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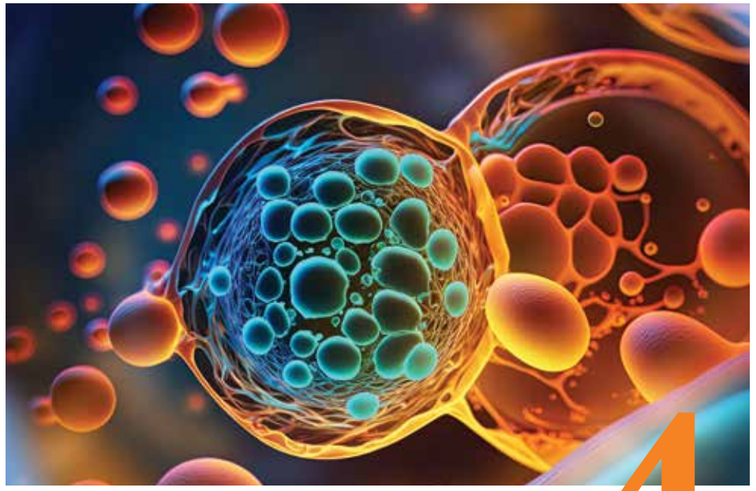

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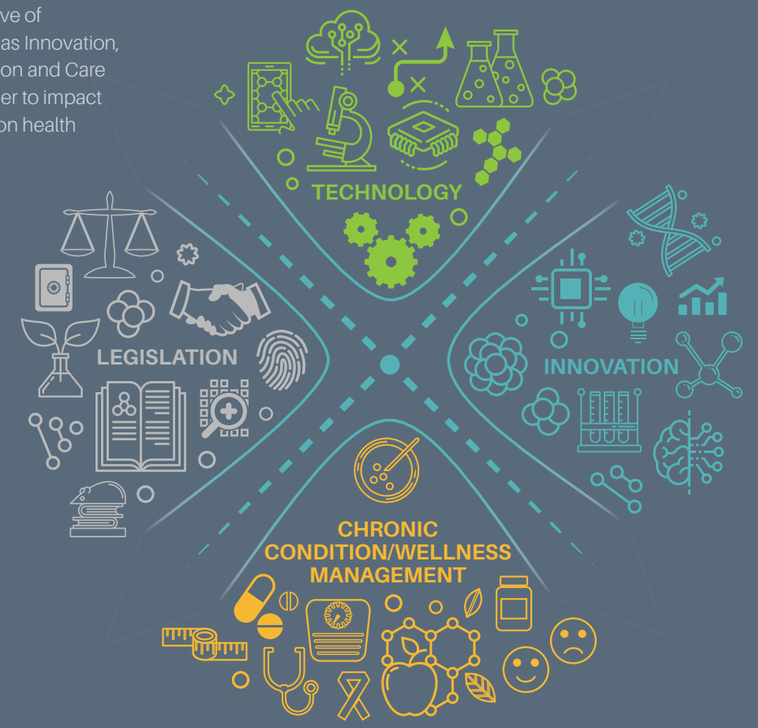
Crossroads

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

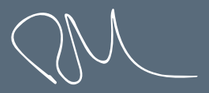


Redefining Personalized Healthcare through Cutting-Edge Research

We have repeatedly seen the power of cutting-edge research to transform the way we diagnose, treat and prevent disease. At the heart of this research are scientists who are pushing the boundaries of our understanding, and developing new technologies and therapies that have the potential to improve countless lives. One such group of researchers, led by Heritage Medical Research Institute Investigator Charles KF Chan, Ph.D., recently published a groundbreaking study in the journal *Science* shedding light on how sex hormones regulate bone regeneration in mice and humans.

This study is particularly exciting because it offers new insights into a long-standing mystery in medicine: Why do men and women differ in their ability to regenerate bone tissue after injury? By revealing that estrogen plays a critical role in this process, and that this mechanism is differentially regulated between males and females, the researchers have opened up new avenues for therapeutic intervention. Their findings suggest that localized estrogen hormone therapy could be an effective strategy for accelerating bone healing, and could have important implications for the treatment of osteoporosis, bone fractures and other conditions.

