



Neuroproteomics and Signalling of Brain Disorders

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*Korea-EU Horizon Europe Researchers Networking Forum
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Composition of the “Neuroproteomics and Signalling of Brain Disorders” team

Permanent scientists



Joël
BOCKAERT
Emeritus



Philippe
MARIN
Team leader



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CLAEYSEN
Researcher



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BÉCAMEL
Associate Professor



Séverine
CHAUMONT-DUBEL
Associate Professor



Éric
THOUVENOT
Professor



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Olivier
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Researcher



Sylvaine
ARTERO
Researcher

Postdocs



Charleine
ZUSSY
Postdoc



Geoffrey
CANET
Postdoc



Léo
BOUSSAMET
Postdoc

PhD Students



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CUREL
PhD



Clémence
QUITTET
PhD



Manon
RIVAL
PhD

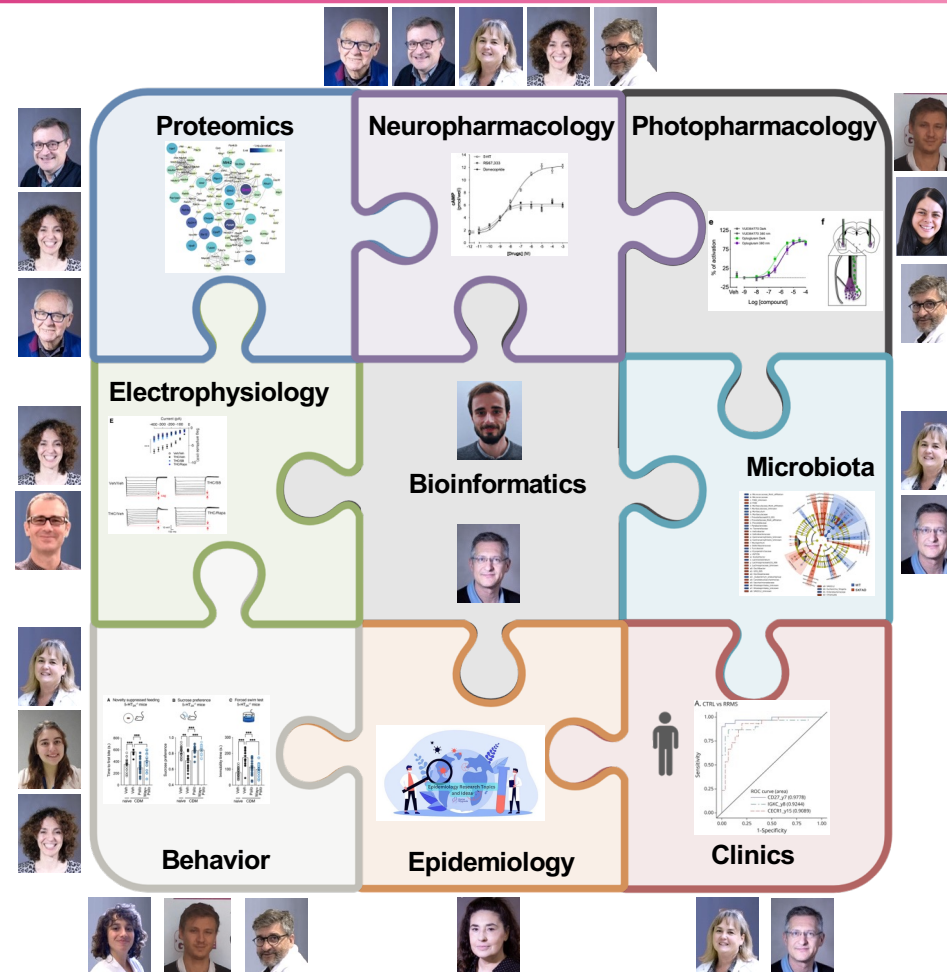


Soufiane
EL-KHAYARI
PhD

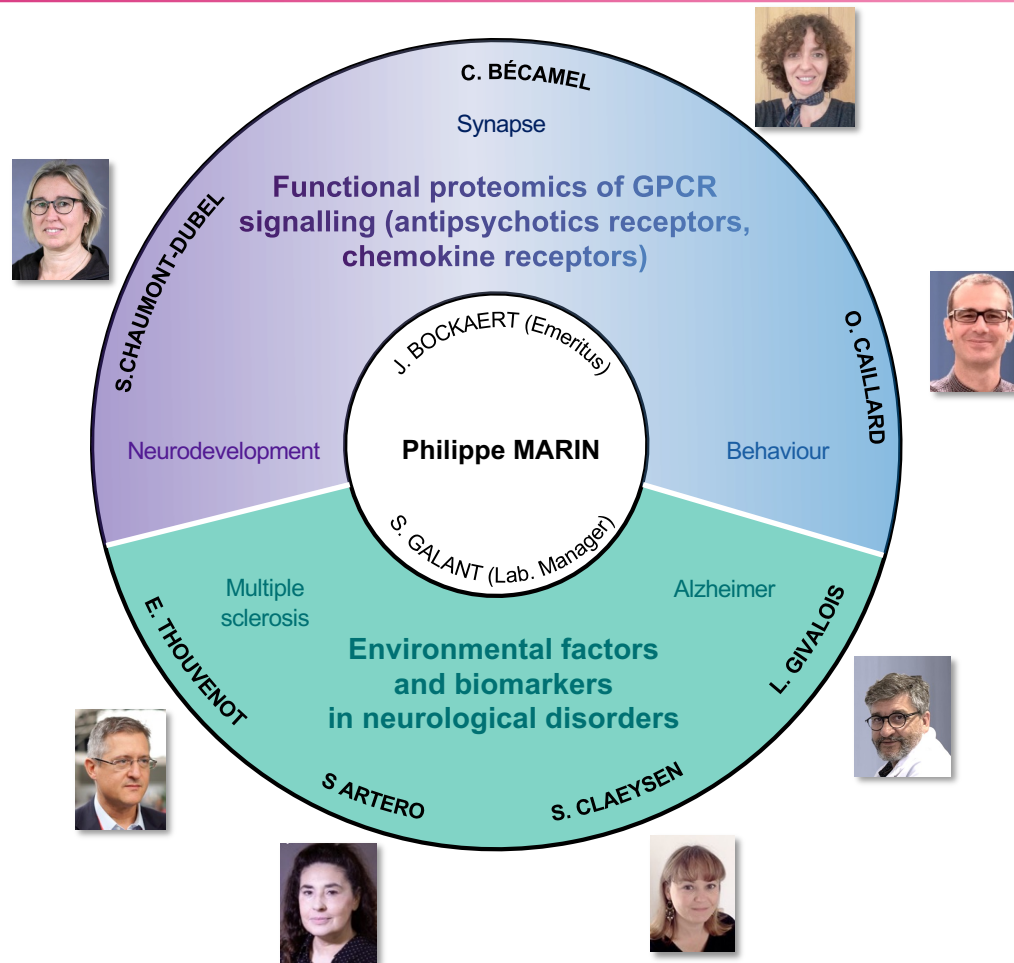


Mehdi
SEKSSAOUI
PhD

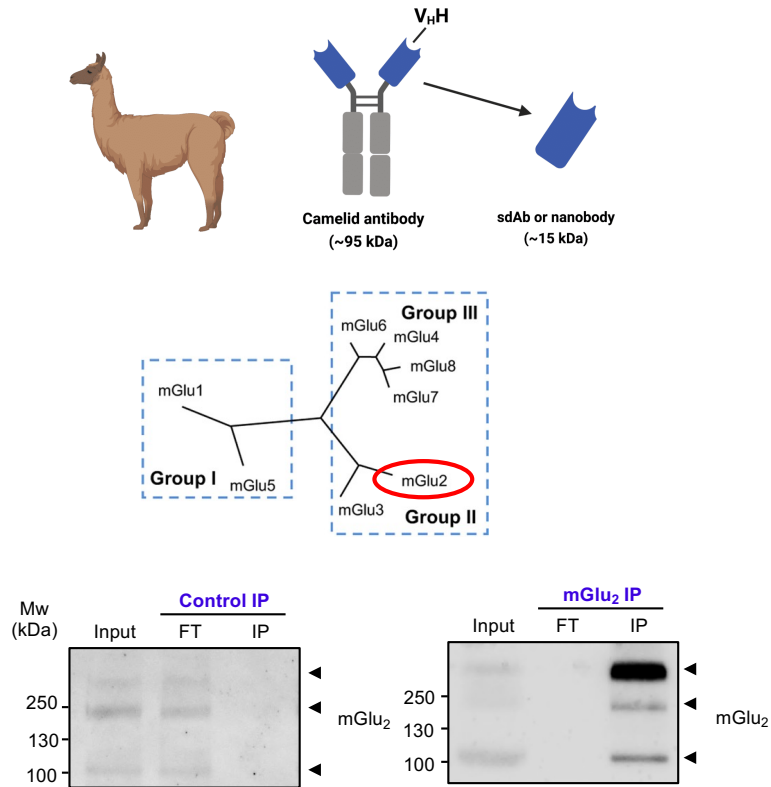
Multiple skills from molecular and cellular approaches to physiological, behavioural and epidemiological studies



Two major topics



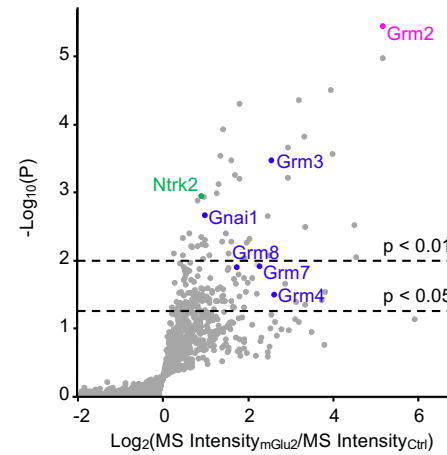
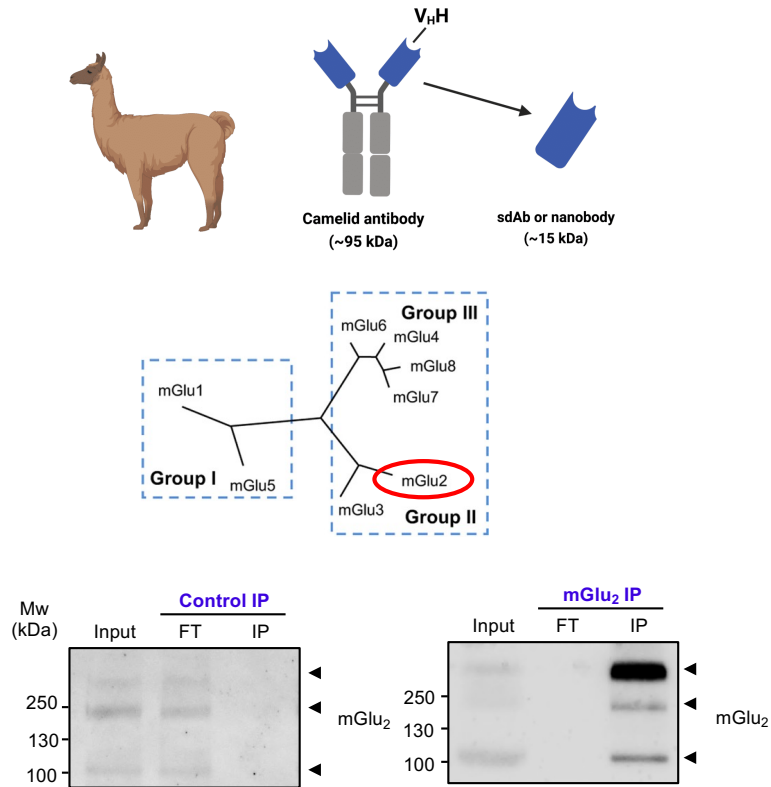
Characterization of the mGlu₂ receptor interactome



Philibert et al. *Sci Adv.* 2024 Jan 26;10(4):eadg1679.

