

# Novel Gene Therapy Treatment for Severe Chronic Pain

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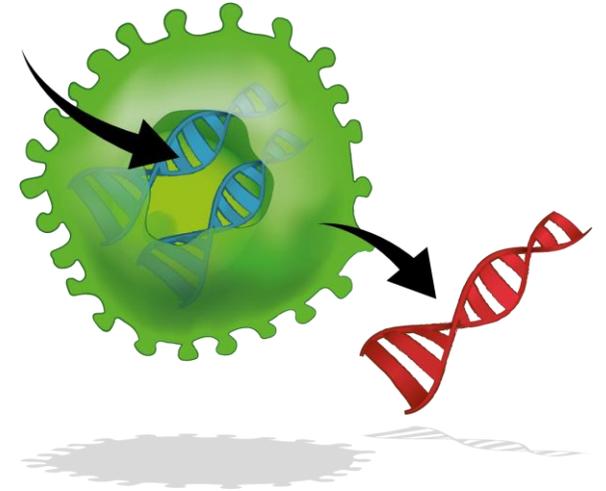
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# CombiGene – a leading Nordic gene therapy company

A public Swedish gene therapy company – founded in 2015

## Expertise covering the central areas of the gene therapy field

Strong team covering all areas in drug development with a track record of taking a Gene Therapy project from scientific finding to out-licensing to Big Pharma



## Project portfolio

Project name	Therapy mode	Indication	Preclinical phase development
CG01	Gene therapy	Epilepsy	<div style="width: 70%;"></div>
COZY01	Peptide	Pain	<div style="width: 50%;"></div>
COZY02	Gene therapy	Pain	<div style="width: 25%;"></div>

# CombiGene Business model – to source and develop assets



## CombiGene seeks:

- Collaborations and/or inlicensing from academia/SME/Pharma
- Gene therapy projects
- CNS and metabolic diseases
- Rare and common diseases (excluding ultra-rare)
- Projects ranging from scientific findings to clinical studies



# COZY The Pain program

# Chronic Pain from a Societal Perspective

## Pain is one of the biggest challenges in healthcare

Between **6 and 8 %** of the world's adult population suffers from severe chronic pain.



## Huge costs for society

Annual medical and indirect costs of various diseases in the United States.

**Pain: USD 635 billion**

**Cardiovascular diseases: USD 309 billion**

**Cancer: USD 243 billion**

**Diabetes: USD 188 billion**

Source: *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Appendix C. The Economic Cost of Pain in the US.* Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Washington (DC); National Academies Press (US); 2011

## Today's pharmaceuticals are insufficient

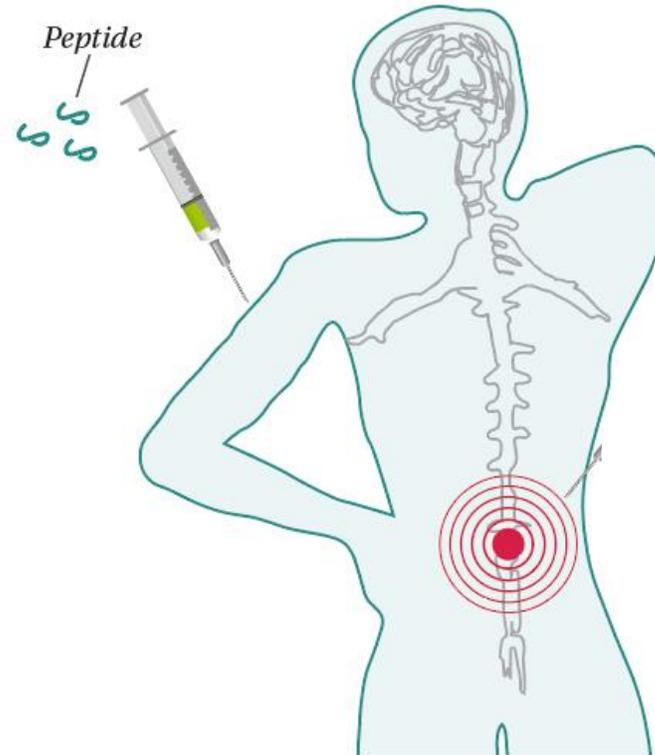
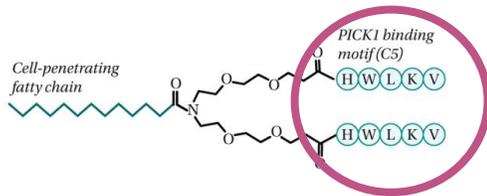
The problem with today's treatments is that they are not specifically developed to treat chronic pain. The pain relief that is achieved therefore often has a number of debilitating side effects such as substance abuse problems,  
**depression, anxiety, fatigue, reduced physical and mental ability.**

