Effects of a Modified Hyaluronan Biopolymer (MHB3^{TM}) on Cartilage Loss in a Monoarthritis Model

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Background: Osteoarthritis (OA) is characterized by the progressive loss of articular cartilage. Eventually, in many cases, the entirety of the articular cartilage in certain diarthrodial joints such as the knee, where the femur and tibia articulate, is lost. Frequently compensation for pain results in a loss of range of motion causing an altered gait and the development of OA in other areas.

Commonly used treatments and medications only provide palliative care. Palliative care is defined as any form of medical care or treatment that concentrates on reducing the severity of disease symptoms, rather than halting or delaying progression of the disease or providing a cure. Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are frequently prescribed or self-administered ad libitum. Types include aspirin, ibuprophen, acetaminophen, and naproxen. Although NSAIDs work well for their intended purpose, long-term use of these drugs can cause stomach problems such as ulcers and bleeding. In April 2005 the FDA asked manufacturers of NSAIDs to include a warning label on their product to alert users of an increased risk for cardiovascular events (heart attacks and strokes) and gastrointestinal bleeding. Certain NSAIDs may also weaken bone and increase the risk of bone fractures.

COX-2 inhibitors (coxibs) are also used to treat symptoms. Coxibs block an inflammation-promoting enzyme called COX-2. This class of drugs was initially believed to work as well as traditional NSAIDs, but with fewer stomach problems. However, numerous reports of heart attacks and strokes have prompted the FDA to re-evaluate the risks and benefits of the COX-2s. Rofecoxib (Vioxx) and valdecoxib (Bextra) have been withdrawn from the US market following reports of heart attacks in some patients taking the drugs. Celecoxib (Celebrex) is still available, but labeled with strong warnings and a recommendation that it be prescribed at the lowest possible dose for the shortest duration possible. However, neither

NSAIDs nor COX-2 inhibitors are known to stop or restore the loss of articular cartilage, which is the hallmark of osteoarthritis and the cause of the symptoms.

Steroids and artificial joint fluid (Synvisc, Hyalgan etc.) can be injected directly into the joint capsule to reduce pain and inflammation for up to six months but have attendant injection site risks and do not improve the underlying cartilage condition.

Natural substances marketed in the United States as dietary supplements are also administered in cases of osteoarthritis. In particular, glucosamine, chondroitin sulfate, and methylsulfonylmethane (MSM) are administered in order to provide some relief from the symptoms of osteoarthritis. However, none of these substances is known to address cartilage loss, the root cause of osteoarthritis symptoms.

We constructed a study using an established histopathological scoring system to evaluate specifically the effects of an orally administered, polydisperse, hyaluronan biopolymer (MHB3, Cogent Solutions Group LLC) in a mouse model of monoarthritis.

Methods: Thirty 10 week old male C57BL/6 mice purchased from Charles Rivers Laboratories were subjected to a meniscotibial ligament transection surgery of the left knee. This surgery creates a slowly advancing instability condition that mimics the loss of articular cartilage in humans with OA. At week six mice were randomly assigned to 5 groups. Group A (Untreated Controls N6) was euthanized, both left and right knees decalcified, paraffin embedded, stained with Saffrin-O and scored (Pritzker *et al.)* to confirm disease onset and cartilage loss. A histopathological score of 1 indicates articular cartilage which is intact and pristine. A score of less than 10 indicates that a great deal of healthy articular cartilage remains. A histopathological score of 24 indicates total loss of articular cartilage as is observed in very severe cases. Following confirmation of cartilage loss at week 6 post surgery Group B (Controls, N6) was gavaged 5 days/week for 3 weeks with saline; Group C (Controls, N6) was gavaged 5 days/week for 6 weeks with saline; Group D (Treated, N6) was gavaged 5 days/week for 3 weeks with MHB3 at a dose of 10mg/kg; and Group E (Treated, N6) was gavaged 5 days/week for 6 weeks with MHB3 at a dose of 10mg/kg. At the end of week 9 Groups B and D were euthanized, their left and right knees scored and compared. At the end of week 12 Groups C and E were euthanized, their left and right knees scored, and compared.

