



Penn Center for Advanced Cartilage Repair and Osteochondritis Dissecans Treatment Update



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Introduction

In January 2013, the proposal to create a Penn Center for Advanced Cartilage Repair and Osteochondritis Dissecans Treatment was supported by L. Scott Levin, M.D., Chair of the Department of Orthopaedic Surgery, and then officially endorsed by J. Larry Jameson, M.D., Ph.D., Dean of the Perelman School of Medicine at the University of Pennsylvania. This Penn Cartilage Center operates as a Type-1 Center within the Department of Orthopaedic Surgery—promoting targeted, inter-disciplinary science and education spanning basic, translational, and clinical research. Over the last year, the Cartilage Center has excelled in this mission.

Cartilage Symposium

We adapted the 8th Penn Cartilage Symposium to a virtual platform, and held this meeting on September 11-12th, 2020. Due to support from our generous sponsors, we were able to offer this educational opportunity for free to anyone interested. While we missed the human teaching lab portion of the program that is typically associated with the in-person symposium, the virtual platform allowed us to hear from speakers around the United States, and abroad. The symposium included basic, translational, and clinical science presentations with the overarching theme of “Enhancing the Quality and Value of Cartilage Repair”. The translational science keynote was given by Alan J. Grodzinsky, Sc.D., a leader in cartilage biomechanics, tissue engineering, and drug delivery from Massachusetts Institute of Technology. Dr. Grodzinsky spoke about the delivery of novel therapeutics for cartilage repair and regeneration. The clinical keynote was given by Tim Spalding, FRCS Ortho, a surgeon and pioneer in meniscal transplantation from England. Mr. Spalding covered the cost-effectiveness of fresh osteochondral allografts and meniscus transplants. These keynote presentations were accompanied by 14 other talks by leading scientists and clinicians. In addition to the talks, there were numerous posters submitted and presented by trainees. We finished the symposium with a virtual mural arts tour of Philadelphia hosted by Mural Arts Philadelphia. Overall, the 8th Penn Cartilage Repair Symposium was a success, and we look forward to meeting in-person next time.

Basic Science and Translational Research

Magneto-driven cell gradients for cartilage tissue engineering

We recently developed a novel cell patterning strategy using magnetic fields to position unlabeled cells in three dimensional hydrogels (Figure 1). A provisional patent has been filed for this invention through the University of Pennsylvania and the Philadelphia CMC VA Hospital (Application No. 63/009,419). We applied this magneto-patterning strategy to create engineered cartilage tissues with native-like cell gradients. This advance permits us to engineer tissues with greater complexity than previously possible. Our findings were recently published in *Advanced Materials*¹, and showcased as the cover image on December 3rd, 2020. In addition to this cover article, Hannah Zlotnick was interviewed on KYW NewsRadio, and a summary of the paper was featured in *Advanced Science News*, and *Penn Medicine News*. We are very excited about this work and we look forward to implanting our magneto-patterned cartilage tissues in a preclinical cartilage defect repair model in the coming year.

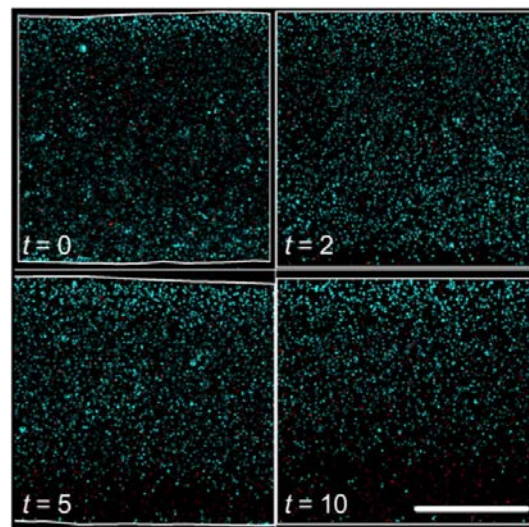


Figure 1. Cell magneto-patterning. Over time the cells (cyan) move upward, away from the magnet positioned underneath. t = time exposed to magnetic field (minutes). Scale bar = 500 μ m.

