NX210c: A PROMISING DRUG CANDIDATE FOR BLOOD BRAIN BARRIER REPAIR IN PARKINSON'S DISEASE

Nicolas Rebergue[1], Chris Greene[2], Matthew Campbell[2], Gwen Fewell[3], Supriya Mahajan[4], Damir Janigro[4], Juliette Le Douce[1], Sébastien Marie[1], Annette Janus[1], Yann Godfrin[1,5] & Sighild Lemarchant[1]

[1]Axoltis Pharma, Lyon, France [2]Smurfit Institute of Genetics, Trinity College Dublin, Dublin, Ireland, [3]SynVivo, Huntsville, USA, [4]Flocel, Cleveland, USA, [5]Godfrin Life-Sciences, Caluire-et-Cuire, France

INTRODUCTION

BBB integrity is altered in Parkinson's disease (PD) which contributes to disease progression and functional impairments. NX210c is a 12-amino acid peptide derived from the SCO-spondin that exerts beneficial effects on cognitive and motor functions in several models of neurodegenerative diseases and CNS injuries such as PD (cf. poster from Dr Sighild Lemarchant), AD, ALS and SCI. We hypothesized that NX210c may contribute to functional recovery by restoring BBB integrity. Here are presented in vitro and in vivo evidences of NX210c effects on BBB permeability and/or tight junction protein levels in mouse endothelial cell (EC) monolayers, in a dynamic human BBB model and in aged C57BL/6J mice.

METHODS

In vitro

Mouse bEnd.3 EC monolayers were treated with NX210c (1, 10, 100 µM) or its vehicle (cell culture water) for 24h. Claudin-5 and occludin protein expression were evaluated respectively by immunofluorescence (N=7-10/group) and western-blot (N=8/group). We also measured permeability of EC monolayers grown on transwell inserts to a 40-kDa-FITC Dextran was measured (N=3/group).

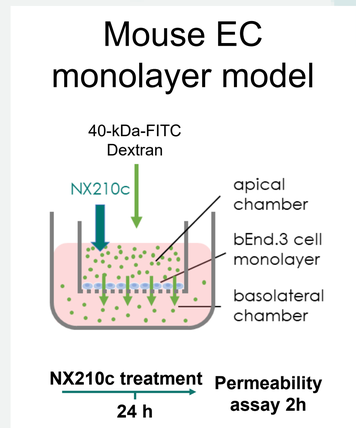
Human BBB-on-chips (human brain microvascular endothelial cells (HBMVECs), pericytes and astrocytes) under shear stress were treated with NX210c (10, 100 µM) or its vehicle for 4h, and the permeability was assessed using 4-kDa-FITC Dextran injected into the vascular channel for 1h (N=4-5/group).

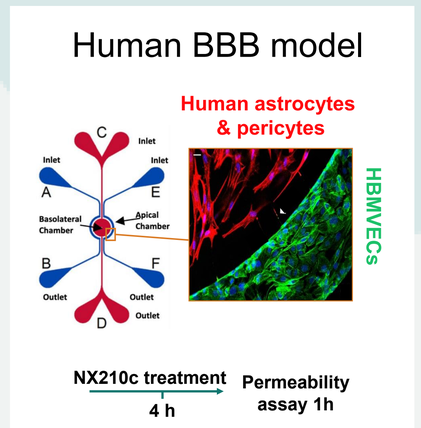
Statistics: ** p<0.01, * p<0.05 vs ctrl

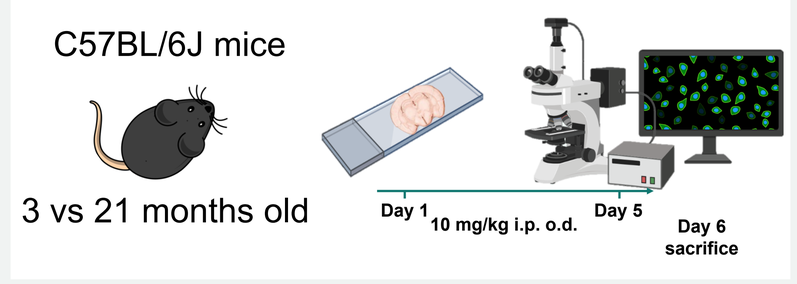
In vivo

3- and 21-month-old C57BL/6J mice were treated intraperitoneally with NX210c at 10 mg/kg or its vehicle (water for injection) for 5 days once a day. Brains were collected at day 6 and tight junction protein expression (claudin-5 and occludin) were analyzed by immunofluorescence in the cortex and the hippocampus (N=5-8/group).

