Osteochondral Repair in the "Red Knee": Impact of Preexisting Meniscus Damage on Graft Function

Brendan D. Stoeckl[1,2], Rachel A. Flaugh[1,2], Akbar N. Syed[3], Elizabeth R. Bernstein[1,2], Emily S. Cook[1,2], Austin C. Jenk[1,2], Lorielle G. Laforest[1,2], Kendall M. Masada[1,2], Carla R. Scanzello[1,2], Liane M. Miller[1,2], Robert L. Mauck[1,2], David R. Steinberg[1,2]

[1]University of Pennsylvania, Philadelphia, PA. [2]CMC Veterans Administration Medical Center, Philadelphia, PA. [3]Children's Hospital of Philadelphia, Philadelphia, PA. **Disclosures:** RLM (5- 4WEB Medical)

INTRODUCTION: Knee osteoarthritis is both common and debilitating, but treatment for end-stage disease is limited to joint replacement [1], which may not be optimal in younger or more active patients given the artificial joint's limited functional lifespan.[2] Biologic cartilage reconstruction with a live graft would be an ideal alternative. This includes osteochondral autografting, where an osteochondral unit from a non-weight bearing portion of the knee is transplanted to the defect site [3]. However, as with all biologic repair solutions, this procedure is only indicated in near-ideal surgical conditions, excluding the vast majority of patients with cartilage damage—the clinically typical "red knee" [4]. Our prior work has demonstrated that reducing inflammation via local targeting of the IL-1 pathway may enhance graft function after osteochondral repair in the minipig [5]. We also developed a Yucatan minipig model of the "red knee" utilizing an enhanced destabilization of the medial meniscus approach [6,7]. However, the efficacy of osteochondral repair in large animal models exhibiting a "red knee" phenotype, while typical in the human population, has not been studied, nor has the utility of therapeutics to rescue such a joint environment to enhance osteochondral repair. In this study we analyze the effects of prior meniscus damage and the degenerative environment that this precipitates on healing and graft function in a porcine model of osteochondral repair.

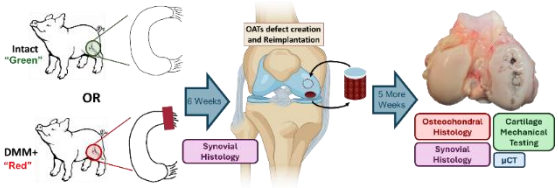

Figure 1: *Study design and timeline*

METHODS: This study utilized skeletally mature castrated male Yucatan minipigs with approval from the institutional animal care and use committee at the University of Pennsylvania. One group, the "red knee" group (N=6) first underwent a unilateral arthroscopic procedure in which a 5mm portion of the anterior medial meniscotibial ligament was resected (DMM+). Six weeks later, a second surgery was performed on the same stifles: A medial parapatellar arthrotomy followed by patellar subluxation and hyperflexion of the stifle to allow for visualization of the medial femoral condyle. Next, a 6mm diameter x 10mm depth defect was created using a standard Arthrex OATS® kit. A second defect, 7mm diameter x 10mm depth was created, and the resulting osteochondral plug was press-fit into the first defect. The empty 7mm defect served as a negative empty control. Each defect was made on the weight-bearing midline of the medial femoral condyle, and their relative positions proximal or distal were alternated between subjects. Synovial fluid and synovium tissue biopsies were obtained at the time of surgery. A second group the "green knee" group (N=5) underwent only the osteochondral autografting procedure (described above) on their naïve intact stifle. Five weeks after the osteochondral procedure, animals were sacrificed (**Fig 1**). Additional synovial fluid and synovium tissue were acquired at the time of sacrifice, and all synovium was fixed, paraffin processed, sectioned, stained with hematoxylin and eosin and scored by 5 blinded observers in four categories of pathology (hyperplasia, inflammation, fibrosis, and vasculature) [9]. Medial femoral condyles were isolated, potted, and indented with a 2mm diameter spherical indenter in the center of each autograft and empty defect. Fifteen-minute duration creep tests at a 0.1N load were fitted to a Hertzian biphasic creep model [8], and values for compressive modulus, tensile modulus, and permeability were determined. Next, osteochondral tissues were scanned by microCT (without and with contrast enhancement), decalcified for 5 weeks, sectioned, and stained with Safranin-O and Fast Green. In all outcomes, unoperated contralateral limbs served as controls. Differences between groups (Intact vs DMM) and between surgical and contralateral knees were evaluated via student's T-tests; differences in synovial scores were evaluated via ANOVA.

