

# Systemic Administration of Novel Hydroxyl Dendrimers to Target Inflammation in Arthritic Tissues

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## Background

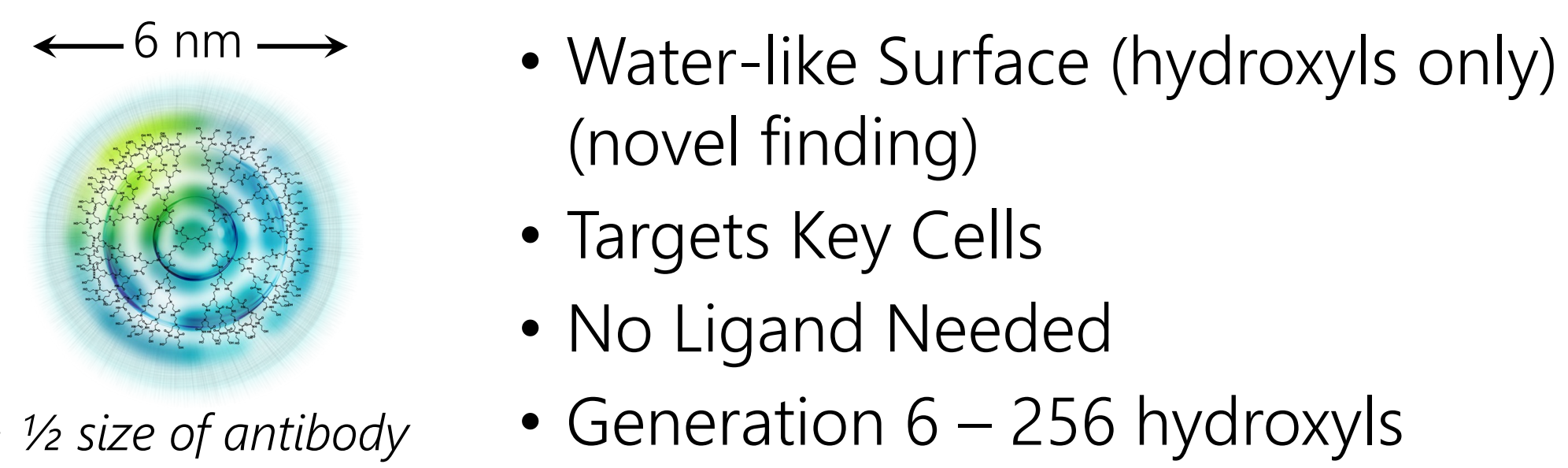
**Problem:** Treatment of autoimmune diseases such as arthritis involves systemic therapies (injectable or oral). Most of the drug administered to patients is not localized to the disease site causing off target toxicity or lack of optimal efficacy.

