

**CR10049, THE FIRST OA-TARGETED KINASE INHIBITOR,
IMPROVES PAIN BEHAVIOUR, RESOLVES INFLAMMATION AND
PRESERVES JOINT STRUCTURE IN SMALL AND LARGE
ANIMAL MODELS**



Disclosure statement

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I have a financial relationship(s) with:

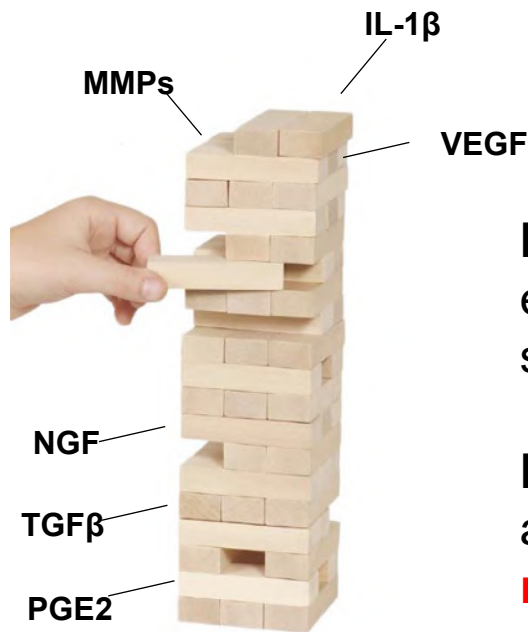
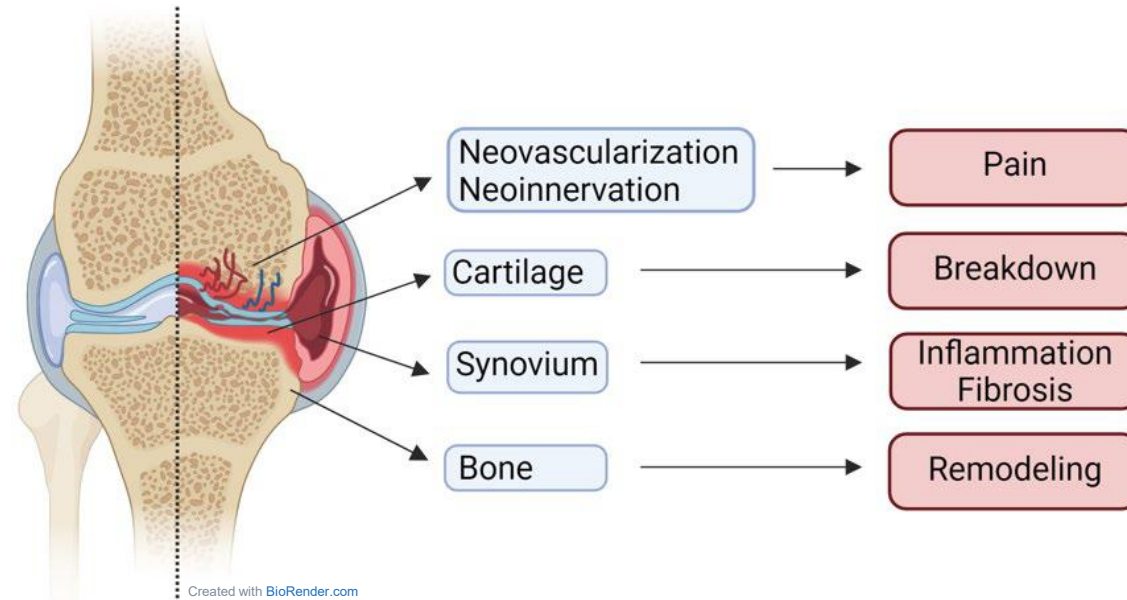
Rottapharm Biotech

My presentation does not include a discussion of off-label or investigational use;
CR10049 is a compound in pre-clinical development.

