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Crossroads

With Dr. Richard Merkin

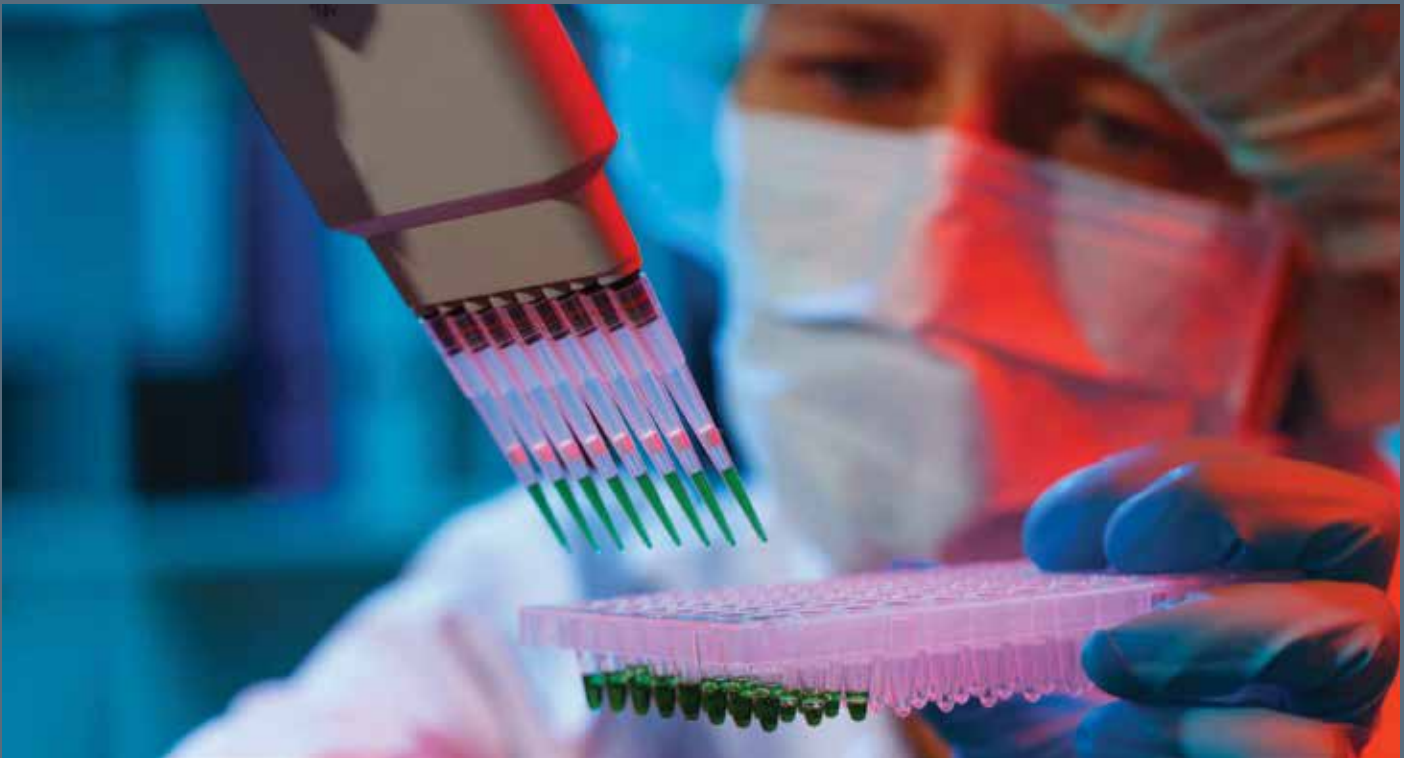
The unique perspective of Richard Merkin, M.D., as Innovation, Technology, Legislation and Care Delivery come together to impact the future of population health



Improving Quality of Life From the Cellular Level



In our youth, we seldom contemplate the wear and tear our bodies will endure over the course of our lifetime. Whether we are athletes participating in sports, staying active through various hobbies and interests, or just living our lives, age and injury will have an impact on our skeletal structure, resulting in decreased overall strength, mobility and functionality over time.



In our feature article, we continue our conversation with Charles KF Chan, Ph.D., Heritage Medical Research Institute (HMRI) Investigator and assistant professor of Surgery, and Michael T. Longaker, M.D., M.B.A., D.Sc., director of Regenerative Medicine at Stanford University School of Medicine, as they focus their efforts on using skeletal stem cells to reverse skeletal aging and help restore vital bone tissue diminished by time, injury or trauma. Joint pain and osteoarthritis caused by injury or trauma may ultimately result in needing invasive joint replacement surgery later in life. Their research findings show promise to alleviate pain, discomfort and lengthy recovery time by offering a much better alternative to traditional surgical methods, thus improving quality of life.

