

The science of surgery

Dr Diana L Farmer and other prominent members of the UC Davis Department of Surgery outline the rich history of innovation within the Department, and describe ongoing cutting-edge research that will improve the lives of patients in the US and around the world



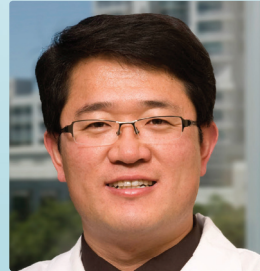
Diana L Farmer, MD



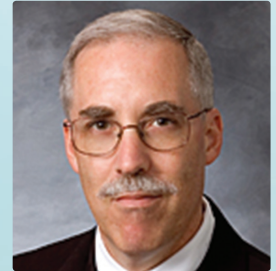
David H Wisner, MD



Claus Sondergaard, PhD



Aijun Wang, PhD



David Greenhalgh, MD

Could you provide an overview of the University of California, Davis (UC Davis) Department of Surgery's history and research strengths?

DF&DW: The UC Davis Department of Surgery encompasses bariatric, burn, cardiothoracic, gastrointestinal, plastic, transplant, trauma and emergency, vascular and oncologic surgery. We also conduct basic, translational and clinical biomedical research in collaboration with a variety of UC Davis divisions, departments and centres, as well as external research partners.

Our research accomplishments date back to the founding of the Department almost 50 years ago. Highlights include:

- The development and validation of nuclear medicine scanning (HIDA) for the diagnosis of acute cholecystitis
- Critical contributions to the development of minimally invasive major cardiac surgery and novel biologics for use in cardiac surgery
- Active utilisation of national databases (such as the 'American College of Surgeons National Surgical Quality Improvement Program' – ACS NSQIP) to investigate questions ranging from prognosis for patients with specific cancers to the impact of resident participation in surgery on patient outcomes
- Forward-thinking research on surgical education, and the intersection of gender, surgery and surgical education

UC Davis also has a long history of leadership in trauma research. The Department has been home to pioneering studies on resuscitating injured patients, including foundational, basic and clinical research on hypertonic and other novel resuscitation fluids. Our research programme on burns is among the best in

the world and features major prospective clinical studies, laboratory-based work on the pathophysiology of burn injury, and basic research on the genetic basis of variable response to injury. These initiatives have led to the development of an Injury and Inflammation Research Center, led by Drs David Greenhalgh, Tina Palmieri and Kiho Cho.

The Center's ongoing research complements that of the Department's Surgical Bioengineering Laboratory (SBL), which focuses on 'biosurgery', or leveraging advances in stem cell biology and tissue engineering to better treat surgical disease.

In what ways is the Department working to combine stem cell engineering and biomaterial technology for the purpose of tissue regeneration?

DF: Our Department is home to the SBL, a hub for faculty, residents, research fellows, graduate students, and undergraduate and post-baccalaureate junior scientists conducting interdisciplinary research to engineer solutions for the full spectrum of surgical disease. Our research team brings together diverse experience from across the health sciences, and draws upon the most up-to-date technologies in regenerative medicine and biomaterials development to tackle some of largest challenges in medicine, including heart disease, spinal cord injury and birth defects.

How are efforts to identify the optimal microenvironment for therapeutic stem cells progressing?

CS: We have only recently started to realise the importance of the extracellular environment in directing the fate of stem and progenitor cells *in vivo* and *in vitro*. Understanding and controlling the mechanical and biochemical environment in which we place our therapeutic cells is the difference between a successful and a failed

therapy. We are currently exploring how we can transplant our therapeutic cells within an extracellular environment that promotes their therapeutic potential, while at the same time ensuring that we optimally match the donor cell to the recipient tissue, in order to afford them the best chance to synergise with the body's own healing response.

The Department is a pioneer in the treatment of foetuses with spinal cord injury (SCI) associated with spina bifida. Can you describe your current work?

AW&DF: We are working at the interface of two novel fields – foetal surgery and tissue engineering. We believe that the foetus is the ideal target for stem cell therapies and other tissue engineering treatments. In normal gestation, stem cells propel the development of the growing foetus. Since the gestational environment is intrinsically welcoming to stem cells, it provides a unique opportunity for biosurgery to repair birth defects, including spina bifida.