The experiments described in this presentation were funded by Rottapharm Biotech.
Rottapharm Biotech employees participated as individual and independent scientists.



Inflammatory osteoarthritis (OA) is a whole joint disease

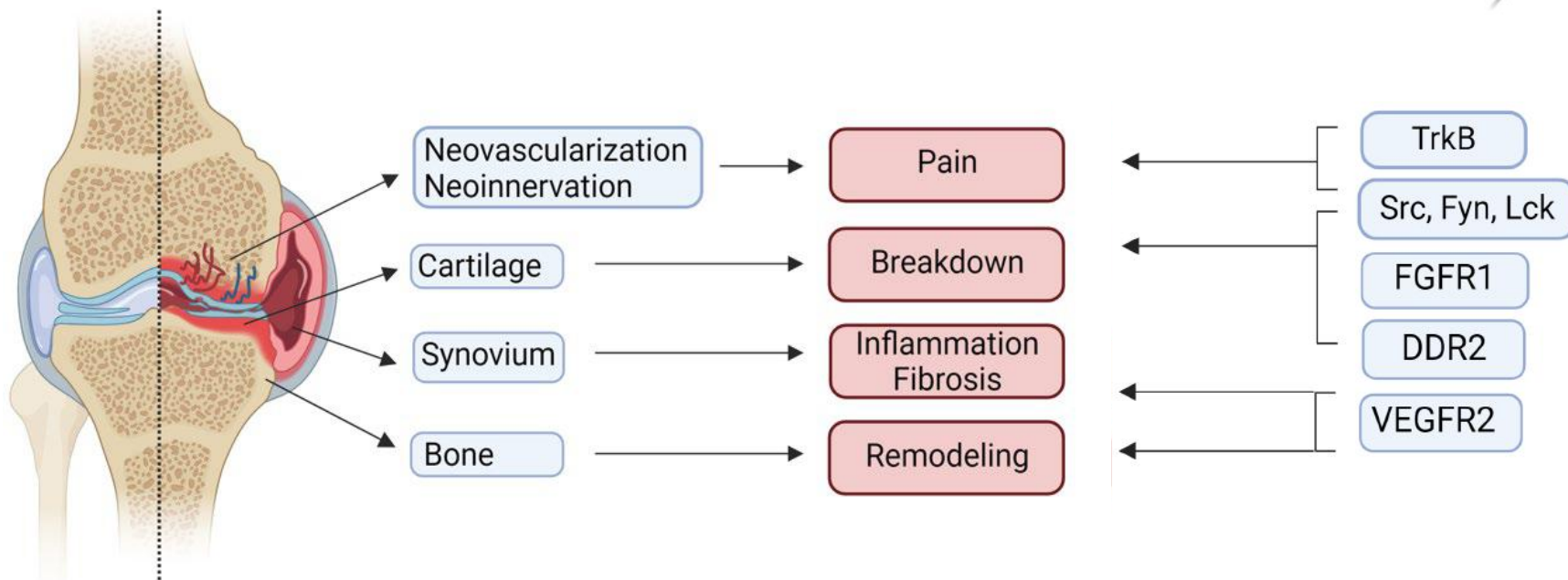


Many factors are involved in the generation of the inflammatory and destructive events in joint tissues affected by OA. Lack of efficacy of compounds targeting one single component suggest a **multiplicity, redundancy** and **synergy** of factors in OA

But no single brick, when eliminated, is sufficient to collapse the whole inflammatory and degradative tower → **the interference with more than one factor is necessary to block all the pathological features of OA**



CR10049 the first OA-targeted kinase inhibitor



CR10049 is an inhibitor designed to target specific kinases involved in OA altered pathways

Inhibition of OA-targeted kinases in the nanomolar range

Kinase	Lck	Src	VEGFR2	Fyn	FGFR1	TrKB	DDR2
IC ₅₀ (nM)	0.04	0.18	6.9	8.1	10.5	16	21



