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BRIGHAM AND WOMEN'S HOSPITAL

ORTHOPEDIC SURGERY ADVANCES

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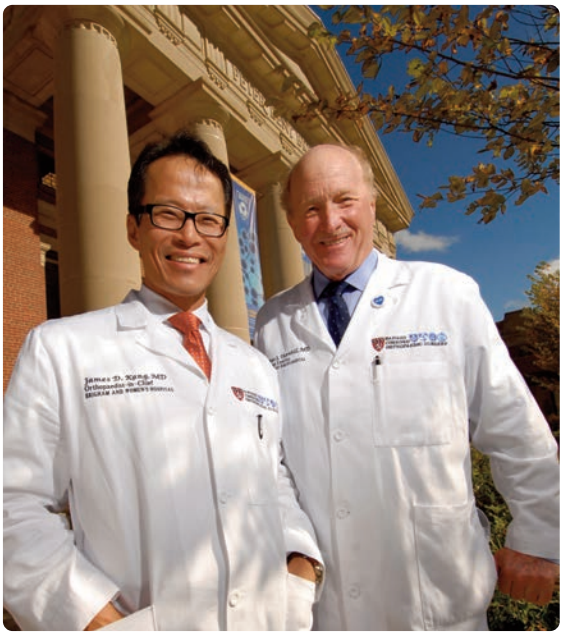
Building on a Strong Foundation: James D. Kang, MD, Appointed New Chairman of Orthopedic Surgery

James D. Kang, MD, has been appointed as Chairman of the Department of Orthopedic Surgery at Brigham and Women's Hospital (BWH) and succeeds Thomas S. Thornhill, MD, who stepped down after more than 20 years of groundbreaking leadership.

Dr. Kang, an internationally recognized expert on the basic science and clinical treatment of intervertebral disc degeneration, discussed his vision of building on the strong foundation that was established by his predecessor.

How do you view optimizing patient care?

"I want to promote interdisciplinary collaborations as a way to improve the care of our patients," Dr. Kang said. "One example of this is our multidisciplinary Metastatic Spine Tumor Board which is very unique in this country. It was originally inspired by one of our faculty, Dr. Mitchel Harris, and involves orthopedic surgeons, neurosurgeons, radiologists, oncologists, radiation therapy, rehab medicine, and bioengineers – so we have all bases covered. The board meets once a week to discuss specific cases in order to optimize the treatment for patients with metastatic tumors of the spine. As a result of this unified team approach, the patient feels comforted knowing that his or her treatment was not determined by just one surgeon or one doctor. I believe that health care professionals in the future will need to work in synergy and across departmental lines to optimize cost and effective patient care."



James D. Kang, MD, the new Chairman of the Department of Orthopedic Surgery, plans to build on the strong foundation established by Thomas S. Thornhill, MD, who stepped down after more than 20 years of groundbreaking leadership.

How does research support this optimization?

"I would like to raise the bar in terms of basic science research with the goal of fostering translational innovations in orthopedic surgery that will shape how patients are treated in the future," he

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Harnessing the Power of Stem Cells and Nanorobots to Enhance Fracture-healing After Trauma

Investigators at Brigham and Women's Hospital (BWH) are performing innovative research into the use of stem cells and nanomedicine to improve fracture-healing after trauma.

"Fracture-healing remains a poorly understood yet vital process for all procedures in orthopedics. From the perspective of a trauma surgeon, a clearer understanding of this essential process and specific areas in which we can impact the consistency of the result would optimize clinical outcomes," explained Mitchel Harris, MD, FACS, Chief, Orthopedic Trauma Service. "We are currently investigating mechanisms whereby we can reinvigorate the vitality of osteoblasts, particularly in the elderly, after fractures. If we can identify factors that improve this process in the geriatric population, we may be able to apply this to the younger population as well. In addition to our cellular work, we are also investigating the nanodelivery of chemicals that work locally but can be administered without surgical intervention."

Julie Glowacki, PhD, Shuanhu Zhou, PhD, and Mitchel Harris, MD, FACS, are leading research into the use of stem cells and nanomedicine to improve fracture-healing after trauma. This research is funded by the Gillian Reny Stepping Strong Fund.

Exploring the Influence of Bone Marrow Hematopoietic Cells on Osteoblast Differentiation

Shuanhu Zhou, PhD, lead researcher in the Department of Orthopedic Surgery, recently discovered that there are paracrine (local) effects of blood-forming hematopoietic cells on human mesenchymal stem cells (hMSCs), which are bone-forming precursors found in bone marrow (*Sci. Rep*. 5, 10573; doi: 10.1038/srep10573 [2015]). According to Dr. Zhou, this discovery may help to identify interventions to prevent age-related changes such as the decline in stem cell function and an increased risk for osteoporosis, bone fractures, and skeletal tissue degradation.