Treatment for burn injury is increasingly focused on treating not just the injury itself, but also the associated long-term physical and psychosocial effects. Could you elaborate on how this shift can be seen within your Department?

DG: The burn team at UC Davis has long had a philosophy that optimising functional and cosmetic outcomes is the number one goal. All burn teams are doing well with survival – but what good is survival if the burn patient never goes back into society? We therefore always endeavour to make skin grafts look as good as possible by trying to place whole sheets of skin as opposed to meshed skin. We always place the thickest skin on hands and faces so that there is less contracture, or shrinkage, of the healed wound.

In addition, we are dedicated to providing strong support for survivors, including being active in groups that teach strategies for going back home and returning to school and work. To this end, I developed the Aftercare-Reintegration Committee of the American Burn Association to work with the Phoenix Society for Burn Survivors to improve strategies for returning to society.

The Department relies extensively on interdisciplinary collaborations, both internally and externally. How important is this approach to its success?

DF: Collaborations are integral to progress, both in research and in the clinical setting. By working closely with experts with diverse backgrounds, we learn to look at challenges in a new light and come up with novel solutions. Our Department seeks to promote interdisciplinary collaboration to improve the care we provide for our patients, both now and in the future.

Internal partnerships allow us to take advantage of the academic richness of UC Davis, which includes the veterinary medical school, medical school and undergraduate campus. Some of our UC Davis partners include the Institute for Population Health Improvement, the Center for Healthcare Policy and Research, the One Health Institute housed in the veterinary school, the large-animal research CENTAUR Program, the Center for Health and Technology, the Institute for Regenerative Cures, and the Comprehensive Cancer Center. External partnerships, such as with industrial corporations, are critical when developing new medical devices or biological products; similarly, close communication with government bodies is a key part of moving our research projects into the clinic.

Dr Farmer, you are an internationally renowned leader in paediatric and foetal surgery. Overall, what do you consider your greatest professional achievement?

DF: It all comes back to the patients. First and foremost, I am a doctor. All that I do is concerned with improving care for patients, from reorganising UC Davis' surgical services to improving educational opportunities for future surgeons. My research has always sought to address the next steps in paediatric and foetal surgery, challenging barriers that limit the success of the treatments we provide for patients. Above all, I am proud of my continued efforts to improve care – in both my own operating room and in the field of paediatric surgery – which I hope have laid a foundation for future advances to be made by the promising young physicians we are training today.

Leading the way

The University of California, Davis Department of Surgery in Sacramento, California, USA, looks set to further improve its reputation for innovative research and training

SURGERY DATES BACK as far as the first human tools. While the central aims of diagnosing, preventing or curing ailments remain essentially unchanged, advances since the Industrial Revolution have transformed surgery from a perilous last resort into a scientific discipline capable of treating many complex diseases and conditions.

Today, surgical science has many fast-evolving frontiers, including regenerative medicine, injury and inflammation, and transplantation. Since its inception almost 50 years ago, the Department of Surgery at the University of California, Davis (UC Davis), USA, has worked at the forefront of surgical science, undertaking groundbreaking research to develop solutions for the full range of surgical disease.

RECREATING THE BODY: REGENERATIVE MEDICINE RESEARCH

Dr Diana L Farmer, MD, an internationally renowned foetal and neonatal surgeon, chairs the Department of Surgery. In collaboration with Dr Aijun Wang, PhD, she also directs the Surgical Bioengineering Laboratory (SBL), which provides a home for the Department's basic and translational researchers who are pursuing stem cell-based treatments for surgical disease.

Farmer's research specialty is the surgical treatment of congenital anomalies (particularly the safety and efficacy of treating spina bifida before birth) and cancer, airway and intestinal

surgeries in newborns. Wang's complementary goal is to develop novel technologies that combine stem cell engineering and biomaterial engineering to promote tissue regeneration. His research focuses on regenerative medicine in the context of congenital anomalies, biomedical engineering of novel scaffolds for implantation and the contribution of stem cells to cardiovascular disease.

