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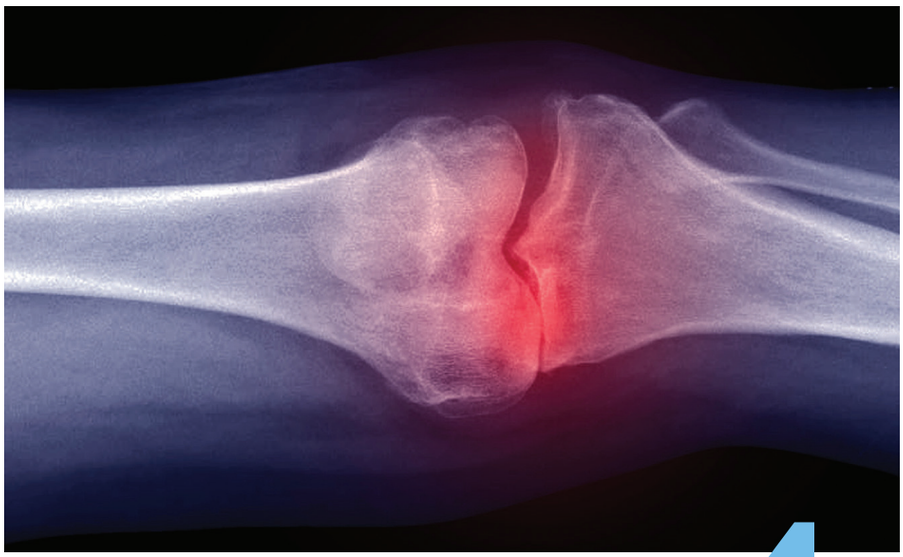

FEATURE STORY

Transforming Cartilage Growth Exploration

Heritage Medical Research Institute Scientists Making Advances at Stanford Medicine

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SUMMER 2021
ISSUE 43

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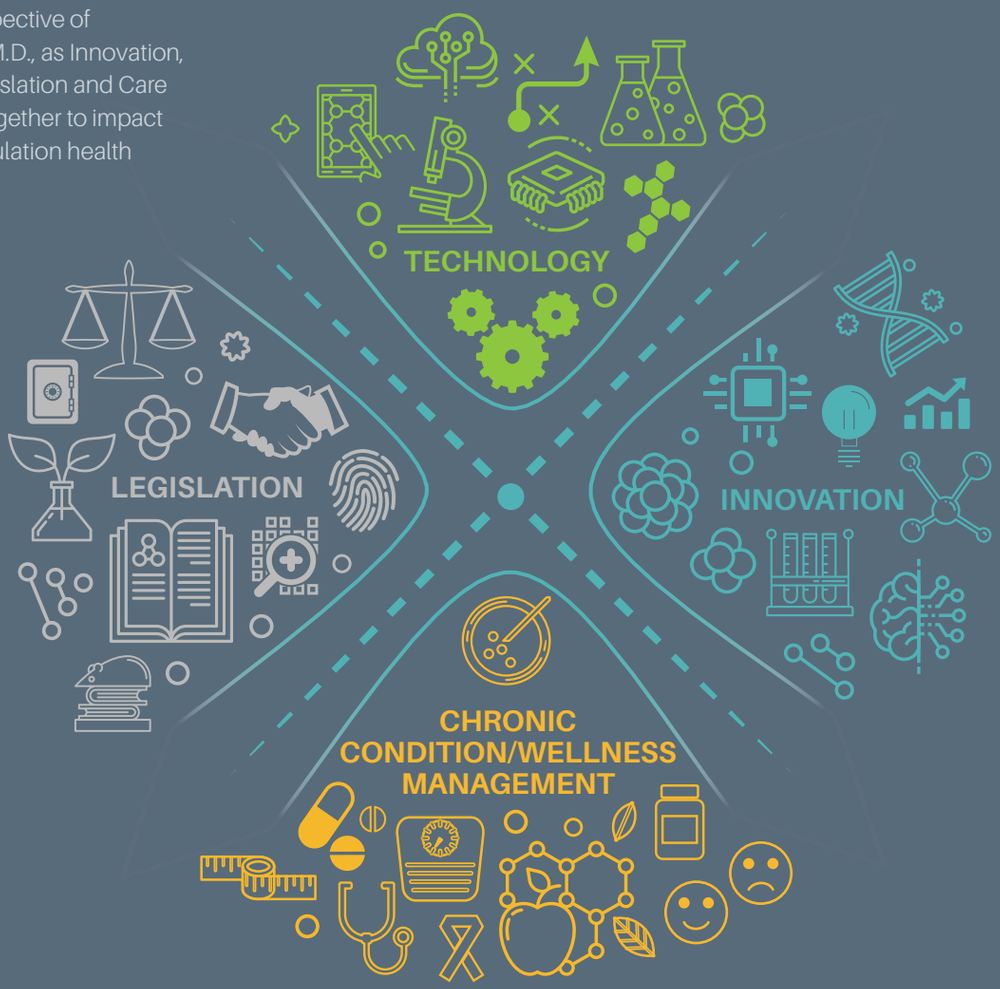
Crossroads

