Role of the Sodium-Calcium Exchanger NCX2 in Oxaliplatin Induced Peripheral Neurotoxicity

Connecting Young Brains to Advance Neuroscience
Naples, June 22-23, 2026

Chiara Invernizzi

PhD student in Neuroscience

Universita' degli Studi di Milano-Bicocca

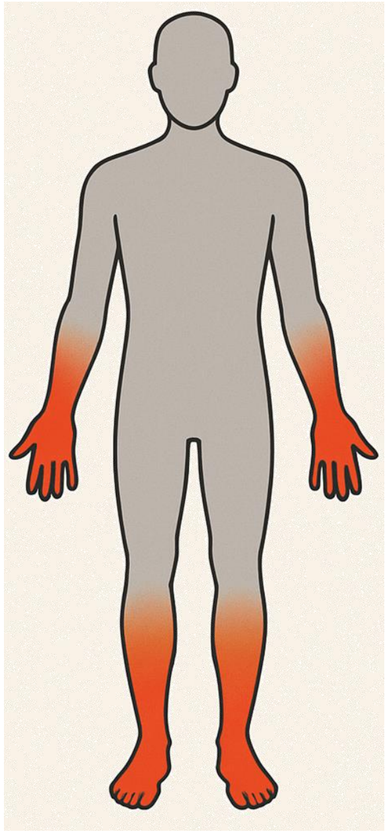
Email: c.invernizzi14@campus.unimib.it

SINS ITALIAN SOCIETY FOR NEUROSCIENCE

Introduction: CIPN

- Chemotherapy-induced peripheral neurotoxicity (CIPN)

- Symptoms:
  - Distal and symmetric upper and lower limb alteration of all **sensory** modalities
  - **Sensory ataxia** and gait abnormalities
  - **Neuropathic pain**



Made with AI (ChatGPT)

«Gloves and socks» distribution

Introduction: Oxaliplatin (OHP)

- OHP is the cornerstone drug for **colorectal cancer**
- Neurotoxicity is the **dose limiting** effect for OHP:

Chronic syndrome
- Long-lasting axonal neuropathy sensory
- Negative (sensory ataxia) and positive (neuropathic pain) symptoms

Acute syndrome
- Transient cold-induced paresthesia (2-3 days after OHP administration)
- Short-term voltage-gated sodium channels (NaV) dysfunction

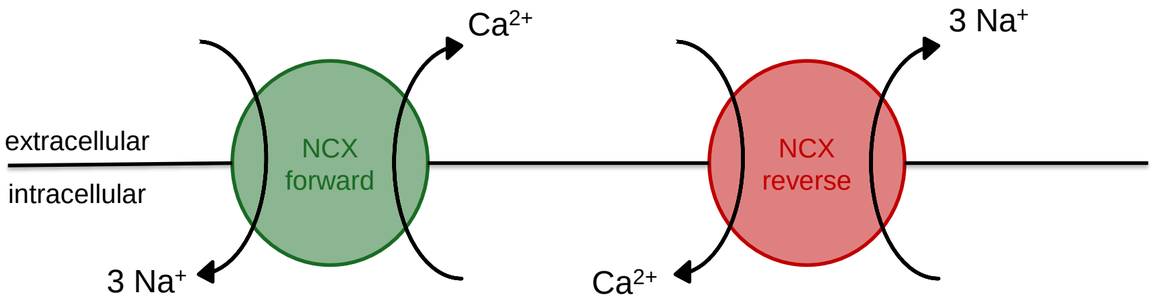
↓

Axonal hyperexcitability

Introduction: Axonal damage

Upstream event → Voltage-gated **sodium channels** impairment → **increase** in **sodium** intracellular levels

Downstream event → **NCX2 reverse mode** activation → Accumulation of intracellular **calcium**