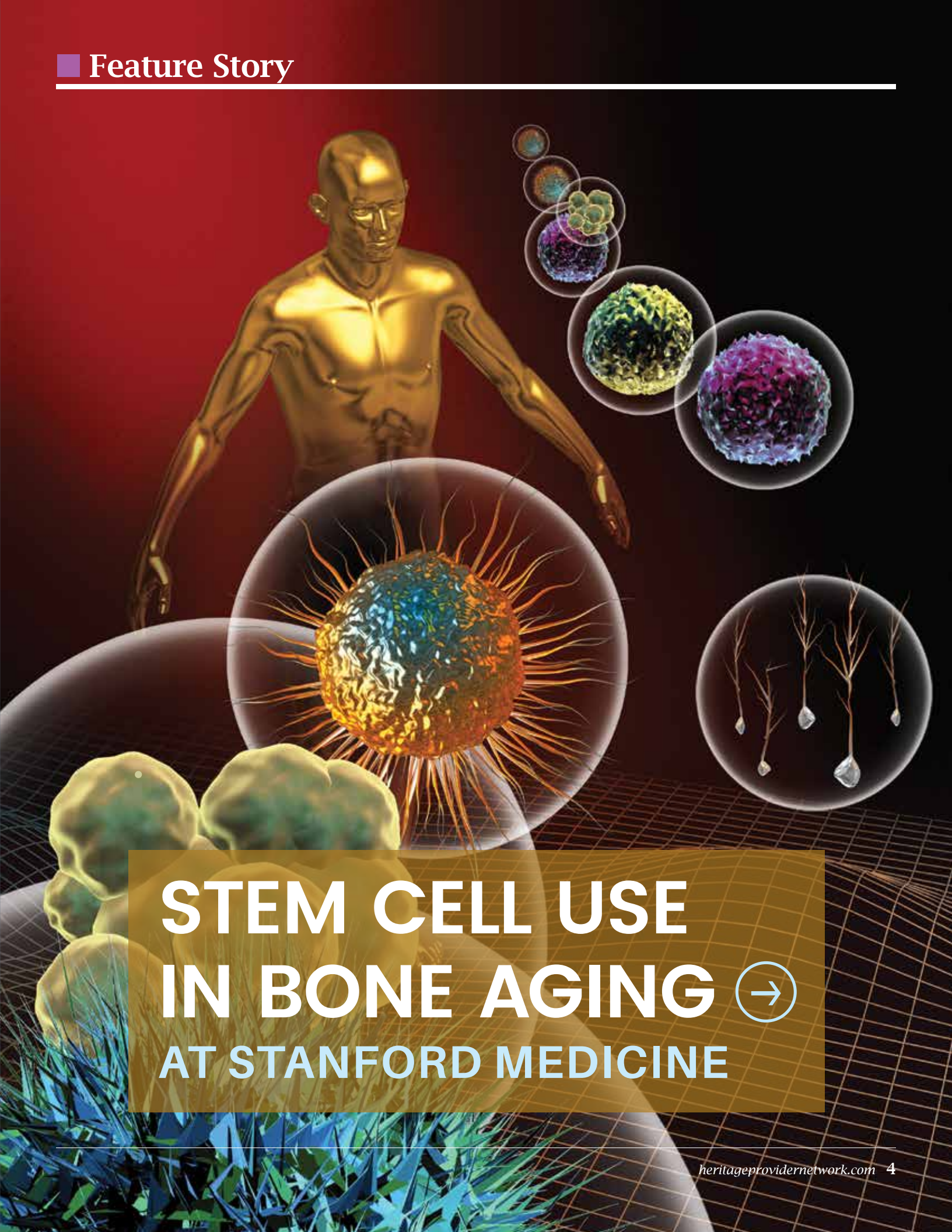
Lastly, as we witness the tragedy and uncertainty unfold around us and across the world, I want to

thank everyone for their continued dedication to the many communities we serve. We are strengthened by our collective devotion to protect the safety of our members and provide care when needed most.

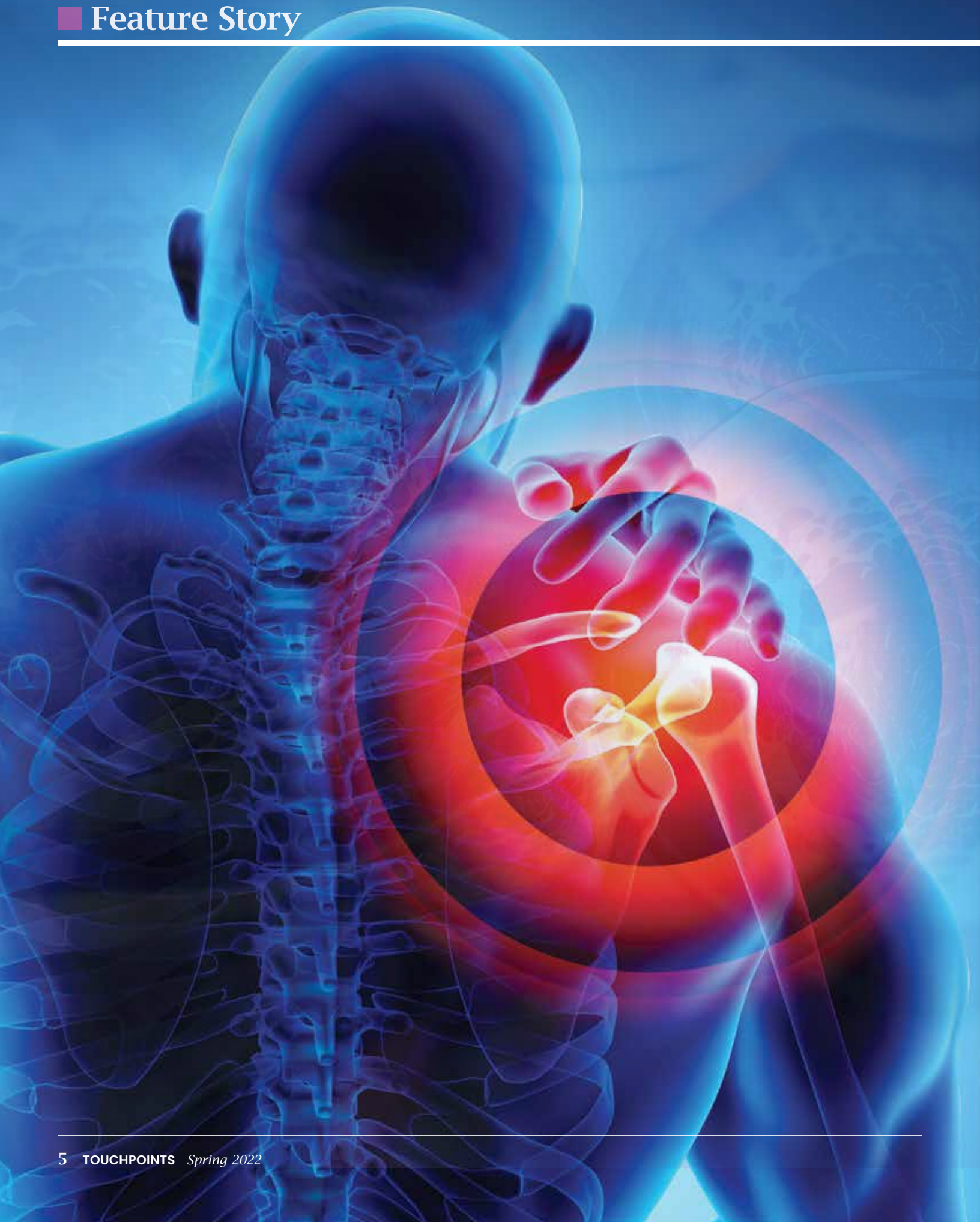
Richard Merkin, M.D.
President and CEO of HPN