Our goal is to drive real change in healthcare, and this research is essential for advancing our understanding of disease and improving patient outcomes. We are proud to be part of a community of researchers, clinicians and healthcare professionals who are working tirelessly to develop new treatments and technologies that have the potential to transform healthcare as we know it.

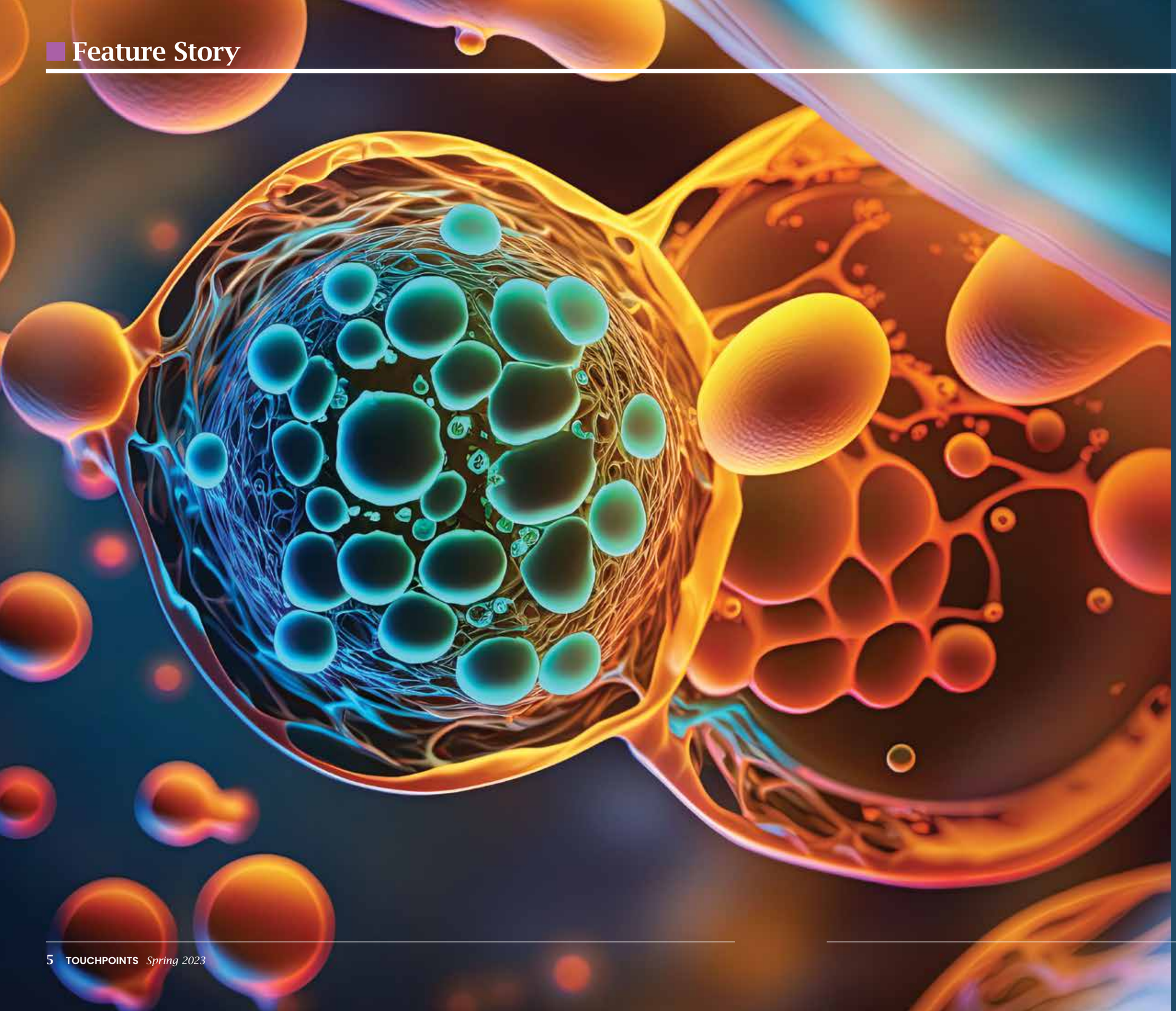


Richard Merkin, M.D.
President and CEO of Heritage Provider Network

Richard Merkin, M.D.