Disdier et al. *Submitted.*

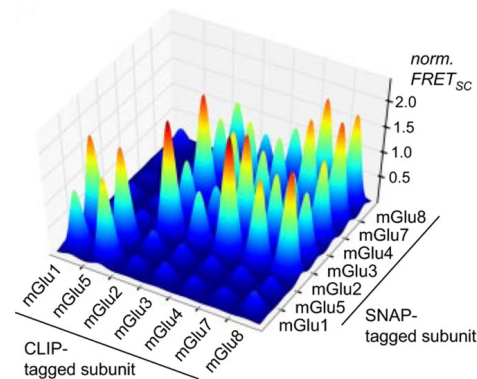
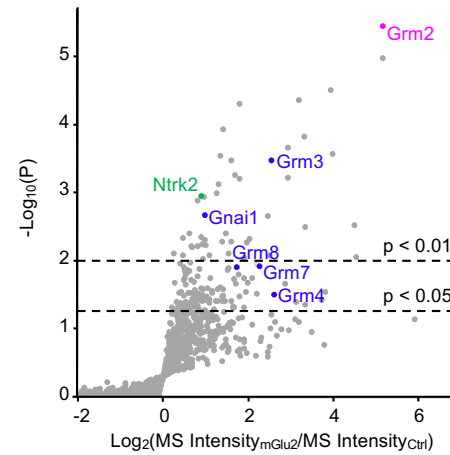
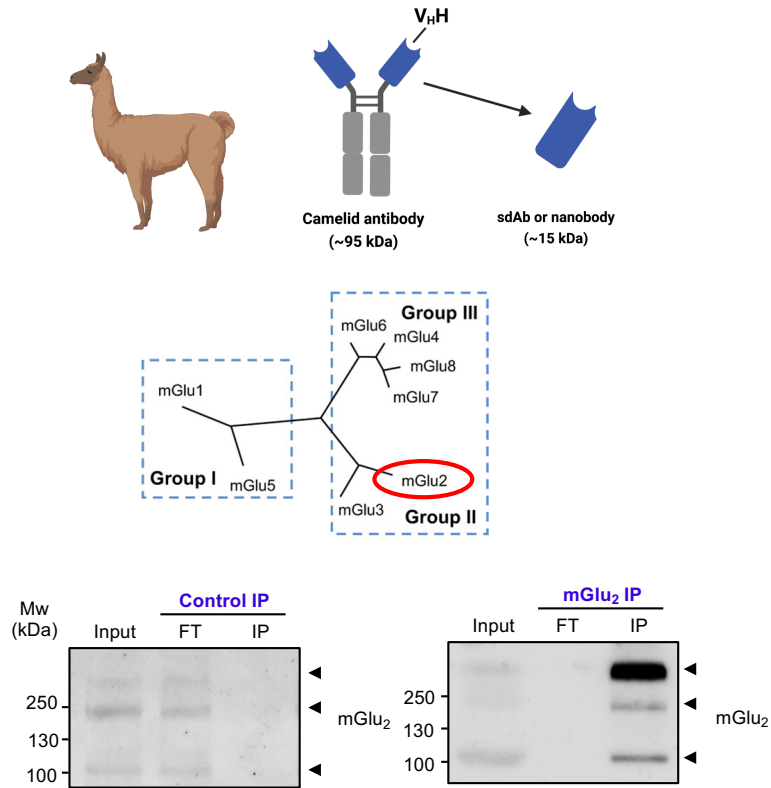
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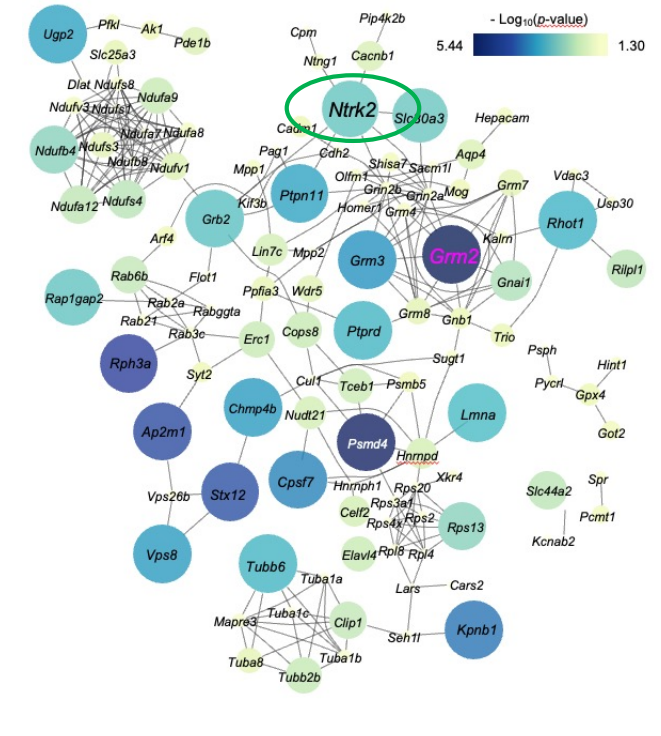
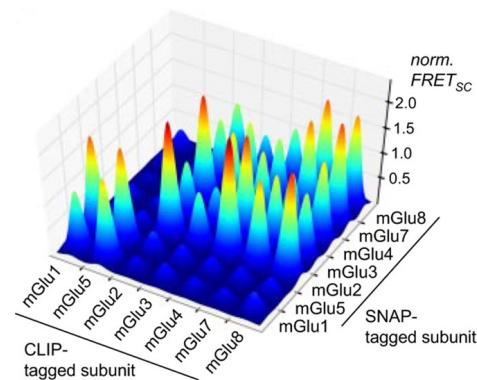
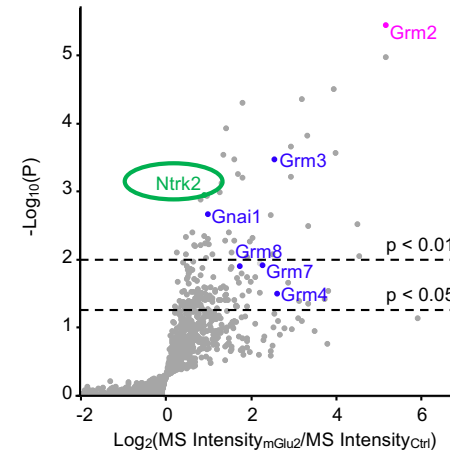
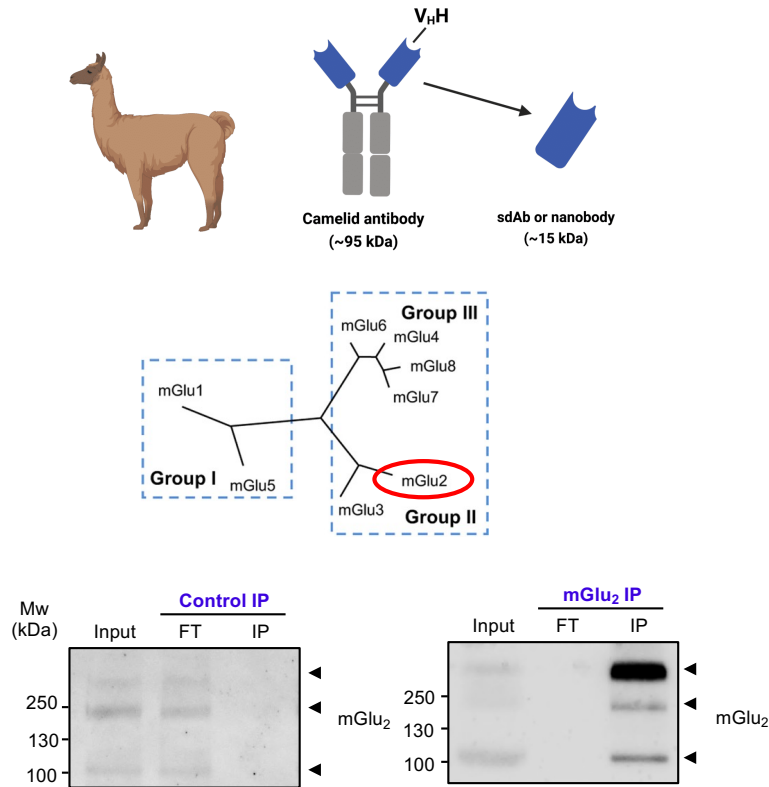
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Characterization of the mGlu₂ receptor interactome



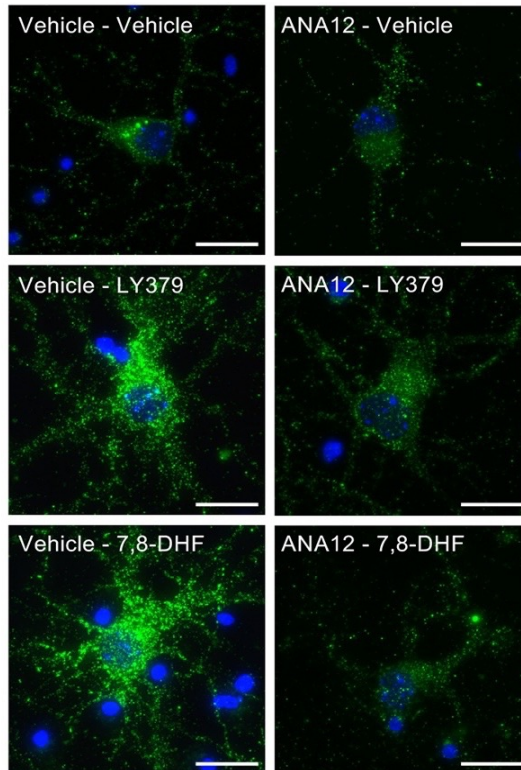
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Disdier et al. *Submitted.*

TrkB transactivation mediates antipsychotic-like effects of mGlu₂ receptor activation

TrkB Activity

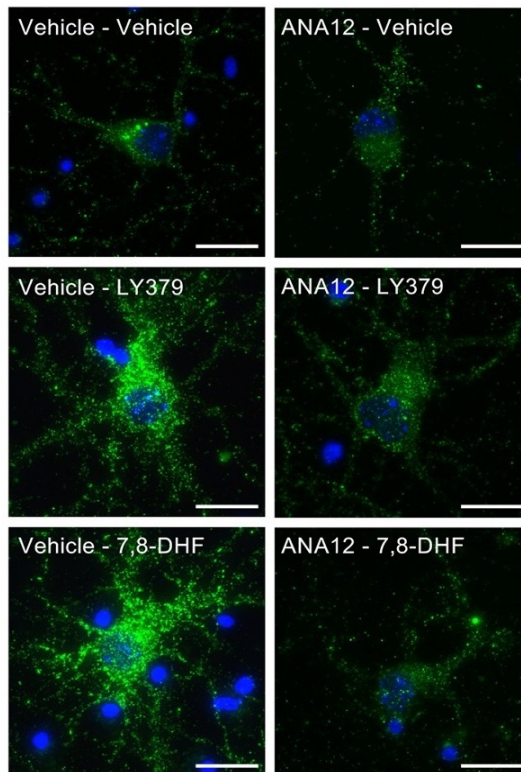
Primary neurons - p-Y⁸¹⁶-TrkB/DAPI



TrkB transactivation mediates the antipsychotic-like effects of mGlu₂ receptor activation