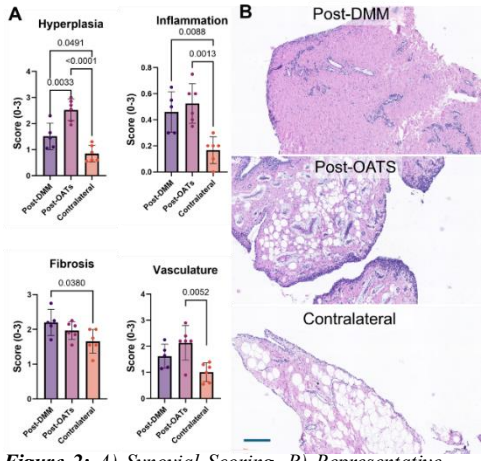

Figure 2: *A) Synovial Scoring. B) Representative H&E-stained synovium. Scale =200µm*

RESULTS: At the time of the OATs surgery (6 weeks post-DMM), synovium showed greater lining hyperplasia, inflammatory cell infiltration, and subintima fibrosis compared to contralateral controls. At sacrifice (5 weeks later, after the OATs procedure, **see Fig 1**), lining hyperplasia continued to evolve, becoming even greater than both the post-DMM timepoint and contralateral limb; the inflammation score remained elevated, and the vascularity score significantly increased in comparison to contralateral; fibrosis partially restored towards contralateral baseline. (**Fig 2**) Cartilage mechanical testing revealed no significant differences in autograft tissue placed into intact naïve knees and those with prior DMM in any parameter (compressive modulus, tensile modulus, permeability). For both groups, the compressive and tensile moduli were significantly lower than that of contralateral cartilage. Only autograft cartilage from joints with prior DMM had increased permeability compared to control (**Fig 3A**). MicroCT demonstrated excellent bony integration, and surface conformation in autografts from both intact and DMM knees, while osteochondral histology in both groups showed poor cartilage integration as well as moderate surface roughening and a minor loss in proteoglycan content within the autograft tissue (**Fig 3B-C**). Quantitative µCT and histopathology analyses are ongoing.

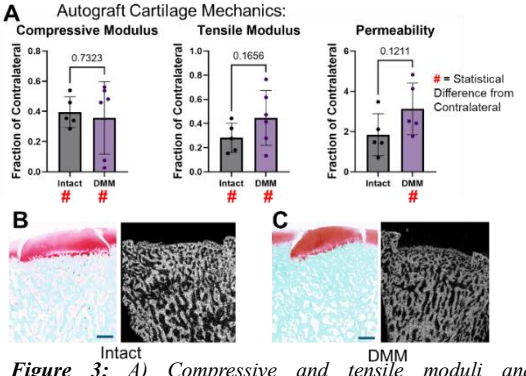

Figure 3: *A) Compressive and tensile moduli and permeability of autografts placed in intact knees and those with prior DMM. (B-C) Representative Safranin-O and Fast green stained histology and sagittal µCT cross sections of autografts in both intact and DMM knees. Scale = 1mm*

DISCUSSION: While our previous work with this large animal model of osteochondral repair showed that blocking IL-1 signaling enhances autograft function, it was interesting to note that even in an ideal surgical scenario (repair in a pristine, healthy knee), autograft tissue showed significant degeneration even at an early timepoint [5]. We hypothesized that surgical insult in and of itself may precipitate an inflammatory joint environment that is detrimental to osteochondral healing. It was therefore the goal of the current study to evaluate the effect of *prior* damage to the joint on healing. We showed little difference between autograft properties when placed in intact knees versus placement into those with prior DMM, and progressing synovial pathology with each subsequent surgical insult. It may be that at this early timepoint, the catabolic joint environment resulting from surgery is indistinguishable from that caused by prior meniscal injury. It remains an open question whether these sources of poor healing resolve at different rates and whether there would be differences between these two groups at longer timepoints. It also remains unanswered whether blocking inflammatory signaling can rescue the degenerative environment of the "red knee" as effectively as it did in the previous study on the "green knee."

CLINICAL RELEVANCE: Most people evaluated clinically for knee injury fall into the "red knee" category—that is, they have underlying mechanical insufficiency or an otherwise degenerative joint— and are therefore contraindicated for the most advanced biologic repair solutions. Despite this, there are few large animal models that evaluate osteochondral repair in such a scenario. This study shows similar repair potential for OCA in healthy and red knees and lays the groundwork for testing the efficacy of adjuvant therapeutics to improve biologic repair.

REFERENCES: [1] Devitt +, *Knee*, 2017. [2] Bayless+, *Lancet*, 2017. [3] Hangody+, *Knee Surgery*, 1997. [4] Martín+ *NRM,* 2019. [5] Stoeckl+, *ORS,* 2025. [6] Stoeckl+, *ORS,* 2024. [7] Meadows+ *JOR*, 2025. [8] Moore+, *J Tribol*, 2016. [9] Bansal+, *OJSM*, 2021

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