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Involvement of Receptor Tropomyosin Kinase type A signaling in Rheumatoid Arthritis using TrkA/C knock-in mice: a multimodal approach

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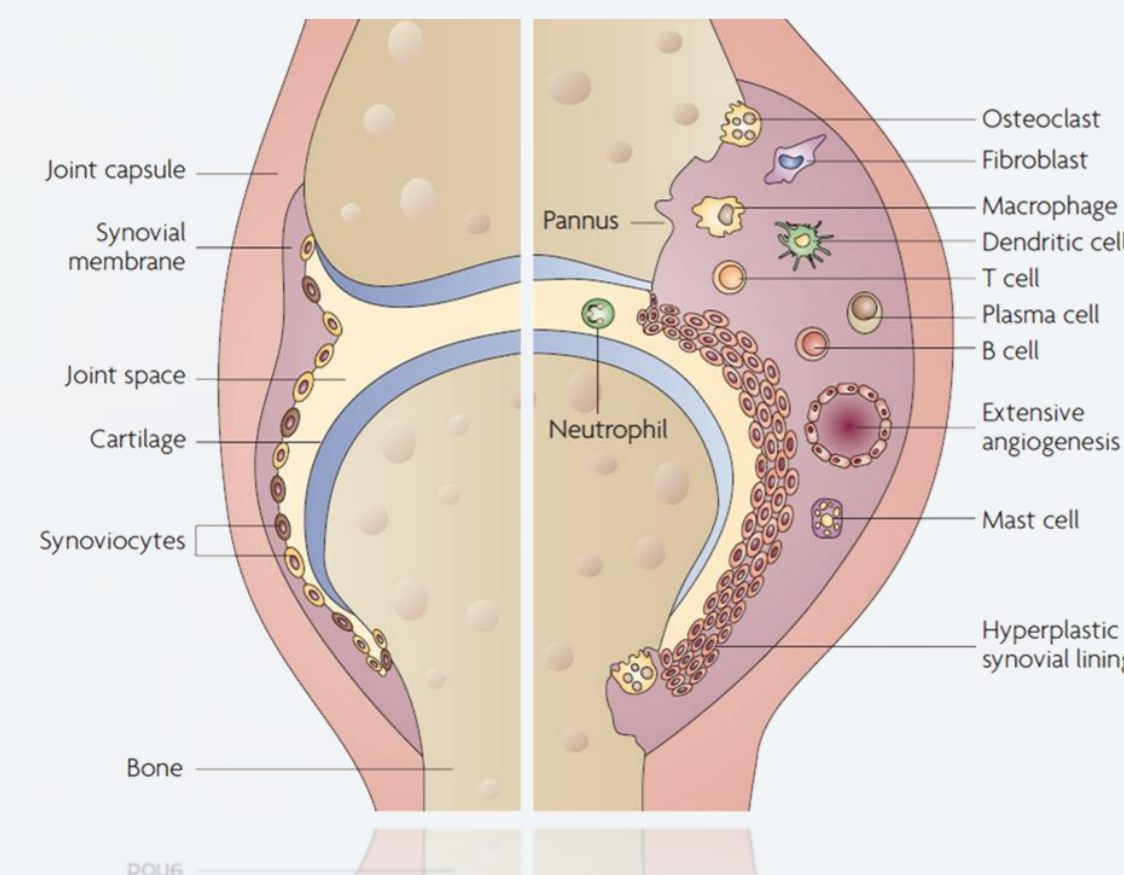
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Introduction

Rheumatoid Arthritis (RA) is an autoimmune disease characterized by articular inflammation, cartilage and bone alterations and is commonly associated with chronic pain which is often refractory to current analgesics.

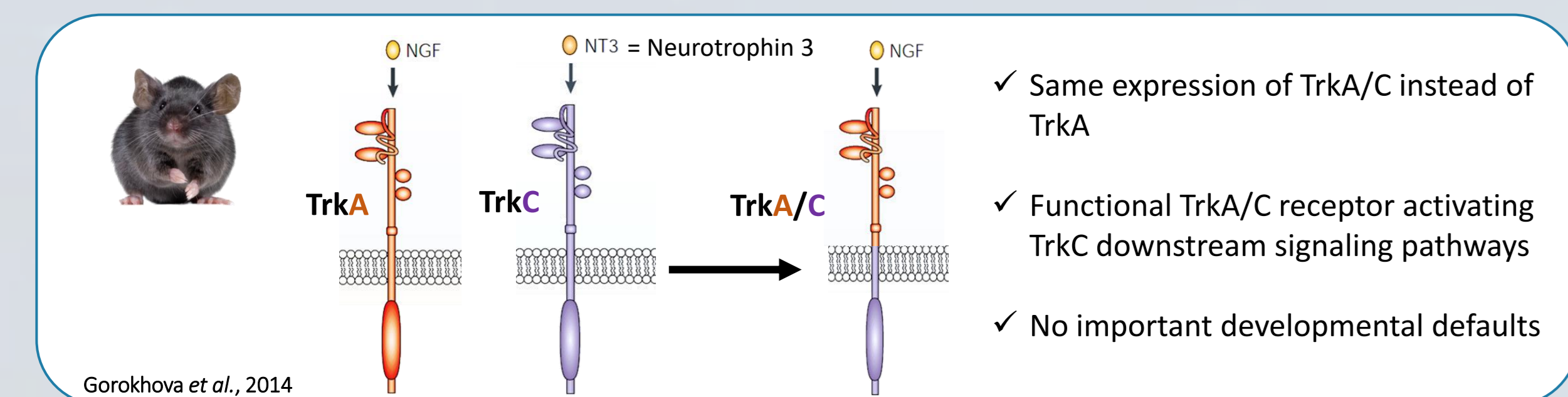
Targeting **Nerve Growth Factor (NGF)**, a neurotrophic factor, is considered a very promising treatment for RA. However, it could lead to serious adverse effects.

