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TrkA-NAM
– Next-generation non-opioid analgesics

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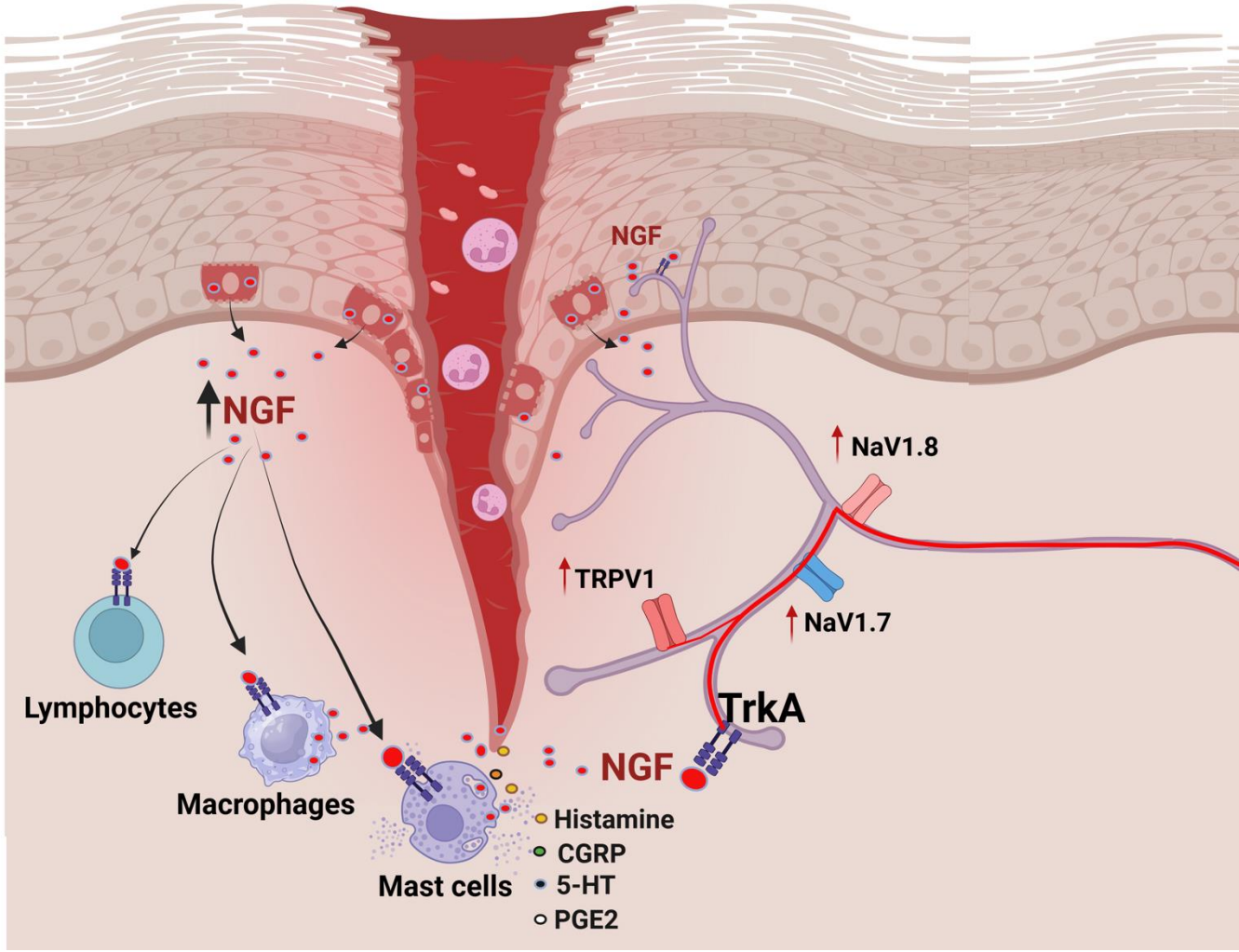
Background and target pathway: NGF/TrkA

Nerve growth factor (NGF) and its receptor TrkA plays an important role in pain sensation and is genetically and clinically validated in humans

- **1. NGF** is released at the site of an injury.
- **2**. **TrkA** is the receptor for NGF and it is located on both neuronal and non-neuronal cells.
- **3.** NGF leads to **inflammation** and **increased neuropathic and nociceptive pain.**
- **4**. Deletion of NGF or TrkA in humans leads to a painless phenotype
- **5. Anti-NGF antibodies** demonstrated a step change in efficacy in several late-stage clinical trials, but side effects limited the clinical usefulness



NGF and TrkA are involved in nociceptive and neuropathic pain signaling

Neurotrophins and mechanisms for targeting NGF/TrkA signaling

- **Neurotrophins binds to Trk-receptors and P75NTR**

NGF regulates multiple pathways such as neuronal survival in the CNS and pain sensation in the PNS.

Multiple attempts has been made to intervene with NGF-signalling:

- **Generation 1 (2000-2008)**

Non-selective Trk-inhibitors (Larotrectinib)

Inhibits TrkA, TrkB and TrkC

- **Generation 2 (2005-2015)**

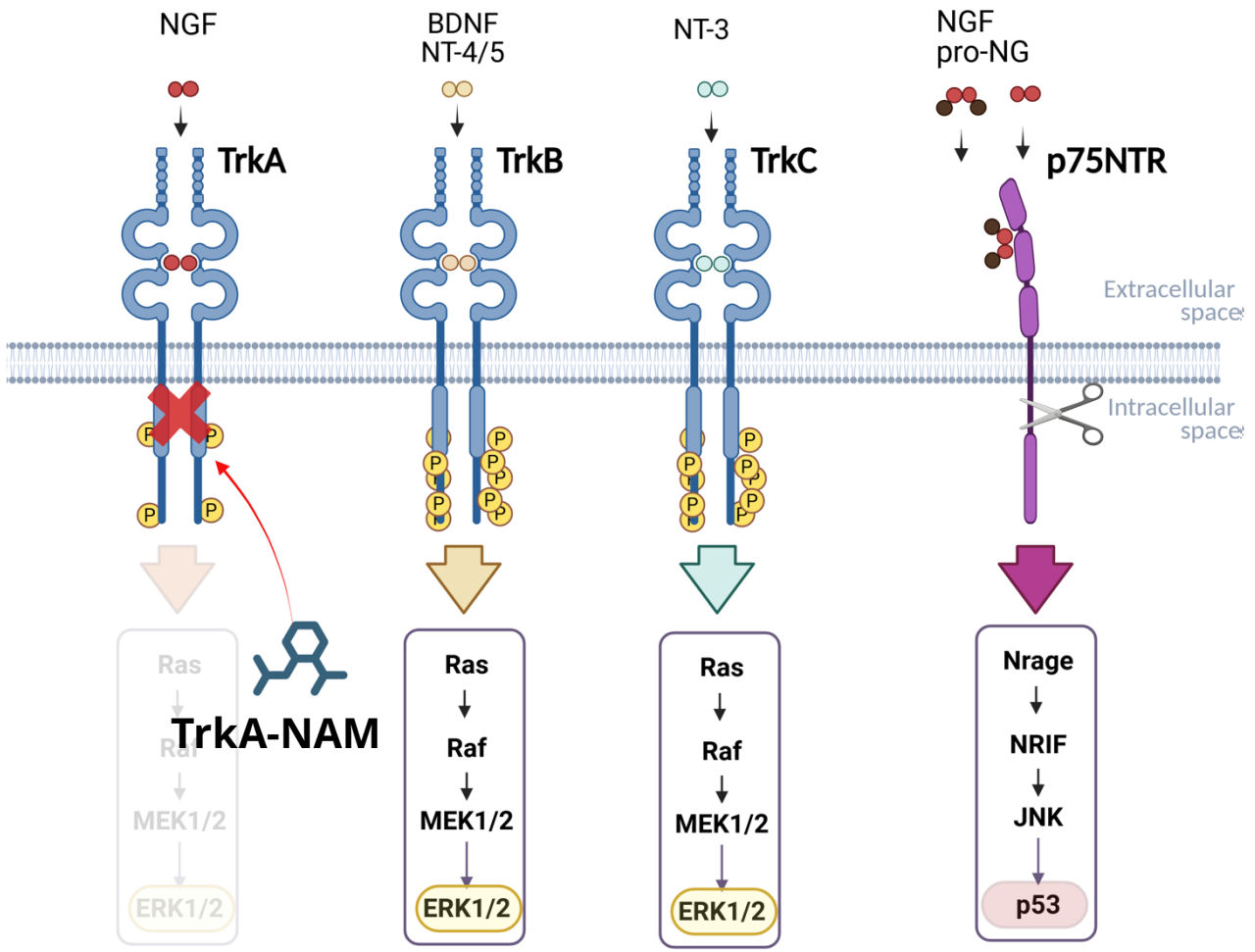
Anti-NGF monoclonal antibodies (Tanezumab)

Inhibits NGF and pro-NGF signalling via TrkA and p75NTR

- **Generation 3 (2015-2026)**

Negative allosteric modulators (NAM) of TrkA (ACD137 and AK1830).

