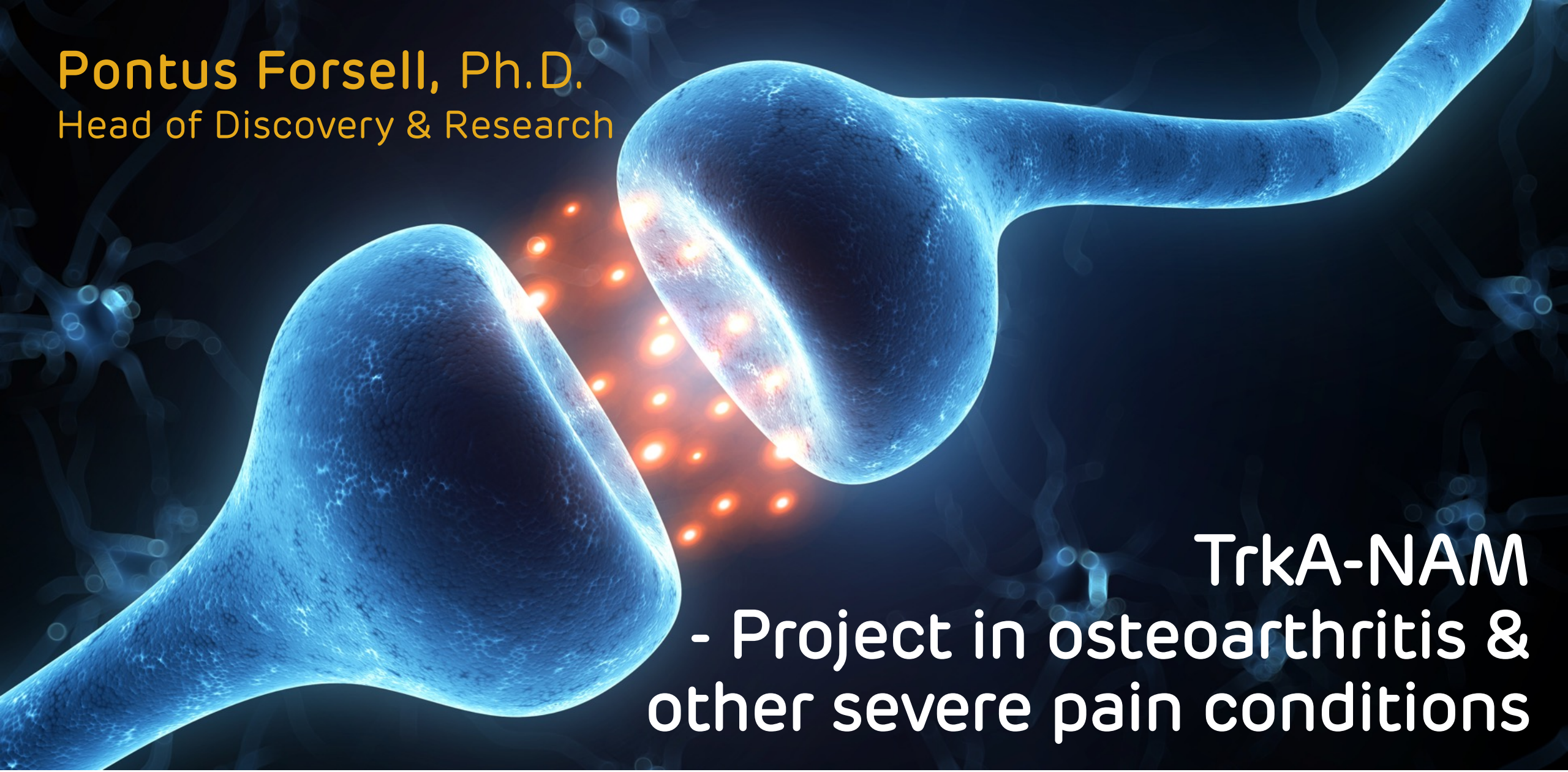
Pontus Forsell, Ph.D.
Head of Discovery & Research