Statistics: ** p<0.01, * p<0.05

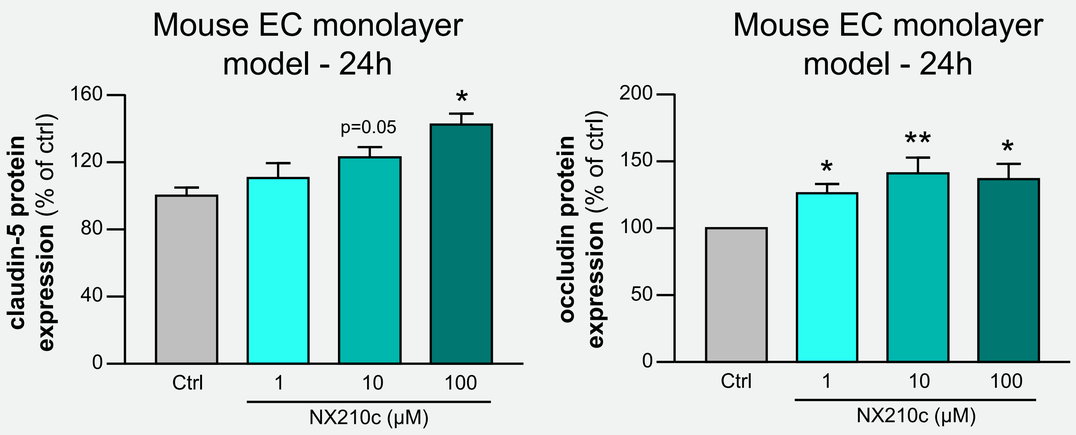




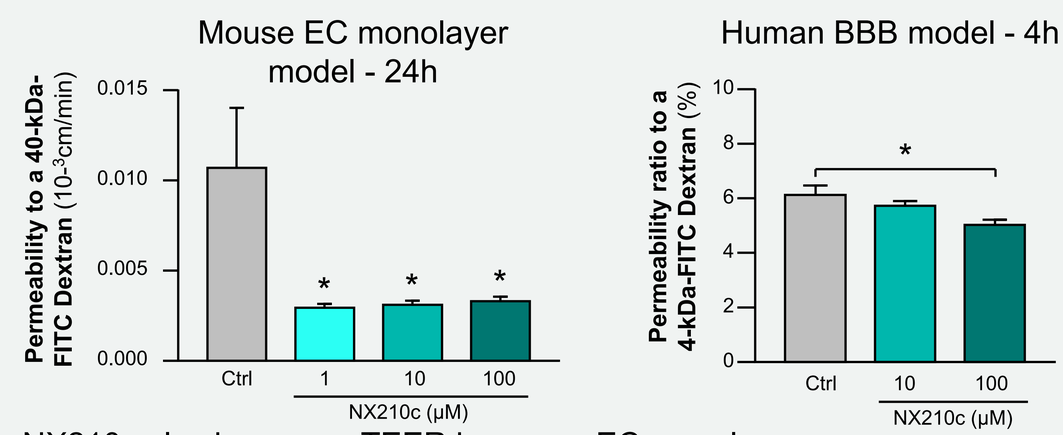


In vitro RESULTS

NX210c increases tight junction protein expression



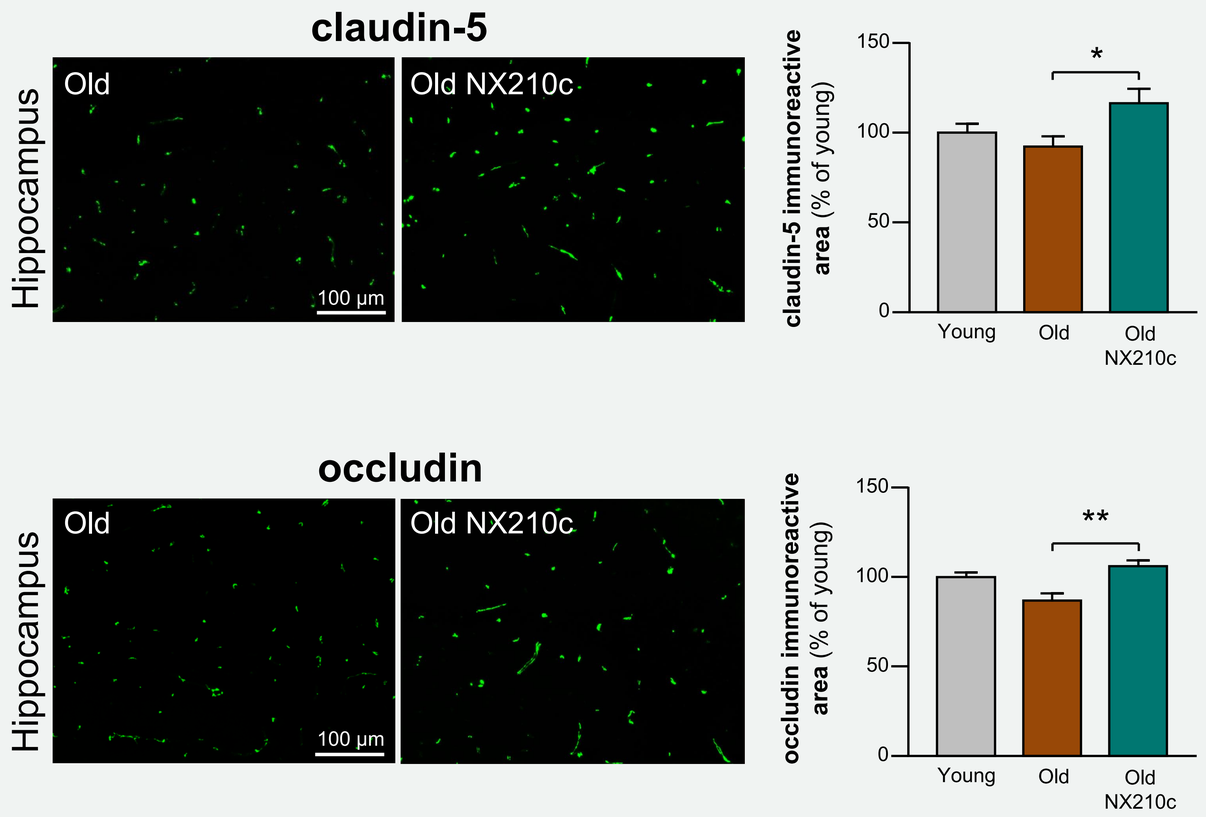
NX210c reduces BBB permeability to FITC Dextrans



NX210c also increases TEER in mouse EC monolayers, as well as in static and dynamic human BBB models (data not shown).

In vivo RESULTS

NX210c increases tight junction protein expression in the brain of old mice



same in cortex (not shown)

CONCLUSIONS & PERSPECTIVES

Overall, NX210c is a promising drug candidate for the treatment of neurological diseases with BBB dysfunctions. Indeed, in 3 different labs, we have shown that NX210c promotes BBB integrity *in vitro* by reducing BBB permeability, increasing TEER (data not shown) and increasing claudin-5 and occludin protein expression. The increase in tight junction protein expression was confirmed *in vivo* in an ageing mouse model.

Top-line results of a phase 1b clinical trial (NCT05827653) confirmed the good safety profile of NX210c and pharmacological effects on BBB. Indeed, a sustained decrease in claudin-5 plasmatic levels was observed with PK/PD relationship in elderly healthy volunteers treated 3x/week for 26 days (results presentation on Sat. 09 auditorium VIII 18h10 by Dr Annette Janus). This phase 1b trial already got authorization to extend to a PD patient cohort. In addition, a phase 2 trial in ALS patients, where BBB is also impaired, is expected to start in 2024.

Scan for more information on NX210c

Disclosures: NR, JLD, SM, AJ, SL are employed by Axoltis Pharma. YG is the CEO and a shareholder of Axoltis Pharma. GF is CEO of Synvivo. DJ is CEO of Flocel.

nrebergue@axoltis.com