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

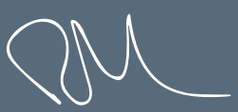


What Time Takes Away, Science Helps Restore

Imagine the ability to turn back time to regain mobility and independence by a process that helps regenerate certain cells in our bodies. What was previously damaged can be renewed with the help of modern science and technology.

In our feature article, we highlight the extraordinary efforts of Dr. Charles KF Chan and Dr. Michael Longaker at Stanford Medicine as we follow their progress into transforming cartilage regeneration using stem cell research. The initial trial delivers promising results that could help alleviate pain and inflammation, further improving the quality of life for millions who suffer from degenerative diseases caused by aging, osteoarthritis and cancer.

And as we transition into further reopening California along with other states across the U.S., our organization remains diligent and steadfast in our commitment to making COVID-19 vaccines available throughout the communities we serve. We encourage everyone to get vaccinated so that we can expeditiously eliminate the spread of the coronavirus, and prevent potential exposure to other variants. Our employees and staff will continue to adhere to the mandated safety guidelines and regulations to ensure proper safety measures in all of our locations while COVID-19 remains a threat. I want to thank everyone for their dedicated service and support as we strive to reach immunity.

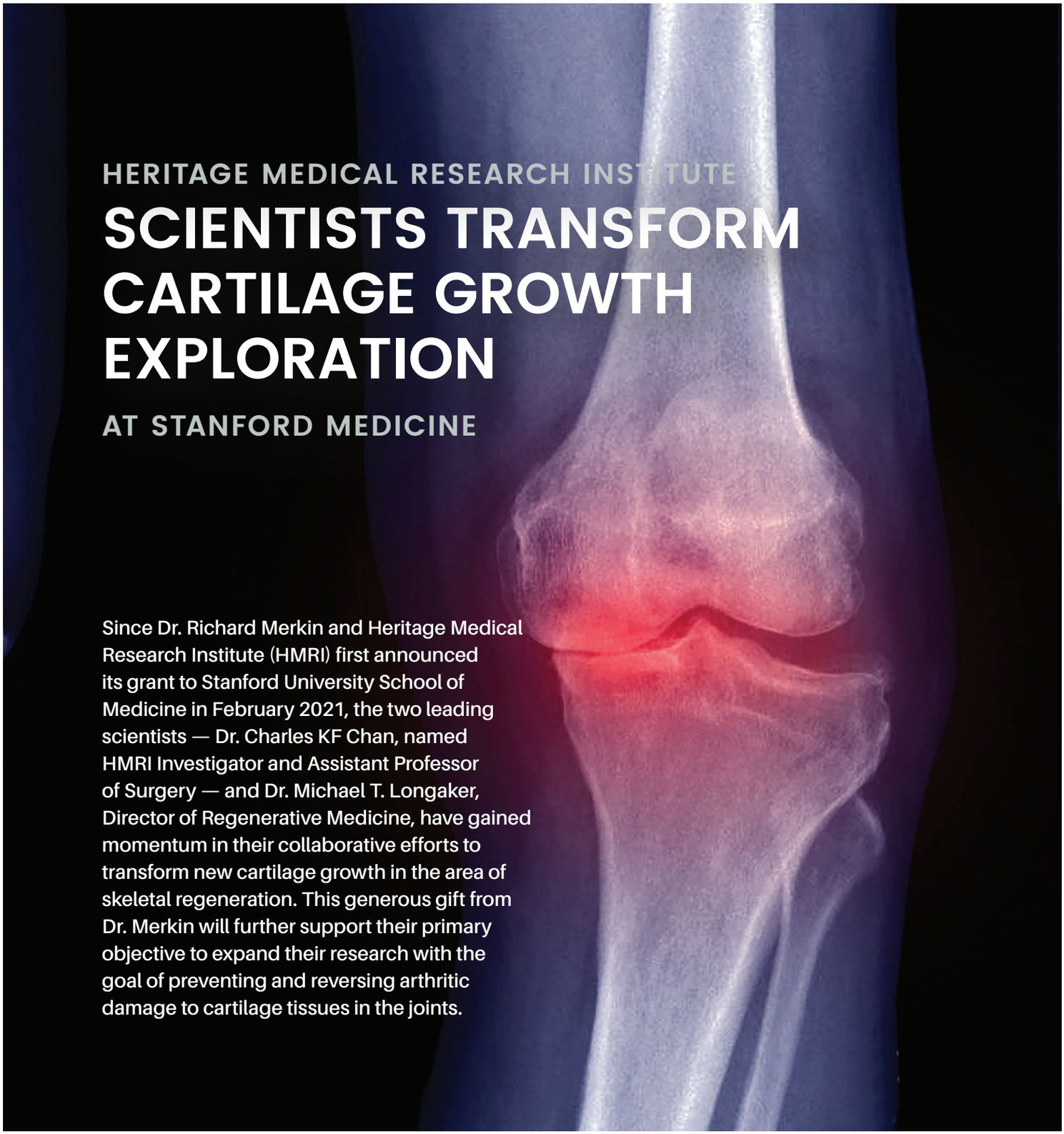


Richard Merkin, M.D.
President and CEO of HPN

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.

CARTILAGE GROWTH EXPLORATION

AT STANFORD MEDICINE



HERITAGE MEDICAL RESEARCH INSTITUTE

SCIENTISTS TRANSFORM CARTILAGE GROWTH EXPLORATION

AT STANFORD MEDICINE

Since Dr. Richard Merkin and Heritage Medical Research Institute (HMRI) first announced its grant to Stanford University School of Medicine in February 2021, the two leading scientists — Dr. Charles KF Chan, named HMRI Investigator and Assistant Professor of Surgery — and Dr. Michael T. Longaker, Director of Regenerative Medicine, have gained momentum in their collaborative efforts to transform new cartilage growth in the area of skeletal regeneration. This generous gift from Dr. Merkin will further support their primary objective to expand their research with the goal of preventing and reversing arthritic damage to cartilage tissues in the joints.

Dr. Merkin was first inspired by their ability to grow new cartilage in mice that suffered from arthritis. The results of their findings indicated that the cartilage appeared normal and remained so for several months.

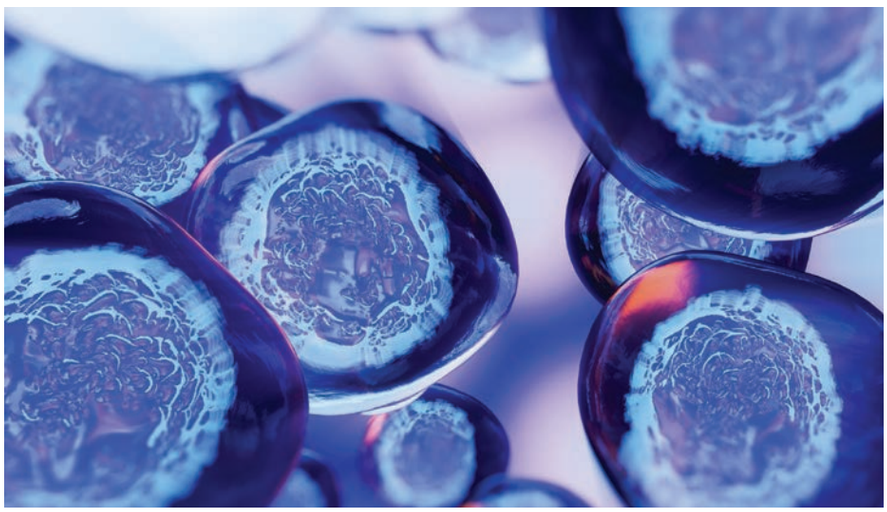
"Once I learned about this remarkable step toward growing new cartilage that scientists previously believed could never grow back once lost, I knew I had to jump onboard and encourage this research that is so vitally promising and exciting."