Selective inhibition of TrkA



TrkA is a validated pathway for the treatment of pain
Allosteric modulators might give opportunity for biased signalling

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Anti-NGF mAbs are effective in different types of pain

Clinical validation by anti-NGF monoclonal antibodies

Company	Drug name	Phase	Indication
Pfizer/Lilly	Tanezumab PF-04383119 RN624	3 3 3 2 3 3 2 2	OA-pain Low back pain Post herpetic neuralgia Diabetic Peripheral Neuropathy Painful bladder Cancer pain Schwannomatosis Chronic pancreatitis
J&J	Fulranumab	3	OA-pain
Regeneron	Fasinumab SAR164877 REGN475	3 3 2 2 2	OA-pain Low back pain Sciatic pain Pancreatitis pain Vertebral fracture pain

Inhibition of NGF/TrkA signaling is an effective analgesic treatment in several pain indications
Anti-NGF mAbs suffer from some adverse events (RPOA) that was dose-limiting

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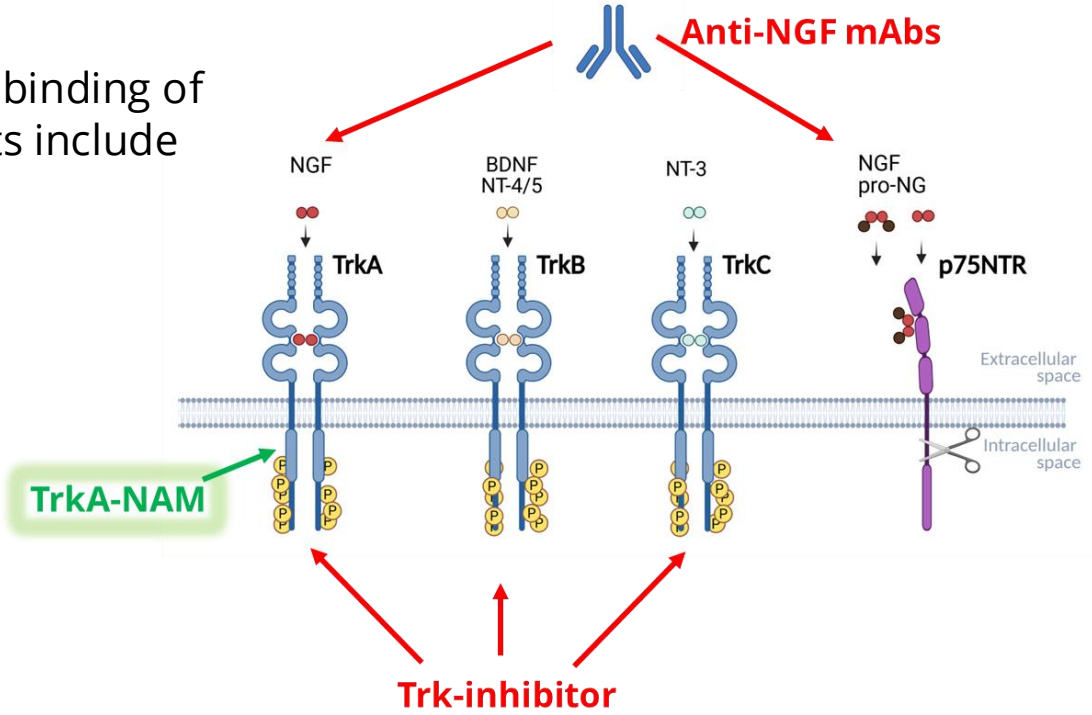
Safety: TrkA-NAM's, a safer mechanism than anti-NGF mAb's?

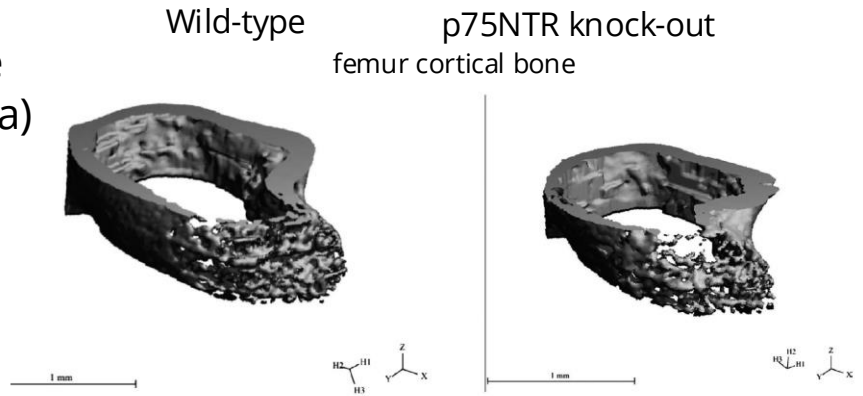
- The anti-NGF antibodies inhibits NGF signaling by blocking binding of NGF and pro-NGF to both TrkA and p75NTR. Adverse events include rapidly progressing OA (RPOA).

- Inhibition of p75NTR might be related to arthropathies:
  - p75NTR is involved in **bone mineralization** and bone homeostasis
  - p75NTR **limits inflammation** in the knee joint

- Trk-inhibitors like Larotrectinib inhibits TrkA, TrkB and TrkC. RPOA has so far not been reported by patients taking Trk-inhibitors.

- TrkA-NAMs have improved CNS safety profile compared to a Trk-inhibitor (Array Biopharma)



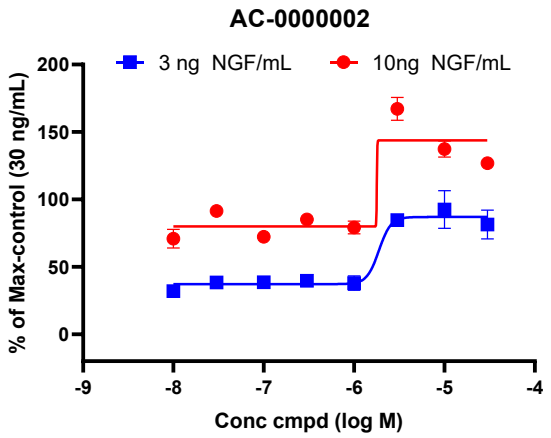


Zhao, Cell Proliferation, 2020

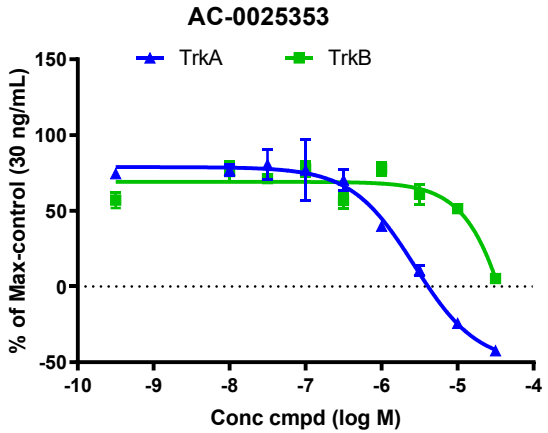
History: AlzeCure's TrkA-NAM program

- **2013**: A compound in series E was identified as a positive allosteric modulator of TrkA
- **2015**: The first TrkA-selective negative allosteric modulator (NAM) in series E was identified
- **2026**: Highly potent, in vivo active and novel TrkA-NAM compounds

