INVITED EDITORIAL

Wound Healing Research at the Hagey Laboratory for Pediatric Regenerative Medicine at Stanford University School of Medicine

Michael S. Hu and Michael T. Longaker*

Hagey Laboratory for Pediatric Regenerative Medicine, Division of Plastic Surgery, Department of Surgery, Stanford University School of Medicine, Stanford, California.

Michael T. Longaker, MD, MBA

Submitted for publication February 26, 2018. Accepted in revised form February 26, 2018.

*Correspondence: Hagey Laboratory for Pediatric Regenerative Medicine, Division of Plastic Surgery, Department of Surgery, Stanford University School of Medicine, 257 Campus Drive, Stanford, CA 94305
(e-mail: longaker@stanford.edu)

INTRODUCTION

The medico-economic burden related to wound healing is enormous and rapidly growing. As the average population ages—with a concomitant increase in comorbidities, such as obesity, diabetes mellitus, and peripheral vascular diseases—there has been an increase in the prevalence of chronic nonhealing wounds.[1] Examples of such wounds include pressure ulcers (bed sores), diabetic foot ulcers, and venous stasis ulcers.[2] In addition to this problem of underhealing, humans are uniquely affected by overhealing, in the form of hypertrophic scars and keloids.[3] Wound healing itself is a complex and metabolically demanding process.[4] Although our understanding of the full spectrum of wound healing has grown tremendously, there remains much to be elucidated.[5] Advances in stem cell biology, materials science, and tissue engineering promise regenerative approaches to wound healing.[6] As such, the Hagey Laboratory for Pediatric Regenerative Medicine at Stanford University School of Medicine has devoted significant effort to studying wound healing and its sequelae.

HAGEY LABORATORY FOR PEDIATRIC REGENERATIVE MEDICINE

The Hagey laboratory is codirected by Dr. Michael T. Longaker and Dr. Geoffrey C. Gurtner. The laboratory itself is a 14,000 square foot two-story building located on the Stanford University campus (Fig. 1). This facility has full capacity for biomolecular/histological analyses, cell culture, and small animal surgery. Centrally located in the Stanford University School of Medicine campus, the Hagey laboratory provides a collaborative scientific environment located within one of the finest bioscience research ecosystems in the world. The new Lorry I. Lokey Stem Cell Research Building with 200,000 gross square feet of space with state-of-the-art equipment and core facilities for histology, imaging, genomics, and cell sorting is located just 50 m from Hagey. It is home to the Institute for Stem Cell Biology and Regenerative Medicine, which is codirected by Dr. Irving L. Weissman, Dr. Michael T. Longaker, and Dr. Maria Grazia Roncarolo. In addition, the Hagey laboratory is just steps from the Center for Clinical Sciences Research (CCSR), Beckman Center for Molecular and Genetic Medicine, James H. Clark Center, and Stanford University Medical Center, providing an abundance of resources, highly collaborative atmosphere that guides multidisciplinary investigator projects, and means for clinical translation. The Department of Comparative Medicine's Veterinary Service Center (VSC) manages multiple nearby animal facilities with 110,000 gross

DOI: 10.1089/wound.2018.0787

Figure 1. The Hagey Laboratory for Pediatric Regenerative Medicine at Stanford University School of Medicine.

square feet of space for housing animals, such as mice, rats, and pigs, for wound healing studies. Finally, situated off Sand Hill Road, notable for its concentration of venture capital firms which have provided early funding for nearly every top Silicon Valley company, the Hagey laboratory sits on prime real estate for crossing the chasm in biomedical technology.

Within the Hagey laboratory are seven Principal Investigators—Dr. Michael T. Longaker, Dr. Geoffrey C. Gurtner, Dr. H. Peter Lorenz, Dr. George P. Yang, Dr. Derrick C. Wan, Dr. James C. Dunn, and Dr. Bill Chiu—with a wide variety of backgrounds and areas of expertise. These include stem cell biology and regenerative medicine, developmental biology, osteoblast and cranial suture biology, craniofacial development and disease, epigenetics, cutaneous wound healing, materials sciences, and tissue engineering. Five of the seven Principal Investigators in the Hagey laboratory study wound healing in its entire breadth and are profiled in the following section.

In addition, over 50 laboratory members comprise the engine that powers this prolific building. Hagey members include senior scientists, visiting scholars, postdoctoral fellows (both MD and PhD), medical scientist training program (MSTP) students, medical students, graduate students, laboratory technicians, undergraduate students, high school students, and office staff (Fig. 2). Stanford University and the Hagey laboratory provide an unparalleled research environment and resources to promote collaboration, growth and development, and career advancement.

