

## OBJECTIVES

- Characterizing the antigen induced arthritis (AIA) rat model using magnetic resonance imaging (MRI) in a longitudinal study
- Validating the efficiency of MRI in assessing synovial and intra-articular oedema as well as bone erosion compared to  $\mu$ CT and conventional histological scoring
- Assessing the effects of an existing anti-rheumatoid arthritis (anti-RA) therapeutic dexamethasone (Dexa) using MRI

## RATIONALE

- With many new anti-RA treatments in preclinical development, cost and time effective assessment methods are needed
- RA assessment using MRI in small animal models of rheumatoid arthritis (RA) is not a commonly used method to date
- Infiltration and erosion histological scoring as well as  $\mu$ CT are the gold standard for measuring bone erosion and tissue inflammation and the most conventionally used in studying new animal models and new therapeutics
- These methods are limited in their ability to study several disease parameters simultaneously and can be labor intensive and expensive if a longitudinal study is pursued

## A Longitudinal Assessment of Disease Parameters in AIA Rat Model Using MRI

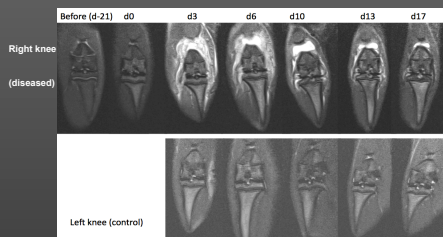


Figure 1

- Figure 1 depicts MR images of the right arthritic knee and the contralateral control acquired by T2 2D-STIR MR sequence illustrating synovial and intra-articular oedema (white signal) on days -21, 0, 3, 6, 10, 13 and 17

- Figure 2: assessment of synovial oedema, intra-articular oedema and erosion using MRI scores. While synovial oedema peaks on days 3 and 6 and then significantly declines, intra-articular oedema peaks on day 10 and slowly decreases. Erosion continues to increase over time up to day 10 and plateaus afterwards

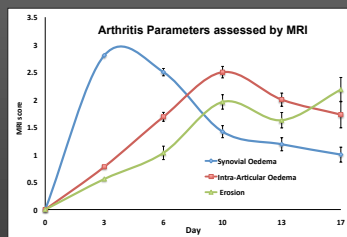
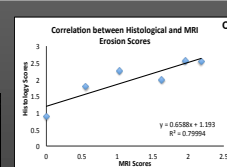
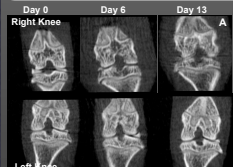


Figure 2

## Validating MRI Efficiency in Detecting Erosion and Inflammation Compared to Histology and $\mu$ CT



- Figure 3: Progress of erosion scored using MRI, histology and  $\mu$ CT shows a similar trend between the three methods (B). A good correlation was found between erosion scores obtained from MRI and histology ( $R^2=0.799$ ) (C) and between MRI and  $\mu$ CT ( $R^2=0.877$ ) (D).

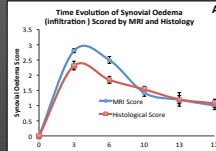
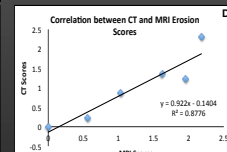
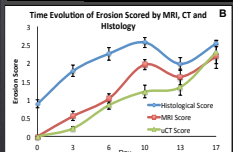


Figure 4



- Figure 4: Progress of inflammation scored using MRI and histology shows a highly similar trend between the two methods (A). A high correlation was found between inflammation scores obtained from MRI and histology ( $R^2=0.938$ ) (B).

