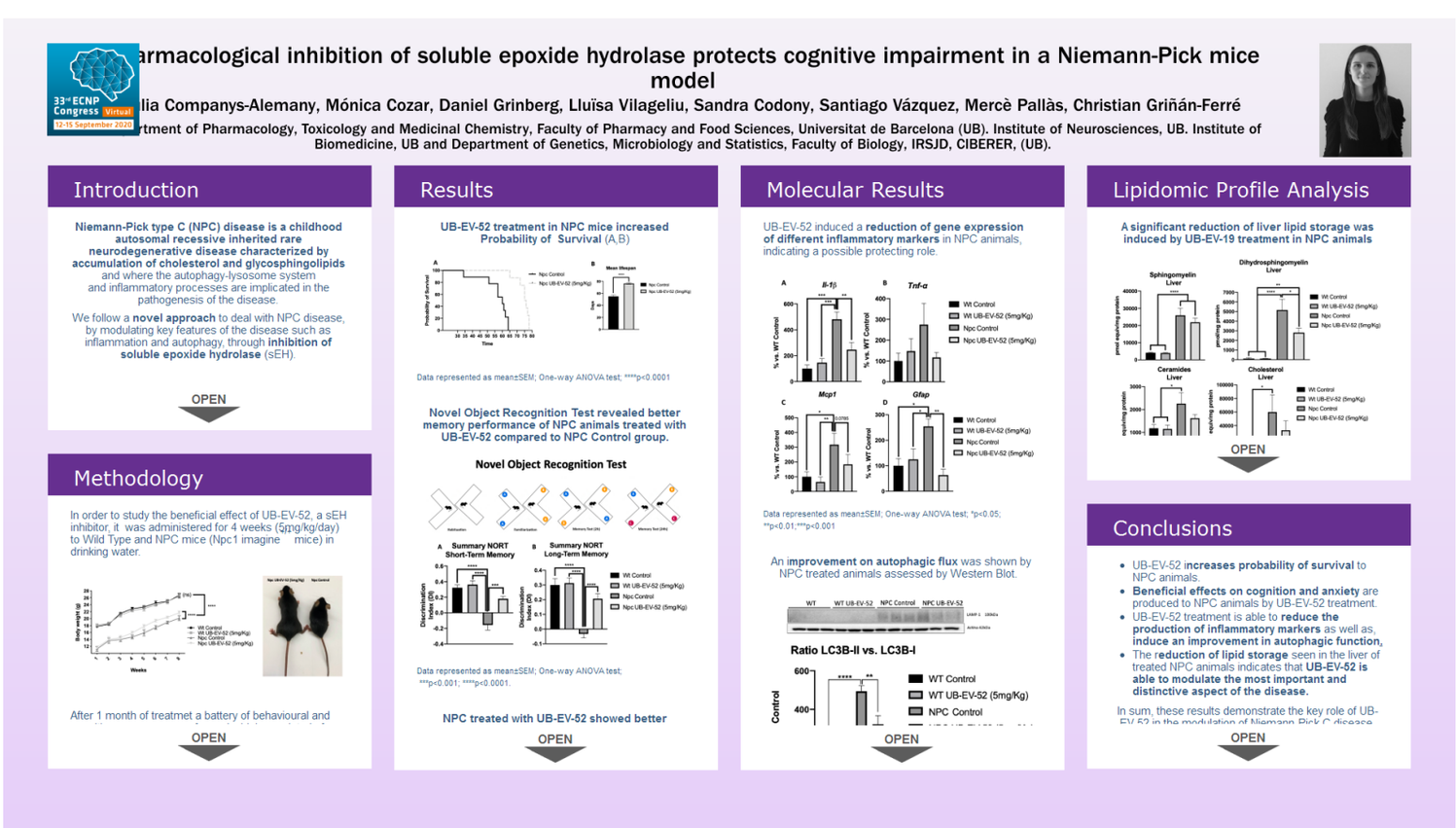
Pharmacological inhibition of soluble epoxide hydrolase protects cognitive impairment in a Niemann-Pick mice model



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Welcome to the future of CNS treatments
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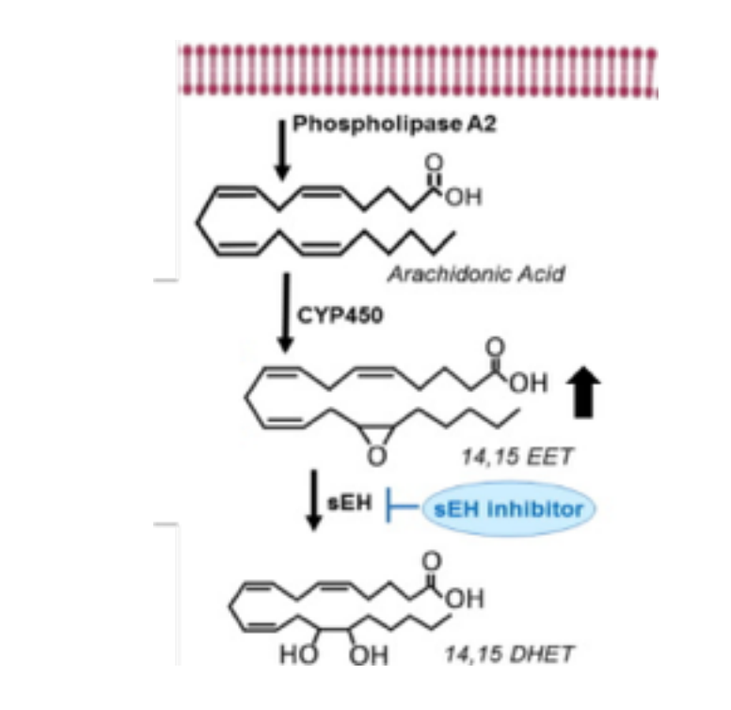
INTRODUCTION

Niemann-Pick type C (NPC) disease is a childhood autosomal recessive inherited rare neurodegenerative disease characterized by accumulation of cholesterol and glycosphingolipids and where the autophagy-lysosome system and inflammatory processes are implicated in the pathogenesis of the disease.