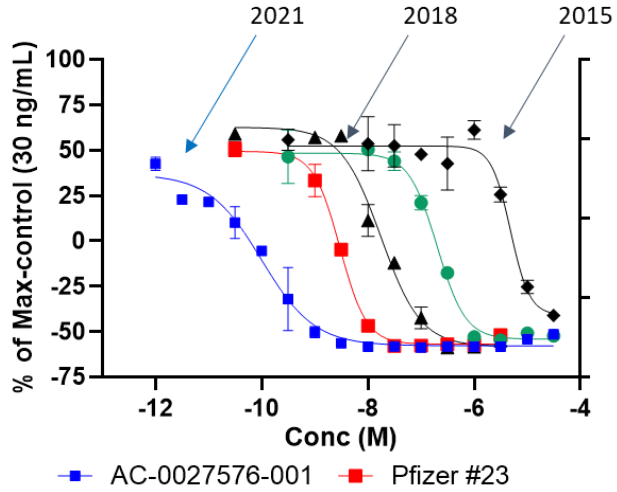
2013
First hit (PAM)



2015
First selective TrkA-NAM



2026
Potent and selective TrkA-NAM's



ACD137 selected as a clinical candidate in 2024

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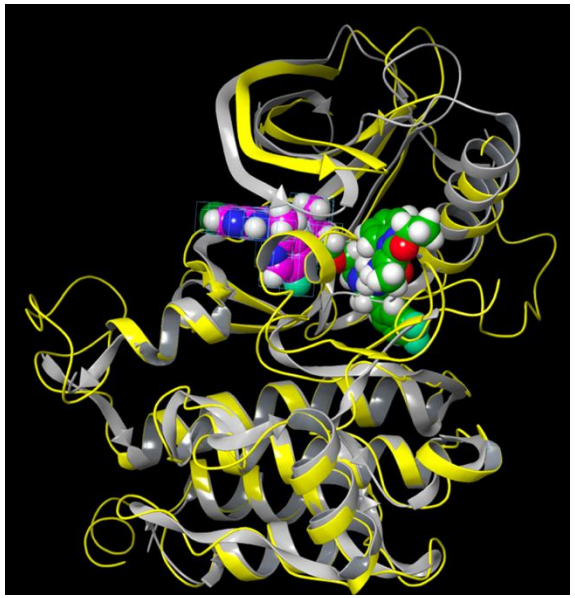
TrkA-NAM program in short

860 compounds has been synthesized and tested

- 3 cmpds with IC50 <10 pM
- 11 cmpds with IC50 <50 pM
- 11 cmpds with IC50 <100 pM
- 89 cmpds with IC50 <1 nM

- Selectivity vs TrkB/TrkC is generally very good, usually >10,000-fold selectivity
- Selectivity towards other receptor tyrosine kinases is very high
- X-ray structure has been solved and binding site identified
- Generally low BBB-permeability leading to low brain exposure
- Several TrkA-NAM molecules including ACD137 have a significant analgesic and anti-inflammatory effect in different in vivo models of pain



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Selectivity for TrkA over TrkB and TrkC

Selectivity towards other Trk-receptors is important, especially with respect to safety.

AlzeCure's TrkA-NAM compounds are very selective for TrkA over TrkB and TrkC compared to other TrkA-NAMs, Trk-inhibitors or anti-NGF antibodies.

Compound	MoA	TrkA IC_{50} (nM)	TrkB IC_{50} (nM)	TrkC IC_{50} (nM)
ACD137	TrkA-NAM	1.2 ± 0.15	20,780± 3,530	21,170 ± 6050
Array compound #1 (Ashai Kasei AK1830)	TrkA-NAM	0.20 ± 0.15	524 ± 148	312 ± 8.8
Pfizer compound #23	TrkA-NAM	0.93 ± 0.35	2030 ± 1034	86± 11.6
Zoetis compound #1	TrkA-NAM	0.46 ± 0.21	27.2 ± 13.8	6.9 ± 2.7
Larotrectinib	Trk-inhibitor	9.6 ± 0.87	9.2 ± 2.0	6.0 ± 2.4
GW441756	Trk-inhibitor	374 ± 66	322 ± 71	72.8
Tanezumab (K_d)*	Anti-NGF mAb	0.001	Not reported	1.0

* Results taken from patents or scientific literature

ACD137 is the most selective molecule investigated
>17,000-fold selective for TrkA over TrkB and TrkC

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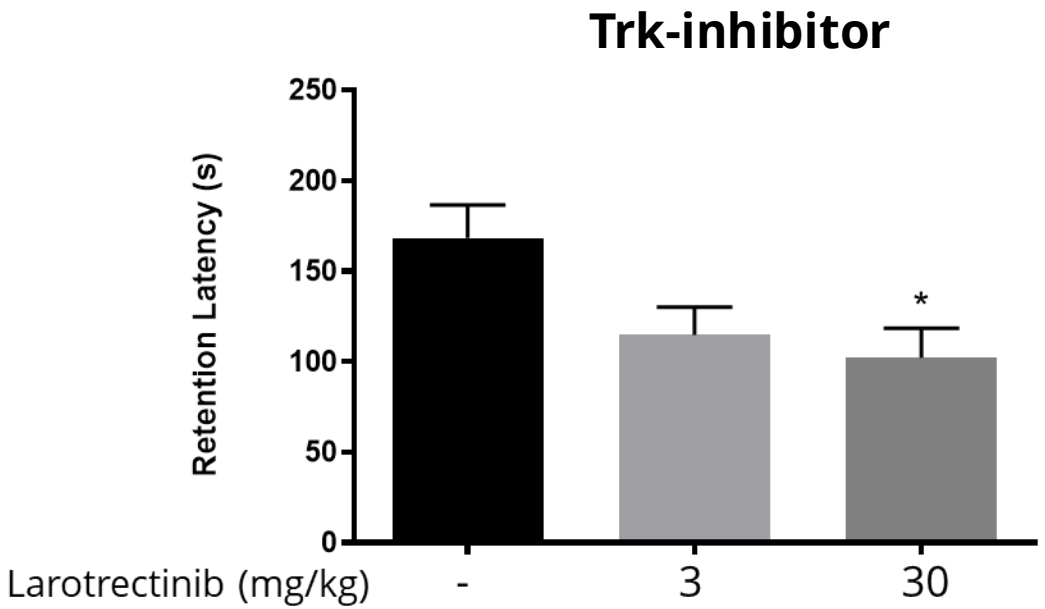
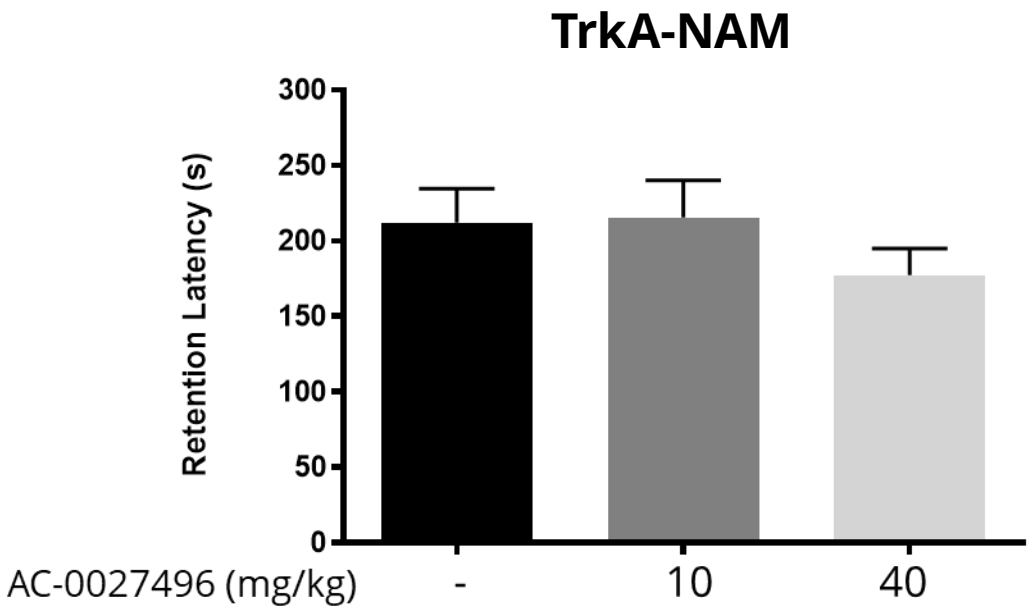
TrkA-NAM does not impair cognition like a Trk-inhibitor does

