May 26, 2026

TrkA-NAM in pain

– Major unmet medical needs & indication areas

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Osteoarthritis Pain – Still a Large Unmet Medical Need

Pain starts mostly when starting physical activity, and after strainful activities.
Later in disease, also at rest and during the night. Pain at rest is more common in hip OA

Stiffness in the morning or after inactivity is usually does not last more than 30 min.
Swelling and edema around the joint is not uncommon
Joints can also become sore to touch

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Osteoarthritis – a Wellknown but Underserved Pain Disorder

- Osteoarthritis (OA) affects 595 million people worldwide and is one of the most rapidly increasing health conditions globally[1], In the US, >14 million adults are affected[2]
- Symptomatic knee OA occurs in 10% men and 13% in women ≥60 years, >14 million in the US[2]
- Not only the knee can be affected, also other joints – hip, spine (lower back and neck), hands
- The prevalence rises with increasing age
- Joint replacement – many want to wait for as long as possible
- Current therapies – NNT and NNH
- The risk for side effects in older individuals

[1]*Hatzikotoulas et al. Nature 2025;* [2]*Zhang et al, Clin Geriatr Med 2010, 2013*

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Current Standard of Care Treatment in Knee OA

- Exercise is a core treatment, both to reduce stiffness and to reduce pain
- Weight reduction
- Pharmacological treatments should always be combined with exercise

Pharmacological treatment	Recommendation/ evidence level
Oral NSAIDs, including celecoxib	High level
Paracetamol	Weak level
Opioids weak	Weak level
Duloxetin	Weak level
Intraarticular corticosteroid injections	High level
Topical NSAID, strong opioids	Not recommended

- Pharmacological treatments are tailored individually based on effects and side effects

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Side Effects of Current Pharmacological Standard of Care

- NSAIDs
  - Gastrointestinal – gastritis, gastric ulcers, diarrhoea, nausea are quite common – approx 25% of patients
  - Cardiovascular – myocardial infarction, cardiac failure – <0.5% of patients
  - Kidney function – approximately 2% of patients, BUT a large proportion of older patients admitted to hospital due to drug side effects have kidney failure caused by NSAIDs
- Paracetamol
  - Very few side effects, but also very low efficacy
- Opioids
  - Constipation in almost all patients
  - Nausea
  - Dizziness - falling
  - Impaired cognition

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What Happened to the NGF Antibody Story?

- Monoclonal anti-NGF antibodies were developed in the 2010-ies, and in PhIII of clinical development for OA pain, neuropathic pain and cancer related pain
- The effect was stunning and dose related
- During the development of Pfizer's tanezumab and other anti-NGF antibodies, Rapidly Progressing OA (RPOA) appeared as an unexpected AE
- Mostly in combination with NSAID as rescue treatment
- RPOA was dose dependent, when risk was lower, efficacy was very low
- As a result, anti-NGF mABs never reached the market
- NGF antibodies have also now been applied in pain management for cats and dogs*

The NGF antibodies have validated NGF as a relevant treatment target in pain
A TrkA-NAM, such as ACD137, can avoid the adverse effects seen with the ABs by being selective for the TrkA receptor