PRINCIPAL INVESTIGATORS

Michael T. Longaker, MD, MBA, DSc (hon), FACS

Dr. Michael T. Longaker is the Deane P. and Louise Mitchell Professor and Vice Chair of the Department of Surgery, Director of the Program in Regenerative Medicine and Children's Surgical Research, and Professor, by courtesy, of the Department of Bioengineering and Department of Materials Science and Engineering. He codirects the Hagey Laboratory for Pediatric Regenerative Medicine where he has recruited five faculty investigators, all of whom are NIH funded.

Dr. Longaker earned his undergraduate degree from Michigan State University, where he played varsity basketball and was a member of the 1979 NCAA Men's Basketball Championship Team. He earned his medical degree from Harvard Medical School. He completed his general surgery residency at the University of California, San Francisco (UCSF), during which he completed a postdoctoral research fellowship in the Fetal Treatment Program under Dr. Michael Harrison and in the laboratory of Dr. Michael Banda in Radiobiology. During this time, he pioneered the discovery of fetal scarless wound healing, a topic he has continued to research. Dr. Longaker then went on to complete plastic surgery residency at New

Figure 2. Members of the Hagey Laboratory for Pediatric Regenerative Medicine at the 2017 holiday party.

York University (NYU) and craniofacial surgery fellowship at the University of California, Los Angeles (UCLA). He also earned an MBA from the University of California, Berkeley and Columbia University, in the inaugural class of their combined program and was elected in Columbia University's Beta Gamma Sigma Honor Society.

Dr. Michael Longaker's extensive research experience includes the cellular and molecular biology of extracellular matrix, fetal scarless wound repair, keloid and hypertrophic scars, and craniofacial development and stem cell biology. With over 1,200 publications to date, his vast research experience provides a unique understanding of wound healing. Dr. Longaker started his research career exploring all aspects of fetal wound healing.[7] Since then, Dr. Longaker has continued to unravel the mystery behind fetal scarless wound regeneration. Although the exact mechanism still remains unknown, his group recently identified a fibroblast subpopulation that is the cellular culprit for fibrosis,[8] giving promise to novel therapeutics to reduce cutaneous scarring. In addition, the Longaker laboratory has studied cell-based therapeutics to accelerate wound repair, exploring genetically modified mesenchymal stromal cells[9] and macrophages/monocytes.[10]

Geoffrey C. Gurtner, MD, FACS

Dr. Geoffrey C. Gurtner is the Johnson and Johnson Distinguished Professor of Surgery, Vice Chairman for Research in the Department of Surgery, and Professor, by courtesy, of Bioengineering and Materials Science. He codirects the Hagey Laboratory for Pediatric Regenerative Medicine with Dr. Longaker. Dr. Gurtner is also the Executive Director of the Stanford Advanced Wound Care Center where he serves as the Principal Investigator of multiple clinical trials involving wound healing. Dr. Gurtner is on the Board of Directors for the Wound Healing Society and Editorial Board for *Advances in Wound Care*.

Dr. Gurtner attended Dartmouth College then UCSF School of Medicine. He received training in general surgery from the Massachusetts General Hospital, followed by a plastic surgery residency at NYU. Dr. Gurtner then went on to complete a microsurgery fellowship at MD Anderson Cancer Center and joined the faculty at NYU, where he served as Program Director and Plastic Surgery Director of the Laboratory for Microvascular Research/Vascular Tissue Engineering. Dr. Gurtner was recruited to the Hagey laboratory in 2005, where he continues to make contributions to the field of wound healing.

The Gurtner laboratory discovered that abnormal response to hypoxia, through inactivation of hypoxia-inducible factor (HIF) 1-alpha, underlies delayed diabetic wound healing[11] and showed that transdermal deferoxamine an iron chelator that increases HIF-1-alpha transactivation prevents pressure-induced diabetic ulcers.[12] In addition, Dr. Gurtner linked mechanical loading to skin fibrosis through focal adhesion kinase (FAK).[13] Based on lessons learned from this work, Dr. Gurtner and Dr. Longaker created a tension off-loading device that has been used to minimize scarring in >40,000 patients to date.[14]

H. Peter Lorenz, MD, FACS

Dr. H. Peter Lorenz is a Professor of Surgery and Plastic and Reconstructive Surgery Service Chief at the Lucile Packard Children's Hospital. He attended UCLA for his undergraduate education, followed by the University of Michigan for medical school. Dr. Lorenz then received training in general surgery at UCSF, during which he spent 3 years as a postdoctoral fellow in the laboratory of Dr. Michael Harrison studying scarless wound healing with Dr. Longaker. Dr. Lorenz then went on to train in plastic surgery at UCLA, followed by a fellowship in craniofacial surgery at Stanford University. He then joined the faculty at UCLA, until being recruited back to Stanford in 2001 by Dr. Longaker.