Results: The average scores in Group A (untreated week 6 baseline) were: left knee 5.33/24; right knee 1.80/24 confirming disease onset. The average scores in Group B (week 9 saline control) were: left knee 10.70/24; right knee 4.17/24. The average scores in Group C (week 12 saline control) were: left knee 12.80/24; right knee 3.40. The average scores of Group D (week 9 MHB3 treated) were: left knee 7.25/24; right knee 2.0/24. The average scores of Group E (week 12 MHB3 treated) were: left knee 7.84/24; right knee 1.08/24.

Conclusion: The results of this study strongly support the disease modifying and chondroprotective benefits of the oral hyaluronan biopolymer MHB3 when used in an established model of osteoarthritis. This is the first time that an orally administered, exogenous hyaluronan biopolymer has been shown to have such benefits.

Figure 1. Group A Untreated Control Left Knee Average Score 5.33/24 Week 6

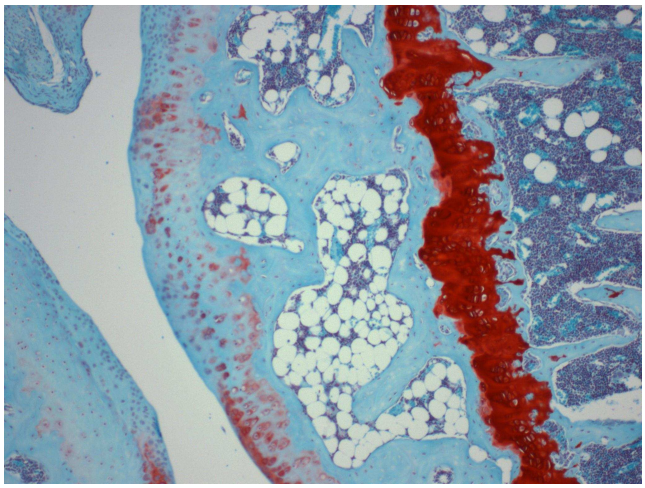

Figure 2. Group A Untreated Control Right Knee Average Score 1.80/24 Week 6

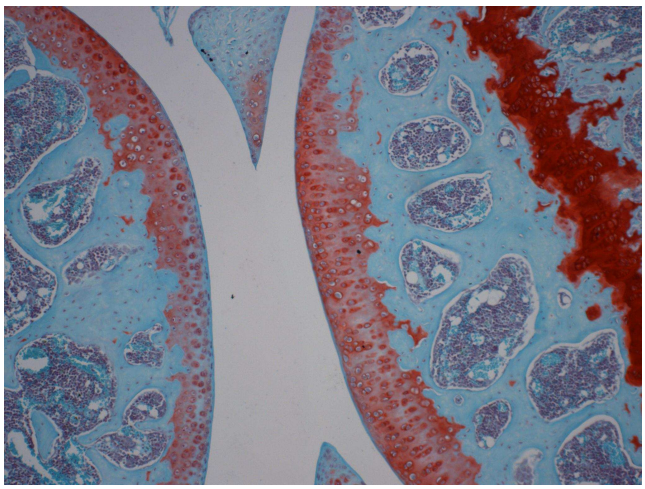

Figure 3. Group B Saline Control Left Knee Average Score 10.7/24 Week 9

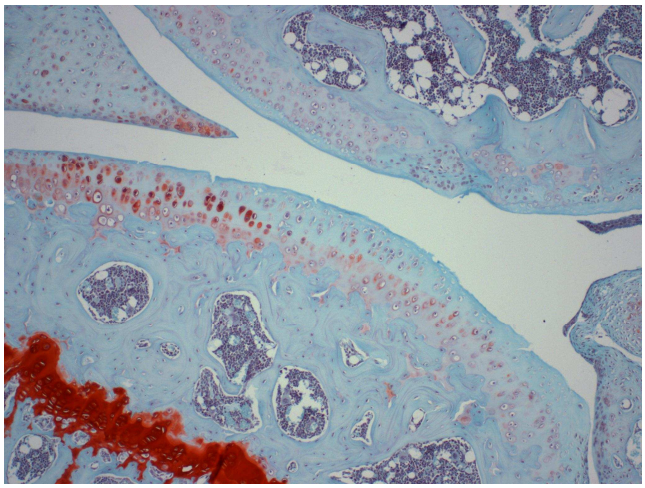

Figure 4. Group B Saline Control Right Knee Average Score 4.17/24 Week 9

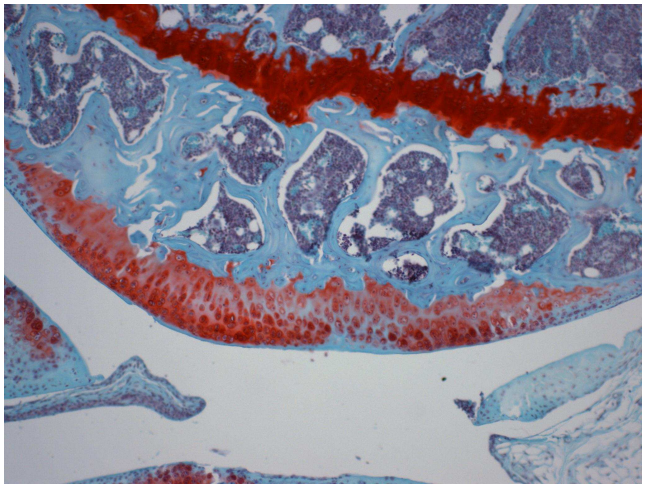