**della Rocca et al, 2025*

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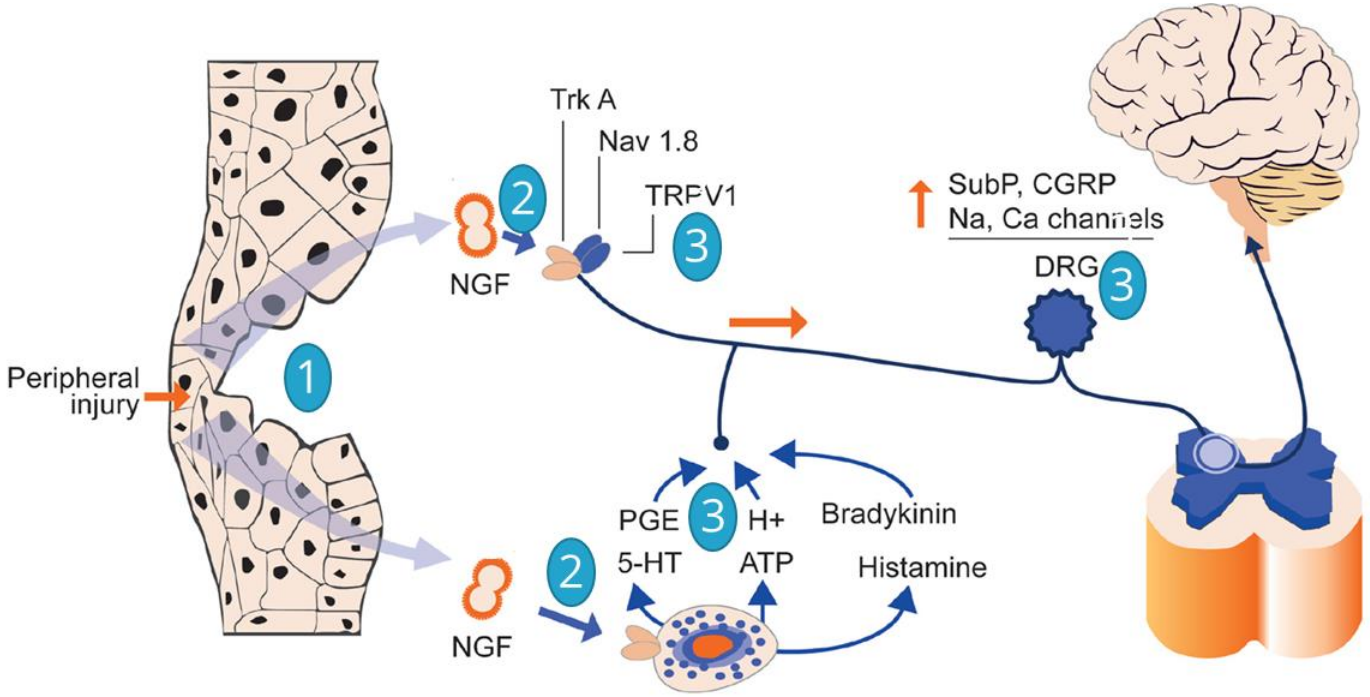
How Does ACD137 Differ from NGF-Antibodies?

Background and target pathway: NGF/TrkA

NGF and its receptor TrkA play an important role in pain sensation and the pathway is both genetically and clinically validated in humans

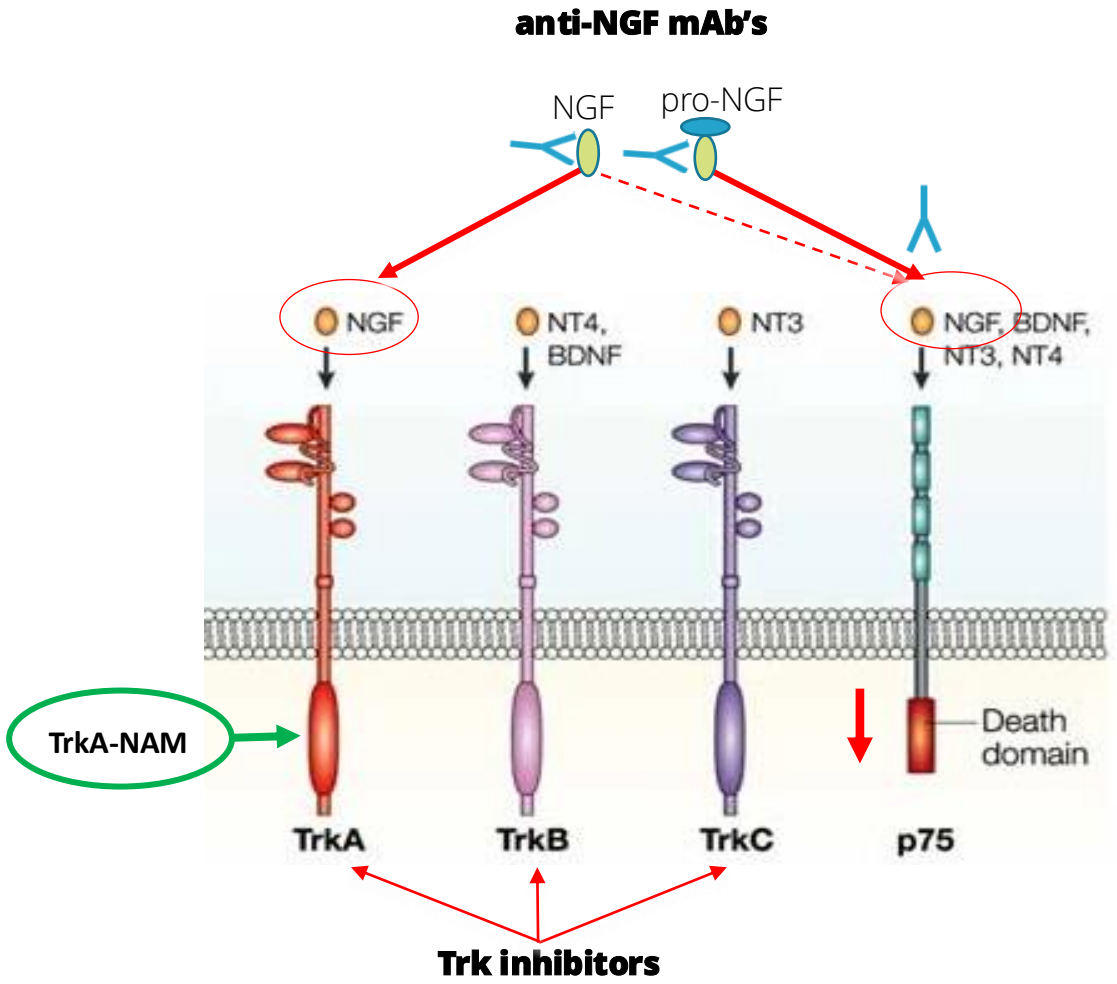
- **1.** NGF is released at the site of an injury.
- **2**. TrkA is the receptor for NGF and it is located on both neuronal and non-neuronal cells.
- **3.** NGF leads to inflammation and increased neuropathic and nociceptive pain.
- **4.** Anti-NGF antibodies, TrkA inhibitors or negative allosteric modulators (NAM) are analgesic in several preclinical models



