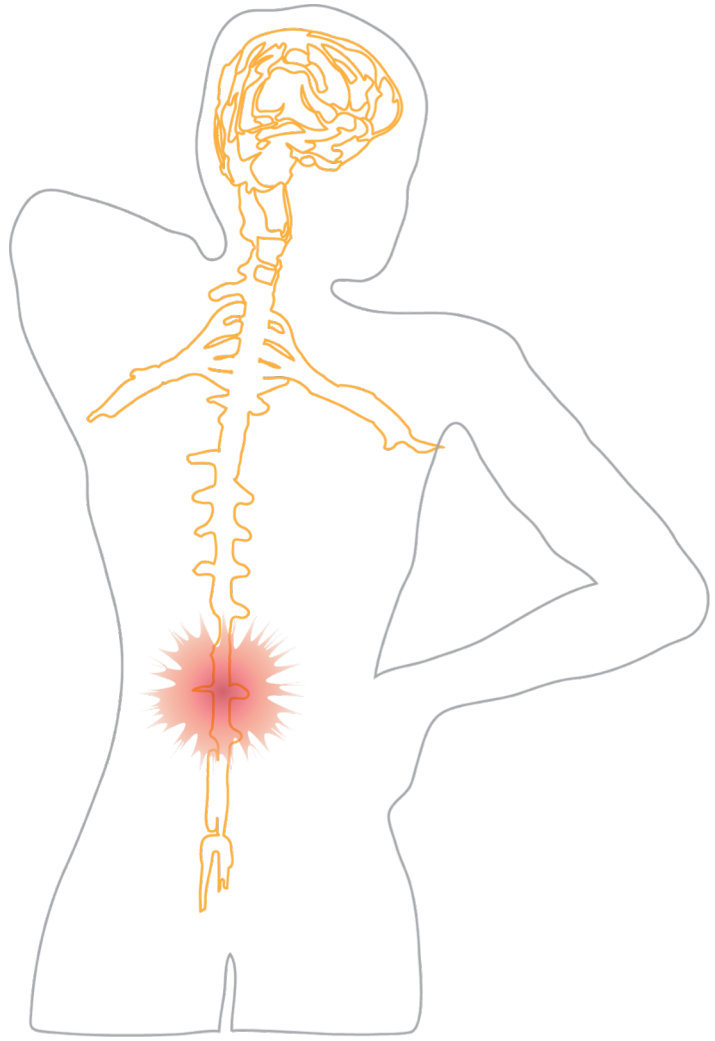
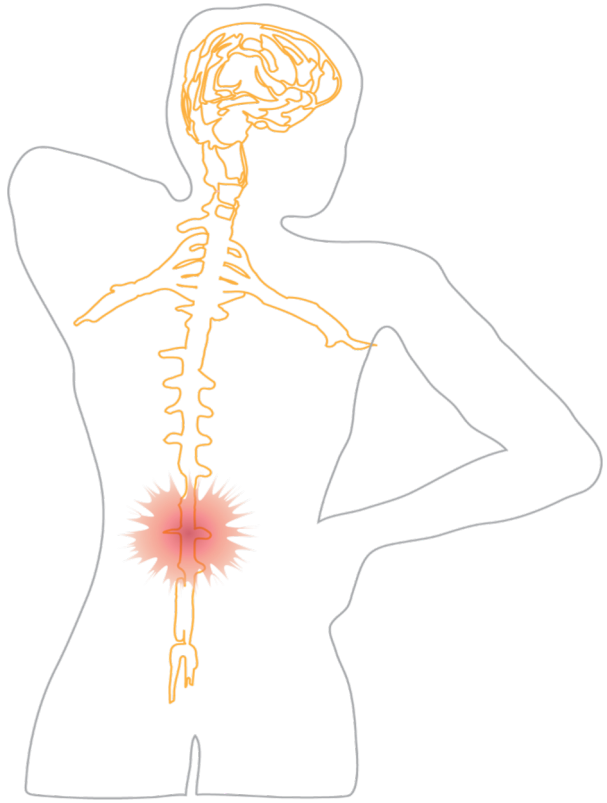
Targeting PICK1 – a novel pharmacological target for chronic pain treatment