**Approach:** Selectively target drug only to disease site to improve therapeutic window and safety profile of the drug.

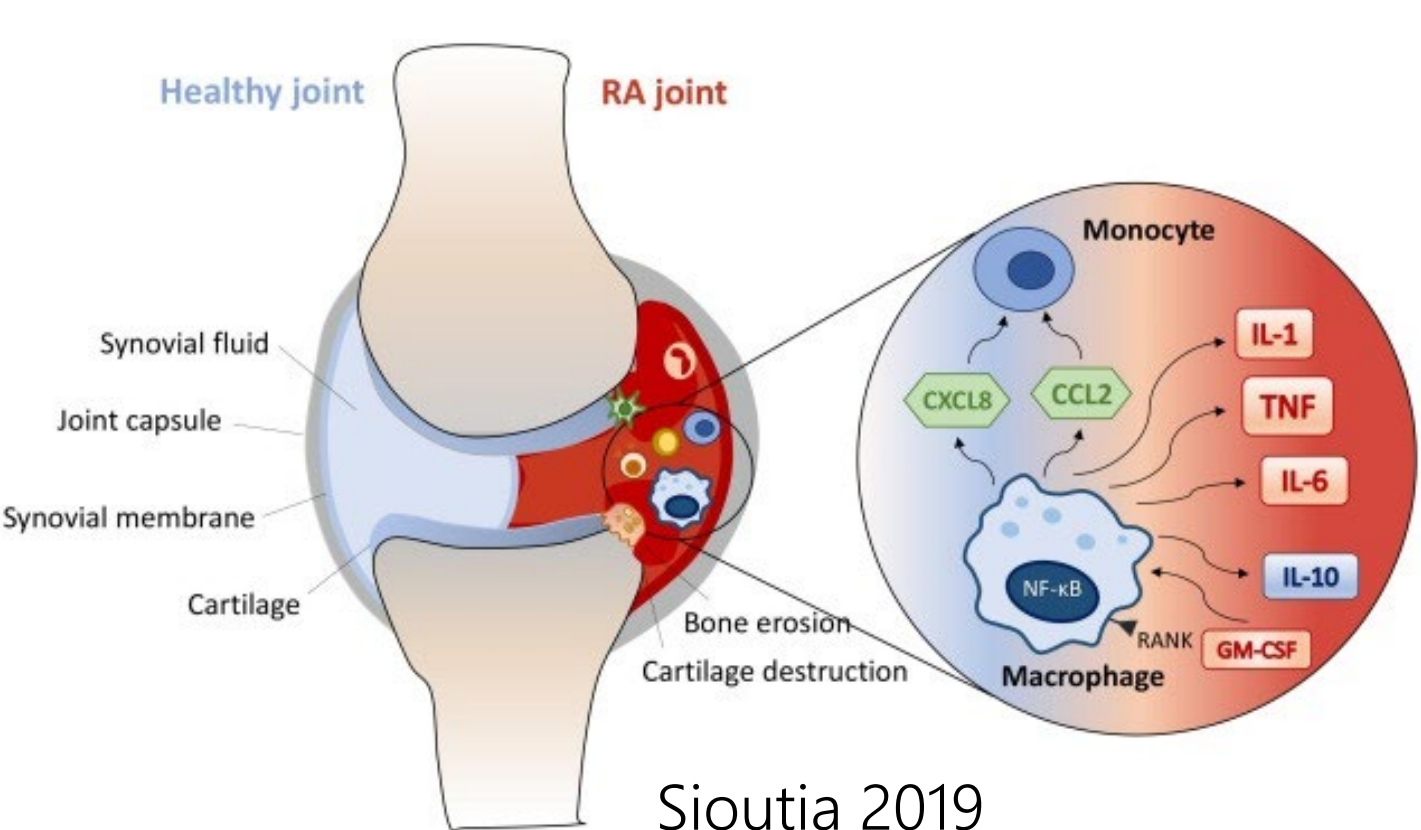
**Goal:** Demonstrate the potential for novel hydroxyl dendrimer (HD) technology to target joint inflammation and bone enabling targeted therapy.

## Hydroxyl Dendrimer (HD) Technology

- Only taken up by reactive inflammatory cells in diseased tissues (broad range of diseases)
- Targeted systemic therapy (Oral or injectable)
  - Crosses tissue barriers (BBB, retina, tumor)
  - Safe at high doses in animals & humans
  - Sustained duration of effect
- Low cost manufacturing, rapid discovery process (Over 65 HDTs to date)
- Broad license to technology from Johns Hopkins University (JHU) (>15 yrs, >\$30 M NIH, >30 JHU collaborators, >70 papers, 22 issued & 50 pending patents)