NGF and TrkA are involved in inflammation as well as in nociceptive and neuropathic pain signaling

Anti-NGF-antibodies are unselective and block all NGF targets

- RPOA seems to be due to an inhibition of the p75 receptor
- This is avoided by ACD137, being selective for the TrkA receptor



Inhibition of p75NTR signaling by anti-NGF mABs might increase inflammation in the knee joint and reduce the natural tissue remodeling/repair of joints, especially when in combination with NSAIDs

ACD137 and its Role in Reducing Pain in Knee Osteoarthritis

Pain and stiffness are present in osteoarthritis

Knee OA causes pain and stiffness, having a great impact of level of daily activity and quality of life

Modulators reduce pain signalling

Negative allosteric modulators of TrkA, such as ACD137 can block the pain induction caused by NGF and thereby reduce OA pain

Improved mobility and wellness

The treatment will lead to less pain and inflammation as well as improved bility for people with knee OA, improving their quality of life

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Chemotherapy Induced Neuropathic Pain

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CINP – a Growing Patient Group

- In 2023, 5-year survival was 85% or more in 25 countries in Europe, North America and Oceania[1]
- In the US, the 5-year relative survival in the US rose from 75% in 1970s to 90% in 2017[1]
- The American Cancer Society today states that common cancer types such as breast cancer and prostate cancer, as well as aggressive forms as testicular cancer, thyroid cancer, and skin melanoma have survival rates of 99-100%.
- An important reason for this is screening programmes, as well as improved treatment regimens.

- Considering the increasing yearly incidence of not the least breast, prostate, colon and lung cancers, the number of individuals is steadily increasing

[1] *Amato et al, Curr Opin Oncol, 2023*

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How Common is Cancer Treatment Related Pain Overall?

- Pain after Irradiation Treatment is high, 38% after ENT-cancers, in general 30-40% (colon and breast cancer)
- Chemotherapy Induced Neuropathic Pain overall is not as well studied epidemiologically, and differs based on type of chemotherapeutic agent and type of malignancy
- The CINP intensity often sets the dose limit for the chemotherapy – an efficacious treatment could help optimization of the chemotherapy and thereby increase effects
- Thus, CINP is very intense in the acute phase, but often attenuates over time, with remaining provoked symptoms in combination with loss of sensation
  - A typical chronic feature is loss of sensitivity in the feet, requiring steady shoes, in combination with ”pins and needles” provoked by cold even at normal ambient temperature

