diagnosis, management and prevention of known and emerging diseases increases the probability of adverse events. There is a severe mismatch between the genetic and ecological complexity of disease emergence and our ability to identify root causes of epidemics. Faster and finer grained surveillance systems are required to identify agents, genotypes, sources, and spread of priority pathogens. At present, infectious disease outbreaks are only recognized by epidemiological investigation after their occurrence. An overarching goal of the Leighton lab is to develop proactive surveillance and infection control systems which recognize disease emergence at the earliest possible stage.

Dr. Leighton uses a novel, but proven, biosensor technology (PlexID) for the rapid, sensitive, cost-effective, and simultaneous detection of a wide range of pathogenic organisms and unexpected emerging infectious organisms. The Respiratory Virus Surveillance (RVS) assay platform was designed to provide identification of most known and emerging respiratory viruses, including influenza, adenovirus, respiratory syncytial virus, bocavirus, metapneumovirus, SARS and other coronaviruses. The Leighton lab has deployed this new viral detection and identification capability to monitor dynamic respiratory viral propagation. The substantial increase in usable knowledge and reduction in outbreak response time from this project will enable actionable design and deployment of countermeasures for patient protection.

In addition, several types of airborne microorganisms and spores cause building acquired infections and communicable disease. We are developing new types of rapid and safe building decontamination technologies to eliminate spores and pathogens from hospital interiors in a single treatment.

2011 Selected Publications

Scientists & Staff
Kavita Lalwani, PhD, Visiting Scientist

“Our research focuses on infectious disease emergence, biosurveillance, medical countermeasures and infection control.”
Investigators

The prevention of many serious infectious diseases by vaccination represents a major public health and biomedical achievement of the twentieth century. However, a clear understanding of the molecular mechanisms underlying vaccine efficacy is still lacking. Dr. Lucas seeks to investigate how immunity is conferred against a class of bacterial pathogens that are coated in a polysaccharide capsule, in particular Haemophilus influenzae type b (Hib), Neisseria meningitidis and Streptococcus pneumoniae.

Although antibodies directed against the capsular polysaccharides that coat these bacteria have been found to protect against infection, studies from the Lucas lab show that some Hib and pneumococcal vaccines induce antibodies that bind the respective capsular polysaccharide with greater affinity than others, and this variation in binding affinity profoundly affects the ability of the antibodies to protect against infection.

The Lucas group is currently elucidating the primary structures of anti-Hib, anti-pneumococcal, and anti-meningococcal polysaccharide antibodies in order to discover the genes encoding these antibodies, and to map the structural determinants of polysaccharide binding affinity and protective efficacy. Dr. Lucas’s research shows significant differences in antibody binding affinity can be linked to subtle variations in amino acid sequence that are acquired as a result of either gene usage or from variation in the levels of somatic hypermutation. The Lucas lab is also trying to discern the relative contributions that these mechanisms play in determining susceptibility to developing invasive bacterial disease. In addition, Dr. Lucas is exploring the molecular ontogeny of the anti-capsular antibody repertoire in human infants using a new method developed by the Lucas group for generating native human monoclonal antibodies. Preliminary results reveal an exceptionally high level of B lymphocyte clonal diversity in the response to vaccination. Moreover, different clones appear in the repertoire during the first 15 months of life, the time period when the infant is receiving repeated vaccinations. Thus, Dr. Lucas is using polysaccharide vaccines as probes to investigate the molecular diversity of protective antibody repertoires. These studies will help unravel the evolutionary and somatic forces shaping human immunity and may enable the design of more effective vaccines.

Scientists & Staff

Leyu Liu, MD, PhD, Associate Staff Scientist
Elias Tsadik, Staff Research Associate

“The goal of our research is to understand the mechanisms by which vaccines elicit protective immunity. In particular, we focus on Haemophilus influenzae type b, Neisseria meningitidis and Streptococcus pneumoniae, bacteria which cause serious infection, especially in children.”

Alexander H. Lucas, PhD
Senior Scientist, Executive Director, CHORI; Senior Vice President, Children’s Hospital & Research Center Oakland
Epigenetics are changes in gene expression that are not the result of specific changes in DNA itself, but in the complex assortment of proteins associated with DNA in chromosomes that regulate DNA expression or silencing. The Martin lab has a broad focus on the role of epigenetic phenomena in animal biology and their mechanisms.

Dr. Martin’s pioneering work on epigenetic inheritance in mammals led to an investigation into the effect of an environmental agent (dietary methyl donors) on the inheritance of silent epigenetic state in agouti viable yellow (Avy) mice, an isogenic model of epigenetic variation and inheritance. Heritable epigenetic changes are epigenetic changes that pass on from one generation to the next. Recent research from the Martin lab shows that exposure to methyl donors over generations produces a progressive shift in the phenotypes within the population, indicating that methyl donors induce a heritable epigenetic change.

In addition, Dr. Martin established that there are numerous “hotspots” of variable CG methylation in the mouse genome and that methyl donors increase the number of such hotspots. Current research in the Martin lab focuses on establishing if the epigenetic variation induced by methyl donors is heritable.

In collaboration with Associate Scientist Dario Boffelli, PhD, and colleagues at UC Berkeley, the Martin group developed a method of analyzing high-throughput sequencing data to produce a genomewide “methyltype”; comparison of humans and closely related apes reveals a set of CG islands that are methylated in the germline, suggesting the possibility that methylation itself is heritable and that germline methylation states constrain somatic function. The labs of Drs. Martin and Boffelli also employ a novel deep sequencing-based methylation mapping method demonstrating that the genome of the fruit fly Drosophila melanogaster, a very broadly used model in animal genetics, is indeed methylated.

**Selected Publications 2011**


**Scientists & Staff**

Denise Muñoz, PhD, Associate Staff Scientist
Joseph Dhabbi, MD, PhD, Assistant Staff Scientist
Mark Wagner, PhD, Postdoctoral Fellow
James Jacobs, MD, MPH, Hematology/Oncology Fellow
Wendy Magis, BS, Volunteer

“Our research focuses on the control of gene expression, particularly on epigenetic mechanisms that regulate gene silencing. We are particularly interested in the inheritance of epigenetic states between generations and the role of this phenomenon in phenotypic variation and disease.”

David I.K. Martin, MD
Scientist, Deputy Director, CHORI
Cardiovascular disease is the most serious and prevalent public health concern of the industrialized world. It is estimated that more than 65 million Americans are afflicted with coronary artery disease, which remains the leading cause of death in this country. One of the most well-known and established risk factors for cardiovascular disease is having elevated blood levels of low-density lipoprotein cholesterol (LDLC). Dr. Medina seeks to identify the molecular mechanisms underlying both variation in individuals’ LDLC and their responses to cholesterol lowering drugs by identifying processes that regulate the proper balance of intracellular cholesterol, or cholesterol homeostasis.

Intracellular cholesterol is derived from two sources, the cell creating cholesterol (through cholesterol biosynthesis) and the cell taking available cholesterol from the blood (through cholesterol uptake pathways). Dr. Medina and her colleagues have recently found that genes involved in the cholesterol biosynthesis and uptake pathways are coordinately regulated at the level of alternative splicing, a process by which various portions of the gene are either included or excised in a functionally relevant manner. Dr. Medina is currently working on identifying the specific splicing factors involved in mediating this response, as well as investigating the interaction between its genetic and environmental regulation. By understanding the molecular determinants of LDLC variation in the blood, Dr. Medina hopes to significantly contribute to our understanding of cardiovascular disease risk, development and treatment.

In collaboration with CHORI Senior Scientist Ronald Krauss, MD, Dr. Medina is also investigating the genetic and molecular determinants underlying inter-individual variation in response to statins, a class of cholesterol lowering drugs. Dr. Medina is integrating clinical trial data with functional cellular studies using a variety of genomic tools and a multidisciplinary approach. The results of this research could significantly improve our ability to identify individuals most likely to achieve cardiovascular benefit from statin treatment, as well as identifying new pharmacologic approaches for increasing statin efficacy.

**Selected Publications 2011**


**Scientists & Staff**

Arnie Acosta, Staff Research Associate III

Aline Cornelius, Staff Research Associate II

Devesh Naidoo, Staff Research Associate I

Kristen Stevens, Staff Research Associate I

Frederick Bauzon, Postdoctoral Fellow I

Eugene Bolotin, Postdoctoral Fellow I

Elizabeth Theusch, Postdoctoral Fellow I

Chi-Yi Yu, Postdoctoral Fellow I

"Our research strives to understand the mechanisms underlying inter-individual variation in risk factors and treatment of cardiovascular disease. We are specifically interested in examining the role of alternative splicing as a mechanism of maintaining intercellular cholesterol homeostasis, and the impact of human genetic variation on this mechanism."
Investigators

“A our lab is investigating mechanisms of pathogenesis and developing vaccines for the prevention of disease caused by Neisseria meningitidis. Also, we are developing vaccines and immunotherapeutic approaches to the treatment of acute lymphoblastic leukemia and metastatic melanoma.”

Gregory R. Moe, PhD
Scientist, CHORI

A major focus of research in the Moe lab is on studies of a sugar molecule, discovered by the Moe group, named neuraminic acid-containing polysialic acid or NeuPSA. Dr. Moe found that NeuPSA is made by several human microbial pathogens, particularly Neisseria meningitidis group B bacteria, but is also produced in large amounts in many human tumors. Currently, the Moe lab is investigating why it is advantageous to pathogenic organisms and cancer cells to make NeuPSA and how targeting the pathway might lead to new approaches to the prevention and treatment of diseases in which NeuPSA has an important role.

Dr. Moe is also investigating a protein produced by meningococcal bacteria specifically in the presence of human serum called TspB. TspB appears to have an important role in causing invasive meningococcal disease. It is hoped that a better understanding of how TspB works may lead to new vaccines for preventing meningococcal disease.

Selected Publications
2011


Scientists & Staff
Mike Kai Wick Cheng, BA, Staff Research Associate I
Mais Müller, PhD, Postdoctoral Fellow
Lindsay Steirer, PhD, Postdoctoral Fellow I
Reduced arginine-bioavailability and nitric oxide (NO) depletion represent a common theme in otherwise genetically distinct blood vessel disorders, or vasculopathies, and can result from a number of mechanisms, including hemolysis, the breakdown of red blood cells. Arginine is an amino acid and nutritional supplement that is metabolized to NO, while NO is a potent vasodilator, responsible for expanding blood vessels. Dysregulated arginine metabolism contributes to many pulmonary disorders including asthma and pulmonary hypertension. The Morris team found that low arginine-bioavailability was a significant mortality risk factor in sickle cell disease (SCD), while others identified it as a more robust biomarker of cardiovascular disease than cholesterol. Together with CHORI Senior Scientist, Frans Kuypers, PhD, and University of Pennsylvania Medical Center’s Mark Gladwin, MD, and Sidney Morris, PhD, Dr. Morris demonstrated that excess arginase, an arginine-consuming enzyme found in most cell types including red blood cells (RBC), is an important mechanism in these multi-factorial conditions.

Dr. Morris is currently R01-funded to evaluate the role of the nutritional supplement, L-glutamine, to increase arginine-bioavailability in hemoglobinopathies, with promising preliminary results. In addition, Dr. Morris’s recent K23/NHLBI-supported trial of arginine therapy demonstrated a reduction of total narcotic use by >50 percent in children with SCD hospitalized for pain receiving arginine compared to placebo. This represents the first successful intervention for sickle cell-related pain that targets the underlying blood vessel constriction. Dr. Morris is actively seeking funding to validate this important observation in a multicenter trial.

Selected Publications 2011


Morris CR, Vichinsky EP. Guilt by missing the association. Blood. [Internet]. 2011 Dec 6. Available from: http://bloodjournal.hematologylibrary.org/content/118/14/3794/reply


Scientists & Staff

David Killilea PhD, Associate Staff Scientist
Jung Suh PhD, Associate Staff Scientist
Patrick Walter, PhD, Staff Scientist

“The goal of my research is to develop a nutritional approach that minimizes inflammation, oxidative stress and morbidity in chronic diseases that share similar mechanisms. Specific research interests include studies relating to asthma, pulmonary hypertension, sickle cell disease, thalassemia, apraxia/autism and nitric oxide biology.”
In humans, apoE is a polymorphic protein with three commonly occurring isoforms: apoE2, apoE3 and apoE4. It is a 2-domain protein: an N-terminal domain with high-affinity LDL receptor binding sites, and a C-terminal domain with high affinity lipoprotein-binding sites. While apoE3 is associated with a normal lipid profile and is generally considered protective against heart disease, apoE4 is considered a risk factor for both cardiovascular and Alzheimer’s disease. While the molecular organization of the N-terminal domain is well understood, those of the C-terminal domain and the various lipid-associated forms of apoE isoforms are not known. Further, the molecular basis of the difference between apoE3 and apoE4 and their role in amyloid pathology, a hallmark feature of Alzheimer’s disease, are not understood.