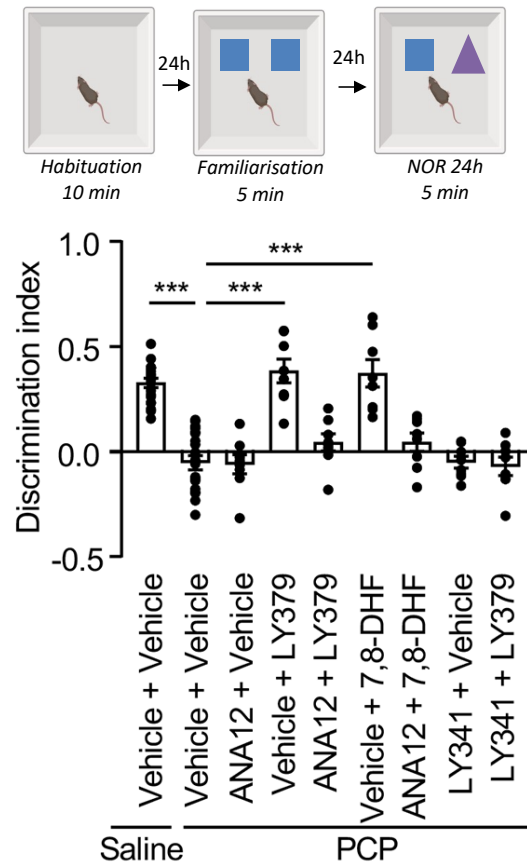
TrkB Activity

Primary neurons - p-Y⁸¹⁶-TrkB/DAPI

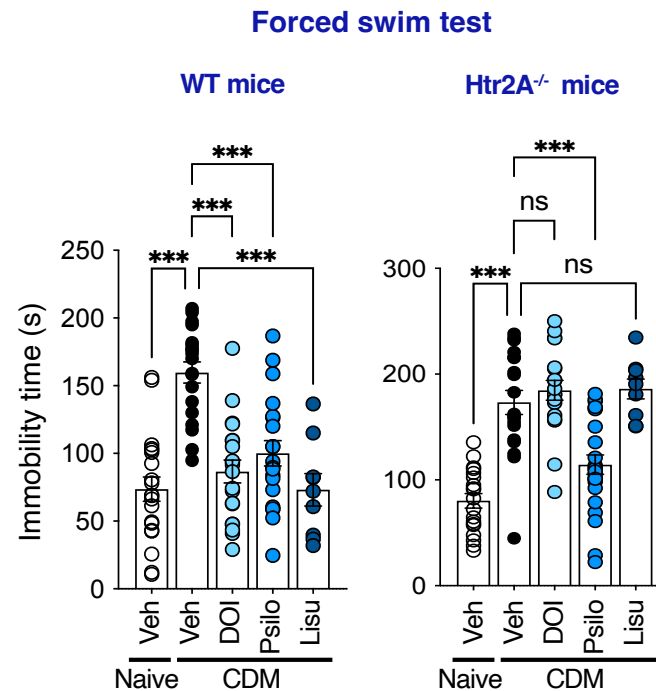
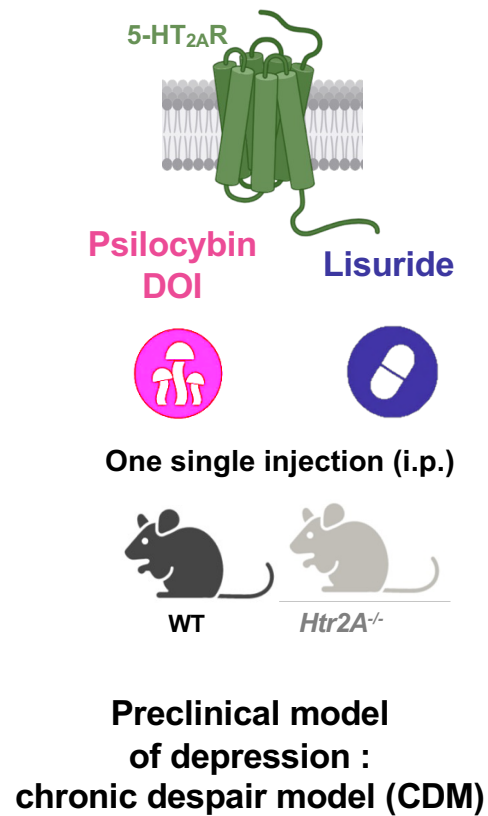


Behaviour

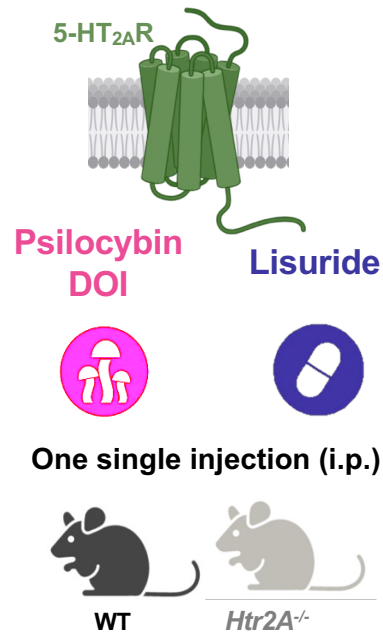
Novel object recognition test



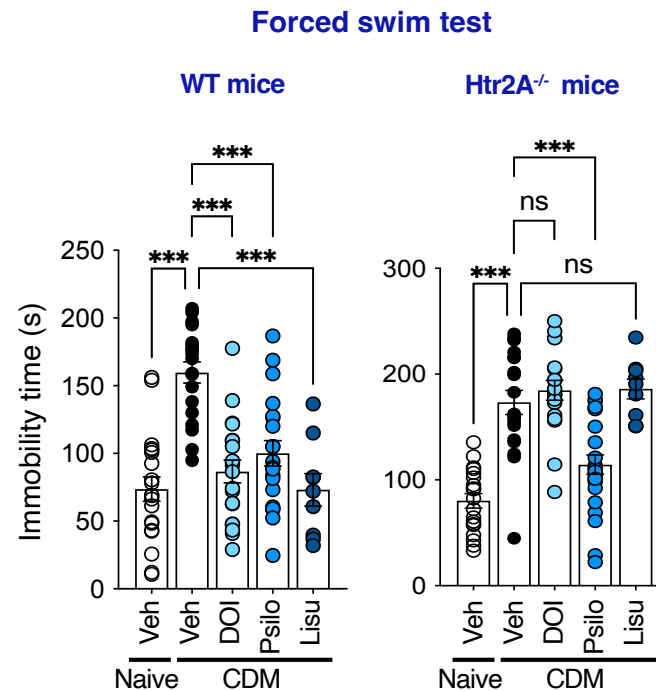
Role of the 5-HT_{2A} receptor in the antidepressant-like effects of psychedelics



Role of the 5-HT_{2A} receptor in the antidepressant-like effects of psychedelics