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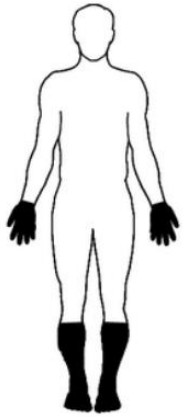
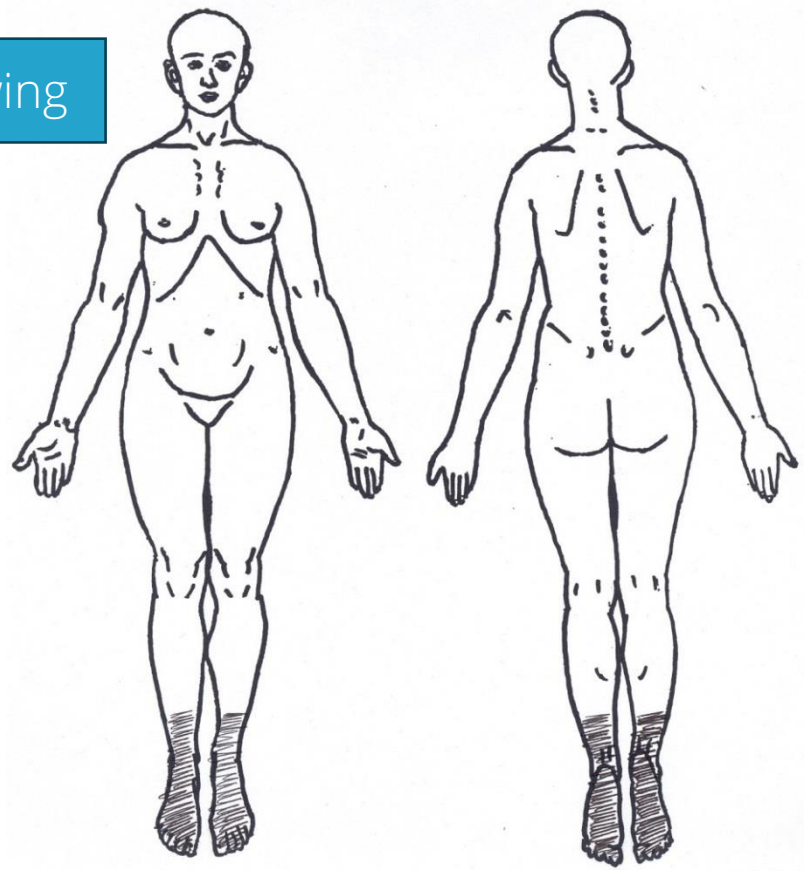
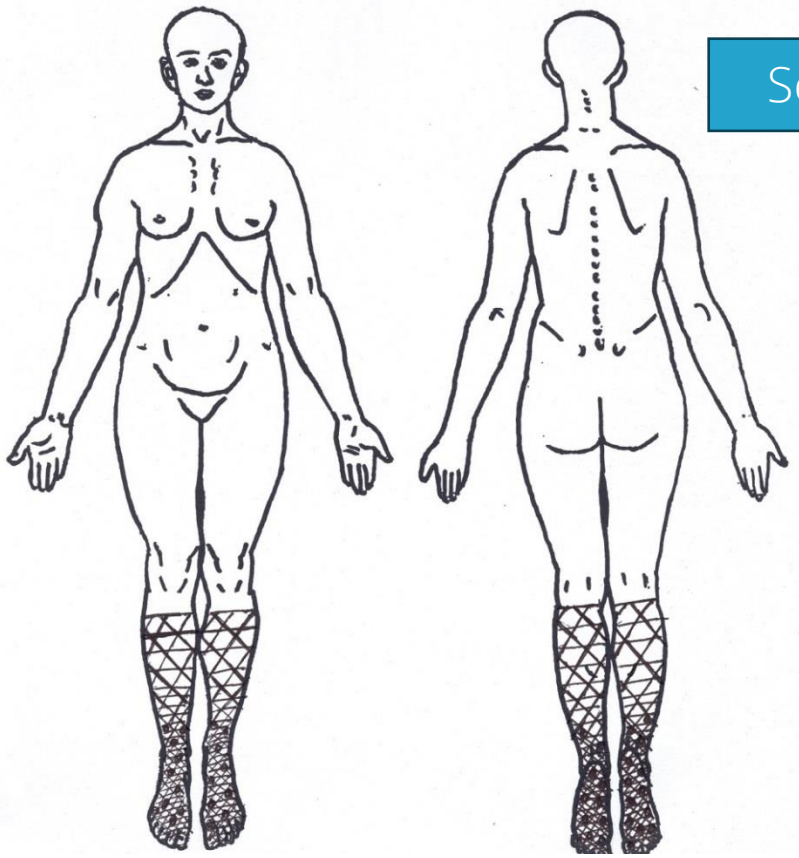
A typical pain drawing of CINP – socks and gloves distribution

