FETAL TREATMENT CENTER

The UCSF Fetal Treatment Center, which performed the world’s first fetal surgery in 1981, continues to develop new interventions for conditions that are most effectively treated before birth.

“We have a whole team of specialists, including pediatric surgeons, high-risk obstetricians, neonatologists, ultrasonographers, nurses and many others who work together to provide the best care for the entire maternal-fetal spectrum,” said Hanmin Lee, MD, chief of the Division of Pediatric Surgery, surgeon in chief of UCSF Benioff Children’s Hospital and Michael R. Harrison, MD, Endowed Chair in Fetal Surgery.

“Our group is very collaborative,” said Lee. “Everyone is geared not only toward outstanding patient care, but the pursuit of novel therapies to improve patient outcomes.”

The center provides consultation to about 500 families annually – from as far away as Siberia, Iceland and Singapore – and performs about 50 fetal surgeries each year. It has also launched two initiatives: the UC Fetal Consortium, led by Lee, which brings together clinicians, researchers and educators at UC San Francisco, UC Davis, UC Irvine, UCLA and UC San Diego to improve maternal, fetal and neonatal outcomes; and the Pediatric Device Consortium, led by the center’s co-founder, Michael R. Harrison, MD, which develops new tools and devices for fetal and pediatric surgery.

Because fetal surgery always involves two patients – the mother and the fetus – and because the major complication of fetal intervention is preterm labor, UCSF has taken a lead role in studying the effectiveness of new procedures to make sure they merit the risk to both patients.

Some of the center’s latest developments include:

- **Spina bifida**: UCSF led the MOMS (Management of Myelomeningocele Study), which was stopped early after demonstrating that prenatal surgery to repair spinal defects significantly reduced the need to shunt fluid away from the brain, improved mental development and motor function, and increased the likelihood that a child would walk unassisted. Fetal intervention for myelomeningocele is now an accepted therapy that is covered by most third-party payers.
LETTER FROM THE CHAIR

In addition to offering the latest treatments to patients, the UCSF Department of Surgery is at the forefront of advancing the standard of care through ambitious research efforts in the clinic and the laboratory. Nearly all of our clinical faculty lead investigations into the causes of disease, and are spearheading projects to develop better therapies. Their wealth of clinical experience helps shape their research questions, and they are ideally positioned to rapidly translate discoveries into new interventions to help patients. These surgeon-scientists also collaborate with a number of other department faculty who are full-time researchers.

This issue’s cover story highlights the UCSF Fetal Treatment Center, the birthplace of fetal surgery. Directed by Hanmin Lee, MD, the center continues to develop more effective, less invasive ways to treat serious congenital conditions that are most effectively addressed before birth. The Fetal Treatment Center also leads efforts across UCSF and the UC system to develop new tools to conduct fetal surgery, and to collaborate in supporting maternal-fetal health.

The UCSF Thoracic Oncology Program, led by David M. Jablons, MD, brings together precision medicine, leading-edge clinical trials and a robust laboratory research program to offer the latest treatments for lung cancer, esophageal cancer, mesothelioma and other thoracic malignancies.

The UCSF Center for Bioengineering and Tissue Regeneration, directed by Valerie Weaver, PhD, integrates the strengths of the physical and life sciences. The center’s researchers are uncovering how force and tension play critical roles in processes ranging from aggressive cancer growth to stem cell differentiation, providing new insights into disease and health.

This issue also features the stem cell research of three of our faculty – fetal and pediatric surgeon Tippi MacKenzie, MD, plastic and reconstructive surgeon Jason Pomerantz, MD, and liver researcher Holger Willenbring, MD, PhD. They are each working to harness the power of regenerative medicine to help patients for whom there are currently few good treatment options.

I am pleased to share these highlights with you, and look forward to updating you as today’s investigations develop into the transformative therapies of tomorrow.