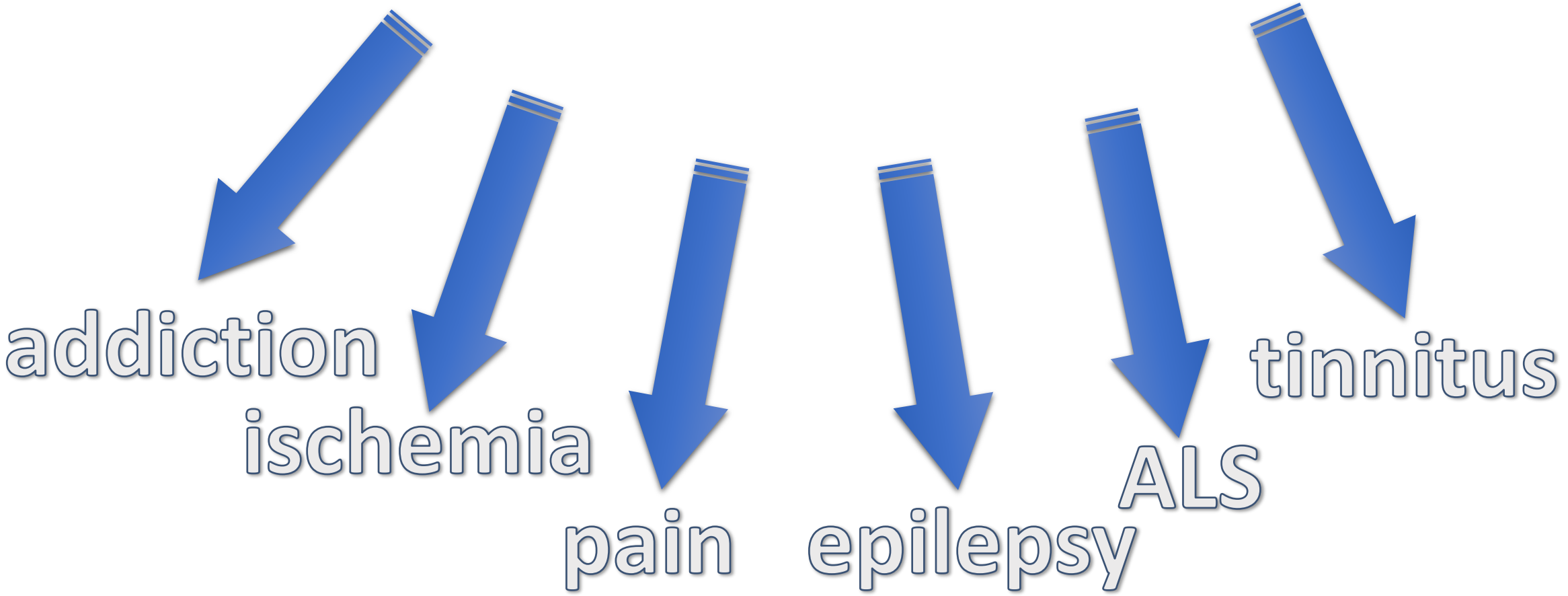


Highlights

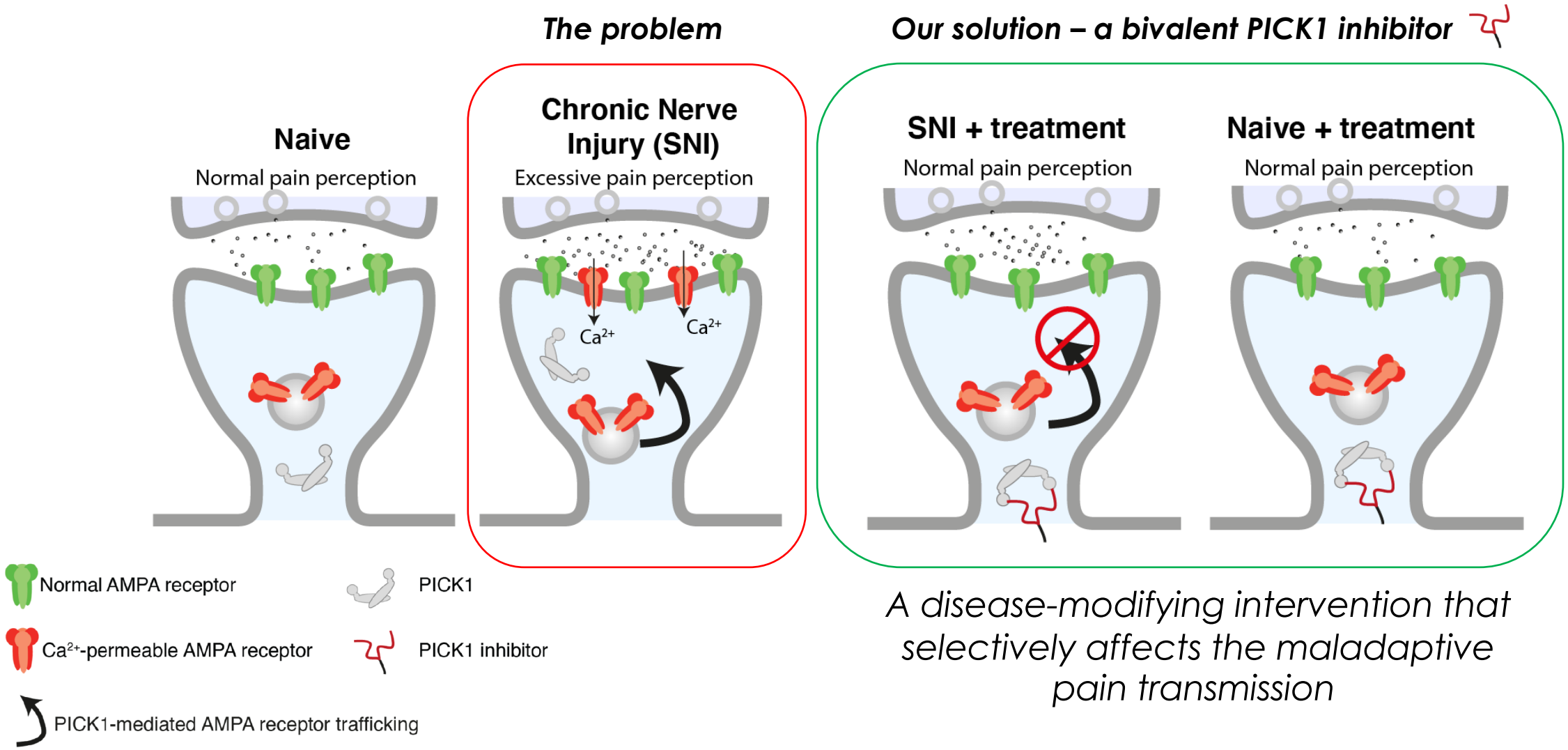
- A novel target in neuropathic pain and addiction treatment has been explored based on solid biological understanding of PICK1 protein
- Is advancing two treatment programs towards the clinic: peptide (lead candidate) and gene therapy (2nd generation)
- Demonstrated profound efficacy in diverse animal models of neuropathic pain
- No on-target side-effects observed



Targeting maladaptive plasticity in disease

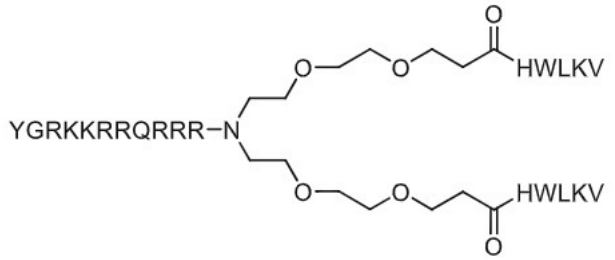


OUR SOLUTION – Preventing maladaptive insertion of calcium-permeable AMPA receptors



A disease-modifying intervention that selectively affects the maladaptive pain transmission

Publications



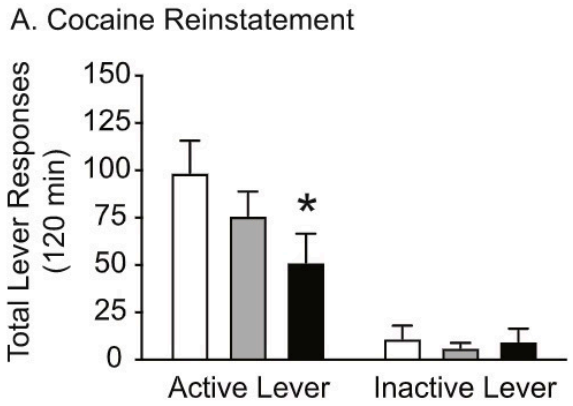
Article

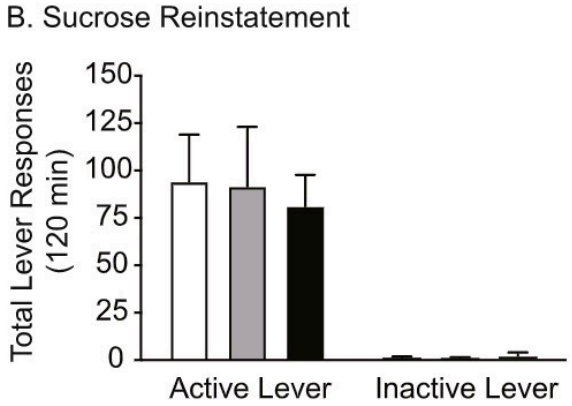
SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

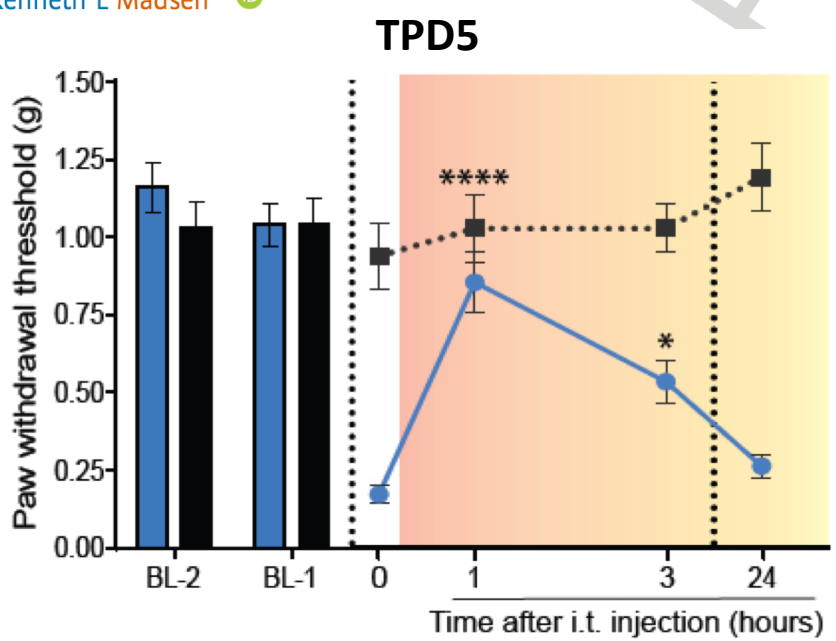
EMBO Molecular Medicine

A high-affinity, bivalent PDZ domain inhibitor complexes PICK1 to alleviate neuropathic pain