CR10049 inhibits inflammation and degradation in *in vitro* OA models

CR10049

- Chondrocytes inflammation
- Chondrocytes calcification
- Cartilage degradation

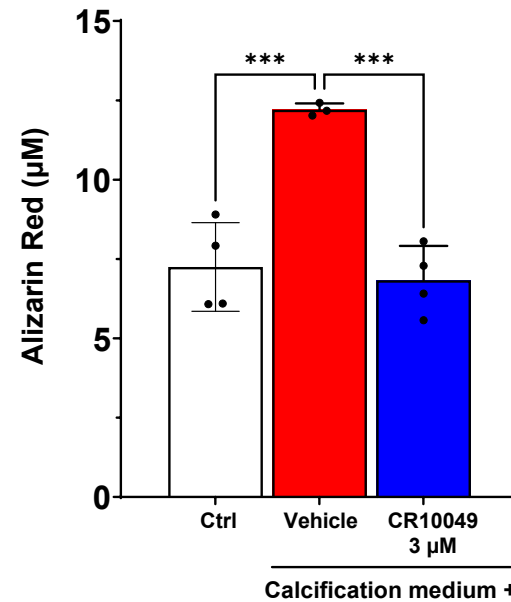
CR10049 inhibits pro-inflammatory and matrix-degrading enzymes expression in articular chondrocytes

Marker	IL-1 β	IL-6	COX2	ADAMTS-5	MMP3	MMP13
IC ₅₀ (nM)	< 10	18	187	34	327	447

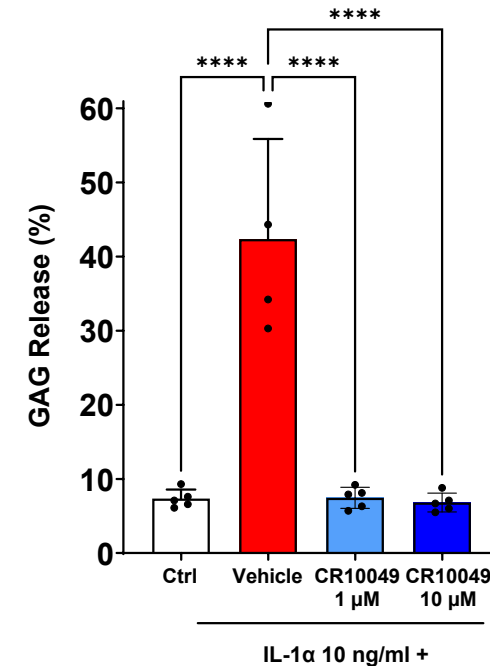
Chondrocytes were stimulated by IL-1 β and gene expression was analysed by qPCR

In preliminary experiments, CR10049 inhibits chondrocytes calcification and cartilage degradation

Chondrocytes calcification



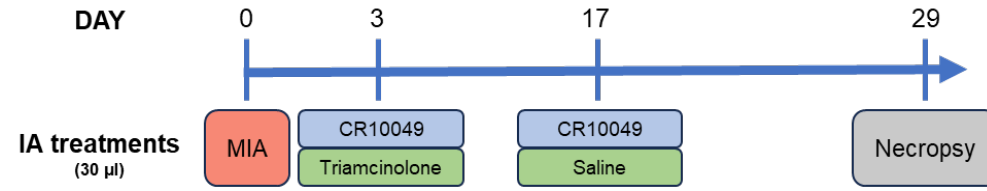
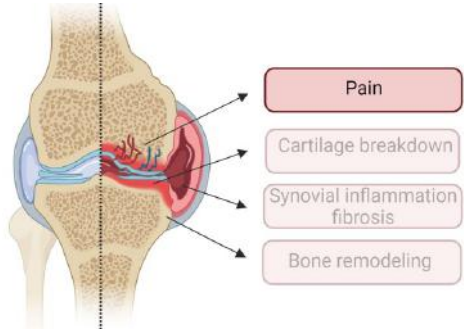
Cartilage degradation