- Naïve mice were subjected to a memory test to address their cognitive function after a single administration of compound
- Compounds were administered by s.c. injection on day 1 before training session. No compound was administered on day 2, when the memory test was performed





A TrkA-NAM molecule (AC-0027496) does not impair cognitive function in mice

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TrkA-NAM / ACD137

- Selective peripheral targeting of TrkA is a promising pathway for pain relief
- AlzeCure has identified highly potent negative allosteric modulator of TrkA
- ACD137 is one the most selective compound for TrkA over TrkB and TrkC that has been tested
- Selectivity for TrkA over other neurotrophin receptors is probably a key feature to obtain a safe compound

- What about efficacy in different models of pain in animals?

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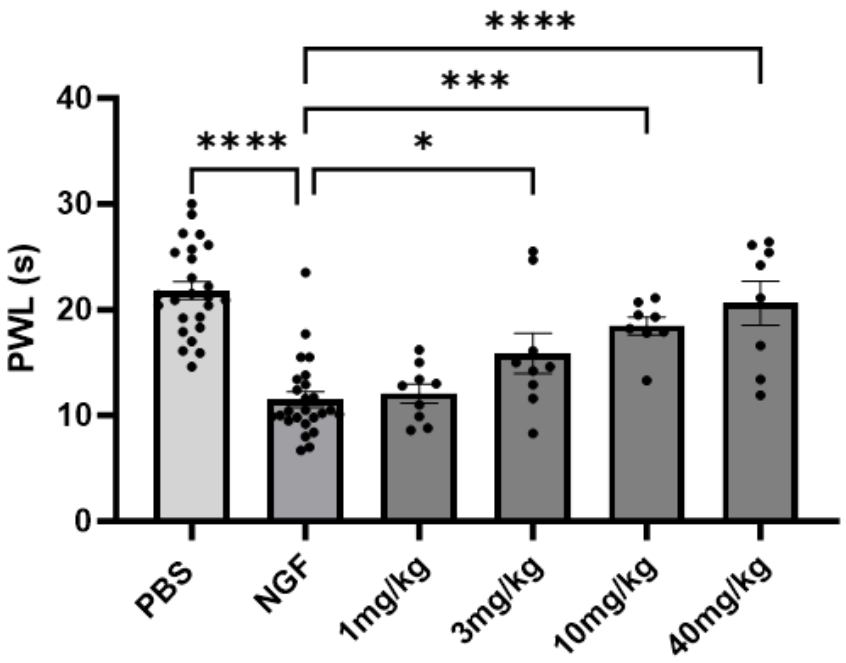
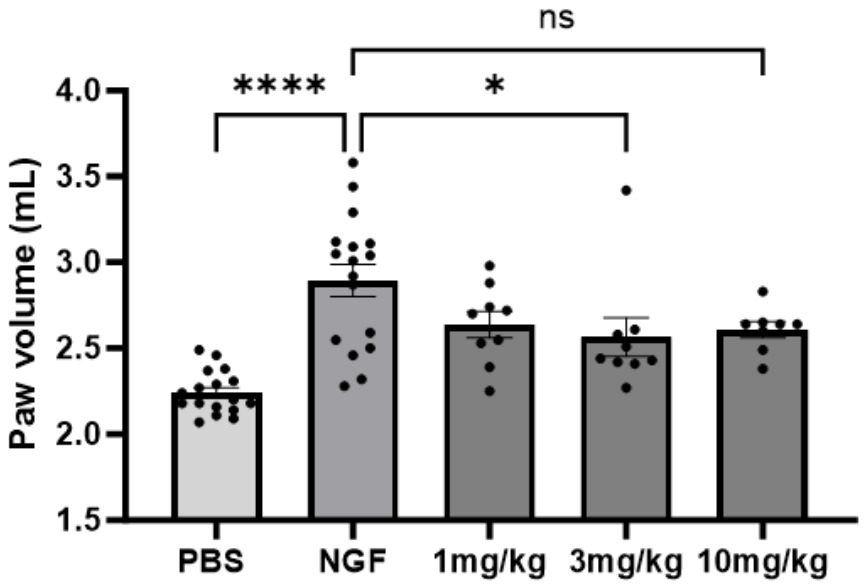
NGF-induced pain and inflammation in rats

Thermal hypersensitivity and inflammation are induced by intradermal injection of 5 μg NGF in the hind paw
ACD137 demonstrates both an analgesic effect and an anti-inflammatory effect.

Analgesic effect



Anti-inflammatory effect



ACD137 shows significant analgesic and anti-inflammatory effects

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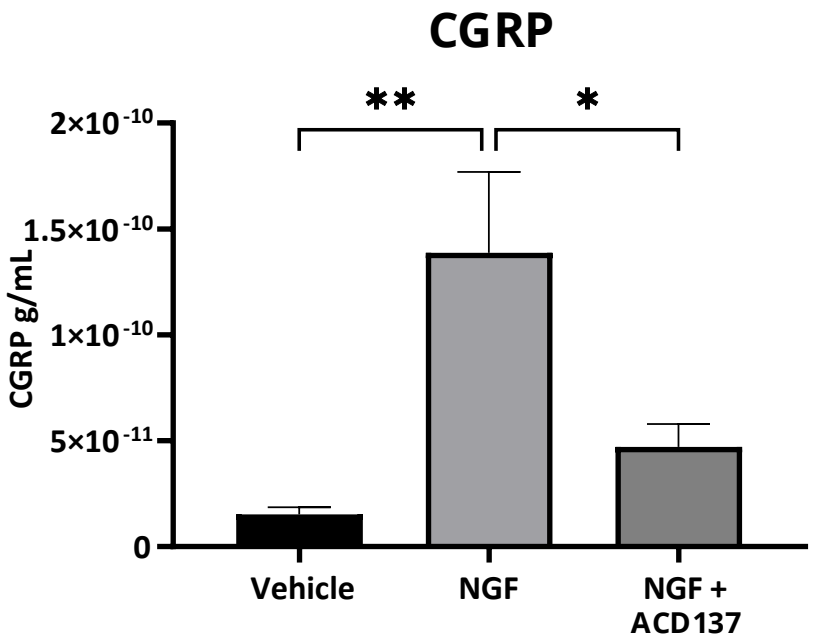
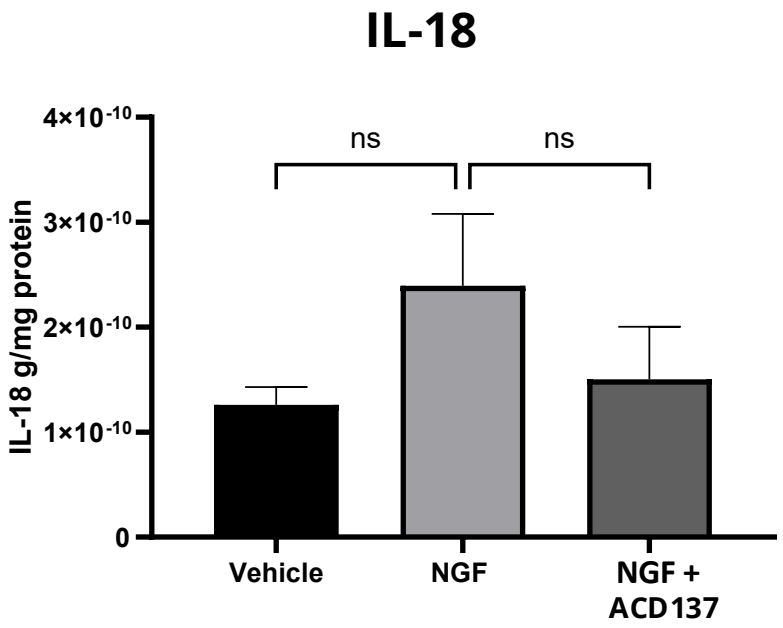
Inflammatory markers in rats

Thermal hypersensitivity and inflammation are induced by intradermal injection of 5 μg NGF.
ACD137 reduces NGF-induced increase in CGRP and IL-18 in skin biopsies from NGF-treated paw.