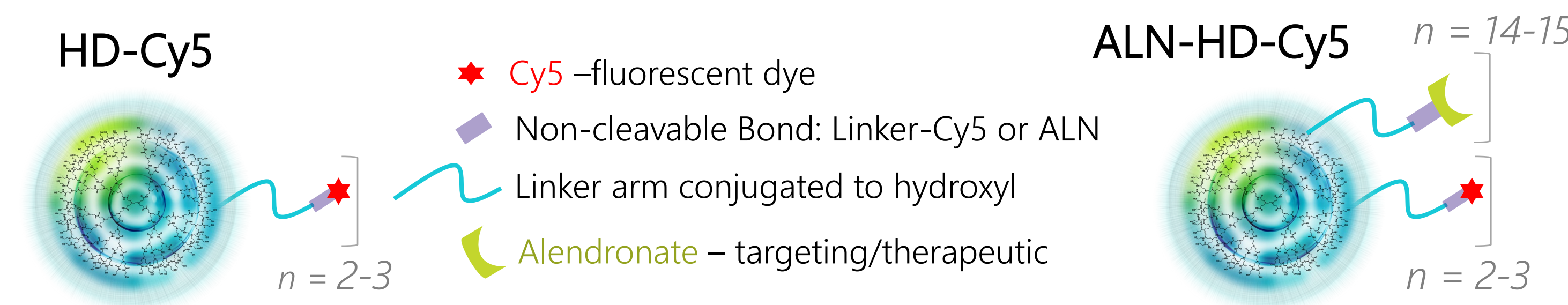


## Macrophage Involvement in Arthritis

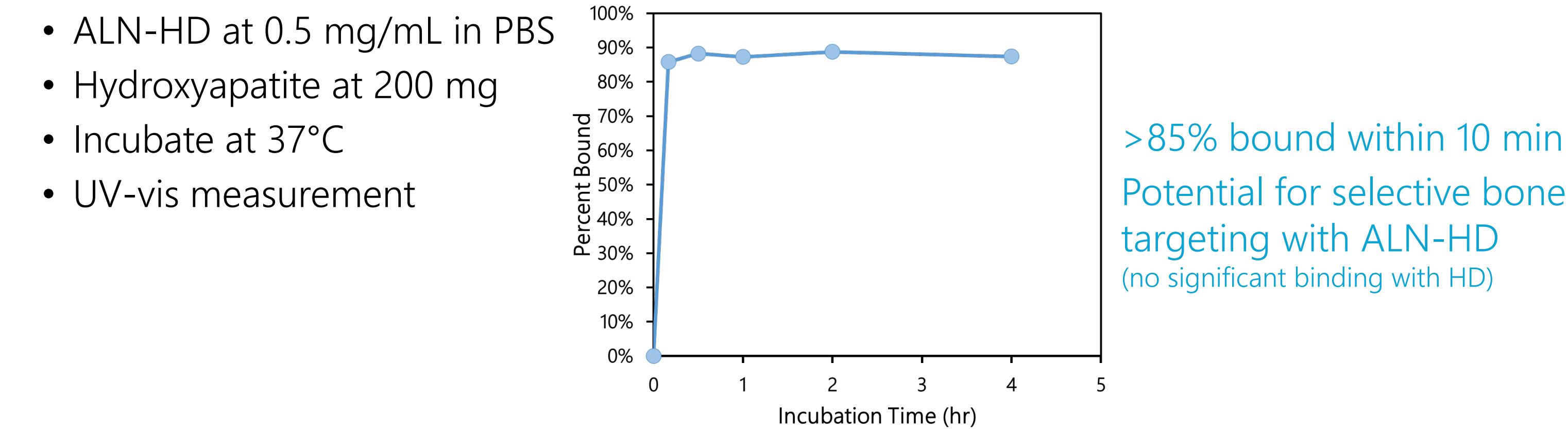


- Macrophage play key role in arthritis – chronic inflammation
- HDs selectively target reactive macrophage in 30+ models and six species including dogs & monkeys (Mishra 2011)
- Potential to further target to bone with alendronate