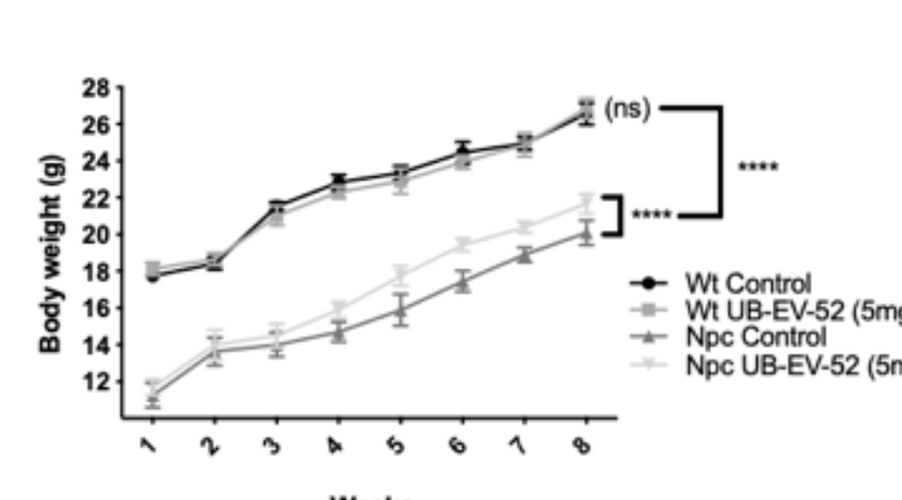
We follow a **novel approach** to deal with NPC disease, by modulating key features of the disease such as inflammation and autophagy, through **inhibition of soluble epoxide hydrolase** (sEH).

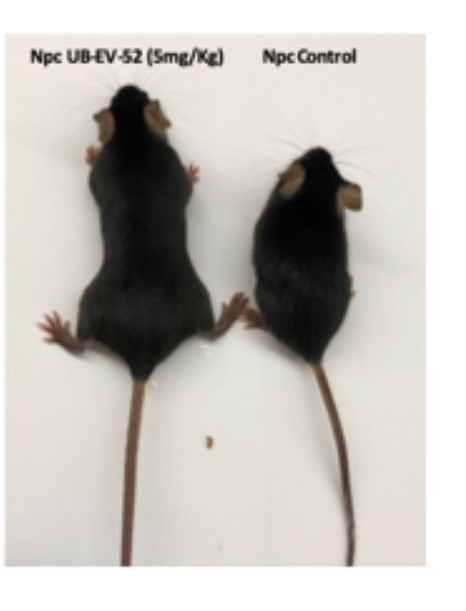
sEH converts epoxyeicosatrienoic acids (EETs) derived from AA by cytochrome P450 epoxygenases, to their corresponding dihydroxyeicosatrienoic acids. EETs have anti-inflammatory properties that are lost after sEH action. Besides, it is well described that increased sEH expression impairs autophagy flux. For this reason, the **aim of the study was to evaluate the effects on cognition and memory, and the molecular changes in autophagy and inflammation pathways induced by a sEH inhibitor on the NPC mice model**.



METHODOLOGY

In order to study the beneficial effect of UB-EV-52, a sEH inhibitor, it was administered for 4 weeks (5mg/kg/day) to Wild Type and NPC mice (Npc1 imagine$^{+/+}$ mice) in drinking water.