Figure 5. Group C Saline Control Left Knee Average Score 12.8/24 Week 12

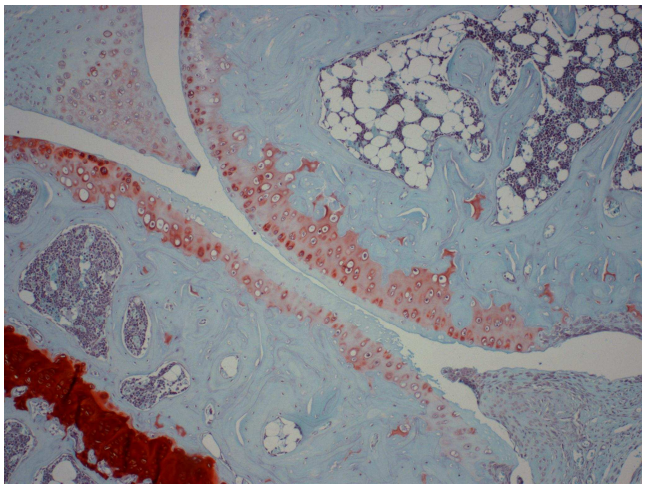

Figure 6. Group C Saline Control Right Knee Average Score 3.40 Week 12

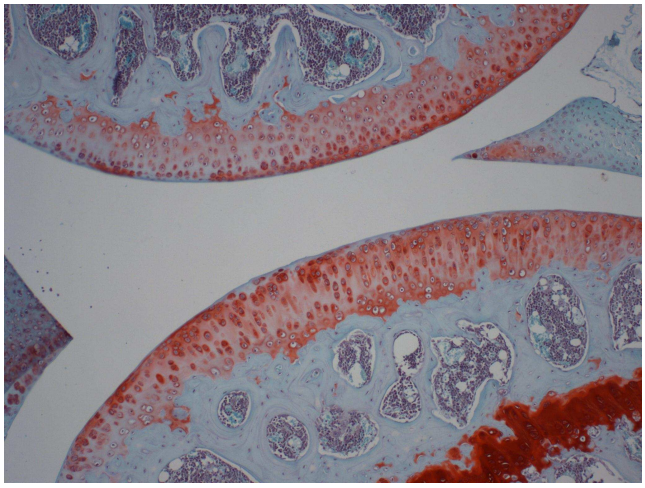

Figure 7. Group D MHB3 Treated Left Knee Average Score 7.25/24 Week 9

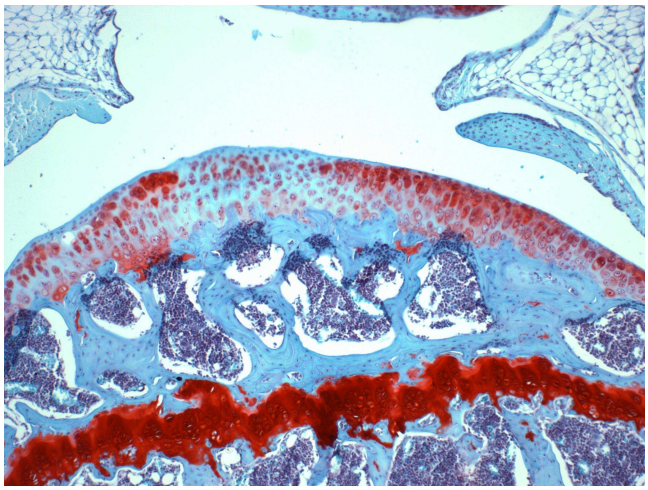

Figure 8. Group D MHB3 Treated Right Knee Average Score 2.00/24 Week 9

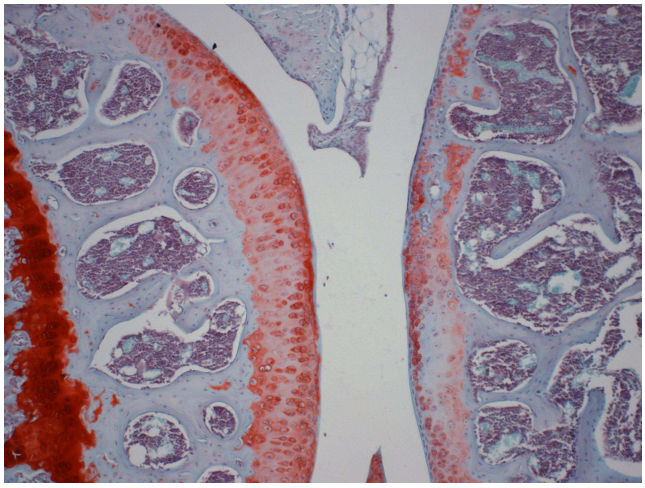

Figure 9. Group E MHB3 Treated Left Knee Average Score 7.84/24 Week 12

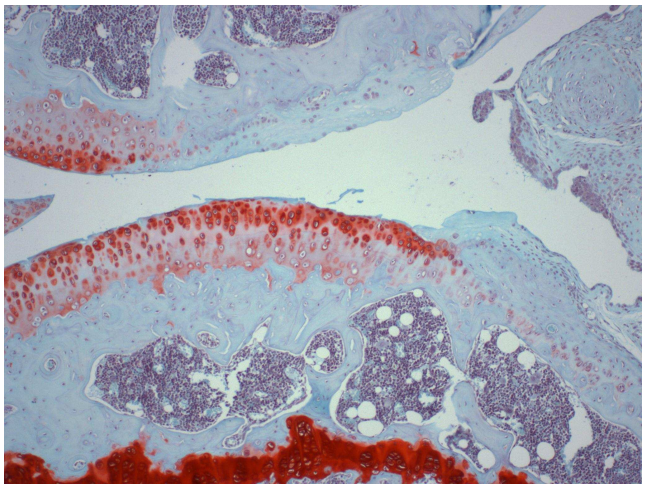

Figure 10. Group MHB3 Treated Right Knee Average Score 1.08/24 Week 12