There are four main areas of research under investigation in the Narayanaswami group: (i) structure-function relationships in apoE using fluorescence and other biophysical approaches; (ii) the role of apoE in cholesterol transport and metabolism at the neurovascular junction; specifically, related to the role of apoE isoforms in the amyloidogenesis process in Alzheimer’s disease and cerebral amyloid angiogenesis at the molecular and cellular levels; (iii) the use of apoE-containing reconstituted HDL as a nanovehicle to transport bioflavonoids in the blood, and lastly; (iv) the effect of second hand smoke exposure on the structure and function of apoE with parallel in vivo and in vitro studies.

Selected Publications 2011


Scientists & Staff

Gursharan Bains, Graduate Student
Roy Hernandez, Graduate Student
Ken Irvine, Graduate Student
Sea Kim, Graduate Student

“Research efforts in our lab are devoted to understanding the role of apolipoprotein E (apoE) in cholesterol metabolism and its relation to cardiovascular disease and Alzheimer’s disease.”
Some diseases result from a mutation in a single gene; however, most diseases are the result of variations in multiple genes. Most of the genes in the human genome have a small number of naturally-occurring variants, termed alleles. Some genes, such as the ones that encode the Human Leukocyte Antigen (HLA) molecules can have thousands of alleles. The products of these genes are important in directing the immune response and the particular alleles and combinations of alleles, observed for HLA genes vary among populations. Comparing multiple populations is essential to both understanding the disease itself and how genes influence disease risk. For example, Dr. Noble’s lab has uncovered multiple instances in which a particular haplotype (or gene combination) commonly found in people of European descent influences type 1 diabetes (T1D) susceptibility in one way, but a closely-related haplotype, specific to Africa in origin, has exactly the opposite effect on T1D risk in other ethnic populations. In addition, the Noble lab has demonstrated that one must consider the combination of all of HLA-encoding genes on both chromosomes to fully understand how HLA is associated with T1D susceptibility. Studying a single gene is not sufficient to understand risk for complex diseases.

In addition to HLA, Dr. Noble’s group studies other genes that might affect susceptibility to T1D, including TNF and the IL-4 receptor. The Noble lab also utilizes their HLA expertise to study disease association with other autoimmune diseases, such as lupus, rheumatoid arthritis, and multiple sclerosis, in collaboration with colleagues at the UC Berkeley and UC San Francisco. In addition, Dr. Noble and her colleagues study the role of HLA in diseases that do not have an obvious autoimmune basis, including age-related macular degeneration and bacterial vaginosis. The ways in which our genes confer susceptibility to disease is a complicated web, which we are beginning to unravel with the aid of cutting edge DNA sequencing technology.

“The focus of our research is to understand the genetic basis of susceptibility to complex diseases and conditions. We have a particular focus on type 1 diabetes (autoimmune diabetes) and on underserved populations, including African American and Hispanic children.”
High density lipoproteins (HDL) are the central theme of the Oda lab. HDL is a major class of lipoprotein and plays a critical role in a wide array of essential biological functions. It is responsible for maintenance of cholesterol homeostasis, modulation of inflammatory response, support of innate immunity (anti-bacterial, anti-viral, and anti-parasitic activities), regulation of glucose metabolism, and has recently been implicated in modulating platelet aggregation.

HDL is traditionally known as the “good cholesterol” due in large measure to the fact that it is the primary mediator of the reverse cholesterol transport pathway (RCT), carrying cholesterol and other lipids from peripheral tissues to the liver, adrenal gland and other steroidogenic organs. HDL is central to the maintenance of a healthy level of lipids within our body’s cells. When there is an imbalance in our cellular lipids, pathologies such as atherosclerosis, a precursor to heart disease, arise. HDL reduces the risk for heart disease through the extraction of excess cholesterol from the artery wall and other peripheral tissues. The primary protein constituent of HDL, apolipoproteinA-I (apoA-I) is a focus of interest in the Oda lab. On HDL, apoA-I performs multiple functions: as a ligand for cell surface receptors; as a mediator of cholesterol and lipid efflux; as a site of enzyme association (paraoxonase and lecithin: cholesterol acyltransferase (LCAT)); and as a key physiological activator of LCAT. HDL derives a large part of its anti-atherogenic character from apoA-I’s ability to execute these functions.

Dr. Oda’s funded research programs are based on HDL’s biological properties and the structure-function of apoA-I. These programs include the NIH-funded investigations of the primary protein component of HDL, apoA-I and the development of NanoDisks as a drug delivery vehicle, as well as the Canadian Institutes of Health Research-funded development of HDL as a preventative of Alzheimer’s disease.
Traditional approaches to vaccine development have proven ineffective for several important diseases. Contemporary vaccine design strategies for these diseases have adopted a “component” or “subunit” approach in which important immunogenic molecules associated with the infectious agent are present in vaccine formulations in place of the killed or attenuated agents more traditionally utilized. The effective design of such vaccines requires an in-depth understanding of the interactions between individual antibody-binding domains (paratopes) and the region of the antigen to which they bind (epitope), as well as a determination of which paratope/epitope interactions are effective in neutralizing the infecting agent.

Dr. Reason’s research seeks to define these interactions directly in humans by first defining the antibody repertoire that arises in response to vaccination or infection, and then by using these reagents to define the “epitopic repertoire” for the antigen as seen by the human host. Both the information and the human monoclonal antibodies generated by this approach can then be individually assayed to determine their efficacy in killing or neutralizing the infectious agent. Together this information identifies the epitope or epitopes that must be present in order for a vaccine to be effective, and in some cases reveals the mechanism by which efficacy is achieved.

Dr. Reason’s group has applied this approach to several serotypes of *Streptococcus pneumoniae*, to soluble toxins from Diphtheria and Anthrax, and to surface proteins associated with *Neisseria meningitidis*. Dr. Reason’s findings have provided significant new information that would not have been obtainable using more traditional techniques of polyclonal serology and may be useful in guiding future subunit vaccine design and development.

**Selected Publications 2011**


**Scientists & Staff**

Jinying Sun, MD, Staff Research Associate I
Investigators

“The goal of our research is to understand factors that regulate plasma lipid homeostasis and cell fate. Ongoing studies are focused on how low density lipoprotein receptor family members modulate plasma cholesterol levels, the mechanism whereby apolipoprotein A-V influences triglyceride metabolism, and the effect of Wnt on stem cell fate.”

Robert O. Ryan, PhD
Senior Scientist, CHORI

The long-term goal of Dr. Ryan’s research is to understand how lipid transport and metabolism are regulated by molecular interactions between lipoproteins and cell surface receptors. Using knowledge of the metabolic roles of apolipoprotein E (apoE) and the low density lipoprotein receptor (LDLR), combined with available structural information, the Ryan lab designs experiments to try to elucidate the elements needed for a productive receptor-ligand interaction. Dr. Ryan has generated a soluble fragment of the LDLR encompassing its seven complement-like ligand binding. In addition, Dr. Ryan is conducting ligand binding and release studies with apoE and proprotein convertase subtilisin kexin type 9 (PCSK9) using LDL-A repeats and the epidermal growth factor precursor homology domain, including its β-propeller segment. Based on the fact that aberrations in the LDLR pathway are positively correlated to onset of cardiovascular disease, Dr. Ryan anticipates that new knowledge gained from these studies will provide insight into molecular mechanisms that regulate vascular cholesterol flux in health and disease.

In other studies, the Ryan lab is exploring the mechanism whereby apolipoprotein A-V modulates plasma triacylglycerol levels in plasma and within hepatocytes. Adeno-associated virus 8 mediated gene transfer studies are underway to introduce variant forms of apoA-V into hypertriglyceremic (HTG) apoa5 (-/-) mice. The ability of specific apoA-V variants to correct the HTG phenotype is under investigation. In other studies expressed protein ligation methodology is being used to reconstruct intact apoA-V from fragments expressed separately in Escherichia coli. Segmental isotope labeled apoA-V will be obtained and used for NMR spectroscopy evaluation of the structural properties of specific regions of apoA-V within the context of the intact protein.

Finally, the morphogen and stem cell fate determinant, Wnt, is under study. The lipid modified Wnt protein has been stably incorporated into discoidal bionanoparticles, termed nanodisks (ND). The biological activity of Wnt ND in stem cell cultures is under investigation.

Selected Publications 2011


Scientists & Staff

Trudy Forte, PhD, Staff Scientist
Jens Simonsen, PhD, Visiting Scientist
Jennifer Beckstead, MSc, Senior Staff Research Associate
Lisa Nelbach, Staff Research Associate II
Francisca Heriyanto, Staff Research Associate I
Xuan Gao, PhD, Postdoctoral Fellow I
Vineeta Sharma, PhD, Postdoctoral Fellow I
Mistuni Ghosh, Graduate Student Researcher
Natasha Crosby, PhD, Volunteer
Betty Su, Volunteer
How does one lipid molecule influence so many different processes? S1P activates signals that stimulate cell survival, migration and proliferation and blocks a form of controlled cell death called apoptosis. S1P can act by stimulating cell surface receptors or by activating other targets within the cell nucleus and cytoplasm. Intracellular levels of S1P are tightly regulated by the actions of three enzymes, which are responsible for its biosynthesis and degradation. By regulating the levels of S1P inside the cell, these enzymes help determine whether an injured cell lives or dies. S1P signaling promotes inflammation, immunity and stem cell functions that together can aid in the repair and regeneration of injured tissues. On the other hand, too much S1P signaling appears to promote injurious levels of inflammation, leading to tissue injury, cancer development and progression. By clarifying the specific roles that S1P signaling plays in these processes, Dr. Saba hopes to target the S1P signaling pathway for therapeutic purposes in degenerative disease, injury, autoimmunity and cancer.

“Our goal is to understand the mechanisms by which cells regulate their growth and how these processes are disrupted in cancer and other diseases. We focus on the signaling and metabolism of a natural lipid called sphingosine-1-phosphate (SIP). SIP is important for many biological functions, including blood vessel development, wound healing, inflammation and immunity.”

Selected Publications 2011


Mesenchymal stem cells (MSC) are cells found in bone marrow, cord blood, embryos, and most recently, in post-birth placenta. Known for being able to differentiate into many different cell types, MSC are used in stem cell transplantation to cure a variety of different diseases. Researchers have long hoped to identify alternative methods for using MSC to treat many different degenerative and fatal diseases as well, such as Alzheimer’s disease or Parkinson’s.

Dr. Serikov’s research focuses on investigating the ways in which MSC might be utilized in the treatment of acute lung diseases, such as sepsis, pneumonia, lung edema, or pulmonary complications of various heart diseases. Acute lung disease, termed Adult Respiratory Distress Syndrome, is an immediate cause of approximately 300,000 deaths annually in the United States. There is no cure for this syndrome and lethality remains at about 40 percent—unchanged in the past 20 years. Novel modes of therapy for this syndrome are in high demand and Dr. Serikov is investigating MSC as a prominent candidate for such therapy.

The Serikov lab has recently characterized MSC obtained from the bone marrow (BM) of transgenic mice. In addition, Dr. Serikov has developed an in vitro model to study MSC transformation into different specialized cell types using a co-culture of MSC and transformed lung epithelial cells. Current studies explore using MSC in acute bacterial and toxic lung injury and stem cell participation in airway epithelial restoration. In collaboration with the University of California, San Francisco, Dr. Serikov recently demonstrated that human BM-derived cells effectively restored functional properties of the human epithelial barrier after acute lung injury. Current studies in collaboration with CHORI Senior Scientist Frans Kuypers, PhD, demonstrated for the first time that human term placenta is a hematopoietic organ and a novel and potent source of hematopoietic stem cells, as well as stromal embryonic-like stem cells with high therapeutic potential.

**Selected Publications 2011**


Currently, the Shackleton-Watson lab focuses on Smith-Lemli-Opitz syndrome (SLOS), a relatively high frequency genetic disease caused by a deficiency in cholesterol synthesis. Cholesterol is essential for cellular structure and function and is central to several biochemical pathways, such as the synthesis of steroid hormones, bile acids and oxysterols. In addition, cholesterol plays a role in early developmental signaling. As a result, SLOS patients suffer a wide variety of symptoms with a broad range of severity caused by the lack of cholesterol synthesis. Ongoing studies use viral vectors to deliver therapeutic genes to mice genetically engineered to display major characteristics of the human SLOS disease. The effects of this gene therapy on the synthesis of cholesterol are monitored by gas chromatography/mass spectrometry, which can quantify sterol metabolites from small blood or tissue samples. Recently published results show, for the first time, that gene therapy administered to SLOS mice can at least partially restore normal cholesterol metabolism. Furthermore, gene therapy appears to improve the rate of weight gain in SLOS mice, which, when untreated, have delayed growth. Although Drs. Shackleton and Watson have not yet cured a SLOS mouse (the nature of the disorder makes this an almost impossible outcome), this novel gene therapy approach shows promise of ameliorating the biochemical basis of this disease and improving the physiological outcome. Future efforts are aimed at improving the extent of vector expression in liver, treating mice at a younger age, and circumventing the blood brain barrier to treat the central nervous system.