TrkA-NAM
- Project in osteoarthritis & other severe pain conditions

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TrkA-NAM: Goal and background

The goal is to develop selective negative allosteric modulators (NAM) of TrkA for the treatment of osteoarthritis (OA) pain and other severe pain disorders

PROJECT OVERVIEW

Validated pathway	› Mutations in NGF* or TrkA leads to loss of pain perception in man › Anti-NGF antibodies is step changing but demonstrate side-effects
TrkA-NAM Lead optimization	› Potent and selective TrkA-NAMs has been synthesised by AlzeCure › Compounds are active both in a model of arthritic pain and in a model of neuropathic pain
Nociceptive and neuropathic pain	› Large unmet medical need for osteoarthritic pain, neuropathic pain and other severe pain disorders, including need for alternatives to opioids › Blockbuster opportunities for a new analgesic therapy that would avoid adverse events

*) NGF = Nerve Growth Factor

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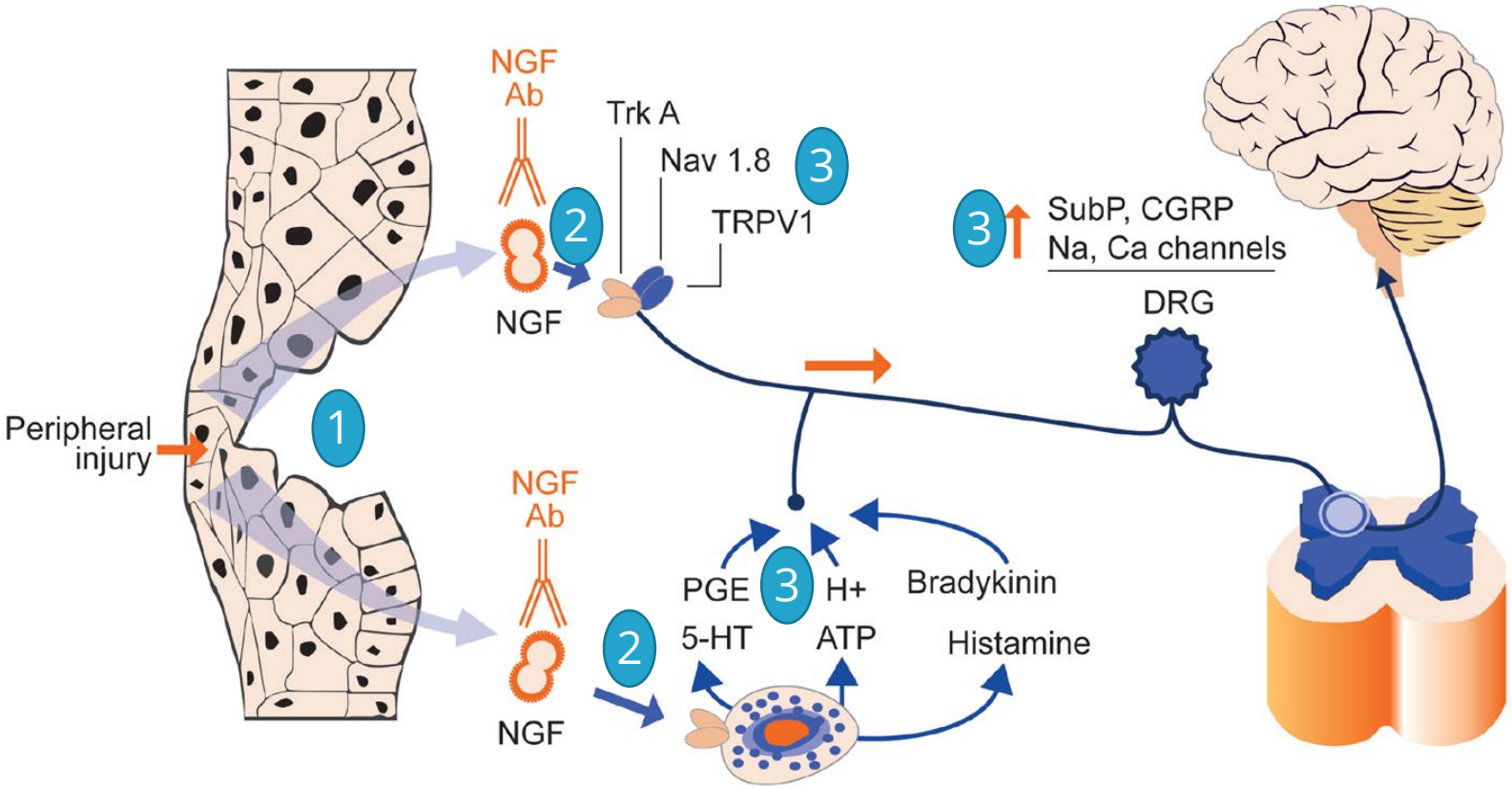
Background: NGF/TrkA and their role in pain sensation