Sodium-calcium exchanger 2

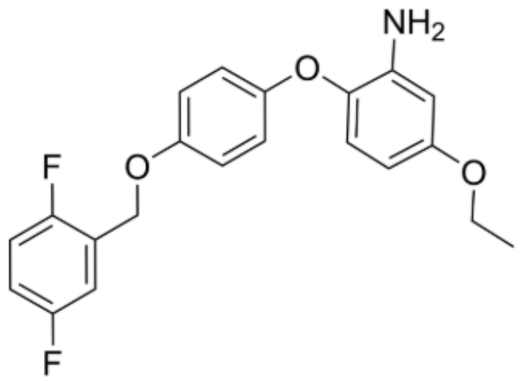
Axonal damage

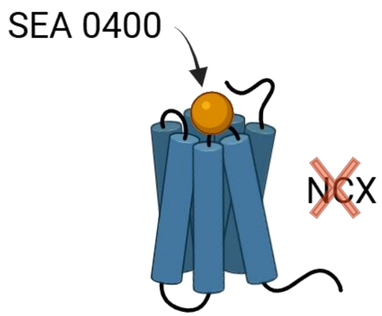
Aim

Investigating:

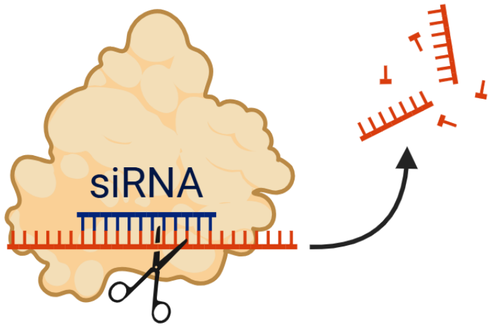
- NCX2 alterations in OHP induced peripheral neurotoxicity
- NCX2 inhibitors as potential neuroprotective agents

SEA0400:
pharmacological inhibition of the transporter





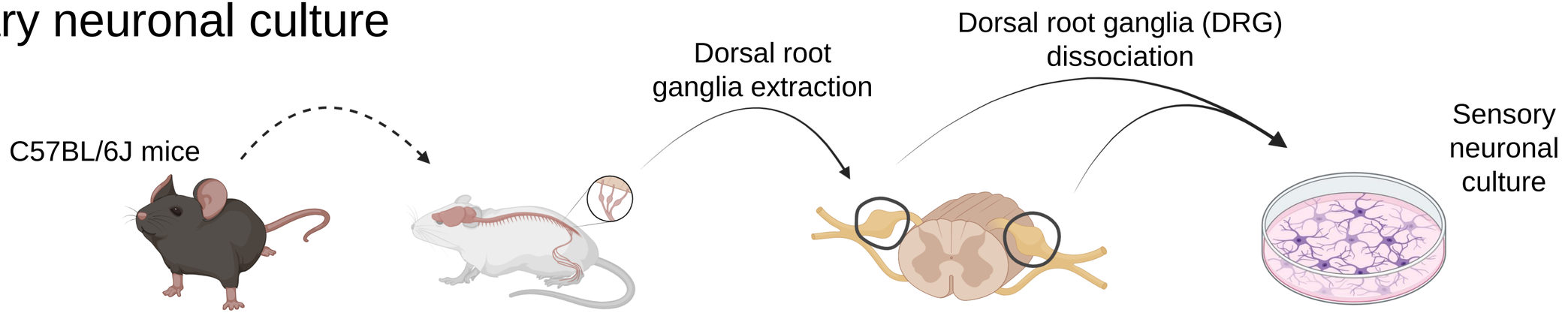
Small interfering RNA (siRNA):
blocking the translation of NCX2