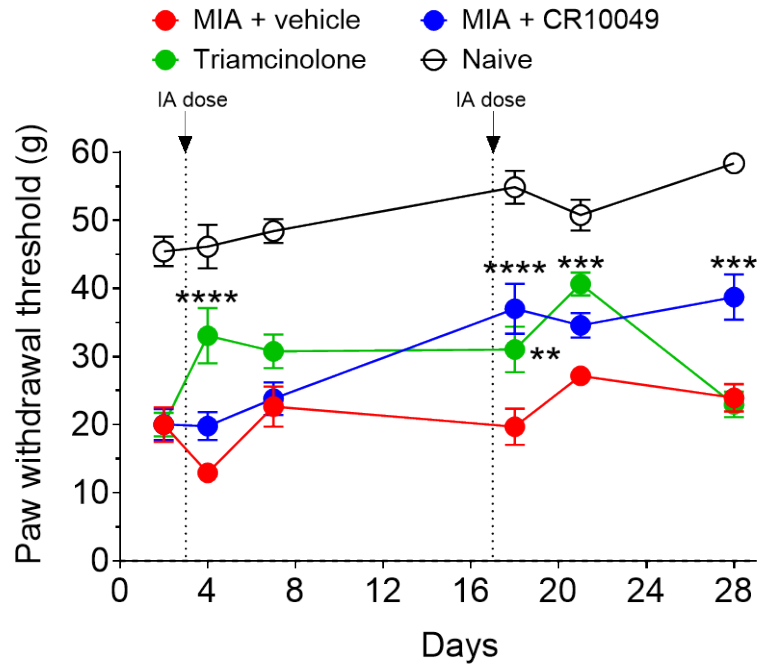
Mean \pm SEM. One way ANOVA with Tukey's multiple comparisons test. *** $p < 0.001$, **** $p < 0.0001$



CR10049 reduces OA-pain in the rat MIA model

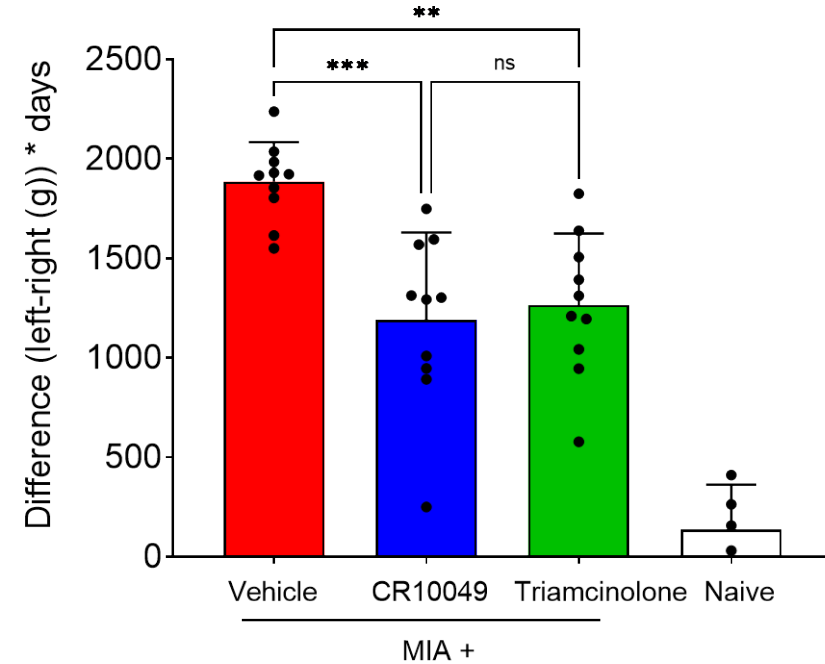


Stimulus-evoked pain Mechanical allodynia - eVon Frey



Mean ± SEM. Two-way ANOVA with Tukey comparisons. **** p < 0.0001, *** p < 0.0005, ** p < 0.001 vs MIA+Vehicle

