Targeting Glia for Pain Therapy

Xalud Therapeutics

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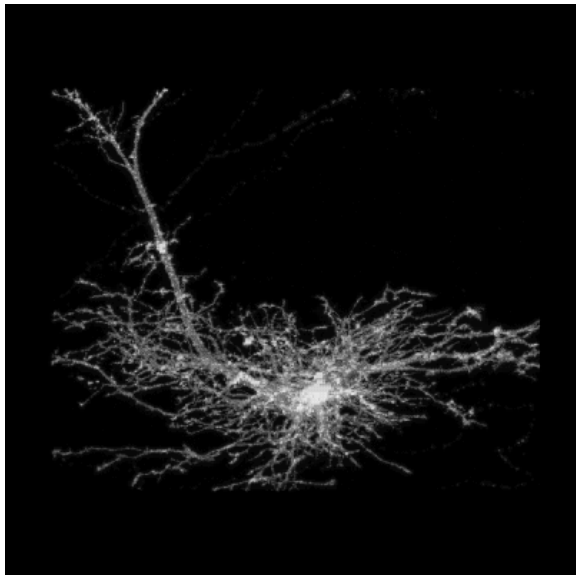
What Have the Past 25 Years Revealed?

- Glia (microglia, astrocytes) are *activated in every clinically relevant model of enhanced pain*:
  - Peripheral nerve injury
  - Chemotherapy-induced pain
  - Bone cancer
  - Multiple sclerosis
  - Spinal cord injury
  - Radiculopathy/herniated discs
  - Rat "migraine", etc.

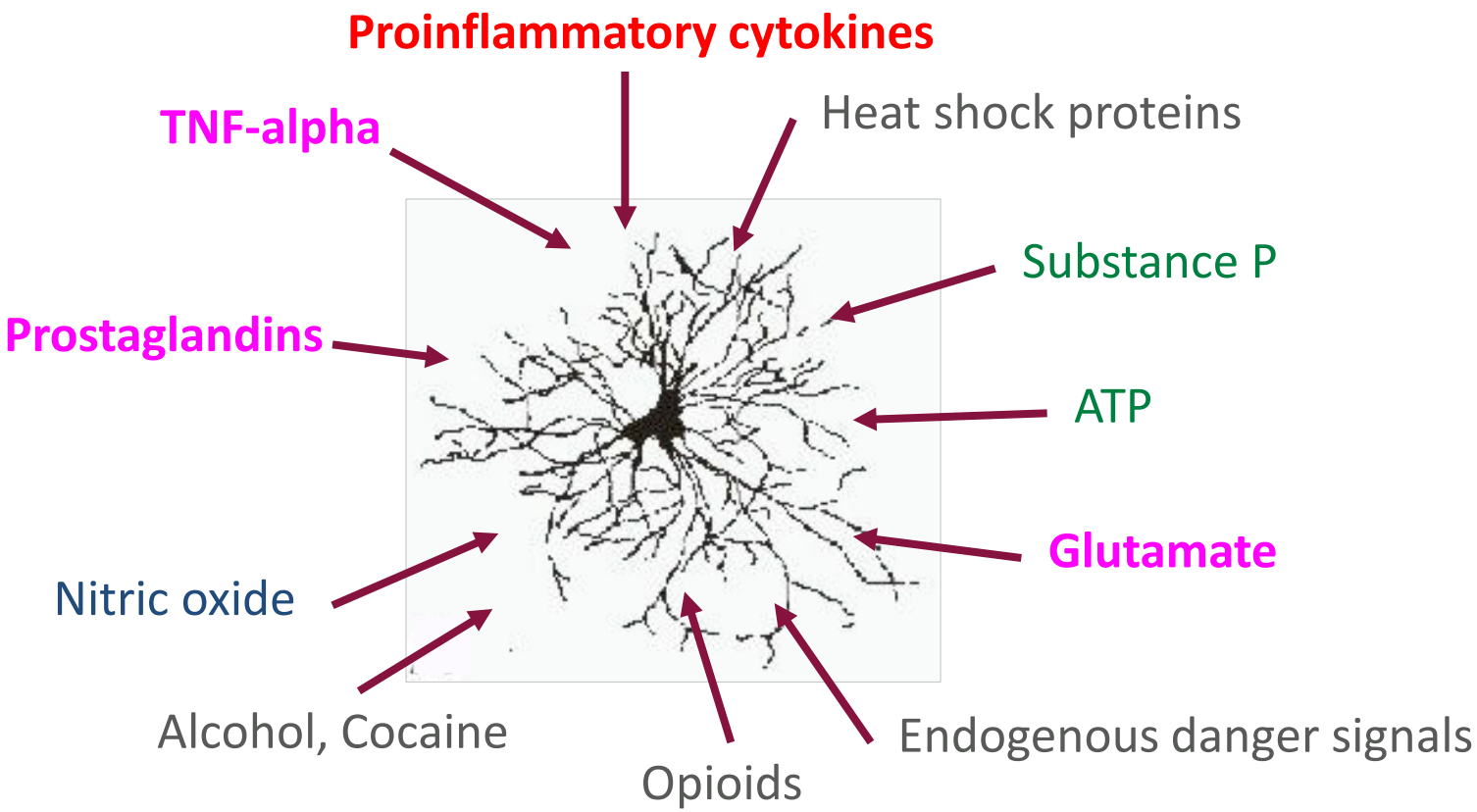


- Suppressing glial activation and pro-inflammatory cytokines:
  - Suppresses pain in every clinically relevant model
  - Returns pain sensitivity to <u>normal</u>

Watkins *et al.*, 2007
Grace *et al.*, 2014

What Activates Glia?