Our aim is to better understand the involvement of specific intracellular signaling pathways activated by NGF through its receptor, the tropomyosine kinase type A (TrkA), in the pathophysiology and associated pain symptoms of RA in order to discover more specific targets.

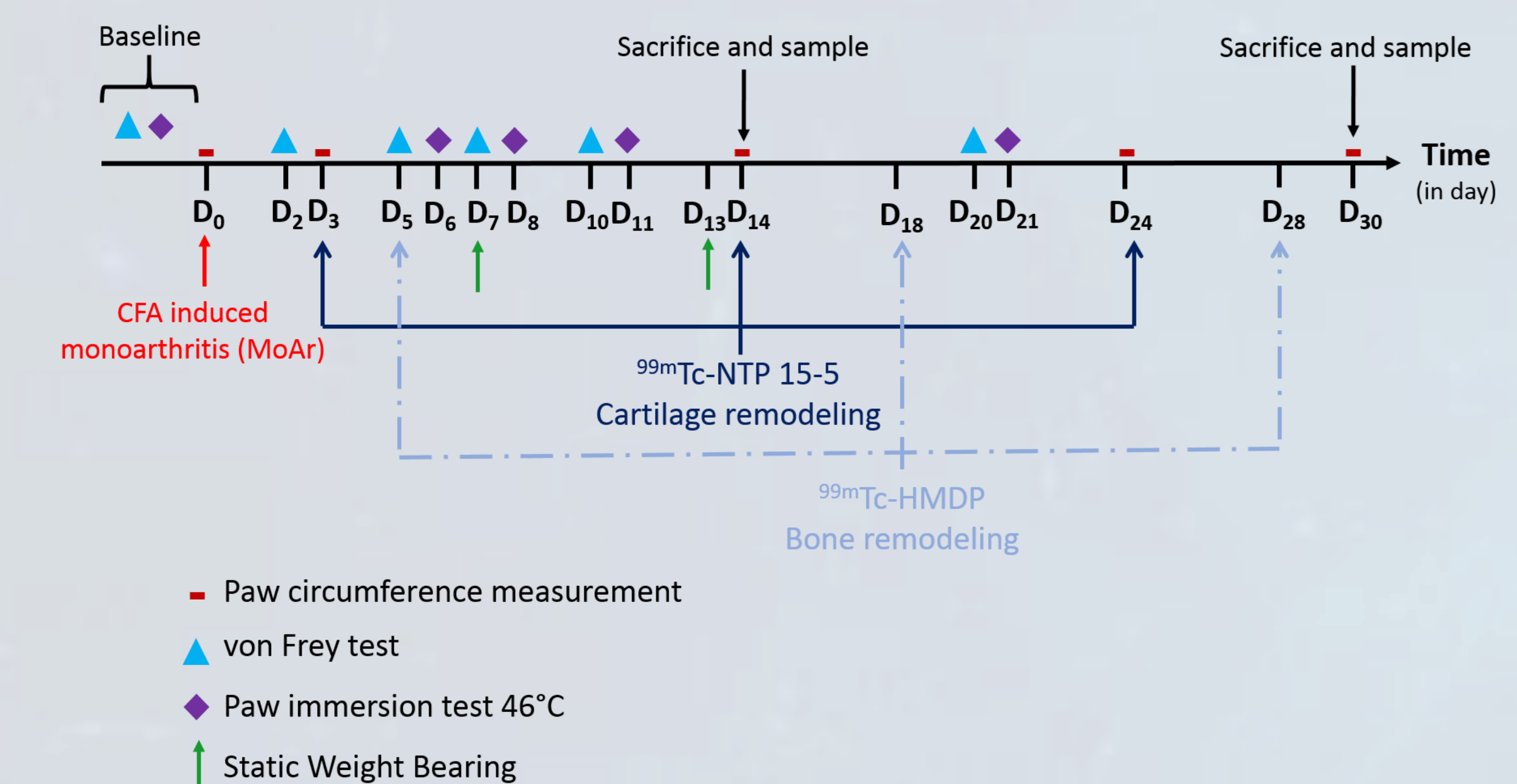


Material & Methods

Genetic model: TrkA/C chimeric knock-in mice



Study design:



Scintigraphic imaging: IMOST

- **Bone remodeling:** ^{99m}Tc-hydroxymethylene diphosphate (HMDP)
- **Cartilage remodeling:** ^{99m}Tc-N-(triethylammonium)-3-propyl-[15]ane-N5 (NTP 15-5)

Immunohistochemistry of the joint:

- Anti-cluster of differentiation 68 (CD68) => monocytes, macrophages, osteoclasts lineage
- Anti-calcitonin gene related peptide (CGRP) => peptidergic nerve fibers