In addition to investigating SLOS, Dr. Shackleton is also heavily involved in collaborative research on other steroid related metabolic conditions, particularly the DSD (disorder of sexual development) condition Cytochrome P450 Oxidoreductase deficiency.

**Selected Publications 2011**


**Scientists & Staff**

Lee Ying, Staff Research Associate I
Crystal Ghosh, Student Volunteer
Sandy Truong, Student Volunteer
“Our research efforts focus on delineating the role of diet in modulating insidious exposure to gut-derived endotoxin, a bacterial cell wall component that can trigger chronic inflammation upon breach of the gut barrier. Chronic inflammation due to gut-derived endotoxin may underpin the insulin resistance, vascular dysfunction, and other metabolic derangements observed in aging and many chronic diseases.”

Mark Shigenaga, PhD
Assistant Scientist, CHORI

Current approaches used to detect the systemic impact of the gut microbiome on the various organ systems of the body are relatively insensitive, including classic techniques directed toward the measurement of gut-derived endotoxin, a bacterial antigen that can provoke innate immune responses implicated in disease risk elevation. Thus, documentation of this event has mostly been confined to extreme inflammatory conditions such as sepsis, burn injury, blunt abdominal trauma, multiple organ dysfunction, etc. Dr. Oda and others postulate that exposure to gut-derived endotoxin at levels difficult to reproducibly track by traditional approaches is capable of triggering the chronic inflammation that drives insulin resistance and risk of common diseases, including cardiovascular disease, diabetes, obesity, and cancer. In an effort to directly link the process by which diet and lifestyle factors contribute to this systemic exposure, methodologies are being developed to sensitively and specifically track the systemic burden of this bacterial antigen. Availability of this tool opens up many opportunities to investigate the role of gut bacteria in human disease and can provide mechanistic insights to the health promoting effects of dietary fiber, fruits and vegetable intake, and metabolic substrates that enhance gut function.

Our second major research topic focuses on identifying widely available, inexpensive, and highly effective dietary components that promote gut health and reduce endotoxin burden through improvements in energy metabolism and gut immunity. Through these studies Dr. Shigenaga hopes to both provide a bridge between gut health, nutrition, and disease and offer inexpensive dietary solutions for improving health and quality of life.

Scientists & Staff
John Gieng, PhD, Postdoctoral Fellow I
Dr. Singer is a pediatric hematologist/oncologist whose interests are in translational and clinical research, primarily in the area of the genetic hemoglobin disease, thalassemia. Dr. Singer has been the principal investigator in several clinical trials in thalassemia. In collaboration with CHORI Senior Scientist, Frans Kuypers, PhD, as well as national and international investigators, Dr. Singer has also investigated the effects of experimental treatments such as hydroxyurea, butyrate and erythropoietin on thalassemia-intermedia, a non-transfusion dependent form of thalassemia. Other research interests include investigating the pathogenesis of decreased fertility in women with thalassemia and the effect of iron on the reproductive system. Through a collaborative study with the UC San Francisco, Dr. Singer helped identify better markers of predictive value for the fertility capacity in women with thalassemia.

In addition, Dr. Singer investigates the pathogenesis of pulmonary hypertension in thalassemia and the specific role of the spleen, platelets and the coagulation system in the progression of this complication. More recent projects involve assessing the specific role of prior splenectomy on the development of pulmonary hypertension in various hematological disorders outside the hemoglobinopathies. Dr. Singer is also exploring the association of hypogonadism and decreased fertility with pituitary iron concentration and is now proposing to investigate the mechanism causing hypogonadism and subfertility in males with thalassemia-induced iron overload.

**Selected Publications 2011**


“The goal of my research is to explore basic science findings in the area of thalassemia and to implement them in patient care.”
Dr. Styles is a pediatric hematologist/oncologist whose research interests are in translational and clinical research. As a national leader in sickle cell disease (SCD) research, Dr. Styles has been the principal investigator on several national, multi-institutional clinical trials in SCD. Working with CHORI Senior Scientist Frans Kuypers, PhD, she identified secretory phospholipase A2 as playing a major role in acute chest syndrome in sickle cell disease. This work culminated in the just completed multi-institutional PROACTIVE trial as part of the NIH SCD Clinical Research Network.

Other recent areas of investigation have included investigating a role for arginine in preventing pain crisis in SCD and the use of statins to reduce inflammation in sickle cell disease and the potential use of a platelet inhibitor to prevent pain crisis.

Lastly, Dr. Styles is exploring the important area of minority health care disparities in pediatric patients with chronic disease. Dr. Styles has a keen interest in mentoring young investigators and was awarded one of only two sickle cell disease NIH K24 Mentoring grants from the NIH in recognition of her work in career development of young investigators. She is an important resource for scientists at CHORI who want to translate their findings from the bench to the bedside.

**Selected Publications 2011**


“The goal of my research is to translate basic science findings in the area of hematology/oncology to patient treatment and care.”

**Lori Styles MD**
Scientist, CHORI; Pediatric Hematologist/Oncologist, Children’s Hospital Oakland
Dr. Test focuses on how manipulations of the complement system affect the antibody response to vaccines, using model vaccines consisting of a pneumococcal capsular polysaccharide coupled to a protein molecule. The complement system is part of the innate immune system and consists of over 30 proteins present either in the bloodstream or on the surface of cells. Originally evolving to kill bacteria directly in the absence of antibody, the complement system also has important effects on the adaptive immune response, which produces antibodies that identify and attack specific bacteria. Administration of vaccines often involves a series of injections given over months or years to generate an antibody response to a particular pathogen. The antibody response to the second or later injection differs from the response to the first injection and is called a secondary or memory response. The secondary response occurs more rapidly than the primary response and consists of antibodies that bind more strongly to the antigen.

Research in the Test lab on the role of the complement system in the antibody response in mice has indicated that depleting complement prior to the first injection of vaccine causes a marked decrease in the primary antibody response, but a very large increase in the antibody response after a second injection. Dr. Test hypothesizes that the persistence of anti-polysaccharide antibody molecules of a specific subclass (IgG1) at the time the second injection of vaccine is given results in partial suppression of the antibody response to the second injection. This suggests that the enhancing effects of complement depletion on the secondary antibody response result from lower circulating levels of IgG1 anti-polysaccharide antibodies coupled with a simultaneous increase in the cells (memory B lymphocytes) that respond to the second dose of vaccine. Current studies aim to confirm this hypothesis and determine how such findings can be applied to enhance the efficacy of vaccines.

**Scientists & Staff**

Lorelle Parker, MS, Staff Research Associate II

“The goal of our research is to better understand the factors that influence the antibody response to vaccines and how those factors can be manipulated to enhance the antibody response, using vaccines against *Streptococcus pneumoniae* bacteria as a model.”
Iron, central to normal health, is often deficient in humans, with 2 billion people suffering from iron deficiency world-wide. Iron can also be in dangerous excesses, however, as in transfusional iron overload or genetic diseases where excess iron is absorbed from food. A protein nanocage, named ferritin, concentrates iron for normal cell nutrition and is also an antioxidant that scavenges reactive iron and oxygen during oxidant stress. Ferritin is required for life. One of the most complicated among known proteins, ferritin regulation is a feedback loop that includes expression of the DNA (gene transcription), regulation of the mRNA (translation), and protein synthesis; loop signals are the cellular amounts of iron and oxygen. The Theil lab is currently characterizing ferritin protein ion channels, catalytic sites, and nucleation channels to manage iron/oxygen chemistry. Curr Opin Chem Biol. 2011 Apr;15(2):304-11.


**Selected Publications 2011**


Scientists & Staff

Rabindra Behera, PhD, Postdoctoral Fellow

Suanjana Haldar PhD, Postdoctoral Fellow

Yuykari Sekine, Volunteer

Ward Hagar, MD, Clinical Collaborator
The Trachtenberg lab studies the roles that human major histocompatibility complex (MHC) and natural killer (NK) cell immunoglobulin-like receptor (KIR) complexes play in health and disease. The MHC, also known as the human leukocyte antigen (HLA) gene complex in man, is integral to the body’s determination of self and non-self as part of the adaptive immune response to pathogens. HLA molecules also act as ligands to KIR molecules, together modulating the immunologic response.

KIR are responsible for activating NK cells, which through their cytolytic or chemokine responses are important as the first line of defense against viruses and tumors. The Trachtenberg group studies the role of HLA and KIR in cancer, autoimmune and infectious diseases, as well as their role in stem cell and organ transplantation. Understanding the population genetics of these highly diverse gene complexes in global populations helps to elucidate their evolution and function and is another focus of the lab. Because of the high complexity of the KIR complex, genetic analysis of the cluster has been slow. To remedy this, the Trachtenberg lab has developed novel KIR genotyping systems, including a SNP-based MALDI-TOF procedure, and a next-generation, clonal sequencing method for simultaneous allelic analysis of all 17 KIR genes. The lab is internationally the most experienced using next-generation sequencing to analyze both the HLA and the KIR complexes. Applying these new methodologies has allowed the Trachtenberg lab to rapidly study large case-control cohorts for analysis of Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), and HIV disease. Moreover, the lab has also been a forerunner in analysis of these immune complexes in large recipient-donor pair cohorts for both stem cell and organ transplantation. These studies help to illuminate the role of the immunologic response in susceptibility to or protection from autoimmune and infectious diseases and its critical role in transplantation.

**Selected Publications 2011**


**Scientists & Staff**

- Martha Ladner, PhD, Associate Staff Scientist
- Jill Hollenbach, PhD, Associate Staff Scientist
- Kazu Osoegawa, PhD, Staff Scientist
- Kathy Houtchens, PhD, MBADS, CGMBS
- John ten Bosch, PhD, D(ABMG), CGMBS
- Damian Goodridge, PhD, Visiting Scholar
- William Pickle, MS, CGMBS, Senior Research Associate
- Franziska Cohen, Staff Research Associate III
- Sherry Hawbecker, Staff Research Associate III
- Fernanda Ribas-Zacarias, Staff Research Associate III
- David Noonan, Staff Research Associate I
- Margaret Vinson, Senior Clinical Laboratory Scientist, CHS, Laboratory Supervisor
- John Agraz, Senior Clinical Laboratory Scientist
- Susan Corkhill, Senior Clinical Lab Scientist
- Kellie Graham, Senior Clinical Lab Scientist
- Kathy Mohr, Senior Clinical Lab Scientist
- Steve Morin, MBA, Senior Clinical Lab Scientist
- Kenneth Plamenco, Senior Clinical Lab Scientist, CHS
- Calvin Ball, Clinical Lab Scientist
- Tricia Lacovangelo, Clinical Lab Scientist

“Our lab focuses on the role of immunogenetic diversity and host immunity in transplantation and disease. In particular, we are interested in the immunogenetics of natural killer cell immunoglobulin-like receptors (KIR) and human leukocyte antigen (HLA) complexes, and the modulation of the immune response by these receptor systems.”
Investigators

“Our research is focused in three areas: 1) examining the associations between autonomic reactivity, clinical severity, family stressors, and mental health symptoms in children with sickle cell disease (SCD); 2) enhancing coordination of service delivery for individuals with SCD in Northern California; and 3) using qualitative and quantitative strategies to develop a health related quality of life measurement system for adults with SCD.”

Marsha J. Treadwell, PhD
Clinical Scientist, CHORI

Previous studies of healthy children have demonstrated a link between autonomic nervous system (ANS) reactivity and health outcomes. There is limited research examining whether ANS reactivity is associated with health outcomes for children with SCD. Dr. Treadwell evaluates ANS reactivity by having children complete standardized protocols measuring ANS responses during rest and challenge conditions in social, cognitive, sensory and emotion domains. The Treadwell lab has found that a sample of children (ages 5 - 8 years) with SCD displayed a different pattern of ANS responses to laboratory challenges compared with children without SCD from the same community, showing sympathetic reactivity in some domains while community children showed parasympathetic withdrawal. Another study demonstrated that children with SCD and the classic ANS reactivity profile (parasympathetic withdrawal and sympathetic activation) in the cognitive and emotion domains were most vulnerable to the effects of stress when family stress was high. Individual differences in ANS reactivity may offer a novel, biologically plausible account for observed variations in physical and mental health outcomes for children with SCD. Costs to patients and families in diminished quality of life and to the health care system could be reduced by further exploration of strategies to identify children with SCD who are most vulnerable to poor outcomes.