Multiple mediators lead to spinal glial activation



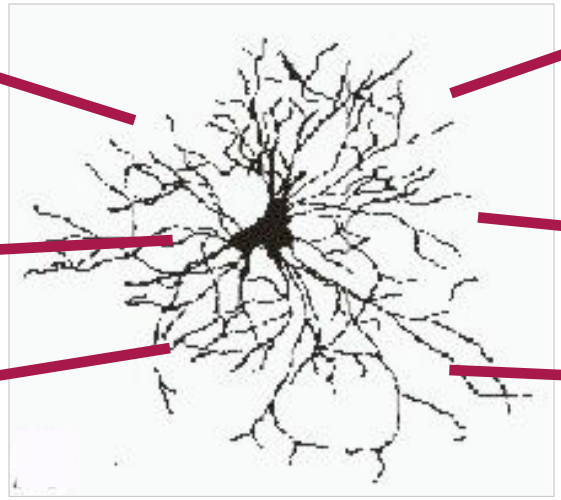
Watkins & Maier, 2003
Hutchinson *et al.*, 2011

Glia Release Pain Enhancing Substances

Arachidonic acid & prostaglandins

Excitatory amino acids

Nerve growth factors



Proinflammatory cytokines

Enkephalinases

Reactive oxygen species; NO

- ***Amplify pain signaling to spinal cord***
- ***Amplify pain transmission to brain***
- ***Upregulate AMPA & NMDA receptor number/function***
- ***Downregulate GABA & outward K^+ currents***
- ***Downregulate glial glutamate transporters & GRK2***

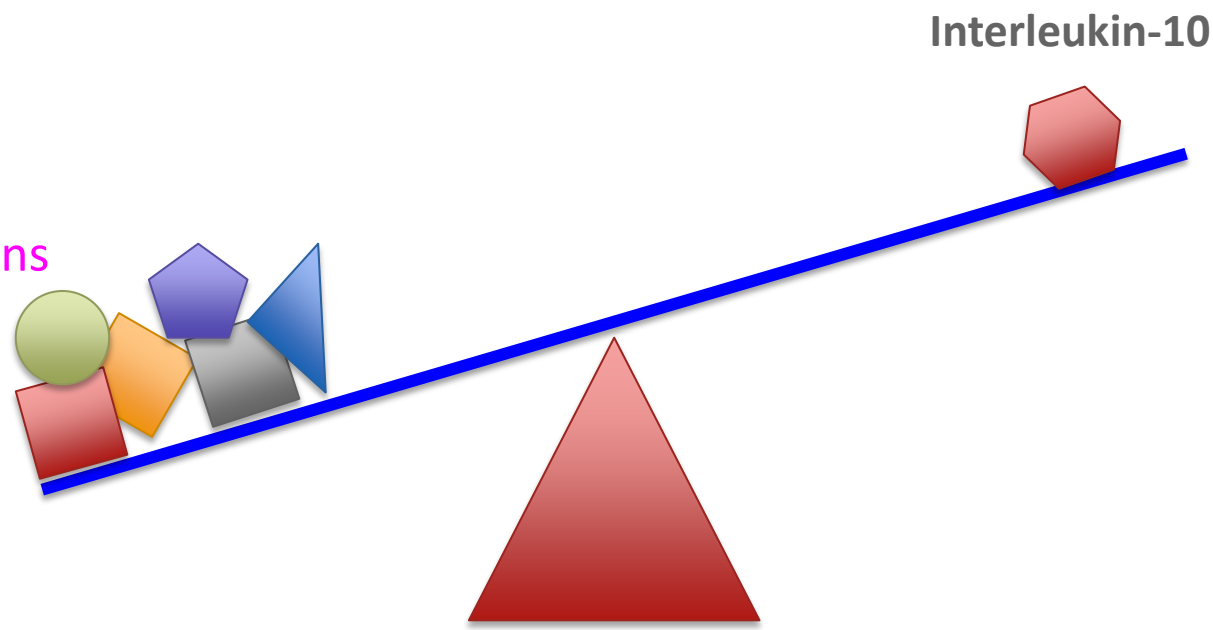
Watkins *et al.*, 2007

Anti-inflammatory Drugs

- TNF receptor antagonists (Etanercept, etc)
- IL-6 antagonist (Tocilizumab)
- COX-2 inhibitors (e.g. Celecoxib)
- Ca^{++} channel inhibitors (Neurontin)
- SNRI's (Riboxetine, Duloxetine)
- Other

Pro- vs Anti-inflammatory Mediators

IL-1β, IL-6
TNF-alpha
CGRP
Substance P
Prostaglandins
ATP
H_2O_2
Fractalkine
Glutamate
Nitric oxide
Endogenous danger signals