Since his postdoctoral research fellowship, Dr. Lorenz has been studying fetal scarless wound regeneration. He demonstrated that fetal scarless wound healing is intrinsic to the tissue[15] and described the transition from fetal scarless to scarring repair in the nonhuman primate.[16] Dr. Lorenz's laboratory group has since identified blood-derived cells that reduce scarring.[17] In addition, his team developed a novel ultraportable negative-pressure wound therapy system[18] that is now commercially available for clinical use.

George P. Yang, MD, PhD, FACS

Dr. George P. Yang is an Associate Professor of Surgery and works clinically at the Palo Alto Veterans Affairs Healthcare System. He is the past President of the Society of University Surgeons (SUS). Dr. Yang received his undergraduate and medical degree from Northwestern University and a PhD in molecular genetics from the University of Illinois College of Medicine. He trained in general surgery at the Stanford University School of Medicine where he stayed on as faculty.

Dr. Yang's wound healing research has focused on stress responses in wound healing pathologies, primarily keloids. He demonstrated that keloid patho-

genesis results from increased transforming growth factor-beta in both keloid keratinocytes and fibroblasts.[19] Dr. Yang's laboratory demonstrated increased FAK complex formation in keloid fibroblasts in response to mechanical strain.[20] By examining transcriptional response to serum stimulation, cooperativity between activator protein-1 and SMAD binding sites was shown to be responsible for activation of connective tissue growth factor transcription.[21] More recently, he has shown that inhibition of the unfolded protein response leads to decreased scar formation.[22]

Derrick C. Wan, MD, FACS

Dr. Derrick C. Wan is an Associate Professor in the Department of Surgery and Director of Maxillofacial Surgery at the Lucile Packard Children's Hospital. In his 6 years since finishing training, Dr. Wan has already made significant contributions to bone tissue engineering with adipose-derived stromal cells and soft tissue reconstruction with fat grafting. Dr. Wan earned his undergraduate degree from Stanford University. He then earned his medical degree at Columbia University and went on to NYU for an internship in general surgery. Dr. Wan underwent further training in general surgery at UCSF during which he spent 2 years as a postdoctoral research fellow in the laboratory of Dr. Michael Longaker. Dr. Wan then completed plastic surgery residency and craniofacial surgery training at UCLA, as well as a microsurgery fellowship at Chang Gung Memorial.

Dr. Wan devotes considerable effort to advancing wound healing research. His laboratory has shown that silencing of PHD-2 accelerated healing of wounds in diabetic mice and perfusion of ischemic hind limbs.[23] In addition, exploiting his expertise with lipoaspirate, the Wan group has shown that $CD248^{+}$ stromal vascular fraction cells accelerated wound healing owing to increased angiogenesis.[24]

ADVANCES IN WOUND CARE

The "Stanford" issue of *Advances in Wound Care* highlights some of the wound healing research being performed in the Hagey Laboratory for Pediatric Regenerative Medicine. Dr. Longaker presents an improved model for detecting closure of full-thickness excisional wounds using K14-cre/mTmG double transgenic mice.[25] He also provides an in-depth review of cutaneous scarring.[26] Dr. Gurtner reviews the role of mechanical forces in wound healing,[27] a field that he has pioneered from bench to bedside. Dr. Lorenz presents two studies using pathway analysis to identify differentially expressed genes and pathways in fetal fibroblasts from scarless and scarring gestational ages[28] and fetal and adult wounds (pending publication). Dr. Yang provides a comprehensive review for the management of pressure ulcers.[29] Finally, Dr. Wan outlines the role of noncoding RNAs in wound healing.[30] In line with the aims and scope of *Advances in Wound Care*, the Hagey Laboratory for Pediatric Regenerative Medicine seeks to progress the field of wound healing by exploring novel basic science, translational, and clinical research approaches. We hope you enjoy our contributions to *Advances in Wound Care*!

AUTHOR DISCLOSURE AND GHOSTWRITING

No competing financial interests exist. The content of this article was expressly written by the authors listed. No ghostwriters were used to write this article.

ABOUT THE AUTHORS

Michael S. Hu, MD, MPH, MS, has had the privilege of spending 5 years as a postdoctoral fellow in the Hagey laboratory under the guidance and mentorship of Dr. H. Peter Lorenz and Dr. Michael T. Longaker. During his tenure, he has focused on studying scarless wound repair, cell-based applications for improving wound healing, and scarring and fibrosis. **Michael T. Longaker, MD, MBA,** is Professor of Surgery and Bioengineering at Stanford. He is the Director of Research for the Program in Regenerative Medicine, Children's Surgical Research, and Division of Plastic and Reconstructive Surgery.

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Abbreviations and Acronyms

CCSR = Center for Clinical Sciences Research
FAK = focal adhesion kinase
HIF = hypoxia-inducible factor
MSTP = medical scientist training program
NYU = New York University
SUS = Society of University Surgeons
UCLA = University of California, Los Angeles
UCSF = University of California, San Francisco
VSC = Veterinary Service Center