In addition, Dr. Treadwell undertakes health services research projects to evaluate strategies to improve access to and follow up with comprehensive and subspecialty care that is patient centered and that promotes positive disease management, with particular focus on youth and adults with SCD in Northern California. In addition, Dr. Treadwell has also conducted a series of focus groups, structured individual interviews and field testing to develop a SCD specific health related quality of life instrument for adults. The Treadwell lab thus translates their research into the design of practice models for the prevention and treatment of SCD related complications.

Selected Publications 2011

The 53rd Annual Meeting of the American Society of Hematology. San Diego, CA; December 10-13, 2011.


Scientists & Staff
Janice Earl, FNP, Nurse Practitioner
Christy Hartshorne, MS, Sickle Cell Nurse
Fernando Barreda, Study Coordinator
Wanda Payton, MA, Social Work Assistant
Dr. Vichinsky’s lab focuses on translational research in hemoglobinopathies and iron disorders. There are 350,000 births per year worldwide of sickle cell disease (SCD) and thalassemia. The research program focuses on the pathophysiology of nitric oxide deficiency, endothelial dysfunction, and inflammation on these diseases. Novel therapies designed to alter these abnormalities are investigated, including fetal hemoglobin modifiers, arginine, anti-inflammatory agents, and transfusion therapy.

The lab is leading three international NIH research investigations, including: the effects of anemia on cognitive function and neuroischemia in SCD; iron metabolism and transport in hemoglobinopathies and the effects of inflammation on iron regulation, and novel iron chelators in the treatment of neurodegenerative diseases secondary to excess brain iron.

**Selected Publications 2011**


**Scientists & Staff**

Ashutosh Lal, MD, Staff Scientist

Patrick Walter, PhD, Staff Scientist

Mahin Azimi, Supervisory Clinical Laboratory Scientist

Marcela Weyhmiller, PhD, Staff Research Associate II

Nancy Sweeters, RN, PNP, Pediatric Nurse Practitioner

Ward Hagar, MD, Director, Adult Sickle Program

Anne Marsh, MD, Hematology/Oncology Fellow

Lynne Neumayr, MD, Administration Director, Sickle Cell Disease Research

Keith Quirolo, MD, Hemoglobinopathy Physician

Kathryn Stewart, Study Coordinator, Hematology

“We are a multidisciplinary research group focused on understanding the epidemiology, pathophysiology, and treatment of hemoglobinopathies and iron disorders, with a focus on developing novel therapies.”
Investigators

“Our research aims to promote maternal and fetal health by optimizing iron and folate nutrition prior to, and during, pregnancy; to understand the role of erythrocytes in general folate nutrition; and to stimulate, support and promote collaborations with international research centers in areas of mutual interest with CHORI scientists.”

Fernando E. Viteri, MD, ScD
Scientist, CHORI

Most women of reproductive age (WRA) even when consuming iron-fortified food have few iron reserves and are at risk for iron deficiency (ID) and anemia (IDA). Pregnancy increases demands for iron, and ID-IDA poses serious health risks, some permanent, for mothers and their babies. Pre-pregnancy iron supplementation can prevent ID-IDA, however. Simultaneously, Dr. Viteri has demonstrated that excess prenatal iron supplementation impairs fetal growth. His lab hypothesizes that during gestation excess iron induces excessive red-blood-cell (RBC) synthesis and oxidative stress, particularly in genetically susceptible populations. Current research addresses these issues and includes scientists in the World Health Organization (WHO), China, Guatemala, Indonesia, Mexico, Spain, and Vietnam. Dr. Viteri’s research has already demonstrated that reducing iron supplementation to once weekly (WIS) is as effective and safer than current daily iron supplementation.

Adding folate (vitamin B9) to pre-pregnancy WIS reduces risk of neural tube defects (NTD). The Viteri lab has shown that with proper doses, weekly folic acid could rapidly achieve and maintain RBC folate levels that prevent NTD. As a result of work at Viteri’s lab and with his collaborators, WHO recommends preventive weekly iron-folate supplementation (WIFS) for WRA prior to pregnancy, primarily for low socioeconomic populations.

Dr. Viteri is also investigating the dynamics of folate in RBC, which have 30 to 40 times more folate than plasma. The hypothesis is that RBC serve as active folate reservoirs that buffer variations in plasma and cellular levels. They have demonstrated that RBC release folate as hemoglobin becomes deoxygenated. The Viteri lab and his collaborators are also looking at common genetic mutations that affect folic acid reduction and the effectiveness of a reduced folate that bypasses those mutations. This research may partially explain the about 30 percent failure to reduce NTD risk of folic-acid-fortified food. Further, the safety of food fortification with folic acid has been questioned because of health risks for the elderly. Targeted WIFS for WRA may be safer than food-fortification.

Selected Publications
2011


Scientists & Staff
Shahana Fedele, Graduate Student
Blanca Ribot, Graduate Student
Willy Gan, Volunteer
Shivani Patel, Volunteer
Sargis Pogosians, Volunteer
Jon Tanaka, Volunteer
Claire White, Volunteer
The major hereditary hemoglobin disorders, sickle cell anemia and thalassemia major, together account for the most common type of genetic disease worldwide, and thus have a profound impact on public health. While there have been advances in supportive care that have improved survival to early adulthood, extensive morbidity that reduces the quality of life and early mortality still plague these disorders. Hematopoietic cell transplantation, in which patients receive stem cells capable of producing healthy blood cells, remains the only curative therapy for hemoglobin disorders. It is applied very infrequently, however, due in part to both a paucity of suitable donors and safety concerns.

Thus, Dr. Walters’ current clinical and laboratory research efforts are focused on expanding new and safer methods of alternative donor transplantation. These efforts include the development of, and participation in, clinical trials of unrelated donor marrow and umbilical cord blood transplantation for hemoglobin disorders and the development of a new trial to test unrelated donor transplantation in young adults with sickle cell anemia.

Dr. Walters is also collaborating with the laboratories of CHORI Senior Scientist Frans Kuypers, PhD, and Clinical Scientist Bindu Kanathezhath, MD, to develop a preclinical model of major histocompatibility complex (MHC)-mismatched transplantation for thalassemia. Clinicians generally try to get as close a match possible between the donor and recipient’s MHC in order to prevent a recipient’s immune system from attacking the newly transplanting cells, in what is called graft versus host disease (GVHD). The novel transplantation model Drs. Walters, Kuypers and Kanathezhath are developing uses donor T-lymphocyte inactivation to prevent GVHD, while still facilitating engraftment after transplantation. If this new method proves successful in the clinic, patients who currently do not have a donor will become eligible for these life-saving transplantation procedures.

Selected Publications 2011


“Our goal is to expand the availability and safety of hematopoietic cell transplantation for sickle cell anemia and thalassemia major, as a curative therapy for these significant hereditary blood diseases.”
Investigators

“We have two goals in our laboratory: 1) to understand and characterize the molecular genetic basis of metabolic disease using mouse models; and 2) to develop and characterize knockout mouse models of disease for use by the biological research community.”

David B. West, PhD
Scientist, CHORI

Obesity and Type 2 Diabetes are serious prevalent conditions that lead to significant morbidity and mortality in our population. There is a major genetic component contributing to risk for developing these diseases and Dr. West is using and developing mouse models in order to identify the genes conferring risk and to characterize their mechanism of action. Dr. West is also collaborating on a project to create and phenotype 312 knockout mouse models. The genes selected to knockout include genes that are putatively involved in many human diseases including metabolic, cardiovascular, infectious diseases and cancer. These knockout models are publicly available and the phenotyping data can be viewed at www.kompphenotype.org.

Selected Publications 2011

Scientists & Staff
Michael Adkisson, Staff Research Associate II
AJ Nava, Staff Research Associate II
Debbie Swinarski, Staff Research Associate II
Julia Kirov, Staff Research Associate I
Current health service and public health studies have dispelled any doubt that income level is the most important predictor of health status in the United States today. Yet even among impoverished populations, certain subgroups suffer disproportionately. Racial/ethnic status and transitional living situations, such as homelessness or living in foster care, have additional effects on health status, and demonstrate the continuing health inequities among certain subgroups in the US population. The economic downturn and high unemployment has exacerbated these effects, as they are more common in communities of color. There is no single type of transitional family. Some are constantly on the move, staying with friends one day and in the living room of family members the next. When they run out of places to stay, some enter homeless shelters. In certain situations, children who had been living with their birth parents are placed in group homes or with foster parents. The constant movement of being in doubled-up situations, homeless shelters and foster homes is part of the cycle of family homelessness.

Dr. Zlotnick’s studies focus on transitional families and health status inequities. The Zlotnick lab has examined the connections between the transitional living situations of homelessness and foster care in childhood, adolescence and adulthood; and has identified risk factors that increase the likelihood that children and their families will enter the cycle of homelessness. Other investigations by the team have started exploring the impact of different services and opportunities to intervene which have the potential to improve the child’s health status or family situation. Dr. Zlotnick has examined the connections between adulthood morbidity and childhood history of homelessness and foster care. In addition, Dr. Zlotnick is beginning the work of identifying evidence-based health care practices that have been effective for children living in transitional families.

**Cheryl Zlotnick, RN, DrPH**

Associate Research Scientist, CHORI

“The major goal of our research program is to identify risk factors, assess needs, measure service utilization and explore the impact of interventions that reduce morbidity in children living in transitional situations (i.e., homeless shelters, doubled-up situations and in foster care). Many studies focus specifically on examining the utility of different interventions such as the integration of primary and mental health care, as well as case management services of children who live in transitional families such as foster care or homelessness.”

— Tammy Tam, PhD, Evaluation Analyst/Scientist
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The general economic environment in the United States has been challenging in recent years. Economic downturns tighten opportunities for both funding and philanthropy. Yet in spite of this difficult climate, CHORI continues to be a thriving research enterprise. Ranked 8th in the nation in 2010 for research grants from the National Institutes of Health (NIH) to children’s hospitals, CHORI’s external funding in 2011 was over $53 million.

In addition, CHORI experienced a 5.2 percent increase in external award funding between 2010 and 2011. This is attributable to the quality and caliber of the individual investigators who comprise CHORI, with 70 percent of our funding coming directly from highly competitive, peer-reviewed NIH awards and other federal funding agencies. CHORI rounded out its federal funding in 2011 with fee-for-service and industry partnerships together totaling 14 percent of its overall budget.

Philanthropy is also a fundamental aspect CHORI’s financial health. The generosity of organizations such as the Clorox Company, which provided a $1 million endowment, and donations from individuals who provided a vital investment in research, comprised five percent of CHORI’s revenue in 2011. Totaling over $2.5 million, these donations enable CHORI to continue its sustained commitment to research aimed at innovative treatments and cures.

### 2011 CHORI Expenditures by Source of Funding

Total $53,409,062

Federal 70%
Other Granting Agencies 11%
Fee for Service 8%
Industry/Pharmaceuticals 6%
Foundation/Donations 5%

### CHORI Growth

1999 - 2012*
CHORI SEMINARS 2011

February 7, 2011. Anne M. Bowcock, PhD, Professor of Genetics, Pediatrics & Medicine, Washington University School of Medicine. “Cancer Genetics in the Era.”

February 8, 2011. Robert H Michell, PhD, FRS; Department of Biochemistry, University of Birmingham, UK. “Inositol Phospholipids: Evolutionary Origins and Accumulation of Functions.”

February 22, 2011. Edward S. Mocarski PhD, Robert W. Woodruff Professor, Georgia Cancer Coalition Scholar, Department of Microbiology & Immunology Emory Vaccine Center, Emory University School of Medicine. “Newly Discovered Cell Death Pathways in Cytomegalovirus Infection and Mammalian Development.”


March 17, 2011. Anna Di Rienzo, PhD, Department of Human Genetics, University of Chicago. “Genetic Adaptations to New Environments in Humans.”


April 11, 2011. Jenifer Allsworth, PhD, Assistant Professor, Department of Obstetrics & Gynecology, Washington University in St. Louis, School of Medicine. “Reducing Unintended Pregnancy: The Contraceptive CHOICE Project.”

April 14, 2011. Andrey Kiselev, PhD, Department of Laboratory Medicine, University of Washington. “Polymorphic Membrane Proteins of Chlamydia: Their Importance in Therapeutic and Vaccine Development.”

April 19, 2011. J. Bruce German, PhD, Professor, Department of Food Science & Technology, Director, Foods for Health Institute, University of California, Davis. “Milk Genomics: From Marsupials to the NICU.”

April 22, 2011. Douglas Grant McFadden, PhD, Professor, Department of Molecular Genetics & Microbiology, University of Florida, College of Medicine. “The Curious Road from Poxvirus Tropism to Oncolytic Virotherapy.”