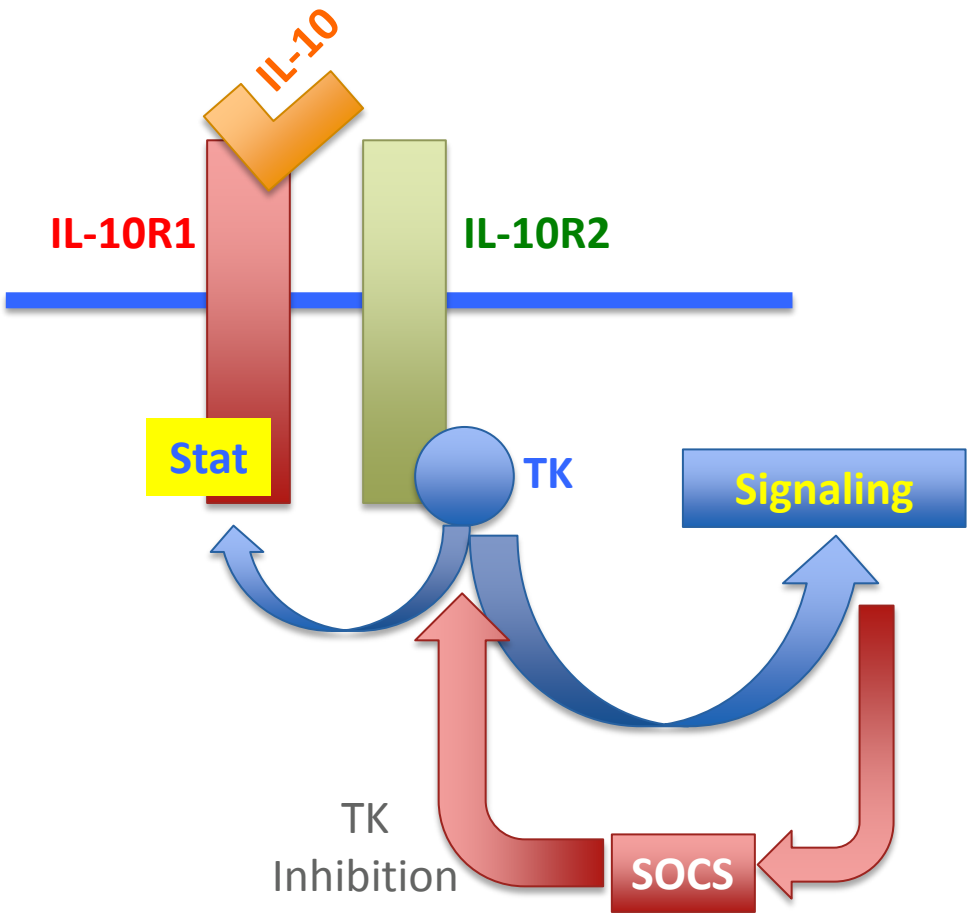
Interleukin-10: A Key Anti-Inflammatory Molecule

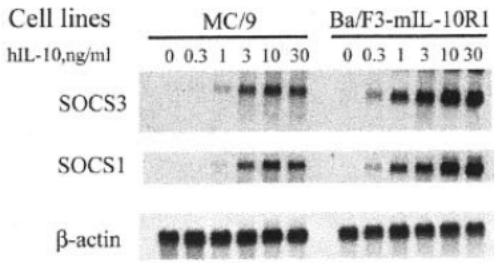
- Broad action against pro-inflammatory mediators
  - Opposes gene activation (p38 MAP kinase, NFκB)
  - Prevents pro-inflammatory cytokine translation, processing, release
  - Increases pro-inflammatory cytokine decoy receptors
  - Decreases membrane-bound pro-inflammatory cytokine receptors
  - Down-regulates reactive oxygen species production
- Normalizes microglial activity
- Highly specific for a single receptor; no off-target
- Human data supports use of IL-10 therapy
  - Pro-inflammatory cytokines are elevated in the CSF of pain patients
  - IL-10 levels are inversely related to severity of pain
  - IL-10 and IL-10R gene polymorphisms associated with pain

Unlocking the Therapeutic Potential of IL-10

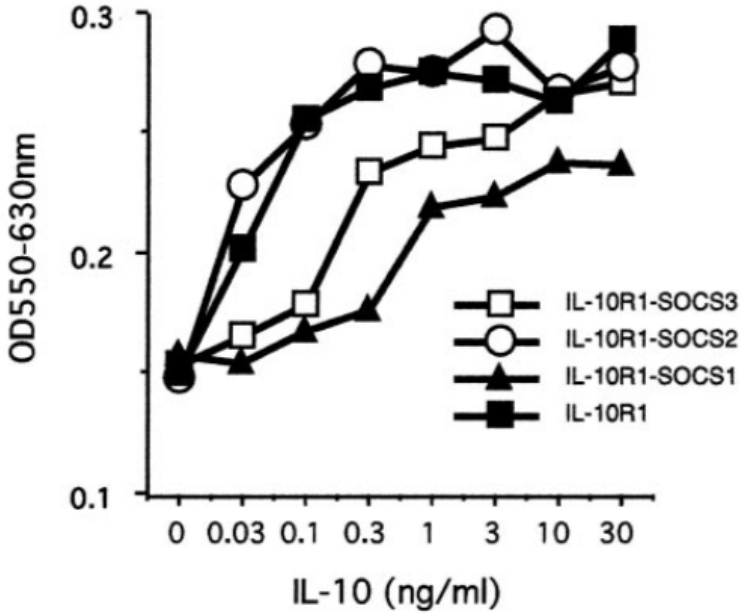
- Recombinant IL-10 Protein: Short circulatory half-life, non-CNS penetrant, safe in clinical IV dosing for IBD
- PEGylated IL-10: longer circulatory half-life ~ 6-8 h; not clinically developed
- Adenovirus IL-10 or AAV2/IL-10: long expression intrathecally but < 1 week efficacy in pain model