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Richard Merkin, M.D.
Healthcare visionary Richard Merkin, M.D., has spent the last 40 years implementing a successful, workable business model to address the needs and challenges of affordable managed healthcare.



**STEM CELL USE
IN BONE AGING →
AT STANFORD MEDICINE**



HERITAGE MEDICAL RESEARCH INSTITUTE

SPONSORS USE OF STEM CELLS TO REVERSE SKELETAL AGING

D Dr. Richard Merkin first took an interest in funding the research of Charles KF Chan, Ph.D., and Michael T. Longaker, M.D., M.B.A., D.Sc., after their initial discovery of transforming cartilage growth to promote skeletal generation. In the Summer 2021 issue of *TouchPoints*, Dr. Chan and Dr. Longaker described how this research will help to prevent and reverse arthritic damage to cartilage tissue in the joints. They are actively working on clinical applications for their scientific findings in hope to one day help the millions of Americans who suffer from joint diseases caused by aging, injury or arthritis.

With continued support from Dr. Merkin and Heritage Medical Research Institute, Drs. Chan and Longaker have further expanded their research by targeting skeletal stem cells in an effort to reverse skeletal aging. Taking their findings to the next level could offer a less invasive, nonsurgical approach to healing and restoring skeletal tissue. If successful, preventing skeletal degeneration could result in replacing joint surgery altogether.



WE PRESENTED OUR QUESTIONS TO DR. CHAN AND DR. LONGAKER TO GAIN DEEPER INSIGHT INTO HOW USING SKELETAL STEM CELLS MAY HELP REVERSE SKELETAL AGING, AND PREVENT OSTEOARTHRITIS BEFORE IT BEGINS.

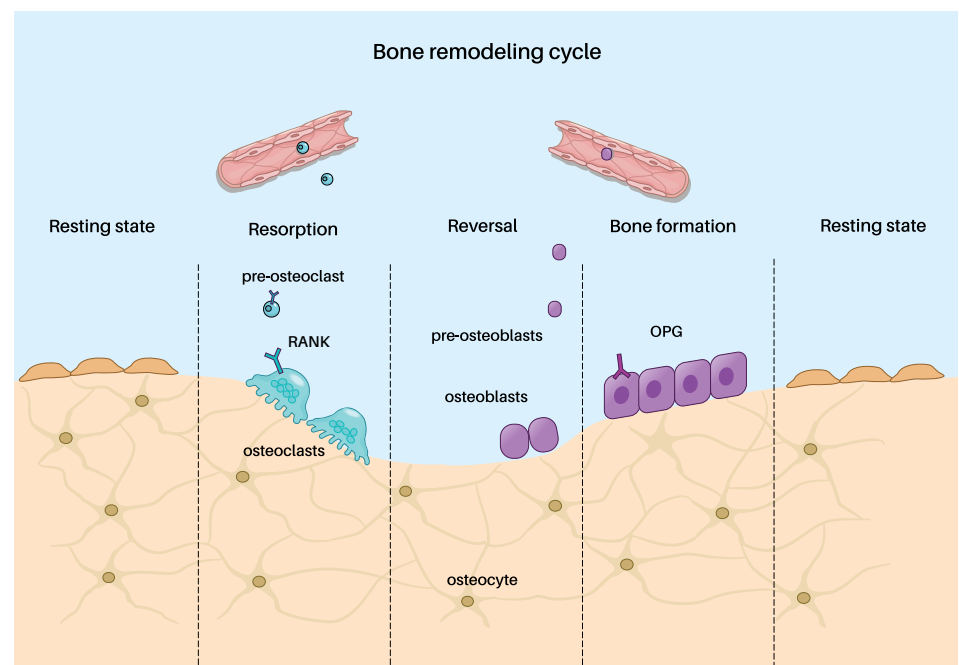
Q: In our previous *TouchPoints* article, you mentioned that you were working on understanding the basis of skeletal aging from the perspective of mouse and human skeletal stem cells (SSCs). Additionally, your team recently found a way to reverse skeletal aging by targeting SSCs as described in *Nature* magazine. What progress have you made in these areas?