# One solution – Two treatment modalities

Same binding motif and mechanism of action

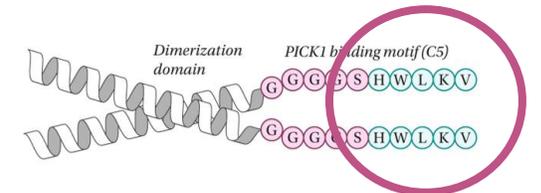
## **COZY01 – a peptide**

– multiple injections during treatment duration



## **COZY02 – a gene therapy**

– one administration



# First indication will be chosen within Neuropathic Pain

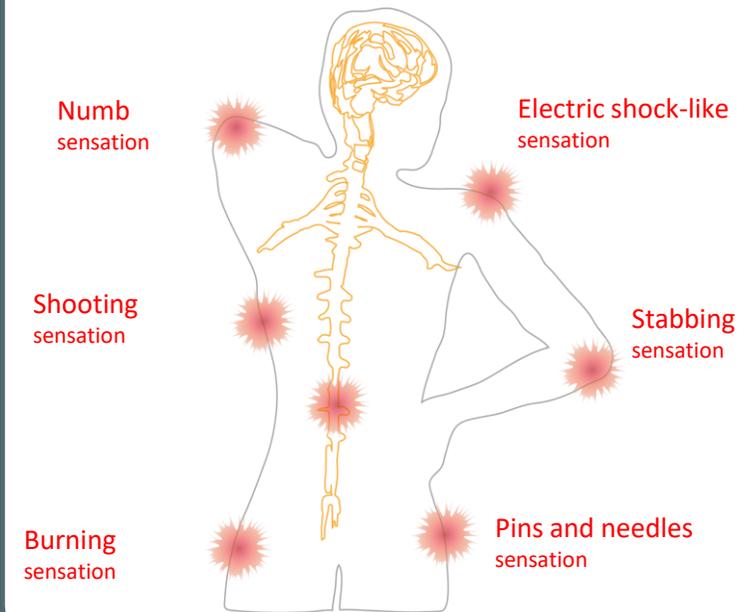
Neuropathic pain (NP) is caused by damage or injury to the nerves

- A biological dysfunction
- Symptoms are abnormal pain from normally non-painful or weakly painful stimuli as well as spontaneous pain
- ~7-10% of adults world-wide

## Common conditions with extensive NP are:

- Diabetic neuropathy (DNP)
- Chemotherapy-induced peripheral neuropathy (CIPN)
- Postherpetic neuralgia
- HIV-associated sensory peripheral neuropathy
- Multiple sclerosis (MS)
- Traumatic nerve lesions incl phantom limb pain (PLP)