IL-10 Signaling





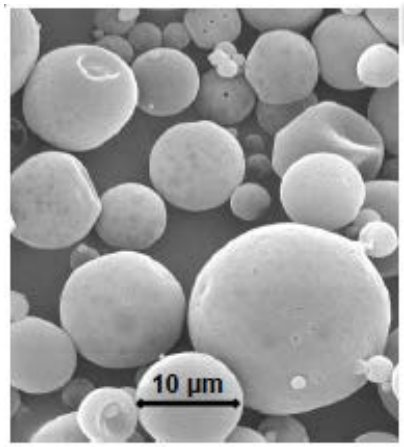
IL-10-dependent growth of BA/F Cells

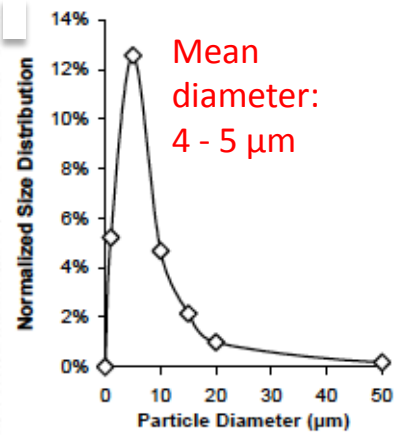


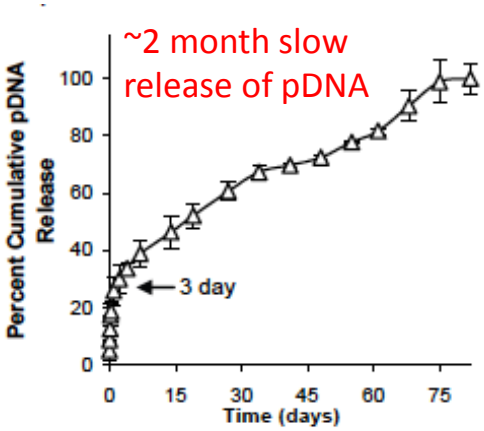
Ding et al., 2003

Plasmid-based Gene Therapy

- PLGA microparticle encapsulation (**XT-101**)
- Intrathecal or intra-articular injections
- Non-narcotic, non-addictive, 12-week efficacy window