Nikolaj R Christensen[1,2,†], Marta De Luca[1,†], Michael B Lever[1], Mette Richner[3], Astrid B Hansen[1], Gith Noes-Holt[1], Kathrine L Jensen[1], Mette Rathje[1], Dennis Bo Jensen[4], Simon Erlendsson[5], Christian RO Bartling[2], Ina Ammendrup-Johnsen[1], Sofie E Pedersen[1], Michèle Schönauer[2], Klaus B Nissen[2], Søren R Midtgaard[6], Kaare Teilum[5], Lise Arleth[6], Andreas T Sørensen[1], Anders Bach[2], Kristian Strømgaard[2], Claire F Meehan[4], Christian B Vægter[3], Ulrik Gether[1] & Kenneth L Madsen[1,*]







Administration of a novel high affinity PICK1 PDZ domain inhibitor attenuates cocaine seeking in rats

Christopher Turner[a,1], Marta De Luca[b,1], Jordan Wolfheimer[a,1], Nicole Hernandez[c], Kenneth Lindegaard Madsen[b], Heath D. Schmidt[a,d,*]

[a] *Department of Biobehavioral Health Sciences, School of Nursing, University of Pennsylvania, Philadelphia, PA, 19104, USA*
[b] *Department of Neurosciences, Faculty of Health Sciences, University of Copenhagen Blegdamsvej 3, DK, 2200, Copenhagen, Denmark*
[c] *Neuroscience Graduate Group, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA*
[d] *Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA*

Neuropharmacology

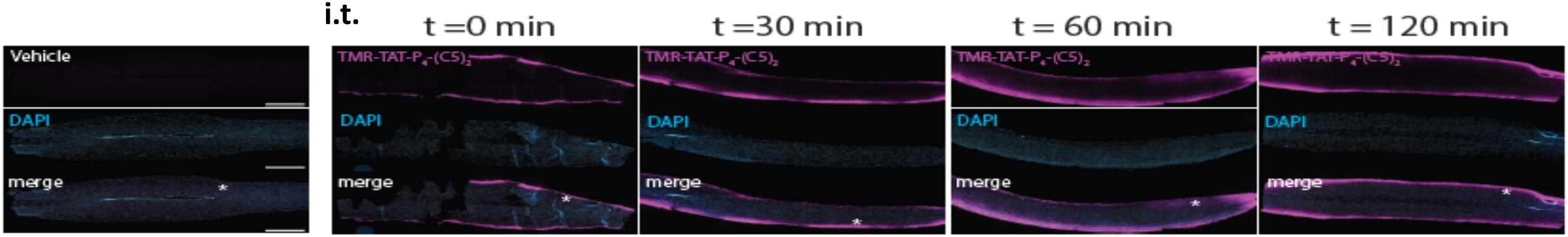
HIGHLIGHTS

- Systemic infusions of the novel PICK1 inhibitor TAT-P_4-$(DATC5)_2$ cross the blood brain barrier and attenuate cocaine seeking.
- TAT-P_4-$(DATC5)_2$ accumulates in medium spiny striatal neurons and binds PICK1.
- Administration of TAT-P_4-$(DATC5)_2$ directly into the nucleus accumbens shell attenuates cocaine, but not sucrose, seeking.

