Small animal studies in osteoarthritis

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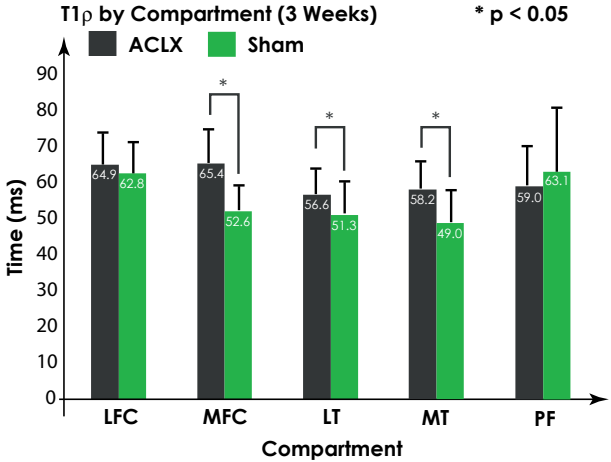
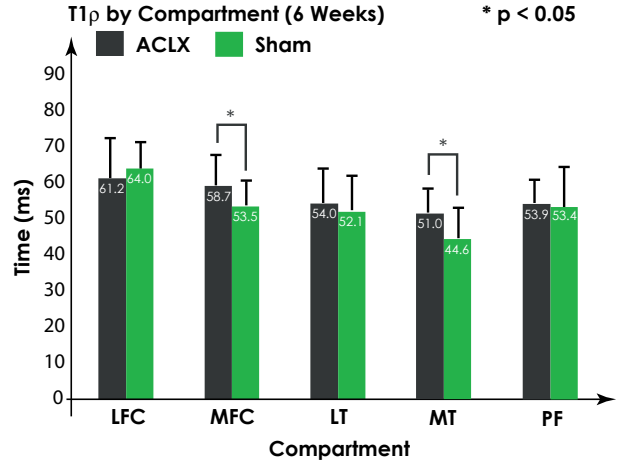
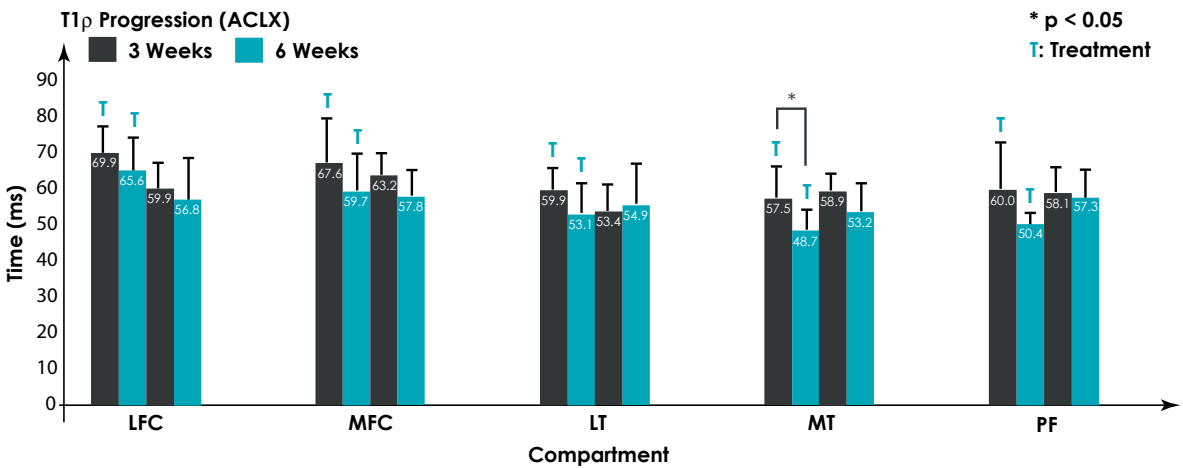
Osteoarthritis (OA) is a chronic degenerative disease characterized primarily by the loss of articular cartilage. Although OA is a very common disease, early diagnosis remains elusive. The development of high field MRI with cartilage-specific imaging allows a quantitative measure of volumetric and biochemical changes of cartilage prior to macro adaptive changes seen on traditional radiographs. Human studies have shown that T1ρ and T2 mapping techniques have the ability to provide highly accurate and quantitative measurements of articular cartilage degeneration in vivo. In addition, the possibility of treating cartilage degeneration pharmacologically is very exciting; however, much work remains to be done before such treatments can be made widely available. For example, in a recent study the effects of doxycycline on osteoarthritis progression were evaluated in a large scale clinical trial using radiographic assessment of joint space narrowing in the medial tibiofemoral compartment as the primary outcome measure. Although the results presented were promising, the statistical significance was small. Using T1ρ and T2 mapping techniques, we have characterized the rabbit anterior cruciate ligament (ACL) transection model of osteoarthritis as an objective model that may be used to assess the effects of doxycycline treatment longitudinally. Longitudinal measurements not only allow us to better account for individual variability, but will also provide us with a unique opportunity to study the natural history of cartilage repair. The goal of this study was to develop an animal model to evaluate treatment of articular cartilage injuries.

The figure illustrates the effect of ACL transection at three and six weeks post surgery. Individual slice data from each compartment were pooled to assess the overall effect of ACL transection on T1ρ and T2 (not shown) data. Data from both the treatment group and the control group were also pooled to increase the statistical validity of the data. Average T1ρ and T2 values for the ACL transection knees were higher than the corresponding values for the contralateral sham operated knees at three and six weeks post surgery. This trend was found to be significant in the MFC, MT and LT at three weeks; T1ρ differences persisted in the MFC and MT and T2 differences persisted in the MFC and LT at six weeks. A significant change was also seen at six weeks in the T2 data in the PF compartment, but in this case was outlier-driven.

To assess the effect of treatment on progression, the data was further broken down into treatment and control cases. The figure contains results for each of these cases in the ACL transection knee. As shown, there was no improvement as judged by imaging parameters in the absence of treatment, and no clear trend emerged as a function of time. In contrast, in the treatment case there was a trend toward improvement over time, and the data became statistically significant in the MT compartment. However, the data indicated that the treated rabbits exhibit some higher initial (three week) values of T2 and T1ρ than the nontreated rabbits, indicating a possible bias.


T1ρ by Compartment (3 Weeks)
* p < 0.05
ACLX
Sham
Time (ms)
Compartment
LFC
MFC
LT
MT
PF
64.9
62.8
65.4
52.6
56.6
51.3
58.2
49.0
59.0
63.1


T1ρ by Compartment (6 Weeks)
* p < 0.05
ACLX
Sham
Time (ms)
Compartment
LFC
MFC
LT
MT
PF
61.2
64.0
58.7
53.5
54.0
52.1
51.0
44.6
53.9
53.4


T1ρ Progression (ACLX)
* p < 0.05
T: Treatment
3 Weeks
6 Weeks
Time (ms)
Compartment
LFC
MFC
LT
MT
PF
69.9
65.6
59.9
56.8
67.6
59.7
63.2
57.8
59.9
53.1
53.4
54.9
57.5
48.7
58.9
53.2
60.0
50.4
58.1
57.3