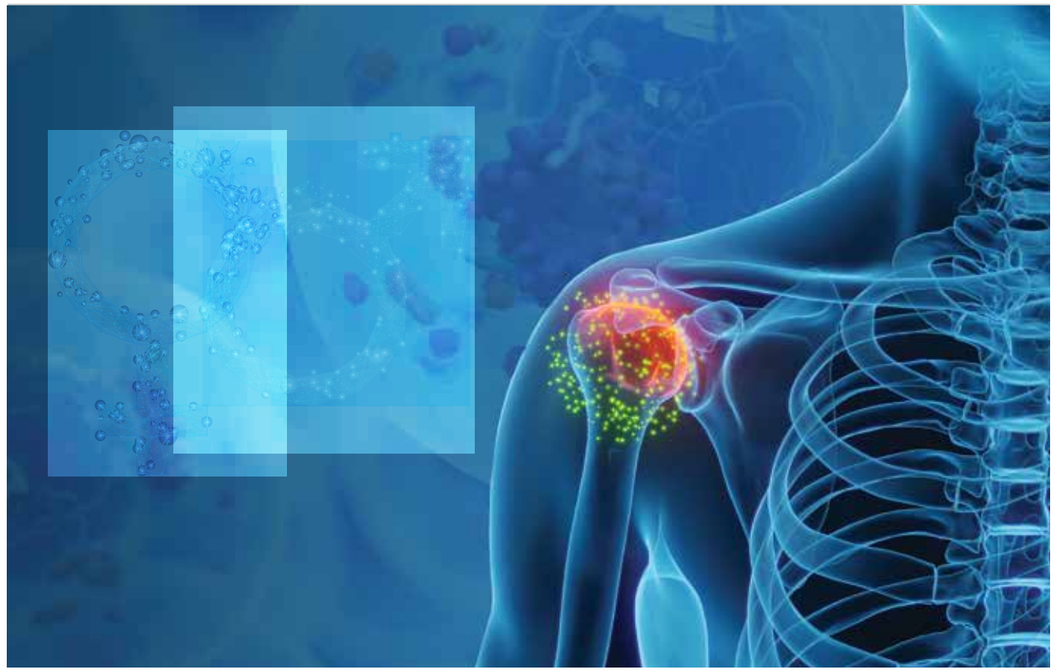
Healthcare visionary Richard Merkin, M.D., has spent the last 40 years implementing a successful, workable business model to address the needs and challenges of affordable managed healthcare.

The Role of Estrogen in Skeletal Regeneration: Sex-Specific Medicine



Uncovering the Role of Estrogen in Skeletal Regeneration: A Breakthrough in Sex-Specific Medicine

Sexual dimorphism is a well-known phenomenon in humans, with differences between males and females spanning physical, physiological and behavioral traits. However, it is only recently that scientists have started to appreciate how sex-specific factors may influence health outcomes, including injury and disease.



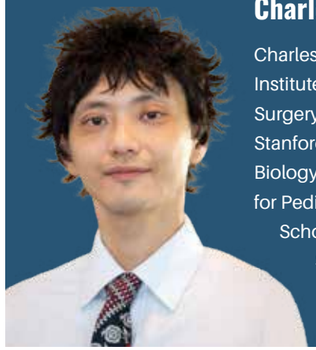
A new study published in the journal *Science* sheds light on how sexually dimorphic mechanisms contribute to skeletal regeneration in humans. Using cutting-edge methods to isolate and analyze human bone progenitor cells, a team of researchers has discovered that estrogen signaling plays a critical role in the regeneration of skeletal tissue, and that this mechanism is differentially regulated between males and females.

To learn more about the implications of these findings for clinical practice, we spoke with Charles KF Chan, Ph.D., a Heritage Medical Research Institute Investigator who led the research team. Dr. Chan is an assistant professor in the Department of Surgery, Division of Plastic and Reconstructive Surgery, at Stanford and is also affiliated with the Stanford Institute for Stem Cell Biology and Regenerative Medicine and Hagey Laboratory for Pediatric Regenerative Medicine. In this interview, we discuss the novel methods used in the study, the significance of the results and the potential applications of this research in healthcare.

Q: Dr. Chan, thank you for speaking with us. Can you tell us about the inspiration behind this study and how it fits into the broader field of bone healing research?