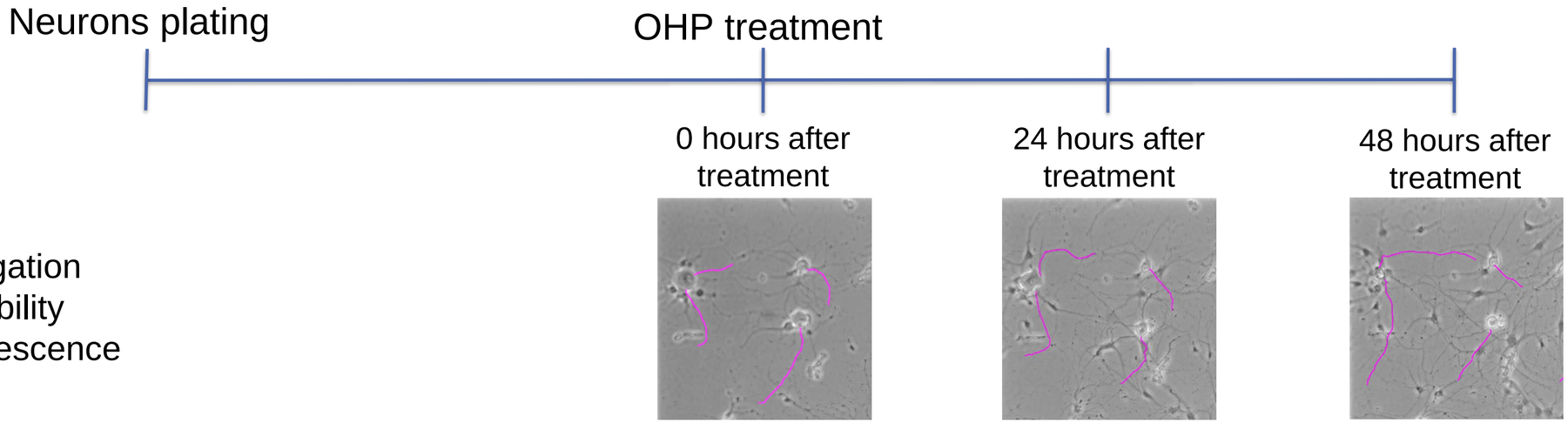
Made with BioRender

Model

Primary neuronal culture

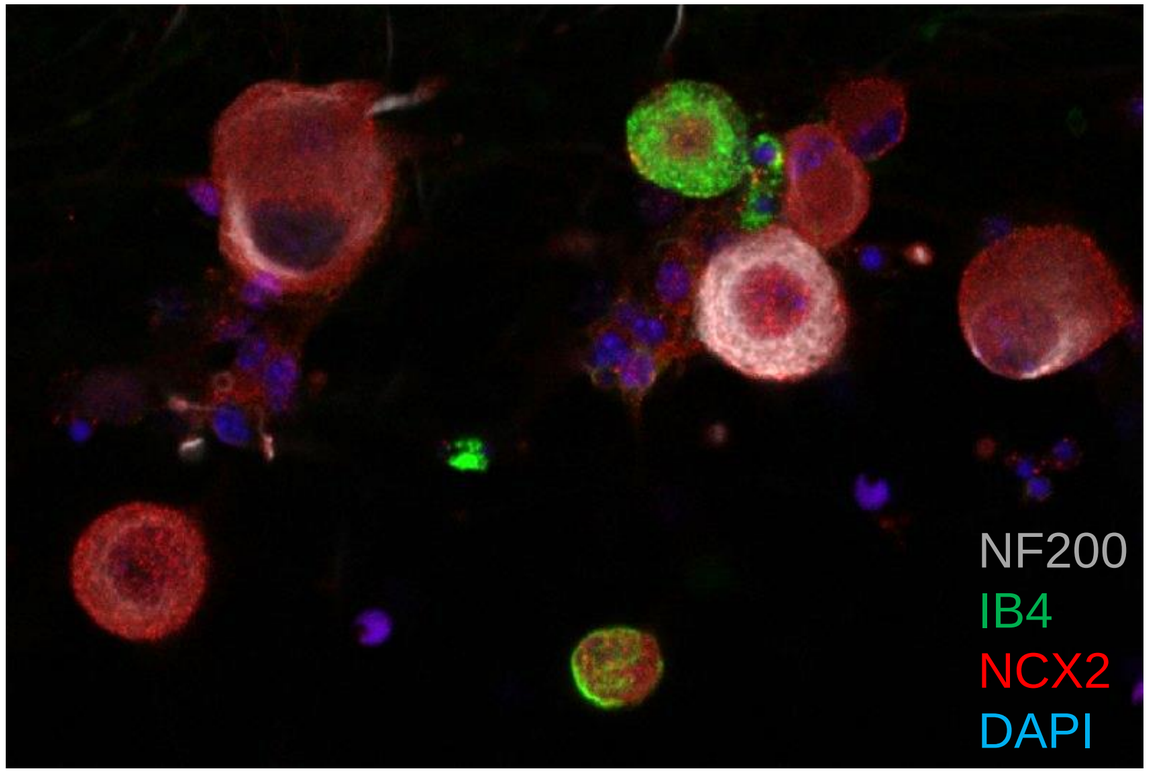


Made with BioRender



Analysis:
Neurite elongation
Neuronal viability