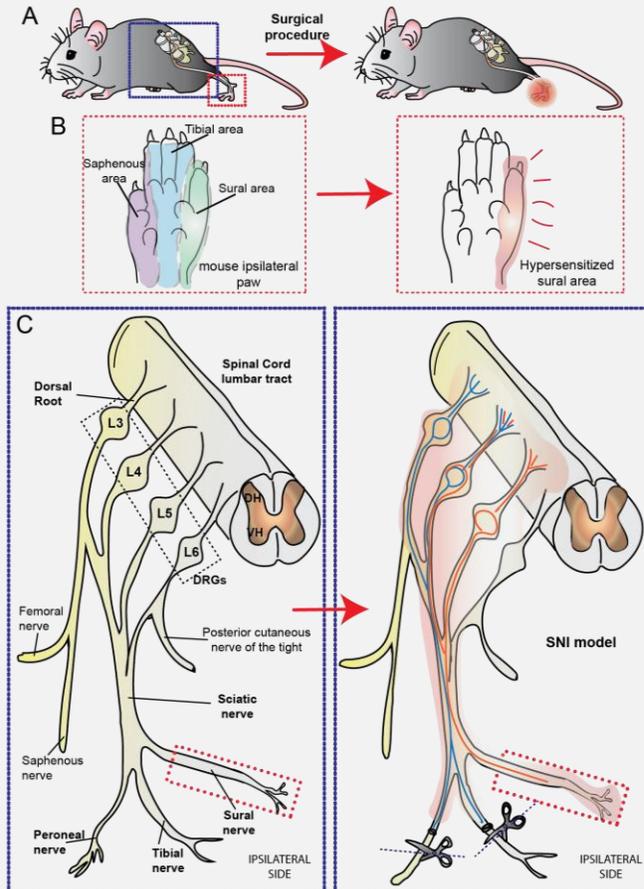
## Typical neuropathic pain symptoms



Limited efficacy of current treatments for NP

# Mouse Neuropathic Pain (NP) model – SNI

## Spared nerve injury (SNI) model of neuropathic pain



Mechanical allodynia tested with von Frey filaments



# Complete Pain Relief in Neuropathic Pain model

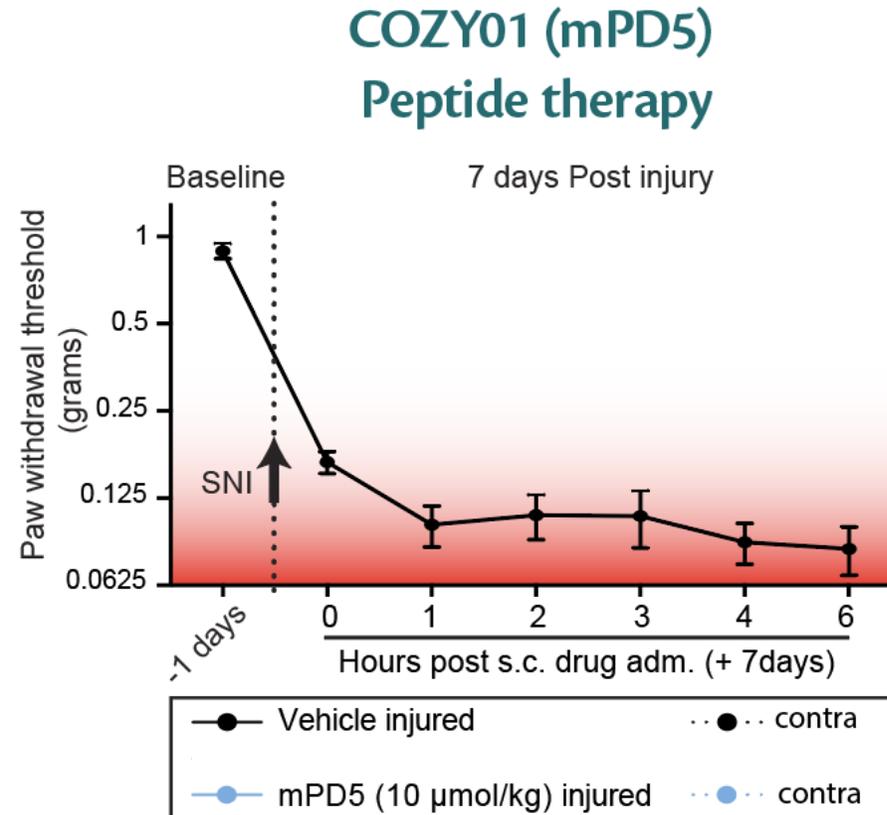
Spared nerve injury (SNI) model

Read-out: mechanical sensitivity

Normal sensitivity



Excessive sensitivity