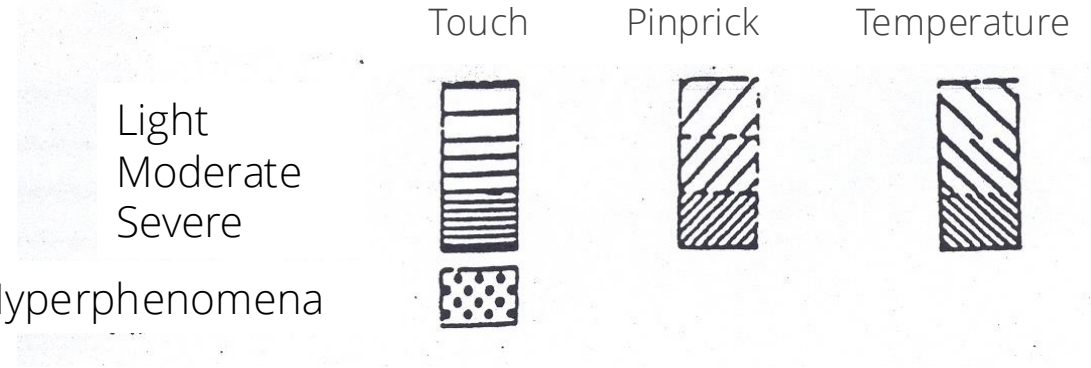
Patient drawing





Sensory testing





What is the Current Standard of Care for CINP?

- The same treatments as for other peripheral neuropathic pains are used:
  - Serotonin Norepinephrine Reuptake Inhibitors (SNRI)
  - Gabapentinoids
  - Tricyclic antidepressants (TCA)
  - Coping strategies

- There are few studies dedicated in CINP on clinicaltrials.gov
  - One NIH-funded study of duloxetine demonstrated significant reduction of pain vs. placebo*
  - Two ongoing studies (Nav1.7-channel blocker; Ca^{2+}-channel blocker)
  - One completed negative study (pregabalin) **

➢ In clinical experience, the treatment success is lower than for other neuropathic pains, i.e. an NNT of 12-15

**) Smith et al, 2013; **) de Andrade et al, 2017*

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Grading of Treatment Related Adverse Events/ Side Effects

No mention of pain or discomfort

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; limiting self-care ADL or severe impact on age-appropriate normal daily activity (pediatric)	Life-threatening consequences; urgent intervention indicated	Death

Definition: A potentially fatal complication of treatment in certain molecular subgroups of leukemia characterized by fever, rash, dyspnea and/or hypoxia, pulmonary infiltrates, peripheral edema with rapid weight gain, pleuropericardial effusion, acute renal failure, disseminated intravascular coagulation (DIC), bone pain and/or hypotension.

Oncology questionnaires do not assess pain as a treatment related side effects
Information to patients mostly rare or non-existing

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Chemotherapy-induced neuropathy - CINP

Supportive Care in Cancer (2020) 28:5933–5941
https://doi.org/10.1007/s00520-020-05438-5

ORIGINAL ARTICLE

Check for updates

Painful and non-painful chemotherapy-induced peripheral neuropathy and quality of life in colorectal cancer survivors: results from the population-based PROFILES registry

C. S. Bonhof[1,2] · H. R. Trompetter[1] · G. Vreugdenhil[3] · L. V. van de Poll-Franse[1,2,4] · F. Mols[1,2]

- Painful CINP was reported by 9% (n = 45) of survivors and non-painful CINP was reported by 22% (n = 103).
- Time since diagnosis was related to CINP
- Time since diagnosis, a higher disease stage, osteoarthritis, and more anxiety symptoms were related to non-painful CINP
- Survivors with painful CINP reported a worse global quality of life
- No differences were found between survivors with non-painful CINP and those without sensory CINP

Painful CINP must be distinguished from non-painful CINP, as only painful CINP was related to a worse HRQoL.

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Many of the Most Common Chemotherapeutic Agents Cause Neuropathy

Physiol. Res. 73: 333-341, 2024 *https://doi.org/10.33549/physiolres.935162*

REVIEW

Biological Mediators and Partial Regulatory Mechanisms on Neuropathic Pain Associated With Chemotherapeutic Agents

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Table 1. Chemotherapeutic agents causing neuropathy.

