NX210c, A PROMISING DRUG CANDIDATE FOR NEURODEGENERATIVE DISEASES

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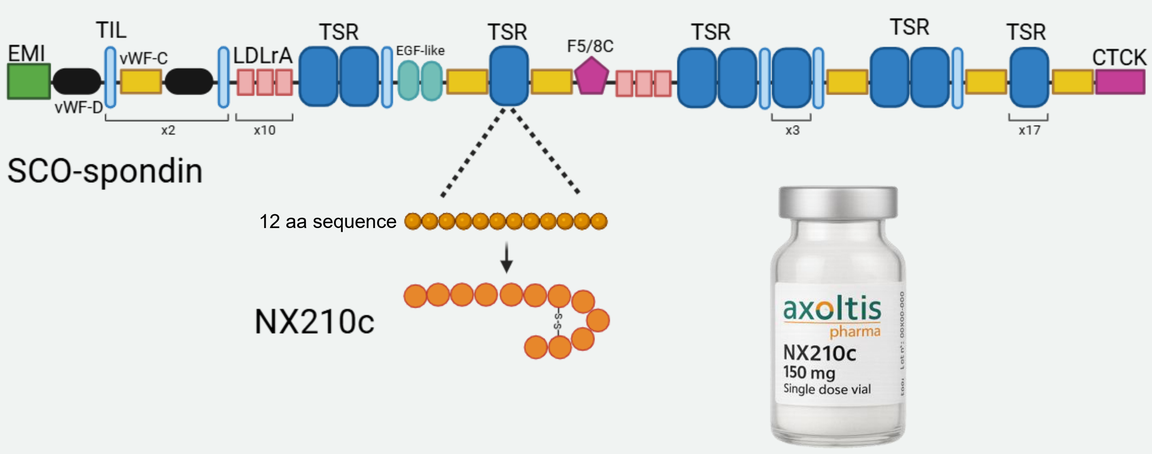
#PO101

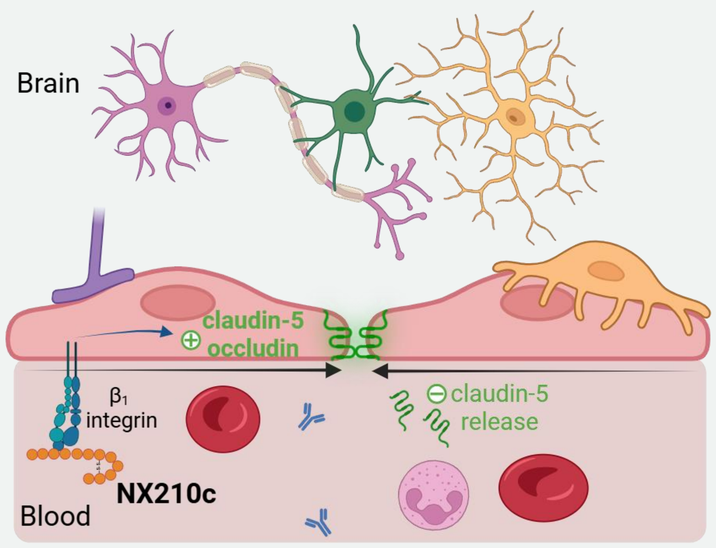
NX210c is a short TSR1 analog from SCO-spondin