# Complete Pain Relief in Neuropathic Pain model

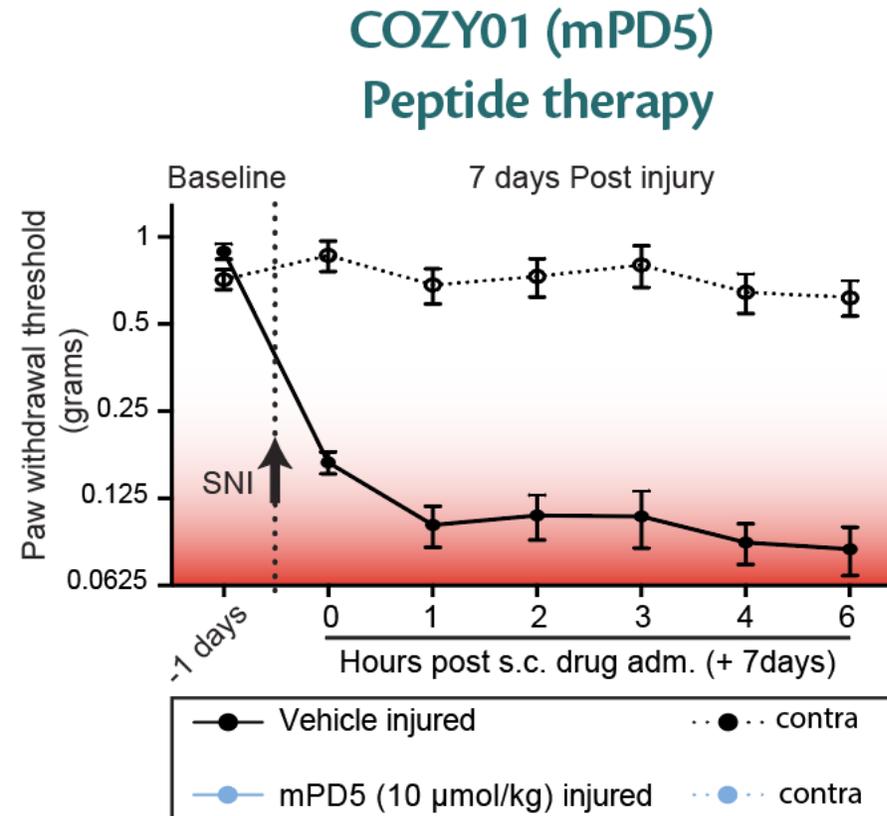
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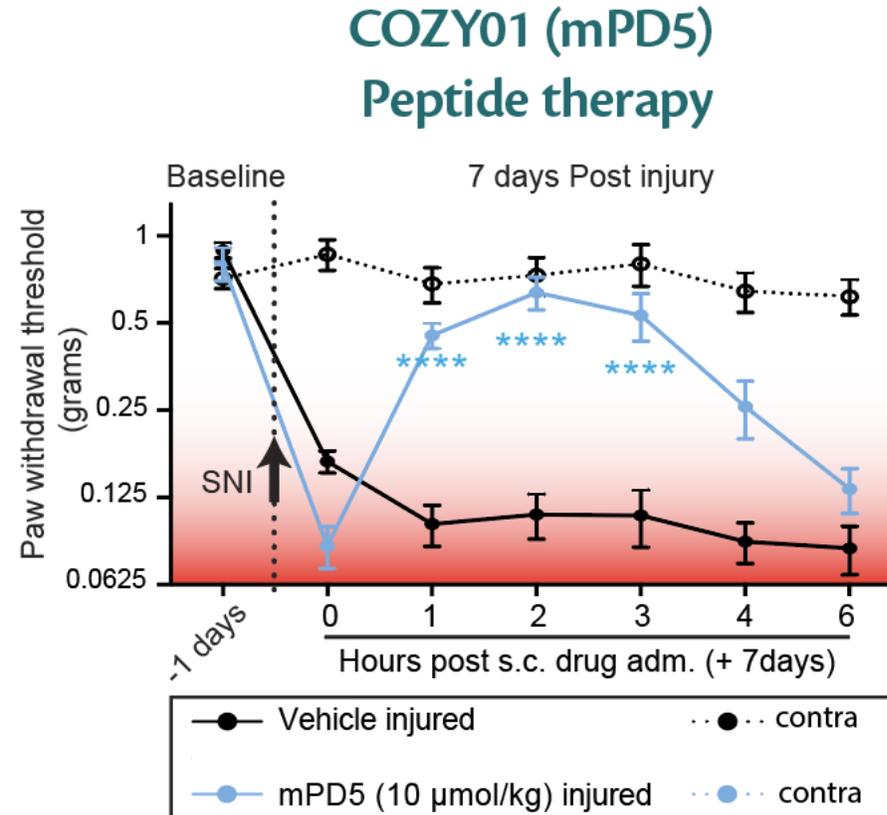
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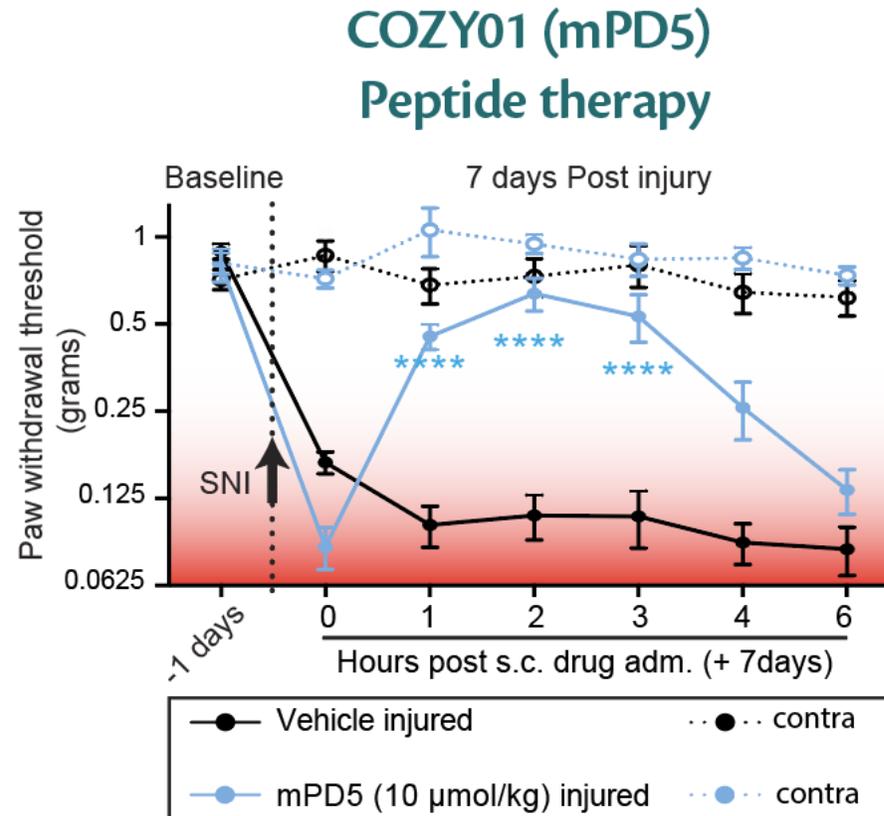
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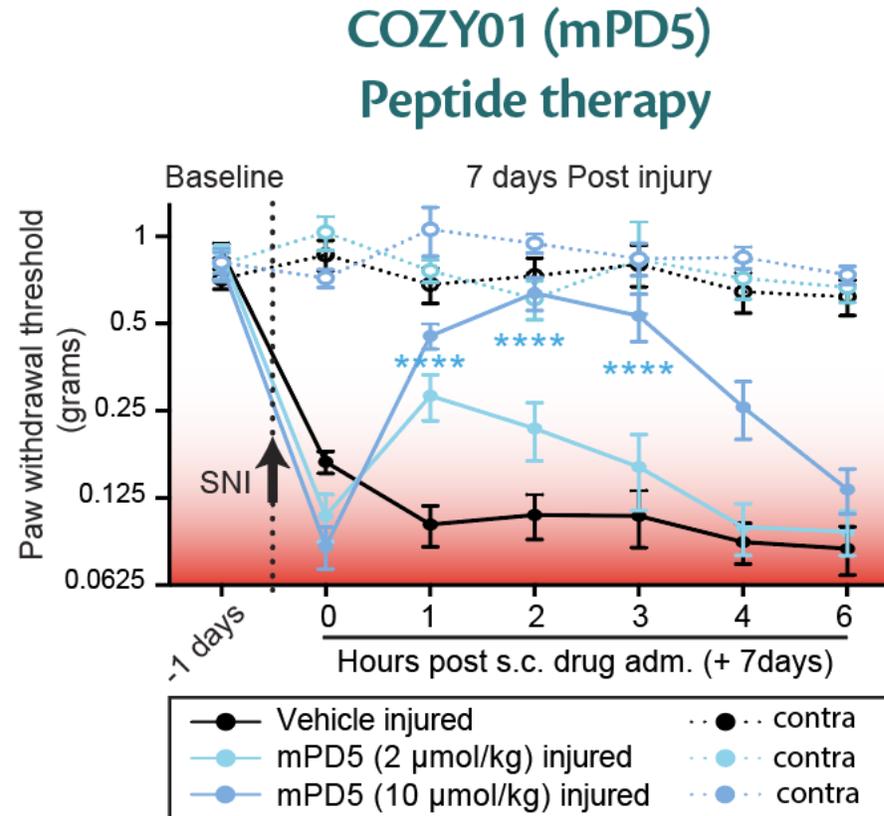
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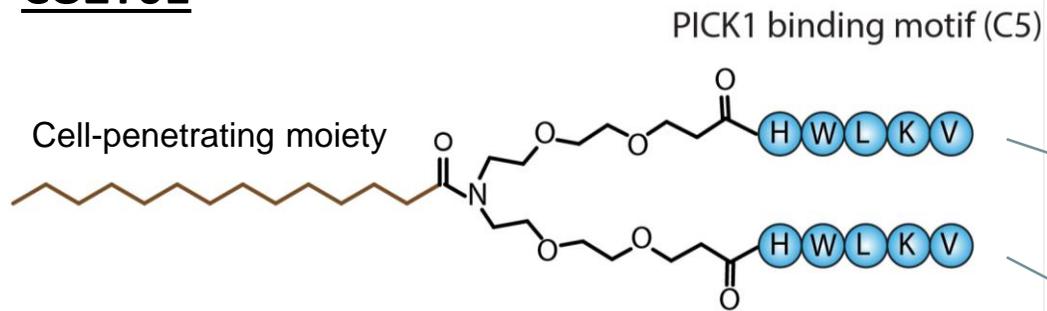
Excessive sensitivity



