

My First Medical Writing

Editorial

In this edition of My First Medical Writing, we welcome one of the first articles written by aspiring medical writer Mayya Sundukova. A physicist by training, Mayya pursued her PhD in neuroscience in SISSA, Italy, studying ion

channels, and then became postdoc at the European Molecular Biology Laboratory in Rome, Italy, to study pain mechanisms and develop tools for neuroscientists. Now, she is exploring several career opportunities in academia and industry and

developing her medical writing skills. It has been a pleasure working with her, seeing her grow day-by-day from constructive feedback, and now publishing her first article in *Medical Writing*.

Evguenia Alechine

Local photoablation of nerves to treat chronic pain

Chronic pain is bad, but no pain can be worse

Chronic pain has a devastating effect on those who suffer from it – almost 20% of adults in Europe.¹ Commonly used treatments block target molecules involved in the origin or maintenance of pain. Probably, there is no ideal molecule to block all types of pain. Nonsteroidal anti-inflammatory drugs, opioids, and antidepressants have limited success in many cases and cause serious side effects because of systemic delivery.² Also, from patients' and doctors' points of view, the adjustment of doses on an individual basis can be challenging.

However, no pain can be even worse. For example, patients with rare hereditary sensory and autonomic neuropathy type 5 (HSAN V) report insensitivity to pain and touch.^{3–5} Mutations in the neuronal growth factor (NGF) gene, which makes the resulting protein unable to function properly, are responsible for the lack of pain. NGF is essential for the development and survival of neurons that transmit pain, touch, and

temperature. Certain mutations in NGF lead to the absence of these neurons in affected patients. As they are unable to receive information about potentially damaging stimuli and dull pain, they suffer from repeated trauma to the joints, skin, and other tissues. Pain insensitivity disease is rare but very dangerous. On the bright side, understanding the role of mutations and characterisation of defective NGF has led to new ideas for treating chronic pain in other people. What if the source of pain could be eliminated locally at its origin – by “silencing” or ablating nerve endings in the skin?

Neuronal growth factor and potential analgesics

NGF has a prominent role in the onset and development of acute and chronic pain states as it binds to TrkA receptors. Apart from being important for nerve survival during development, in the adult nervous system TrkA receptors are expressed on sensory nerves that transmit pain and touch information.⁶ Volunteers

receiving NGF injections have reported enhanced responses to pain.⁷ A treatment based on blocking NGF with antibodies has provided pain relief in animal models and humans,⁸ but clinical studies were put on hold due to safety issues and side effects caused by systemic application.⁹

This article reviews a novel approach for pain treatment that was developed by my colleagues at European Molecular Biology Laboratory.¹⁰ Mutant NGF protein was used to stop pain at the periphery by locally photoablating pain-transmitting nerves with light-activated photosensitisers (Figure 1).

Light-activated therapy or photoablation for nerves in the skin

Light-activated therapy based on cell-targeted delivery of photosensitiser IRDye[®]700Dx (IR700) emerged in 2011 in cancer treatment and has been subject to clinical trials.^{11,12} The

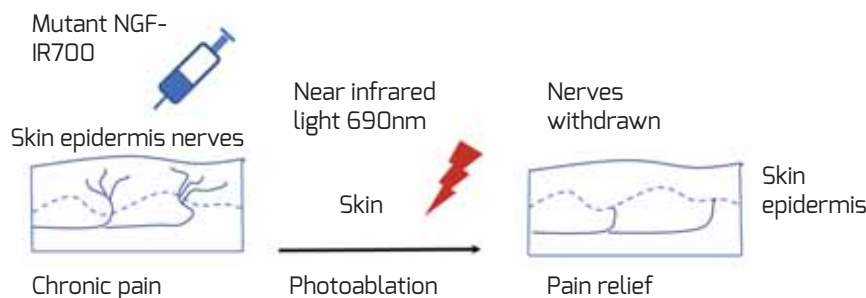


Figure 1.

Scheme for novel pain therapy. Mutant NGF protein was labelled with photosensitiser IR700 and injected into the skin of mice with chronic pain. Protein bound to pain-transmitting nerves, which express TrkA. Near-infrared light illumination activated the photosensitiser linked to the nerves and led to their photoablation. Nerves withdrew, stopping pain perception.

SECTION EDITOR



Evguenia Alechine

ealechine@epsilonosci.com

approach relies on the targeted delivery of light-sensitive IR700 molecules to cells *in vivo*, thus sparing all off-target cells, and local near-infrared laser light application to activate the photosensitizer. Near-infrared light is harmless to living tissues and penetrates deeper than visible light, thereby allowing light to be applied to deeper layers of skin, muscles, or joints. Upon light activation, the photosensitizer IR700 releases reactive oxygen species, leading to cell death.

For pain treatment with light-activated therapy, knowledge about NGF mutations in patients with hereditary sensory and autonomic neuropathy came in handy. One particular mutation leads to a defective NGF protein that can bind the TrkA receptor but is unable to activate cell signalling, and therefore cannot evoke pain by itself.^{3,7} Engineered mutant NGF protein was labelled with IR700 and tested on cells *in vitro* and in mice *in vivo*.¹⁰ The mutant protein bound to TrkA-positive cells, and after exposure to near-infrared laser light, induced cell death within 1 day. Mutant NGF-IR700 was injected into the skin of mice and exposed to the light. Behavioural signs of pain were measured, such as paw withdrawal upon touching with special nylon fibres, a paint brush, or hot/cold stimuli.¹³ As expected, mice that received mutant NGF-IR700 and light showed no sensitivity to touch, due to specific local photoablation of pain-transmitting nerve endings in the skin.

Success of photoablation in preclinical pain models

Photoablation technology based on mutant NGF was successful in pain relief in preclinical models, where chronic pain arises from tissue injury.¹⁰ In different pain models, inactive bacteria were injected into the skin in a model of inflammation, a branch of sensory nerves that innervate the skin was cut in a nerve trauma model, and a toxic chemical was injected into the knee in a model of osteoarthritis and joint pain. After injury, mice would rapidly withdraw their paws when gently touched, showing behavioural signs of pain. Mutant NGF-IR700 was injected into the injury site and locally exposed to near-infrared light. After three consecutive days of treatment the mice were behaving normally without signs of pain, as before the injury. The effect lasted for at least 3 weeks. Authors counted the number of pain-transmitting nerves in skin sections from experimental and control mice. After the end of therapy, the nerves had withdrawn from the skin due to photoablation, blocking pain perception. However, 1 month after the end of the treatment, the nerves had grown back, and pain perception was recovered.

Perspectives

Results obtained in preclinical studies highlight the promise of photoablation therapy in humans. In the quest for more patient-friendly drug formulations (to replace injections), effective delivery of NGF-IR700 via a cream or micro-emulsion was established. Previously, a cream formulation containing a photosensitizer was used to treat a chronic skin itch condition in mice.¹⁵ Therefore, local non-invasive application and photoactivation of NGF-IR700 could provide a flexible option for personalised pain treatment based on the patient's sensations of pain and touch in the affected area, with minimal side effects.

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Mayya Sundukova
Rome, Italy
mayya.sundukova@gmail.com