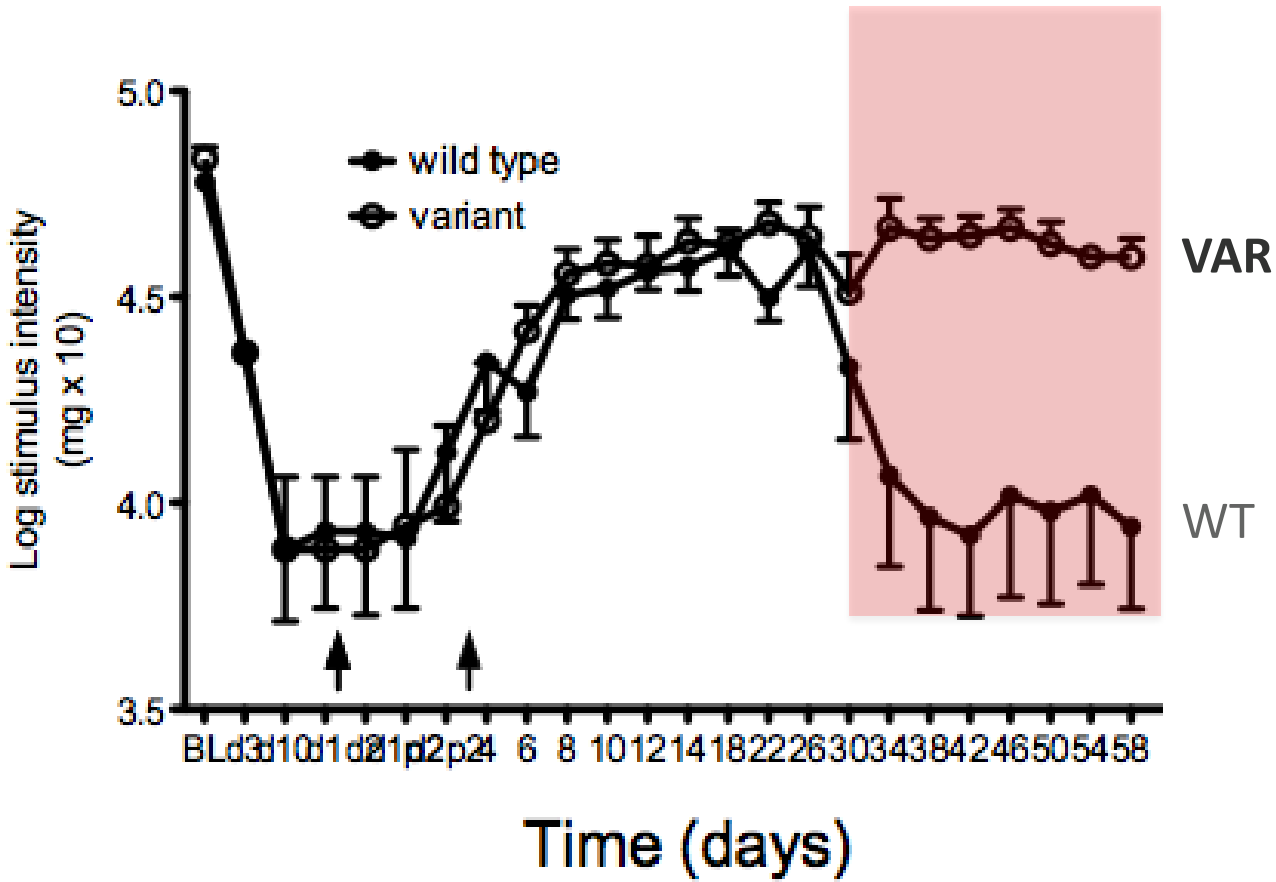




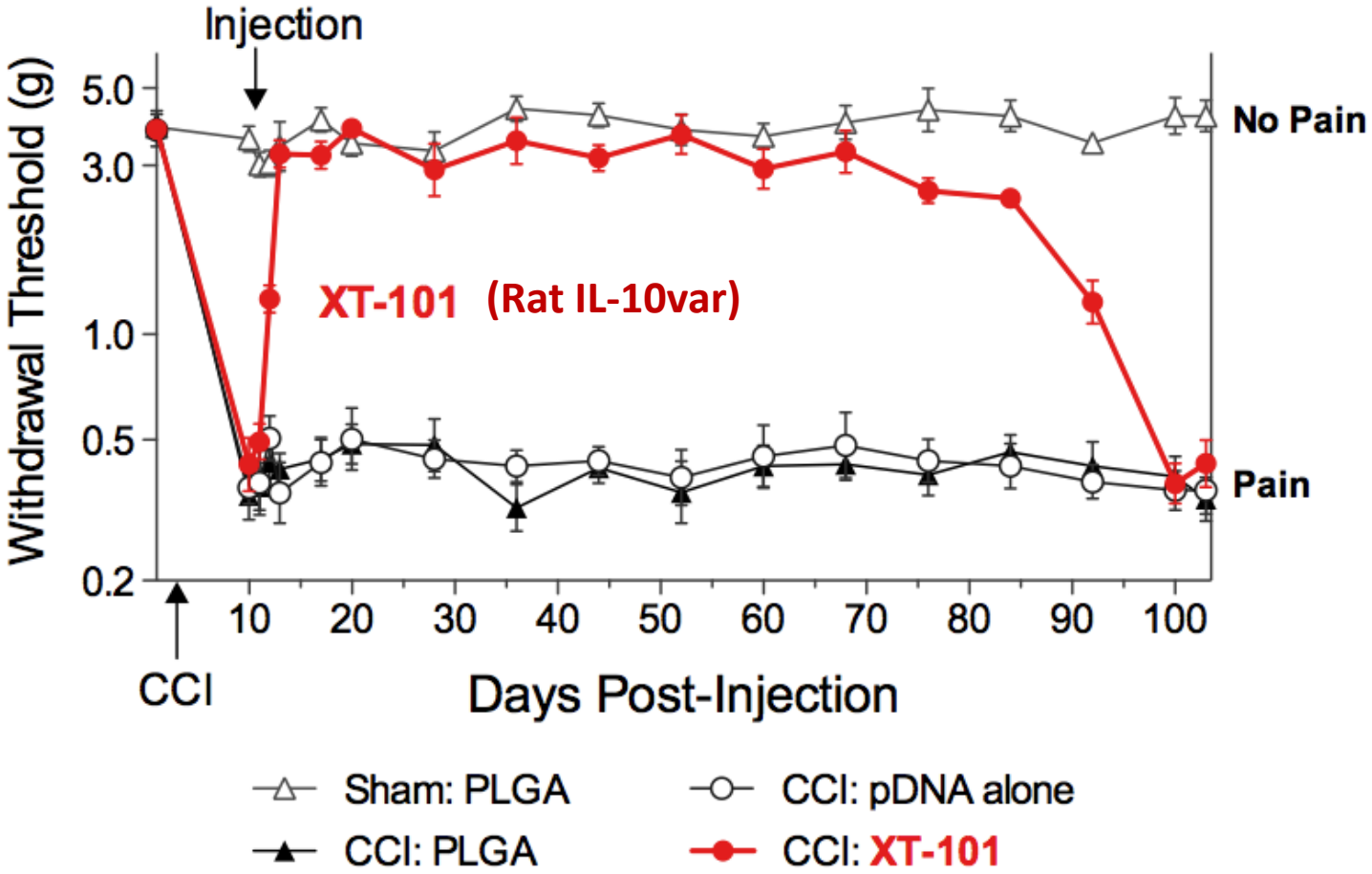


Point mutation in IL-10 makes it more effective

Rat CCI Neuropathic Pain Model



Single Dose XT-101 Produces Durable Pain Reversal (CCI)