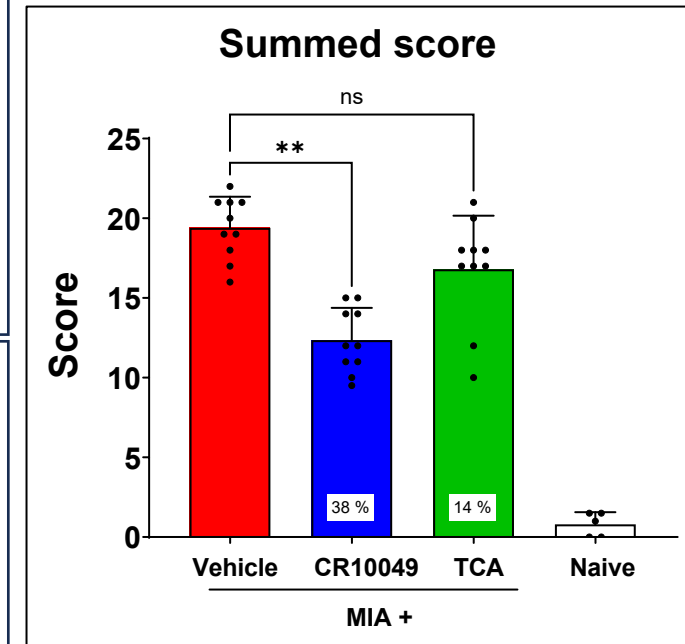
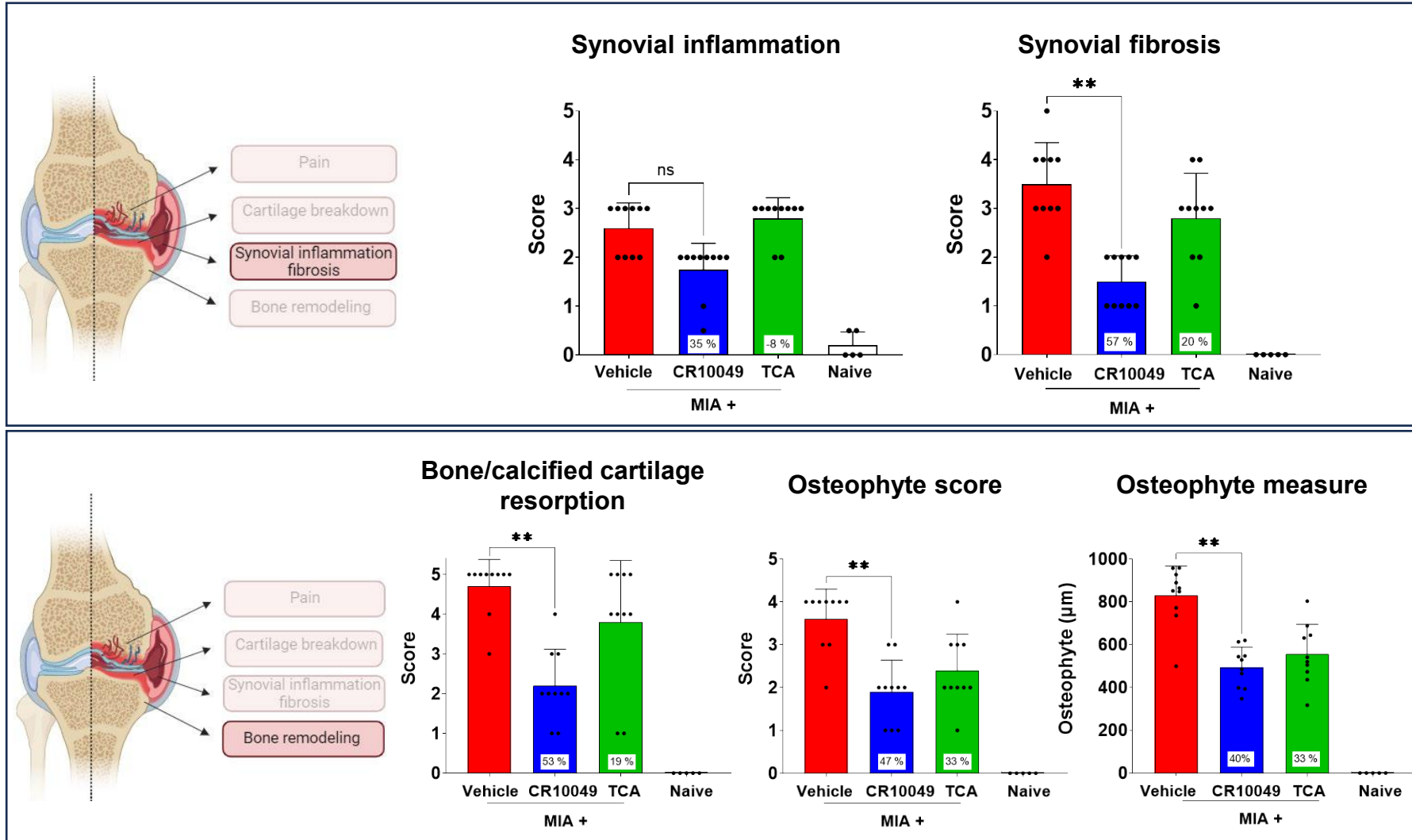
Non-evoked pain Weight Bearing (AUC D2-D28)