May 3, 2011. Shiniro Yokoyama, MD, PhD, Professor, Department of Biochemistry, Nagoya City University Graduate School of Medical Sciences & Department of Food and Nutritional Sciences, Chubu University. “Biosynthesis of HDL by the ABCA1 Pathway as a Potential Pharmacological Target for Anti-atherogenesis Treatment.”


June 7, 2011. David J. Segal, PhD, Associate Professor, Genome Center and Department of Biochemistry and Molecular Disease, University of California, Davis. “Dissecting the Genetic Architecture of Common Diseases by Genome Engineering.”

June 20, 2011. Michael Fietz, PhD, Head, National Referral Laboratory, SA Pathology (at Women’s and Children’s Hospital), Australia. “Continuing Evolution of Mucopolysaccharidoses Testing: Aiming to Diagnose Quickly, Early and Effectively.”

July 25, 2011 Charles H. King, MD, MS, Professor of International Health, Center for Global Health and Diseases Case Western Reserve University, Cleveland, OH and Uriel Kitron, PhD, MPH, Chair, Department of Environmental Studies, Emory University, Atlanta, Georgia. “Microscope to Macrocope: Understanding the Role of Environmental Complexity in Disease Causation.”

September 13, 2011. Gabriella Loots, PhD, Assistant Adjunct Professor/Biomedical Scientist, University of California, Merced & Lawrence Livermore, National Laboratory. “Mining the Human Genome for Functional Elements.”

September 17, 2011. Theil Fest 2011 Symposium, Tuesday, September 27, 2011 Jennifer Manilay, PhD, Assistant Professor, School of Natural Sciences, University of California, Merced. “Embryonic Stem Cell-Derived Hematopoietic Progenitor Cells: Challenges in Development, Differentiation, and Immunogenicity.”

October 4, 2011. John P. Mordes, MD, Professor of Medicine, University of Massachusetts Medical School. “Genetics of Juvenile Diabetes: Still Room for Surprises?”

October 11, 2011. Bill Usinger, PhD, Vice President, R&D, Trellis Bioscience, LLC. “Mining Blood for Therapeutic Antibodies to Treat Infectious Disease.”

October 18, 2011. Rajesh Kumar, MD, Attending Physician, Division of Allergy, Children’s Memorial Hospital. “Another Look at Asthma Disparities.”

October 24, 2011. Mark A. Atkinsion, PhD, Professor, Department of Pathology, University of Florida. “The Role for the Gut Microbiome in Type 1 Diabetes.”

November 1, 2011. Daisy Sahoo, PhD, Assistant Professor of Medicine, Division of Endocrinology, Metabolism, and Clinical Nutrition, Medical College of Wisconsin. “The HDL Receptor: How Structural Ambiguities Affect Cholesterol Transport Efficiency.”


November 15, 2011. Shukry Habib, Dr. rer. nat., Postdoctoral Research Fellow, Departments of Developmental Biology/Howard Hughes Medical Institute, Stanford University. “Can External Cues Induce Asymmetric Division of Stem Cells?”

November 22, 2011. Hussein Yassin, MD, Director, Lipid Clinic, Assistant Professor, Division of Endocrinology, University of Arizona. “HDL Proteomics in Cardiovascular Disease.”

December 6, 2011. Distinguished Speaker, Glenn D. Prestwich, PhD, Presidential Professor, and Director, Center for Therapeutic Biomaterials, Department of Medicinal Chemistry, The University of Utah. “From Organic Chemistry to Regenerative Medicine: Realizing the Promise of Translational Research.”

December 7, 2011. Lawrence L. Rudel, PhD, FAHA, Professor, Wake Forest University School of Medicine. “Cholesteryl Oleate and ACAT2: Underappreciated Villains in Atherosclerosis.”
Institutional Review Board at CHORI

The Children’s Hospital & Research Center Oakland has an active Institutional Review Board (IRB) that oversees the compliance to all federal regulations to protect the rights and welfare of human subjects who have volunteered to participate in research studies. Our IRB ensures that all ethical and regulatory issues have been addressed in accordance with federal regulations. All research protocols involving human subjects are reviewed to consider ethical issues, investigators’ potential conflicts of interest, potential benefits versus risks, and assurance that appropriate consent procedures are used.

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Denyse Pettersson, CIM, CIP, IRB Manager
Brigid Roy, Administrative Coordinator

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Horst Fischer, PhD
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Carla Golden, MD
Carlyle Hedrick, PhD
Rebecca Landes, JD
Jacqueline Madden, RN, PNP
Evelyn Mascarenas, MSW
Steven Oakes, PharmD
Denyse Pettersson, CIM, CIP
Elizabeth Trachtenberg, PhD
Robin Winokur, MD

National Institutes of Health Funded Grants

<table>
<thead>
<tr>
<th>SOURCE: GRANT NUMBER</th>
<th>PRINCIPAL INVESTIGATOR; PROJECT TITLE, PROJECT PERIOD</th>
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</thead>
<tbody>
<tr>
<td>Bay Area Tumor Institute: U10CA45461 (Subaward Contract # 23 CCOP-CHO)</td>
<td>Feusner, James, MD; CCOP Consortium Agreement. 06/01/10-05/31/11</td>
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<tr>
<td>Board of Trustees of the Leland Stanford Junior University (Subaward: 4U19AI090019-02)</td>
<td>Lucas, Alexander, PhD; Vaccination and Infection: Indicators of Immunological Health and Responsiveness. 07/18/11-06/30/12</td>
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<tr>
<td>California Pacific Medical Center Research Institute 1R01EY019900-01A1 (Subaward No. 2803264-5124, PO # 116863)</td>
<td>Noble, Janelle, PhD; Immune Response Gene Polymorphisms and AMD: Examining HLA-KIR Epistasis. 09/30/10-08/31/14</td>
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<td>Case Western: 1R03HD058587-01A2</td>
<td>LaBeaud, Desiree, MD; The Effects of Polyparasitism on Vaccine Response. 05/01/10-04/30/12</td>
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<td>Children’s Hospital Boston: 1R01AI084011-01A1 (Subaward)</td>
<td>Flori, Heidi, MD; Genetic Epidemiology of Life-Threatening Influenza Infection in Children. 11/10/09-05/31/12</td>
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<tr>
<td>Children’s Hospital Boston: 1R34HL018785-01A1 (Subaward)</td>
<td>Vichinsky, Elliott, MD; Comparative Effectiveness of Strategies to Improve Iron Chelation in Thalassemia. 08/15/11-06/30/13</td>
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<tr>
<td>Children’s Hospital Los Angeles: 5U54 HL090511-03 (Subaward Agreement #390 Amendment 5)</td>
<td>Lubin, Bertram, MD; Basic and Translational Research Program. 06/22/09-02/29/12</td>
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<tr>
<td>Children’s Hospital of Philadelphia: 5R01HL098087-02 (Subaward #95106 RSUB)</td>
<td>Flori, Heidi, MD; Impact of Pharmacology on Duration of Ventilation in Patients with Respiratory Failure. 06/01/10-05/31/12</td>
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<td>Lawrence Berkeley National Laboratory: 1R01HL091495-01A1 (Subaward No. 6884471)</td>
<td>Boffelli, Dario, PhD; Comparative Genomics of Non-Coding Regions to Facilitate Translation Research. 06/01/09-03/31/13</td>
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<td>Lypro Biosciences, Inc: (Subaward No. 4U19AI090019-02)</td>
<td>Oda, Michael, PhD; NanoDisk-Amphotericin B Therapy for Aspergillosis. 05/04/10-07/01/12</td>
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<td>Medical College of Wisconsin Purchased Services Agreement: 5R01HL95410-02 (Subaward)</td>
<td>Flori, Heidi, MD; Purchased Services Agreement for Genetic Variation and Biomarkers in Children with Acute Lung Injury. 05/01/04-03/30/12</td>
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<td>National Cancer Institute: 5R01CA142879-02</td>
<td>Epstein, Jr., Ervin, MD; Vitamin D3 Inhibition of Hedgehog Signaling and Cancer Chemoprevention. 07/12/10-05/31/15</td>
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<td>National Cancer Institute: 5R01CA116984-06 (NCE)</td>
<td>Epstein, Jr., Ervin, MD; Chemoprevention of Basal Cell Carcinomas with Tazarotene. 05/01/10-05/30/11</td>
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<td>National Cancer Institute: 1K22CA163969-01</td>
<td>Munoz, Denise, PhD; Epigenetic Role of AID in the Epithelial-Mesenchymal Transition in Breast Cancer. 09/21/2011-08/31/2014</td>
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<td>SOURCE: GRANT NUMBER</td>
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<td>National Cancer Institute: 5R01CA129438-05</td>
<td>Saba, Julie, MD, PhD; SIP Lyase in Colon Cancer. 09/21/07-07/31/12</td>
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<tr>
<td>National Center for Complementary and Alternative Medicine (AT): 5R21AT004493-03</td>
<td>Ames, Bruce, PhD; Antioxidant Therapy to Reduce Inflammation in Sickle Cell Disease. 02/01/07-01/31/13</td>
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<tr>
<td>National Center for Complementary and Alternative Medicine: 5R21AT005336-02 (NCE)</td>
<td>Saba, Julie, MD, PhD; Soy Sphingadienes and Related Compounds in Colon Cancer Chemoprevention and Treat(ment). 09/01/09-07/31/12</td>
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<td>National Childhood Cancer Foundation: U10 CA98543-07 (Subaward 98543-1053)</td>
<td>Feusner, James, MD; Children’s Oncology Group Chair’s Grant. 03/01/08 - 02/28/14</td>
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<td>National Childhood Cancer Foundation Agreement: U01HL69254 (Subaward No.69254-1046)</td>
<td>Walters, Mark, MD; BMT Clinical Research Network Data Coordinating Center. 09/01/09-09/30/12</td>