A: The physical differences between men and women are not only visible in external characteristics but also in their skeletal structure and health. Menopause, which is associated with a significant drop in estrogen levels, often leads to osteoporosis, a common problem in women. Research shows that up to 20% of bone loss can occur during these stages, and approximately 1 in 10 women over the age of 60 are affected by osteoporosis worldwide. Moreover, 1 in 2 postmenopausal women will have osteoporosis, and most will experience a fracture during their lifetime. Shockingly, the absolute mortality risk within one year post-fracture was 12.5% in women with fractures, highlighting the significance of addressing bone health concerns in both men and women.

Previous studies suggest that the decrease in estrogen levels is linked to an increase in bone resorption by osteoclasts, the cells responsible for bone turnover. However, it is still unclear how estrogen affects bone formatting skeletal stem cells or if there is any difference in the way bone structures in men and women differ. Additionally, we were interested in understanding what happens to bone structure after gender reassignment procedures. The study found that the sex-specific effects of estrogen on bone formation were controlled by skeletal stem cells.



Charles KF Chan, Ph.D.

Charles KF Chan, Ph.D., is a 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.

Q: What led your team to investigate the role of sexually dimorphic estrogen sensing in skeletal stem cells in bone formation and estrogen action in bones?

A: The regulation of skeletal stem cells (SSCs) has been an important area of interest in our lab. We are particularly interested in understanding the influence of local and systemic factors. Previous research has demonstrated that SSCs are primarily under local regulatory control within their microenvironment, and manipulating this environment can lead to cartilage regeneration and bone rejuvenation. However, the role of systemic signals in SSC regulation remains unknown. Additionally, most research on stem cells has primarily focused on males, with little known about how systemic hormones, such as estrogen, can affect SSCs in females. Given the essential role that SSCs play in bone and cartilage regeneration, as well as in the production of stromal cells for the immune system, understanding the impact of hormonal signaling on SSCs is crucial. Interestingly, our research suggests that the signaling may be direct rather than indirect, which has important implications for understanding how SSCs are regulated systemically.

Q: The study used a variety of techniques to investigate the role of estrogen in skeletal regeneration. Can you discuss the strengths and limitations of these techniques in the context of this study?

A: In our research, we utilized flow cytometry as a precise method for isolating and characterizing skeletal stem cells. This approach offers a higher degree of accuracy compared to less exacting methods, such as plastic plate adherence, previously used by other investigators. The use of flow cytometry allowed us to achieve higher purity of the stem cells, enabling us to better distinguish whether a particular cell activity, such as bone formation, is derived from stem cells or other types of cells. It also allowed us to determine whether the effects of hormones were directly on the stem cells

"The skeletal stem cells' delivery of estrogen could significantly reverse osteoporosis."

~ Charles KF Chan, Ph.D.

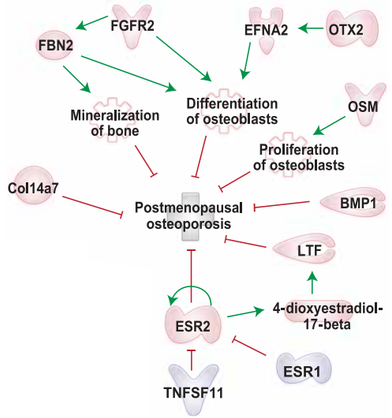
or indirectly through the action of co-purified cells. The precise isolation and characterization of stem cells are essential for understanding their mechanisms of action and ultimately developing more effective treatments for conditions such as bone loss and degeneration.

Q: Can you talk about any particularly surprising or unexpected findings that you've encountered in your research?
A: We were surprised that estrogen didn't have the same effect on skeletal stem cells in males.