~ Dr. Richard Merkin

"This work represents critical breakthroughs toward the advancement of treating more than 50 million people who suffer from common knee and hip pain related to osteoarthritis," said Dr. Merkin. "Once I learned about this remarkable step toward growing new cartilage that scientists previously believed could never grow back once lost, I knew I had to jump onboard and encourage this research that is so vitally promising and exciting," he continued.

Dr. Chan added, "Stem cells are the rare 'seed' cells responsible for making and regenerating new tissues. This grant will propel our search for new ways to awaken sleeping stem cells in the body to regenerate diseased, injured, or aged skeletal tissues, including bone, cartilage, blood stem cell-supporting stromal cells and possibly spinal disc and tendons."

In an in-depth Q&A session, Chan and Longaker further shared detailed insights into their novel approaches for cartilage growth as their techniques hope to one day alleviate pain and suffering from those affected by cartilage loss from degenerative disc diseases, osteoarthritis, osteoporosis, aging and cancer.



Q: Heritage Medical Research Institute (HMRI) is an enthusiastic supporter of your lab's research at Stanford. Landing on such a groundbreaking discovery, can you explain how your work has evolved since beginning your investigation into cartilage regeneration?

A: We are so grateful for the instrumental and generous support of the Heritage Medical Research Institute, which we hope will accelerate our team's effort to create new possibilities for patients everywhere who suffer from conditions involving cartilage degeneration.

Until our recent findings, we, like many others thought that cartilage in people and mice could not regenerate. However, our impression began to evolve once we had identified the skeletal stem cell or SSC. Stem cells are often described as the "seeds" of the body and they are normally very rare. In the case of the SSC, their frequency is fewer than 1 in 100,000 in adult bones, but the scarcity is generally not a problem as SSC exhibits the hallmark characteristics of a true stem cell, that is, self-renewal and multi-potentiality. Self-renewal refers to the ability of a dividing cell to generate at least one daughter cell that has the same capabilities as itself. Without this trait, the stem cell pools will quickly become exhausted. Fortunately, many stem cell types can not only self-renew but can even switch between making one copy, or multiple copies of themselves to grow and replenish the stem cell pool when the body is growing or healing from an injury.

Multi-potentiality refers to stem cells' ability to produce downstream cell types with multiple characteristics. In the case of the SSC, we find that it is the source of progenitor cells that turn into the cells of bone, cartilage, and fibroblast bone marrow stromal tissues. Understanding that SSC is the origin of all three of these very different cell and tissue types was a revelation for us especially as it started to point us towards an explanation as to why cartilage appears not to be able to regenerate. The first possibility that we tested was that adult cartilage no longer possesses stem cells. This we found was not true. While the frequency of SSC certainly declines with increasing maturation and becomes very diminished by adolescence, they are still detectable in adult cartilage tissue, and even in aged animals. Moreover, these remaining SSC could be 'activated' by injury to dramatically expand and form new skeletal tissues. This injury-mediated activation of SSC is also seen in bone fractures and is key for the ability of bones to heal themselves even after complete fractures where the bone is broken completely in half. So this paradoxical finding, that bone can

"Stem cells are often described as the "seeds" of the body and they are normally very rare."

regenerate but cartilage cannot, though SSCs are activated in both cases led us to ask what happens to the activated SSCs in the cartilage case. It turns out that while SSCs in injured bone eventually turn into bone cell types, the SSCs in injured cartilage become other cell types besides cartilage, such as bone and fibroblast stromal cells, but not cartilage. What is happening in the case of cartilage is that the SSCs are not receiving the right signals to become cartilage.

By comparing activated SSCs in bone rather than cartilage, we were finally able to identify a specific combination of signaling molecules that must be delivered to SSCs in cartilage in order for them to make cartilage, and no other tissues like bone and fibroblast stromal cells. When these signals were delivered, we observed robust and lasting regeneration of cartilage that healed cartilage injuries in small animals, and restored their ability to move around without pain or discomfort. Now our goal is to scale up the approach so that it works on larger animals, of course including human patients.