*Dose-dependent reversal of hypersensitivity*

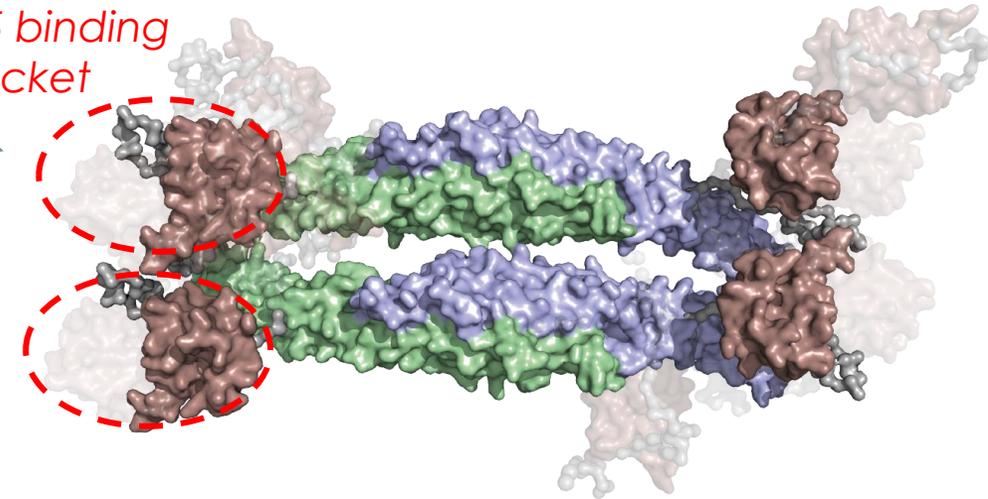
# Dimeric peptide ligands enable high-affinity blockade of PICK1

## COZY01



PICK1 – the target protein

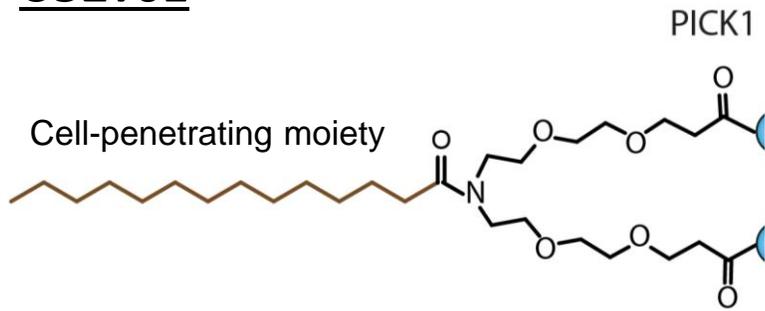
Two C5 binding pocket



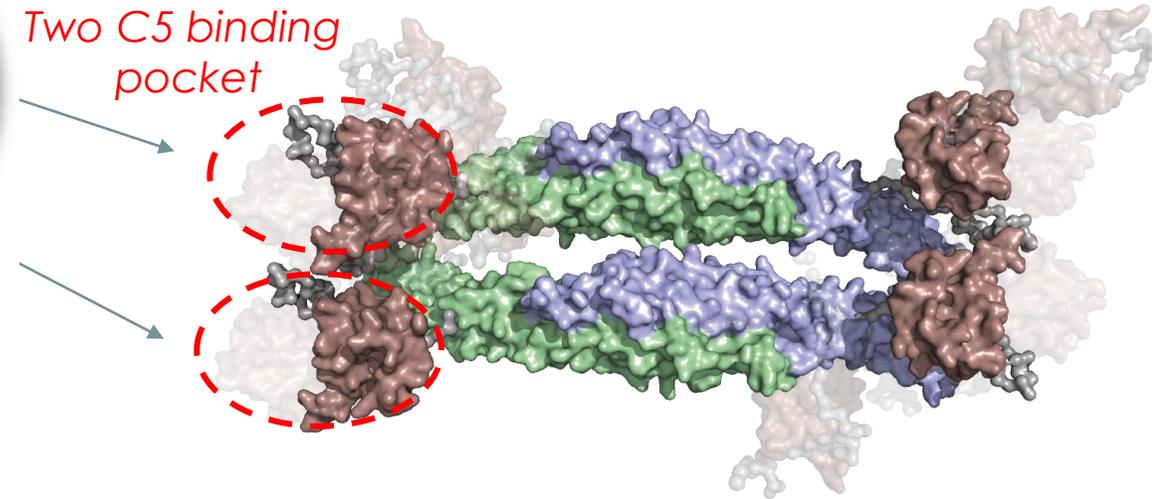
Christensen, De Luca et al, EMBO Mol. Med. 2020