Sincerely,

Nancy L. Ascher, MD, PhD
Professor and Chair, Department of Surgery
Isis Distinguished Professor in Transplantation
Leon Goldman, MD Distinguished Professor in Surgery
Force and tension are phenomena more commonly associated with designing an artificial hip than studying cancer development. However, the UCSF Center for Bioengineering and Tissue Regeneration, led by biochemist Valerie Weaver, PhD, is investigating how these tenets of physics play an integral role at the cellular level of health and disease.

For example, by measuring the level of force in cells, Weaver has discovered that breast tumors have a high level of stiffness compared to normal breast tissue—and that inhibiting this stiffness can prevent cancer progression, while increasing it can make the cancer more aggressive.

“The whole idea of bioengineering is supposed to be interdisciplinary, but at many institutions, these departments focus heavily on engineering, with a little bit of biology,” said Weaver. To bridge this divide, the center helps researchers combine physical and life sciences approaches to problems such as cancer growth and stem cell differentiation.

With major support from the Hofmann Family Foundation, the center houses 20 researchers and trains visiting scholars from as far away as Switzerland and Argentina. Researchers learn to use tools such as spinning disk confocal microscopy, which can image live cells, and atomic force microscopy, which can image and measure matter at the nanoscale. The center also partners with many other researchers on projects including:

- **Aggressive cancer cells and force:** Weaver and her team have discovered that high levels of force in aggressive tumor cells appear to hyperactivate growth-promoting signaling in cells, enabling cancer cells to survive within the circulation and metastasize. The group is also investigating the nano-architecture of the receptors, and how physical force in the cell’s environment can produce “spatial mutations” that alter the way a tumor cell communicates.

- **Targeting aggressive breast cancers:** The center has discovered that tissue force alters micro RNAs, which are small noncoding RNAs that repress levels of a critical tumor suppressor gene called PTEN. Loss of the PTEN protein has been linked to development of many cancers, including breast and brain. By developing a therapeutic to prevent increases in tissue forces, investigators may be able to prevent cancer by restoring PTEN expression. Because these noncoding RNAs often circulate in the blood, they could form the basis of a new diagnostic tool for early detection of cancer progression.

Weaver and Stanford biophysicist Jan Liphardt, PhD, lead the Bay Area Physical Sciences-Oncology Center, which includes 15 investigators from multiple institutions and which received an $18 million, multiyear grant from the National Cancer Institute. Weaver and Liphardt are investigating how cells communicate mechanically over long distances through connective tissue and studying how these connections promote malignant transformation. Weaver is also investigating better ways to treat African American women with aggressive breast cancers.

- **Preventing breast cancer:** Weaver’s group found that lipophilic statins used to treat cardiovascular disease also have off-target effects that may reduce tissue tension. They are conducting preclinical studies to determine whether statins could be effective in preventing breast cancer. Because these drugs are well tolerated and inexpensive, they could be particularly useful for prevention efforts.

- **Pancreatic cancer:** Weaver’s research is investigating connections among rigidity, aggressiveness, force and inflammation in pancreatic tumors.

- **Imaging brain cancer:** Weaver and brain tumor researcher Gabriele Bergers, PhD, are using state-of-the-art MRI imaging to study the interplay among interstitial pressure, extracellular matrix stiffness and cell tension in gliomas. The group predicts that high forces experienced by brain tumors contribute to their aggressive, treatment-resistant nature.

- **Stem cell differentiation:** By investigating the role of force in human embryonic stem cell differentiation, Weaver’s team has developed a new model of the formation of a mesenchymal progenitor—a precursor to muscle, cardiac tissue, cartilage, blood, bone and connective tissue. Previous methods achieved only a 3 percent to 5 percent efficiency in differentiating embryonic stem cells into mesenchymal progenitor cells; Weaver’s team has increased this efficiency to as high as 50 percent to 60 percent. Because these cells can be differentiated into a plethora of tissue types, the findings could enhance tissue regeneration.