Results

Figure 1: Similar edema development following arthritis induction in the different genotypes

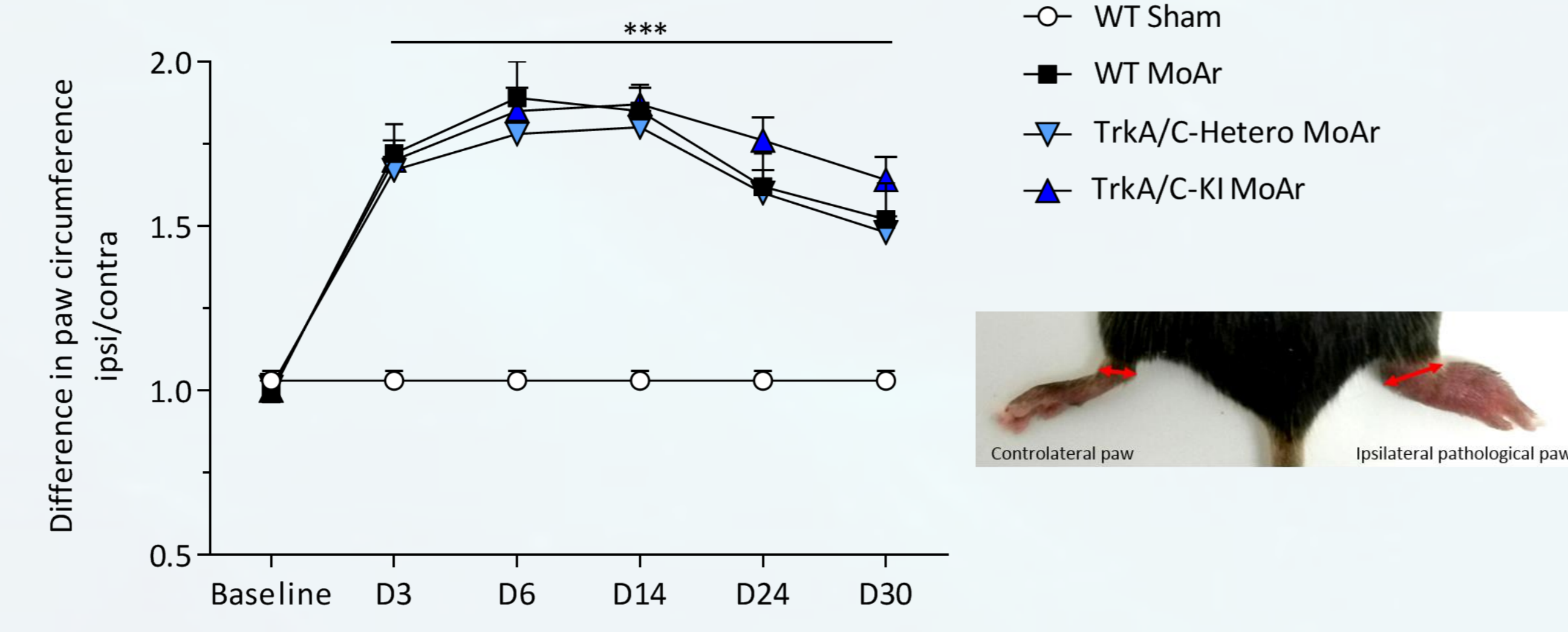


Figure 2: TrkA/C knock-in mice exhibit a specific loss of mechanical hypersensitivity (allodynia and weight bearing) compared to WT mice following arthritis