# Dimeric peptide ligands enable high-affinity blockade of PICK1

## COZY01



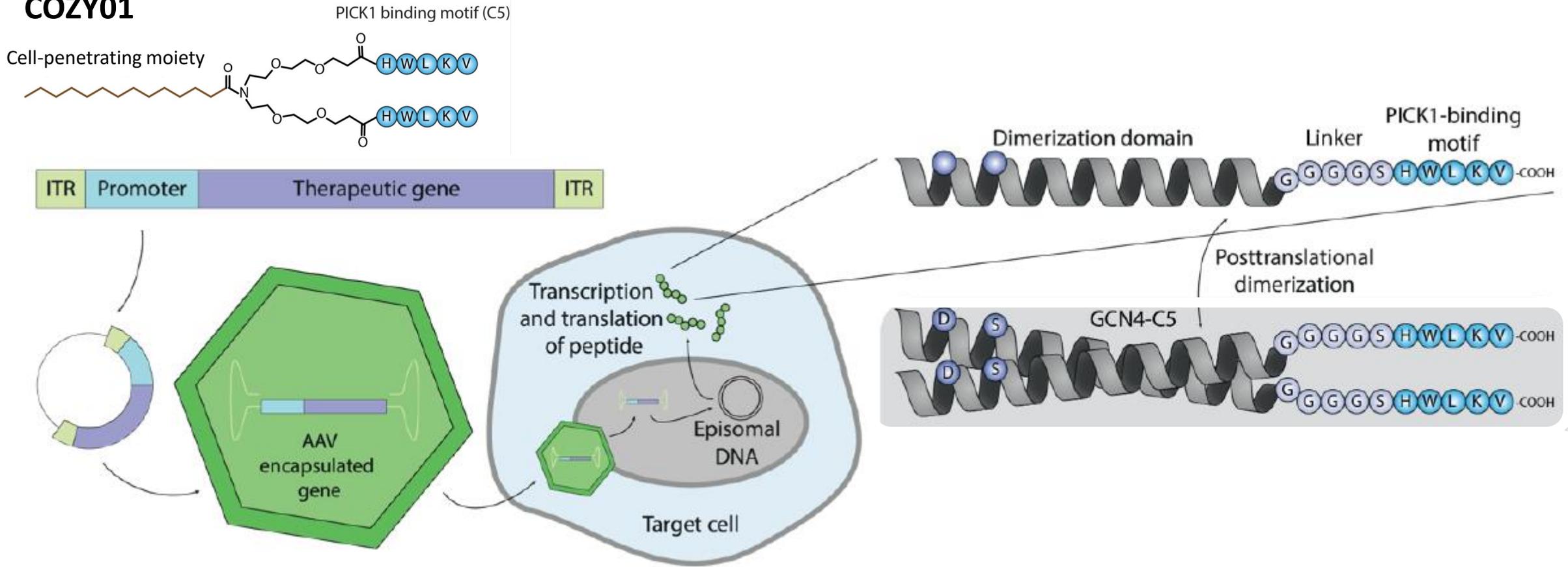
## PICK1 – the target protein



Christensen, De Luca et al, EMBO Mol. Med. 2020

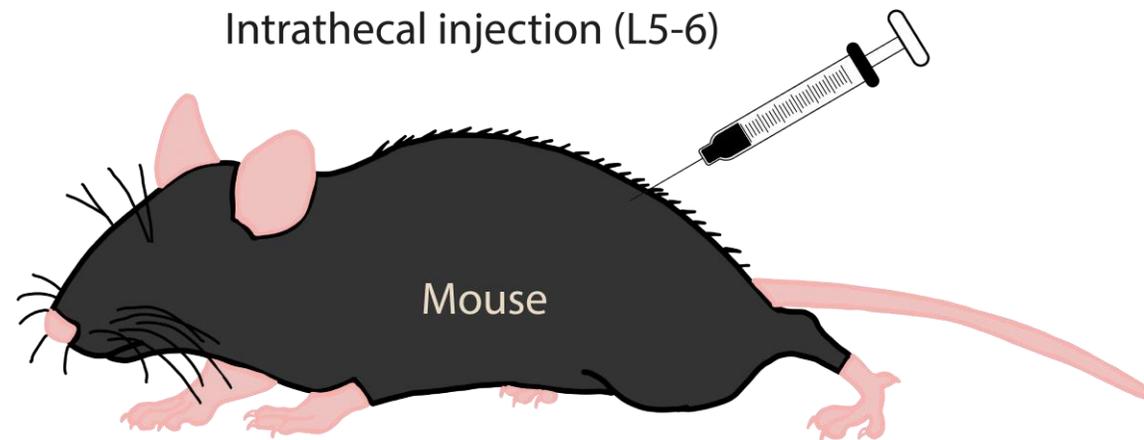
# An AAV-based platform for targeting PICK1: from DNA to peptide

## COZY01



# PICK1 inhibitor delivered through AAV

- The prototype vectors were produced by adherent HEK293T triple transfection method
- Most *in vivo* studies have used AAV8
- The gene cassette is driven by the human synapsin promoter (hSyn)