## HD Construct Design



## Hydroxyapatite Binding



## Collagen Induced Arthritis (CIA) Model

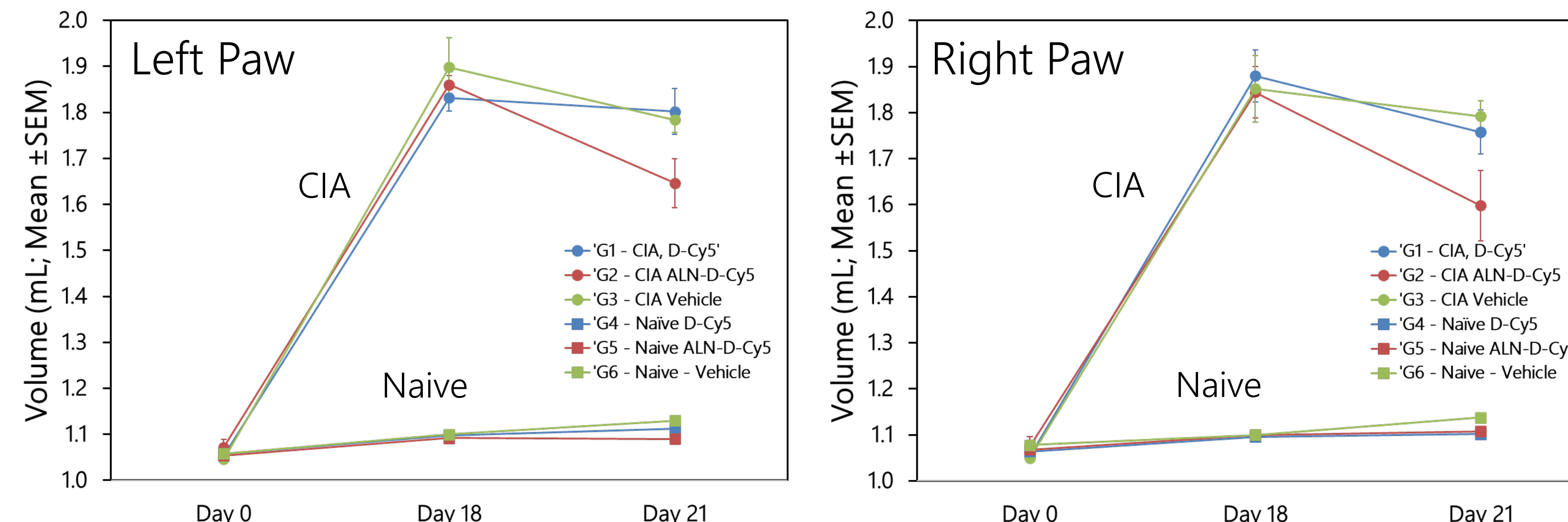
### Female Lewis Rats

5 per group; Single IV dose of 50 mg/kg HD-Cy5, ALN-HD-Cy5 or Vehicle on Day 19  
CIA induced on Day 1 & 7 with intradermal doses of type II bovine collagen in IFA

Groups	Treatment
1	CIA HD-Cy5
2	CIA ALN-HD-Cy5
3	CIA Vehicle
4	Naïve HD-Cy5
5	Naïve ALN-HD-Cy5
6	Naïve Vehicle