Weaver and Holger Willenbring, MD, PhD, are also investigating how force regulates stem cell differentiation into liver progenitor cells. (Please see related article on the following page.)

**FOR MORE INFORMATION:**
Visit weaverlab.surgery.ucsf.edu.
STEM CELL RESEARCH

Not only does UCSF offer state-of-the-art surgical procedures, but its researchers and surgeon-scientists are developing new approaches to advance the standard of care. “Our faculty includes a number of outstanding researchers who are developing novel stem cell therapies to treat a wide range of conditions, including sickle-cell anemia, muscle injury and liver disease,” said Nancy L. Ascher, MD, PhD, chair of the UCSF Department of Surgery, Isis Distinguished Professor in Transplantation and Leon Goldman, MD Distinguished Professor in Surgery. “With support from the California Institute for Regenerative Medicine and other organizations, our researchers are helping to create therapies of the future.”

- Fetal stem cell transplantation:
  Congenital stem cell disorders such as sickle-cell anemia and alpha thalassemia can be treated after birth with bone marrow transplant, but that procedure carries significant morbidity and requires immunosuppression. Tippi MacKenzie, MD, a fetal and pediatric surgeon and director of research for the UCSF Fetal Treatment Center, is developing methods to transplant stem cells in utero to replace the fetus’s own missing or mutated stem cells. Early in gestation, the fetus’s immune system is more plastic and can potentially be trained to tolerate transplanted cells.

  In collaboration with immunologist Qizhi Tang, PhD, director of the Transplantation Research Laboratory, MacKenzie is studying maternal-fetal cellular trafficking. They discovered that the mother’s immune system is the main rejector of transplanted stem cells, and that matching transplanted cells to the mother’s immune system enables good engraftment into the fetus. They are also investigating maternal-fetal cellular trafficking to understand how maternal-fetal tolerance is broken during preterm labor.

  MacKenzie and Tang are also working to mitigate ongoing loss of engraftment following fetal stem cell transplantation, and to develop a conditioning protocol that frees up space in the fetus’s bone marrow for transplanted stem cells to engraft.

  “Fetal surgery was born from a desire to correct fetal anatomic disorders, such as big lung masses or tumors,” said MacKenzie. “Now that techniques have been developed to safely image and access the fetus, we can potentially increase the scope of diseases to include those that are not fatal but are still quite devastating.”

- Reconstructing muscle with stem cells: Many disorders involve muscles too small to be treated by current techniques of muscle flaps or transfers. Examples include traumatic injuries or diseases affecting eye, face and hand muscles, and muscular problems of small sphincters throughout the body. Jason Pomerantz, MD, surgical director of the UCSF Center for Craniofacial Anomalies, is developing methods to isolate skeletal muscle stem cells called satellite cells, and autologously transplant them to regenerate small muscles. “In these conditions for which we aim to develop applications in the nearer term, there is already a nerve, blood vessel and scaffold in place – presumably well-poised to incorporate healthy muscle cells,” said Pomerantz. He hopes that eventually the principles and techniques will be applied to treat large defects by engineering of entire muscles.

  Pomerantz is also exploring the possibility of using satellite cells to treat otherwise irreversible muscle atrophy due to nerve injury, which typically occurs if reinnervation is significantly delayed. By replenishing affected muscles with fresh, transplanted satellite cells at the time of reinnervation, Pomerantz’s group hopes to stimulate muscle recovery.

  Pomerantz is also investigating whether transiently disabling some tumor suppressor genes can enable a temporary reversal of terminal differentiation – in which stem cells eventually commit to becoming mature cells and stop dividing. Reversing terminal differentiation could allow cells to regenerate, similar to the way newts can regrow limbs and other important tissues.

  “My research is a natural extension of plastic and reconstructive surgery, which has always been about restoring normal form and function,” said Pomerantz. “The aim of our work is to extend the types of conditions that we can treat effectively.”