Immunofluorescence

Results: NCX2 in DRG neuronal populations

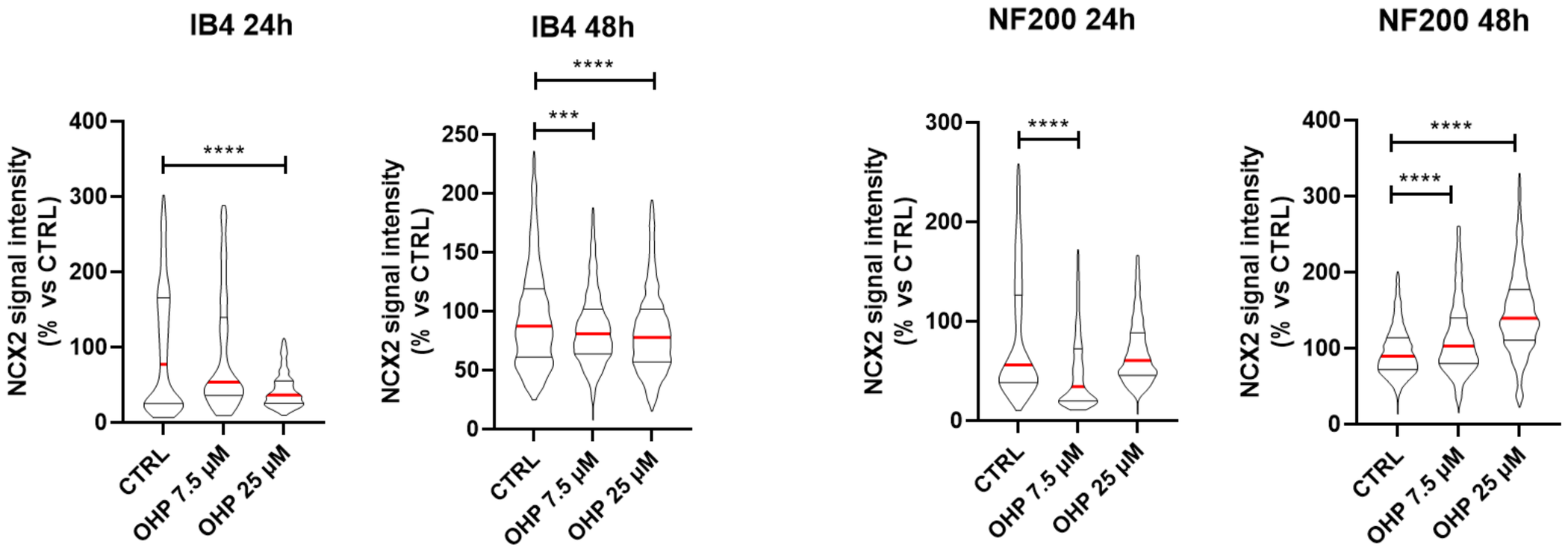


IB4+ neurons
- Small diameter sensory neurons
- Non-peptidergic nociceptive fibers (C fibers)