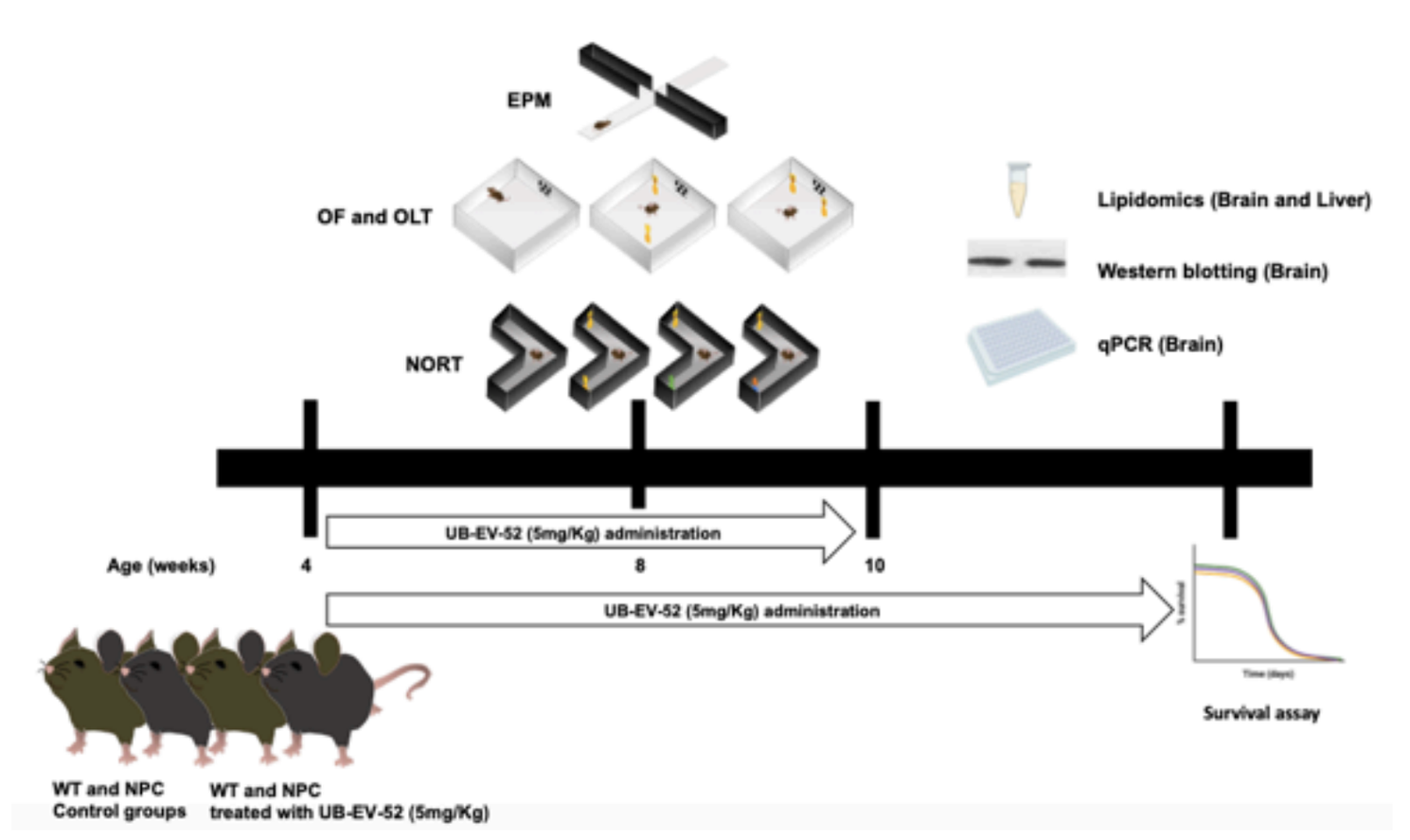




After 1 month of treatmet a battery of behavioural and cognitive assays was performed which consisted of:

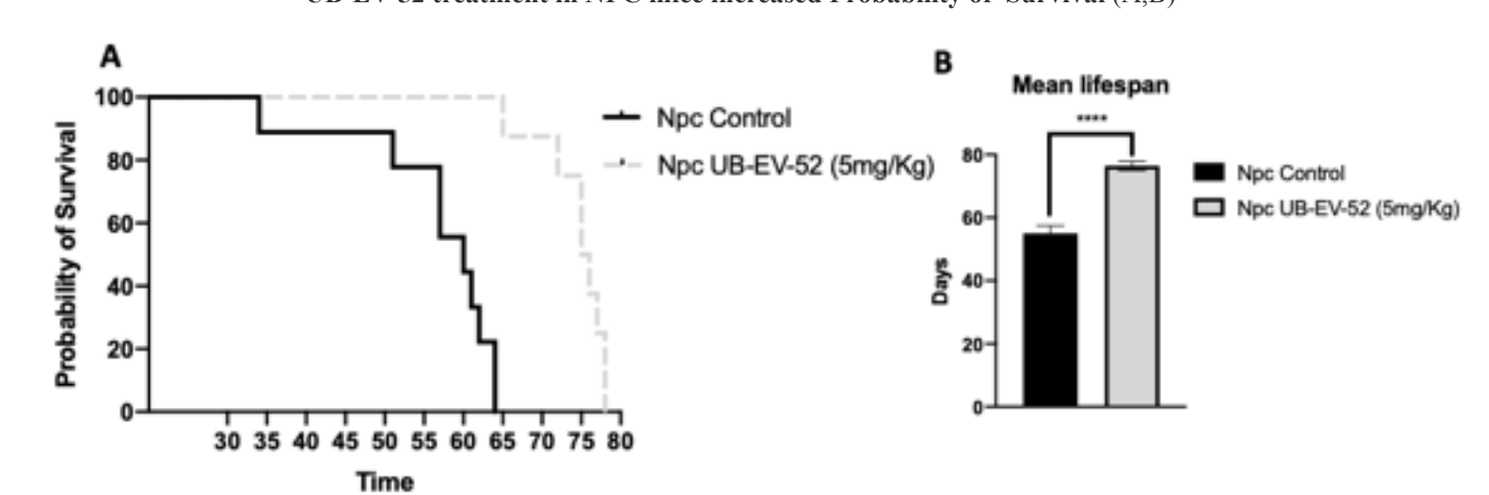
- Novel Object Recognition Test (NORT) to study short and long-term memories.
- Open Field test (OF) to asses locomotor activity and also parameters of anxiety.
- Object Location Test (OLT) which is an idoneal test to asses spatial memory.

After 10 weeks since they were born, the animals were euthanized and molecular assays were performed in order to evaluate gene expression, protein expression and their lipidomic profile.