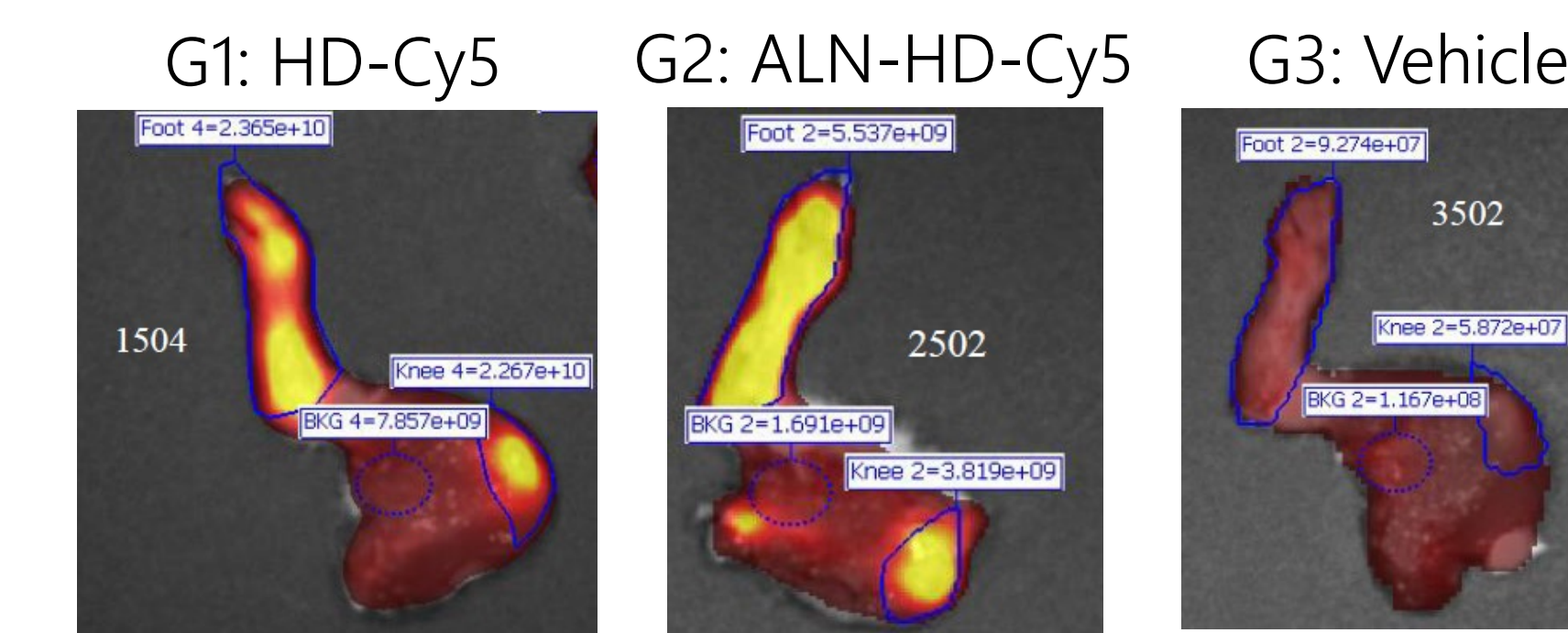
Paw volume Day 0, 18 (randomization), and 21; Sacrifice Day 21 (48 hr post-dose)  
Limbs, liver and kidneys collected for analyses; IVIS Spectrum CT analysis of left limbs, liver and kidneys  
Histological analysis of right limbs