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<tr>
<td>National Childhood Cancer Foundation Agreement: U01HL69254 (Subaward Agreement No.69254-1046 Clinical Study Protocol Rider #0601)</td>
<td>Walters, Mark, MD; Unrelated Donor Hematopoietic Cell Transplantation for Children with Severe Sickle Cell Disease Using a Reduced Intensity Conditioning Regimen - BMT CTN Protocol #0601. 01/04/11-01/31/13</td>
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<tr>
<td>National Heart, Lung, and Blood Institute: 5R01 HL084474-04</td>
<td>Boffelli, Dario, PhD; Identification of Primate-Specific Regulatory Elements of Cholesterol Homeostasis. 04/04/07-03/31/12</td>
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<td>National Heart, Lung, and Blood Institute: 5R01 HL077708-05 (NCE)</td>
<td>Lammer, Edward J., MD; Conotruncal Defects: Genetic and Nutritional Risk. 05/01/06-04/30/12</td>
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<tr>
<td>National Heart, Lung, and Blood Institute: 5R01 HL096365-03 (MPI)</td>
<td>Lubin, Bertram, MD, Narayanaswami, Vansanthi, PhD (MPI); Short-Term Research Education Program to Increase Diversity in Health Related Research. 04/01/09-03/31/14</td>
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<tr>
<td>National Heart, Lung, and Blood Institute: 5R01 HL104133-02</td>
<td>Ryan, Robert, PhD; Wnt Signaling and Hematopoietic Stem Cells. 08/01/10-07/31/12</td>
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<tr>
<td>National Heart, Lung, and Blood Institute: 5U01HL083704-05 (NCE)</td>
<td>Walters, Mark, MD; Northern California Consortium for Sickle Cell Disease. 04/18/06-03/31/12</td>
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<td>National Human Genome Research Institute: 5U01HG004080-05 (ARRA)(NCE)</td>
<td>de Jong, Pieter, PhD; High-throughput Targeted Mutagenesis of Mouse Stem Cell Lines. 09/30/09-08/31/12</td>
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<tr>
<td>National Human Genome Research Institute: 5U01HG004080-05 (NCE)</td>
<td>de Jong, Pieter, PhD; High-throughput Targeted Mutagenesis of Mouse Stem Cell Lines. 09/07/06-08/31/12</td>
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<tr>
<td>National Institute of Allergy and Infectious Diseases: 5R01AI079955-04</td>
<td>Beemink, Peter, PhD; Identification of Vaccine Antigens Based on Expression in Blood. 09/24/08-08/31/12</td>
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<td>National Institute of Allergy &amp; Infectious Disease: 5R01AI059647-05 (2nd NCE)</td>
<td>Dean, Deborah, MD; C. Trachomatis Genomics, Strain Typing, and Evolution. 04/01/07-03/31/11</td>
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<td>National Institute of Allergy and Infectious Diseases: 1R56AI078419-01AI (NCE)</td>
<td>Dean, Deborah, MD; The Influence of Negative Regulators of Inflammation on C. Trachomatis Infections. 09/09/10-08/31/12</td>
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<td>National Institute of Allergy and Infectious Diseases: 2U01A1067068-06</td>
<td>Erlich, Henry, PhD; Trachtenberg, Elizabeth, PhD; (MPI); HLA and KIR Genomics in Inflammatory Bowel Disease. 09/20/05-07/31/15</td>
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<tr>
<td>National Institute of Allergy and Infectious Diseases: 5R01AI082263-03</td>
<td>Granoff, Dan, MD; An Engineered Meningococcal OMV Vaccine for Africa Against All Capsular Groups. 01/01/10-12/31/13</td>
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<tr>
<td>SOURCE: GRANT NUMBER</td>
<td>PRINCIPAL INVESTIGATOR; PROJECT TITLE. PROJECT PERIOD</td>
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<td>National Institute of Allergy &amp; Infectious Disease: 5R01AI046464-10</td>
<td>Granoff, Dan, MD; Novel Vaccine Strategies for Prevention of N. Meningitidis Group B Disease. 12/01/99-05/31/14</td>
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<td>National Institute of Allergy &amp; Infectious Disease: 1R21AI0868481-02</td>
<td>Hertel, Laura, PhD; RASCAL: A New Tropism Determinant Encoded by Human Cytomegalovirus? 12/03/10-11/30/12</td>
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<td>National Institute Allergy and Infectious Diseases: 5R01AI092508-23 (NCE)</td>
<td>Lucas, Alexander, PhD; Polysaccharide Antibody Repertoires. 09/01/88-04/30/12</td>
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<td>National Institute of Allergy &amp; Infectious Disease: 5R21AI090345-02</td>
<td>Moe, Greg, PhD; Neisseria Meningitidis Ig Binding Protein Vaccine. 05/01/10-04/30/12</td>
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<td>National Institute of Allergy and Infectious Diseases: 1R01AI0961554-05 (NCE)</td>
<td>Ryan, Robert, PhD; Leishmaniasis Treatment: Macrophage Scavenger Receptor. 06/01/06-06/30/12</td>
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<tr>
<td>National Institute of Allergy and Infectious Diseases 5U01AI067068-07</td>
<td>Trachtenberg, Elizabeth, PhD (NIH PI: Erlich, Henry, PhD); HLA and KIR Genomics in Inflammatory Bowel Disease (Supplement: Development of Superior HLA Genotyping Using Nanofluidics and Next-Generation Sequencing). 08/01/11-07/31/12</td>
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<td>National Institute of Allergy and Infectious Diseases: 3U01AI067068-05S1 (ARRA)</td>
<td>Trachtenberg, Elizabeth, PhD (NIH PI: Erlich, Henry, PhD); The Role of HLA and KIR in Rheumatoid Arthritis and Crohn's Disease. 09/12/09-02/28/12</td>
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<td>National Institute of Arthritis and Musculoskeletal and Skin Diseases: SK01AR053496-05</td>
<td>Jawaeheer, Damini, PhD; Gender Differences in Outcomes and Genetic Associations of Rheumatoid Arthritis. 05/01/07-04/30/12</td>
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<td>National Institute of Arthritis and Musculoskeletal and Skin Diseases: 5R21AR057931-02 (Revised #1) (NCE)</td>
<td>Jawaeheer, Damini, PhD; Gene Expression Profiling in a Prospective Rheumatoid Arthritis and Skin Diseases. 04/12/10-01-31/13</td>
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<td>National Institute of Child Health &amp; Human Development: 2R01HD053036-06</td>
<td>Shackleton, Cedric, PhD, DSc and Watson, Gordon, PhD; Pathogenesis/Treatment-Inherited Cholesterol Deficiency. 04/15/06-01/31/16</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases: SRCIDKO86472-02 (ARRA)(NCE)</td>
<td>Krauss, Ronald, MD; Effects of Resistant Starch on Lipid and Glucose Metabolism in Insulin Resistance. 09/30/09-08/31/12</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases: ST32DK078514-10</td>
<td>Kuypers, Frans, PhD; Training: Hematology, Immunology &amp; Stem Cell Biology. 07/01/00-08/31/12</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases: IR2DK080428-02 (ARRA)(NCE)</td>
<td>Martin, David, MD; A High-throughput Screen for Candidate Agents that may Reverse Gamma-globin Silencing. 07/01/09-06/30/12</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases: SRO1DK06722-08</td>
<td>Noble, Janelle, PhD; The Genetic Basis of Type 1 Diabetes Autoimmunity in African Americans. 04/01/02-03/31/14</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases: SRCIDKO20251-33S1 (ARRA - SUPPLEMENT)(NCE)</td>
<td>Theil, Elizabeth, PhD (MPI: Goss, Dixie, PhD); Ferritin: Protein /mRNA/DNA in Fe/O Regulation / Metabolism. 08/01/77-08/31/12</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases 5R01GM066954-07</td>
<td>Vichinsky, Elliott, MD / John Brooke Porter; Modulation of Iron Deposition in SCD and Other Hemoglobinopathies. 08/01/00-07/31/12</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases: 5R01DS25124-01A1</td>
<td>West, David, PhD; Genes on Chromosome 17 Regulating % Body Fat in the Mouse. 09/10/10-07/31/14</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases: 1R56DK084357-01A1</td>
<td>West, David, PhD; Rapid Identification of Obesity and t2D QtGs In a large B6x129 09/10-07/31/14</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases: 7R01DK090479-02</td>
<td>Wu, Wen-Shu, PhD; Role of Slug in Hematopoietic Stem Cell Regeneration. 01/01/12-07/31/16</td>
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<td>National Institute of General Medical Sciences: 5R01GM066954-07</td>
<td>Saba, Julie, MD, PhD; Sphingolipid Metabolism in Drosophila Development. 09/01/03-02/28/14</td>
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<td>National Institute of Allergy &amp; Infectious Disease: 5R01AI061354-05 (NCE)</td>
<td>Ryan, Robert, PhD; Leishmaniasis Treatment: Macrophage Scavenger Receptor. 06/01/06-06/30/12</td>
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<td>National Institute of Arthritis and Musculoskeletal and Skin Diseases: 5K01AR053496-05</td>
<td>Ryan, Robert, PhD; leishmaniasis treatment: Macrophage Scavenger Receptor. 06/01/06-06/30/12</td>
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<td>National Institute of Arthritis and Musculoskeletal and Skin Diseases: 5R01AI064314-04 (NCE)</td>
<td>Moe, Greg, PhD; Unique Neisseria Meningitidis B Capsular Epitopes. 05/19-06-04/30/11</td>
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<td>National Institute of Allergy and Infectious Diseases: 5R21AI090345-02</td>
<td>Moe, Greg, PhD; Unique Neisseria Meningitidis B Capsular Epitopes. 05/19-06-04/30/11</td>
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“National Institute on Aging: SRCIA036203-02 (ARRA)(NCE)”