NF200+ neurons
- Medium/large diameter myelinated neurons
- Mechanoceptive and proprioceptive fibers (Aβ/Aδ fibers)

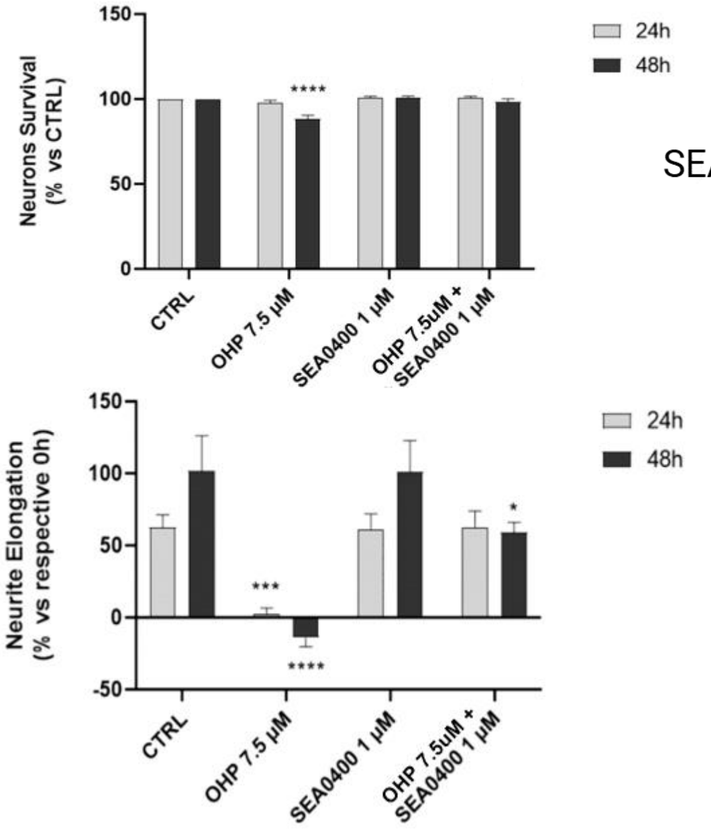
Results: NCX2 in DRG neuronal populations

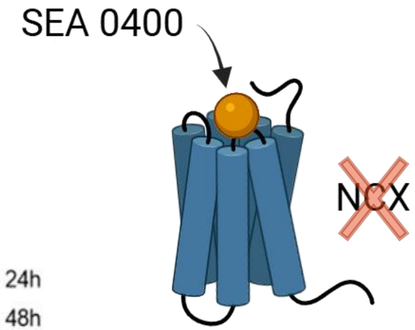
Immunofluorescence: NCX2 signal in IB4+ and NF200+ neurons



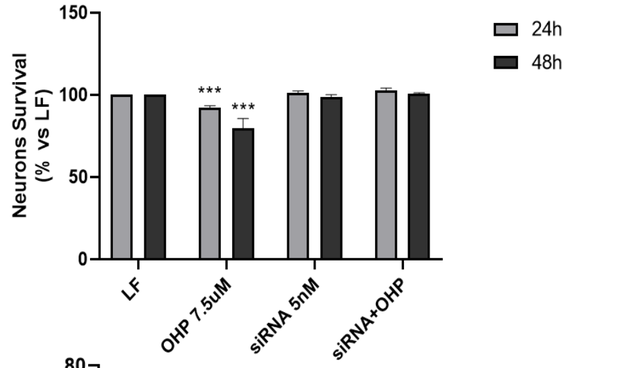
Results: NCX2 inhibition

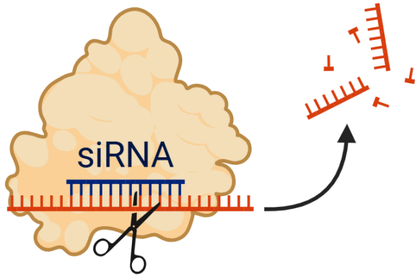
SEA0400: pharmacological inhibition of the transporter (3 hours pretreatment)