- **1.** NGF is released at the site of an injury.
- **2.** TrkA is the receptor for NGF and it is located on neuronal and on non-neuronal cells.
- **3.** NGF leads to increased pain in several different ways.



NGF and TrkA are involved in pain signaling in both nociceptive and neuropathic pain

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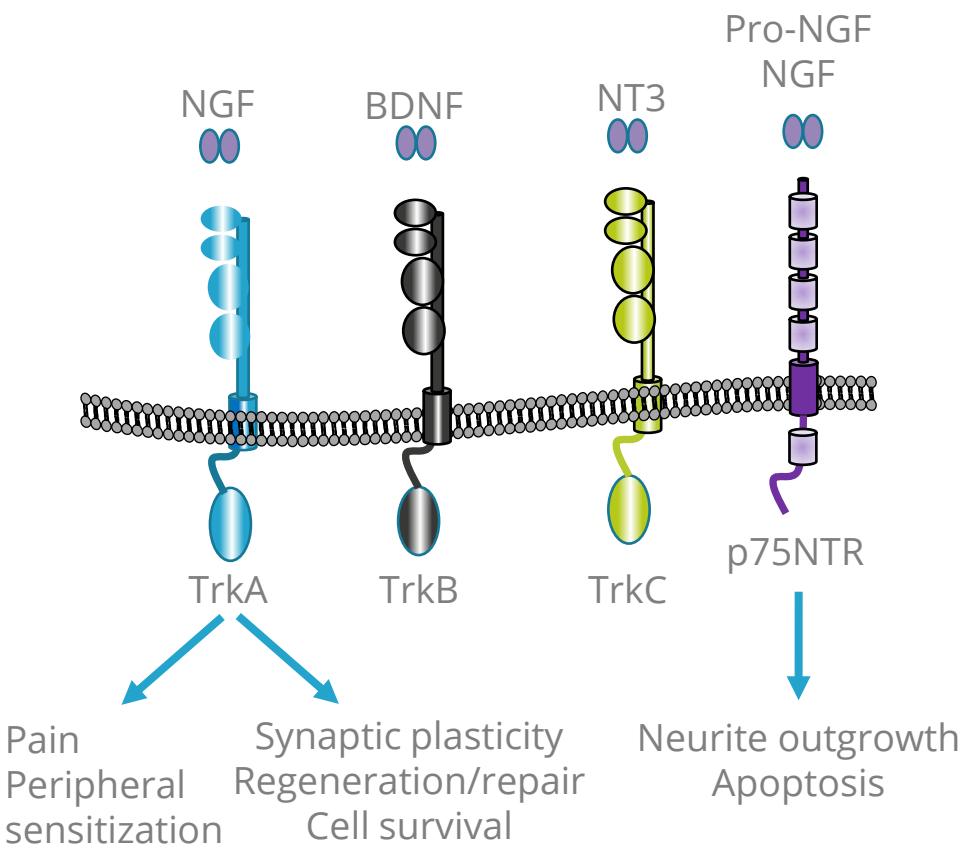
Background: NGF signalling is mediated by its receptors TrkA and p75NTR