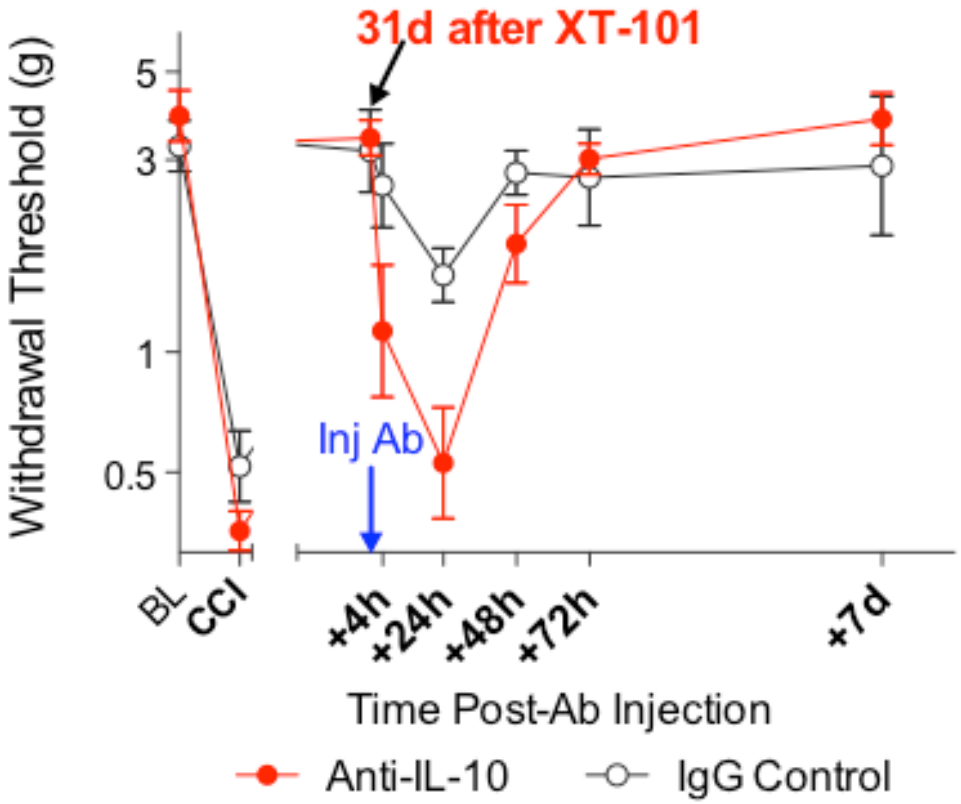


n=6/group

Soderquist *et al.*, 2010

IL-10 Expression Drives XT-101 Efficacy

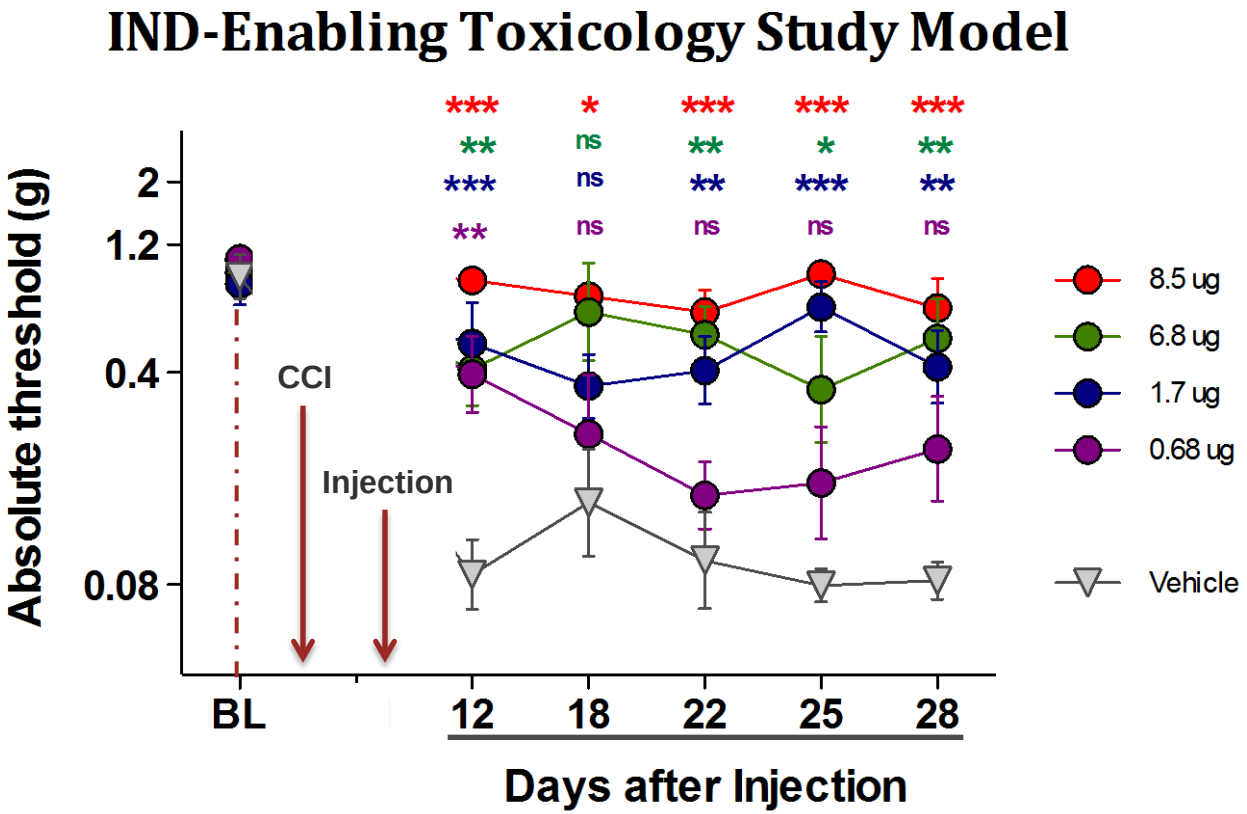
Neutralizing IL-10 antibody blocks the reversal