Hydrogel-mediated reinforcement and sealing of cartilage defects

Over the past few years, we have developed a novel biomaterial system to stabilize damaged cartilage tissue. Our modified hyaluronic acid system is applied to cartilage tissue, diffuses in, and is crosslinked into place with a light source, fortifying the existing tissue. Moreover, we can introduce various biochemical and biophysical cues to this new environment. For example, we conjugated a peptide sequence that enhanced the adhesion and response of stem cells at the damaged cartilage surface and guided these cells towards the formation of a sealant layer with the intent of preventing further cartilage deterioration. Recently, with the support of the Penn Health-Tech Pilot Funding program, we conducted a pilot study in a large animal model (Yucatan minipig) and are currently finishing evaluation of the therapeutic benefit of our approach. This multi-phasic system (Reinforcement and Sealing) has already displayed promising outcomes, resulting in a pending patent application and the formation of Forsagen LLC, a startup company attempting to further translate and commercialize this technology.

Improving marrow stimulation techniques for cartilage repair

We have recently formed a new collaboration with sports medicine surgeon Jason L. Koh, M.D., from NorthShore Medical Group in Glenview, IL, and the team at Marrow Access Technologies. This group has recently developed a spring-loaded needle device (SmartShot) to improve upon traditional awl-based microfracture. Their device creates repeatable marrow stimulation holes that are smaller in diameter and deeper than awl-based holes. This collaboration has allowed us to compare the current clinical marrow stimulation strategies (mallet and awl, drill and K-wire) to the Marrow Access Technologies' needle-based device. For this study, we utilized a large animal model of cartilage defect repair. We found that the needle-based device reduces bone resorption typically observed post-microfracture (Figure 2). We also

discovered that drilling with a K-wire leads to significant bone compaction around the hole site, and this compaction leads to delayed bony healing. The results of this study were presented at the recent virtual Orthopaedic Research Society Meeting in an abstract entitled, "Marked differences in local bone remodeling based on marrow stimulation technique in a large animal."

Bioprinted composite scaffolds for cartilage repair

As part of a research consortium with the AO Foundation, we have recently developed fiber-reinforced hydrogels with the requisite mechanical properties and physiochemical properties to promote cartilage repair within focal defects. To create these composite scaffolds, we leverage melt electrowriting (MEW) to first form polycaprolactone (PCL) meshes composed of microscale fibers. Thereafter, precursor hyaluronic acid (HA) hydrogel components are filled within these PCL meshes before being cured via visible light crosslinking. The resultant composites possess compressive properties that are <50-fold larger than hydrogels alone and ,10-fold larger than PCL meshes alone. Since the HA hydrogel prevents PCL fibers from buckling under compression, the total load-carrying capacity of the scaffolds synergistically increases when hydrogels and meshes are combined together. Moreover, mesenchymal stromal cells embedded within these composites readily form and disperse extracellular matrix towards the formation of neocartilage. We are currently evaluating the therapeutic potential of these composite scaffolds in a large animal model (Yucatan minipig) of articular cartilage damage, and preliminary results for this ongoing study were recently presented at the 2020 World Biomaterials Congress Virtual Meeting in an abstract entitled, "Engineering MEW-Reinforced Hydrogels to Enhance the Mechanics of Cartilage Constructs."

Clinical Research

ROCK (Research in OsteoChondritis of the Knee) Prospective Cohort Study

The ROCK Prospective Cohort was created by the osteochondritis dissecans (OCD) study group, ROCK. ROCK is dedicated to determining the optimal treatment for OCD—a focal, idiopathic alteration of subchondral bone with risk for instability and disruption of adjacent articular cartilage that may result in premature osteoarthritis. Since its inception in 2013, the ROCK Prospective Cohort has become one of the largest cartilage cohorts in the world. This study aims to develop a comprehensive database of predictors and outcomes for patients who are diagnosed with OCD of the knee by following their course of care for up to 50 years. In addition to prior ROCK publications on the novel and reliable classification of OCD lesions and healing using x-rays^{2,3} and arthroscopy⁴, the ROCK group published a substantial work on the reliability of MRI features⁵ last year. The Institutional Review Board-approved home of the cohort is the University of Pennsylvania under Principal Investigator James L. Carey,

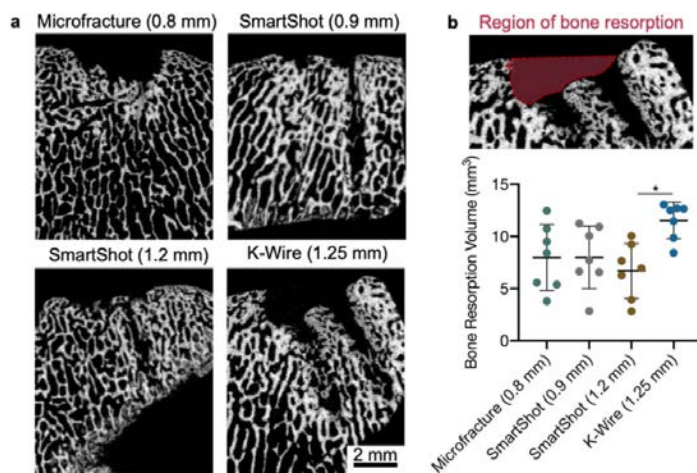


Figure 2. Global bony response underneath cartilage defects treated with different marrow stimulation techniques. **(A)** Representative μ CT images from each marrow stimulation group. **(B)** 3D quantification of bone resorption 4 weeks post-surgery. * $p < 0.05$.