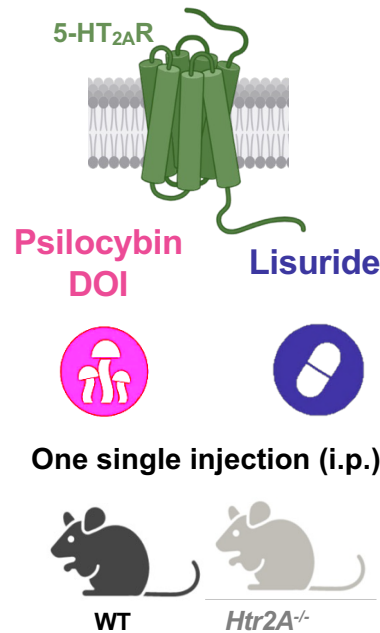


**Preclinical model
of depression :
chronic despair model (CDM)**



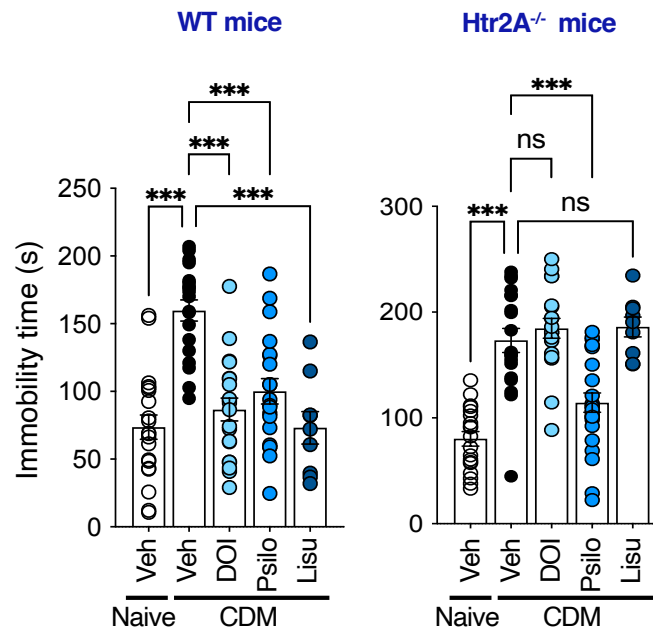
Psychedelic properties of 5-HT_{2A}R agonists are not necessary for their antidepressant activity

Role of the 5-HT_{2A} receptor in the antidepressant-like effects of psychedelics



**Preclinical model
of depression :
chronic despair model (CDM)**

Forced swim test

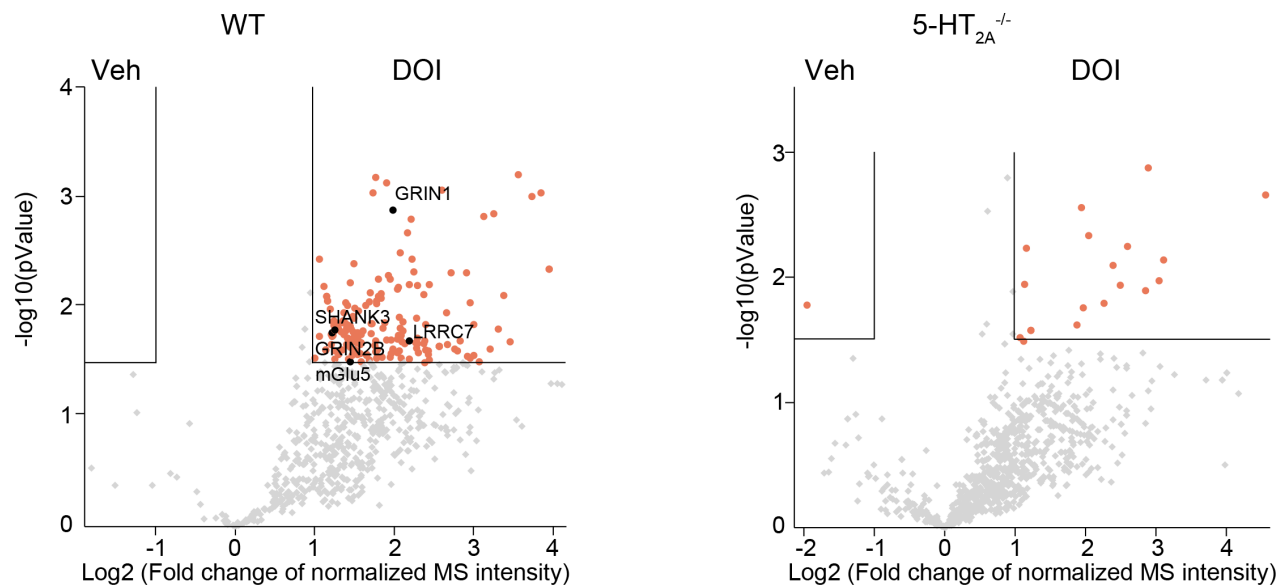


Psychedelic properties of 5-HT_{2A}R agonists are not necessary for their antidepressant activity

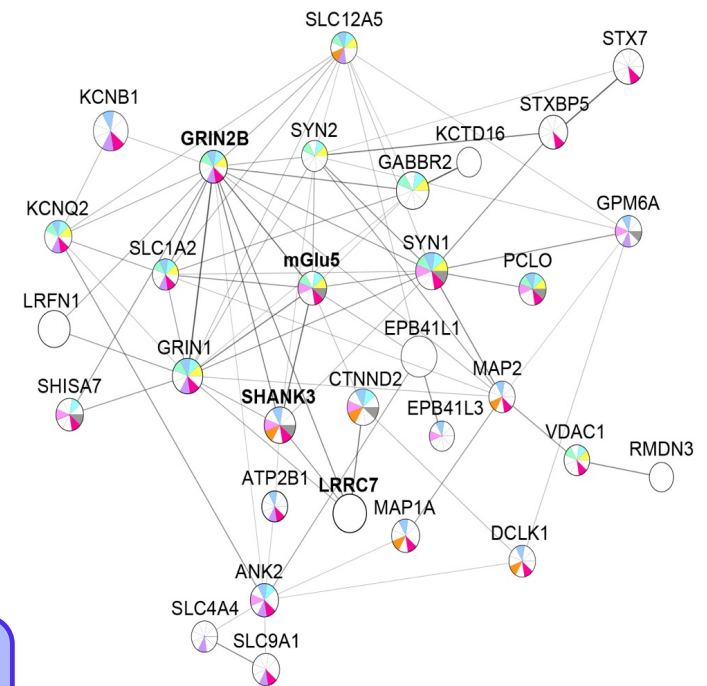
The 5-HT_{2A}R is NOT required for the antidepressant-like effects of psilocybin

Characterization of psychedelic-dependent synaptic phosphoproteome in mouse prefrontal cortex

980 phosphorylated residues on 351 unique proteins (>1/3 regulated by DOI administration)