Dr. Zhou found that certain soluble factors that are secreted by hematopoietic cells may contribute to osteoblast differentiation and inhibit the senescence of bone-forming cells. Dr. Zhou reported that these factors may allow hematopoietic cells to interact with hMSCs. Of particular note, he found that the secreted factor TNF-α (tumor necrosis factor α), a multifunctional protein that increases with age, inhibits the proliferation and differentiation of osteoblasts.

"Our bench studies with human skeletal cells could identify potential interventions for senile osteoporosis and bone fracture and may lead to novel therapeutic strategies to prevent skeletal tissue degeneration and loss in the aging population," noted Dr. Zhou. In addition, future therapeutic strategies could target the interaction between hematopoietic cells and mesenchymal stem cells in order to potentially restore skeletal tissue.

"This study identifies the ways in which marrow hematopoietic cells influence osteoblast differentiation and identifies new targets for optimizing skeletal health," said Julie Glowacki, PhD, Director of the Skeletal Biology Laboratory.

Exploring Vitamin-D Metabolism and Regulation in Pediatric MSCs

Another area of groundbreaking research at BWH pertains to the role of activated vitamin D in osteoblast differentiation. Dr. Glowacki explained, "One of the reasons that vitamin-D sufficiency is important for skeletal health is that osteoblast differentiation is directly stimulated by activated vitamin D. Several years ago, we discovered that MSCs have the biochemical machinery to synthesize and activate vitamin D, thus making these cells both a source of and a target of active vitamin D."

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Mitchel Harris, MD, FACS
Chief, Orthopedic Trauma Service,
Brigham and Women's Hospital

Julie Glowacki, PhD
Director, Skeletal Biology Laboratory,
Brigham and Women's Hospital

Shuanhu Zhou, PhD
Lead Researcher,
Department of Orthopedic Surgery
Brigham and Women's Hospital

BWH Stem Cell Research for Cartilage Repair

Researchers at Brigham and Women's Hospital (BWH) have assembled a unique interdisciplinary team of nationally and internationally recognized experts in stem cell, regenerative medicine, and tissue engineering research, dedicated to the mission of applying the principles of engineering and the life sciences toward the development of groundbreaking diagnostic and therapeutic interventions.

The BWH Regenerative Medicine Center, led by cardiologist Richard Lee, MD, represents a unique collaboration of basic scientists and clinicians, from across several specialties, with the goal of bringing life-changing ideas "from the bench to the bedside."

Within the Regenerative Medicine Center, orthopedic surgeon Andreas H. Gomoll, MD, leads the Orthopedic Regenerative Medicine Program. "There are many places that do excellent clinical work, and there are many places that do excellent basic-science work. But I believe we have done a remarkable job of combining the two and focusing on translational medicine," explained Dr. Gomoll.

Researching Umbilical Cord and Amniotic Stem Cells for Cartilage Repair

Currently, the Program's primary research focus is in joint preservation and therapeutics that can delay, or potentially even negate the need for total knee replacement—including cartilage transplantation, osteotomy, and, more recently, the use of stem cells.

"Unlike labs around the world that are doing research on stem cells on a basic science level, we have taken our research into the clinical space," Dr. Gomoll said. "The FDA does not regulate the use of stem cells, provided they are not cultured or significantly manipulated during processing. There are many clinics in the U.S. that use various forms of stem cell injections on a daily basis without supporting data. Our group decided that we wanted to pursue clinical use of stem cells, but we wanted to do it in an academic environment, based on data. We are now at the bedside but conducting the research in a clinical trial environment, collecting data and following patients with lab and imaging studies."

Dr. Gomoll is currently conducting clinical studies on the use of various types of stem cells for cartilage repair.

Cartistem Trial

This study, involving 12 patients at two U.S. sites, is a fully enrolled multicenter FDA Phase I/II trial investigating the safety of using umbilical cord blood mesenchymal stem cells (MSCs) for surgical cartilage repair in the knee.

"We are treating cartilage defects in the knee, but instead of using currently available cartilage transplants, we are using stem cells derived from umbilical cord blood taken after healthy deliveries. So essentially these are very early-stage mesenchymal stem cells," he said. "The MSCs are grown in culture and mixed with hyaluronan, making a gel, which is then pasted into the defect during a surgical procedure. The postoperative treatment is the same as that following conventional cartilage repair, and the patients are followed for two years with MRI scans to ensure that there are no complications and the cartilage defects heal. The study is ongoing, but the initial results are very promising. Next will be a much larger Phase III trial focusing on efficacy."

ReNu Trial

This is a multicenter, randomized controlled trial involving 200 patients in which amniotic stem cell injections will be compared with injections of placebo (saline) and viscosupplementation for the treatment of knee osteoarthritis. "The main goal is to provide patients with symptomatic relief, rather than tissue regeneration," Dr. Gomoll said. "The latter would be a desirable long term goal, but it remains to be seen whether tissue healing could be achieved with an injection only."