A: The skeletal system provides structure for organs and locomotion, as well as regulation of mineral homeostasis and adult hematopoiesis. As a result, skeletal dysfunction also underlies a broad spectrum of health conditions and physiological disorders, ranging from congenital to age-related diseases, such as osteoporosis and osteoarthritis to nonhealing skeletal injury and cancer. The physical integrity of bone is controlled by two opposing processes: bone formation by bone making cells called osteoblasts, and bone absorption by bone eating cells called osteoclasts. Osteoblasts are formed by skeletal stem cells (SSCs), while osteoclasts are made by blood forming hematopoietic stem cells (HSCs). The continuing process of bone formation with bone absorption helps

keep the physical makeup of bones in optimal form, as if you have a pair of brick masons, one that continuously takes out bad bricks and old, cracked cement, and another that continuously installs new bricks with fresh cement.

For reasons that are not well understood, aging leads to a misbalance of bone formation and bone absorption, which results in

more bone being diminished instead of new bone being made. This leads to thinning of the bone (osteoporosis) and an inability of bone to repair itself well. Age-related osteoporosis is a key cause of morbidity as we get older, leading to poor posture from compressive bone fractures to our spine, and even affects our appearance since our muscles and skin are all ultimately attached to our bones.

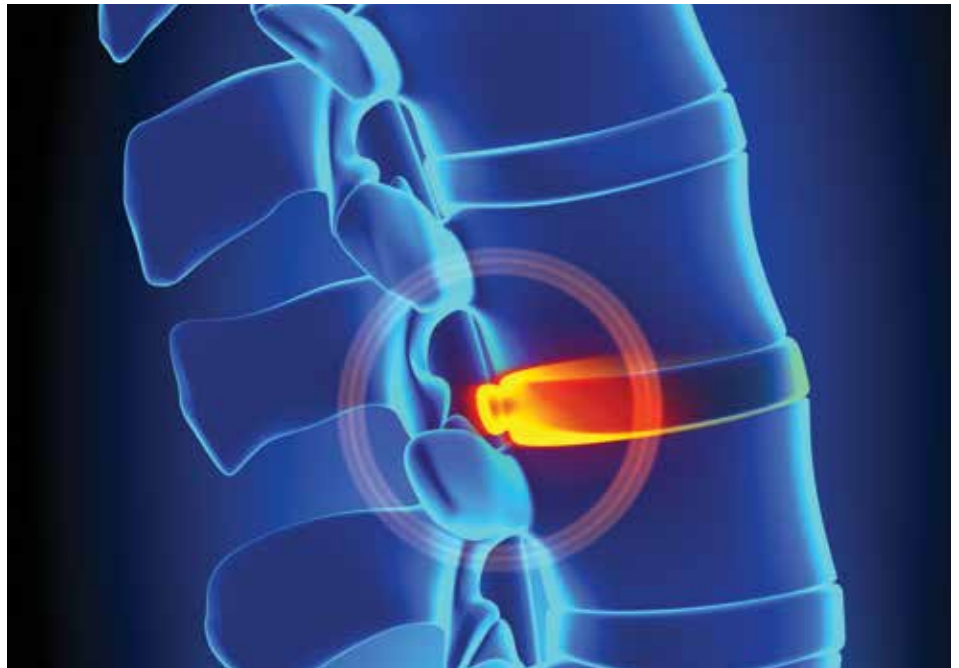




In our recent studies in mice (*Nature* 2021), we found that age-related changes to bone, including less osteoblasts and more osteoclasts are both due to age-related changes in SSCs. Aged SSCs make less bone forming osteoblasts, but also release signals that cause HSCs to make more osteoclasts as well as other inflammatory cell types. These inflammatory cell types also attack other tissues, including lung and blood vessels, and may be a factor in why older patients tend to have poorer responses to infectious diseases, including COVID-19.

We are now following up these studies by comparing mouse and human skeletal stem cell aging. In a recent study that we published in the journal *Aging Cell*, we find that human SSCs are also affected by aging in a similar manner as mouse SSCs. We have also identified a drug, SRT3025, that appears to be capable of reversing human SSCs in vitro and we are now conducting additional studies to determine if it works in vivo and if it is safe to use long-term.

It is notable that we are developing new ways to reverse SSC aging as most drugs that are now used to treat osteoporosis are directed against the inflammatory cell types and the osteoclasts. Since we now see that SSC aging actually leads to overproduction of inflammatory cell types, it may be possible that new drugs targeting SSC aging could be further ranging by stimulating bone formation as well as reducing bone absorption and inflammation at the same time.



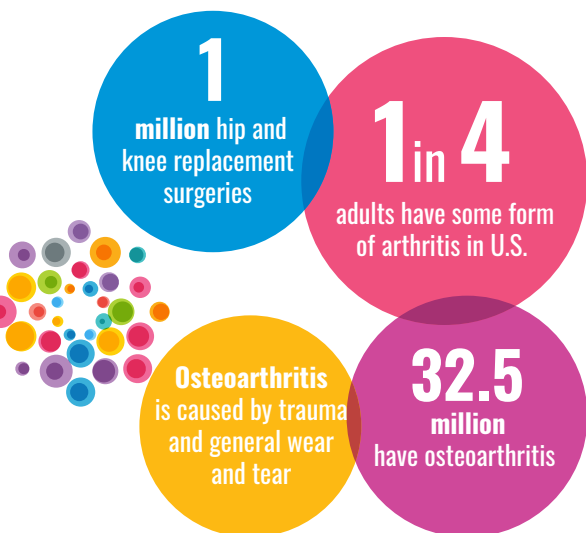
“Using an approach similar to what we showed for articulating joints, we are finding that it is also possible to regenerate spinal disc tissues.”