# Can one injection with a gene therapy relief the pain?

Spared nerve injury (SNI) model

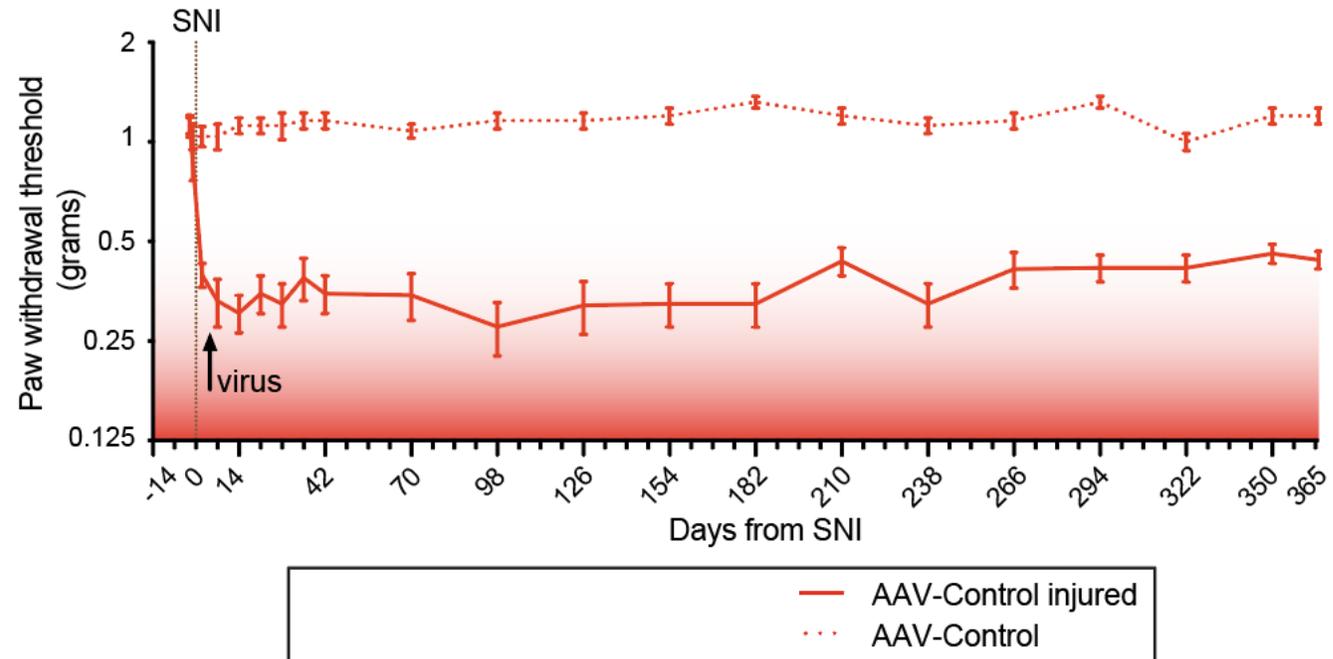
Read-out: mechanical sensitivity

Normal sensitivity



Excessive sensitivity

## AAV-C5 weak dimer Gene therapy



# Long-term Pain Relief in Neuropathic pain model

Spared nerve injury (SNI) model

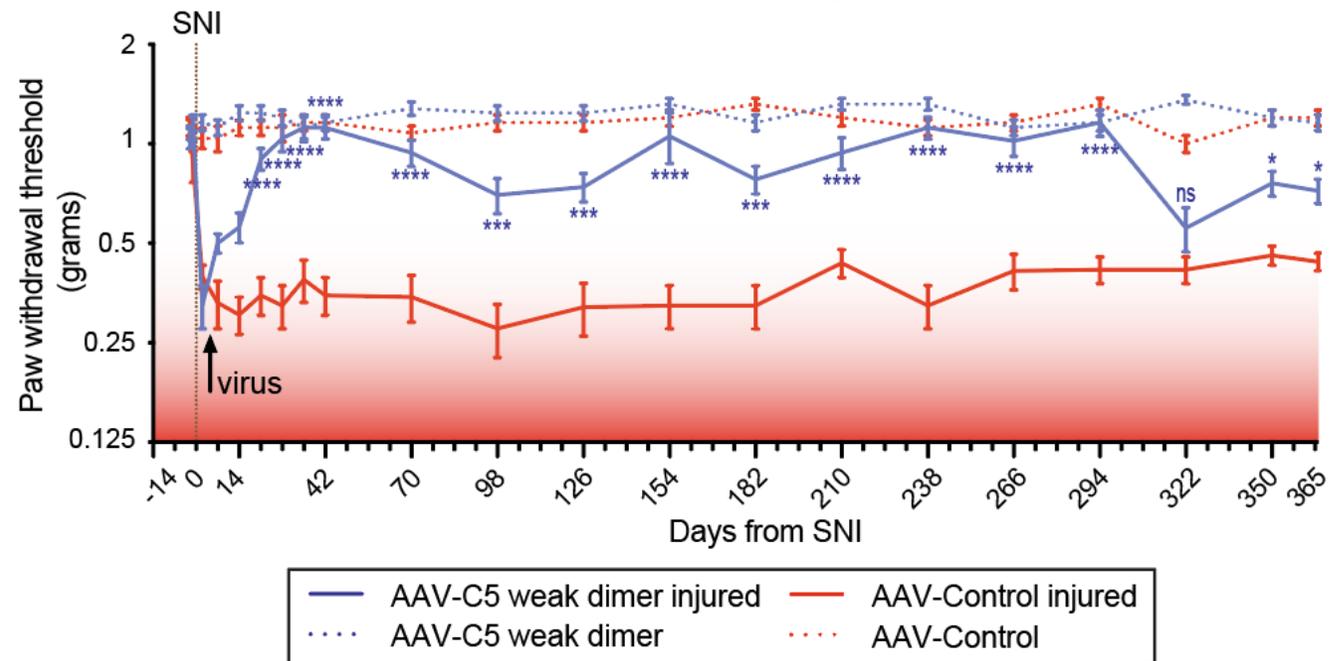
Read-out: mechanical sensitivity

Normal sensitivity



Excessive sensitivity

## AAV-C5 weak dimer Gene therapy



*Reversal of hypersensitivity*

# Administration of AAV in the chronic SNI phase

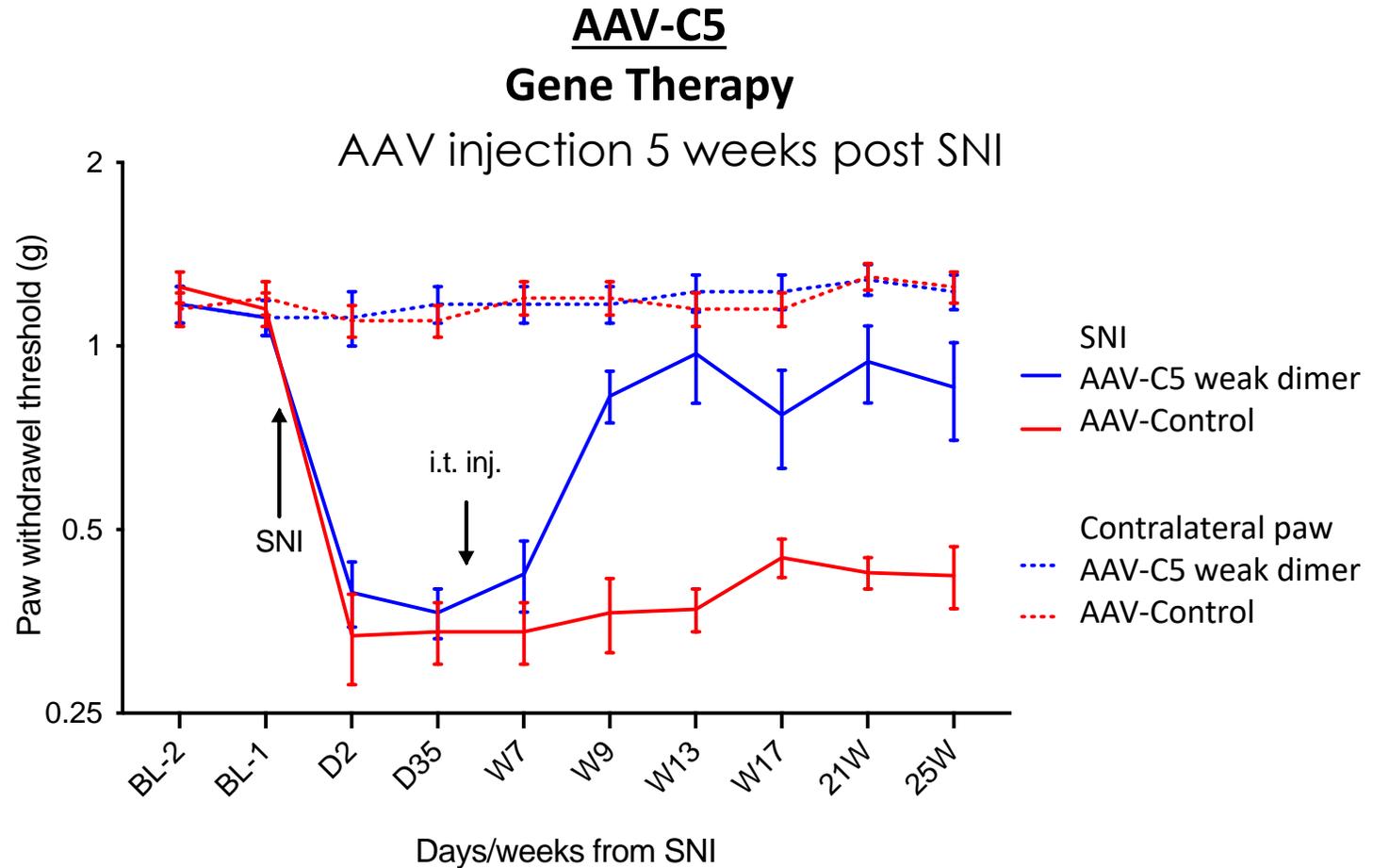
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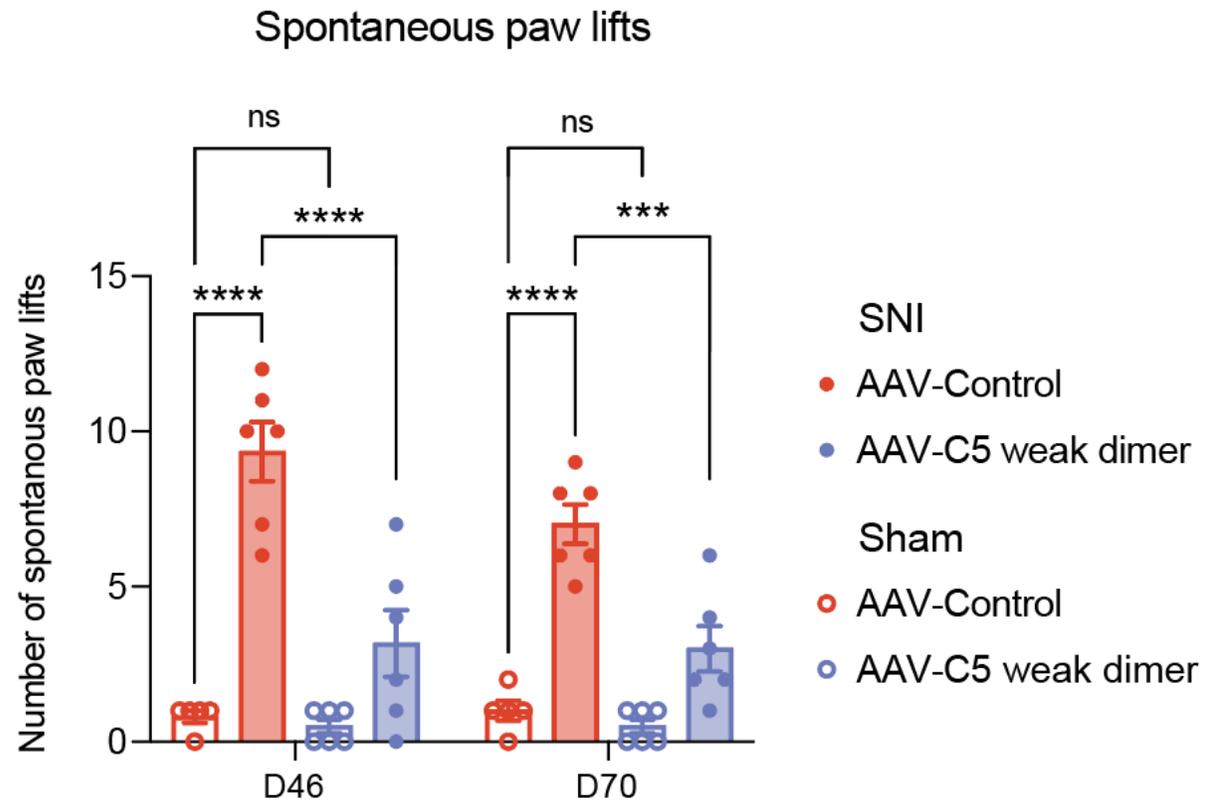


Excessive sensitivity



*Reversal of hypersensitivity after AAV treatment in the chronic phase*

# Effect on spontaneous pain - SNI model



*Effect on spontaneous pain (SNI AAV-C5 vs SNI AAV-Control)*

# Summary of the COZY program

## COZY01 and COZY02 Efficacy shown in several pain models (SNI, CFA, STZ)

- Data has been verified by academic collaborators and CRO
- Efficacy in **both genders**
- Mode of action is peripheral and **without abuse liability**
- Effect on **spontaneous pain**
- **None** of the treatments/modalities affects **normal sensory perception**
- No side-effects on learning & memory, or on locomotion & balance

⇒ **Peptide CD candidate selected and AAV lead candidate is currently being finalized**



# Thank you!

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