- NGF belongs to the neurotrophins, also including BDNF, NT3 and NT4, that are essential for the central and peripheral nervous systems.
- Neurotrophins bind to TrkA, B or C-receptors and to the p75NTR receptor.
- The Trk-receptors are the target for our positive allosteric modulators in NeuroRestore.

- TrkA is the target for TrkA-NAM.
- Small molecules has advantages over antibodies, and they can have complementary roles in pain.



TrkA-NAM is a more selective mechanism than Trk-inhibitors or anti-NGF antibodies.

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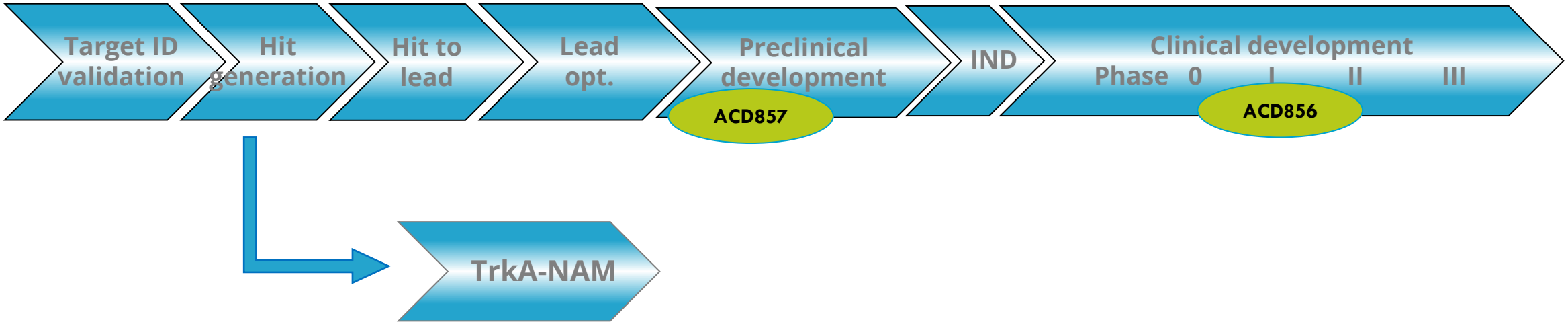
Background: AlzeCure's TrkA-NAM program

AlzeCure's TrkA-NAM program originates from the NeuroRestore platform

NeuroRestore, positive allosteric modulators of Trk-receptors



TrkA-NAM, negative allosteric modulator of TrkA

The identification of TrkA-NAM adds further value to our shareholders in a cost-effective manner

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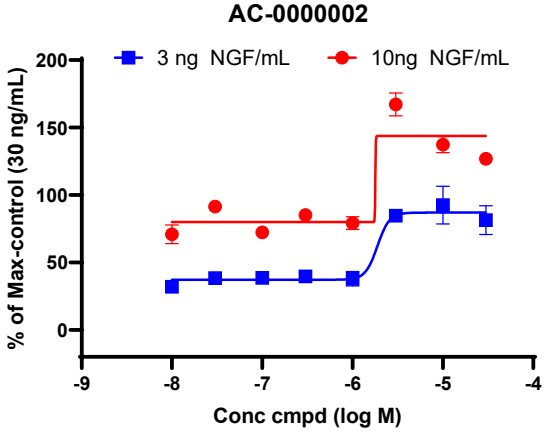
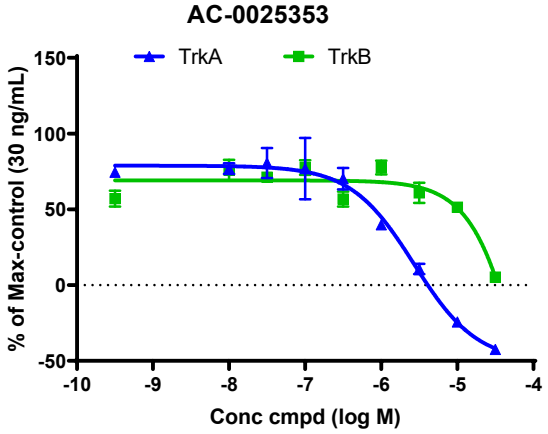
History: AlzeCure's TrkA-NAM program