Q: Your team has also discovered ways to apply cartilage regeneration technology toward regenerating spinal discs. Can you elaborate more on this research?

A: While we have found that SSCs in limbs can make bone and cartilage, SSCs in the spine can also make spinal discs. However, we are still in the midst of finding the right signals that direct SSCs to form the right ration of fibrous disc tissues. Using an approach similar to what we showed for articulating joints, we are finding that

it is also possible to regenerate spinal disc tissues. However, SSC formation of disc tissues appears to require a different combination of factors than what we observed in cartilage. The arrangement of the tissues in the spinal disc is also important, as it is intricately patterned and mixes compositions of fibrous and cartilage tissues arranged in layers within one another. We are now working on 3D printing methods to formulate scaffolds that will release factors spatially so that we can induce these structures in newly regenerating disc tissues.

Lives affected by the numbers



■ The Centers for Disease Control and Prevention (CDC) estimates that 1 in 4 (or 54.4 million) American adults have some form of arthritis, a figure that is projected to reach 78 million by the year 2040. While there are estimated to be more than 100 types of arthritis, osteoarthritis is the most common form of arthritis, affecting 32.5 million U.S. adults.

■ Osteoarthritis, caused by trauma and general wear and tear on the body, is the leading cause for joint replacement surgery in the U.S.

■ Almost 1 million hip and knee replacement surgeries are performed each year in the U.S. alone, making it one of the most common orthopedic procedures performed today.

Source: Centers for Disease Control and Prevention

Q: How do SSC and cartilage regeneration integrate in order to work successfully, specifically in the steps necessary to begin human clinical trials?

A: As previously described in our *Nature Medicine* 2020 paper, a combination of factors could induce durable regeneration of lost cartilage in mice and also in human joint tissues that had been xenografted into immunodeficient mice. We are now conducting follow-up studies in mini pigs and canines to test additional variations in the scaffolds that we design to find the optimum combination for stable cartilage regeneration. Some the questions that we are hoping to determine are: How can we formulate more durable

scaffolds? How do we refine the surgical techniques for installing the scaffolds arthroscopically? How do we vary the approach to treat different joints?

Q: What significant roles do age and gender play with respect to the outcome of this study, given the differences in how male and female hormones can affect regeneration?

A: Male and female bones grow and repair differently and we also find that SSCs exhibit sexual dimorphism in terms of their skeletogenic ability and their response to male and female hormones. We are currently studying these differences and have another manuscript in revision at *Nature Communications* where

we examine the mechanism of sexual dimorphism in SSCs more closely. We are also establishing new methods to deliver male and female hormones to skeletal tissues by fusing them to nanoparticles that bind to SSCs specifically.

Q: How excited are you about this discovery and its potential impact on the millions of people who stand to benefit from such anti-aging technologies?

A: We are extremely enthusiastic about the potential of this technology. New generations of stem cell targeting anti-aging technologies are much more specific and sophisticated than previous approaches and we are now seeing

results that we didn't think were possible even a mere five years ago. It is useful to think of stem cells as the meristems of the body, and if we can keep them healthy and functioning properly, then we should be able to stay in good health as we get older.

Q: Is there anything else you would like to share about this research?

A: We would like to again express our immense gratitude to Dr. Merkin and Heritage Medical Research Institute (HMRI) for their generous support of our research. It is truly remarkable that there is a healthcare entity like HMRI that is so invested in making the most advanced healthcare available that they would also invest in initial research and the development of new drugs and treatments that could help address unmet needs.

Q: What is next on the horizon after reversing skeletal aging and cartilage regeneration?

A: We are currently focused on our skeletal aging therapies and cartilage regeneration techniques at the moment. However, we believe that the general strategy that we have established for identifying druggable targets in stem cell aging could likely be applied toward a wide variety of other important tissues, including the heart, blood vessels, skin and brain.

Source: med.stanford.edu/news/all-news/2021/08/old-skeletal-stem-cells-interfere-with-healing-study-finds.html



Charles KF Chan, Ph.D.

Heritage Medical Research Institute Investigator, Assistant Professor, Department of Surgery, Division of Plastic and Reconstructive Surgery; Stanford Immunology Faculty Institute for Stem Cell Biology and Regenerative Medicine; Hagey Laboratory for Pediatric Regenerative Medicine; DiGenova Faculty Scholar 2021; PCF Young Investigator 2013; Stanford School of Medicine; Stanford University

Dr. Charles KF Chan's research focuses on the biology of aging in stem cells and stem cell niches. Niches are the highly specialized but poorly understood microenvironments that regulate stem cell activity. Using a reductionist approach, he pioneered techniques to identify and isolate stem/progenitor cells of individual tissue types, including bone, cartilage and blood vessels. His team was the first to identify mouse and human skeletal stem cells, which have the ability to make bone, cartilage, bone marrow and tendons, but not fat. With these studies as a foundation, Dr. Chan and his group are working to understand how aging affects stem cells in mammals, while developing new therapies to reverse the effects of aging to cure age-related diseases, such as atherosclerosis, anemia, osteoporosis and osteoarthritis.