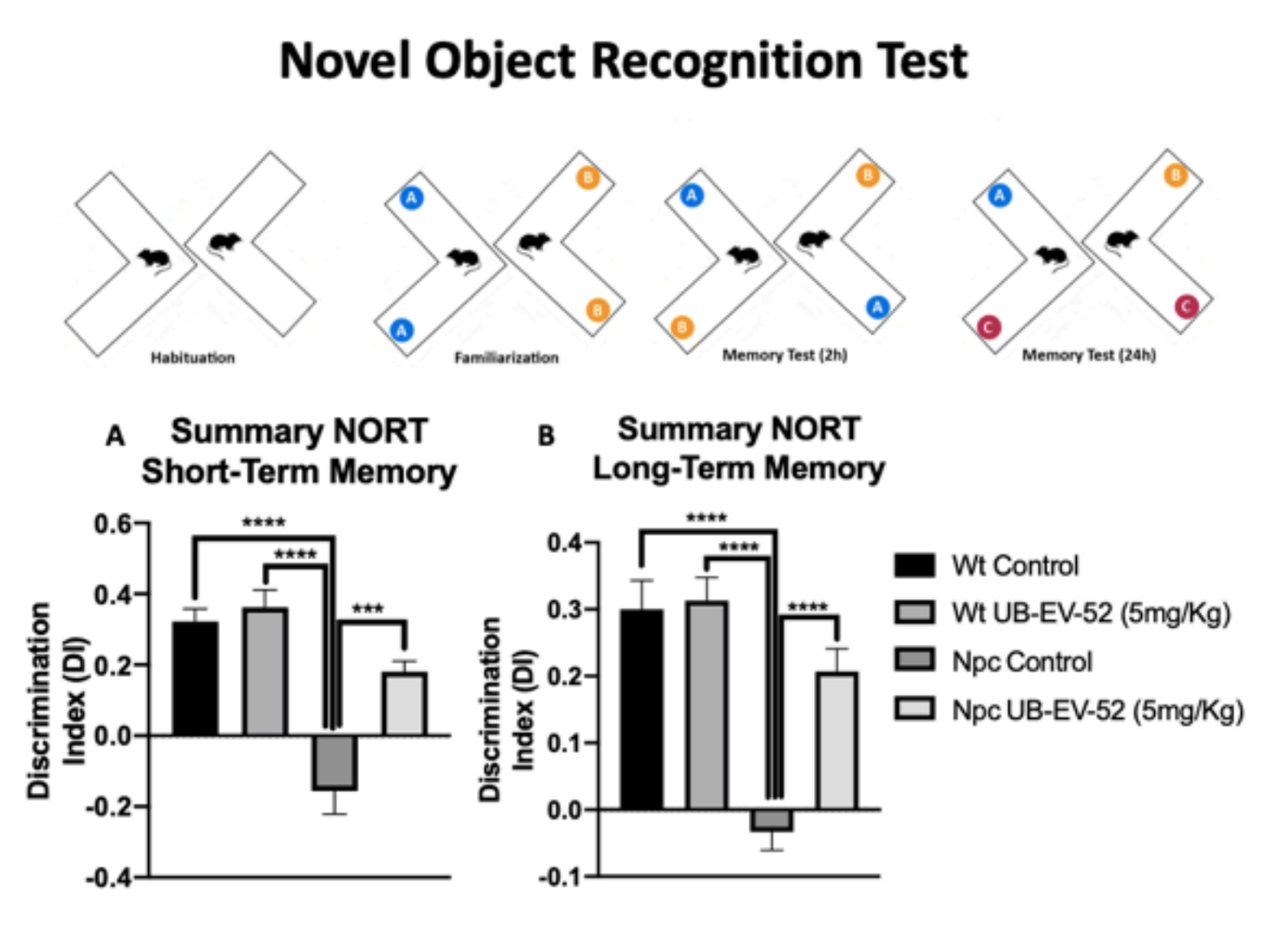
RESULTS

UB-EV-52 treatment in NPC mice increased Probability of Survival (A,B)



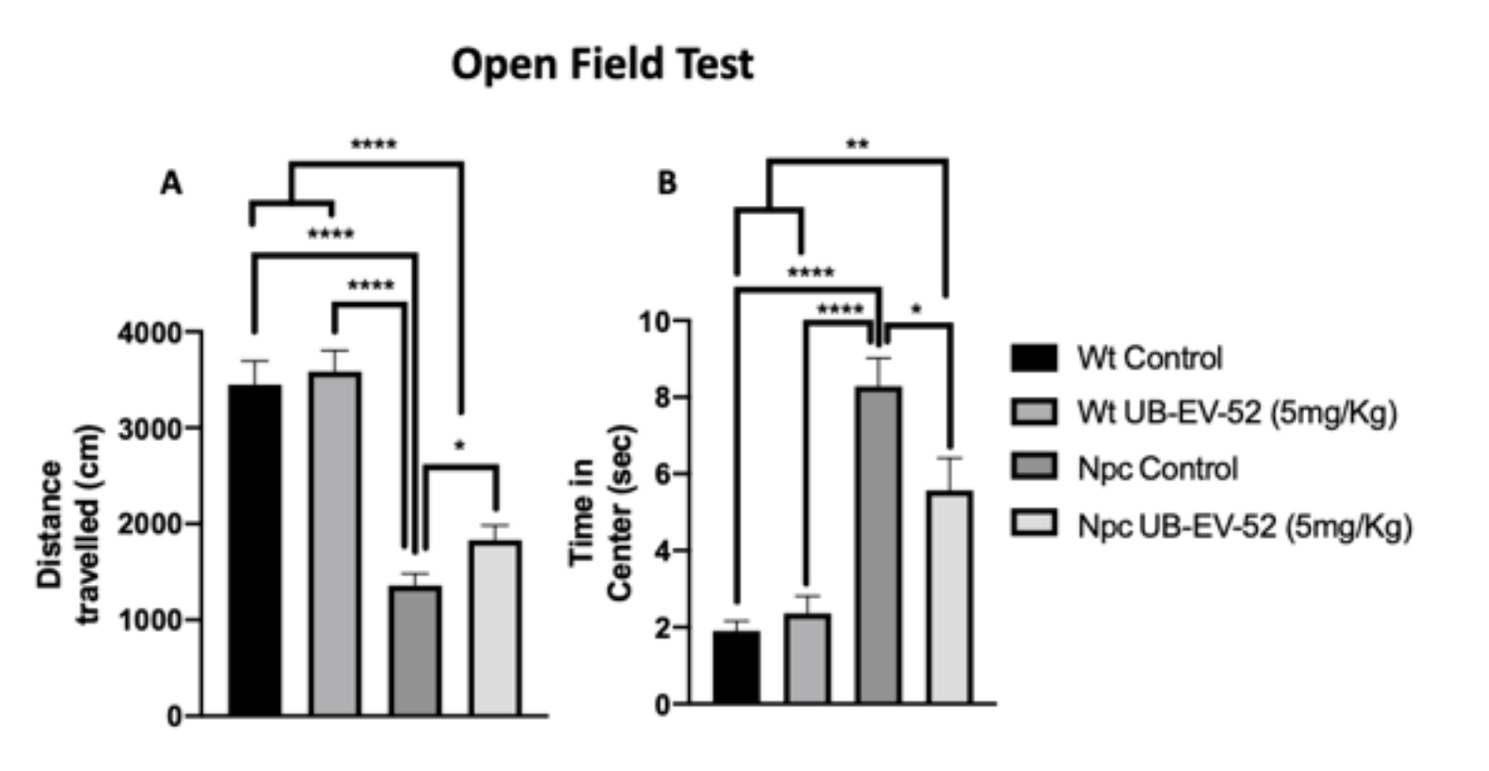
Data represented as mean±SEM; One-way ANOVA test; ****p<0.0001

Novel Object Recognition Test revealed better memory performance of NPC animals treated with UB-EV-52 compared to NPC Control group.