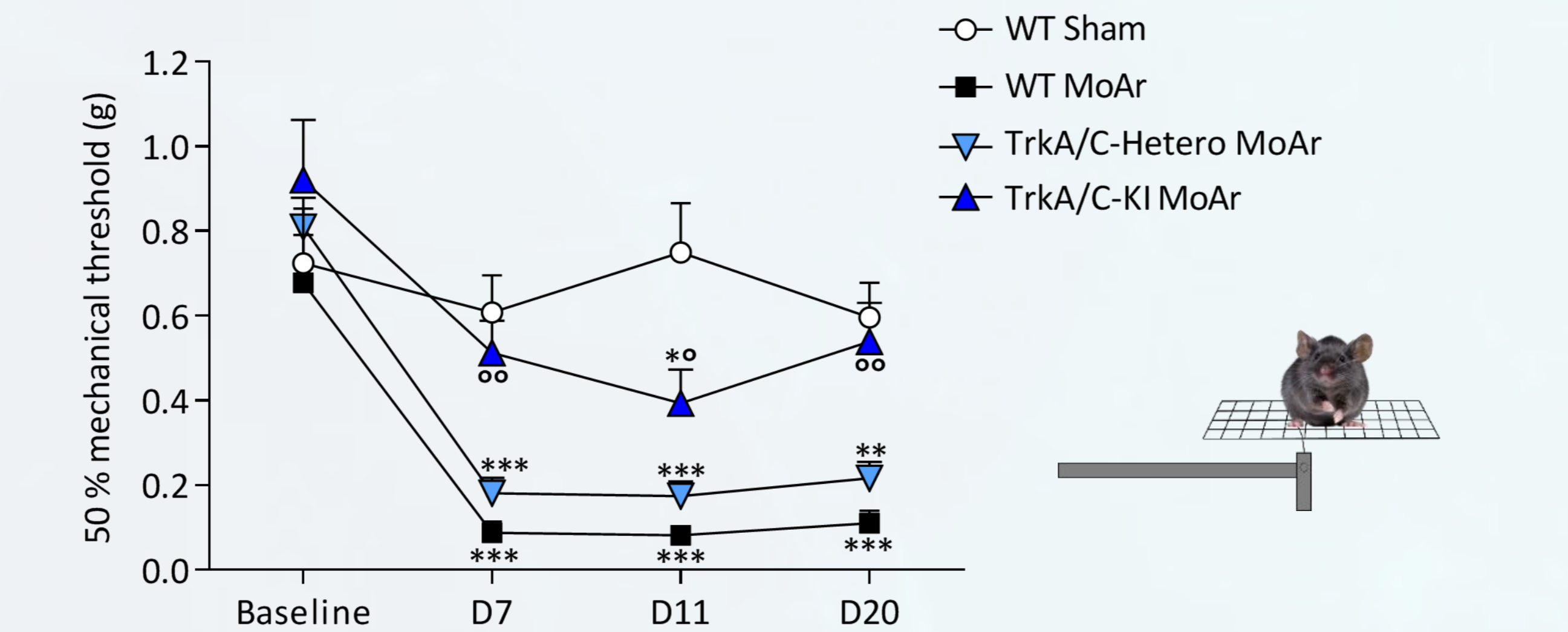


Figure 3: Increase in bone but not cartilage remodeling is reduced in TrkA/C knock-in mice compared to WT mice following arthritis

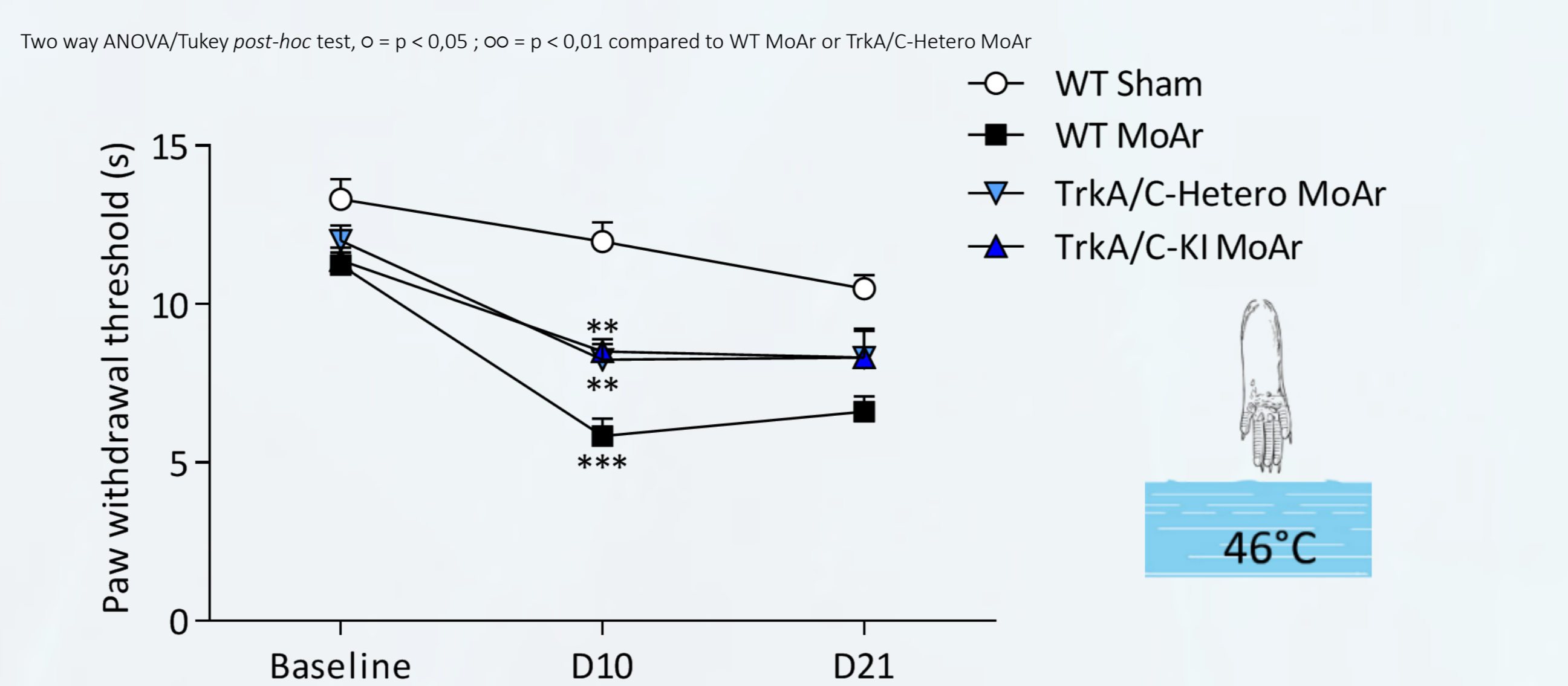
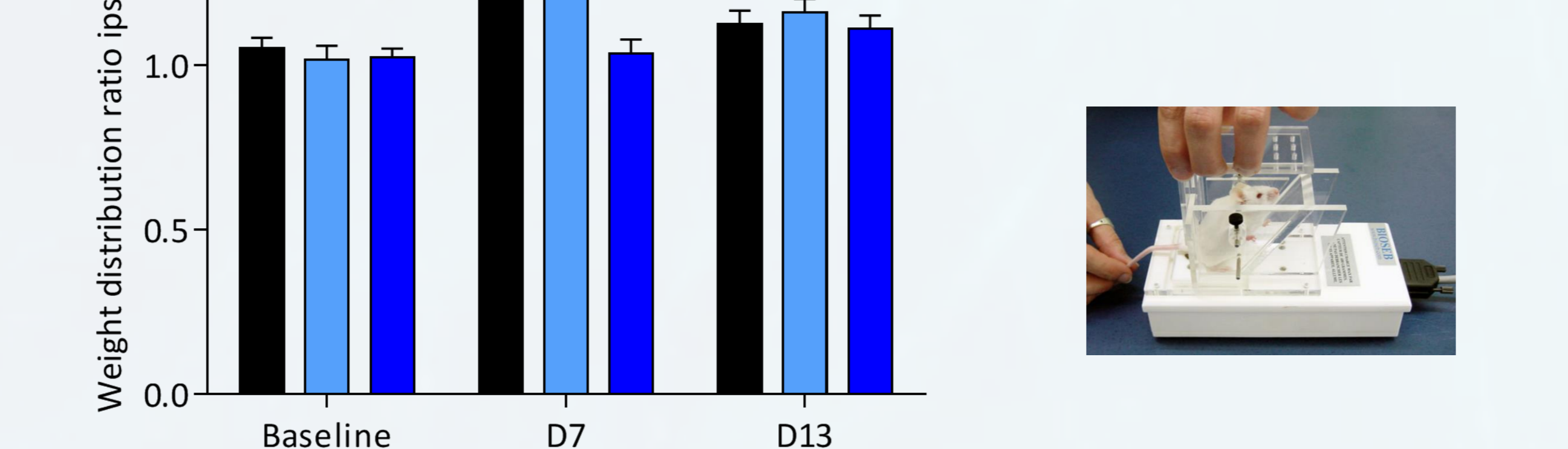