Michael T. Longaker, M.D., M.B.A., D.Sc. (hon), FACS

Deane P. and Louise Mitchell Professor and Vice Chair; Co-Director, Stanford Institute for Stem Cell Biology and Regenerative Medicine; Director, Children's Surgical Research; Director, Program in Regenerative Medicine; Professor, by Courtesy, of Bioengineering; Professor, by Courtesy, Department of Materials Science and Engineering; Stanford University School of Medicine

Dr. Michael Longaker's research experience focuses on wound repair and fibrosis, with specific applications to the differences between fetal and postnatal wound healing, and the biology of keloids and hypertrophic scars. Most recently, his research has focused on skeletal stem cells, activation in fibroblasts and mesenchymal cells from adipose tissue and their applications for tissue repair, replacement and regeneration. Dr. Longaker has published over 1,300 papers.

DESERT OASIS HEALTHCARE

Partners With America's Charities to Support Employees Facing Financial Hardship Through New SAFE Fund

On December 8, 2021, in Palm Springs, CA — “Every day, our employees show our collective commitment to the health and well-being of our thousands of members.

This has never been truer than during 2020 and 2021 as we’ve battled COVID-19 together,” said Marc Hoffing, M.D., medical director of Desert Oasis Healthcare. “We want to make sure that our employees understand we appreciate how much they do for those we serve on a daily basis. That’s why we are so pleased to announce the launch of our Supportive Assistance for Employees Fund — or its shorter name, the SAFE Fund.”

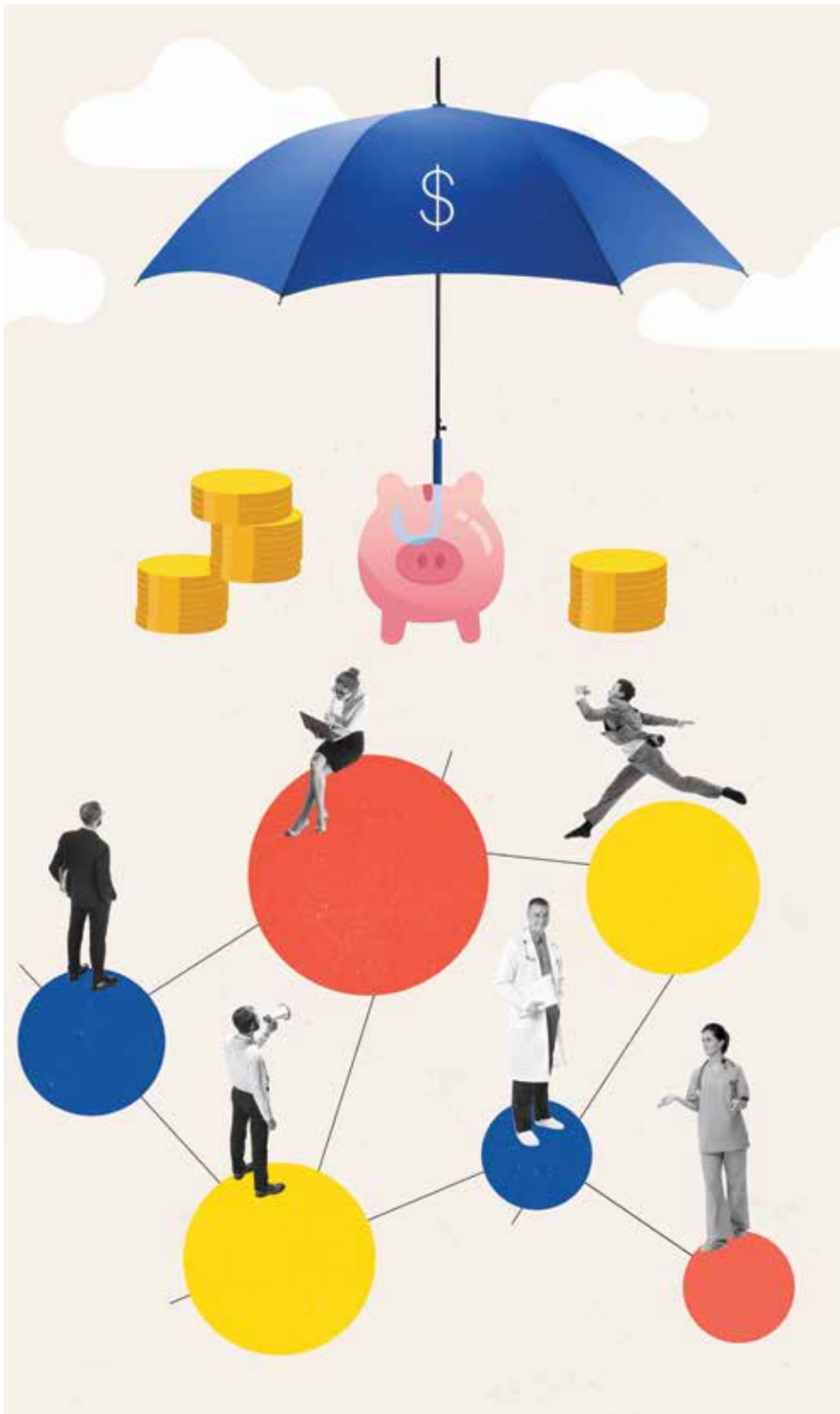
In partnership with America’s Charities, the SAFE Fund will provide financial assistance to eligible employees of Desert Oasis Healthcare (DOHC) and Family Hospice Care facing difficult or unforeseen circumstances. DOHC has provided the initial seed funding and will match total donations, dollar for dollar, up to \$25,000 a year.

“Corporate social responsibility is more than what you do for others — it’s also about what you do for your own

employees,” said Jim Starr, president and CEO of America’s Charities. “We are thrilled to help Desert Oasis Healthcare continue making a significant difference in the lives of their employees and their communities.” America’s Charities has more than 40 years of proven charitable funds management and employee engagement expertise. All grants made from the funds will be tax-free, providing maximum support to employees when they need it.