Category	**Examples**	**Treatment**
Proteasome inhibitors	Bortezomib	Multiple myeloma certain types of lymphoma [47,48]
Platinum-based compounds	Oxaliplatin, cisplatin carboplatin	Solid tumors, i.e., stomach, liver, lung, ovarian, brain, uterine cancers [49]
Taxanes	Paclitaxel, docetaxel cabazitaxel	Ovarian, breast, on-small cell lung, and prostate cancers [48,50]
Vinca alkaloids	Vincristine, vindesine, vinblastine, vinorelbine	Hodgkin lymphoma, testicular cancer, and non-small cell lung cancer [51]
Epothilones	Ixabepilone	Non-small lung, ovarian, and prostate cancers [52]
Immunomodulatory drugs	Thalidomide	multiple myeloma [53]

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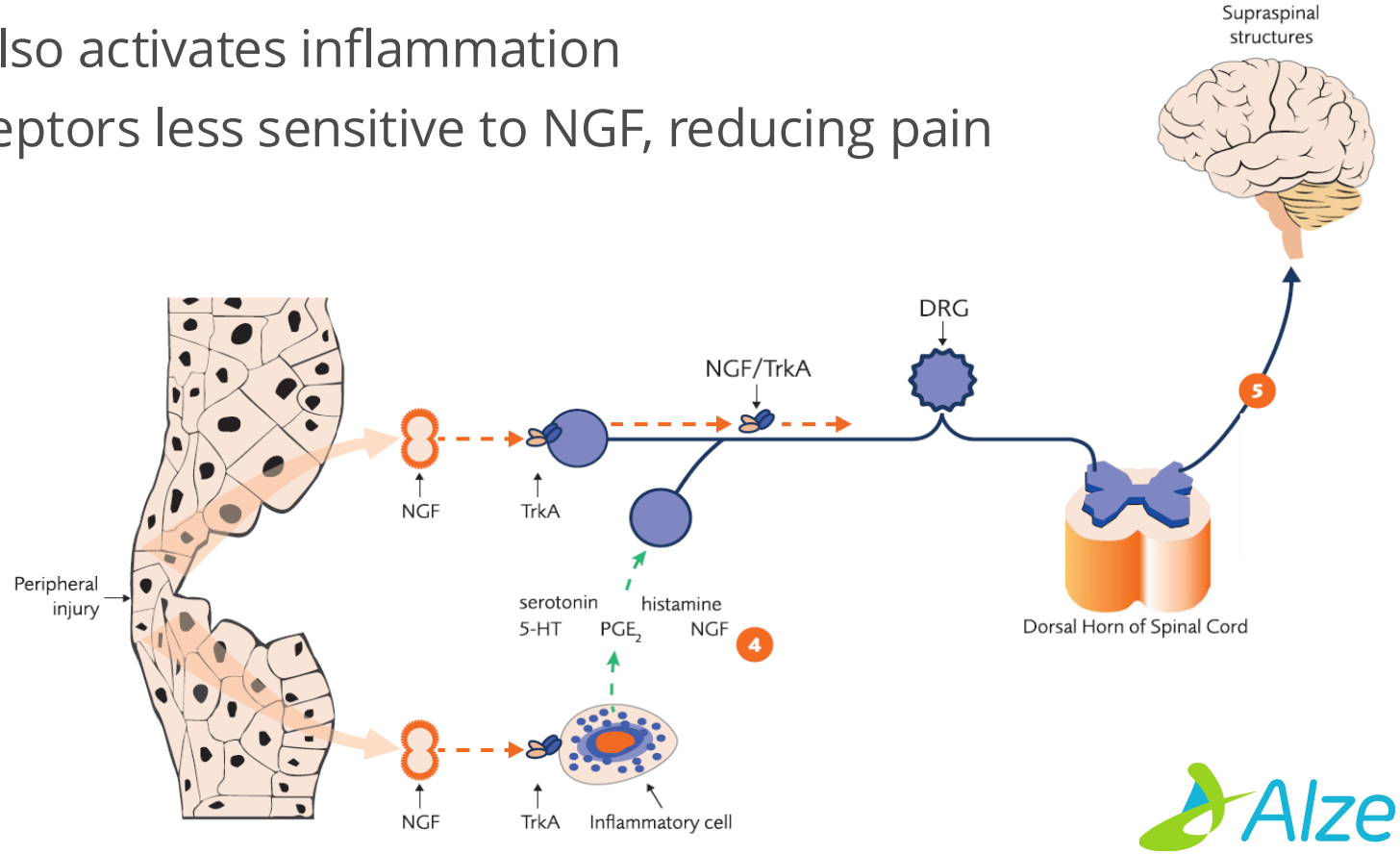
How Does TrkA-NAM Work in Reducing CINP Pain?