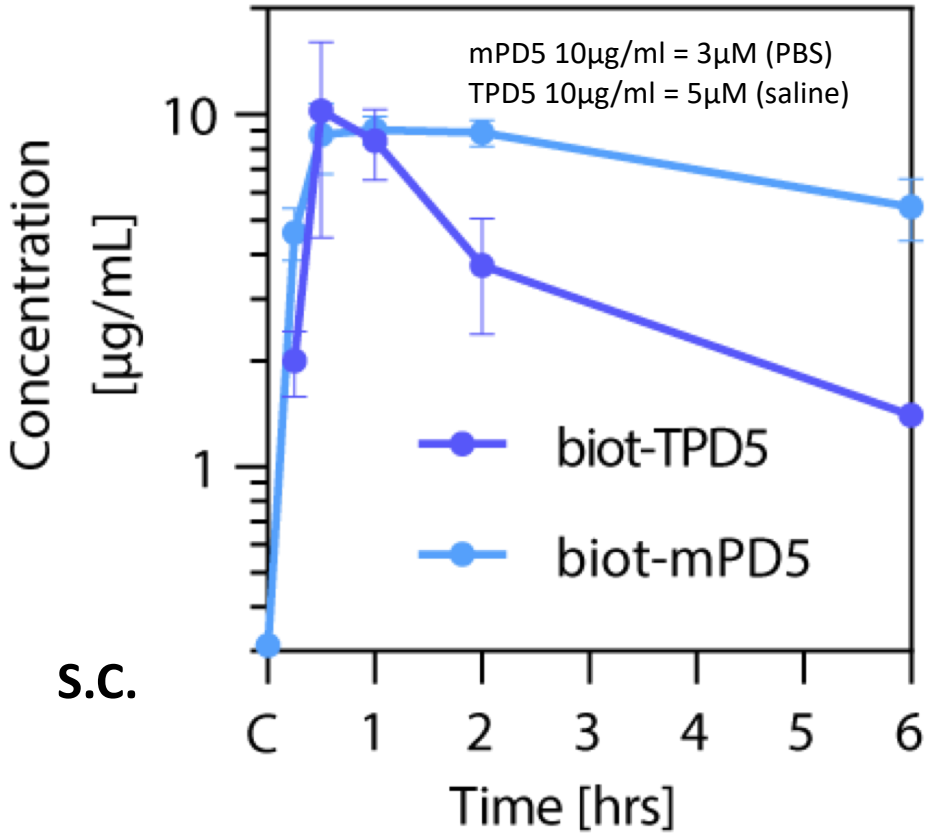
Kinetics

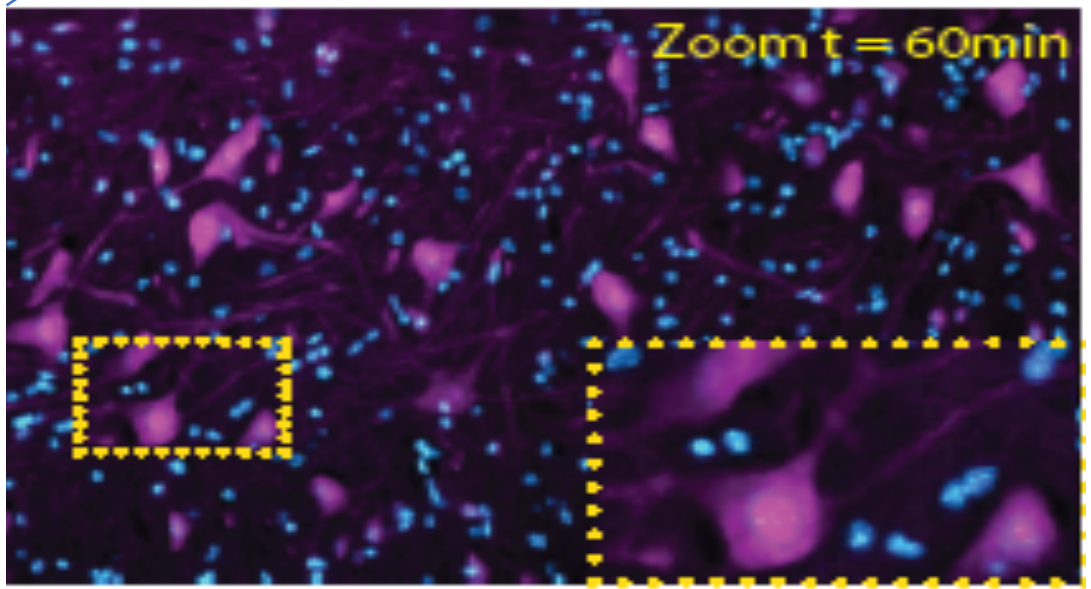
Christensen, De Luca et al., EMBO Molecular Medicine, 2020

i.t.



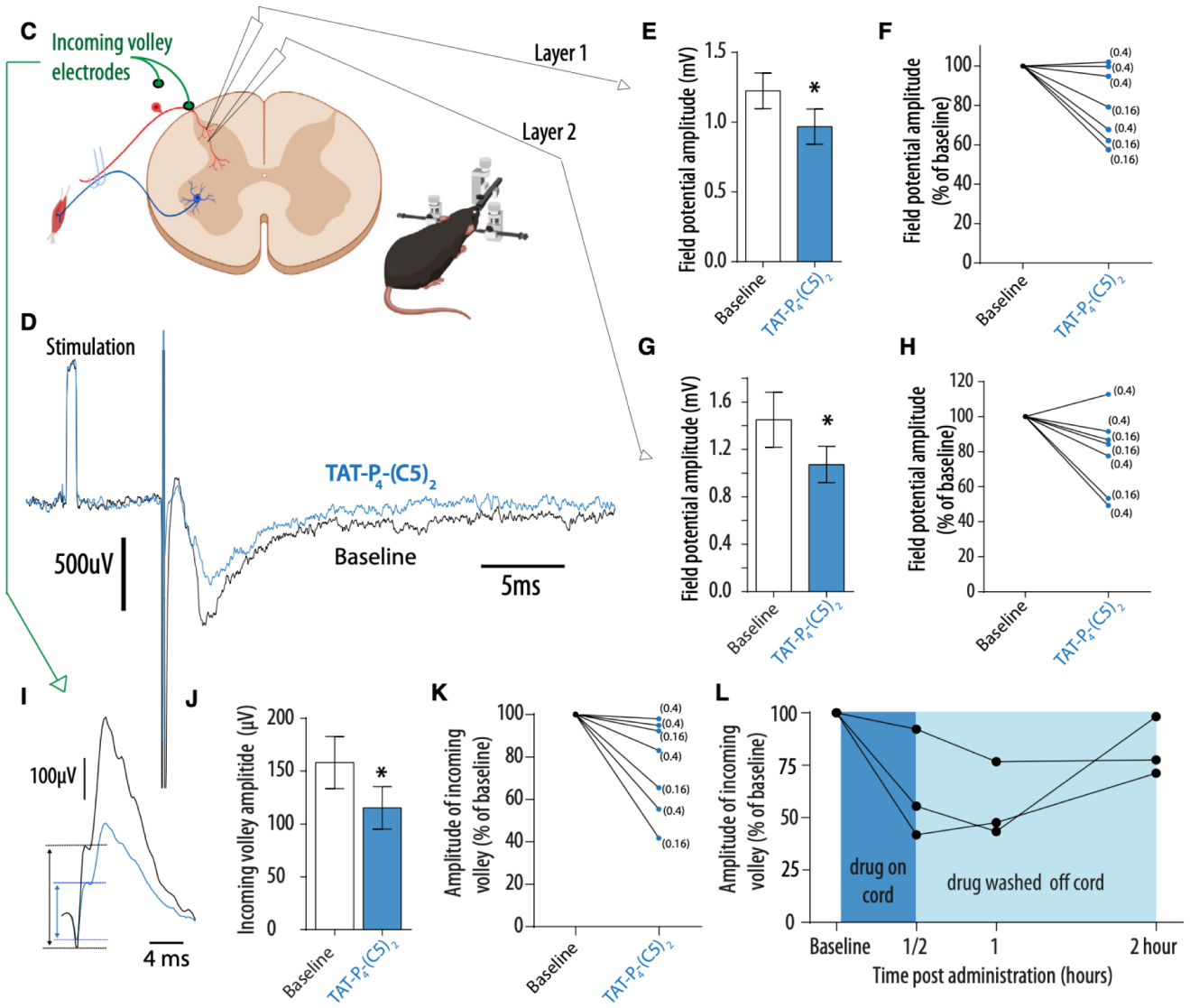
s.c.





Conclusion: TPD5 enter spinal cord and neurons

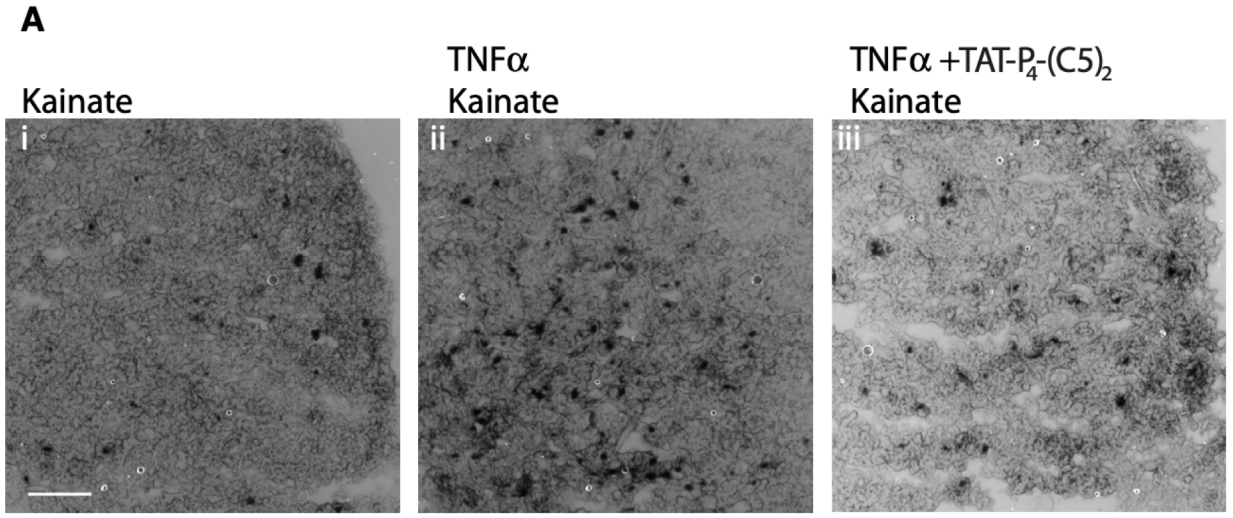
In vivo e.phys recordings in spinal cord from SNI animals