- Liver disease: A pediatrician by training, Holger Willenbring, MD, PhD, and his group are working on developing autologous liver cell therapies for patients with severe liver diseases. They have found ways to turn human skin cells into hepatocytes that, after transplantation into a mouse liver, engraft, mature and expand, making

  A liver section from a mouse transplanted with hepatocytes generated by reprogramming of human fibroblasts. The human cells are red, both mouse and human nuclei are blue, and nuclei of dividing cells are green.
For decades, we haven’t seen much progress in the way we manage patients with severe liver diseases, but there is a lot happening right now in liver research,” said Willenbring. “I think we’re going to see many advances in the coming years, and we are quite excited about the potential of our investigations.”

FOR MORE INFORMATION:
- pedsurglab.surgery.ucsf.edu/research/mackenzie-lab.aspx
- plastic.surgery.ucsf.edu/faculty/faculty/jason-h-pomerantz,-md.aspx
- willenbringlab.surgery.ucsf.edu

Michael Harrison, MD, founder and director emeritus of the Fetal Treatment Center at UCSF Benioff Children’s Hospital and director of the UCSF Pediatric Device Consortium, received the Ronald McDonald House Charities Medical Award of Excellence.

Il-Jin Kim, PhD, received a grant from the Mesothelioma Applied Research Foundation to study novel fusion and tumor-specific isoform candidates in malignant pleural mesothelioma, with the ultimate goal of identifying therapeutic targets.

Peter Stock, MD, PhD, was named president-elect of the American Society of Transplant Surgeons. The society’s mission is to advance the art and science of transplant surgery through leadership, advocacy, education and training. Stock’s clinical investigations were also instrumental in leading to the passage of the HIV Organ Policy Equity (HOPE) Act in 2013, which lifted the ban on research for transplanting organs between HIV-positive donors and recipients.

Gregory P. Victorino, MD, director of trauma services for the UCSF-East Bay Surgery Program, who leads Highland Hospital’s Surgery Trauma Center in Oakland, Calif., received the Siren Award from the Alameda County Emergency Medical Services Agency.

Flavio Vincenti, MD, is the principal investigator of a seven-year, $17 million multicenter study through the National Institutes of Health to determine if regulatory T cells or a drug now used to treat rheumatoid arthritis can effectively support long-term health of kidney transplant recipients. The study’s goal is to reduce or eliminate inflammation in kidney transplants, prevent functional decline and maximize long-term organ survival.

Valerie Weaver, PhD, was inducted into the American Institute for Medical and Biological Engineering’s College of Fellows, Class of 2014. She also received the American Society for Cell Biology’s Women in Cell Biology Mid-Career Award for excellence in interdisciplinary science and outstanding mentoring.

Endowed Chair
Gordon A. Cohen, MD, PhD, MBA, was named the Julien I. E. Hoffman, MD, Endowed Chair in Cardiac Surgery.
HORACIC ONCOLOGY PROGRAM

The UCSF Thoracic Oncology Program offers a precision medicine approach, customizing treatment plans to match the molecular signature of each patient’s cancer. The program brings together an outstanding team of surgeons, medical oncologists, radiation oncologists, interventional radiologists and laboratory researchers who are pioneering innovative therapies for lung cancer, esophageal cancer, mesothelioma and other thoracic malignancies.

“We have more in-house experience than any other thoracic oncology program in the country in collecting, safeguarding and interrogating resected tumors,” said Jablons. “By genetically sequencing and analyzing each patient’s tissue, we are unlocking the biological secrets of their malignancy to guide both immediate and long-term treatment. We also apply a systems biology approach, comparing hundreds of patient samples to tease out underlying patterns of disease and identify novel therapeutic targets, for which we are developing powerful new therapeutics.”