Together, Farmer and Wang are investigating a variety of approaches to promote healing or regeneration in the context of spina bifida. "Examples include the development of nanofibrous scaffolds with stem cells to guide nerve regrowth, and the establishment of novel stem cell-based therapies to promote healing and preservation of damaged spinal cord tissue," Wang explains. "Our preclinical studies have yielded incredibly promising results, revealing that foetal treatment may significantly improve spinal cord repair and motor function."

Another pioneering collaboration within the SBL has been forged between Drs Claus Sondergaard, PhD, and W Douglas Boyd, MD. Their research – developing a stem cell-based treatment for heart disease – builds upon the rapidly growing body of work investigating the differences between different populations of stem cells and the importance of the microenvironment in determining therapeutic efficacy. Stem cells were first thought to be incredibly plastic, or capable of differentiating into any cell type under the necessary conditions. "We now know that this happens at an insignificant scale, if at all, and many of our current efforts concentrate on better matching up types of stem cells with the disease we intend to cure," Sondergaard elaborates. "Thus, a brain cell will be replaced by a neural stem cell, a beta cell with a pancreatic stem cell, and so forth." In Sondergaard and Boyd's work, cell types that play a supportive role in the regeneration of diseased tissues and organs may be used to boost the body's intrinsic healing capacity. "We are currently trying to identify the optimal combination of cells and microenvironment to achieve maximal regenerative effect in our disease model," Sondergaard explains.

The SBL's research in tissue engineering – synthesising replacements for damaged tissues and thus eliminating donor site morbidity – extends into plastic surgery. A research group led by Dr David Sahar, MD, focuses on adipose-derived stem cells (ASCs), which can be obtained from fat samples. "An ongoing project in our lab seeks to answer the question of whether ASCs will be effective for the repair of acute and chronic calvarial bone defects," Sahar states.

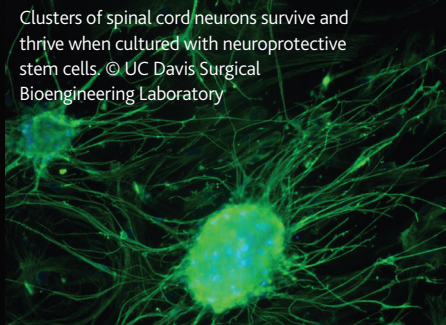
Sahar's team is also seeking a new treatment method for infantile hemangioma (IH) – a debilitating childhood disease. IHs are benign, vascular tumours affecting 5-10 per cent of all infants. While the tumours are nonthreatening, they can leave unsightly scars in head and neck regions, potentially leading to social problems in later life. Recent research led by Dr Sahar's protégé, Dr Hakan Orbay, targets different aspects of the disease process by combining photodynamic therapy and pharmacotherapy delivered by a nanoparticle carrier. This multifaceted treatment approach has the potential to prevent the disfiguring consequences of IHs and may have an enormous impact on patients' quality of life.

INVESTIGATING INJURY AND INFLAMMATION

The Injury and Inflammation Research Center studies a range of groundbreaking topics including novel signals that might influence the systemic response to injury, the activity of sections of DNA that invade other sections, and how variations in steroid receptors allow some patients to recover more successfully than others.

Associate Professor Kiho Cho, PhD, looks beyond genes to understand how the rest of human DNA – particularly endogenous retroelements, which are sequences originally derived from a virus – function in human health. These remnants of ancient viral intruders are generally thought to be harmless, but Cho's pioneering work suggests otherwise and that better understanding their role may be instrumental

Clusters of spinal cord neurons survive and thrive when cultured with neuroprotective stem cells. © UC Davis Surgical Bioengineering Laboratory





A night view of the UC Davis Medical Center.
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INTELLIGENCE

UC DAVIS DEPARTMENT OF SURGERY

OBJECTIVES

- To pioneer new regenerative medicine therapies for devastating surgical diseases, ranging from improving motor recovery following peripheral nerve injury to repairing a heart damaged by coronary artery disease
- To set a new 'gold standard' for care following injury by illuminating the interplay of inter-individual physiological variability and the healing process, with a particular focus on inflammation
- To equip the next generation of surgeon-researchers with the skills and the knowledge to tackle the largest problems in global surgery, public policy, and basic, clinical and translational medicine