- **NGF antibodies have shown promise in alleviating chemotherapy-induced peripheral neuropathy (CIPN) pain, but been halted**
- The TrkA-receptors are present on the sensory nerves, so a stimulation of them, by NGF, gives rise to pain.
- TrkA-receptor stimulation also activates inflammation
- TrkA-NAM makes these receptors less sensitive to NGF, reducing pain and inflammation



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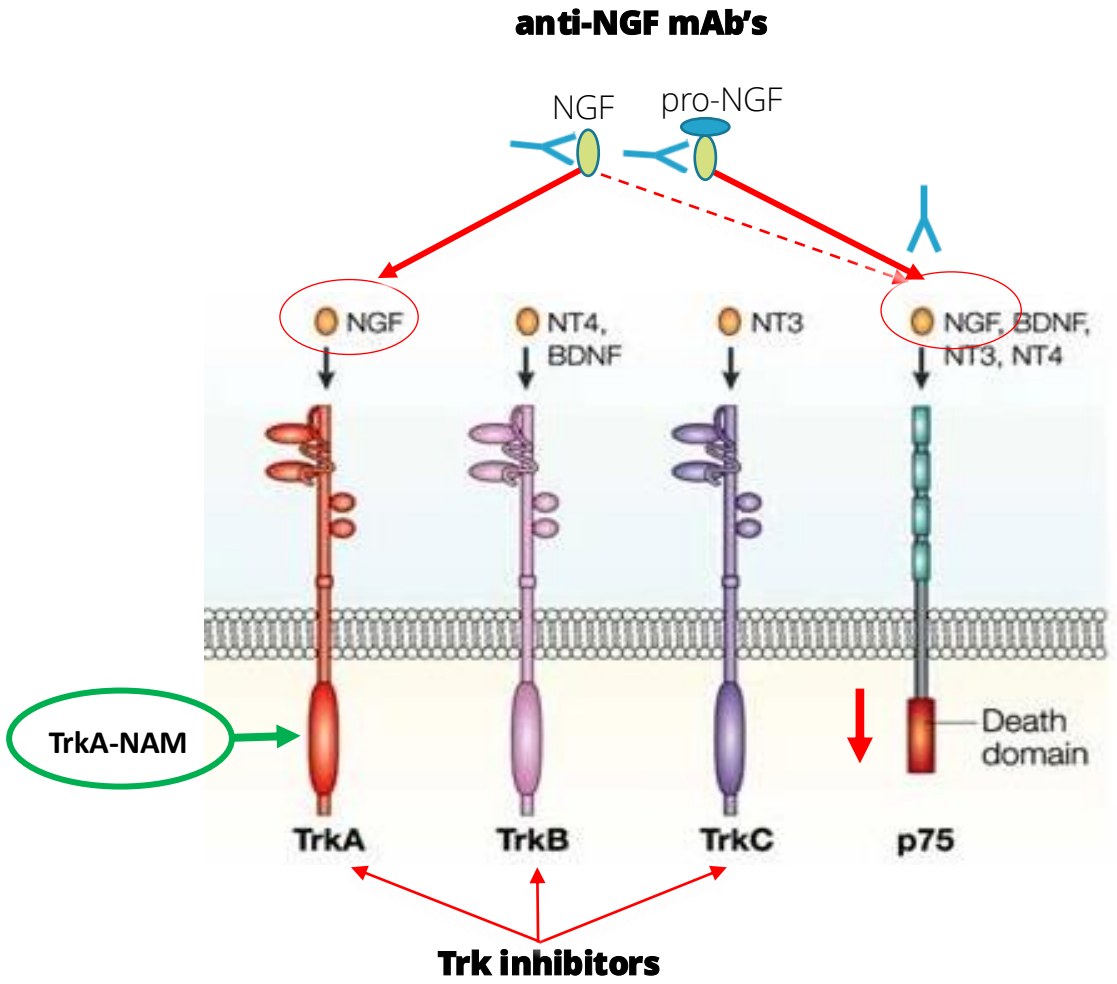

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Summary

- Osteoarthritis pain affects >500 million people worldwide, and increases with age
- Current therapies are not very efficacious and have limited efficacy and tolerability