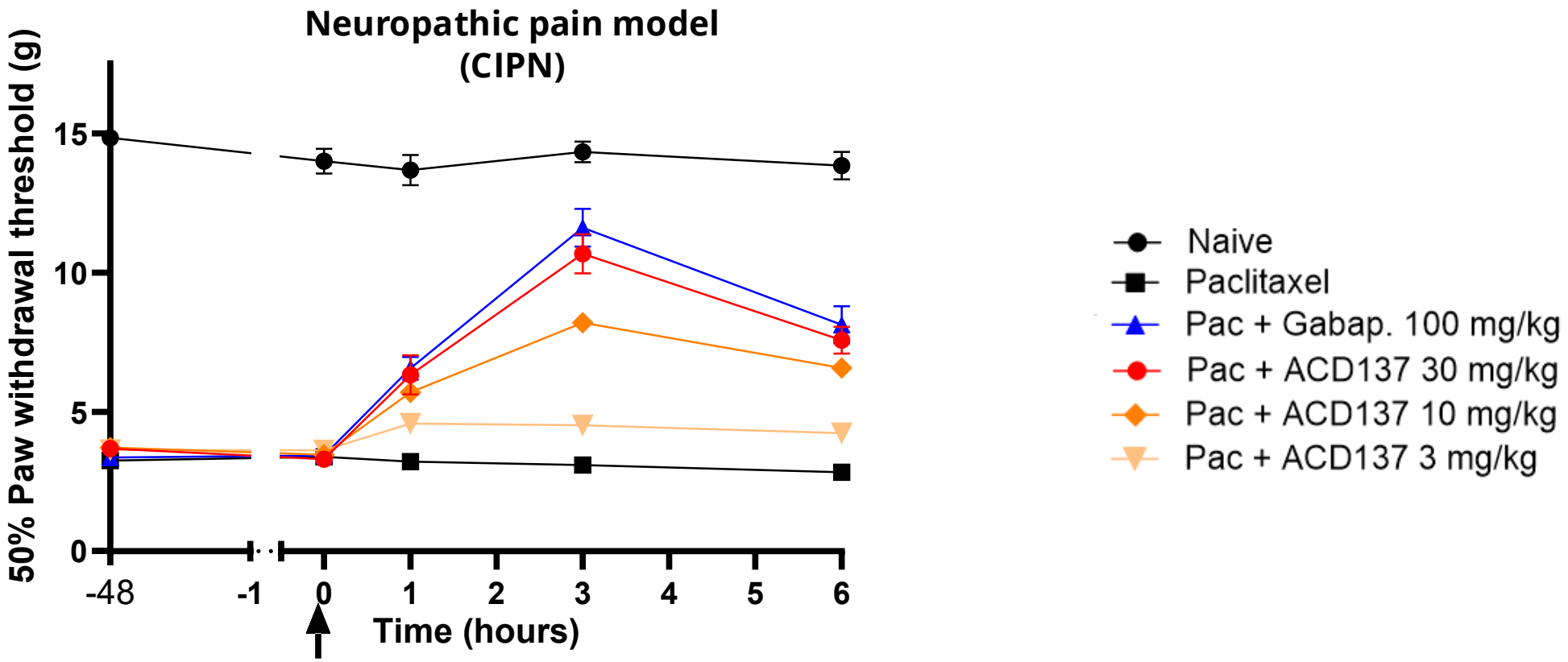




ACD137 significantly reduce levels of CGRP in skin biopsies

Effects of ACD137 in a model of neuropathic pain (chemotherapy-induced peripheral neuropathy (CIPN))

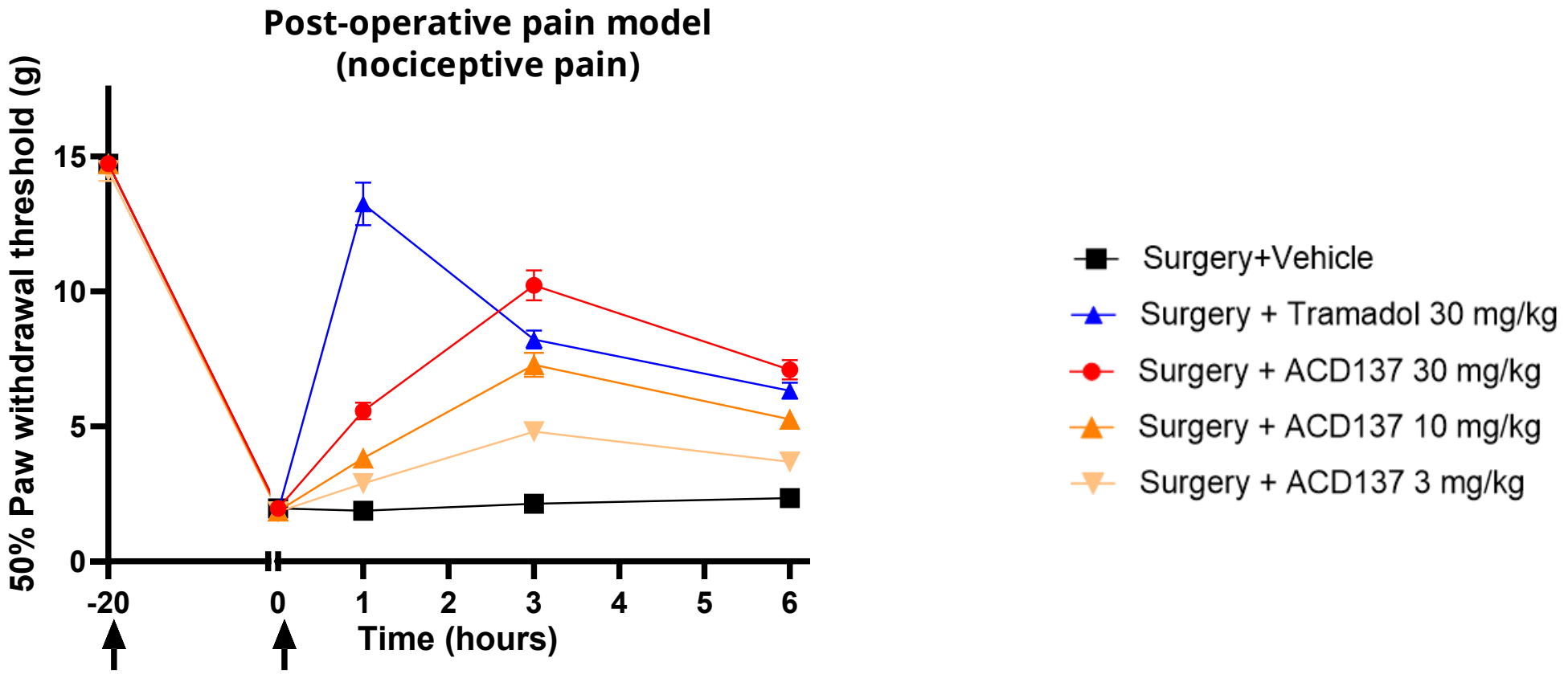
Peripheral neuropathy was induced by repeated injections of Paclitaxel
ACD137 or Gabapentin were administered orally and pain assessment was performed at 1, 3 and 6 hours post-dose