Figure 4: TrkA/C knock-in mice exhibit no increase of monocytes-macrophages-osteoclasts lineage in the pathological paw 14 and 30 days after arthritis

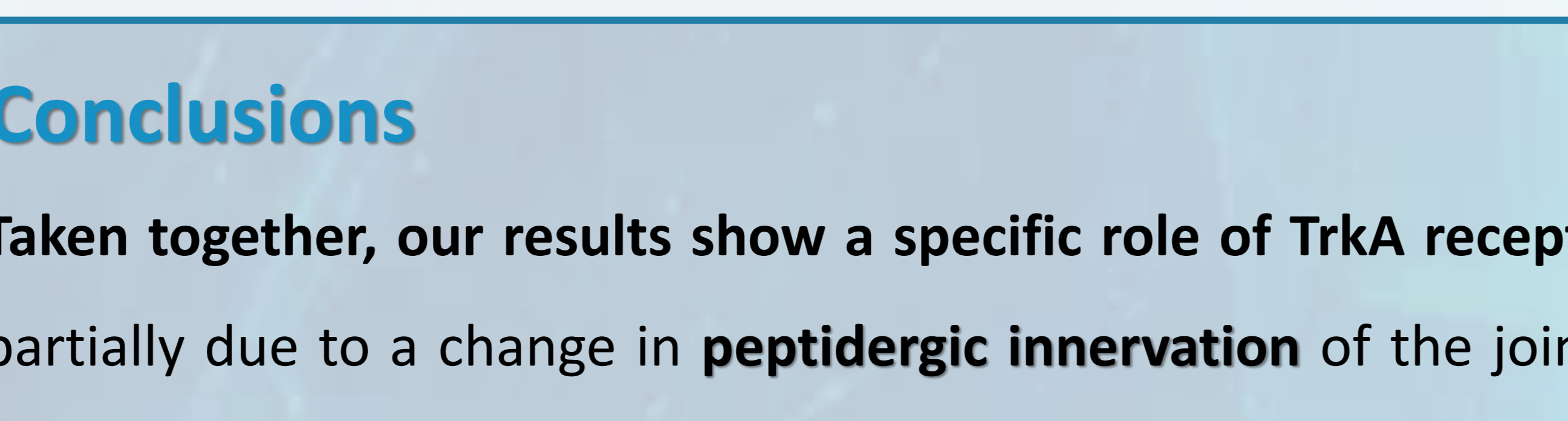


Figure 5: Lack of peripheral peptidergic fibers sprouting in TrkA/C knock-in mice compared to WT mice 14 days after arthritis