- **2013**: A positive allosteric modulator of TrkA was identified
- **2015**: The first TrkA-selective negative allosteric modulator was identified
- **2020**: Highly potent and in vivo active TrkA-NAM compounds

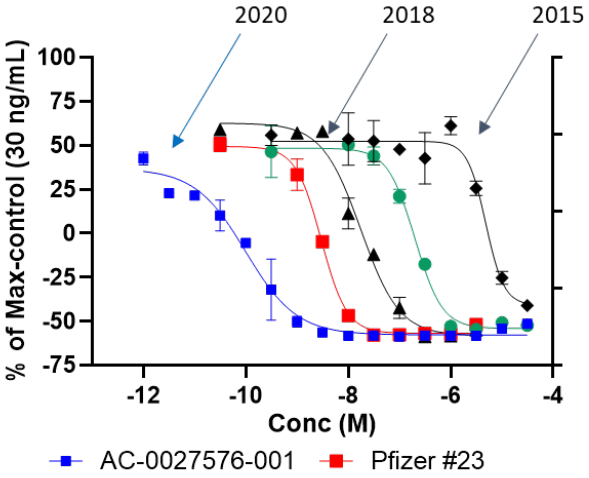
2013
First hit (NeroRestore)



2015
First selective TrkA-NAM



2020
Potent and selective TrkA-NAM's



Many compounds available for selection and development

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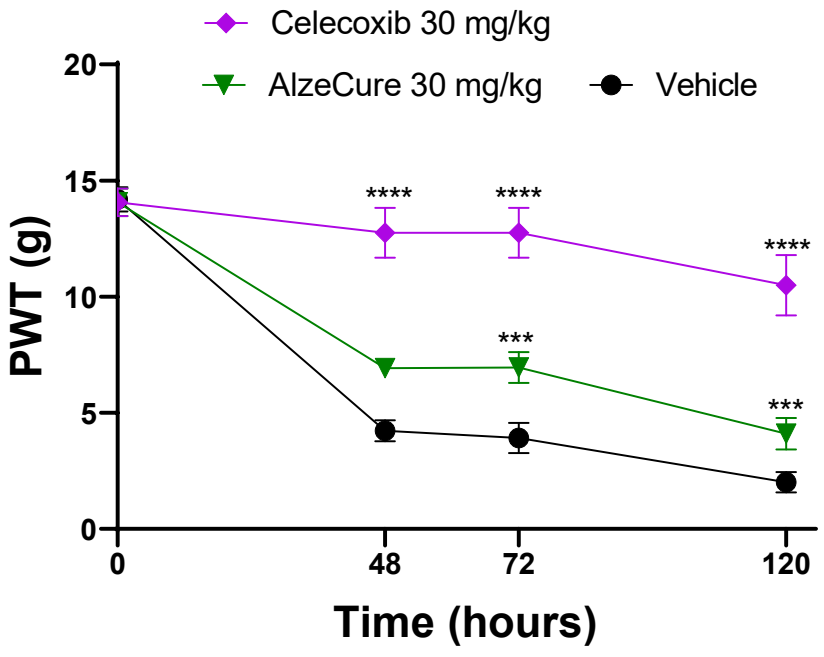
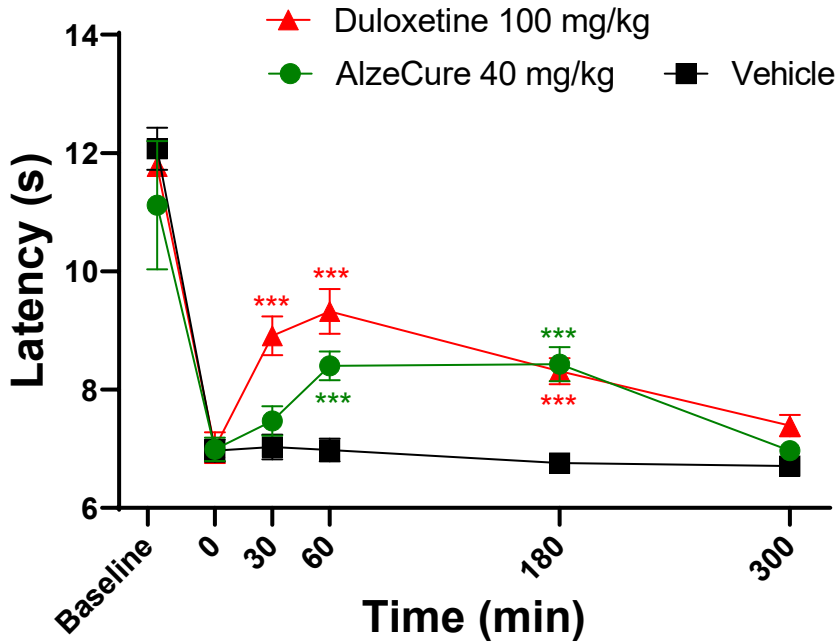
Efficacy: TrkA-NAM's are effective in different pain models