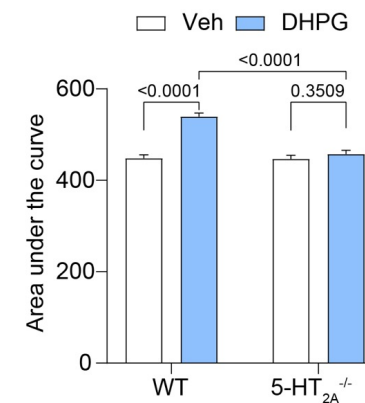
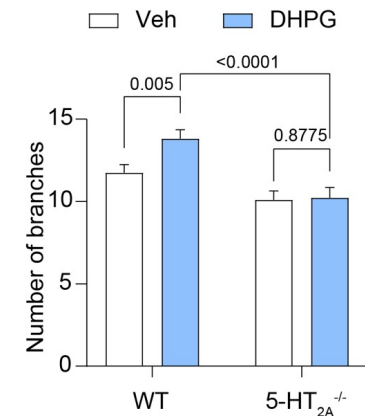
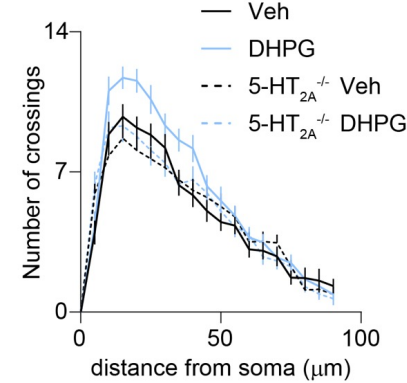
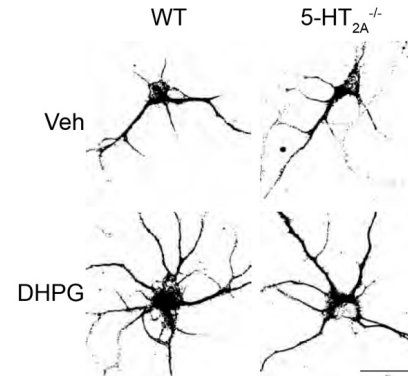
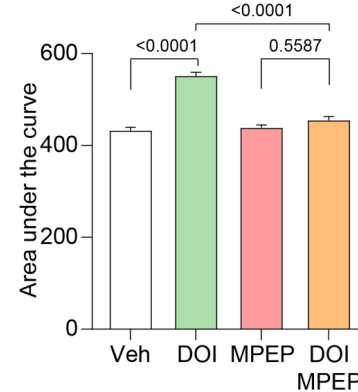
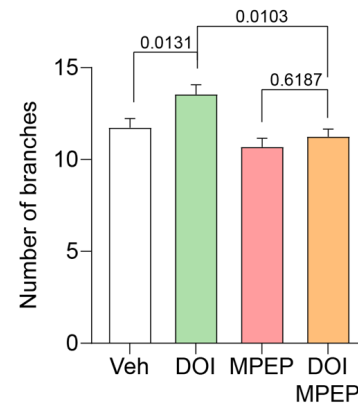
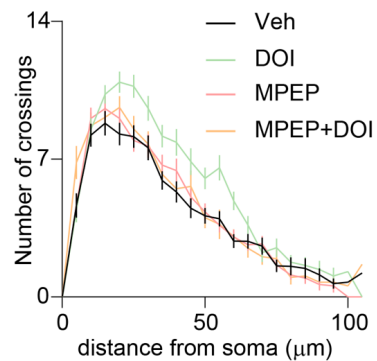
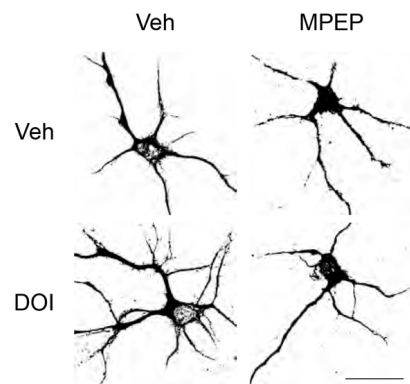


mGlu₅ receptor signalosome



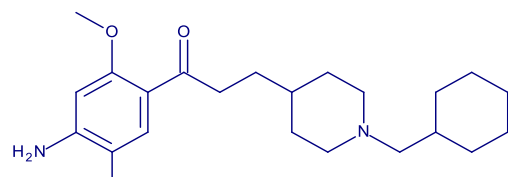
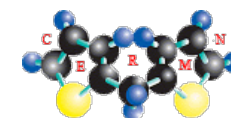
Stimulation of prefrontal 5-HT_{2A} receptors induces substantial changes in synaptic phosphoproteome that might contribute to structural plasticity

Impact on structural plasticity induced by 5-HT_{2A} receptor stimulation

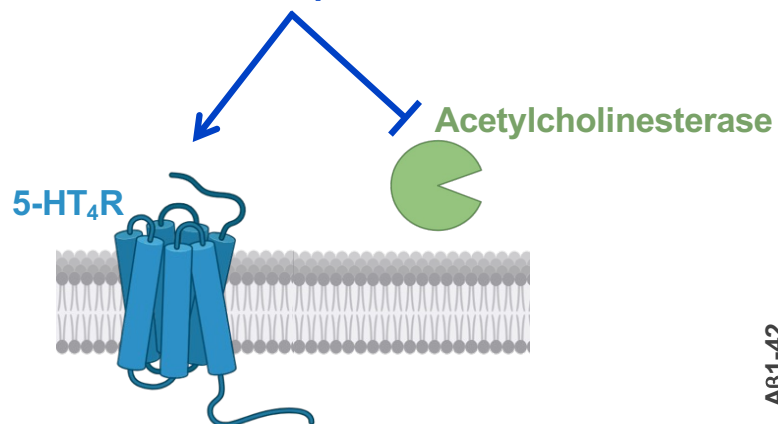


A reciprocal interplay between 5-HT_{2A} and mGlu₅ receptors triggers structural plasticity in primary cortical neurons.

Preclinical development of donecopride, a multi-target ligand

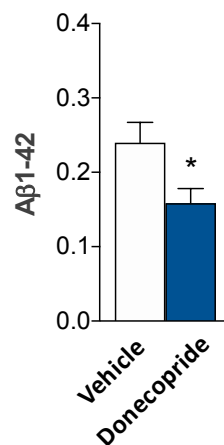


Donecopride

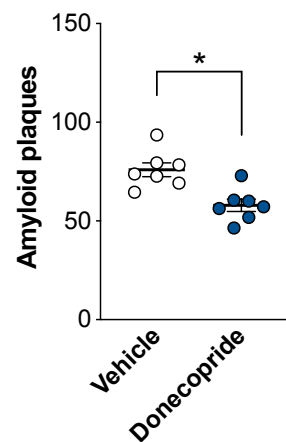


Donecopride
(1 mg/kg twice a week i.p., 3 months)

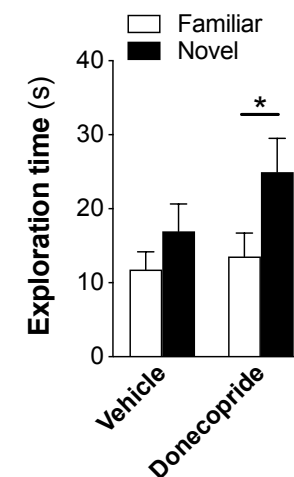
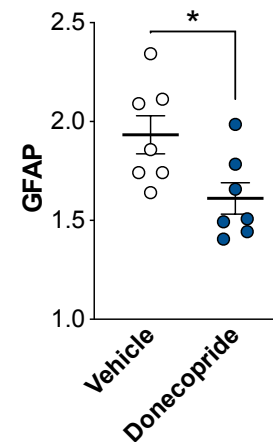
A β load



Plaques



Inflammation

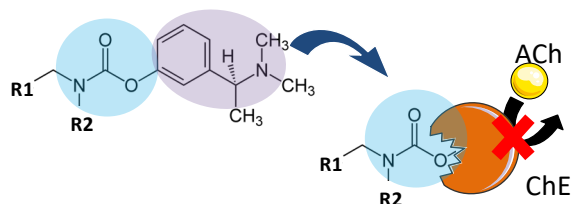


Dallemagne P, Rochais C & Claeysen S
WO 2020065028 & WO 2020064979, 2020
 Lecoutey C et al., **PNAS**, 2014
 Rochais C et al. **J Med Chem**, 2015
 Rochais C et al. **Brit J Pharmacol**, 2020