In addition to the new SAFE Fund and its generous employee benefits package, DOHC also offers a GuidanceResources® Program, available at no cost to DOHC employees or their dependents. On a 24/7 basis, the program includes confidential counseling on personal issues, financial information, resources and tools; legal information, resources and consultation, and more.

DOHC and its 1,100+ employees have supported a variety of local nonprofit organization partners in their communities for years with money, in-kind donations, and the volunteer time of management and staff. These nonprofit partners benefit food insecurity, services to seniors and youth, chronic and terminal health conditions, and so much more. Although DOHC had already provided \$200,000 in support in 2021, it celebrated its 40th anniversary on July 1 by awarding an additional \$40,000. Community votes on the DOHC website determined these awards: mydohc.com/vote.

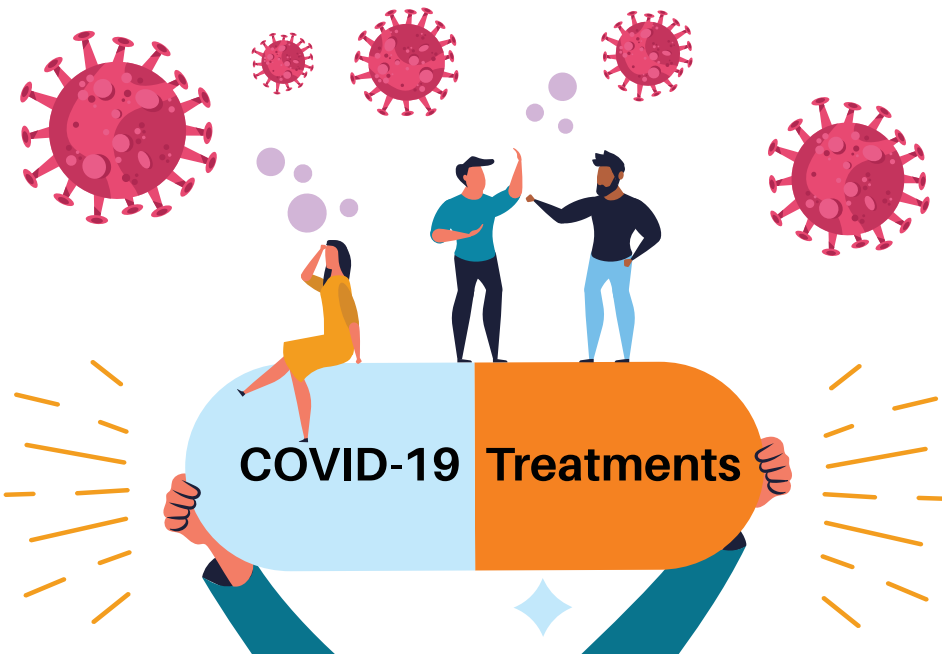


ABOUT
Desert Oasis Healthcare

Formed in 1981 as one of the first medical groups in the desert communities of Southern California, Desert Oasis Healthcare (DOHC) continues to advance with changes in the healthcare market. DOHC provides primary and immediate care, home health, palliative care, clinical research studies and other services to more than 60,000 members/patients living in the Greater Coachella Valley and the Morongo Basin of Riverside and San Bernardino counties. The multidisciplinary and comprehensive care programs of DOHC are committed to educating individuals on preventive health care in their daily lives, reflected in the DOHC motto, "Your Health. Your Life. Our Passion." For more information, visit mydohc.com.

ABOUT
America's Charities

America's Charities helps the nation's most trusted charities generate sustainable income through workplace giving and by inspiring employers and individuals to support the charities of their choice. As a 501(c)(3) membership-based nonprofit, America's Charities acts as a bond between employers, charities and employee donors. For more information, visit charities.org.



DESERT OASIS HEALTHCARE

Provides Ease of Access to COVID-19 Treatments

A recent New York Times article entitled “When My Mom Got COVID-19, I Went Searching for Pfizer’s Pills” told the reporter’s personal story of frustration in accessing treatment options. Meanwhile, Desert Oasis Healthcare (DOHC) has worked hard to provide COVID-19 treatment options for patients in its service area of the Coachella Valley and the high desert communities of Riverside and San Bernardino counties.

However, with variants like Omicron bringing higher COVID-19 positivity rates, the demand for the treatment drugs sometimes exceeds available supply. “We’ve set up COVID-19 treatment tents in Palm Springs and Indio, where our

providers, nurses and pharmacists are working together to prioritize the needs of those in our community who are seeking care,” said Marc Hoffing, M.D., DOHC medical director. “Our clinical teams can triage patients by assessing those needing

immediate treatment by us, as opposed to those who can safely weather their illness at home, and those who really need to be seen at the hospital.”

A good working relationship with the county allowed DOHC to be one of only four sites in Riverside County offering a range of therapies. These include all three IV (intravenous) monoclonal antibody treatments – Bamlanivumab/Etesevimab, REGEN-COV and Sotrovimab — as well as the two oral antivirals, Paxlovid and Molnupiravir. “As one of the only local nonpharmacy sites, we offer therapy to our entire community, not just our members,” said Lindsey Valenzuela, Pharm.D. and AVP of Population Health Integration. “We review each positive case to evaluate which therapies are appropriate, given the patient’s medications, kidney function, ability to adhere to oral drug therapy versus a one-time IV treatment, and our availability of the appropriate drug.”