KEY COLLABORATORS

UC Davis/CIRM Institute for Regenerative Cures • UC Davis CENTAUR Program • UC Davis School of Veterinary Medicine One Health Institute • UC Davis Center for Health and Technology • UC Davis Institute for Population Health Improvement • UC Davis Center for Healthcare Policy and Research • UC Davis Comprehensive Cancer Center

FUNDING

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DIANA L FARMER, MD, is the Chair of the UC Davis Department of Surgery, Surgeon-in-Chief of the UC Davis Children's Hospital, and a practicing paediatric and foetal surgeon. She has conducted notable research on surgical treatment and stem cell-based therapies for congenital anomalies. She has also ardently advocated for the emerging field of global surgery.

in developing a new generation of treatments for patients with afflictions as diverse as burn traumas, autoimmune disease and cancer.

Like Cho, the work of Dr David Greenhalgh, MD, touches on the role of endogenous retroviruses and transposable elements in the response to injury. His research also addresses contributing factors that can lead to multiple organ failure following trauma: "The dead tissue of a burn acts as a stimulus for inflammation (just like a splinter)," Greenhalgh points out. "We are now finding that early excision of the burns seems to improve the chances of surviving a major trauma."

As Director of the Burns Data Coordination Center at UC Davis, Dr Tina Palmieri, MD, also plays a key role within the Department of Surgery. Funding from the US Department of Defense allows her to study the impact of blood transfusions on survival and infection rates among burns patients. Palmieri also investigates the body's response to acute stress and the long-term psychosocial impact of burn injury.

TRAINING TOMORROW'S SURGEON-RESEARCHERS

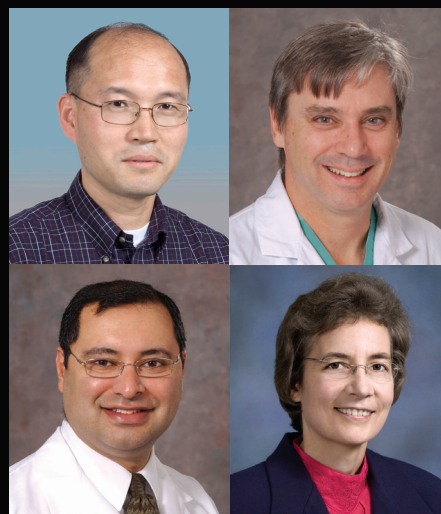
The Department has spent the last three years working hard to evaluate, improve and streamline its training options for prospective and current residents. This concentrated effort has resulted in the launch of three distinct training tracks, each offering residents tailored educational, research and clinical experiences.

The Global and Rural Surgery track is a pathway close to Farmer's heart: "The type of training necessary to be skilled in a rural healthcare environment is similar to that required in an international or global health setting," she notes, reflecting on her own training experiences in rural USA and Africa. Trainees in this track have the opportunity to receive clinical training in South Africa, Tanzania and rural northern California. Meanwhile, the Comparative Effectiveness and Public Policy track provides residents with experienced

research mentors who guide them through the process of formulating a research question, designing a study, collecting and interpreting data, and effecting policy change. Residents participating in the Surgical Scientist track are also connected with a research mentor, but with a focus on basic, translational or clinical research training. Project topics range from developing novel surgical devices to developing new therapies for cancer treatment.

Given the Department's dedication to both research and surgical education, it is unsurprising that it looks to the future by extending surgical educational experiences to pre-medical undergraduate and post-baccalaureate students. "We are looking forward to further supporting the UC Davis Pre-Medical Surgical Internship, Mentorship and Research Program," Farmer enthusiastically states, "which was founded in 2003 with the goal of inspiring students from diverse backgrounds to enter the medical profession and specialise in general surgery".

Clockwise from top left: Dr Kiho Cho, PhD; Dr W Douglas Boyd, MD; Dr Tina Palmieri, MD; Dr David Sahar, MD.



UC DAVIS
HEALTH SYSTEM