- Chemotherapy induced neuropathic pain (CINP) is a growing with the increasing successful cancer treatments and increased survival times
- Approximately 9-10% of chemotherapy treated patients develop Chronic CINP
- CINP is a peripheral neuropathic pain, specifically sensitive to thermal stimulation
- Current treatments for neuropathic pain do not work very well

- Based on data with NGF-antibodies, NGF is a validated target for OA pain and relevant also for CINP
- ACD137, not having the side effect profile of the NGF-antibodies, is a very promising candidate for the treatment of acute and chronic CINP

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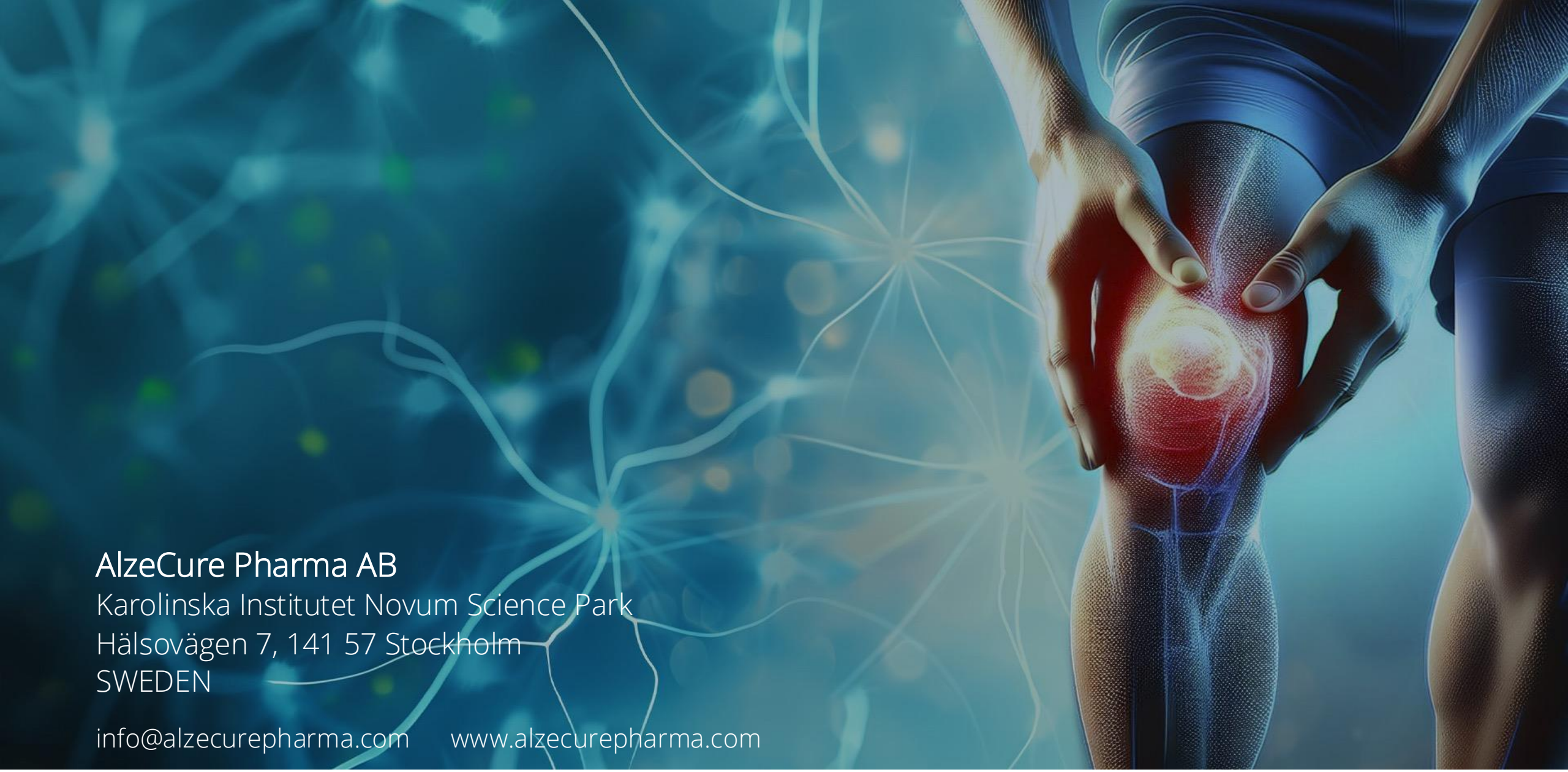

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