of neuropathic pain, even after 30 days of XT-101-driven efficacy



Rat IL-10var pDNA

Soderquist *et al.*, 2010

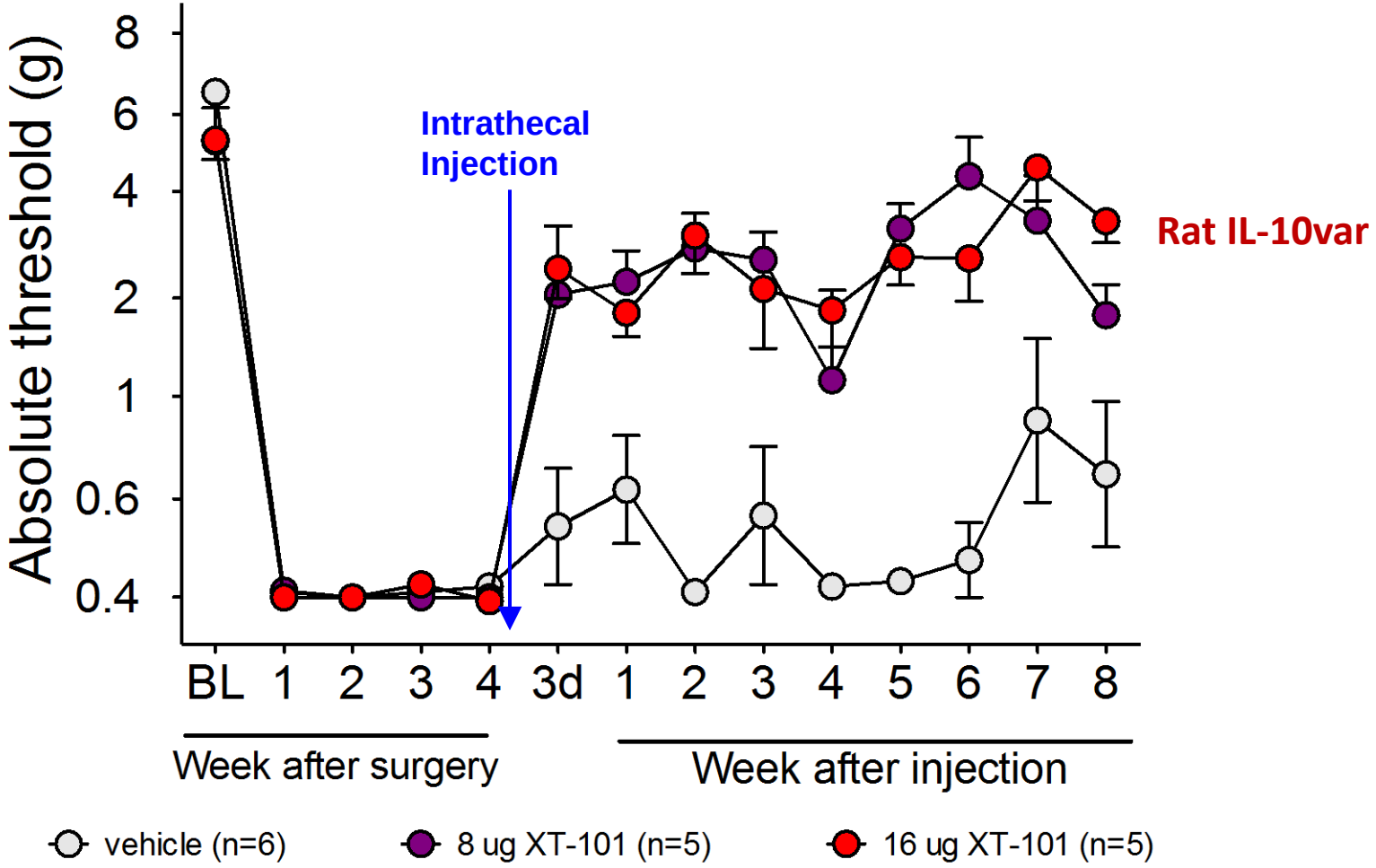
XT-101 Efficacy Is Dose-Dependent in Mouse CCI