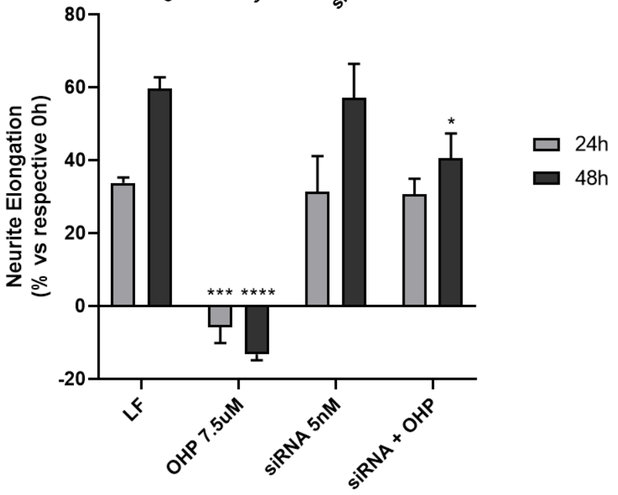




Small interfering RNA (siRNA): blocking the translation of NCX2





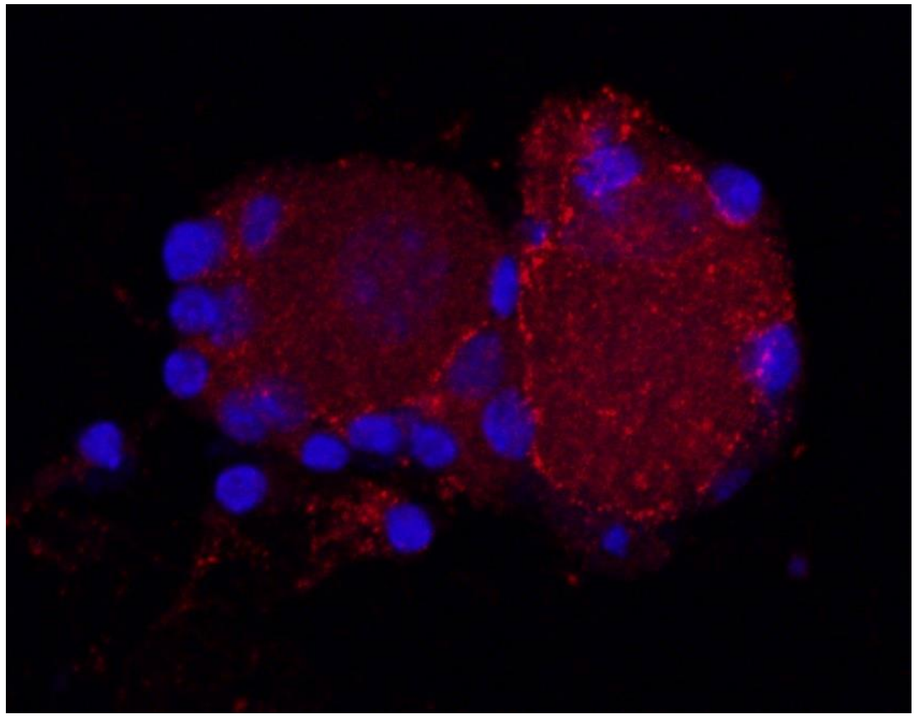


Materials and methods