Amer, Bruce, PhD; mtDNA Mutation/Heteroplasmy: a Sensitive Functional Biomarker of Oxidative Stress. 09/30/09-08/31/12

National Institute on Aging: 7R01AG040182-02

Wu, Wen-Shu, PhD; Regulatory Role of Transcription Factor Slug in Aging. 08/01/11-07/31/16

NetBio: 1R43AI096768-01 (Subaward)

Dean, Deborah, MD; A Rapid Point-of-Care Diagnostic for Neisseria Gonorhroeae STDs. 07/05/11 - 06/30/13

NetBio: 1R43AI084206-01 (MPI Subaward Agreement 203) (NCE)

Dean, Deborah, MD; Sponsored Research Agreement for A Diagnostic Test For Chlamydia Trachomatris. 07/15/09-06/30/12

New England Research Institute: 5U01HL065238 (Sub Award)

Vichinsky, Elliott, MD; Thalassemia Clinical Research Network - A Longitudinal Cohort Study of Patients with Thalassemia (TLC). 03/01-07-Completion
<table>
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<tr>
<td>New England Research Institutes, Inc. (NERI): U01 HL065238</td>
<td>Vichinsky, Elliott, MD; Thalassemia Clinical Research Network - A Phase IIA Study of Subcutaneous 5-AZA-2’ Deoxycytidine (Dectitabine) in Patients with Thalassemia Intermedia. 08/18/08-Completion</td>
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<td>New England Research Institutes, Inc.: U01HL065238-08</td>
<td>Vichinsky, Elliott, MD/Foote, Drucilla, PNP; Assessment of Pain Survey. 03/01/09-Completion</td>
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<tr>
<td>New England Research Institutes, Inc.: U01HL065238-08</td>
<td>Vichinsky, Elliott, MD/Drucilla, PNP; Thalassemia Clinical Research Network - Assessment of Pain in Transfusion Dependent Patients with Thalassemia during Transfusion Crisis. 03/01/09-Completion</td>
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<td>New England Research Institutes, Inc.: U01HL065238-08</td>
<td>Vichinsky, Elliott, MD/Drucilla, PNP; Thalassemia Clinical Research Network: Pilot of Oral Sildenafil for the Treatment of Pulmonary Hypertension in Thalassemia with Comparison to Controls (PHT). 03/01/09-Completion</td>
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<tr>
<td>New England Research Institutes, Inc.: SCDCRN</td>
<td>Walters, Mark, MD; Preventing Acute Chest Syndrome by Transfusion (PROACTIVE) Feasibility Study. 01/14/09-Completion</td>
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<tr>
<td>New England Research Institutes, Inc./ Washington University Medical Center: U01HL065238 (Subaward)</td>
<td>Walters, Mark, MD; TCRN-NMD 0901-Related Donor Hematopoietic Cell Transplantation for Children with Severe Thalassemia Using a Reduced Intensity Conditioning Regimen (The URTH Trial). 08/01/09-Completion</td>
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<td>New England Research Institutes, Inc.: SCDCRN</td>
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<td>Department of Health and Human Services/Health Resources and Service Administration: 2H12HA00072-15-00</td>
<td>Barba, Daniel, Esq; Family Care Network. 08/01/97-07/31/12</td>
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<td>Department of Health and Human Services/Health Resources and Service Administration: 5H80CS00052-11-00</td>
<td>Zlotnick, Cheryl, MS, MPH, DrPH; Health Center Cluster. 11/01/01-10/31/15</td>
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<td>Department of Health and Human Services/Maternal Child Health Bureau 5 H46MC00250-09-00</td>
<td>Morris, Claudia, MD; Glutamine therapy for Hemolysis-Associated pulmonary Hypertension. 04/01/09-03/31/13</td>
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<td>Easter Seals Northern California</td>
<td>Greenwald, Sue, LICSW; Consultation and Training Team (CATT) Services.</td>
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<td>Emmaus Medical, Inc. Protocol GLUSC09-01</td>
<td>Vichinsky, Elliott, MD; A Phase III, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study of L-Glutamine Therapy for Sickle Cell Anemia and Sickle BO-Thalassemia. 08/23/10-12/31/13</td>
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<td>Every Child Counts</td>
<td>Meade, Kelly, MD; Providing Asthma Education and Services to Children Age 0 to 5 and Their Families. 07/01/11-06/30/13</td>
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<td>Every Child Counts, First 5 Alameda County</td>
<td>Greenwald, Sue, LICSW; Consultation with Agencies Funded by the FSAC 2009-2011 Community Grants Initiative Neighborhood Partnership Program Planning and Providing School Readiness Services for Families with Children with Special Needs in Community-Based Settings.</td>
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<td>Every Child Counts, First 5 Alameda County</td>
<td>Greenwald, Sue, LICSW; Support to Providers Who Work with Latino Families Serving Children 0-5 Years Old.</td>
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<td>Every Child Counts, First 5 Alameda County, Contract FSS2009-11-09</td>
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<td>Every Child Counts, First 5 Alameda County, Contract FSS2009-11-11</td>
<td>Greenwald, Sue, LICSW: Every Child Counts (ECC) - Special Start. 07/01/09-06/30/11</td>
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<td>Family Support Services of the Bay Area</td>
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<td>Farr Family</td>
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<td>FDA: Food and Drug Administration; 5R01FD003531-03 NCE</td>
<td>Morris, Claudia, MD; Glutamine Therapy for Hemolysis-Associated Pulmonary Hypertension. 04/01/09-03/31/13</td>
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<td>FerroKin BioSciences, Inc: Protocol FBS0701</td>
<td>Harmatz, Paul, MD; A Phase 2, 2 Open Label, Multi-Center, Single-Dose Pharmacokinetics, and Multiple Dose Study of the Safety, Efficacy and Tolerability of FBS0701 in a Pediatric Population with Transfusional Iron Overload. 07/22/11</td>
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<td>FerroKin BioSciences, Inc: Protocol FBS0701-CTP-03</td>
<td>Harmatz, Paul, MD; A Phase Ib Open Label, Multi-Center, Escalating Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of FBS0701 in Patients with Transfusional Iron Overload. 10/28/09-Completion</td>
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<td>First 5 Alameda County, Every Child Counts</td>
<td>Greenwald, Sue, LICSW: Parent Infant Program. 7/1/11-6/30/13</td>
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<td>Genentech Research Payment and Supply Agreement; Protocol number SHH4437G</td>
<td>Epstein, Jr., Ervin, MD ; An Open-Label, Multicenter Extension Study of GDC-0449 (Hedgehog Pathway Inhibitor) In Patients Treated With GDC-0449 In A Previous Genentech-Sponsored Phase I or Phase II Cancer Study. 05/31/11-Completion</td>
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<td>Genentech Research Payment and Supply Agreement; Protocol number SHH4685s</td>
<td>Epstein, Jr., Ervin, MD; A Phase II Randomized, Double-Blind, Vehicle-Controlled, Clinical Trial of GDC-0449 And Placebo Each Taken Once-Daily For 18 Months In Subjects With Basal Cell Nevoid Syndrome. 07/29/09-12/15/11</td>
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<td>Genzyme Corporation Service Agreement</td>
<td>Harmatz, Paul, MD; Service Agreement. 05/10/10- Ongoing</td>
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<td>Gilead</td>
<td>Ramdeholl, Shanta, RN; Rapid HIV Testing at a Juvenile Justice Center.</td>
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<td>Gilead Sciences, Inc.: Protocol No. GS-US-174-0115</td>
<td>Harmatz, Paul, MD; A Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety, and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Adolescents with Chronic Hepatitis B Infection. 10/17/08-Completion</td>
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<td>Global Blood Targeting, Inc.</td>
<td>Vichinsky, Elliott, MD; Global Blood Targeting. 08/25/11-08/24/12</td>
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<td>Harvest Plus Challenge Program; Agreement # 8229; (Centro Internacional de Agricultura Tropical - CIAT; International Food Policy Research Institute - IFPRI)</td>
<td>King, Janet, PhD; Testing Novel Biomarkers of Zinc Status for Use in Human Zinc Supplementation Trials. 10/01/10-10/31/12</td>
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<td>Hearst Foundation (NCE)</td>
<td>Treadwell, Marsha, PhD; Improving School Success for Children with Chronic and Life Threatening Conditions: The Hematology/Oncology School Integration Project. 06/01/09-09/30/11</td>
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<td>Helen Keller International - Service Contract</td>
<td>Killilea, David, PhD; Analysis of 1,925 Plasma Samples. 06/22/10-Ongoing</td>
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<td>HemaQuest Pharmaceuticals, Inc. Protocol HQP 1001-SCD-006</td>
<td>Neumayr, Lynn, MD; A Randomized, Open-Label, Multi-Dose Study of HQK-1001 in Subjects with Sickle Cell Disease. 04/04/11-Completion</td>
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<td>Hoffman-La Roche Inc. Protocol No. NP25138C</td>
<td>Petru, Ann, MD; An Open Label Prospective, Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Intravenous Otse tantirv (Tamiflu) in the Treatment of Infants Less than One Year of Age with Influenza Infection. 10/05/10-Completion</td>
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<td>Hoffman-La Roche Inc. Protocol No. NP25139</td>
<td>Petru, Ann, MD; An Open Label Prospective, Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Intravenous Otse tantirv (Tamiflu) in the Treatment of Children 1 to 12 Years of Age with Confirmed Influenza Infection. 02/09/10-Completion</td>
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<td>Hyundai Motor America</td>
<td>Feusner, James, MD; Hyundai Hope on Wheels 2010 Hope Grant. 10/01/10-12/01/11</td>
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<td>INO Therapeutics LLC Site Agreement for Investigator Initiated Clinical Study</td>
<td>Durand, David, MD; Trial of Late Surfactant (TOLSURF) to Prevent BPD in Preterm Infants Receiving INO. 03/28/11-03/28/13</td>
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<td>INO Therapeutics: BALLR4</td>
<td>Durand, David, MD; Trial of Late Surfactant to Prevent BPD: A Pilot Study in Ventilated Preterm Neonates Receiving Inhaled Nitric Oxide (BALLR4). 05/21/08-Ongoing</td>
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<td>Inspire Pharmaceuticals Protocol 08-108</td>
<td>Hardy, Karen, MD; A Multi-Center, Double-Blind, Placebo-Controlled Randomized, Efficacy and Safety Study of Denufosol Tetrasodium (INS37217) Inhalation Solution in Patients with Mild Cystic Fibrosis Lung Disease. 09/11/06-Ongoing</td>
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<td>Inspire Pharmaceuticals Protocol 08-110</td>
<td>Hardy, Karen, MD; A Phase 3, International, Multi-Center, Randomized Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Denufosol Tetrasodium Inhalation Solution in Patients with Cystic Fibrosis Lung Disease and FEV &gt; 75% but &lt;=110% Predicted. 01/09/09-Ongoing</td>
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<td>Inspire Pharmaceuticals Protocol 08-114</td>
<td>Hardy, Karen, MD; Study 08-114: Open-label Extension of Study 08-110—A Multi-Center Study of Denufosol Tetrasodium Inhalation Solution in Patients with Cystic Fibrosis Lung Disease. 08/03/10-Ongoing</td>
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<td>Irving Harris Foundation</td>
<td>Greenwald, Sue, LICSW; Infant-Family Mental Health Training. 07/01/12-06/30/15</td>
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<td>J.M. Long Foundation</td>
<td>Luster, Marsha/Willoughby, Mary/Newman, Vivienne; Pediatric Palliative Care Program. 2010-2011</td>
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<td>Jewish Family &amp; Children's Services of the East Bay</td>
<td>Greenwald, Sue, LICSW; Early Intervention Services - Early Childhood Mental Health Program/Parent Infant Program. 07/01/10-06/30/11</td>
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<td>Johnson &amp; Johnson Clinical Agreement #270097</td>
<td>Lund, Carolyn, RN, MS; The First Bath in Term and Late-Preterm Infants: Impact of Two Bathing Techniques on Skin Function. 02/01/11-01/31/13</td>
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<td>Johnson &amp; Johnson Protocol DORIPED3002; Phase 3</td>
<td>Kuhlanjan, Julie, MD; A Prospective, Randomized, Double-Blind, Multicenter Study to Establish the Safety and Tolerability of Doripenem Compared with Ceftazidime in Hospitalized Children With Complicated Urinary Tract Infections.</td>
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<td>La Familia (Amendment to Memorandum of Services)</td>
<td>Greenwald, Sue, LICSW; Consultation and Training Team (CATT) Services.</td>
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<td>La Familia (Second Amendment to Memorandum of Services)</td>
<td>Greenwald, Sue, LICSW; Consultation and Training Team (CATT) Services.</td>
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<td>Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center Cost Reimbursement Consortium Agreement</td>
<td>Harmatz, Paul, MD; A Study of Intrathecal Enzyme Replacement for Cognitive Decline in Mucopolysaccharidosis I. 09/30/10-10/01/12</td>
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<td>Macy's Foundation</td>
<td>Petru, Ann, MD; Pediatric HIV/AIDS Program. 01/01/11-12/31/11</td>
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<td>McKesson Foundation</td>
<td>Olson, Jennifer, MD; To Pilot Diabetes Sensor Project.</td>
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<td>MediResource Meeting Support Agreement</td>
<td>Harmatz, Paul, MD; Preceptorship Meeting for Education and Training Purposes January 11-13, 2011. 11/1/10-Completion</td>
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<td>Merck &amp; Co., Inc., US External Non-Clinical Study Agreement (IISP); # 38797</td>
<td>Krauss, Ronald, MD; Genetic Variation Affecting PCSK9 Regulation of LDLR. 12/02/10-12/01/12</td>
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<td>Miscellaneous Funders</td>
<td>Vichinsky, Elliott, MD; Evaluation of the Presence of XMRV and/or MLV-Related Viruses in Blood Samples of Chronically Transfused Thalassemia and Sickle Cell Patients. 01/24/11-12/31/11</td>
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<td>National Marrow Donor Program</td>
<td>Walters, Mark MD; Forms Competition. 01/01/07-Completion</td>
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<td>Novartis CICL670AUS38</td>
<td>Vichinsky, Elliott, MD; A 5-Year, Prospective, Non-Interventional, Multi-Center Registry in Sickle Cell Disease Patients. 12/01/09-12/31/17</td>
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<td>Novartis CICL670AUS42T</td>
<td>Walter, Patrick, PhD; Modulation of the Innate Immune Response in Thalassemia Major by Chelation. 09/01/10-04/30/12</td>
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<td>Novartis ICL670A 2209</td>
<td>Vichinsky, Elliott, MD; A Randomized, Double-Blind, Placebo-Controlled, Phase II Study to Evaluate the Efficacy and Safety of Deferasirox (ICL670, Exjade) in Non-Transfusion-Dependent Thalassemia Patients with Iron Overload. 01/01/09-03/27/13</td>
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<td>Novartis Vaccines and Diagnostics, Inc., V59P21</td>
<td>Azimi, Parvin, MD; A Phase 3, Open-Label, Randomized, Multi-Center Study to Evaluate the Safety and Immunogenicity of ProQuad Vaccine When Administered Concomitantly with Novartis Meningococcal ACWY Conjugate Vaccine to Healthy Toddlers. 07/24/08-01/31/12</td>
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<td>Novartis Vaccines and Diagnostics, Srl; Sponsored Research Agreement for the 287 Study</td>
<td>Granoff, Dan, MD; Sponsored Research Related to the Development of Opsonophagocytosis Assays for Measuring Serum Opsonic Activity (“OPA”) to Neisseria Meningitides Group B. 06/12/09-06/12/10</td>
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<td>Novartis; CICL670AUS24T</td>