Charles KF Chan, Ph.D.

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 is an Assistant Professor at the Stem Cell Institute and the Department of Surgery, Division of Plastic and Reconstructive Surgery at Stanford School of Medicine. His 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 cell (SSC), 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., MBA, DSc (hon), FACS

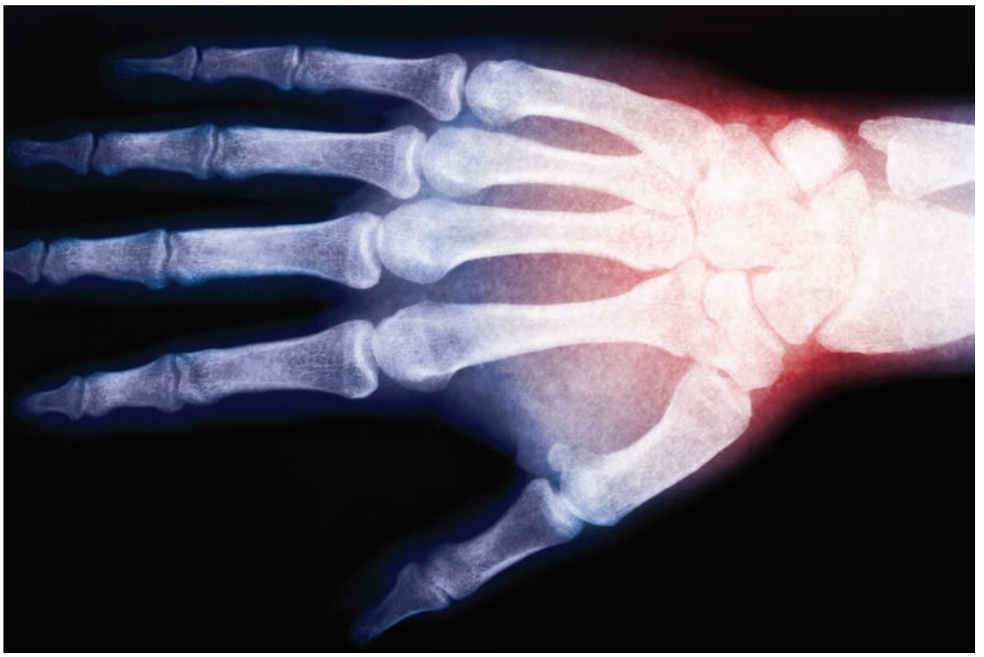
Deane P. and Louise Mitchell Professor and Vice Chair; Co-Director, Stanford Institute for Stem Cell Biology and Regenerative Medicine; Director, Children's Surgical Research; Director, Program in Regenerative Medicine; Professor, by Courtesy, of Bioengineering; Professor, by Courtesy, Department of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

Q: What led you to this field of study?

A: Living in remarkable times, balanced against growing environmental challenges, there is also a revolution in terms of our understanding of human biology, and in the development of biomedical innovation which is creating new paradigms for medicine and global health. For the first time reversing the effects of aging, and curing cancer, have become tangible, attainable goals. Aging has always fascinated me both as a biological phenomenon as well as its close associations to highly prevalent diseases such as cancer and cardiovascular disorders. However, it wasn't until the remarkable "Dolly" experiments on nuclear transfer and somatic cell reprogramming by Ian Wilmut and Keith Campbell (inspired by earlier work by John Gurdon) that I realized that therapeutic cloning and molecular rejuvenation might be feasible. Campbell, Wilmut and Gurdon et al.'s results suggested that the genetic clock of a cell could be fully reversed, nearly to time zero by transferring the nucleus of a fully differentiated cell into the immature environment of a fertilized egg.

Motivated by these findings, I decided to investigate the genetics of differentiation from the stem cell perspective at Stanford with Irv Weissman, which subsequently led me to identify the cells that form the regulatory environment (or niches) of blood forming stem cells. I then worked with Michael Longaker to show that the niche forming cells for blood stem cells are actually derived from another type of stem cell, the skeletal stem cell. Now in my own group, I am applying the most state-of-the-art techniques to characterize the molecular changes that tissue-specific stem cells undergo with age in hope of finding new ways to rejuvenate tissues by revitalizing their stem cell niches.