ACD137 significantly reduces mechanical allodynia in a model of neuropathic pain

Effects of ACD137 in a model of nociceptive pain

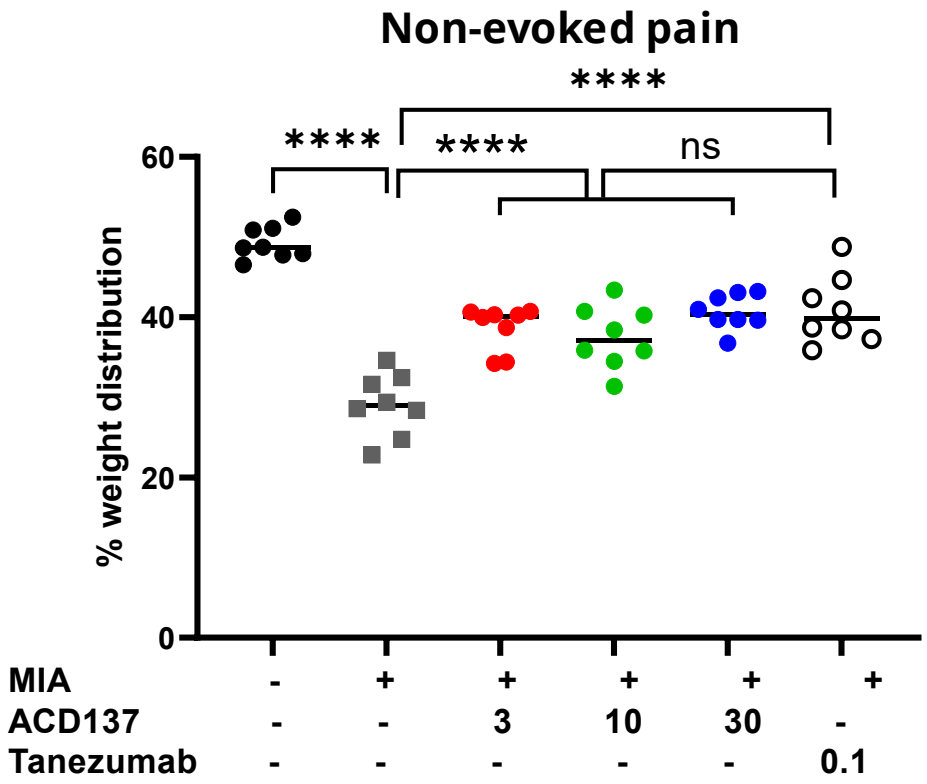
- Post-operative pain was studied in a model of incisional pain (Brennan model)
- ACD137 was administered by oral gavage, and pain assessments were performed at 1-, 3- and 6-hours post-dose

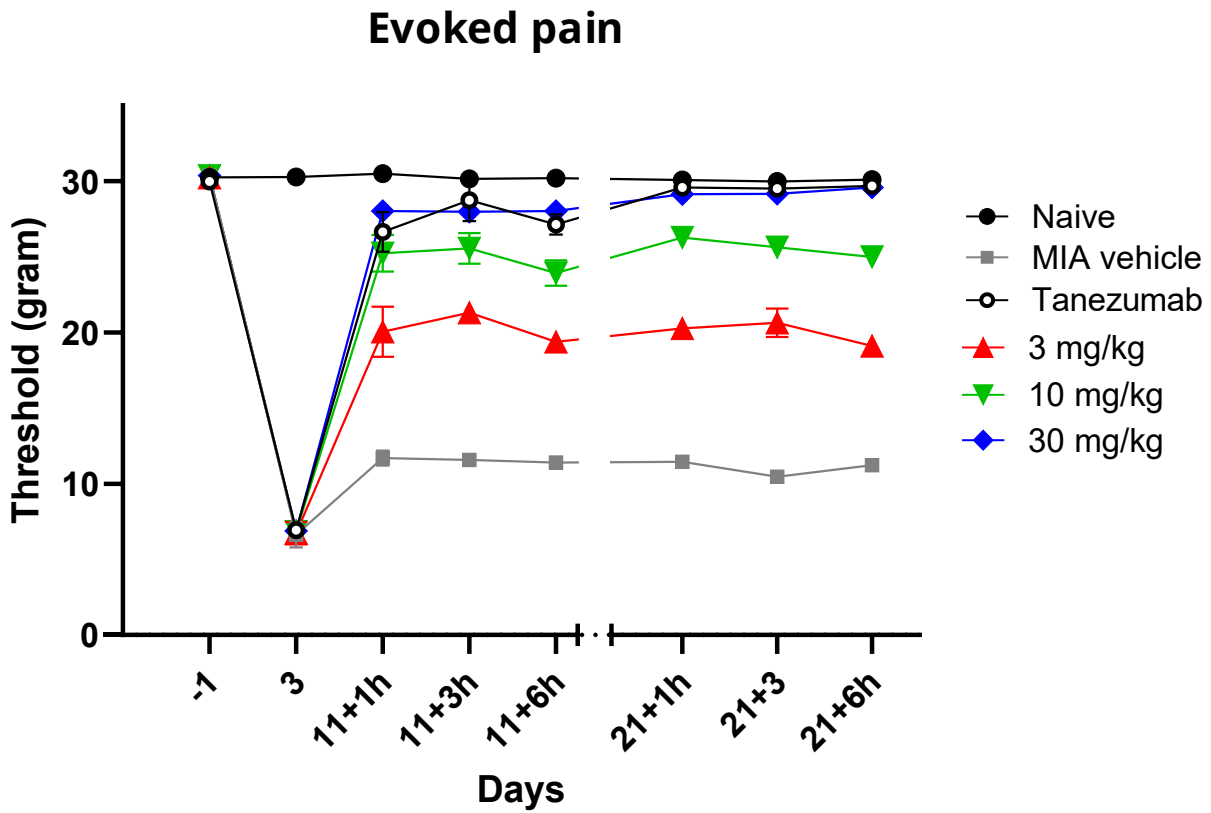


ACD137 significantly reduce mechanical allodynia in a model of nociceptive pain

TrkA-NAM: equivalent pain relief as anti-NGF antibody in a model of OA

Arthritis was induced by injecting mono-iodo acetate (MIA) in the knee joint of the left hind leg
ACD137 was administered twice daily by oral gavage for 18 days from day 3 to 21
Pain was assessed by weight bearing (non evoked pain) and mechanical allodynia (evoked pain)





