Evaluation of clinical analgesics in a nonhuman primate model of knee osteoarthritis

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Goals

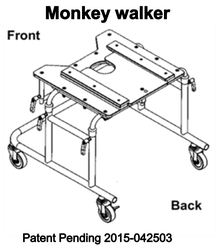
- ❑ **Behavioral characterization of a nonhuman primate model of knee osteoarthritis.**
- ❑ **Pharmacological validation of a nonhuman primate model of OA pain with clinically used analgesics.**
- ❑ **In vivo imaging of the knee joint.**

Methods

Animals
Young adult cynomolgus macaques (SNBL, Japan).

Behavioral assessments
Weight bearing: Macaques were restrained in a monkey walker and weight bearing of the left and right legs were measured using scales. Normal weight bearing is 50%.

Knee pressure threshold: Pressure threshold was measured using a hand-held pressure meter. The amount of force needed to evoke a withdrawal response was recorded. The maximum threshold was 3 kg. Ipsilateral knee pressure threshold was reported as a % of the contralateral, uninjured knee. Normal knee pressure is 100% of the contralateral knee.



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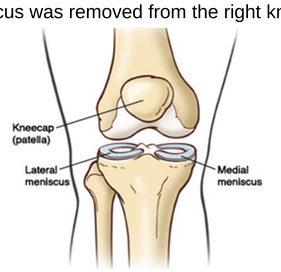
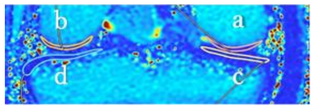
Medial Meniscectomy (MMx)
Following baseline testing and exercise training, under anesthesia, the medial meniscus was removed from the right knee.



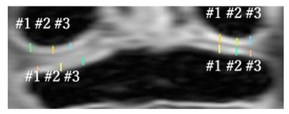
In vivo imaging over time
Knee joints were imaged 6, 8, and 18 weeks following MMx using a 3.0 T-MRI (Signa EXCITE HDxt, GE Healthcare). N = 4, data expressed as mean ±S.E.

T2 maps were created from multi-echo data using Osirix (Pimexo, Bernex, Switzerland). A coronal section of the center of the knee joint was selected and T2 values (msec) were recorded in four regions of interest (ROI).

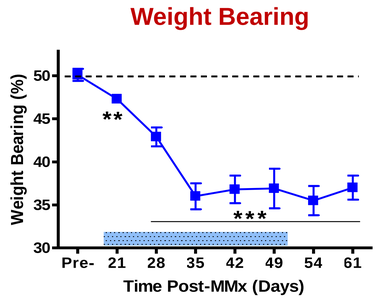


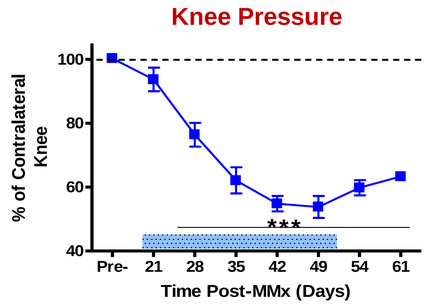
a-medial femur; **b**-lateral femur; **c**-medial tibia; **d**-lateral tibia.

3D-SPGR images were registered from T2 maps and **cartilage thickness** (mm) was measured at three areas within each of the four ROIs. Cartilage thickness at each ROI was the average of three measurements.