"We are actively working on clinical applications for our scientific findings to help the millions of Americans who suffer from joint diseases brought on by arthritis, injury, or aging."

Q: How is your technology able to simulate comparable mechanical properties to natural cartilage?

A: Our technology involves activating sleeping stem cells normally residing within cartilage tissues to expand and to make new, true cartilage. Since these are in fact newly generated true cartilage, we are relieved and encouraged that they also have comparable mechanical properties as natural cartilage.

Q: What had previously made cartilage regeneration seem unlikely in adults?

A: Adult cartilage is very avascular and not connected to blood supplies that are normally required for new tissues to grow so one might expect

that this lack of access to essential blood flow is functionally linked to the seeming inability of cartilage to regenerate in adults.

Q: Current treatments for damaged cartilage have their limitations. How has your work surrounding the identification of human skeletal stem cells helped to address these limitations?

A: Current treatments for damaged cartilage included analgesics for pain relief and joint replacement procedures. The limitations of symptom control are that the pain burden is very high and the relief is only temporary. Joint replacement can provide durable symptom control, however the procedure to replace the diseased joint with the prosthetic device is highly invasive. Moreover, the prostheses have limited life spans and are not suitable for some patients who have weakened bones such as the elderly, or for younger individuals whose longer lifespan would extend beyond that of the devices, thus requiring eventual replacement through another highly invasive surgery. We are hoping to achieve better outcomes using a strategy to replace "like with like" by actually resurfacing the damaged joints with new cartilage.

Q: Right now, research has been focused on cartilage replenishment in mice. What is the next phase of investigation?

A: Our next step is to scale up the technology for testing in larger animals such as dogs and sheep. We will then proceed with applications to begin clinical trials.

"Our technology involves activating sleeping stem cells normally residing within cartilage tissues to expand and to make new, true cartilage."

Q: As an HMRI Investigator, how will Heritage Provider Network's support speed the translation of the new technology from mice to humans?

A: The funding is essential for supporting our efforts to scaling up the technology for use in larger animals including developing new material to deliver the cartilage, including new minimally-invasive arthroscopic procedures for introducing the scaffolds.

Q: What is the expected timeline for human clinical trials?

A: We hope that the large animal studies can be completed in around 24 months, followed by applications to begin clinical trials which may require an additional 12 months.

Q: What are some of the first potential future clinical applications of your findings, and how can they benefit the nearly 1 in 4 Americans suffering from arthritis?

A: We are actively working on clinical applications for our scientific findings to help the millions of Americans who suffer from joint diseases brought on by arthritis, injury, or aging.

Q: Your lab is involved in research at the forefront of scientific discovery. Is there anything else you would like to share about your work?

A: We are working on understanding the basis of skeletal aging from the perspective of mouse and human skeletal stem cells. Our team recently found a way to reverse skeletal aging by targeting SSC which will be described in an upcoming manuscript in *Nature*. We are also finding ways to apply our cartilage regeneration technology toward regenerating spinal discs.

Merkin Family Foundation Announces Gift Establishing

The Merkin Peripheral Neuropathy and Nerve Regeneration Center

at Johns Hopkins Medicine

On March 30, 2021, the Merkin Family Foundation announced a gift establishing the Merkin Peripheral Neuropathy and Nerve Regeneration Center at Johns Hopkins Medicine supporting further research within the Department of Neurology. The Merkin Family Foundation was founded by visionary healthcare executive Richard Merkin, M.D.

The gift will create an exciting new Discovery Fund for the center's initial research activities including supporting interdisciplinary teams working to significantly expedite nerve regeneration research and understanding underlying causes and progression as well as identifying new regenerative therapies.

It also supports basic research that will fuel new drug discoveries, translational and clinical studies, and integrate patients' experience with new therapies including finding biomarkers of nerve degeneration that potentially will help millions of people currently suffering from pain, decreased mobility and degenerative nerve loss that affects motor skills including those used for walking.