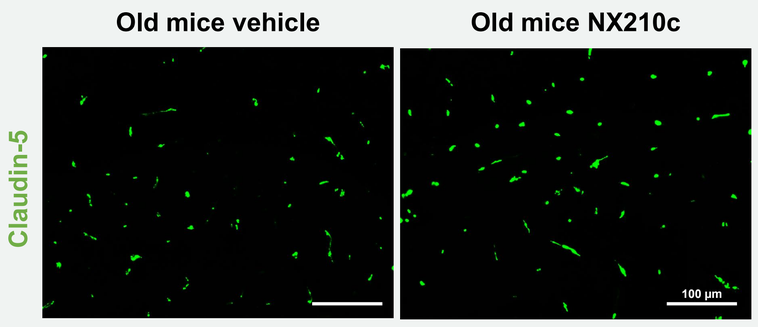
NX210c is **a 12 amino acid peptide** derived from the **most conserved sequence** of the ThromboSpondin type 1 Repeat (**TSR1**) from the SubCommissural organ (**SCO**)-spondin protein. This **matricellular protein** is secreted during embryogenesis where it mediates **neuronal development** (differentiation, migration and survival of neuroepithelium) and regulates **cerebrospinal fluid activity**. Its action is mediated through cell-cell and cell-matrix critical interactions via direct contact with **multiple ligands**, **notably β_1-integrin** (Sepúlveda et al., 2021). This confers **combined properties** to NX210c such as **BBB integrity strengthening, neuroprotection to glutamate excitotoxicity, neurotransmission enhancement whilst also creating conditions that may support myelin repair.**



NX210c mechanism of action

BBB integrity strengthening

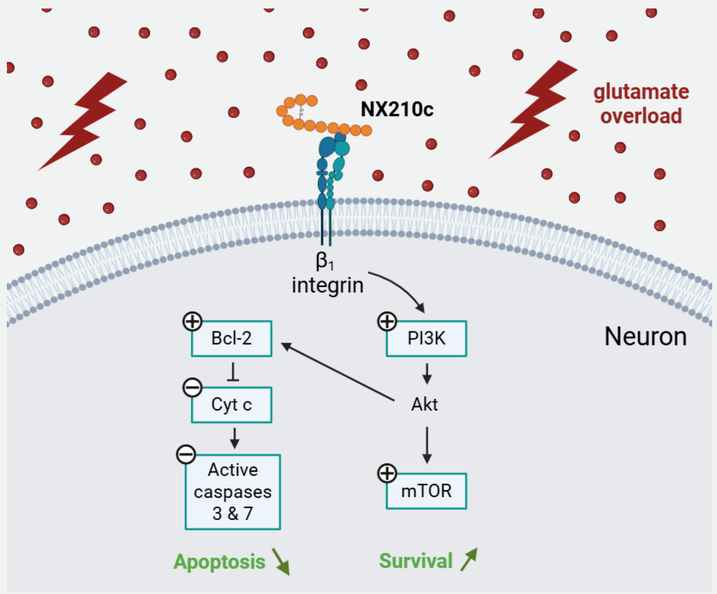


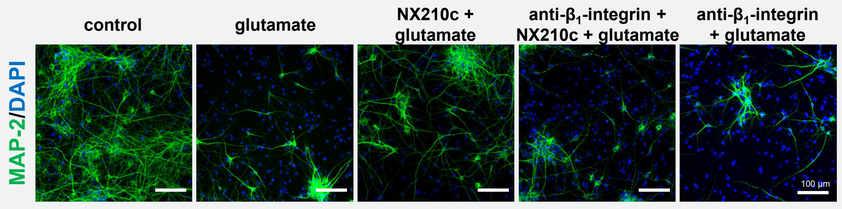


Repeated systemic NX210c administrations (10 mg/kg for 5 days once/d) increases claudin-5 protein levels in the hippocampus of 21-month-old mice (***Greene & Rebergue et al., 2024***).

- **Increases tight junction expression**
- **Decreases BBB permeability**
- **Decreases claudin-5 blood release**