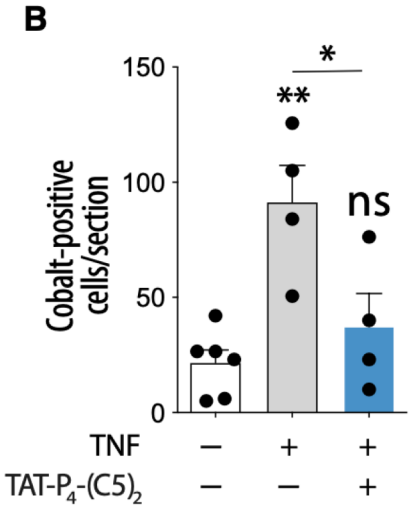


Christensen, De Luca et al., EMBO Molecular Medicine, 2020

Conclusion: TPD5 reduces hyperexcitability both pre- and postsynaptically

Cobalt influx through (CP-AMPARs) from spinal cord sections

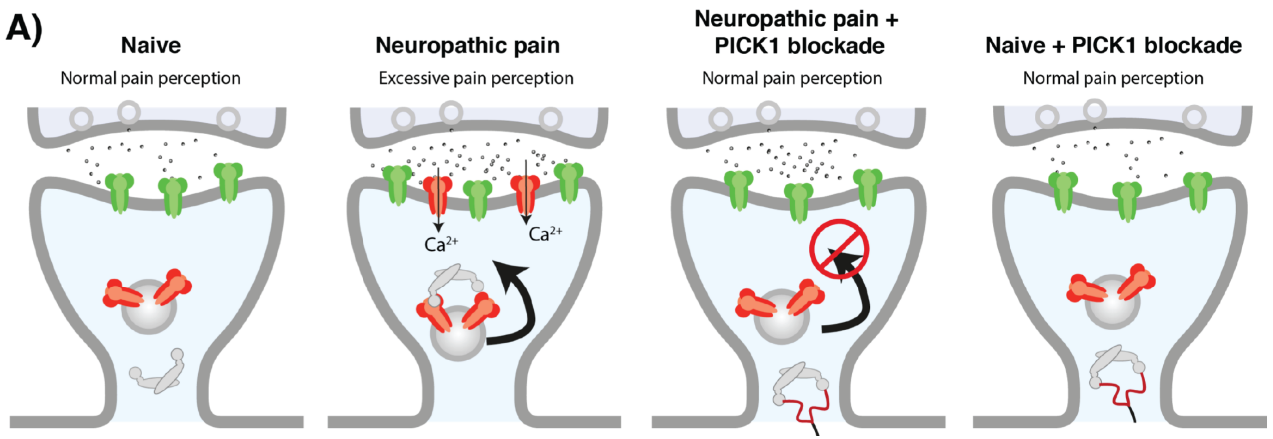


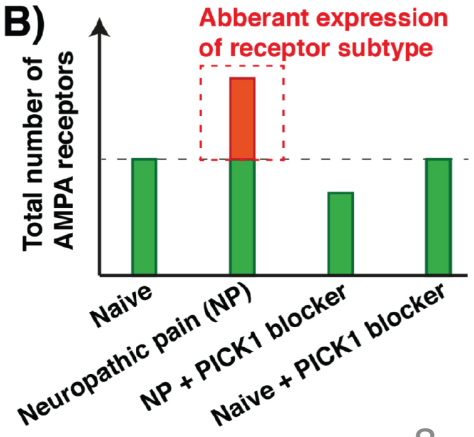


Conclusion: TPD5 reduces Ca^{2+} influx induced by TNF

Christensen, De Luca et al., EMBO Molecular Medicine, 2020

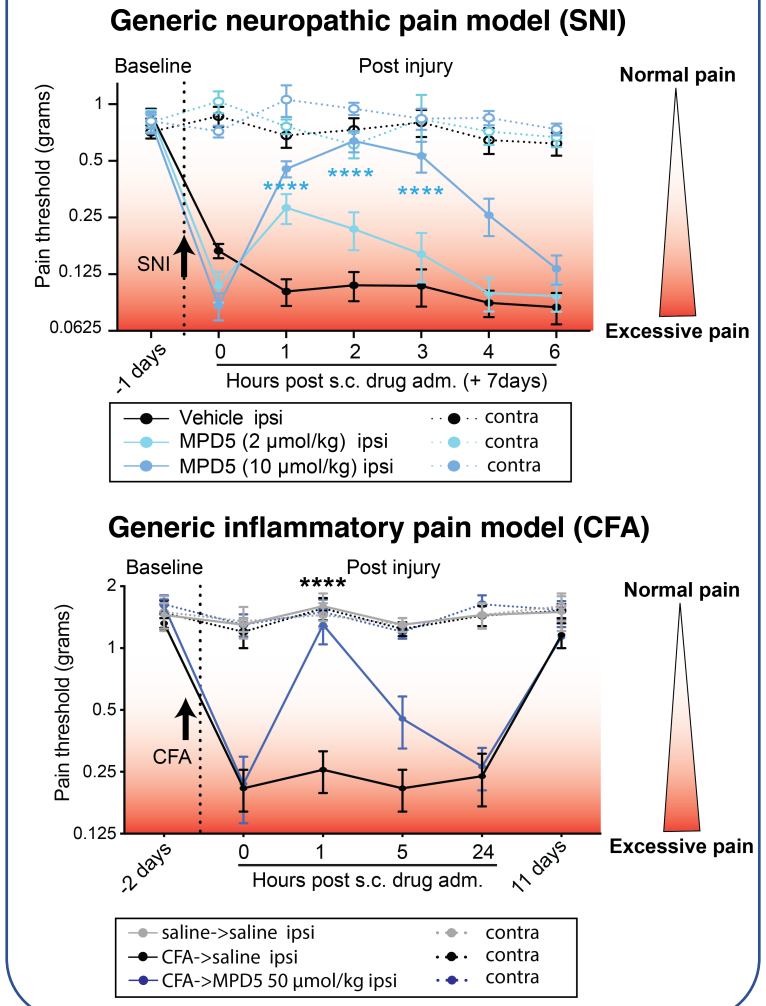
Original and present MoA working model



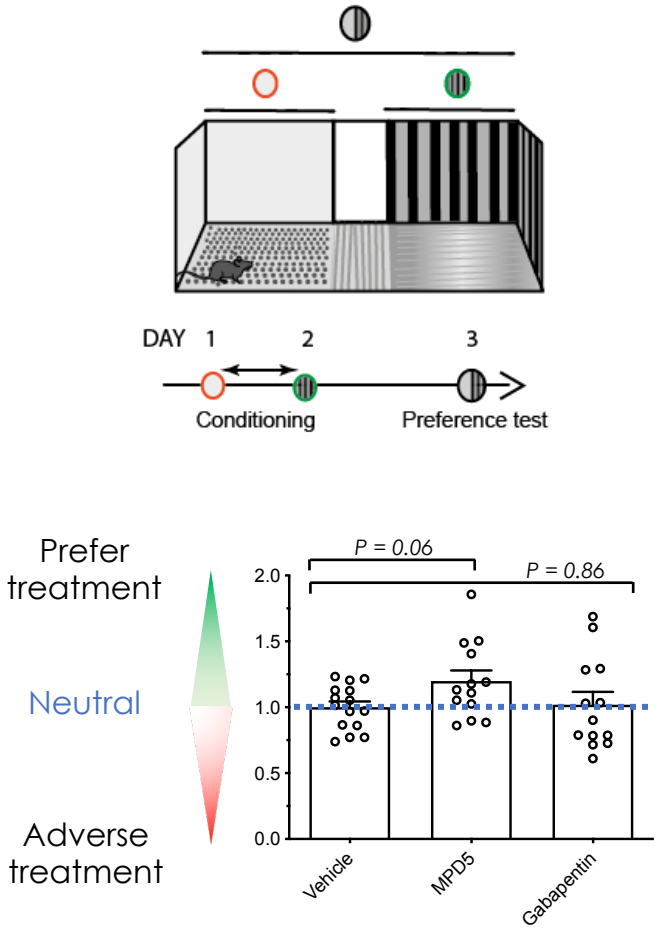


Efficacy across etiology and modality

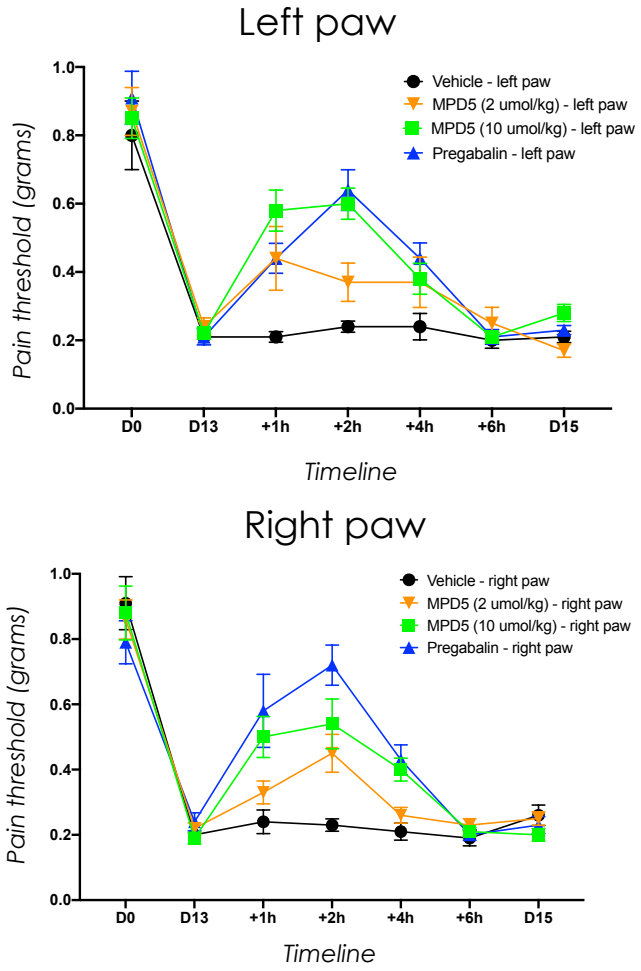
SNI and CFA model (mechanical allodynia)