ACD137 have similar analgesic effect as the anti-NGF antibody Tanezumab

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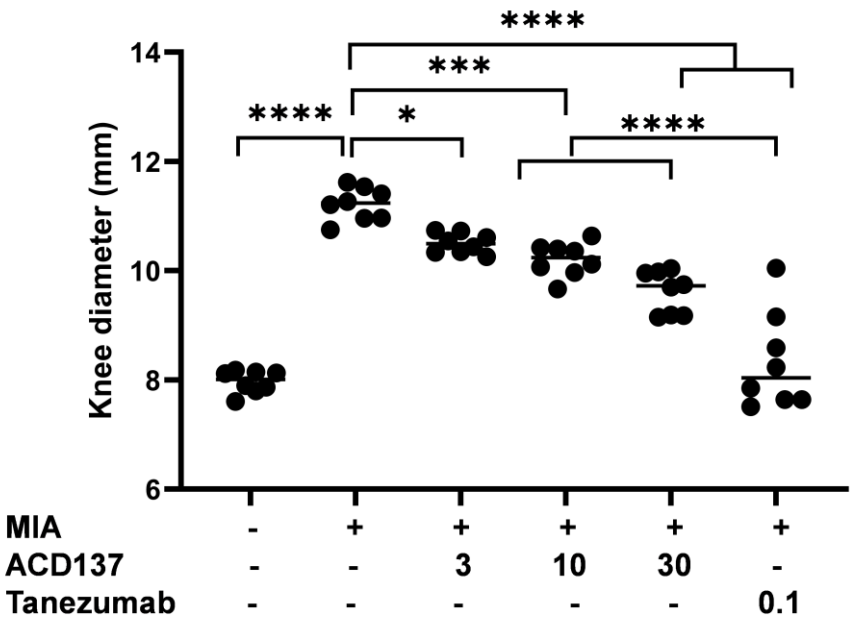
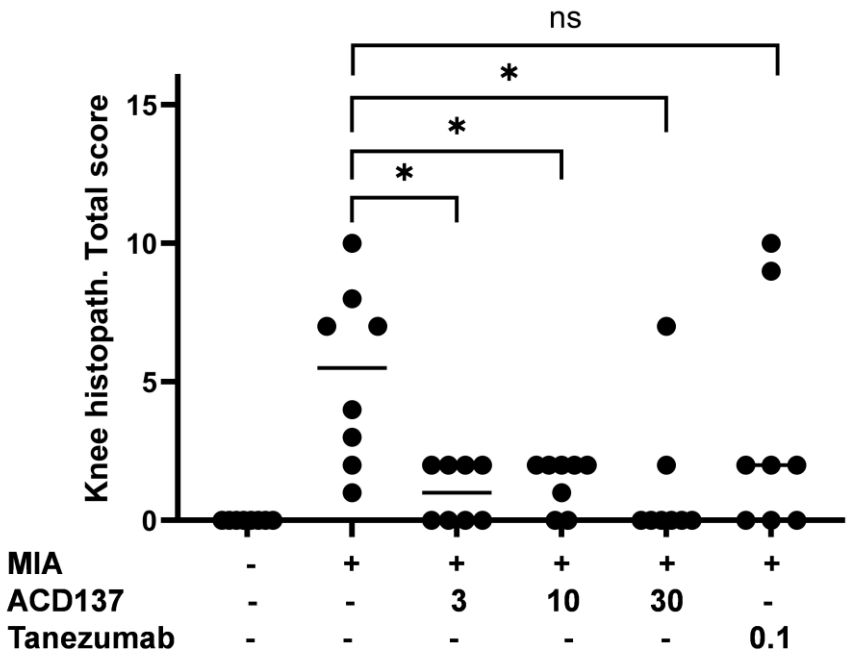
Effects of ACD137 in a rat model of osteoarthritis

Arthritis was induced by injecting mono-iodo acetate (MIA) in the knee joint of the left hind leg
ACD137 was administered twice daily by oral gavage for 18 days from day 3 to 21
Knee joint diameter was used a measure of inflammation and joint pathology was scored by modified Mankin scoring

Inflammation

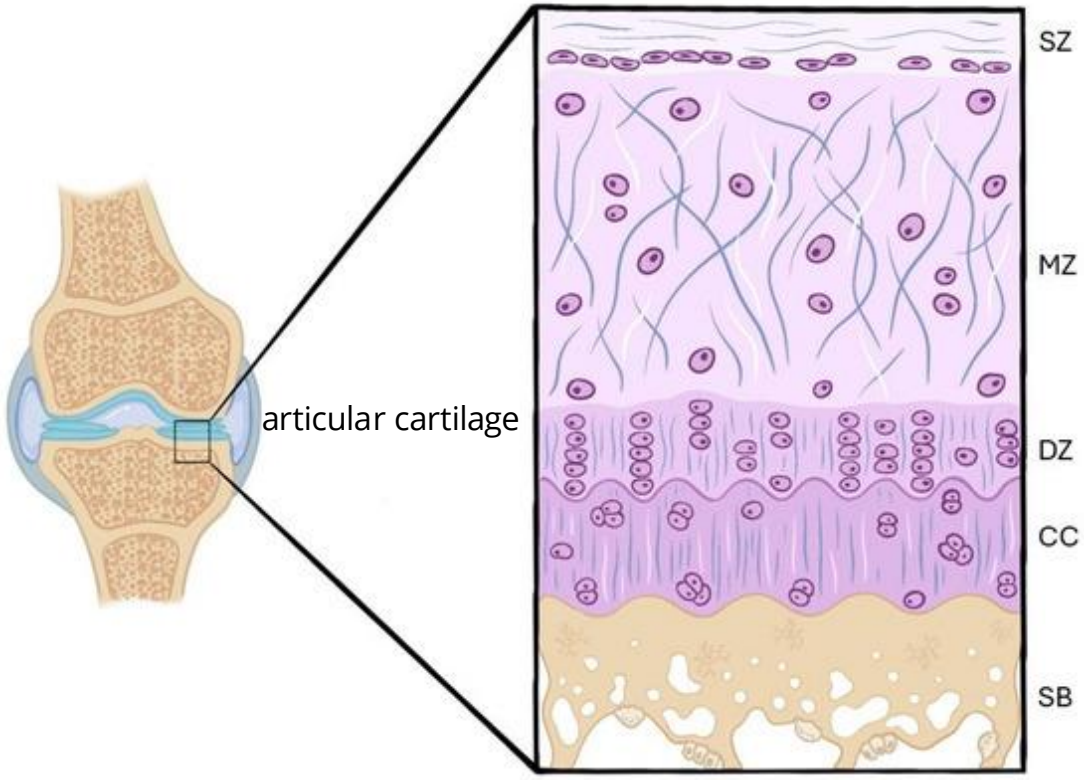


Joint pathology

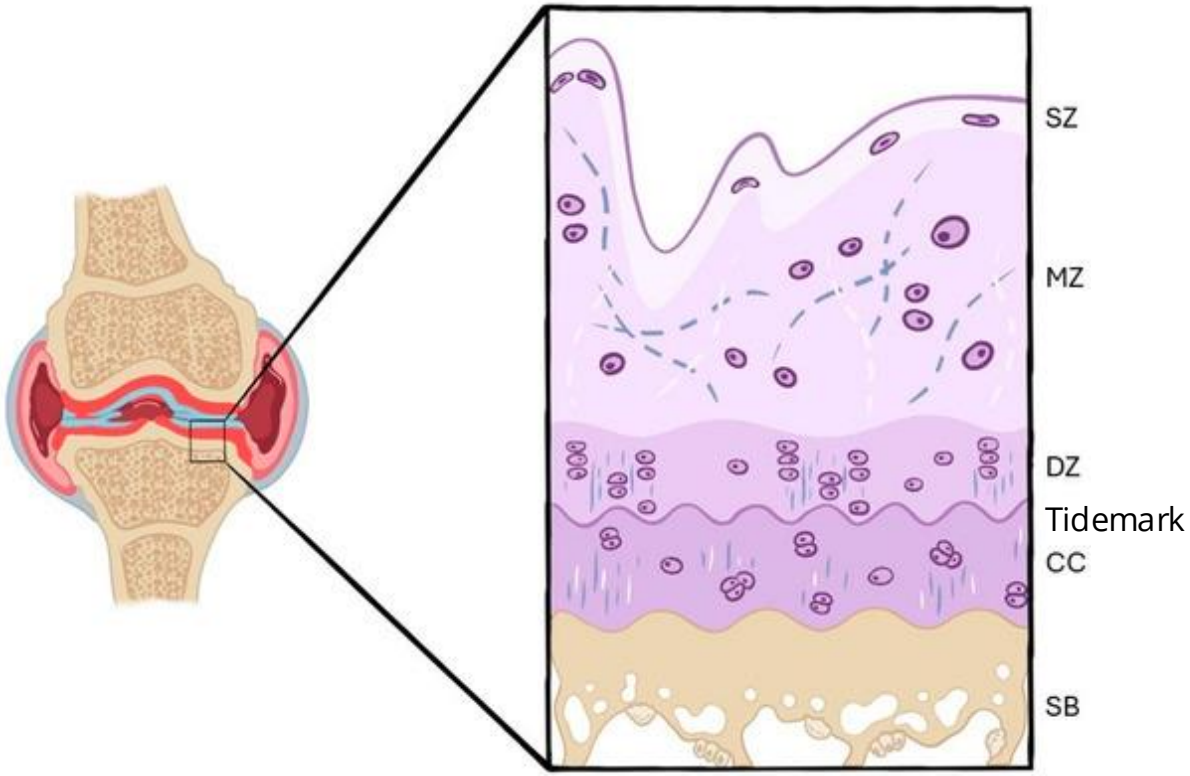


ACD137 have analgesic, anti-inflammatory and joint protective effects in the knee joint
ACD137 have similar analgesic effect as Tanezumab

Changes in the articular cartilage in the presence of OA



SZ—superficial zone
MZ—middle zone
DZ—deep zone
CC—calcified cartilage
SB—subchondral bone



Osteoarthritis: progressive structural disorganization, loss of chondrocytes, cellular abnormalities, and disruption of the collagen fiber network, together with subchondral bone thickening and sclerosis.