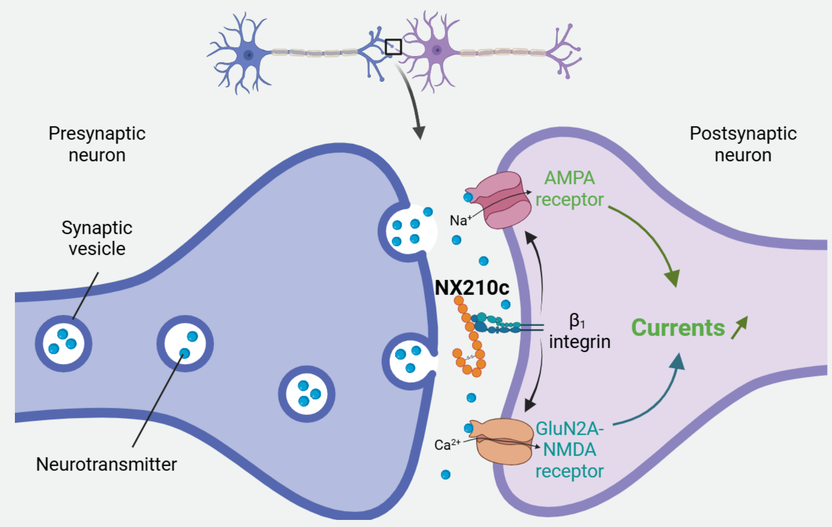
Neuroprotection against glutamate overload

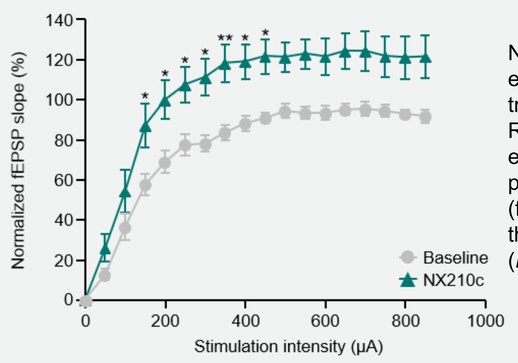




NX210c (250 µg/mL for 48h) protects rat cortical neurons from glutamate-induced excitotoxicity (20 µM for 20 min). β1-integrin blockade prevents NX210c effect (***Delétage et al., 2021***).

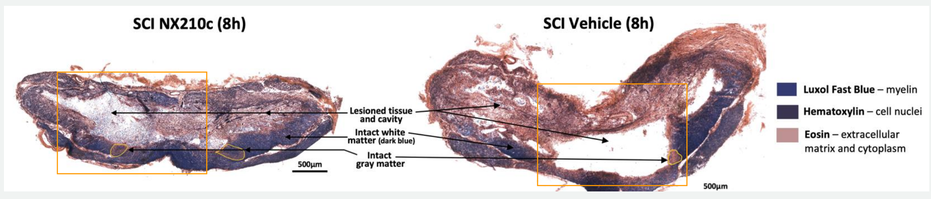
Neurotransmission





NX210c (250 µg/mL) enhances basal synaptic transmission.
Representative traces of extracellular field excitatory postsynaptic potentials (fEPSP) from the thalamocortical region (***Lemarchant et al., 2022***).

Remyelination

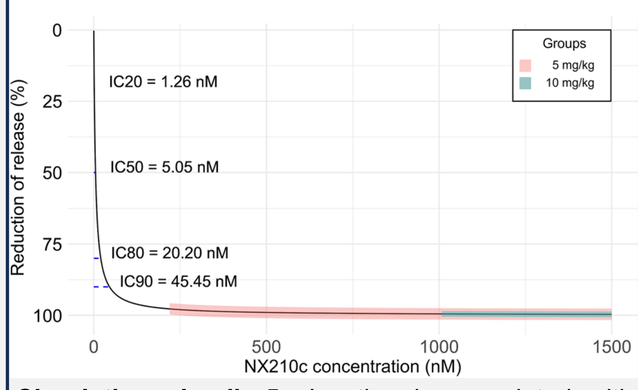


Daily systemic administration of NX210c (8 mg/kg for 8 weeks once/d) promotes tissue preservation after cervical Spinal Cord Injury (SCI) in a model of rats (***Punjani et al., 2025***).