The Thoracic Oncology Program currently offers nearly 10 clinical trials and is pursuing many ambitious initiatives, including:

- **Stratifying lung cancer risk:** UC San Francisco researchers recently published studies in The Lancet and the Journal of the American Medical Association describing a novel molecular assay that more accurately predicts mortality due to cancer recurrence following surgery for stage I lung cancer. Medical oncologist Thierry Jahan, MD, is now leading an international trial to determine whether early-stage lung cancer patients identified as high-risk experience improved survival if they receive chemotherapy prior to any detectable recurrence.

- **Mesothelioma program:** Instead of relying solely on morphologic criteria, the Thoracic Oncology Program’s researchers are uncovering the molecular underpinnings of mesothelioma. UCSF has a robust tissue bank with hundreds of well-annotated specimens of resected mesotheliomas, and is rigorously sequencing these samples and analyzing their gene expression and mutation status.

- **Esophageal program:** UCSF Medical Center offers combined modality therapy for early-stage through locally advanced stage III esophageal cancer. Patients receive chemotherapy, radiation and surgery, with a general surgeon performing minimally invasive laparoscopic gastric mobilization and a thoracic surgeon performing minimally invasive or limited thoracotomy and esophagectomy. Compared with open surgery, this combined surgical approach has significantly reduced complications and improved patient outcomes.

- **Medicinal chemistry core:** The Thoracic Oncology Program has recruited a team of medicinal chemists who are developing novel cancer drugs in-house, assisted by computer modeling. The team is currently pursuing four different stem cell pathways, and is close to submitting an Investigational New Drug application to the FDA for its Gli inhibitor, which targets a gene critical to multiple cancer signaling pathways.

- **Cancer stem cells:** Malignant tumors are composed of several different types of cancer cells. Although chemotherapy is toxic to most of these cell types, molecular geneticist Biao He, PhD, has led efforts to isolate a very small, elite subpopulation of cancer stem cells. These cells not only survive conventional chemotherapy, but are enriched by it, since chemotherapy eliminates other cancer cells, which compete for resources. The team has also found that its Gli inhibitor is highly effective in disabling these cancer stem cells.

- **Systems genetics and network analysis:** Il-Jin Kim, PhD, an applied genomics researcher, has led genetic analysis of malignant pleural mesotheliomas, identifying key genes that were upregulated or downregulated compared to normal matched tissue samples. This study will expand in an upcoming collaboration with New York University, helping to validate new therapeutic targets. Kim and his team have also analyzed matched tumor-normal tissue samples from 100 lung cancer patients, identifying about 1,000 genes that are active in lung cancer development. They mapped out a network analysis to identify genes that appear to be central to tumor cell replication but are not highly active in normal cells — making them promising targets for future drug development.

“Our laboratory discoveries rapidly translate into the clinic,” said Jablons. “The UCSF Thoracic Oncology Program offers care that is second to none. Our advanced approach is powered by the molecular revolution, our exceptional surgical skills and outstanding pre- and postoperative care. For patients with lung cancer, mesothelioma and other thoracic malignancies, there is no better center for state-of-the-art care.”

CONSULTATIONS AND REFERRALS:

Visit top.surgery.ucsf.edu or call (415) 885-3882.
- **Congenital diaphragmatic hernia (CDH):** This condition occurs when a hole in the fetus’s diaphragm allows the abdominal organs to migrate into the chest, severely restricting lung growth. UCSF developed an intervention, inserting a balloon to occlude the trachea, which blocks escape of fluids from the lungs and forces them to expand. The fetus is delivered using the ex utero intrapartum treatment (EXIT) procedure, an extraordinary C-section in which the fetus remains connected to the placenta until the balloon is removed and the newly delivered baby can breathe on his or her own. The hole in the diaphragm is easily corrected after birth.

UCSF is participating in an FDA-sponsored trial of temporary tracheal occlusion, in which the balloon is removed after about six weeks. This eliminates the need for the EXIT procedure, and may also support improved development of type II pneumocytes, which produce a protein important to proper lung function.