Principal investigator: S. Claeysen

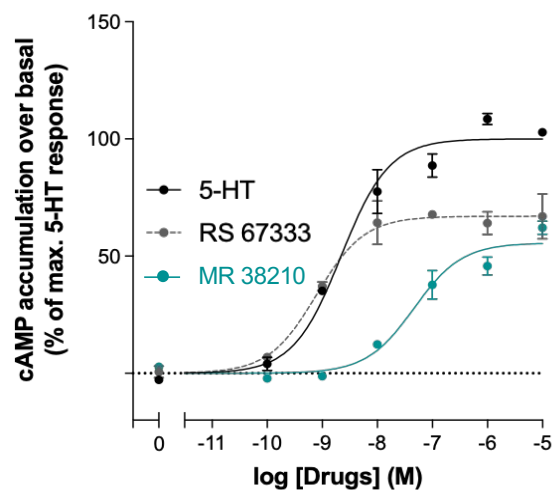
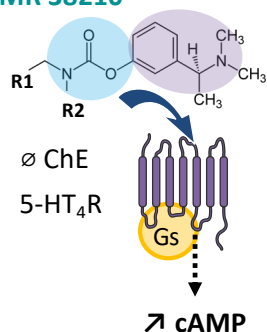
Development of multi-target prodrugs with potential therapeutic interest in Alzheimer's disease

MR 38210: a selective inhibitor of BChE and a 5-HT₄R partial agonist prodrug



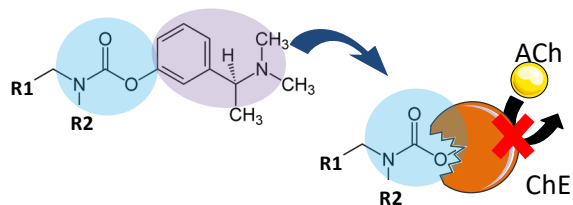
	AChE	BChE
IC ₅₀	117 nM	7.6 nM

MR 38210



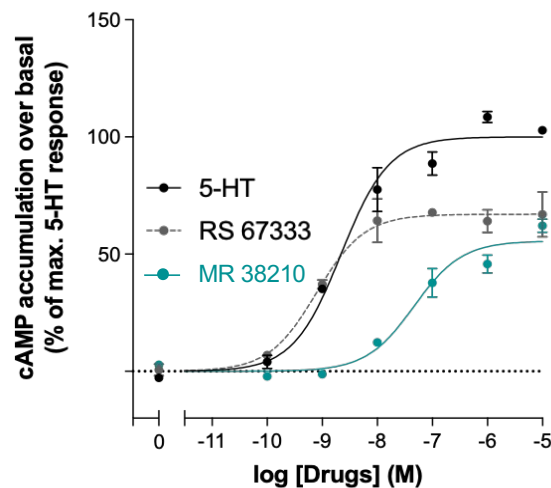
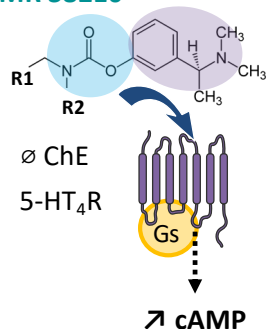
Development of multi-target prodrugs with potential therapeutic interest in Alzheimer's disease

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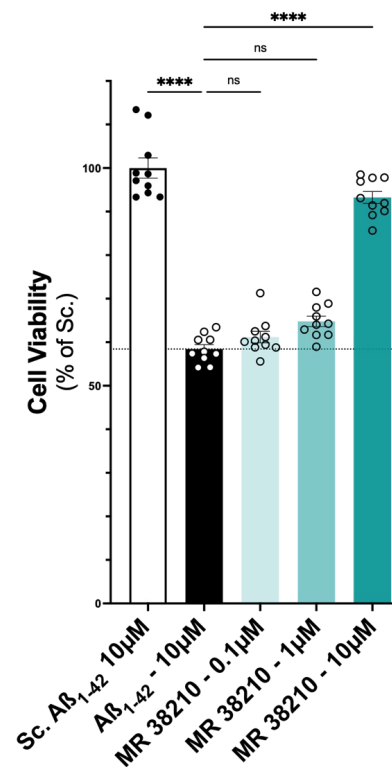


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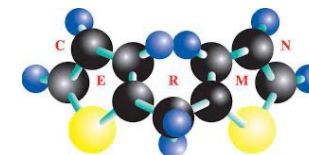
MR 38210



10 μ M oA β_{1-42}



COMETE
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Chronic administration of MR38210 slows down the development of memory deficits in 5xFAD mice



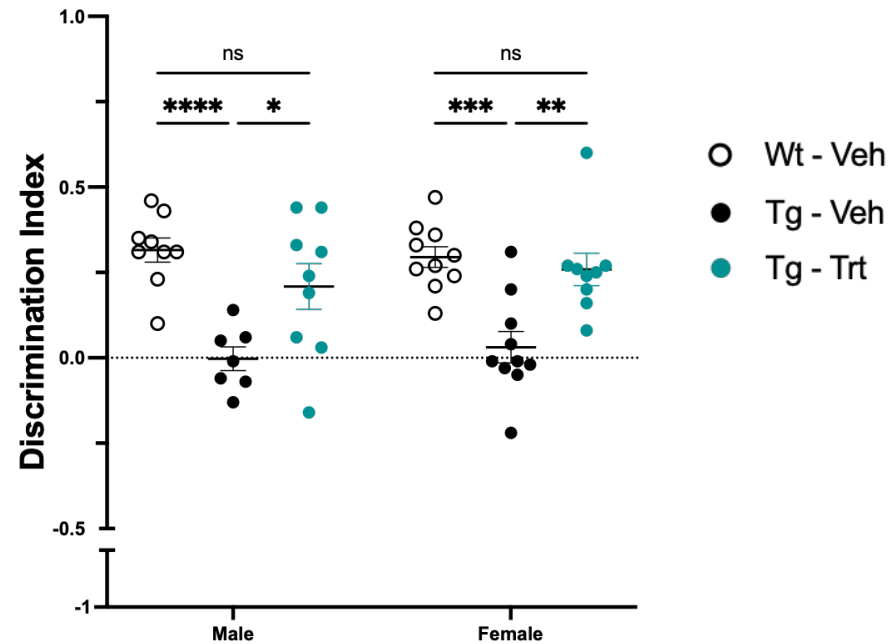
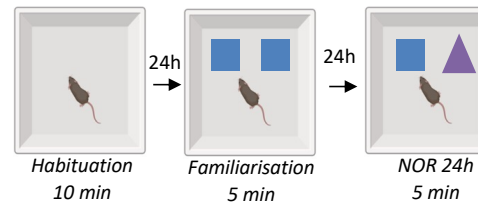
Transgenic (Tg) 5xFAD mouse model

Formulation

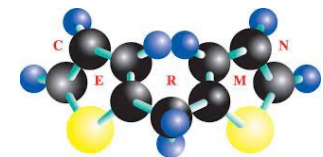


Encapsulation in muco-adhesive thermosensitive gel-loaded liposomes for intranasal delivery for 22 weeks (2-6 months)

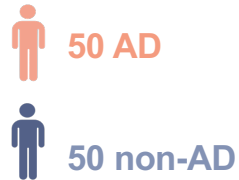
Novel object recognition test



COMETE
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Microbiota and Alzheimer's disease: the MICMALZ study