NX210c Biomarkers and dose determination

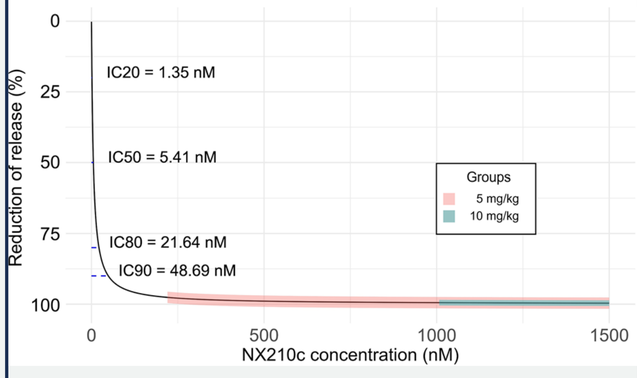
The **Multiple Ascending Dose Study** (NCT05827653, ***Janus et al., 2024***) was a randomized, double-blind, placebo-controlled study that evaluated 5 and 10 mg/kg (i.v. 3x/w 4-weeks) of **NX210c** in Healthy Elderly Volunteers (>55 years old). Statistical analysis of blood and cerebrospinal fluid biomarkers showed significance of numerous fluid biomarkers. **PK/PD modelling methods identified relationships between NX210c pharmacokinetic and claudin-5, neurofilament light chain (NfL), and SPARCL-1.**

Reduction of claudin-5 release



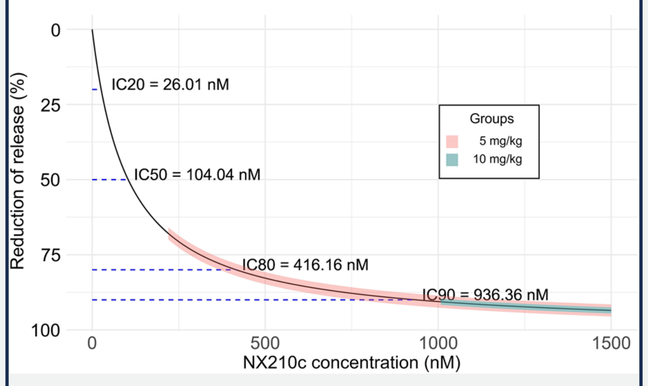
Circulating claudin-5 elevation is associated with BBB disruption. Its **reduction may contribute to restoring vascular integrity.**

Reduction of NfL release



NfL is a marker of neuro-axonal injury. Its **decrease suggests a potential neuroprotective effect.**

Reduction of SPARCL-1 release



SPARCL-1 (from *reactive* astrocytes) is critical for synaptic connectivity; **release reduction** aligns with **restoration of CNS homeostasis**.

A PKPD model of SPARCL-1 simulated dose effect of 2.5, 5, 7.5 and 10 mg/kg NX210c was performed. **Reduction in SPARCL-1** (release) ranged from ~70-85% with lower dose NX210c while an effect of 90% **production inhibition** was demonstrated with 10 mg/kg.

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Conclusion

NX210c is a promising drug candidate which, acting as a TSR-1 analog, may offer a novel therapeutic strategy for neurodegenerative disease involving BBB breakdown such as ALS. Based on the phase 1b *in silico* analysis of claudin-5, homocysteine, NfL and SPARCL-1 for which a PKPD relationship was revealed, doses of 5 and 10 mg/kg intravenously administrated 3 times per week for 4 weeks were selected for the phase II trial SEALS in 80 ALS patients. It also guided the selection of NfL and the quotient of cerebrospinal fluid to blood albumin (Qalb) as primary endpoints.

NX210c has been evaluated in SEALS clinical trial, go to poster #PO108 and #PO127.

Disclosures:
AJ, NR, JL and SM are employed by Axoltis Pharma. AJ is consultant for Axoltis Pharma. FS, PB and DR are employed by InSilicoTrials.

The Phase II clinical trial “SEALS” includes AURALS collaborative project which is granted by France 2030, La Région Auvergne-Rhône-Alpes, bpifrance SERVIR L’AVENIR

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