- **Twin-twin transfusion syndrome:** Monochorionic pregnancies, in which two fetuses share a placenta, can develop complications if twins share interconnected blood vessels and there is significant transfer of blood from one twin to the other. UCSF helped lead randomized clinical trials demonstrating that laser photocoagulation of the inter-twin vessels resulted in better outcomes compared to standard therapy of amnioreduction, in which amniotic fluid was removed from one of the fetuses.

- **Amniotic bands:** Occasionally, bands can form across the amniotic cavity, likely related to membrane problems with the amniotic chorion. These bands can wrap around a fetus’s limb like a tourniquet, sometimes resulting in amputation. Fetuses with preserved blood inflow but compromised outflow to the affected limb are most likely to benefit from surgical intervention, which uses a laser fiber and sometimes a micrograsper to divide the band and remove the constriction.

- **Congenital pulmonary airway malformation (CPAM):** Also known as congenital cystic adenomatoid malformations (CCAMs), this disorder is characterized by immature lung tissue that grows rapidly. Without surgical intervention, in the past fetuses experienced 100 percent mortality; even with surgery, many died or developed lifelong disabilities. Lee discovered that a simple steroid injection into the mother enabled the vast majority of affected fetuses to deliver at term with almost no disabilities, likely a result of the steroid’s twofold effect of causing cystic lung tissue to mature and also preventing that tissue from growing at an abnormal rate.

UCSF Medical Center now offers an experimental intervention in an effort to restore normal circulation while the heart is still developing. In a process similar to angioplasty, a needle with a narrow, hollow bore is inserted through the mother’s abdomen and uterus, through the fetus’s chest and into its left ventricle. A balloon-tipped catheter is inserted through the needle over a thin guide wire and positioned across the stenotic valve. The balloon is inflated several times to open the valve.

UCSF has performed four of these procedures since 2008, and is actively recruiting for a clinical trial. “One of the biggest challenges with this disease is that there is no animal model,” said Anita Moon-Grady, MD, director of the UCSF Fetal Cardiovascular Program. “We are very clear that this procedure is not a cure – it is experimental – but we may be able to change the baby’s long-term outcomes, which otherwise can be quite poor.”

Prompt referral is essential, since the procedure can only be performed after 18 weeks, when the fetus is large enough to accommodate the equipment, and before 31 weeks, to minimize risk of preterm delivery. “Any decrease in ventricular function should be easily recognizable on a standard 16- or 18-week obstetric [anatomy] ultrasound,” said Moon-Grady. “If there’s any suspicion, obstetricians should send the patient to us for evaluation expeditiously.”

- **Fetal cardiac intervention:** Aortic stenosis in the fetus can result in hypoplastic left heart syndrome (HLHS), in which babies are born without a functioning left ventricle. Even with major surgical interventions, over 25 percent of these children will die before age 5. For those who survive, expected lifespan is 20 to 30 years at best, with significant functional and neurodevelopmental limitations.
The Fetal Treatment Center provides expert help for many other conditions, and also collaborates with others to develop new treatments for fetuses and children. For example, the center’s clinical trials core helped support a phase I clinical trial led by David Rowitch, MD, PhD, chief of neonatology at UCSF Benioff Children’s Hospital, that showed transplanting neural stem cells into the brains of pediatric patients with Pelizaeus-Merzbacher disease was safe, and that the cells engrafted and appeared to produce myelin.

“Taking care of fetuses allows us to provide a continuum of care from before birth, through delivery and neonatal life,” said Lee. “We’ve been doing this longer than anybody else in the world, and feel we are the best people to take care of fetuses and babies with congenital anomalies.”

CONSULTATIONS AND REFERRALS:
For more information, please visit fetus.ucsfmedicalcenter.org, email the Fetal Treatment Center at fetus@surgery.ucsf.edu or call 1 (800) RX-FETUS (1-800-793-3887) or (415) 476-0445.