"I'm very pleased this gift will establish the Johns Hopkins Merkin Peripheral Neuropathy and Nerve Regeneration Center, providing these research teams with new and exciting opportunities to change how and why

"I'm very pleased this gift will establish the Johns Hopkins Merkin Peripheral Neuropathy and Nerve Regeneration Center, providing these research teams with new and exciting opportunities to change how and why nerve loss occurs, opening doors for prevention and new discoveries."

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

nerve loss occurs, opening doors for prevention and new discoveries," said Dr. Merkin.

Dr. Ahmet Hoke, Director of the Neuromuscular Division and Professor of Neurology in the Department, will be the inaugural director of the Merkin Center. Dr. Hoke focuses on neuromuscular diseases with a particular interest in peripheral nerve diseases.

"The Merkin Center will create a platform for speeding up the research in this area," said Dr. Hoke. "We are looking forward to investing in pilot projects to stimulate research and attract new investigators to the field."

How Arizona Priority Care Works With Members Post-COVID-19

Most people who have COVID-19 recover completely within a few weeks. But some people, even those who had mild versions of the disease, continue to experience symptoms after their initial recovery and in some cases, for months. The virus can damage the lungs, heart, and brain, which increases the risk of long-term health problems. Notably, most of the member population at Arizona Priority Care (AZPC) are older adults, who are most likely to experience lingering COVID-19 symptoms such as fatigue, shortness of breath, cough, joint and muscle pain, chest pain, memory, concentration, or sleep problems, organ damage, and more.

Arizona Priority Care has employed a team of nurse practitioners and other healthcare professionals that work with members to plan for and address any acute or chronic illness, including post-COVID-19. The goals of this team are to become familiar with each member, follow-up with them once they are out of the hospital or skilled nursing facility, and address any barriers that may prevent them from reaching their highest level of health and recovery possible. AZPC is uniquely equipped to provide this level of support through various care coordination services.

Through the Home Wellness Program, members can get help scheduling a follow-up visit with a nurse practitioner, complex care manager (RN), and/or a licensed social worker, establishing communication with their PCP, accessing community resources, and completing important medical documents like advance directives. Additionally, members receive a medication review and physical assessment.

The Complex Care Management (CCM) program assists the primary clinician with managing the care of members with multiple and complex medical conditions. In this program, a registered nurse care manager (RN CM), a licensed medical social worker (LMSW), the patient and their family, as well as the physician(s) work together to achieve the best health possible. The RN CM will go to the member's home for a face-to-face visit, create a care plan and will follow up monthly thereafter. They will keep the primary clinician and specialist(s) up to date on any identified issues. Also, the LMSW will work to address the social determinants of the member's health, including completion of advance directives, help with applying for Medicaid, long-term care, Meals on Wheels, and address other social needs.

Close follow-up is provided to ensure members have the proper education and resources in order to maintain their health and to avoid utilizations, if possible.

Telephonic Care Management (TCM) is a program for members who do not require intense interventions, but may need some additional guidance such as referrals to community resources, finding a doctor, or monthly check-ins over the phone with an AZPC nurse. The TCM program serves as a means of encouraging wellness through frequent communication and ongoing healthcare education.

The Social Services program's primary goal is to provide each member with information, resources, and ongoing support. A licensed social worker will assist with solving social issues that affect a member's overall health. The social worker will provide education and assistance with advance directives such as durable power of attorney, medical power of attorney, or a living will. They can also help apply for Medicaid and long-term care services.

Finally, AZPC's COVID-19 Care Program is provided to members who test positive for COVID-19. When a member receives a positive test result, AZPC is sent an alert from the Health Information System (HIE), Sonora Quest Labs, or from a hospital admission. An RN Care Manager will call the member to ask them how they are feeling and what symptoms they are exhibiting. w A member may receive a referral to an infectious disease specialist if warranted, and can virtually visit with an NP. Members are provided with a COVID-19 care program letter that includes informational hand-outs about the disease and what to do, plus a COVID-19 care package that includes a cloth AZPC mask, sanitizer spray bottle, mini tissue pack, digital thermometer, and a pulse oximeter (for members who have a respiratory diagnosis). Those who have received this information and the care package have provided very positive feedback.

As research is ongoing, it is recommended that doctors closely monitor people who have become sick with the coronavirus to see how their organs are functioning after recovery. AZPC's various care coordination programs will help deliver the care and attention members need to stay on top of their health post-COVID-19.