Almost since the beginning of the pandemic, Dr. Valenzuela and Dr. Brian Hodgkins, Pharm.D. and EVP of Clinical Operations have been providing weekly clinical updates and answering local radio listener questions on “The Joey English Show.” Dr. Hodgkins added, “For two years, DOHC front-line and support teams have risen to a new challenge in doing what we all do best: serving our members and the community as a whole.”

ARIZONA PRIORITY CARE

Develops Comprehensive Plan to Better Manage Patient Information

Arizona Priority Care has developed a comprehensive plan to manage patients in the Centers for Medicare & Medicaid Services (CMS) Global and Professional Direct Contracting (GPDC) program.

The initial step was to identify the population of interest — Direct Contracting Entity (DCE) members utilizing hospital services. This involved working closely with Contexture, formerly known as Health Current, a local health information exchange. Contexture receives data for all patients who receive hospital services throughout Arizona. However, data integrity issues were identified involving health care systems and their use of HL7 standards that resulted in incorrect assignment of Admission/Discharge/Transfer orders. After much research was completed, these problems were corrected. In addition to this, CMS files did not include a member's contact information (e.g., phone number). With the help of Contexture, we are able to obtain this data. Finally, an automated process was developed to enable the transmission of a report from the health information exchange detailing all member hospital utilization over the past 24 hours, which is then uploaded into internal systems. Member information includes their name, contact information,



facility, dates of service and hospital status (observation vs. inpatient).

Next, a clinical case management outreach plan was developed. Dedicated nurses contact members by telephone after hospital discharge. Depending on a patient's needs, home visits with a clinical nurse, nurse practitioner and/or social worker may be scheduled. Clinical care pathways focusing on diabetes, chronic obstructive pulmonary disease and congestive heart failure for at-risk members are also in development.

Meetings with aligned physician offices have proven to help close the clinical

documentation gap. The providers are often unaware of a patient's hospitalization and lack hospital records, so processes are now in place to provide them with all the relevant clinical information to ensure there is thorough and timely follow up.

Ultimately, customized reporting will demonstrate the impact on member outcomes and hospital admissions by these case management efforts and determine if participation in the CMS GPDC model of care is successful.

HERITAGE SIERRA MEDICAL GROUP

Launches Community Engagement Department to Provide Health Education to Communities



In February 2022, Heritage Sierra Medical Group launched its new Community Engagement department to help provide health education and resources to the communities of Palmdale, Lancaster and Santa Clarita.

This has allowed community residents to participate in educational presentations facilitated by esteemed primary care providers (Eric Fernandez, M.D., Paula Bailey-Walton, M.D., and Marina Gold, M.D.) and learn about COVID-19 care, pain management, women's health, preventive care, geriatric care, nutrition and more.

In addition to providing health education, Heritage Sierra Medical Group has distributed, 1,000+ complimentary wellness kits to program attendees.

Each wellness kit includes a variety of resources ranging from recipe guides, exercise bands, COVID-conscious door

openers, stress relievers, vaccine card protectors, Band-Aids, masks, hand sanitizers, geriatric tools for mobility and more.

The Community Engagement department continues to develop additional resources and seminars and has partnered with the community centers of Santa Clarita and the Antelope Valley to provide health and wellness education to all ages.

Heritage Provider Network Affiliated Medical Groups

THE LARGEST INTEGRATED PHYSICIAN-LED MEDICAL GROUP NATIONALLY

For more than 30 years, Heritage Provider Network (HPN) has provided quality, cost-effective healthcare to the communities we serve. Today, HPN and its affiliates manage the healthcare of more than 1 million individuals. Our network has thousands of primary care physicians and specialists and hundreds of hospitals.

ADOC Medical Group

adoc.us

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Orange, CA 92868
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Arizona Priority Care

azprioritycare.com

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585 N. Juniper Drive, Suite 200
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Counties Served: Maricopa and areas of Pinal (Casa Grande Area)

Bakersfield Family Medical Center

bfmc.com

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Bakersfield, CA 93309
Counties Served: Kern

Coastal Communities

Physician Network

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1305 Marsh St.
San Luis Obispo, CA 93401
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Desert Oasis Healthcare

mydohc.com

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Palm Springs, CA 92262
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HealthCare Partners, IPA

hcpipa.com

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Heritage Colorado Care

heritagecolorado.com

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Heritage New York Medical, P.C.

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Garden City, NY 11530
Counties Served: Bronx, Brooklyn, Manhattan, Nassau, Queens, Suffolk and Westchester

Heritage Sierra Medical Group

sierramedicalgroup.com

Phone: (661) 945-9411
44469 N. 10th St.
West Lancaster, CA 93534
Counties Served: Kern, Los Angeles and San Bernardino

Heritage Victor Valley Medical Group

hvvvmg.com

Phone: (760) 245-4747
12370 Hesperia Road, Suite 6
Victorville, CA 92395
Counties Served: Los Angeles and San Bernardino

High Desert Medical Group

hdmg.net

Phone: (661) 945-5984
43839 N. 15th St. West
Lancaster, CA 93534
Counties Served: Kern and Los Angeles

Lakeside Community Healthcare

lakesidemed.com

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Regal Medical Group

regalmed.com

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touchpoints

Heritage Provider Network
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Northridge, CA 91325-5810

Our Awards

Recognition of Commitment and Excellence

The recognition we have received demonstrates our practices in excellence. We're proud to be awarded for our commitment to our members and our community.



Wellness Excellence Award in Health Education — Southern California Foundation for Health Care



Top Ten Physician Medical Networks in California by America's Physician Groups



NCQA Certification for Utilization Management and Credentialing



Elite Status of Excellence for the Standards of Medical Care by America's Physician Groups



Recognized by the Integrated Healthcare Association for our diabetic registries