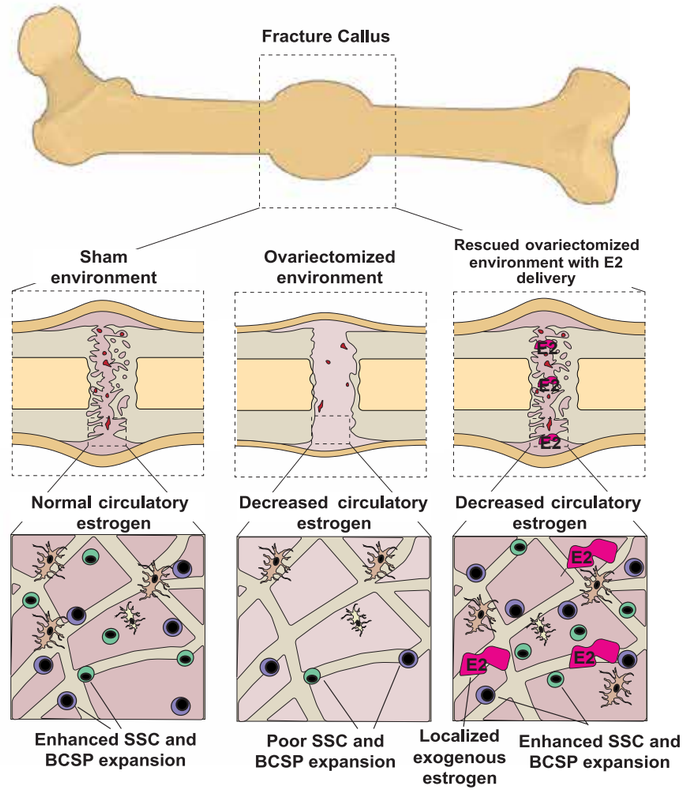
Q: Why doesn't estrogen work for male SSCs and what implications does this have for bone fracture treatments in men?
A: It appears that SSCs in men do not express the same set of estrogen receptors as women. Women express both estrogen receptors 1 and 2 while men only express estrogen receptor 1 but not 2. Many of estrogen's effects on SSCs seems to be mediated through estrogen receptor 2. It is possible that the male sex hormone, testosterone will promote SSC activity in men.

Q: Could you explain more about how the team's findings could have a significant impact on the treatment of osteoporosis?
A: Our finding suggests that the SSCs' delivery of estrogen could significantly reverse osteoporosis. We are now working on an antibody drug conjugate that would deliver estrogen to skeletal tissues by linking estrogen to an antibody that recognizes proteins that are specifically expressed on the surface of SSCs. Such an approach is already used clinically to target cancer.

Q: What are the risks associated with systemic estrogen injections for building up bones and how do the team's findings offer an alternative strategy for treating bone fractures in women?
A: Research has shown that women who took combined hormone therapy or estrogen alone were at an elevated risk of stroke, blood clots and heart attack. However, it is important to note that for women in both groups, this risk returned to normal levels after they stopped taking the medication. In addition to these risks, there is also an increased risk of cancer associated with hormone therapy use. Despite the benefits of hormone therapy in managing menopausal symptoms, it is essential to carefully weigh the potential risks and benefits before starting this type of treatment. Regular monitoring and follow-up with a healthcare provider can help minimize the risks associated with hormone therapy use. Alternatively, we could work to identify the specific targets of the hormone therapies in terms of cell types, which could help us establish more ways to target the hormone therapy for repairing specific tissues, such as bones, while avoiding tissues that could respond adversely, such as blood vessel tissues.



Q: Could you elaborate on how the findings have implications for gender reaffirmation surgeries and dental implant surgeries?
A: Our data suggests that hormone therapy may be less effective for reshaping skeletal features in male to female transitions in gender reaffirmation surgeries. In osteoporotic women, localized estrogen delivery may significantly improve the stability of implants.



Q: When do you hope to begin clinical trials for this new approach to treating bone fractures?
A: We are working with clinical teams to develop products, such as estrogen eluting fixation pins or dental implants, which could be tested in large animal models. If the data seems favorable, then we hope to initiate clinical trials.

Q: The authors suggest that the identification of a sex-specific mechanism controlling skeletal regeneration has broader implications for the study of other organ systems. Can the findings of this study inform our understanding of how hormonal signaling influences stem cell behavior and tissue regeneration in other organ systems beyond the skeletal system?
A: This study suggests that other types of stem cells which maintain other organs may also be subjected to regulating sex hormones, but that there may be cell-intrinsic differences between male and females that affect their response to these hormones. Since SSCs also form the cells of the bone marrow stromal cells that regulate formation of blood and immune cells, it is also possible that hormone therapy to SSCs may help reverse age-related changes to the immune systems, such as the age-related expansion of inflammatory cell production.

