#### THE P75<sup>NTR</sup> ANTAGONIST THX-B IMPROVES VOIDING BEHAVIOUR AND REDUCES **ABSTRACT #106 BLADDER CONTRACTILITY IN AGING MICE** The authors have no 🐯 McGill

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potential conflict of interest

## INTRODUCTION

- •Overactive bladder syndrome (OAB) presents the symptoms of urgency, with or without urge incontinence, usually with increased daytime frequency and nocturia, as defined by the International Continence Society.
- •The Nerve Growth Factor (NGF) is a survival factor essential for nervous system health and homeostasis. It binds mostly TrkA receptor.
- •Precursor proNGF binds p75<sup>NTR</sup> receptor to promote inflammation and cell apoptosis. levels Decreased of NGF, and lower NGF/proNGF ratio have been reported in urine samples of aging female patients with OAB<sup>1</sup>.
- •Antagonism of the proNGF receptor, p75<sup>NTR</sup> by the compound THX-B restored NGF levels and increase the NGF/proNGF ratio in mice with diabetic voiding dysfunction<sup>2</sup>.

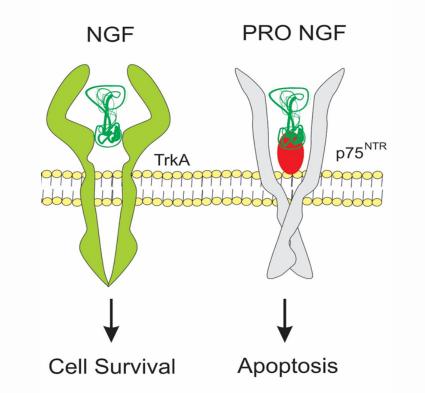


Figure 1. NGF binds TrkA to activate cell survival pathways. ProNGF binds p75NTR to activate apoptotic and inflammatory pathways<sup>3</sup>.

### Urine of aging females with OAB

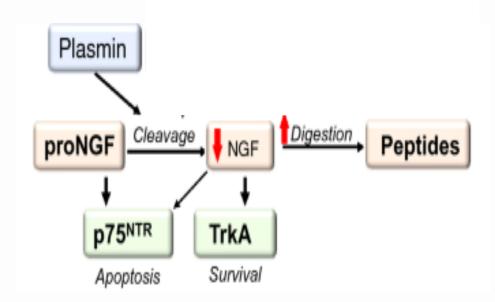


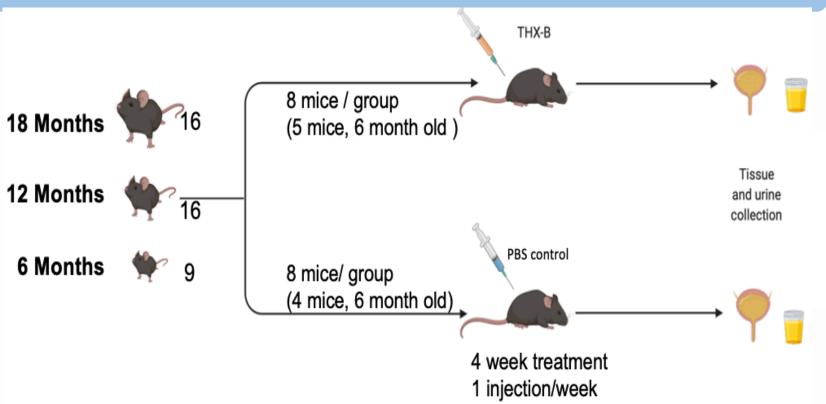
Figure 2. Urinary levels of NGF and related enzymes in aging female patients with OAB<sup>1</sup>.

## **OBJECTIVE**

To assess the behavioural and functional benefits of treating aging mice bladders with a p75<sup>NTR</sup> antagonist, THX-B.

# **METHODS AND EXPERIMENTAL DESIGN**

Male C57BL/6J mice of 6-, 12- and 18-months were injected intraperitoneal with either PBS (control) or THX-B (50 µg) once weekly for four weeks. Mice were separated based on age and expression of urinary p75<sup>NTR</sup> extracellular domain. Voiding behaviours and patterns, notably, total urine volume, volume of urine, and frequency of urination were assessed using voiding spot assay biweekly. Bladders were collected for organ bath, which evaluated bladder contractility using electrical field stimulation (EFS), KCI and carbachol.