TrkA-NAM's have been demonstrated to have analgesic effects in several acute or chronic pain models

Model of osteoarthritis pain



Model of neuropathic pain



AlzeCure's TrkA-NAM is effective in both osteoarthritis pain and neuropathic pain models

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Competition: Limited competition with small molecule approach

Compound	Company	TrkA (nM)	TrkB (nM)	TrkA vs TrkB	Status	Indication
AC-0027628	**AlzeCure**	**0.004**	**1800**	**450,000**	**Preclin**	**OA* & other pain conditions**
Cmpd #10	Array Bio. Ashai Kasei	0.038	210	5,500	Phase 2	OA LBP^
Cmpd #23	Pfizer	0.64	145	230	inactive	OA
Cmpd #1	Merck	99	>81000	>820	inactive	OA

AlzeCure has synthesized novel and highly potent and selective TrkA-NAM's

*) OA = Osteoarthritis ^) LBP = Lower Back Pain

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Summary

- NGF and TrkA is involved in pain sensation and validated targets
- Selective TrkA-NAM's could be a safer approach than anti-NGF antibodies
- AlzeCure have identified potent, selective and in vivo active TrkA-NAM's
- Preclinical characterization of compounds are ongoing
- Limited competition with respect to small molecule approach

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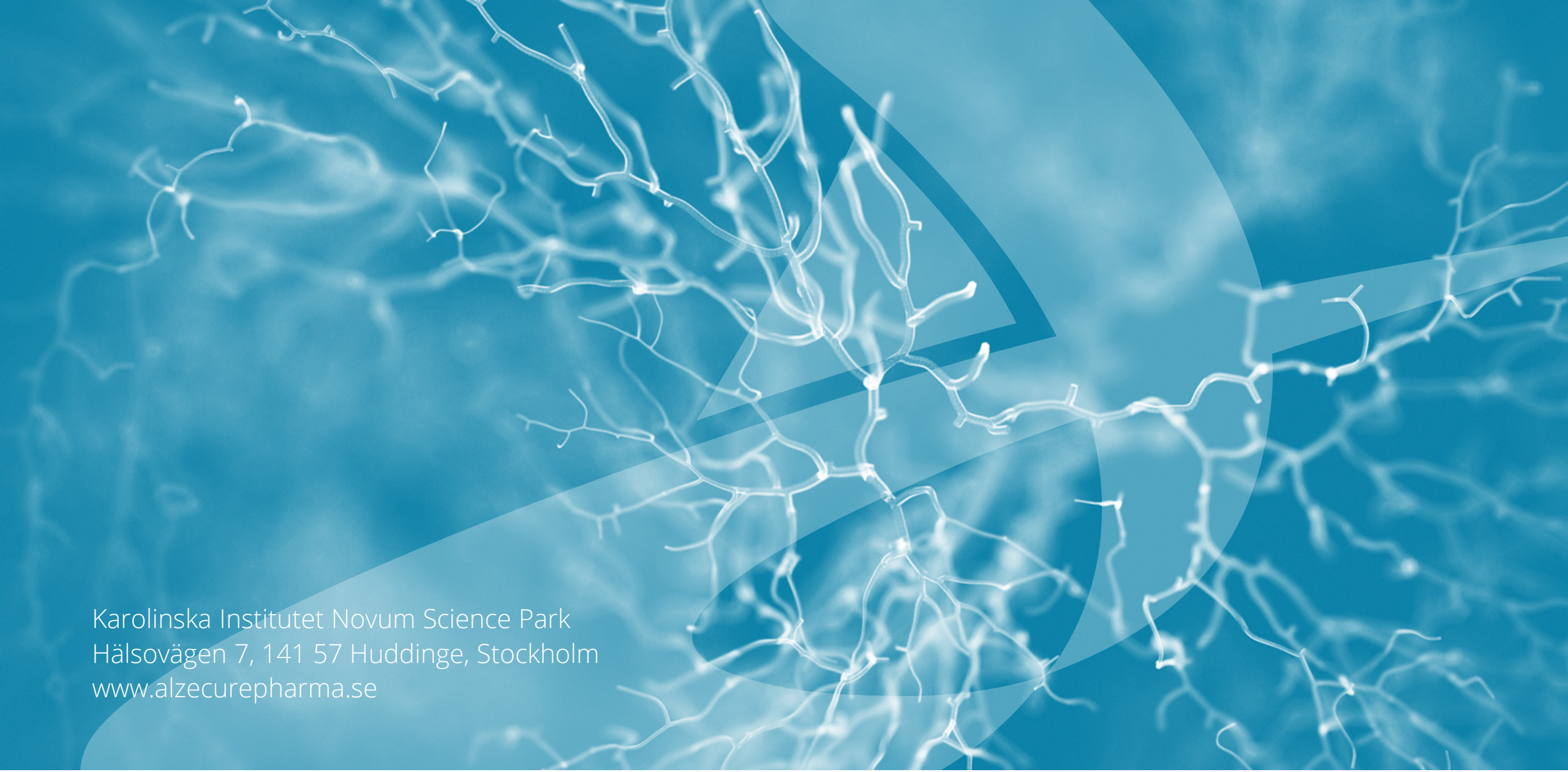