<td>Vichinsky, Elliott, MD; Safety of Deferasirox (ICL670) and Deferoxamine (Desferal or DFO) Combined Chelation Therapy in Patients with Transfusion Dependent Thalassemia and Iron Overload. 10/15/07-12/31/13</td>
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<td>Novartis; CTA - ICL670A/Study2411/Center: #511</td>
<td>Vichinsky, Elliott, MD; A Five Year Observational Study (Registry) of Children Aged 2 to &lt;6 Years at Enrollment with Transfusion Dependent Hemoglobinopathies Treated with Deferasirox. 02/01/07-10/30/13</td>
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<td>Novartis; RAD0001M 2301</td>
<td>Brown, Candida, MD; A Randomized, Double-Blind, Placebo-Controlled Study of RAD001 in the Treatment of Patients with Subependymal Giant Cell Astrocytomas (SEGA) Associated with Tuberous Sclerosis Complex (TSC). 01/27/09-09/12/13</td>
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<td>Novo Nordisk Inc Study ID HGH-2149</td>
<td>Ahmad, Tariq, MD; The ANSWER Program American Norditropin Studies: Web Enabled Research. An Observational Study (Registry) Assessing Treatment Outcomes and Safety for Children and Adults Who Are Prescribed Norditropin (Human Growth Hormone). 01/20/11-Completion</td>
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<td>Oakland City Council Resolution No. 82433 (Federal Funds), First Amendment</td>
<td>Greenwald, Sue, LICSW; Early Start Mental Health Consultation services. 01/01/10-01/30/11</td>
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<td>Oakland Unified School District</td>
<td>Mary Kelley; To Perform the Ultimate Review, Supervision, and Responsibility of OUSD. 08/31/10-08/30/12</td>
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<td>Pfizer Inc. Protocol # A8851008</td>
<td>Lee, Brian, MD; A Prospective, Open Label Study to Assess the Pharmacokinetics, Safety &amp; Efficacy of Anidulafungin When Used to Treat Children with Invasive Candidiasis, including Candidaemia. 07/14/08-ongoing</td>
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<td>Pfizer Inc. Protocol #A1501080</td>
<td>Kulhanjian, Julie, MD; A Prospective, Open Label, Non-Randomized, Multi-Center Study to Investigate the Safety and Tolerability of Voriconazole as Primary Therapy for Treatment of Invasive Aspergillosis and Molds such as Scedosporium or Fusarium Species in Pediatric Patients. 06/04/09-ongoing</td>
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<td>Pfizer Inc. Protocol #A8851009</td>
<td>Lee, Brian, MD; A Prospective, Randomized Trial Comparing the Efficacy of Anidulafungin and Voriconazole in Combination to that of Voriconazole Alone When Used for Primary Therapy of Proven or Probable Invasive Aspergillosis. 07/14/08-ongoing</td>
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<td>Pfizer Inc. Protocol #TRN 87-052-45 [CCID# A6281276]</td>
<td>Olson, Jennifer MD; Pfizer International Growth Study (KIGS). 11/30/09-Completion</td>
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<td>Pharmaceutical Product Development/Medimmune Protocol No. MI-CP110</td>
<td>Azimi, Parvin, MD; A Pivotal Phase 3 Study of MEDI-524 (NumaxTM), an Enhanced Potency Humanized Respiratory Syncytial Virus (RVS) Monoclonal Antibody, for the Prophylaxis of Serious RVS Disease in High-Risk Children.</td>
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<td>Pharmaceutical Product Development/Medimmune Protocol No. MI-MA213</td>
<td>Azimi, Parvin, MD; An Observational Prospective Study to Assess the Outcomes and Risk Factors of RSV Infection Among Premature Infants (32-35 weeks Gestational Age).</td>
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<td>Prometheus Therapeutics &amp; Diagnostics Study No. 10BD09</td>
<td>Ali, Sabina, MD; Procurement of Blood Samples from Pediatric Subjects for Use in the Development of Gastrointestinal Disease Test. 02/23/11-Completion</td>
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<td>Public Health Foundation Enterprises Inc.: 3USCI123677-05S4 (Subaward project number 2367/001.001) (ARRA)</td>
<td>Azimi, Parvin, MD; ELC 317 Rotavirus-ARRA. 09/01/10-12/31/11</td>
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<td>Principal Investigator; Project Title; Project Period</td>
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<td>Public Health Foundation Enterprises, Inc.: 1US0DD000568-01 (Subaward Project Number 2328.002.001)</td>
<td>Vichinsky, Elliott, MD; California Hemoglobinopathies Surveillance Initiative (CHSI). 03/01/10-02/11/11</td>
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<td>Public Health Institute through Centers for Disease Control; Grant Agreement # 1016281</td>
<td>Lewis, Gena, MD; CSPLAT Environmental Health Curriculum. 10/01/10-09/29/11</td>
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<td>Robert Crose</td>
<td>Greenwald, Sue, LICSW; Early Childhood Mental Health Program (CATT).</td>
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<td>Robert James Frascino AIDS Foundation</td>
<td>Petru, Anna, MD; Pediatric HIV/AIDS Program. 2010-2011</td>
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<td>S.D. Bechtel, Jr. Foundation</td>
<td>Sawyer, Aenor, MD; Pediatric Bone Health Consortium. 01/01/10-01/12</td>
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<td>San Francisco AIDS Foundation</td>
<td>Petru, Anna, MD; Pediatric HIV/AIDS Program. 2010-2011</td>
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<td>Sanofi Pasteur Inc.</td>
<td>Granoff, Dan, MD; Human Sera for Complement; Collection of Sera from Previously Identified Donors (Sanofi Study). 01/01-03/31/12</td>
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<td>Santa Clara County Office of Education</td>
<td>Greenwald, Sue, LICSW; Early Childhood Mental Health Program (CATT).</td>
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<td>Shire Human Genetic Therapies, Inc.</td>
<td>Harmatz, Paul, MD; A Multicenter Open-Label Study of Gene-Activated® Human Glucocerebrosidase (GA-GCB) Enzyme Replacement Therapy in Patients with Type 1 Gaucher Disease Previously Treated with Imiglucerase; Clinical Protocol No. TKT034. 09/27/07-Completion</td>
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<td>Shire Human Genetic Therapies, Inc.</td>
<td>Harmatz, Paul, MD; A Phase II Open-Label Clinical Study of the Efficacy and Safety of Recombinant Human N-Acetylgalactosamine 4-Sulfates (rhASB) Enzyme Replacement Therapy in Patients with Mucopolysaccharidosis. 08/04/06-Completion</td>
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<td>Shire Human Genetic Therapies, Inc.</td>
<td>Harmatz, Paul, MD; An Open-Label Extension Study of Gene-Activated® Human Glucocerebrosidase (GA-GCB) Enzyme Replacement Therapy in Patients with Type 1 Gaucher Disease Previously Treated with Imiglucerase TKT 044. 07/27/09-Completion</td>
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<td>Shire Human Genetic Therapies, Inc. Protocol HGT-GCB-058</td>
<td>Harmatz, Paul, MD; A Multicenter Open-Label Treatment Protocol to Observe the Safety of Gene-Activated Human Glucocerebrosidase (GA-GCB, Velaglucerase alfa) Enzyme Replacement Therapy in Newly Diagnosed or Previously Treated (with Imiglucerase) Patients with Type 1 Gaucher Disease. 12/15/09-10/31/11</td>
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<td>Shire Human Genetic Therapies, Inc. Protocol HGT-REP-059</td>
<td>Harmatz, Paul, MD; An Open-Label Treatment Protocol to Evaluate the Safety of Replagal Treatment in Patients with Fabry Disease. 07/14/10-12/16/11</td>
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<td>St. Baldrick’s Foundation</td>
<td>Hankin, Dina PhD; Pediatric Oncology Long Term Follow-Up. 12/01/11-11/30/12</td>
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<td>St. Jude Children’s Research Hospital, Inc.</td>
<td>Treadwell, Marsha, PhD; Consulting Services Agreement (mentorship to Dr. Jerlym Porter. 02/01/11-11/30/11</td>
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<td>State of California Public Health 10-EN002 A2</td>
<td>Olson, Jennifer; Newborn Screening Program Endocrine Centers. 07/01/10-09/30/10</td>
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<td>State of California: 10-MC-002 A2</td>
<td>Watson, John, MD; Newborn Screening Program. 07/01/10-06/30/11</td>
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<td>State Street Foundation</td>
<td>Magaña, Tomás, MD; JJC Healthy Pathways. 01/01/11-12/31/11</td>
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<td>Stephen Bechtel Fund</td>
<td>Suh, Jung, PhD; Redox Metabolomics Study. 05/29/09-05/28/12</td>
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<td>Strike 3 Foundation</td>
<td>Orren, Pam and Hankin, Dina; Teen Cancer Support Group Program and the Siblings Program. 2011-2012</td>
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<td>The Board of Trustees of the Leland Stanford University: 6U0DD000489-03 (Subaward 27159960-50754-B)</td>
<td>Lammer, Edward, MD; California Center of the NBSPS - Finding Causes and Preventives of Birth Defects. 12/01/08-11/30/13</td>
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<td>The California Endowment, File No. 20081942 (NCE)</td>
<td>Magaña, Tomás, MD; FACES For the Future. 05/01/09-08/31/11</td>
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<td>The California Wellness Foundation - 2009-138</td>
<td>Magaña, Tomás, MD; FACES For the Future. 07/01/09-06/30/12</td>
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<td>The Center for Comprehensive Care &amp; Diagnosis of Inherited Blood Disorders/Health Resources and Services Administration (HRSA): 7H30MC21656-01</td>
<td>Matsunaga, Alison, MD; Region IX Comprehensive Hemophilia Care Program. 04/01/11-05/31/11</td>
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<td>The Hospital for Sick Children: 019468-001 (Subaward)</td>
<td>Feusner, James, MD; Predicting the Risk of Infections in Canadian Children Receiving Chemotherapy for Acute Myeloid Leukemia. 07/01/08-Completion</td>
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<td>The Nemours Foundation</td>
<td>Fung, Ellen, PhD, RD; A Multi-Center Pilot and Feasibility Study of Low Magnitude Mechanical Stimuli to Improve Bone Mass in Children and Adolescents with Cerebral Palsy. 10/01/10-Completion</td>
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<td>The Regents of the University of California, San Francisco Campus, Cardio Vascular Research Institute: Contract # 9000008848</td>
<td>Serikov, Vladimir, MD, PhD; To Render Samples of Immunohistochemical Analysis of Lung Tissue, Cell Cultures and Mesenchymal Stem Cell Cultures on “As Needed” Basis to UCSF’s Cardio Vascular Research Institute. 02/01/06-01/31/10</td>
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<td>SOURCE: GRANT NUMBER</td>
<td>PRINCIPAL INVESTIGATOR; PROJECT TITLE, PROJECT PERIOD</td>
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<td>The Regents of The University of New Mexico (UNM)</td>
<td>Greenwald, Sue, LICSW; Professional Consultation and Training Provided by Children's Hospital &amp; Research Center at Oakland.</td>
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<td>The Spanish Speaking Unity Council</td>
<td>Greenwald, Sue, LICSW; Consultation and Training Team (CATT) Services.</td>
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<td>The University of Western Ontario (Subaward)</td>
<td>Hertel, Laura, PhD; Human Cytomegalovirus Tropism for Dendritic Cells and Fibroblasts. 01/01-03/31/15</td>
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<td>The William G Irwin Charity Foundation</td>
<td>Wen, Andrew, MD; Equipment for Cardio-Pulmonary Exercise Testing Program.</td>
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<td>Tiburcio Vasquez Health Center</td>
<td>Greenwald, Sue, LICSW; Consultation and Training Team (CATT) Services.</td>
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<td>Tobacco-Related Disease Research Program: University of California; Agreement no. 18KT-0021</td>
<td>Cavigiolio, Giorgio, PhD; Impact of Tobacco-Smoke on Apolipoprotein Exchangeability. 07/01-09/30/12</td>
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<td>Tobacco-Related Disease Research Program: University of California: 17RT-0165 (NCE)</td>
<td>Narayanaswami, Vasanthy, PhD; ApoE Related Effect of Smoking in Cardiovascular Disease. 07/01-08/30/11</td>
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<td>Trio Foundation</td>
<td>Greenwald, Sue, LICSW; Promoting Positive Reunification for Previously Incarcerated Parents and their Young Children: A Pilot Intervention Model. 2011-2012</td>
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<td>United States Department of Agriculture</td>
<td>de Jong, Pieter, PhD; Lobolly Pine Genome Project. 02/01-01/31/16</td>
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<td>United States Department of Agriculture: Award No 2010-65200-20491</td>
<td>Fung, Ellen, PhD, RD; Testing the Calcium DRI in Pregnancy: a Study of Bone Health in Black and White Women. 02/01-01/31/13</td>
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<td>United States Department of Agriculture: Award No. 2009-65109-05760</td>
<td>Dean, Deborah, MD; Genome Sequencing and Evolution of Chlamydophila and Chlamydia Species of Animal Origin. 09/01-09/30/12</td>
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<td>University of British Columbia: MOP-106706 (Subaward)</td>
<td>Oda, Michael, PhD; Development of Nanodisks as Novel Therapeutic Agents for Alzheimer’s Disease. 04/01-09/30/15</td>
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<td>University of California, Berkeley: TG2-01164, (Subaward #00007113 Amendment 3)</td>
<td>Walters, Mark, MD/Ellen Robey (UC Berkeley); Interdisciplinary Training in Stem Cell Biology, Engineering and Medicine. 01/01-09/30/12</td>
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<td>University of California, Los Angeles: DR1-01452 (Subaward agreement # 2301-5-NA586)</td>
<td>Walters, Mark, MD; Stem Cell Gene Therapy for Sickle Cell Disease. 05/01-09/28/14</td>
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<td>University of California, San Francisco (Subaward 6651tc)</td>
<td>Illek, Beate, PhD; CFTR Expression Levels and CFTR Function: Transgene Versus Endogenous. 12/01-12/30/11</td>
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<td>University of California, San Francisco; CA Endowment 20072103</td>
<td>Juarez, Lourdes, PNP; Disparities in Pediatric Obesity: Bridging the Gap. 02/01-09/30/11</td>
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<td>University of California, San Francisco: (Subaward SAGE-0001)</td>
<td>Benson, Mindy, MSn, PNP; Asthma Research. 10/01-09/12/31</td>
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<td>University of Colorado: SPO # 0000046648</td>
<td>Eriich, Henry, PhD; PCR-Based Genetic Screening Including the HLA-DR and DQ Genes for the TEDDY Study. 12/21/05-Completion</td>
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<td>University of Minnesota Subaward</td>
<td>Harmatz, Paul, MD; Longitudinal Studies of Brain Structure and Function in MPS Disorders. 07/01-12/31/14</td>
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<td>University of Southern California -Children's Hospital Los Angeles Institutes for Pediatric Clinical Research (Amendment)</td>
<td>Hastings, Caroline, MD; Therapeutic Advances in Childhood Leukemia Consortium (TAACL). 07/01-07-Completion</td>
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<td>Various Granting Agencies</td>
<td>Krauss, Ronald, MD; Lipoprotein Research. 09/15-04/Ongoing</td>
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<td>Vitapath Genetics Agreement 196</td>
<td>Lammer, Edward J., MD; Genetics Research. 09/01-08/31/12</td>
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<td>WestEd Contract S11-067</td>
<td>Greenwald, Sue, LICSW; Consultation and Training Team (CATT) Services.</td>
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<td>WestEd Subaward/ First 5 California Contract No. CCFC 7219, WestEd# 66042 s10-114</td>
<td>Greenwald, Sue, LICSW; Training, Technical Assistance, and Work Force Development Project.</td>
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