### ALN-HD-Cy5 (single dose) ~10% Reduction in Paw Volume



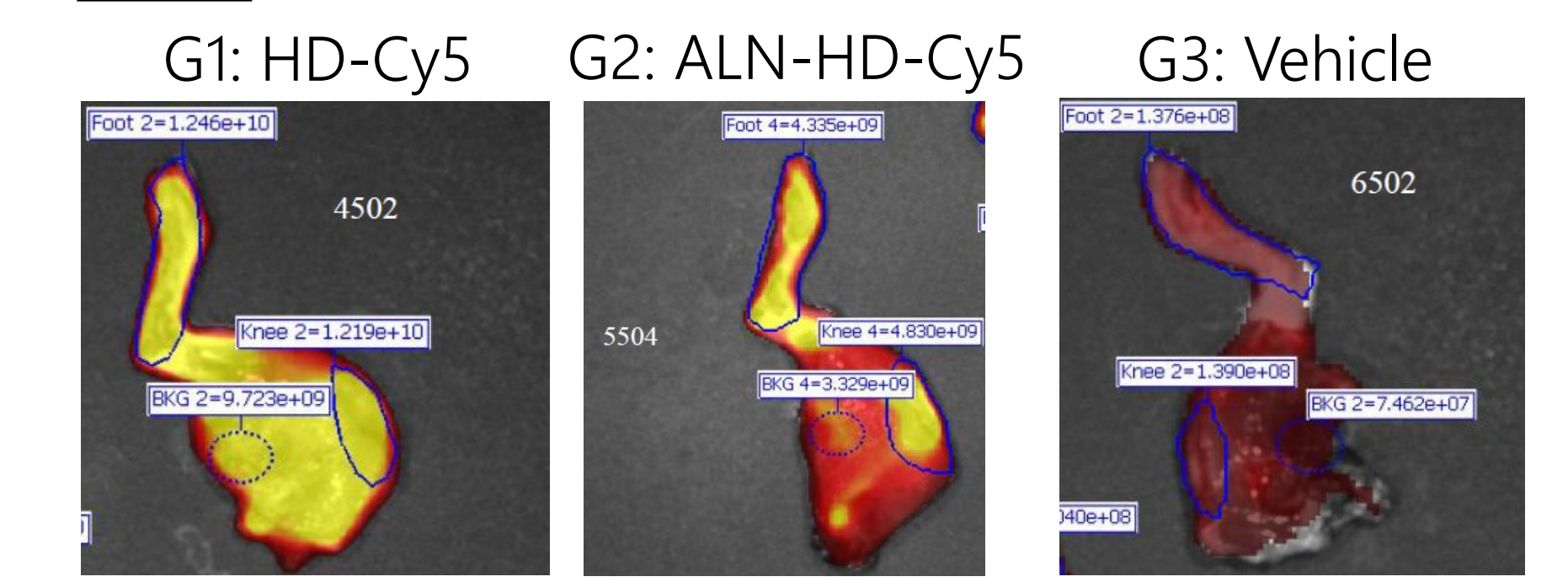
## IVIS Imaging of Hindlimbs

### CIA Rats

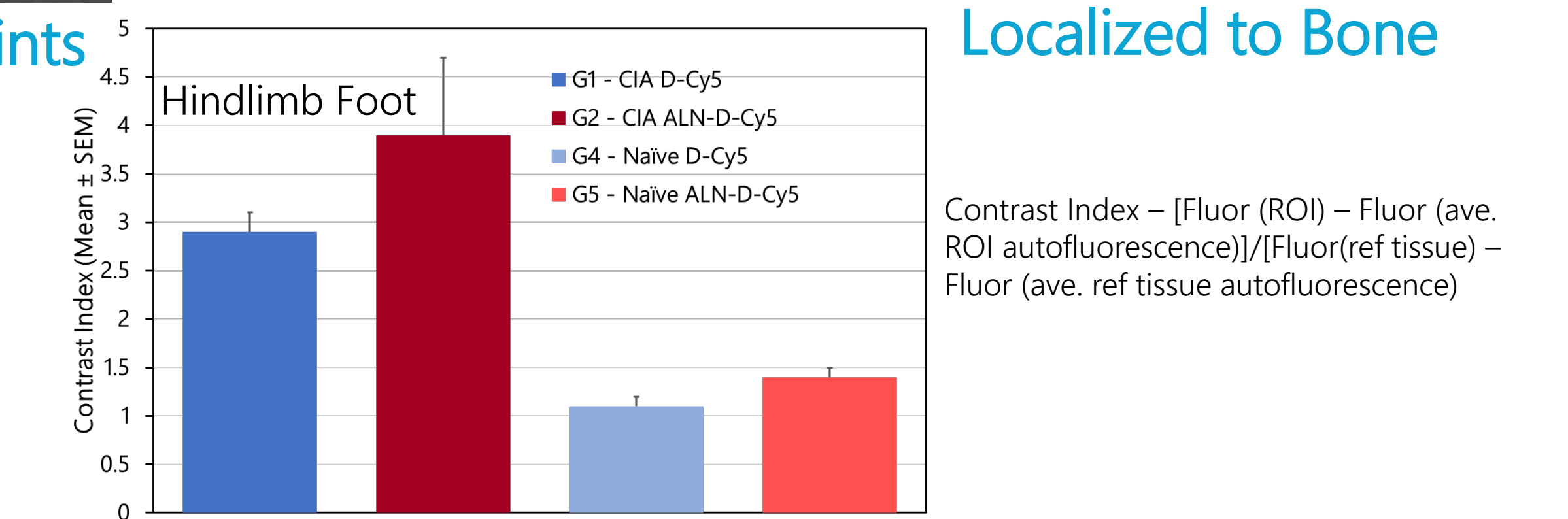


Localized to arthritic joints

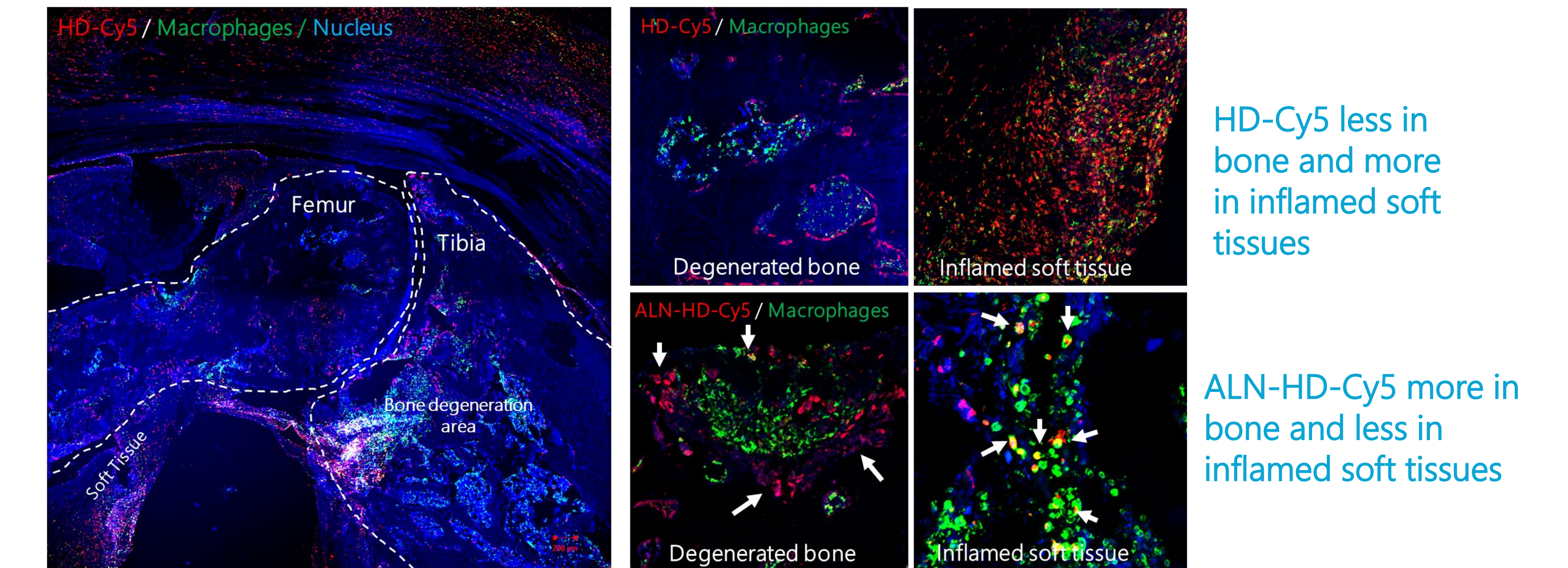
### Naive



Localized to Bone



## Histology of Hindlimbs



HD-Cy5 less in bone and more in inflamed soft tissues

ALN-HD-Cy5 more in bone and less in inflamed soft tissues

## Conclusions & Next Steps

- Systemically administered HDs localize to arthritic tissues demonstrating selective targeting to reactive macrophage (HD-Cy5) and bone (ALN-HD-Cy5)
- HDs have been demonstrated to only be taken up by reactive inflammatory cells in animal models
- HDs are excreted intact in the urine in humans (Phase 1 study) and animals
- HD therapeutics (HDTs) have been designed to deliver drugs specifically to arthritic tissues
- HDTs with a novel JAK1 inhibitor and anti-inflammatory agent have been prepared for future preclinical efficacy studies

## Acknowledgements & References

We thank Charles River Laboratories for the animal work and Siva Kambhampati for the histology work.  
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Mishra MK, Kotta K, Hali M, Wykes S, Gerard HC, Hudson AP, Whittum-Hudson JA, Kannan RM. PAMAM dendrimer-azithromycin conjugate nanodevices for the treatment of Chlamydia trachomatis infections. *Nanomedicine*. 2011 Dec;7(6):935-44. doi: 10.1016/j.nano.2011.04.008. Epub 2011 May 19.