Mean ± SEM. One way ANOVA with Tukey's multiple comparisons test. * p < 0.05, *** p < 0.001



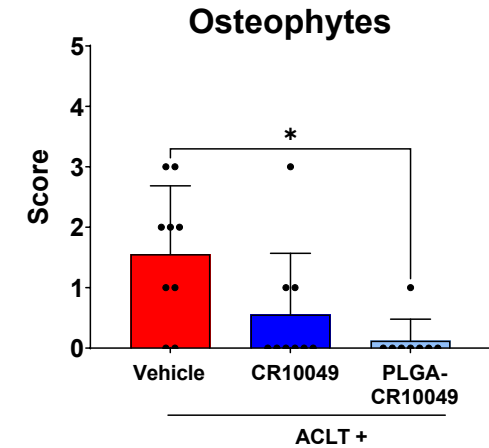
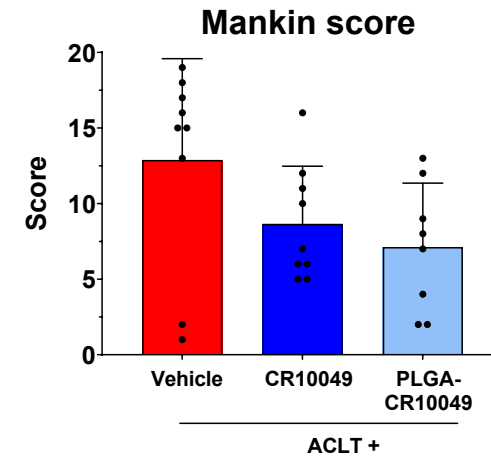
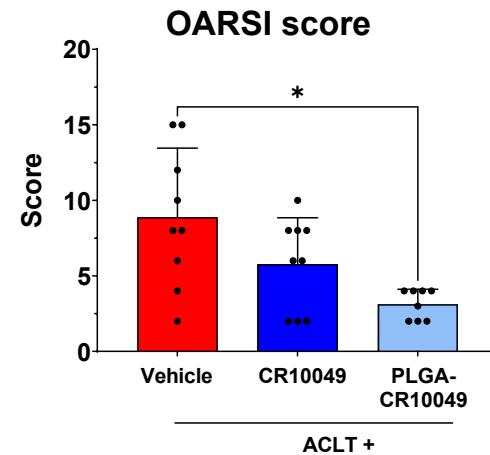
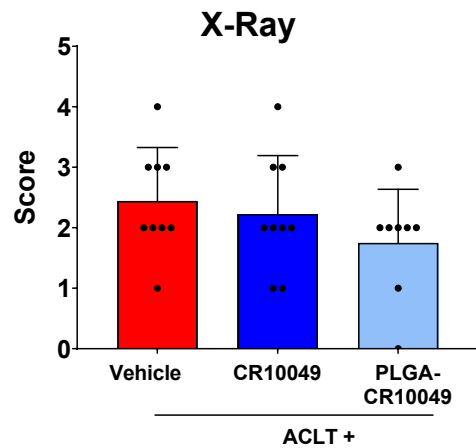
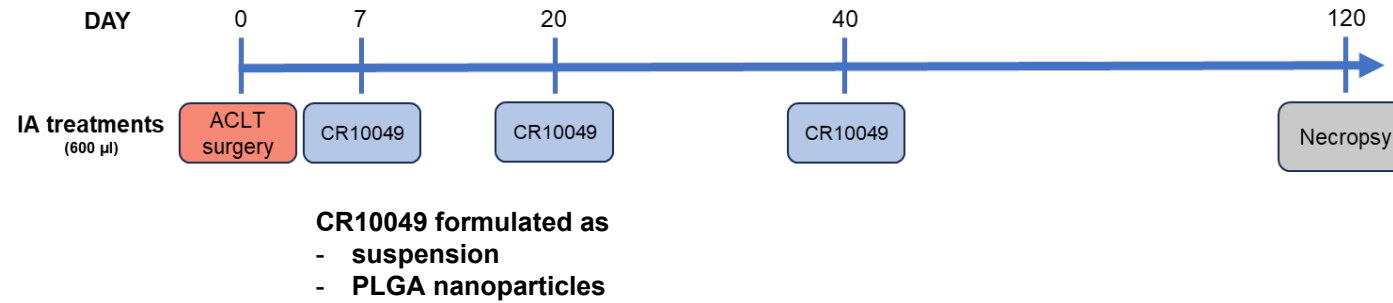
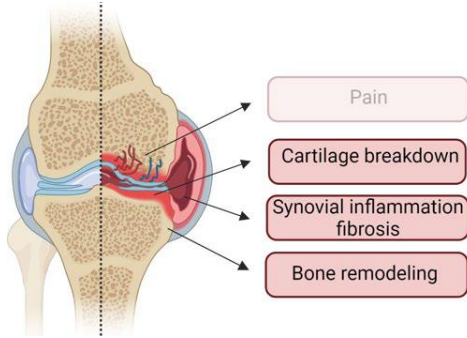
CR10049 improves the joint structure in the rat MIA model



Mean ± SD. One way ANOVA Kruskal–Wallis with Dunn's multiple comparisons test; ** p<0.005. % of decrease compared to vehicle within the bar graph



CR10049 improves the joint structure in the rabbit ACLT model



PLGA = Poly (lactic-co-glycolic acid)



CR10049 a symptom- and disease-modifying drug for inflammatory OA

- ▶ CR10049 is a small molecule targeting **multiple OA-involved kinases**
- ▶ CR10049 inhibits inflammation and degradation in *in vitro* OA models
- ▶ In a **small animal OA model** (rat MIA) CR10049 demonstrates:
 - ▶ similar potency to triamcinolone on two different **pain** assessments. Triamcinolone is active already at early stages, while CR10049 is active later, on established OA
 - ▶ a relevant effect on **histological parameters** of the joint i.e. synovial inflammation and fibrosis, bone erosion, osteophyte formation, cartilage calcification and resorption
- ▶ In a **large animal model** (rabbit ACLT) CR10049 shows:
 - ▶ a significant effect on **joint structure**, with the reduction of the OARSI score and an evident reduction in osteophyte formation

CR10049

a candidate multi-targeted therapy blocking multiple signalling pathways and simultaneously acting on all joint tissues

Thank you



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