## RESULTS

тнх-в

тнх-в

тнх-в

тнх-в

PBS

e (μL) per Micturitio

тнх-в

тнх-в

18 Month-Old

тнх-в

PBS

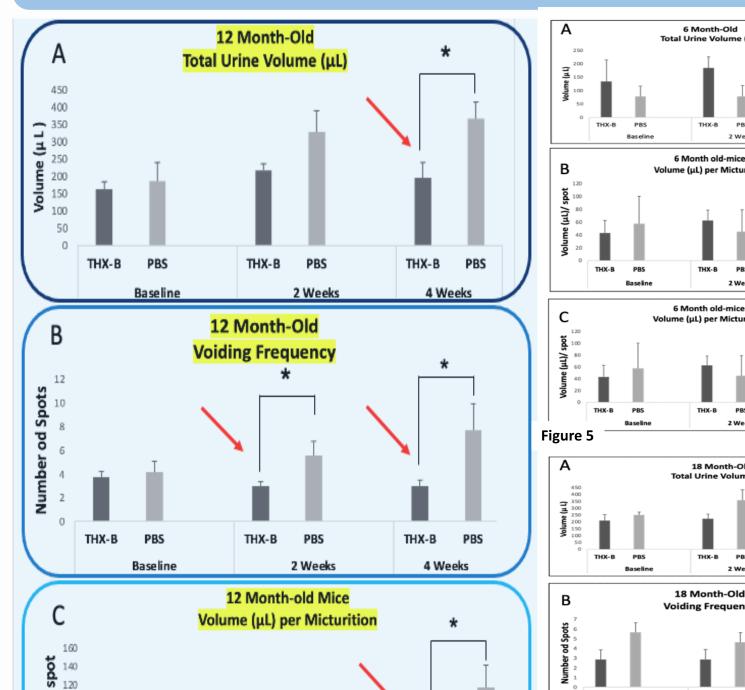
2 Week

PBS

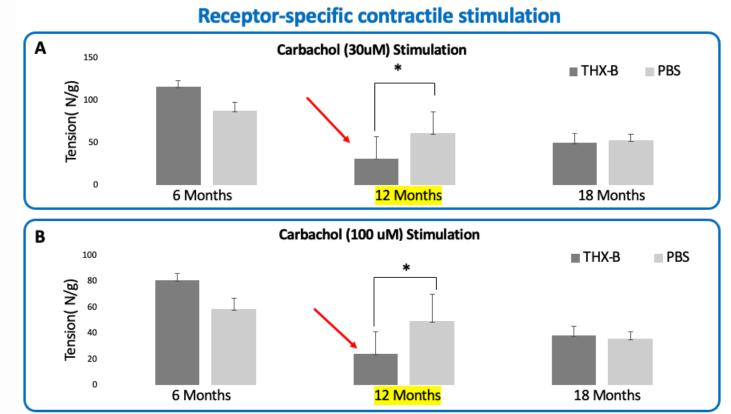
PBS

2 Week

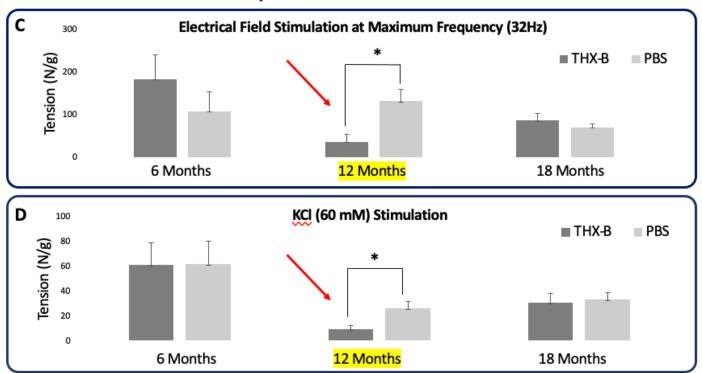
### 12-month-old treated mice showed lower total urine volume, volume/micturition and voiding frequency



## 12-month-old treated mice responded less to contractile stimuli



#### Non-specific contractile stimulation



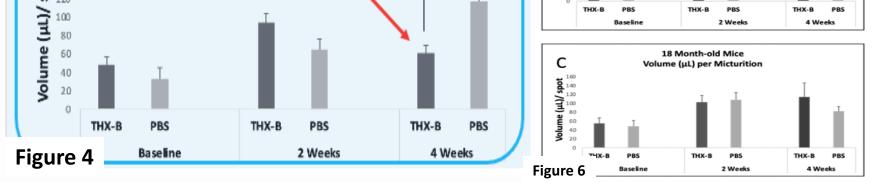


Figure 4, 5 & 6. Voiding Spot Assay (VSA) over a 4 hour period. Figure 4: 12 month-old mice; Figure 5: 6-month-old mice; Figure 6: 18-month-old mice. (A) Total urine volume (µL) voided, (B) Voiding frequency measured by number of spots, (C) Mean volume ( $\mu$ L) per micturition measured by volume per spot; n=4-8 mice in each group at each time point. All comparisons were done using student t-test. \*P <0.05

## **CONCLUSIONS**

- Improvements in bladder behaviour and activity were observed only in 12-month-old treated mice.
- Our results are in accordance with our previous studies and suggest that THX-B could be a new pharmacological tool for improving OAB.
- Future studies aimed at understanding the expression of p75<sup>NTR</sup> in relation to the aging bladder will help understand the mechanism of p75<sup>NTR</sup> antagonism in the aging bladder.

Figure 7. Contractile characteristics of 6-month, 12-month, and 18-month-old mice bladder strips. (A) Electrical field stimulation at maximum frequency (32 Hz). (B) Response to 60 mM KCI stimulation. (C) Response to carbachol at 30µM and (D) 100µM. n= 3-8 bladder strips, each strip comes from individual bladders of mice from each group. Student ttest. \*p<0.05

# REFERENCES

- 1. Mossa AH, Cammisotto PG, Shamout S, Campeau L. Imbalance of nerve growth factor metabolism in aging women with overactive bladder syndrome. World J Urol. 2021 Jun;39(6):2055-2063. doi: 10.1007/s00345-020-03422-6. Epub 2020 Sep 1. PMID: 32870355. 2. Mossa, Abubakr H et al. "Antagonism of proNGF or its receptor p75<sup>NTR</sup> reverses remodelling and improves bladder function in a mouse model of diabetic voiding dysfunction." Diabetologia vol. 63,9 (2020): 1932-1946.
- 3.Amidfar, M., de Oliveira, J., Kucharska, E., Budni, J. & Kim, Y.-K. The role of CREB and BDNF in neurobiology and treatment of Alzheimer's disease. Life Sciences 257, 118020, (2020).