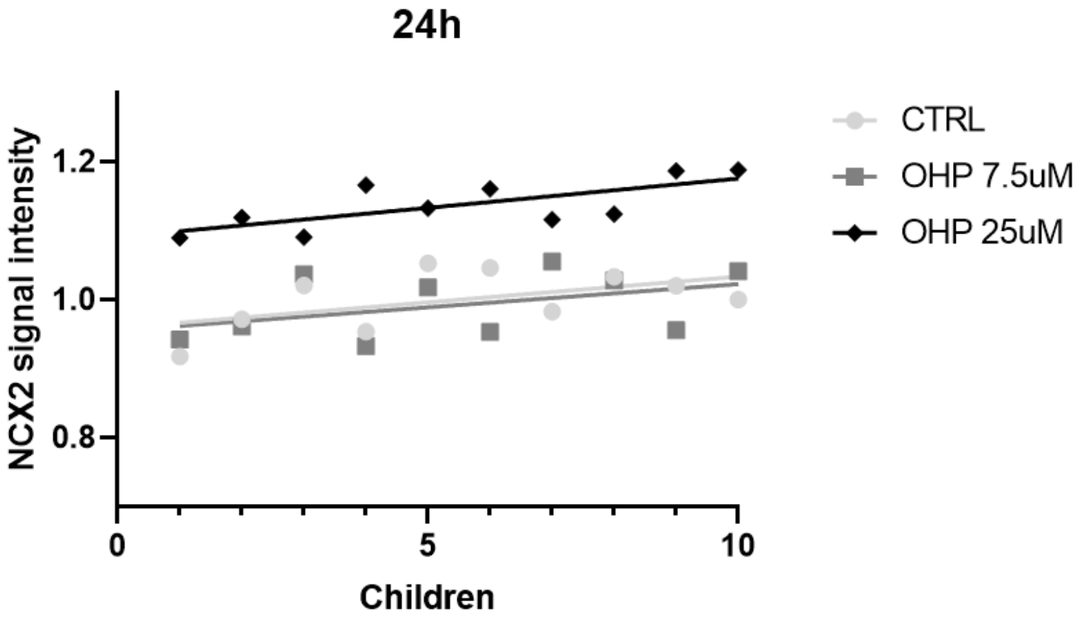
ARIVIS software to analyse IF images

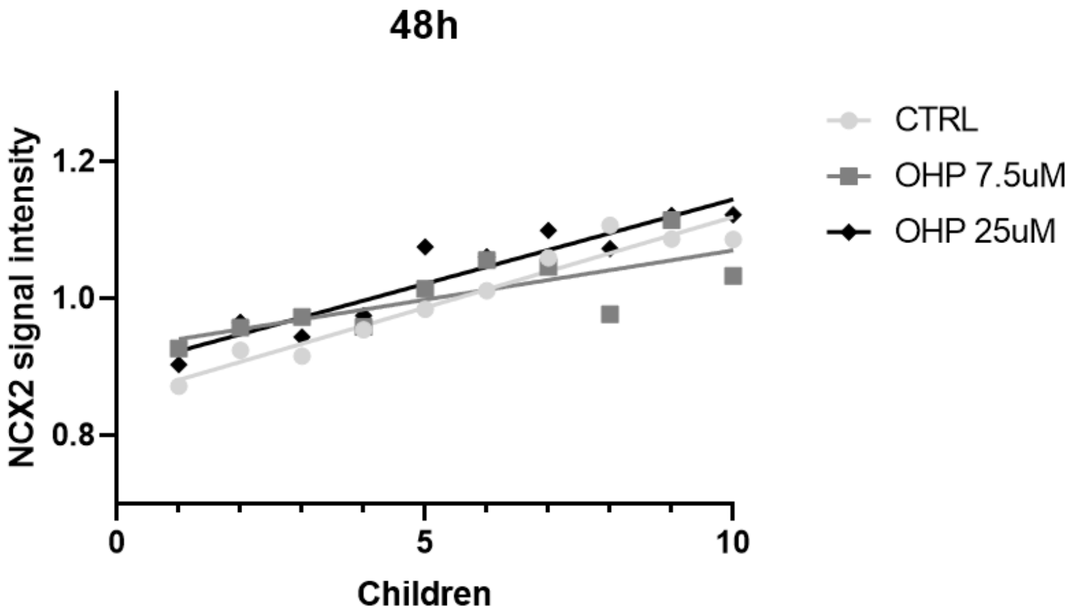
– Counting the number of satellite cells around each neuron (**children**)