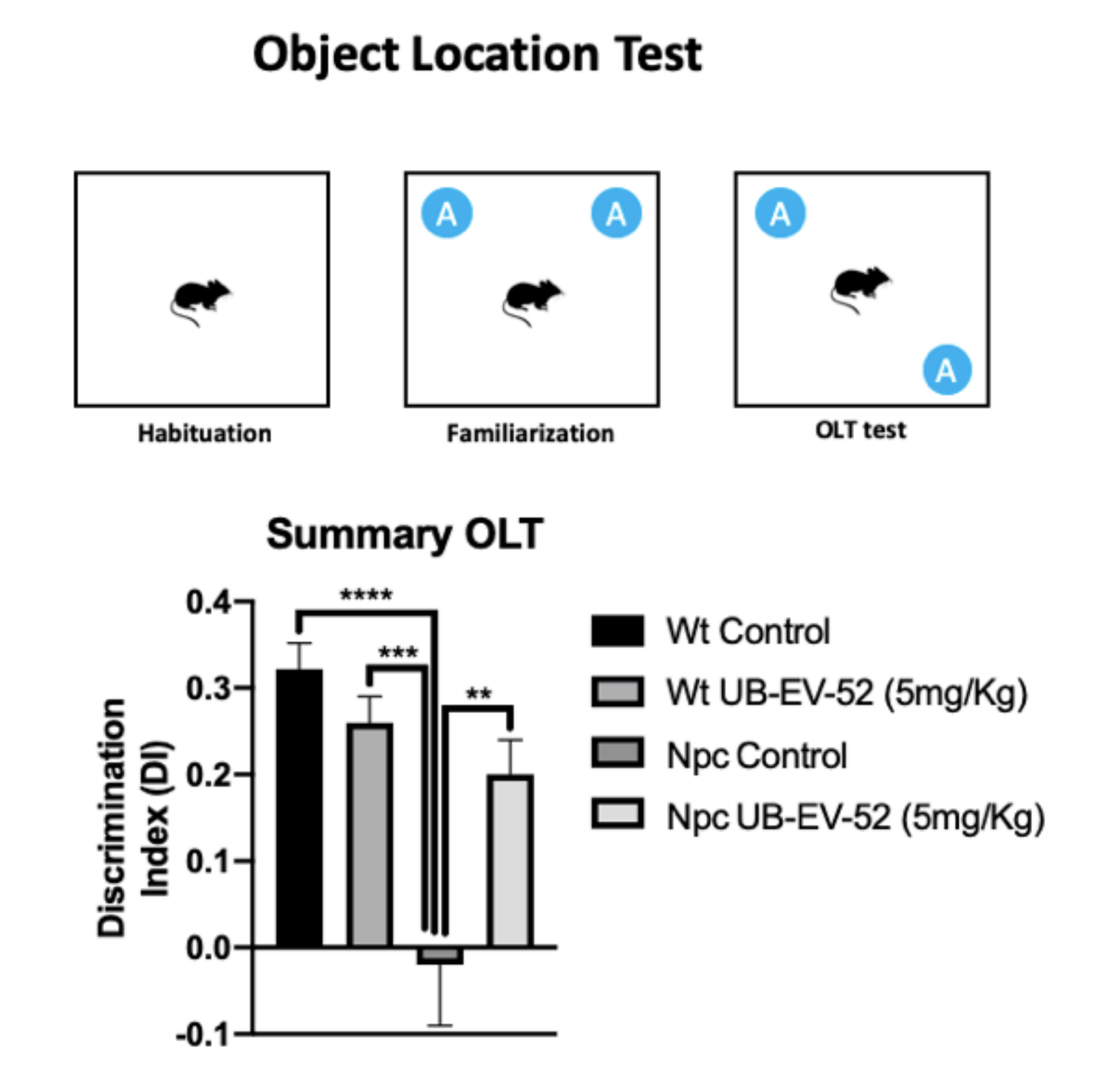
Data represented as mean±SEM; One-way ANOVA test; ***p<0.001; ****p<0.0001.

NPC treated with UB-EV-52 showed better locomotor activity and less anxiety according to Open Field Test.



Data represented as mean±SEM; One-way ANOVA test; *p<0.05; **p<0.01; ****p<0.0001