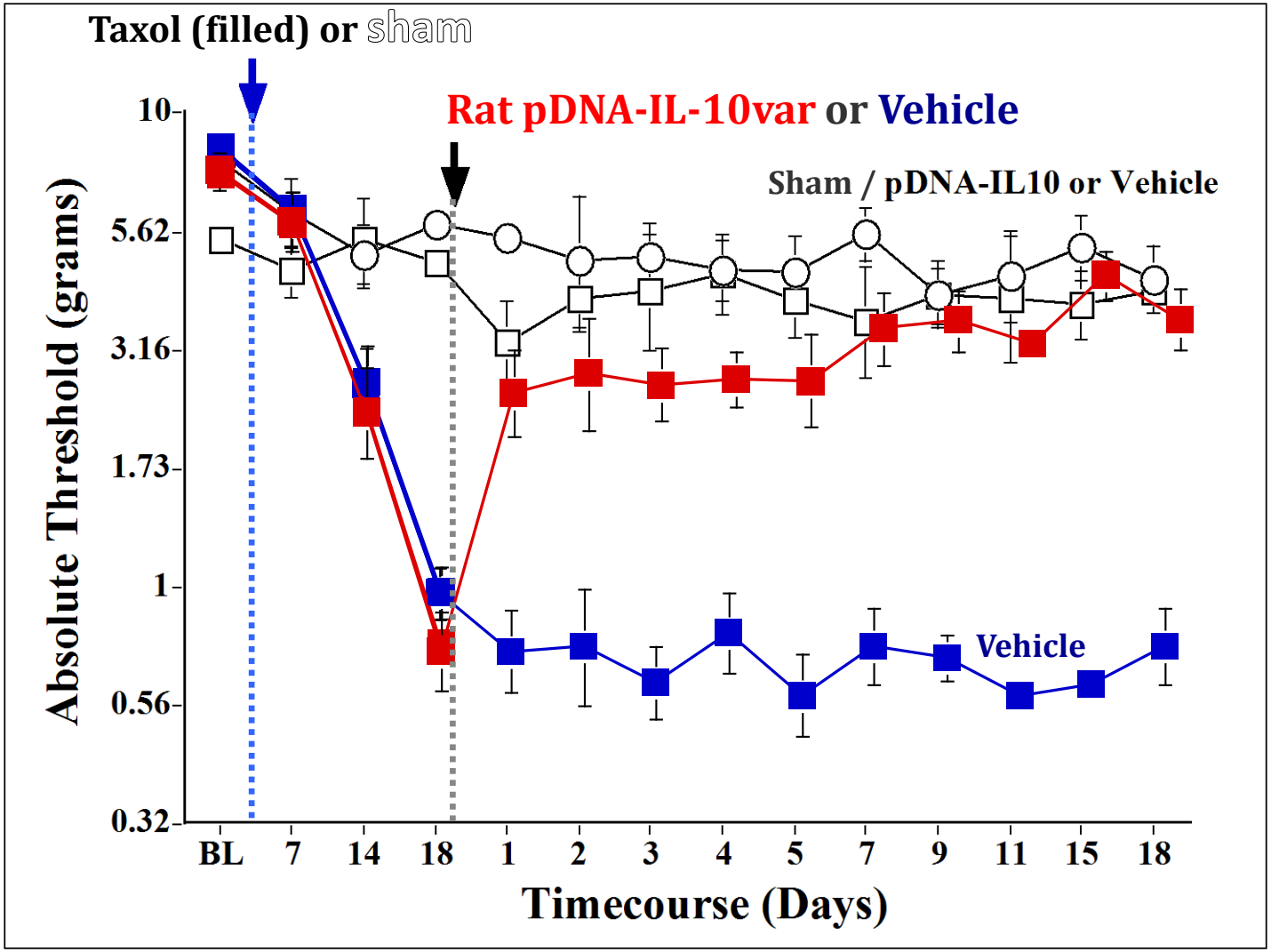
Human IL-10var pDNA

XT-101 Efficacy in the Rat Chung Model

Multiple replicate studies demonstrate dose-related response



Intrathecal IL-10 Plasmid Therapy Reverses Paclitaxel-Induced Neuropathic Pain



NEUROPATHIC PAIN - INTRATHECAL

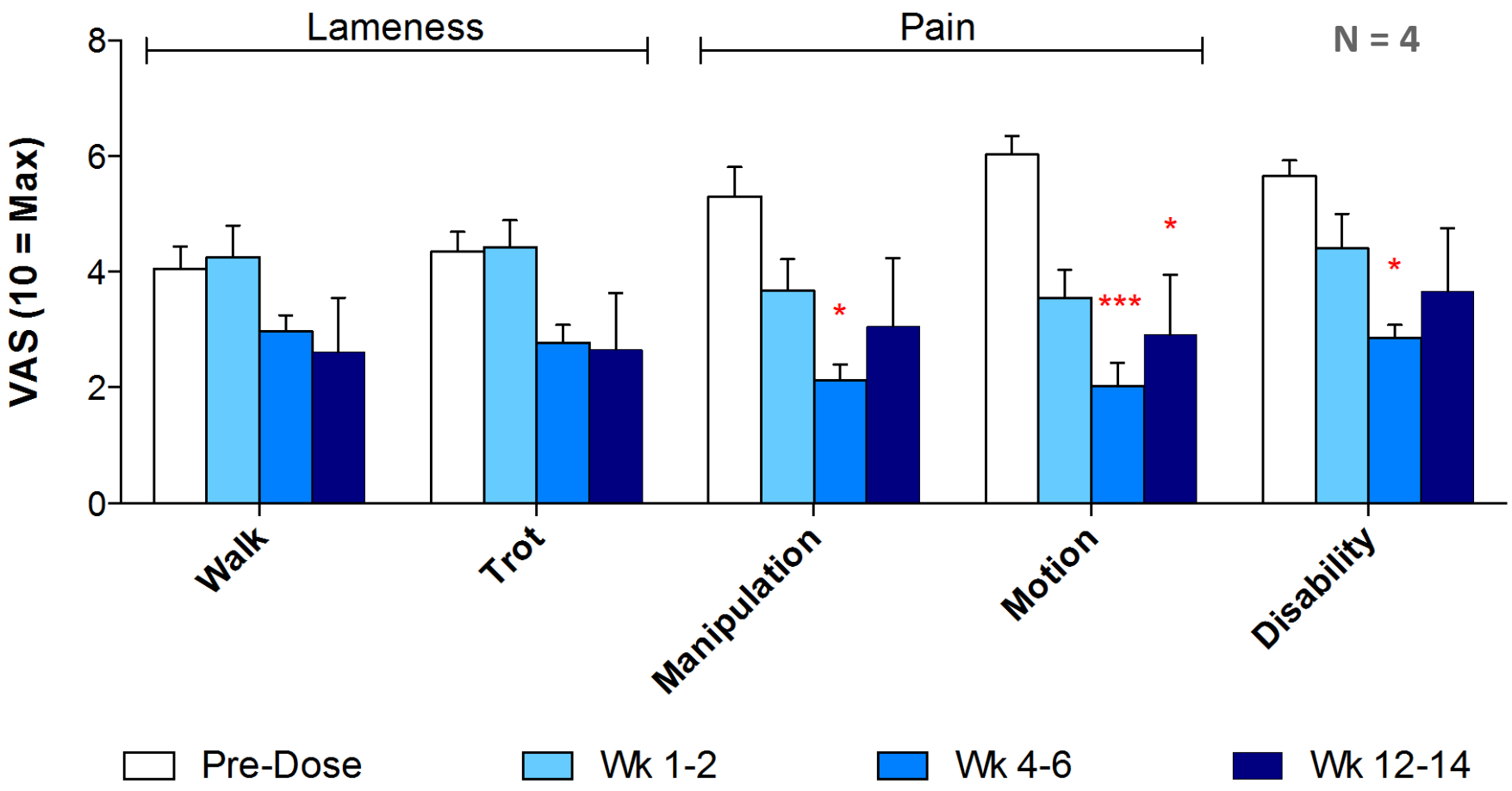
XT-101: Osteoarthritis Pilot Study

- *Case Selection*: Companion dogs with debilitating osteoarthritic pain in one or more joints with longstanding disease; standard therapies failed – euthanasia candidate
- Owners and clinician blind to administration; placebo-controlled
- *Dose*: Standard 1.0 mL dose volume
- *Study Design*: Under inhalation anesthesia, a single dose active or placebo was delivered by acute intra-articular injection to the affected joint per standard clinical practice.
- *Clinical Assessments*: Owner CBPI behavioral assessment, veterinarian clinical VAS for pain and mobility, goniometry

OSTEOARTHRITIS / INTRA-ARTICULAR

XT-101: Canine Clinical Assessments

Significant positive changes in pain and function that improve over time



Summary of Pilot Canine OA Study

- 2 of 3 active therapy dogs show clear improvement in clinical assessments, joint flexion in at least one joint
- All active therapy dogs show improvement in extension of at least one joint (no placebo dogs show improvement)
- Very well tolerated in both fore- and hind-limb injections

Excellent IND-Enabling Toxicology Results

- Single intrathecal administration of XT-101 expressing human IL-10 transgene in CCI mice
  - Thirty day in-life portion with efficacy testing
  - Gross necropsy, histopathology, clinical chemistry, and systemic human IL-10 protein assessed at d30
- No significant XT-101-related findings in gross necropsy, histopathology, or clinical chemistry
- Dose-related efficacy through end of study
- Systemic human IL-10 protein below limit of detection
- NOAEL at maximum feasible dose

Summary

- Intrathecal IL-10 plasmid therapy suppresses neuropathic pain for 12 weeks
- Injection of IL-10 plasmid into OA joints improves joint function and reduces pain
- Clinical trials in neuropathic pain and OA planned for 2016

Acknowledgments

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