(For more information on these trials, contact Dr. Gomoll at (617) 732-9813 or cartilage@partners.org)

Honing in on the Next Major Advance in Cartilage Repair

Dr. Gomoll and colleagues at BWH are setting their focus on the next major advance in cartilage repair. "We are looking to improve outcomes through new methods and expand indications for cartilage repair in patients with more advanced disease who, at the moment, are not indicated for this treatment."

"We previously thought that, when stem cells were injected into the defect, they turned into cartilage cells and produced cartilage. Now we are beginning to understand that stem cells influence the mechanisms of other cells," explained Dr. Gomoll. "They have anti-inflammatory effects, they modulate the local immune system, and they can help recruit other local cells to do the repair. Inflammation is a big part of cartilage disease and osteoarthritis, and it turns out that stem cells have pretty strong anti-inflammatory effects. So they can help repair the defect, but they can also effect change throughout the entire joint."

Andreas H. Gomoll, MD
Orthopedic Surgeon,
Brigham and Women's Hospital

Access to our Orthopedic Surgery Services

Contact our Physician Liaison Ellen Steward who can provide direct assistance with patient referrals and consultations. Ellen can be reached at **(617) 582-4733** or **esteward@partners.org**.

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said. "I am going to key in heavily on innovation, starting at the basic science level and will no doubt require a close working partnership between our clinicians and basic scientists. My focal point will be around tissue-engineering and regeneration and on utilizing the resources available here at Brigham and Women's in a multidisciplinary fashion to recruit researchers to help shape the future of musculoskeletal care."

What is one of the biggest challenges facing orthopedic surgeons?

"As we move toward value-based medicine, we must continue to do everything we can to maintain the high quality of care that we are already providing, but also do it in a cost-effective manner," he said. "This implies that we surgeons need to be acutely aware of the costs associated with the care that is provided. As a major push for the Department, Drs. Jeffrey Katz and Elena Losina, who currently have an outstanding clinical research program in our Department, will spearhead a more broad initiative in making the collection of patient reported outcomes an integral part of delivering advanced orthopedic care. This will not only allow our clinicians to critically evaluate individual surgical outcomes in their patients but will also allow for maintaining a large database for population-based clinical outcomes research."

What are your overarching goals for the future of the Department?

"At BWH there is a unique opportunity to make a positive impact and to guide strategic changes for the future," said Dr. Kang. "Dr. Thornhill built an outstanding clinical orthopedic program here at Brigham and Women's Hospital. My goal is to take what he has built and continue to raise the bar in every aspect of academic medicine."

Harnessing the Power of Stem Cells and Nanorobots to Enhance Fracture-healing After Trauma...

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In a recent study, Dr. Glowacki and colleagues observed an unexpected difference in vitamin D metabolism in MSCs from boys and girls, a difference that is not found in cells from adults (*J Steroid Biochem Mol Biol.* 2015 Sep 15. pii: S0960-070[15]30085-6). The MSCs were obtained as excess bone graft discarded during the course of surgical repair of the orofacial cleft in children between eight and 12 years of age. Significantly higher levels of the enzymes and receptors involved in vitamin-D synthesis and activation were found in MSCs from boys than in those from girls. The differences ranged from 2.6 to 3.5-fold. It was possible to dramatically increase the levels in cells from girls by treating them with a vitamin-D precursor molecule or with an estrogen as an in vitro mimic of puberty. These discoveries indicate how puberty may trigger systems in the body to support the pubertal growth spurt differently in boys and girls. They also may indicate a relative vitamin D-deficiency in prepubescent girls as compared with boys. Current research is focused on determining the significance of these findings and to finding ways to translate them to ensure skeletal health in children.

(For more information on this research, contact Dr. Glowacki at jglowacki@bwh.harvard.edu)

Using Nanodrones to Fight Infection and Enhance Bone-Healing Following Trauma

Omid Farokhzad, MD, Director of the Laboratory of Nanomedicine and Biomaterials within the Department of Anesthesiology, Perioperative and Pain Medicine, and colleagues are conducting groundbreaking research involving the use of "nanodrones" to address the problem of bacterial infections and lack of new bone growth in patients who undergo orthopedic trauma surgery.

Injuries resulting from severe trauma are often challenging because they are associated with large open bone fractures that are prone to high rates of infection. In such cases, orthopedic trauma surgeons are faced with the challenge of simultaneously stabilizing the bone injury, preventing infection, and promoting bone-healing.

The current standard of care is rudimentary: a cement paste containing antibiotics is molded into the open fracture, and the wound is closed. The disadvantages of this method are that only a fraction of the antibiotic is released from the cement spacer, the patient requires an additional operation for cement removal, and the cement can cause bacterial biofilms to grow, leading to further infection.

Dr. Farokhzad and colleagues are addressing these challenges by developing very small biodegradable robots called nanomedicines that can deliver antibiotics to target bacteria and other drugs to promote bone growth and wound-healing. The advantages of this approach are that bacterial infections are minimized or eradicated, natural bone growth is accelerated, and the patient will not need follow-up surgery as the moldable matrix can biodegrade in the body, leaving new bone in its place.