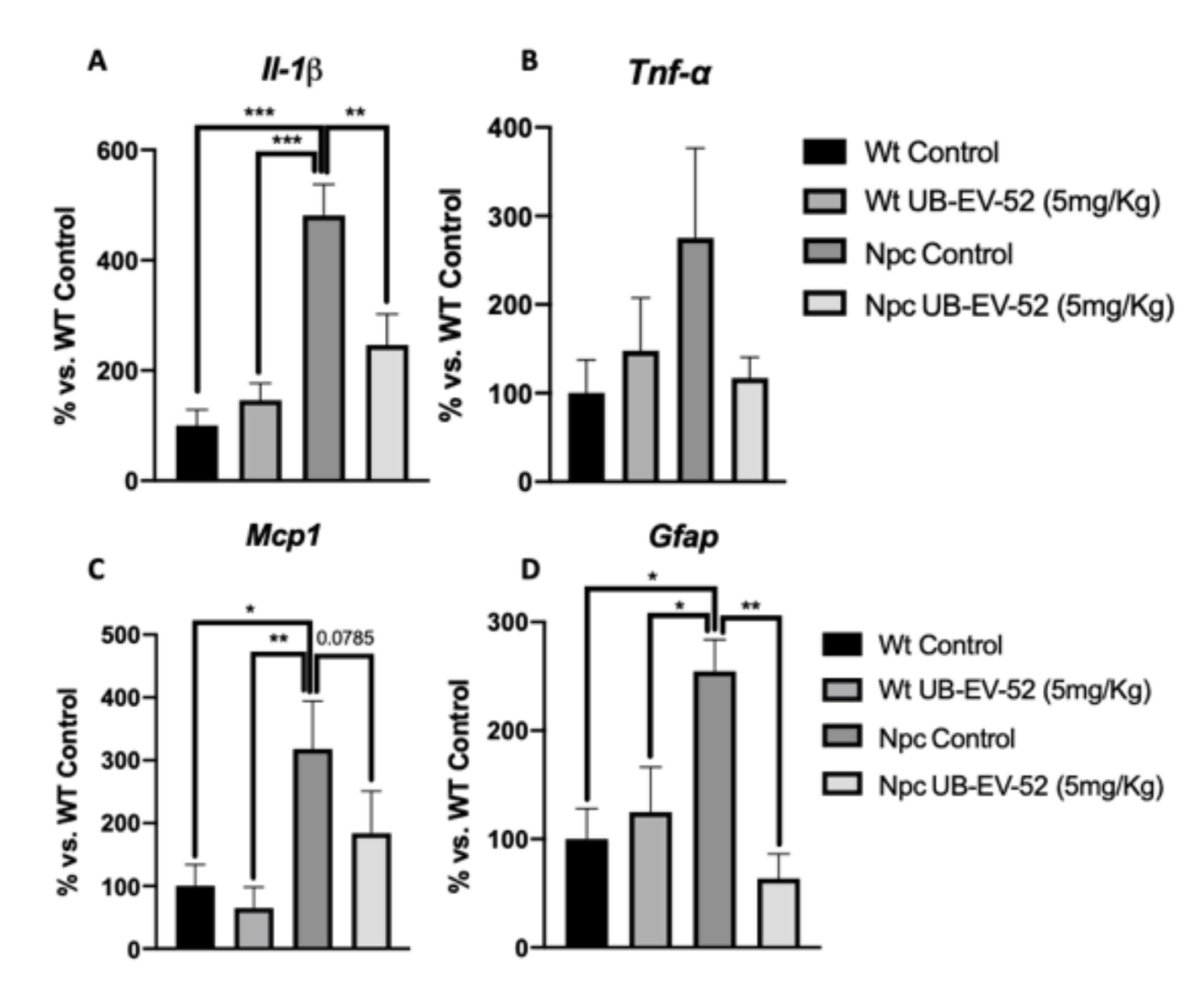
Object Location Test showed a significant improvement in spatial memory in NPC treated animals compared to Control group



Data represented as mean±SEM; One-way ANOVA test; **p<0.01; ***p<0.001; ****p<0.0001