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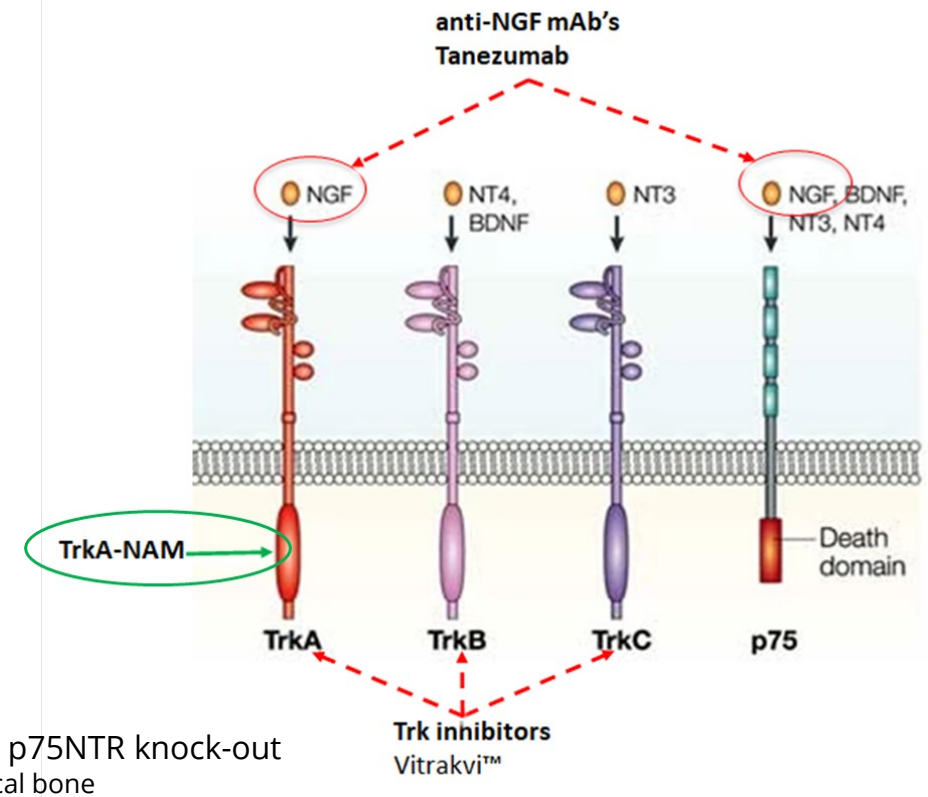
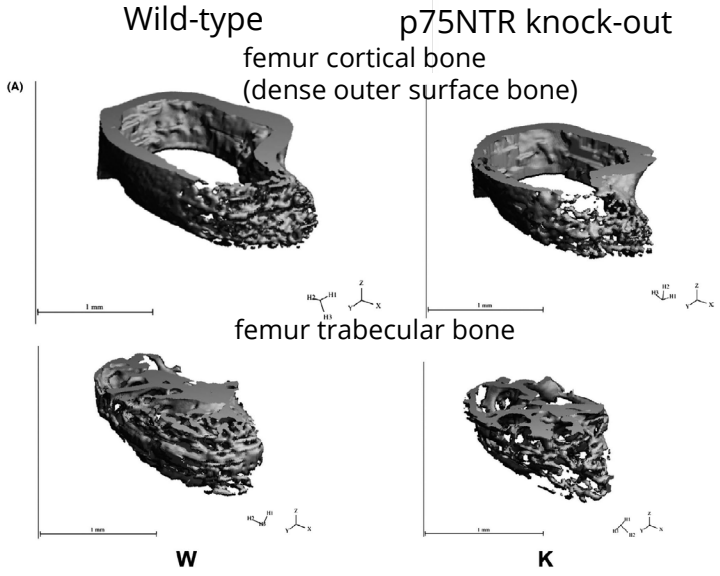
Safety: TrkA-NAM, a safer mechanism?

- 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).
- The painless NGF-R100W leads to loss of binding to p75NTR
- Knock out of p75 in animals leads to reduced bone mineralization
- Trk-inhibitors like Vitrakvi or ASP7962 inhibits TrkA, TrkB and TrkC. RPOA has not been reported by patients taking Trk-inhibitors.
- TrkA-NAMs have improved safety profile (CNS and weight) as compared to a Trk-inhibitor (Array Biopharma).
- Ashai Kasei is currently testing a TrkA-NAM in two phase 2 trials, a total of 800 patients (OA and LBP)





"p75NTR-knockout mice showed obvious bone loss in both the femur trabecular and cortical bone, implying that the osteogenic potential was remarkably decreased in the absence of p75NTR."
Zhao, Cell Proliferation, 2020

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