Sabucedo-Suárez et al., IJMS, 2025

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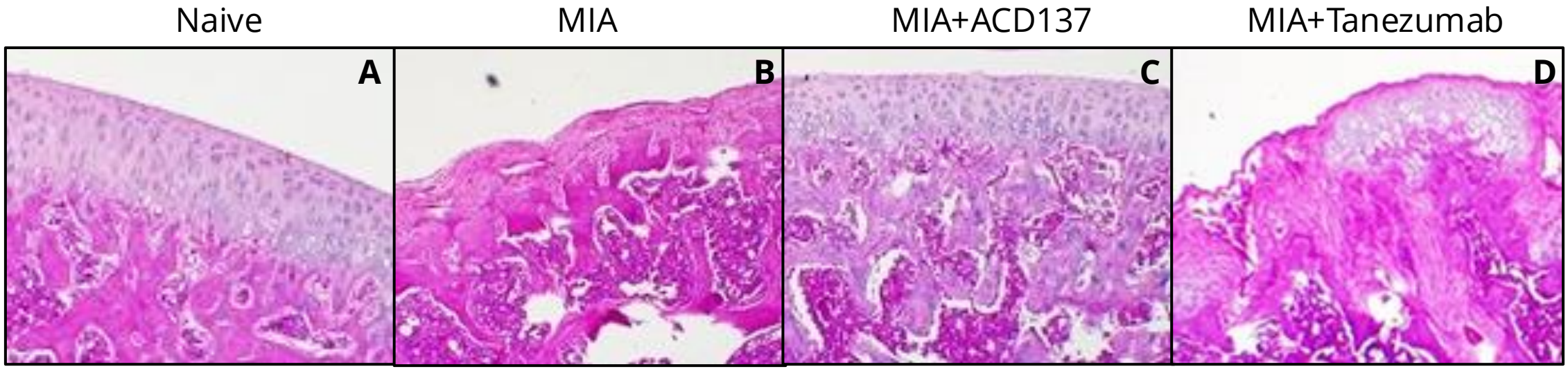
Changes in the articular cartilage in the MIA-model of OA



Representative images of knee joint histopathology.

A. naïve animal showing normal histology with articular cartilage, clear cellular structure and intact tidemark.
B. vehicle-treated MIA animals showing damage in articular cartilage and cellular abnormalities with destroyed tidemark.
C. 30 mg/kg ACD137: normal histology with articular cartilage, clear cellular structure and intact tidemark.
D. 0.1 mg/kg tanezumab: damage in articular cartilage and cellular abnormalities with destroyed tidemark.

All sections were stained with hematoxylin and eosin and pictures were taken using 4X magnification.

ACD137 protects knee joint from degenerative processes

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Summary TrkA-NAM / ACD137

ACD137 :

- Was identified internally by a rigorous medicinal chemistry program
- Is a highly selective and potent negative allosteric modulators of TrkA
- Has analgesic effects in models of both neuropathic and nociceptive pain
- Has anti-inflammatory and protective effects in the knee joint in a rodent model of OA
- Has similar analgesic efficacy as the anti-NGF antibody Tanezumab
- Is currently in preclinical development

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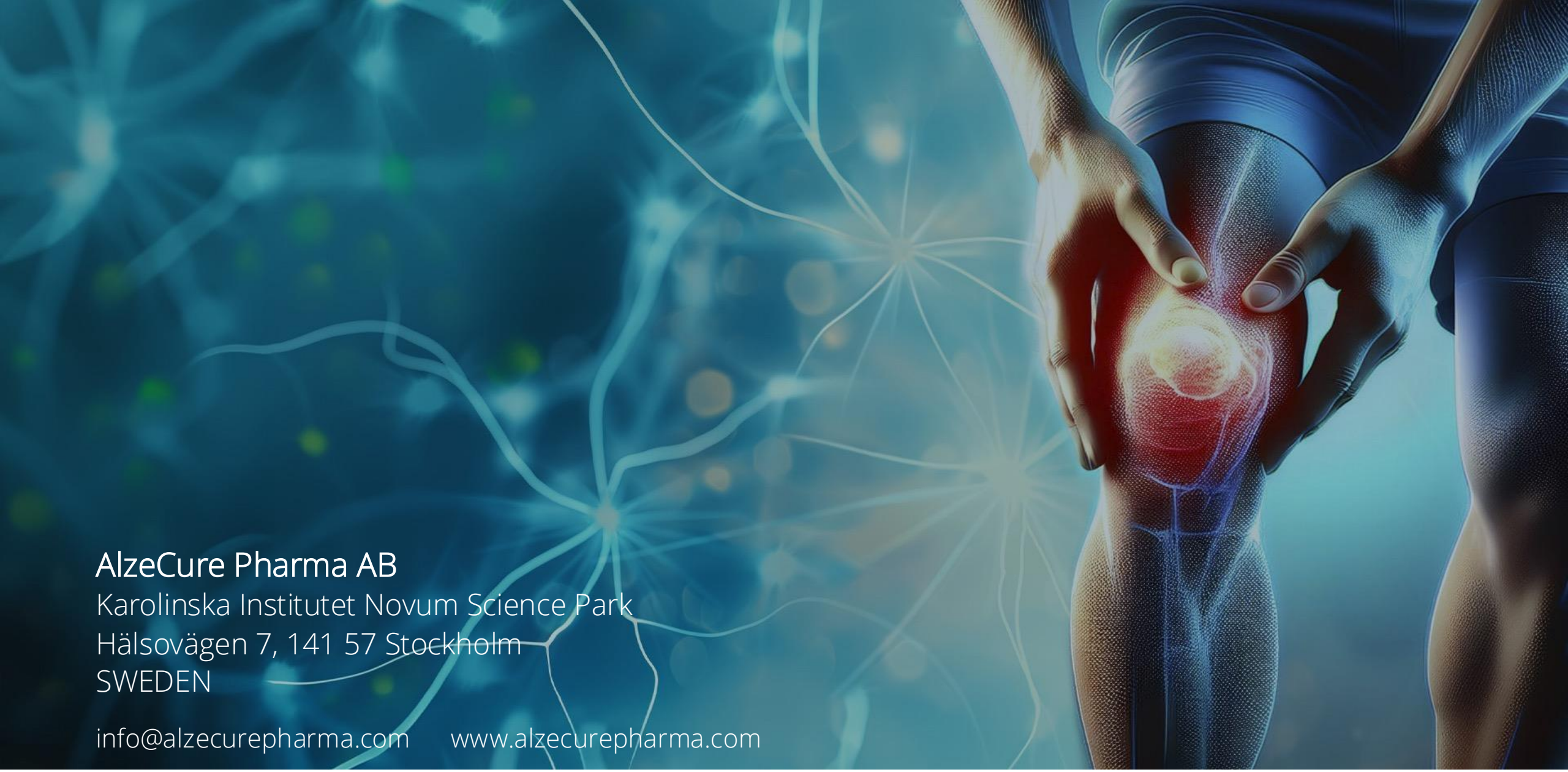

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