Q: Do you have any plans to further investigate the role of sexually dimorphic estrogen sensing in SSCs and, if so, what questions do you hope to answer?
A: We are interested in further learning how estrogen signaling controls different aspects of SSC activity, including expansion and differentiation into skeletal tissues such as bone, cartilage, spinal discs, tendons and bone marrow stromal tissues. We are also interested in finding out how the estrogen sensing is first established, for instance during embryonic development. And, of course, how we can turn these findings into therapies.

Q: What are the most important takeaways from this study that you hope readers will understand, and how might this research impact the field of bone biology?
A: One of the most important take homes is that some of the physical differences between males and females are regulated at the level of stem cells, such as the SSCs. This is at the level of receptors that are expressed by the stem cells which determines if they could receive sex regulating hormones, such as estrogen or testosterone. These signals are important in regulating the ability of SSCs to maintain bones or to repair them after an injury.

BFMC Oak Tree Tehachapi Clinic Unveils Impressive Expansion

The picturesque town of Tehachapi, California is home to one of the four Bakersfield Family Medical Center (BFMC) staff model clinics in Kern County. With a population of 14,414 and an elevation of 3970 feet, the mountain town lies 35 miles southeast of Bakersfield.

In October 2022, the BFMC Oak Tree Tehachapi Clinic marked a significant milestone with the relocation of its facility after 30 years. The clinic has moved from a residential area to a nicely renovated medical office building, prominently positioned on a central thoroughfare in the charming town.

The modern facility offers double the space of the previous one and a bright office area with high ceilings. Visitors can easily find the clinic, thanks to its eye-catching signage. The expanded Procedures area now includes new services like infusions, and the facility also boasts on-site X-ray and lab draw services, ample parking and an accessible entrance.

As one of BFMC's busiest clinics, the Oak Tree Tehachapi Clinic is proud to have increased its team of providers. Three physicians and three nurse practitioners offer exceptional primary care to both BFMC and High Desert members.

The excitement surrounding the clinic's relocation was evident at its open house event. A large crowd, including long-standing and multigenerational BFMC members, gathered to enjoy the festivities. Attendees appreciated the upgraded office and the convenient location. The event also sparked increased interest in BFMC membership, with many guests asking about accessing BFMC providers.

The Oak Tree Tehachapi Clinic's recent expansion demonstrates its commitment to delivering top-quality care to Tehachapi members. With its larger, modern facility, the clinic is well-prepared to continue providing excellent service for years to come.

"Visitors can easily find the clinic, thanks to its eye-catching signage."

Desert Oasis Healthcare Launches Pilot Partnership with Google Health's Care Studio

Desert Oasis Healthcare (DOHC) is proud to announce a pilot partnership with Google Health's Care Studio, aimed at enhancing the efficiency and effectiveness of its Senior Wellness Clinics. These clinics play a vital role in DOHC's preventive care model, catering to a population with complex medical histories and often managing multiple chronic conditions.

One of the challenges faced by DOHC clinicians is the fragmentation of patient data across various information systems. To ensure optimal patient care, it is crucial for healthcare providers to have comprehensive access to patient histories. DOHC is committed to streamlining this process, enabling clinicians to have all necessary data at their fingertips.

Care Studio from Google Health offers a solution to these information challenges by providing a unified view of patient data. Leveraging Google Health's advanced, medicallytuned artificial intelligence search capabilities, Care Studio can effectively search through scanned faxes and PDF documents to retrieve pertinent medical information. The platform also includes a "Conditions" feature that presents a concise summary of a patient's medical conditions, accompanied by relevant context and related information, such as labs, medications and diagnostic reports.

Prioritizing patient privacy and security, Care Studio creates a longitudinal health record encompassing all recorded patient encounters. For more information on how Care Studio from Google Health achieves this, visit https://youtu.be/ChHrquai48E.

The pilot study will commence in 2023, initially involving a small group of participants. As DOHC evaluates the platform's value to clinicians, the number of patients participating in the study is expected to grow. Over time, other user groups within DOHC are also anticipated to adopt Care Studio.

It is important to note that all patient information shared with Google Health by DOHC is protected under HIPAA (Health Information Portability and Protection Act of 1996), a federal law safeguarding sensitive patient information. Data shared will be used exclusively to provide Care Studio services to DOHC.

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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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