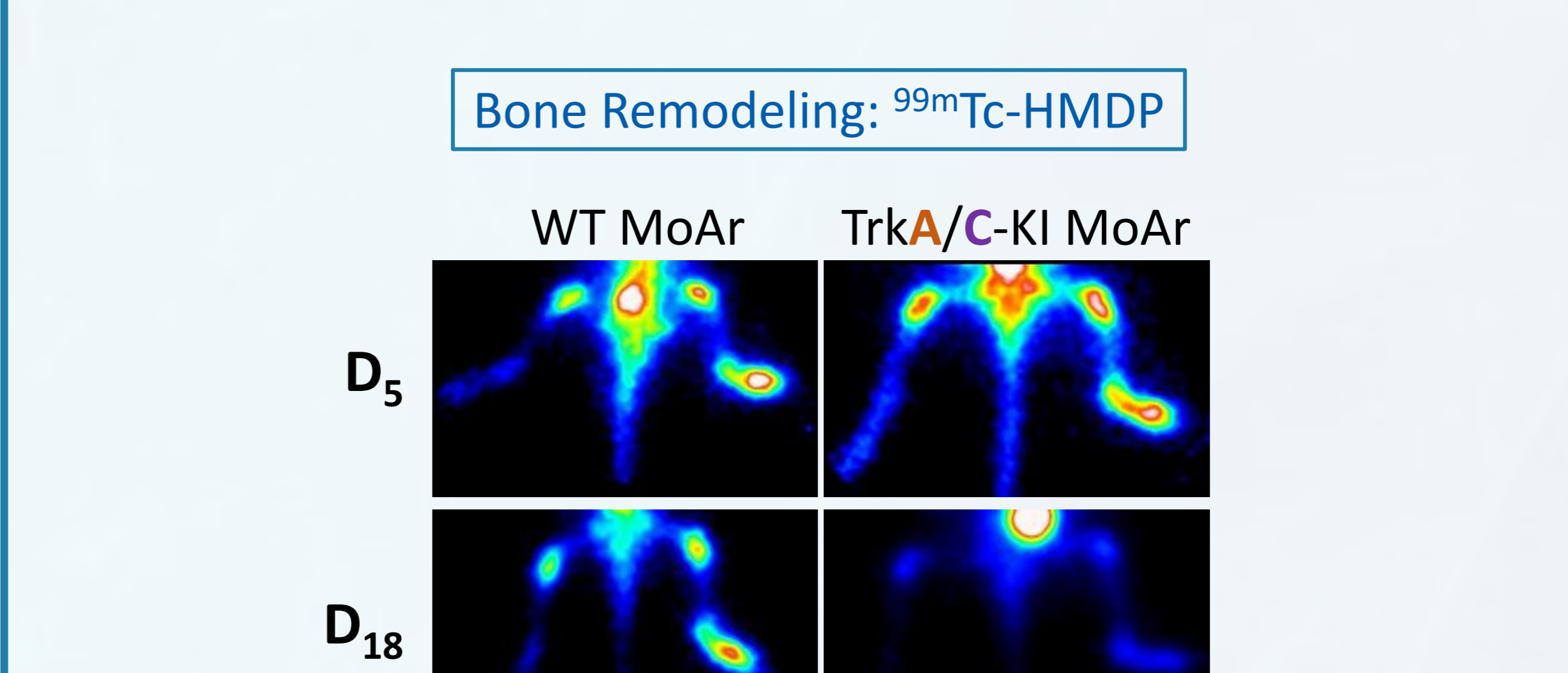


Figure 6: Lack of peripheral peptidergic fibers sprouting in TrkA/C knock-in mice compared to WT mice 14 days after arthritis