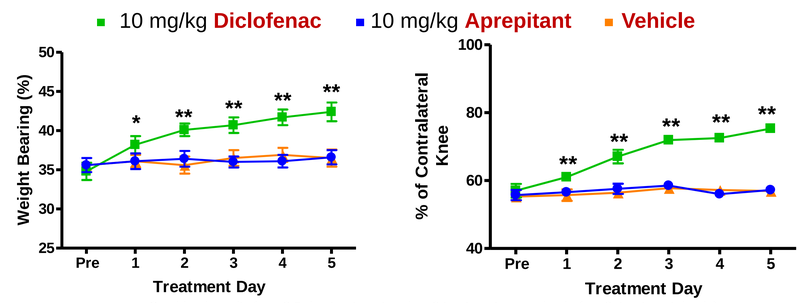


Pain Assessment



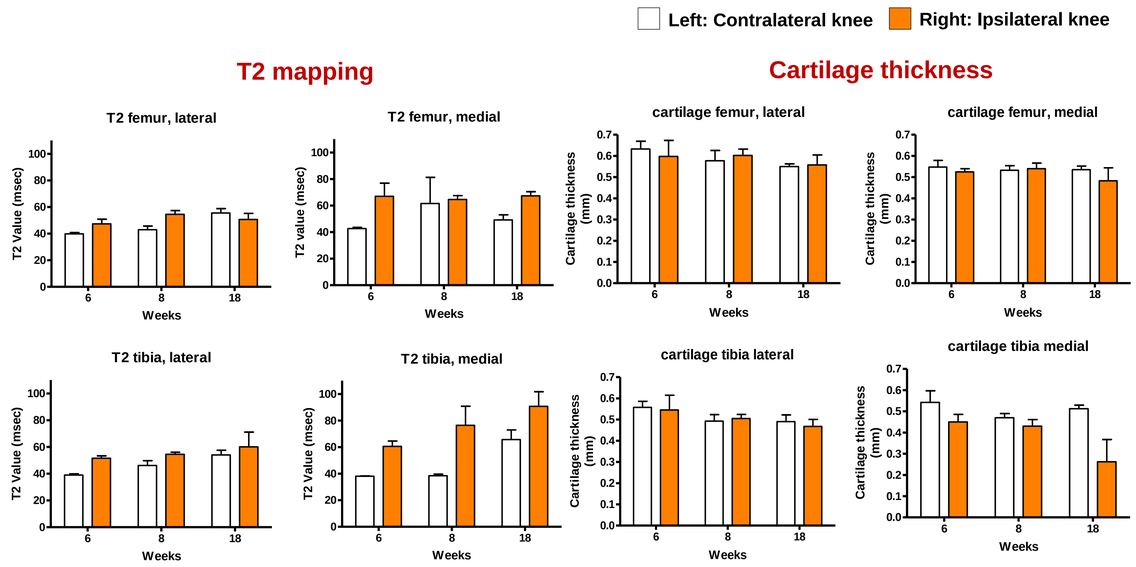


Blue bar = exercise period (50 jumps, once per day, five days a week.)
N = 9. Mean ± S.E. $^{**}p < 0.01$ vs. Pre; $^{***}p < 0.001$ vs. Pre

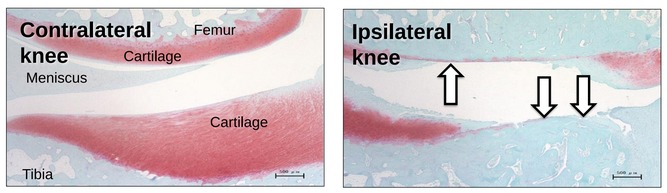


Combined results from 3 5-day treatment cycles, 3 treatment groups/cycle (n = 3 treatments/cycle)
N = 9. Mean ± S.E. $^{*}p < 0.05$ vs. Pre, $^{**}p < 0.01$ vs. Pre.

Imaging Results



Representative photomicrograph of knee joint pathology 4 months after MMx. Note the loss of cartilage (arrows) and exposure of subchondral bone.
Scale bar = 500 µm.



Conclusions

- ❑ **Potential species-based difference in responsiveness to clinical OA analgesics.**
- ❑ **Need for disease-modifying drugs in addition to drugs that relieve pain.**
- ❑ **Nonhuman primate model as a surrogate model of clinical OA.**

Summary

Preclinical success = clinical efficacy?

Drug/Mechanism	Rodent models	Clinical activity	NHP OA model
Morphine/μ-opioid receptor	MIA, CFA	Yes	Yes
Diclofenac/COX-2	MIA, CFA	Yes	Yes
Aprepitant/NK1 receptor antagonist	CFA	No	No
Duloxetine/serotonin-norepinephrine reuptake inhibitor	MIA	Yes	Yes
Pregabalin/α2δ ligand	MIA,CFA	No	No
Fatty acid amide hydrolase inhibitor	MIA, CFA	No	?
TRPV1 antagonist	MIA, CFA	No	?
Dopamine receptor (D3) agonist	MIA	No	?
δ-opioid receptor agonist	CFA	No	?
Matrix metalloproteinase inhibitor (nonselective)	MIA, MMx	No	?

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