CFA model (spontaneous pain)



STZ model (mechanical allodynia)



Phenotype Expertise(Fr)/University of Copenhagen(DK)/University of Aarhus(DK)

Unpublished

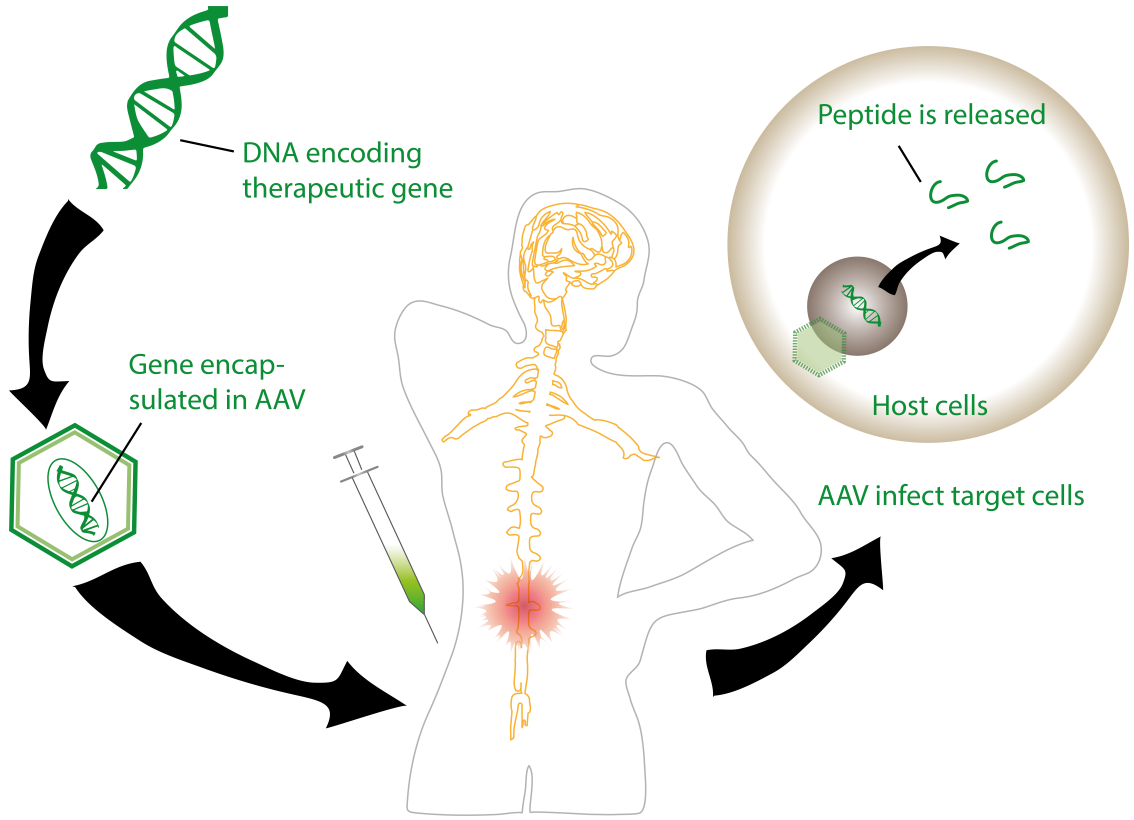
AAV a 2nd generation delivery platform

Product portfolio strategy

Administration of synthetic peptide has been selected for initial PoC in humans to optimize timelines and mitigate risk

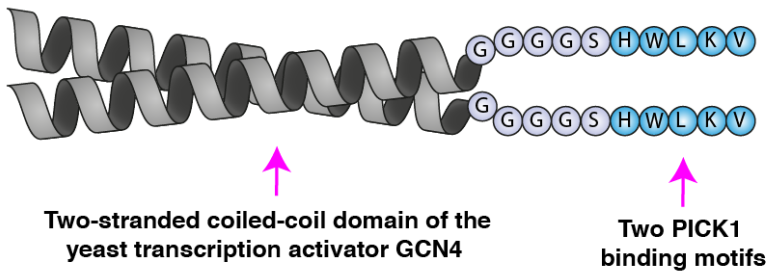
Animal studies confirm gene therapy as potent 2nd generation product or viable backup to the peptide approach

Positive patient response to MPD5 treatment can gate for gene therapy intervention (mitigating route through regulatory pathway)