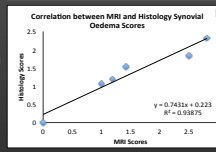


Figure 4

## ACKNOWLEDGEMENTS

- HUG Radiology, CIBM
- Work was funded by the EU Commission Research Committee (Grant Agreement number: NMP4-LA-2009-228929) as part of the NanoDIAra project

## METHODS

- AIA was induced in the right knee of 70 female Lewis rats as described previously by Oelzner et al. 2010 while the left served as an internal control
- Knees were scanned using MRI and  $\mu$ CT on days: 0, 3, 6, 10, 13, 17 post-induction using Siemens 3T clinical scanner with 4cm loop coil and Skyscan-1076 scanner respectively
- Four to ten animals were sacrificed at each time point, paraffin embedded and H&E stained; erosion and infiltration were performed as described previously (Koenders et al. 2005)
- T2 2D-STIR MR sequence was used for oedema (TR/TE 3700/20ms, resolution 0.156mm) and 3D-GRE (VIBE) MR sequence was used for bone erosion (TR/TE 14.3/5.9ms, resolution 0.31mm)
- Nine animals of this group were Dexa treated intraperitoneally (dose: 4, 4, 2mg/kg on day 2, 4, 8) scanned on days 3, 6, 10 and sacrificed on day 10
- On MR images, intra-articular oedema, synovial oedema and erosion were scored based on an blinded clinical scoring (1-3) and  $\mu$ CT images were also clinically scored for erosion in 6 different sites on the joint plateau and articular notch (1-3 scoring system) by blinded observer and the mean of those 6 sites was plotted

## Evaluating the Effect of Dexamethasone Using MRI Compared to Histology and $\mu$ CT

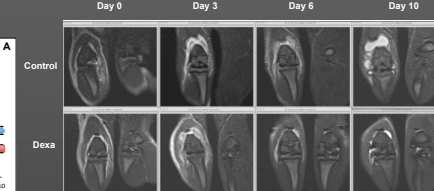
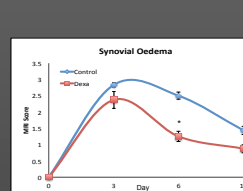
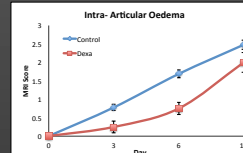


Figure 5

- Figure 5: MR images of Dexa treated and control animals showing significant decrease of inflammation with time



- Figure 6: Dexa treatment significantly decreased synovial inflammation on Day 6 (A) and lower effect on intra-articular oedema (B) scored on MRI. Erosion is significantly inhibited on day 10 (C) and this was confirmed by  $\mu$ CT scores (figure 7). \*  $P<0.05$

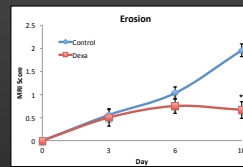


Figure 6

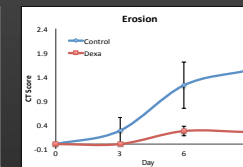


Figure 7

- On day 10 similar trends are seen between inflammation scores obtained by MRI and histology for Dexa treated and control groups (figure 8). \*  $P<0.05$

- Erosion scores of the two groups on day 10 measured by MRI, histology and  $\mu$ CT are significantly different (figure 9). \*  $P<0.05$

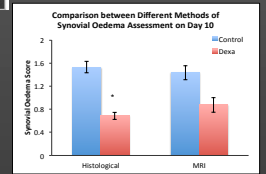


Figure 8

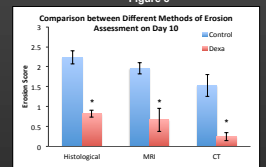


Figure 9

## DISCUSSION

- Using MRI multiple disease parameters (synovial oedema, intra-articular oedema and erosion) can be evaluated overtime and repeated measurements can be performed on the same animal
- Two of the disease parameters (synovial oedema and erosion) can only be measured using two different techniques (histology and  $\mu$ CT) while MRI offers one step solution for both parameters in addition to depicting a third parameter (intra-articular oedema) only seen on MRI
- Following the same animal overtime can decrease the number of animals needed to conduct a longitudinal study
- While histology and  $\mu$ CT possess higher resolution to measure erosion, we were able to demonstrate that MRI has sufficient sensitivity to characterize erosion in AIA model in presence and absence of anti-RA treatment
- MRI predicted with very high accuracy synovial inflammation even in absence of a contrast agent using the T2 2D-STIR sequence