Introduction: Osteoarthritis (OA) is a painful, chronic, incurable disease that affects diarthrodial joints by progressively breaking down of hyaline cartilage. The syndrome is characterized clinically by pain, deformity and limitation of motion and pathologically by focal erosive lesions, cartilage destruction, subchondral bony sclerosis, cyst formation and marginal osteophytes. According to the Arthritis Foundation and the World Health Organization (WHO), OA afflicts 27M in the US and 200M worldwide. Most current therapies focus on pain control and improved function. Traditional treatments have included weight loss, exercise, activity modification, assistive devices (canes, walkers), NSAIDs, and intra-articular therapy with corticosteroids or hyaluronic acid (HA) viscosupplements. When these methods fail, the last option is total joint arthroplasty (i.e., knee or hip replacement). Viscosupplementation is a procedure where the viscous properties of synovial joint fluid are enhanced by the intra-articular injection of a viscous liquid (generally HA or HA derivatives). This therapy approved by the FDA in 1997 has seen its effectiveness challenged. The results of a recent meta-analysis of the clinical trials show that viscosupplements were only 8% more effective than intra-articular saline injections in relieving patient pain. More importantly, viscosupplements have never been shown to improve joint lubrication, to be chondroprotective or to slow the rate of cartilage degradation. We hypothesized that, unlike HA-base viscosupplements, a novel formulation with superior characteristics in lubrication, shock absorption, and residence time might provide beneficial effects in osteoarthritic joints by slowing down the progression of the cartilage wear. Herein, we report the potential of a novel synthetic viscosupplement (Flex590) which exhibits good mechanical characteristics, significantly longer in vivo residence time (compare to HA), and chondroprotection efficacy in vivo.

Materials and Methods:
Rheological measurements were performed on a RA 100 controlled stress rheometer from TA Instrument equipped with a peltier temperature control and a 40 mm aluminum cone plate (2° angle). Coefficient of frictions were measured on steel-on-steel surfaces using 40 mm parallel steel plate and compared it to the bovine synovial fluid and Synvisc®. Biocompatibility tests were performed by Toxikon Corporation (Bedford, MA) under ISO-10993 and FDA C951-5 guidelines. These tests include: Klignman guinea pig maximization test; intracutaneous injection test; 14-day systemic toxicity observation for a single dose; intraperitoneal injection in mice; Ames reverse mutation assay; two-week muscle implant test; agar diffusion test; and cytotoxicity.

Evaluation of residence time: Residence time of the viscosupplement was evaluated in a 14-week-old New Zealand White rabbit knee joint (n=4). 100 µL of the viscosupplement was intra-articularly administered into a knee joint capsule. The animals were kept for 11 days, and the synovial fluid was collected and quantified by agarose gel electrophoresis.

Rat meniscal tear OA model: The basic study design and animal used were approved by the Institutional Animal Care and Use Committee at Bolder BioPATH (Boulder, CO). Male Lewis rats were randomized to groups (n=20) and the right knees were prepared for surgery. A skin incision was made over the medial aspect of the knee and the medial collateral ligament was exposed by blunt dissection, and then transected. The medial meniscus was reflected medially and a cut was made through the full thickness to simulate a complete tear. The skin was closed with a suture. Dosing: 0.25 and 1% solution, a single 40 µL solution via an intra-articular injection one week post surgery, with 40 µL of vehicle (saline) as a control. Groups were terminated 3 weeks post injection for histological evaluation of the treated joint. Data were analyzed using a Student’s t-test or Mann-Whitney U test (non-parametric). When test-article significance is found, data were analyzed again, across all groups, using a one-way analysis of variance (1-way ANOVA) or Kruskal-Wallis test (non-parametric), along with the appropriate multiple comparison post-test. Significance for all tests is set at p<0.05.

Results and Discussion:
Rheological study of the Flex590 solution, showed a trend equivalent to the healthy synovial fluid at higher shear rates (≤10² s⁻¹) (data not shown). Lubricating property of the Flex590 is similar to synovial fluid and significantly better than the HA product, Synvisc® (data not shown). The Flex590 polymer passed all biocompatibility tests evaluated in a range of concentrations relevant to intended clinical use (data not shown). Seventy-five percent of the original concentration of Flex590 was retained 11 days after intraarticularly injection into a rabbit knee joint (data not shown). the efficacy of the Flex590 (two concentration: 0.5 wt% and 1 wt%) was further evaluated in the OA animal model, rat meniscal tear, and the degree of chondroprotection was evaluated with three criteria, substantial cartilage degradation width, osteophyte formation, and total joint score (Figure 1, * = P<0.05 vs saline control). The results clearly indicated chondroprotection with a trend in a dose-dependent manner vs. saline control. Although incapacity testing (static) suggested a slight but significant decrease in load bearing on the test days (data not shown), Bone score and gait analysis (data not shown) showed no statistically significant difference between the treated and the control joint during the 3-week post injection period, supporting the hypothesis that chondroprotection was due to the treatment and not by reducing loading on the joints.

Conclusion: We have hypothesized that a novel viscosupplement that exhibits superior lubrication, shock absorption with a long residence time would delay cartilage wear. To test this hypothesis, we have designed a novel synthetic viscosupplement polymer (Flex590) solely for its mechanical performance to protect cartilage wear. This novel viscosupplement exhibits better rheological and lubrication properties than Synvisc and is more similar to native healthy synovial fluid. The Flex590 formulation was also found to be non-cytotoxic and showed chondroprotection in vivo. To our knowledge, this is the first clear demonstration of efficacious viscosupplementation using a synthetic polymer. We plan to further evaluate the Flex590 viscosupplement as a potential treatment for OA in extended biocompatibility, ADME, and efficacy in a larger animal studies. In this larger animal model, we believe pain relief along with chondroprotection should be critical evaluation factors.


Figure 1: Results of Flex590 on OA rat meniscal tear model: A) substantial cartilage degradation width, B) osteophyte formation, C) total joint score, D) bone score (* = P<0.05 vs saline control).