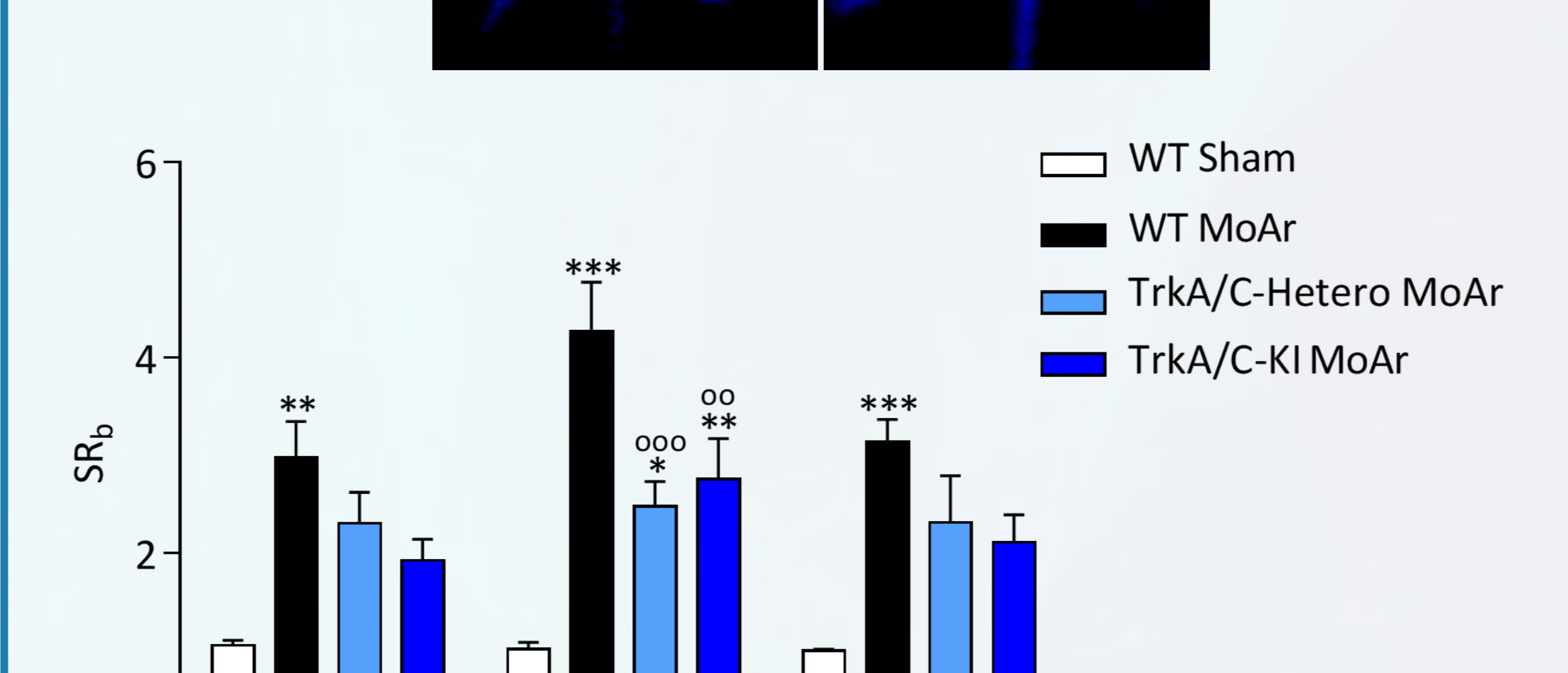


Figure 7: Lack of peripheral peptidergic fibers sprouting in TrkA/C knock-in mice compared to WT mice 14 days after arthritis