– Considering the correlation between the intensity of **NCX2** fluorescent **signal** and the number of children, analysing the difference between CTRL and OHP-treated neurons



Results: NCX2 involvement in OIPN





CTRL – OHP 25uM
Pvalue <0.0001

Discussion

NCX2 signal is different between IB4+ and NF200+ neurons

IB4+ neurons
(nociceptive fibers)

↓

NCX2 is **downregulated**
→ axonal damage is minor
→ these fibers are less affected in OHP-treated patients

NF200+ neurons
(meccanoceptive and proprioceptive fibers)

↓

NCX2 is **upregulated**
→ reverse mode
→ axonal damage is severe
→ these fibers are more affected in OHP-treated patients

Conclusion

- The changes in NCX2 expression after OHP exposure could be due to the **altered ion exchange** due to reverse mode activation
- These results **support** the potential **pivotal role of NCX2** in OHP-related axonal damage
- **NCX2 inhibition** reverts most of neurotoxic effects of low-dose of OHP
  - SEA0400 reverts completely 7.5uM OHP treatment at 24 hours; not completely at 48 hours
  - siRNA transfection also completely deletes 7.5uM OHP treatment effect on neurite elongation and neuron survival at 24 hours, but still not completely at 48 hours

In vivo studies coming next ←

Thanks to
Experimental Neurology Unit

And special thanks to

Dr. Paola Alberti, MD, PhD

Dr. Sara Di Girolamo, PhD

Dr. Mario Mauri, PhD

Prof. Nick Housley, PhD

PHD PROGRAM IN
NEUROSCIENCE

NEUROSCIENZE
DOTTORATO DI RICERCA

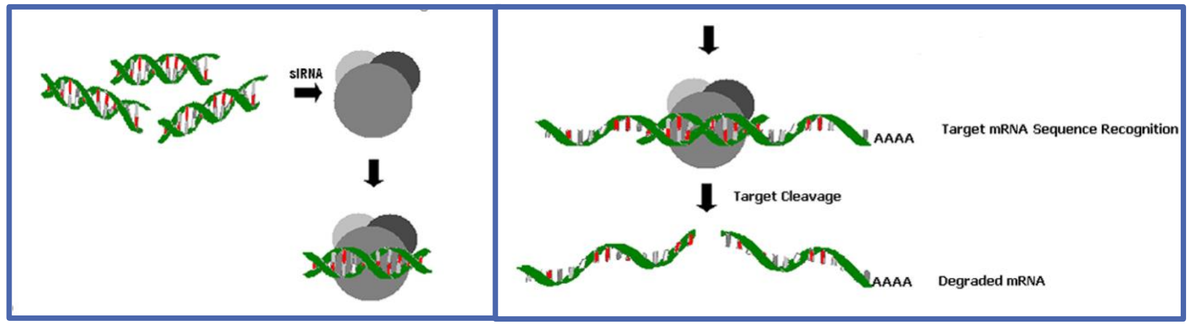
Materials and methods

NCX2 inhibition

SEA0400: pharmacological inhibition of NCX2 protein

- Small-molecule pharmacological inhibitor used as a research tool to investigate calcium homeostasis and ion transport mechanisms in excitable cells.
- Extensively employed in preclinical studies to explore the role of NCX in physiological and pathological conditions.
- Aspecific: it inhibits all the three isoforms of NCX (NCX1-NCX2-NCX3)

Small interfering RNA (siRNA): blocking the translation of NCX2 gene



- Short segments of RNA that efficiently inactivate genes
- More suitable than transgenic animals, because they can be transferred to the **bed-side** (already in use for transthyretin-mediated amyloidosis treatment)
- siRNAs utility has been hampered by **instability**: they need a **vehicle** to reach the target without being degraded