High Desert Medical Group Opens Major Vaccine Site at Antelope Valley Fair Grounds

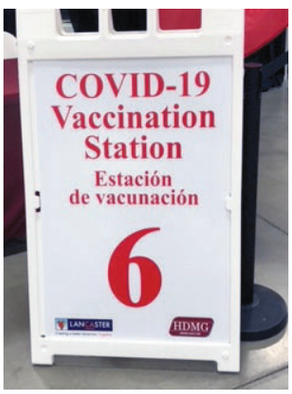
High Desert Medical Group (HDMG), in partnership with the City of Lancaster, opened a major expansion site at the Antelope Valley Fairgrounds for administering vaccinations against COVID-19 in April, with the goal of administering 4,000 vaccine shots a week. “Should availability of vaccines increase, we stand ready to increase that number,” HDMG Administrator Rafael Gonzalez said.

The site opened in the Van Dam Pavilion, and operates from 9 a.m. to 4 p.m. Monday through Friday. As stated by Gonzalez, "This was the work of our partnership with the City of Lancaster, and our remarkable staff team at High Desert Medical Group. Really, they all pitched in and made it happen. We have a great staff."

The new site joins an existing site that the City and Kaiser Permanente are operating at the Fairgrounds. Gonzalez said the partnership evolved from an initiative taken by Lancaster Mayor, R. Rex Parris, after Mayor

Parris called him and offered his help and resources towards a mass vaccination initiative.

With the Mayor's help, High Desert Medical Group and the City of Lancaster can achieve their goal of rapidly expanding the number of shots that will be provided in the Antelope Valley. "Since we are vaccinating around 1,000 of our own members along with community members at HDMG, the Mayor agreed to assign several of his staff to assist with implementing a concurrent program," Gonzalez said. "The city really provided everything we needed in infrastructure and everything that we asked for. What speaks volumes is the help we have secured from student nurses — the nursing programs both at Antelope Valley College, along with Career Care Institute give an abundance of help," Gonzalez said.



The project is led by Dr. Eric Oak and clinical project manager Ada Patterson, who have both worked with the motivated HDMG team. The High Desert Medical Group site currently has the two-dose Moderna COVID-19 vaccine.

The goal is to keep a vaccine team at HDMG, while shifting the majority of resources to combine them with the AV Fairgrounds team. This partnership has given the residents of the Antelope Valley another option for vaccines and helped to accelerate the Parris vaccination goal of 10,000 a week.

DESERT OASIS HEALTHCARE'S

Mobile Health Clinic is on the Move

On its March 11, 2021 maiden voyage, the new mobile health clinic from Desert Oasis Healthcare (DOHC) offered COVID-19 vaccines, along with check-ups for patients of Will Family Medicine in the Eastern Coachella Valley of Riverside County. DOHC pharmacists provided vaccines, enrolled patients with diabetes and/or elevated blood pressure and blood glucose in special programs, and supplied blood pressure cuffs, glucometers and other necessary devices.

Since that first outing, the HIPAA-compliant, air-conditioned mobile health clinic with two exam rooms has traveled to a variety of locations in the Coachella Valley and in the high-desert communities of San Bernardino County that DOHC serves. With its own power generator, the mobile health clinic is self-contained, with instant access to health records and educational materials. More remote locations, where there is often a short supply of primary care providers (PCPs), are now accessible and patients can avoid unnecessary — and sometimes costly — visits to the emergency room.

Now, DOHC can bring team-based care to individuals and families of all ages, along with video visits to PCPs, specialists and other partners. DOHC knows that as many as 10% of their senior members are not accessing care within a calendar year, meaning that chronic conditions are not being identified and/or managed. Now, the mobile health clinic allows DOHC to bring necessary treatment and annual senior wellness visits directly to members.

"Even while masking up and following all necessary COVID safety protocols, our mobile health clinic has allowed us to restart our health fairs with employer groups, senior centers, and other community events in a new and exciting way," said Dr. Teresa Hodgkins, PharmD and VP of Clinical Quality Initiatives. "During this year that marks our 40th anniversary as one of the first medical groups to serve the desert communities, we are so eager to continue sharing our passion for great healthcare with our members and the greater community."

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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

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