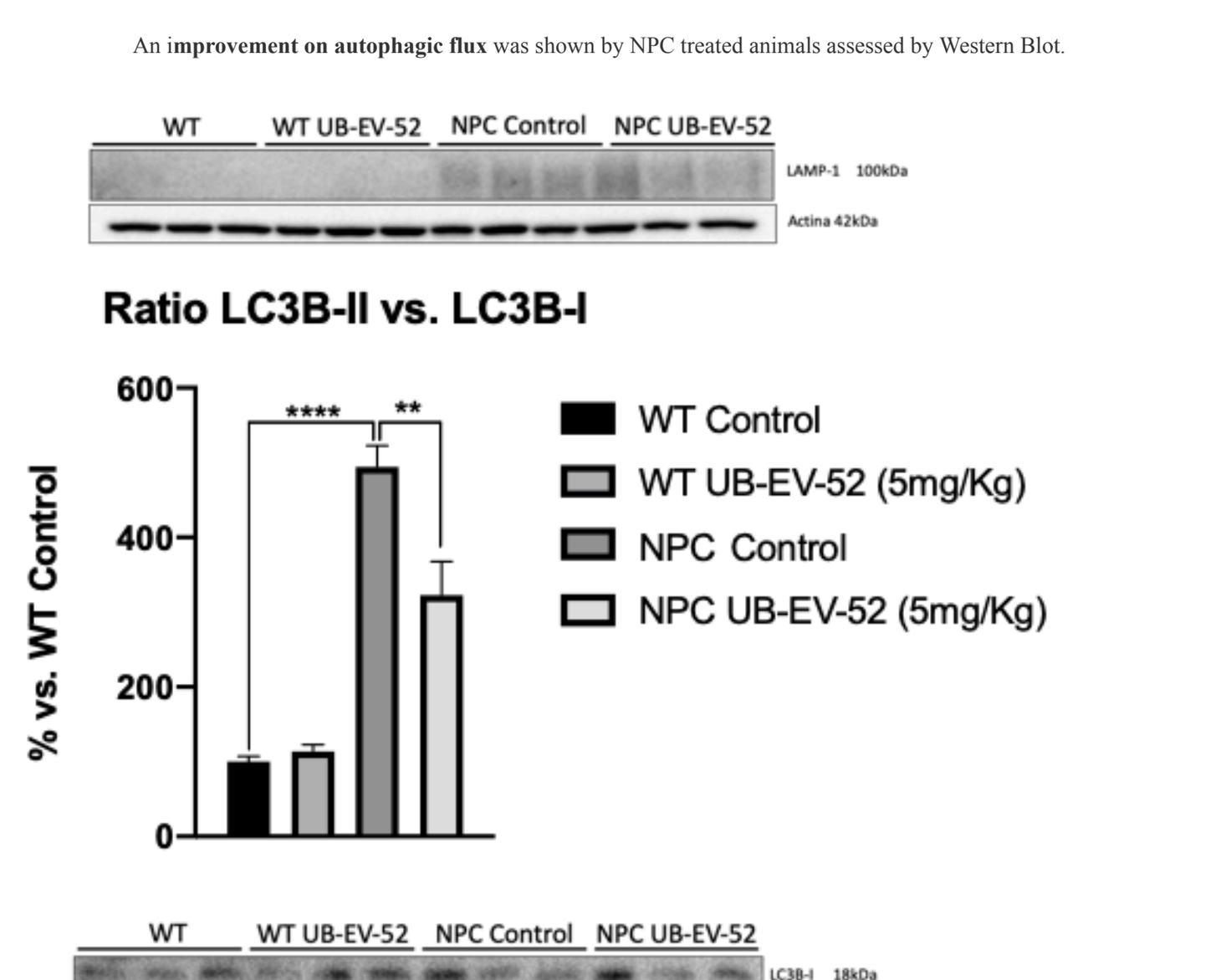
MOLECULAR RESULTS

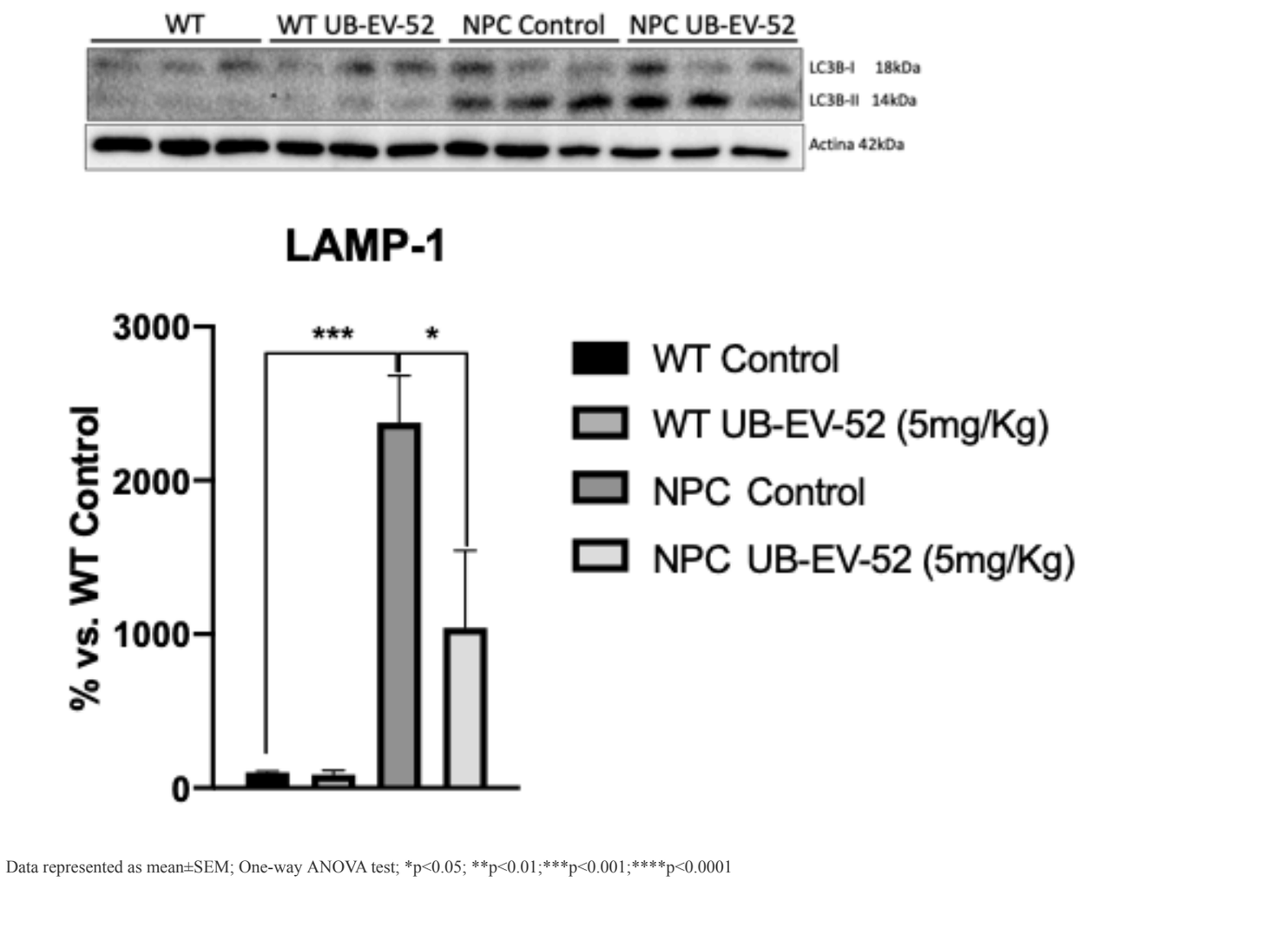
UB-EV-52 induced a **reduction of gene expression of different inflammatory markers** in NPC animals, indicating a possible protecting role.



Data represented as mean±SEM; One-way ANOVA test; *p<0.05; **p<0.01;***p<0.001

An i**mprovement on autophagic flux** was shown by NPC treated animals assessed by Western Blot.