Gene therapy fully relieve abnormal pain in animal models

A



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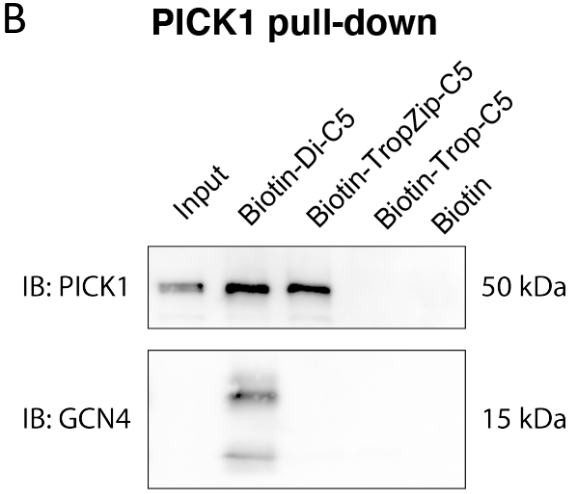

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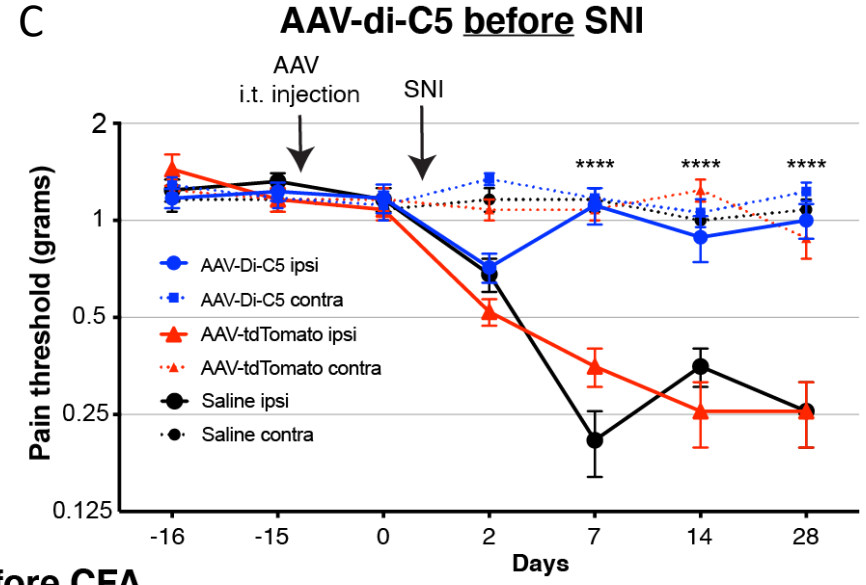

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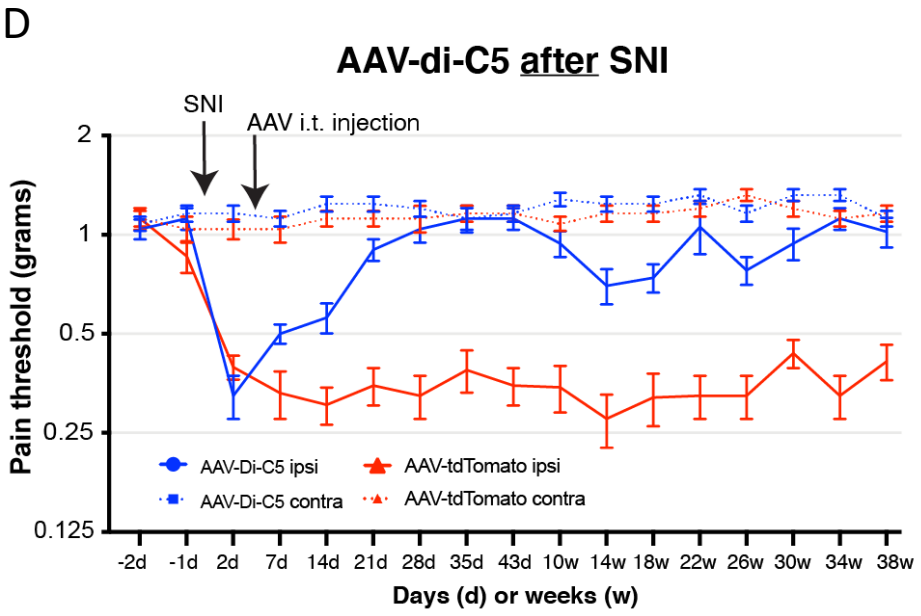

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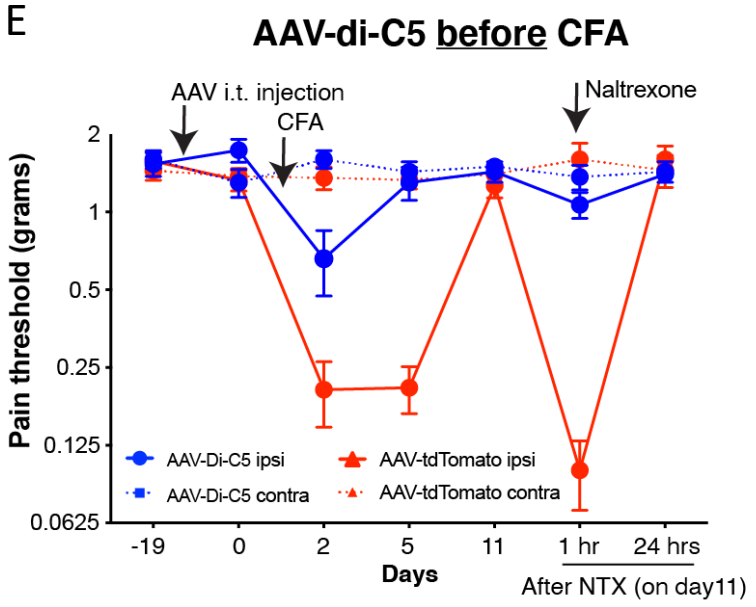

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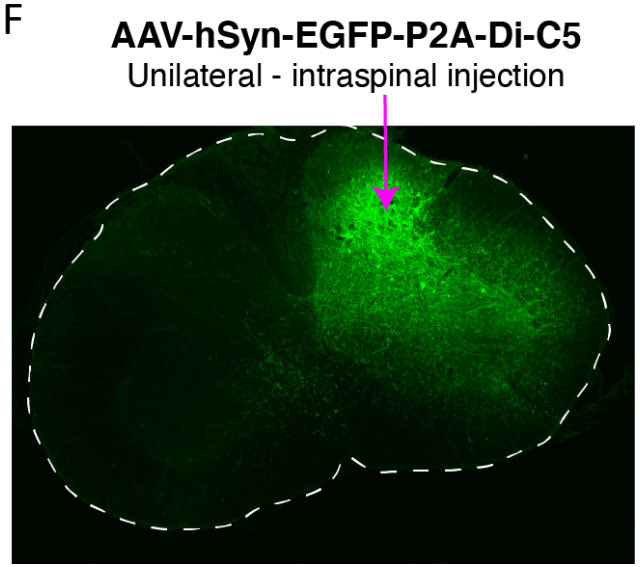