M.D., M.P.H., and the study is now comprised of 26 surgeons and 29 research coordinators at 19 institutions across the country and throughout the world. Management of the study has also expanded to Children's Hospital of Philadelphia (CHOP) under Principal Investigator Theodore J. Ganley, M.D., who also currently serves as President of the ROCK study group. Penn serves as the compliance center for the ROCK Prospective Cohort and CHOP serves the data coordinating center. To date, there are over 1400 knees enrolled in the cohort. As enrollment continues, additional studies and analyses are underway, including a recently submitted descriptive epidemiology study of the first 1000 patients.

PEAK (PEdiatric Autologous cultured chondrocytes treatment of cartilage defects in the Knee)

As thought leaders in research on osteochondral defects, Dr. Carey and Dr. Ganley were invited by Vericel to lead a trial in accordance with the Pediatric Research Equity Act and to serve as Steering Committee members. The purpose of this investigation is to compare the efficacy and safety of MACI (autologous cultured chondrocytes on porcine collagen membrane) versus microfracture for treating patients with symptomatic articular chondral defects or osteochondral defects of the knee. The prospective, multicenter, open-label, parallel group FDA clinical trial will include 45 patients aged 10 to 17 years who are randomized to receive either MACI or microfracture treatment. Randomization will be done in 2:1 ratio where 30 patients will be enrolled for MACI and 15 for microfracture. Currently, the accepted standard of care treatment for treating smaller osteochondral defects is microfracture. MACI treatment includes two steps where first a screening arthroscopy and cartilage biopsy are performed after ensuring at least one symptomatic knee lesion with a size of more than 2 cm². The biopsy cells are sent to Vericel to culture chondrocytes and ultimately to seed them on the collagen membrane. The second step is implantation of MACI via arthrotomy within approximately 5 to 12 weeks from the initial biopsy visit. Patients within both arms are followed

prospectively for 2 years post-treatment. Enrollment has been underway and, currently, CHOP has enrolled 8 subjects and Penn has enrolled 1 subject. CHOP leads nationwide enrollment of the trial despite delays and restrictions due to the COVID-19 pandemic.

Clinical Volumes

With respect to clinical care, the Penn Center for Advanced Cartilage Repair and Osteochondritis Dissecans Treatment remains one of the highest volume centers for autologous chondrocyte implantation and for meniscus allograft transplantation in the world. In addition, surgeons perform many cases of fresh osteochondral allograft transplantation, osteochondral autograft transfer, and microfracture (including autologous matrix-induced chondrogenesis). Second-look arthroscopy is performed when appropriate to assess healing and to refine function. The cartilage center attracts patients on a national and international level, which has been facilitated over the past year by implementation of virtual telemedicine visits.

Summary

Despite the challenges of a pandemic, the Penn Cartilage Center continued to serve as an intellectual common space for interdisciplinary education and research, linking basic science, translational studies, and clinical research.

References

1. Zlotnick HM, Clark AT, Gullbrand SE, et al. Magneto-driven gradients of diamagnetic objects for engineering complex tissues. *Advanced Materials*. 2020;32:1-6.
2. Wall EJ, Polousky JD, Shea KG, et al. Novel radiographic feature classification of knee osteochondritis dissecans: a multi-center reliability study. *Am J Sports Med*. 2015;43:303-9.
3. Wall EJ, Milewski MD, Carey JL, et al. The reliability of assessing radiographic healing of osteochondritis dissecans of the knee. *Am J Sports Med*. 2017;45:1370-5.
4. Carey JL, Wall EJ, Grimm NL, et al. Novel arthroscopic classification of osteochondritis dissecans of the knee: a multi-center reliability study. *Am J Sports Med*. 2016;44:1694-8.
5. Fabricant PD, Milewski MD, Kostyun RO, et al. Osteochondritis dissecans of the knee: an interrater reliability study of magnetic resonance imaging characteristics. *Am J Sports Med*. 2020;48:2221-9.