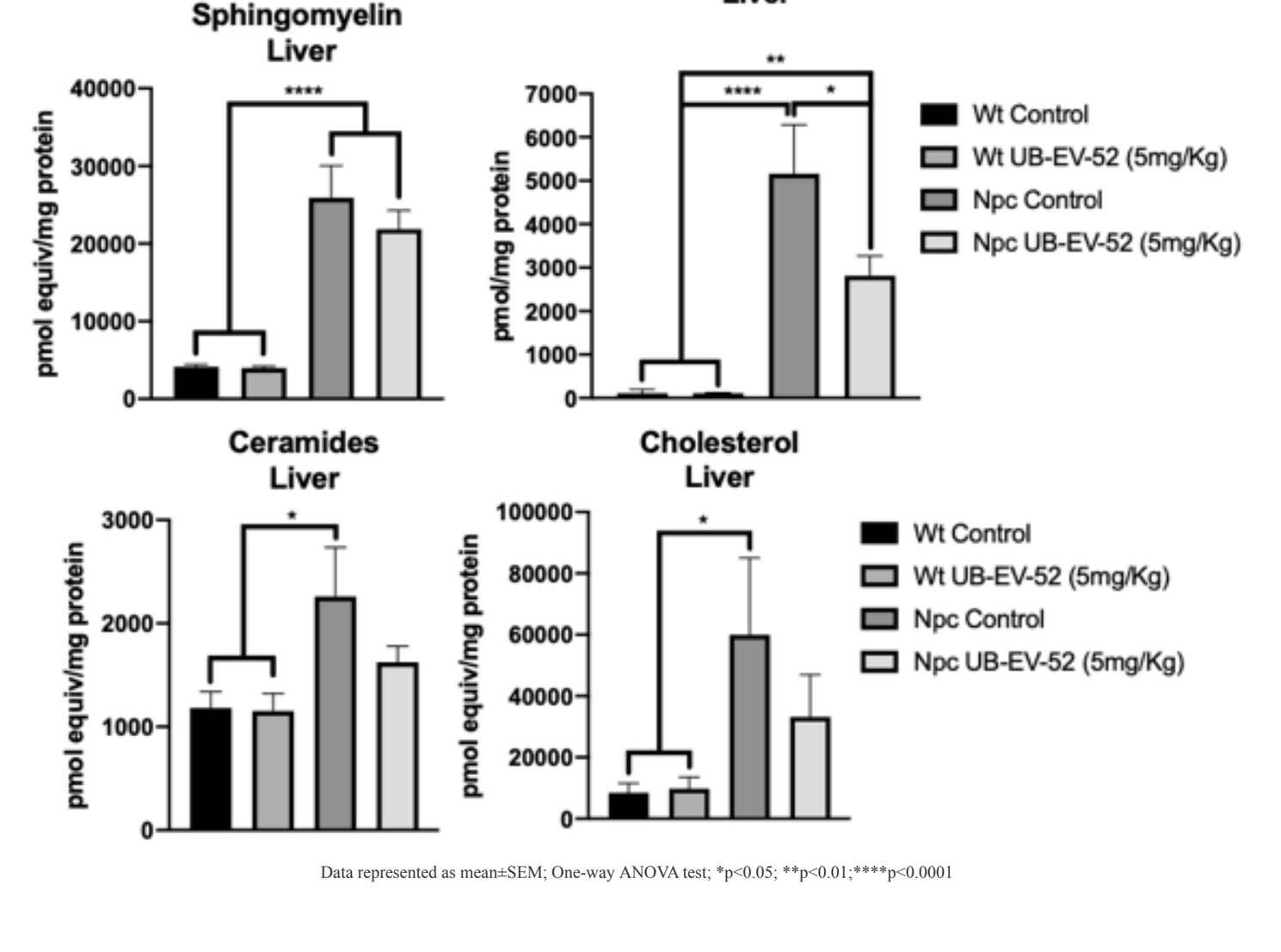




Data represented as mean±SEM; One-way ANOVA test; *p<0.05; **p<0.01;***p<0.001;****p<0.0001

LIPIDOMIC PROFILE ANALYSIS

A significant reduction of liver lipid storage was induced by UB-EV-19 treatment in NPC animals



Data represented as mean±SEM; One-way ANOVA test; *p<0.05; **p<0.01;****p<0.0001

CONCLUSIONS

- UB-EV-52 i**ncreases probability of survival** to NPC animals.
- **Beneficial effects on cognition and anxiety** are produced to NPC animals by UB-EV-52 treatment.
- UB-EV-52 treatment is able to **reduce the production of inflammatory markers** as well as, **induce an improvement in autophagic function.**
- The r**eduction of lipid storage** seen in the liver of treated NPC animals indicates that **UB-EV-52 is able to modulate the most important and distinctive aspect of the disease.**

In sum, these results demonstrate the key role of UB-EV-52 in the modulation of Niemann-Pick C disease, being a **promising disease modifying therapy.**

DISCLOSURES

AUTHOR INFORMATION

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ABSTRACT

Niemann-Pick type C (NPC) disease is a childhood autosomal recessive inherited rare neurodegenerative disease characterized by accumulation of cholesterol and glycosphingolipids. Furthermore, the autophagy-lysosome system, which is one of the main intracellular proteolytic mechanisms responsible for the clearance of unwanted macromolecules and inflammatory process are implicated in the pathogenesis of the disease. Taking into account these mechanisms, we follow a novel approach to deal with NPC disease, by modulating key features of the disease such as inflammation and autophagy, through inhibition of soluble epoxide hydrolase (sEH). sEH converts epoxyeicosatrienoic acids derived from AA by cytochrome P450 epoxygenases, to their corresponding dihydroxyeicosatrienoic acids. EETs have anti-inflammatory properties that are lost after sEH action. Besides, it is well described that increased sEH expression impairs autophagy flux. For this reason, the aim of the study was to evaluate the effects on cognition and memory, and the molecular changes in autophagy and inflammation pathways induced by a sEH inhibitor on the NPC mice model. Data analysis was conducted using GraphPad Prism ver. 8. Strain and treatment effects were compared using One-way analysis of variance (ANOVA) followed by tukey post-hoc analysis. Cognitive analysis was performed blindly. In order to study the beneficial effect of UB-EV-52, a sEH inhibitor, was administered for 4 weeks (5mg/kg/day) to NPC mice (Npc1 imagine+/+ mice). The battery of behavioural assays consisted of novel object recognition test (NORT), open field test (OF) and object location test (OLT). The treatment produced an improvement in short- and long-term memory, as well as in spatial memory in treated NPC mice, showing a better cognitive performance. Additionally, the treatment improved motor capabilities in treated NPC mice. Moreover, treatment increased the lifespan by 25% and reduced gene expression of the inflammatory markers (p.e. Il-1β and Cox2 diminution) and improved oxidative stress markers (iNOS and Hmox1) in treated NPC mice group. Regarding autophagic flux, we evaluated autophagy markers through western blot (WB) and surprisingly we found significant reduced levels of the ratio LC3B-II/LC3B-I and also a significant reduction of hippocampal protein levels of lysosomal associated membrane protein 1 (LAMP-1) in the NPC-disease treated group compared to non-treated, but a slight modification in p62 and Beclin-1 protein levels were shown in NPC treated animals. Moreover, to demonstrate the beneficial effect on the characteristic traits of the disease, a lipidomic profile study was performed and the results showed reduced accumulation of cholesterol and sphingolipids in treated NPC mice compared to non-treated groups. Our results suggest that pharmacological inhibition of sEH ameliorate most of the characteristic traits of the NPC in mice, demonstrating that sEH can be considered a potential therapeutic strategy for NPC disease. Funds: Ministerio de Economía y Competitividad of Spain (SAF2016-77703, PID2019-106285RB), Llavor (2018 LLAV 00007, AGAUR, Catalonia) and FEDER funds. References

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