Unpublished

Test of putative on-target effects of PICK1 inhibition

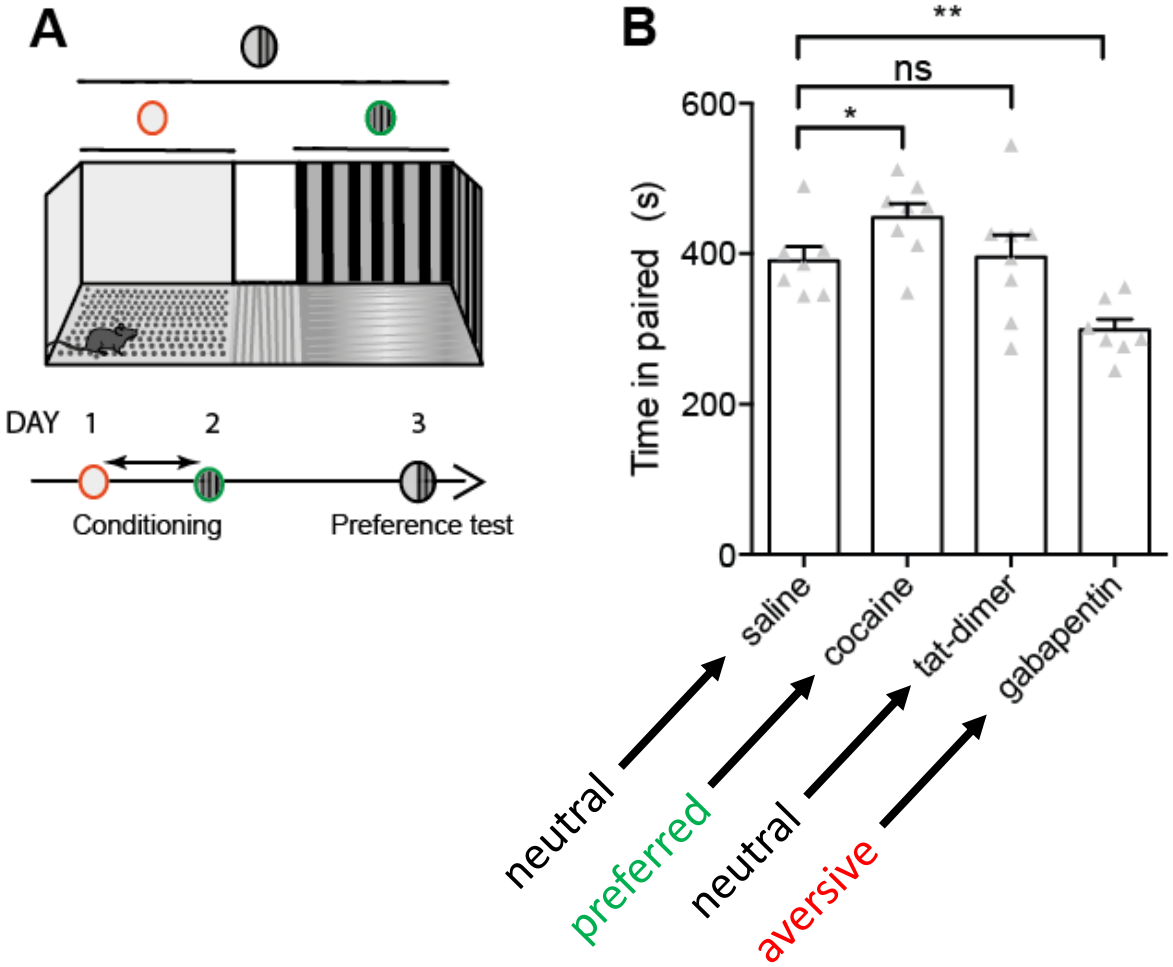
- **PICK1 is involved in insulin granule biogenesis**
  - **DATA**: No effect on insulin levels and glucose metabolism after daily administration of MPD5 for 7 consecutive days
- **PICK1 is involved in synaptic transmission**
  - **DATA:** No effect on basal locomotion or balance (MPD5 and AAV-C5)
- **PICK1 is involved in synaptic plasticity underlying learning and memory**
  - **DATA:** No effect on spatial learning and memory retrieval (testing MPD5 in the Barnes Maze)
- **PICK1 has a role in addiction**
  - **DATA:** No abuse liability of TPD5 and MPD5 (contextual place preference test)
  - **DATA:** TPD5 attenuates cocaine seeking (published results, see link below)
- **Male PICK1 KO mice are infertile**
  - No assessment made
- **PICK1 KO mice reported to facilitate the induction of absence epilepsy**
  - No assessment made – but no phenotype observed (TPD5, MPD5, AAV-C5)

Link to TDP5 and cocaine addiction: https://doi.org/10.1016/j.neuropharm.2019.107901

Test of putative on-target effects of PICK1 inhibition

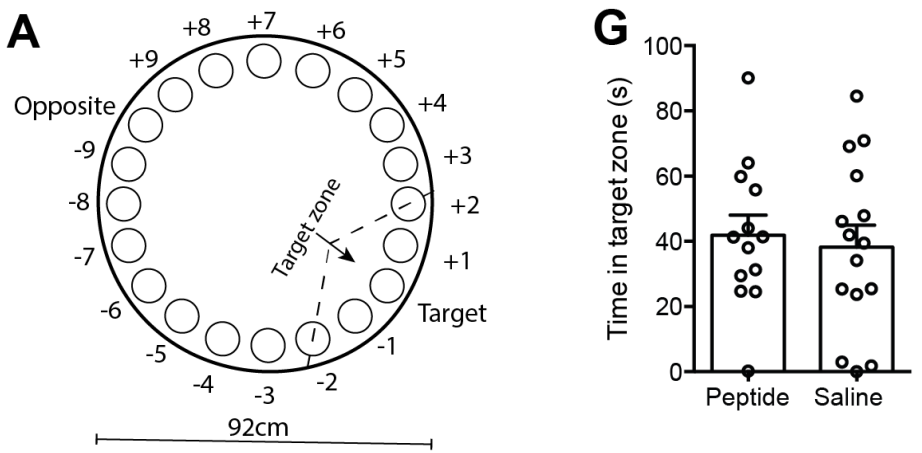
Neutral abuse liability profile

Single exposure place preference (sePP)

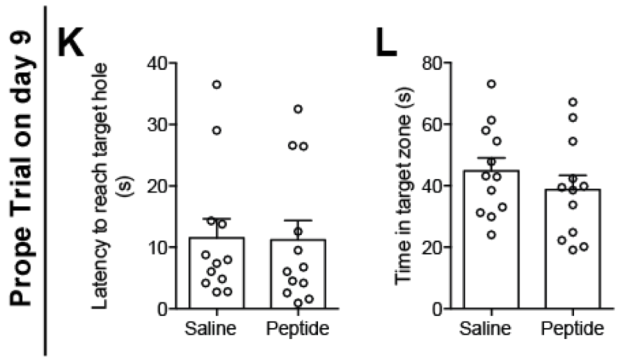


No effect on memory performance

Barnes maze (memory recall)



Barnes maze (reversal learning)



Existing IP position of DolorestBio's technology

Synthetic peptides

PCT appl. WO2020083905
Inhibitors of PICK1 and uses thereof

Priority appl. EP20161524
A fatty acid bivalent inhibitor targeting PICK1

Gene therapy – recombinant peptides

PCT appl. WO2020083916
Virally expressed inhibitors of PDZ domains, such as PICK1 and uses thereof

Priority appl. EP20161493
Viral multimeric peptide constructs for targeting PDZ domains

Third-party overview

No immediate blocking third-party patent positions

Exclusive license from UCPH