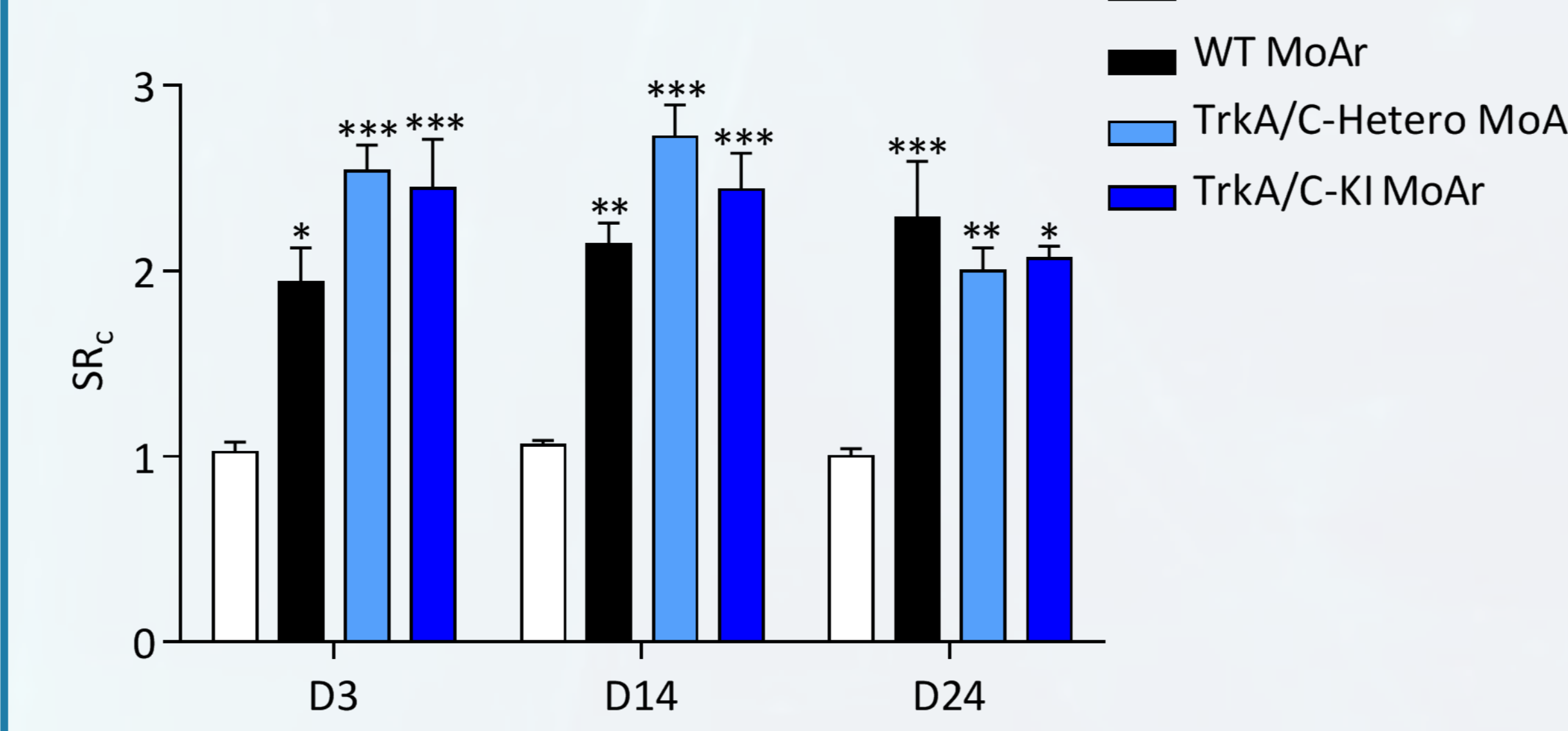
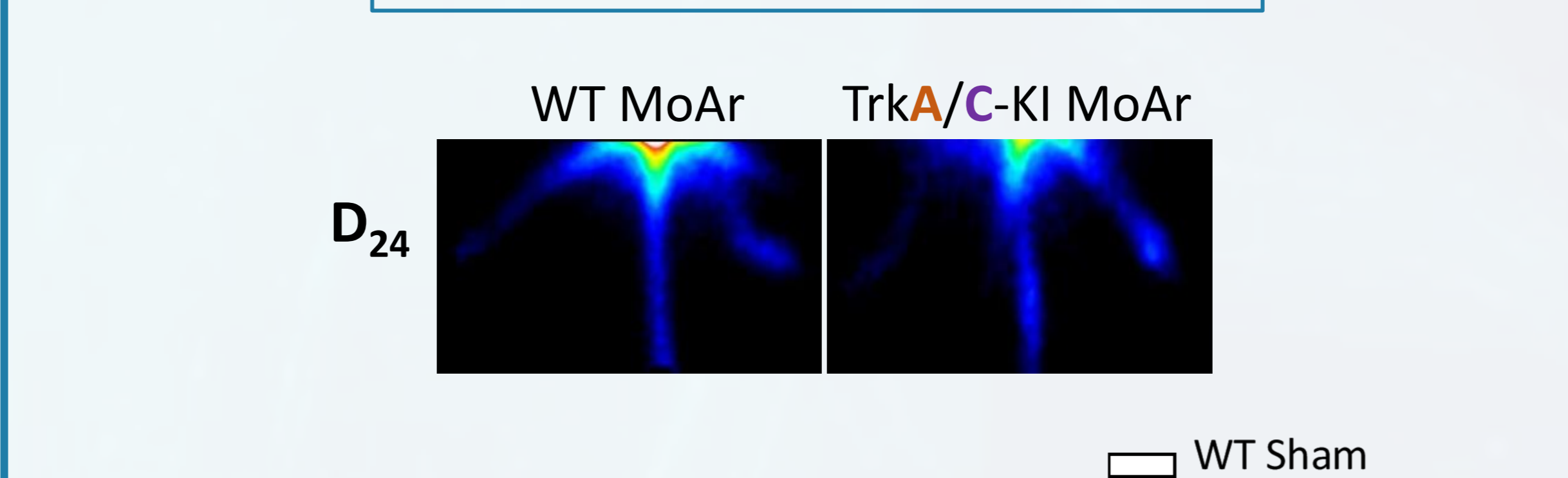
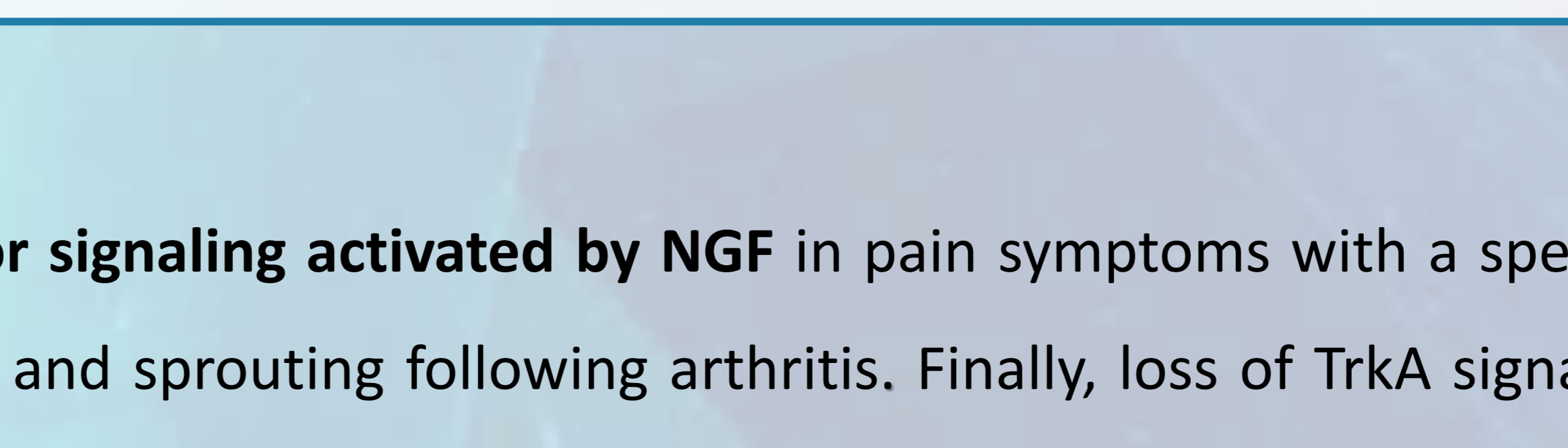


Figure 8: Lack of peripheral peptidergic fibers sprouting in TrkA/C knock-in mice compared to WT mice 14 days after arthritis



Conclusions

Taken together, our results show a specific role of TrkA receptor signaling activated by NGF in pain symptoms with a specific impact on **mechanical hypersensitivity** which could be partially due to a change in **peptidergic innervation** of the joint and sprouting following arthritis. Finally, loss of TrkA signaling pathways activation seems to impact **bone remodeling** following arthritis. We are currently investigating the TrkA signaling pathways involved in pain at the level of the dorsal root ganglia and in bone remodeling in osteoclast cultures.