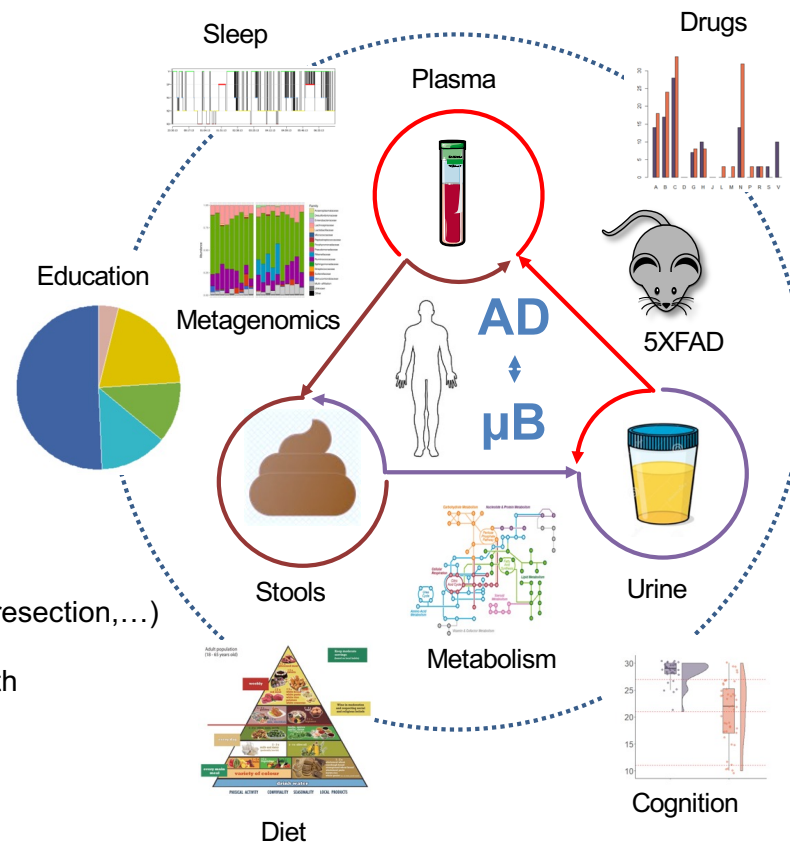


Inclusion criteria

- Woman/man
- 50-85 years old
- ATN Criteria (Albert MS 2011)
- $10 \leq \text{MMSE} \leq 30$
- vs. **memory complain**

Main exclusion criteria

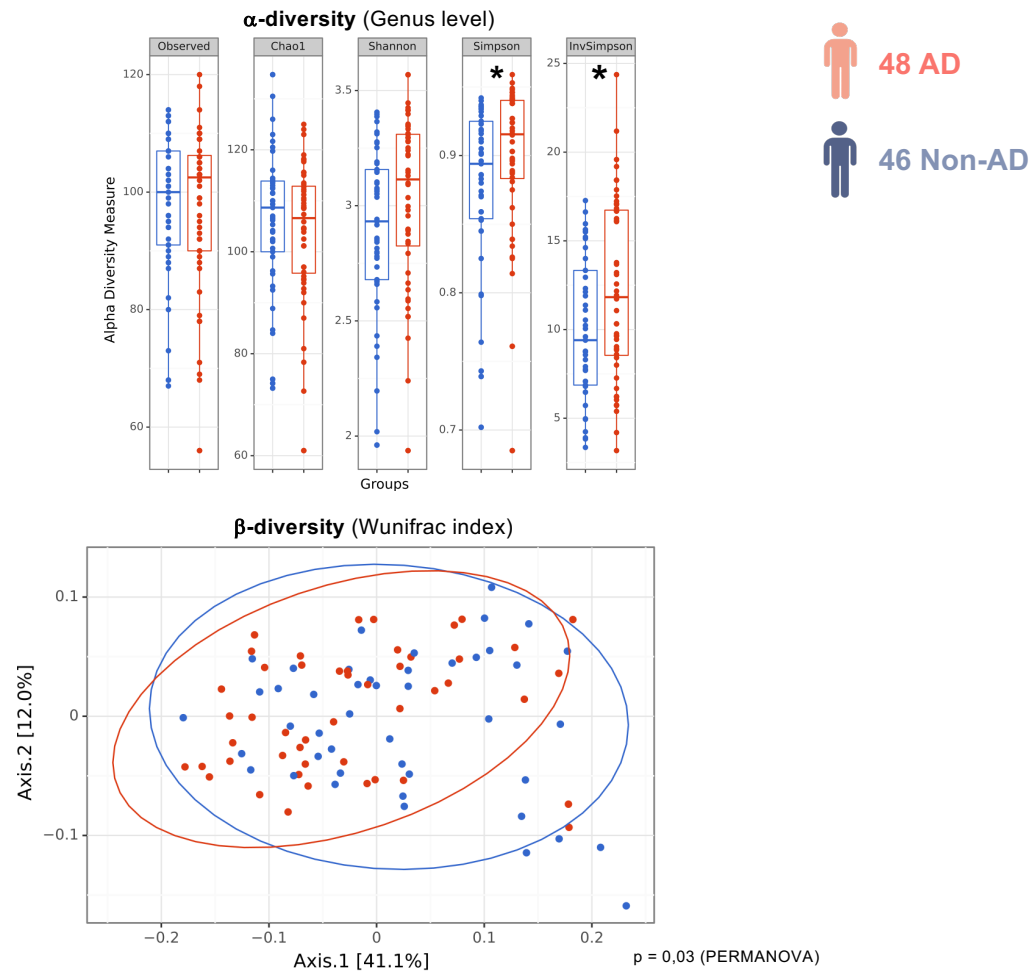
- Gastro-intestinal pathologies (neoplasia, resection,...)
- Chronic use of laxatives
- Antibiotic treatment in the preceding month



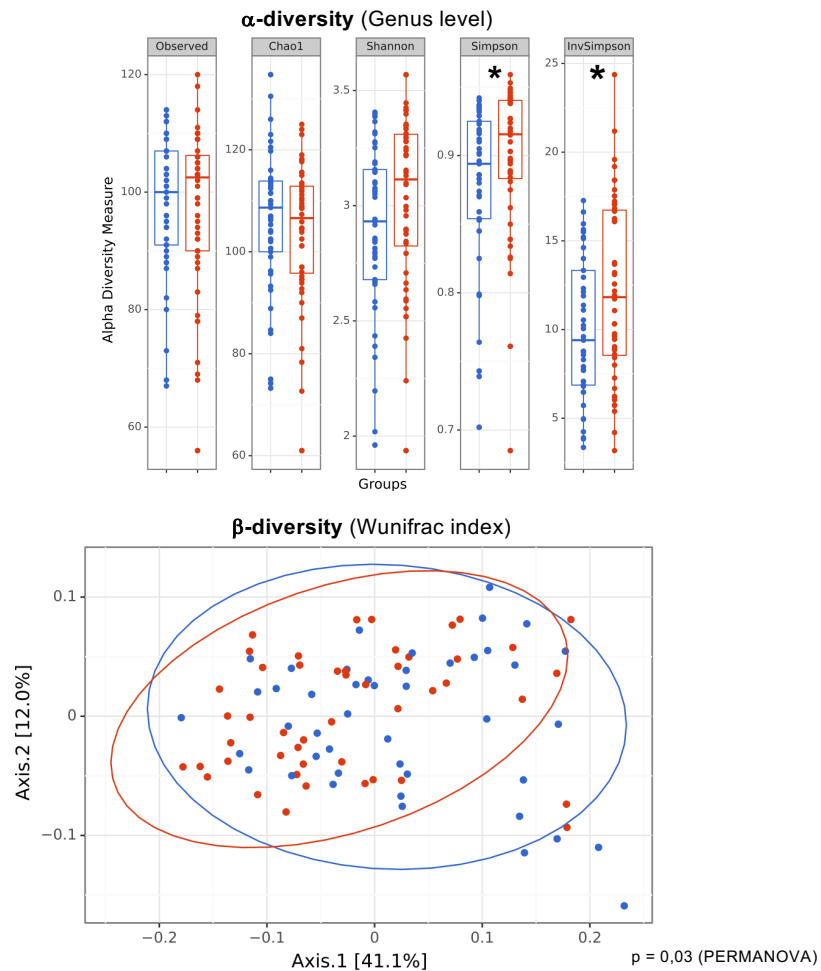
Pr. Audrey Gabelle
Dr. Karim Bennys

Principal investigator: S. Claeysen

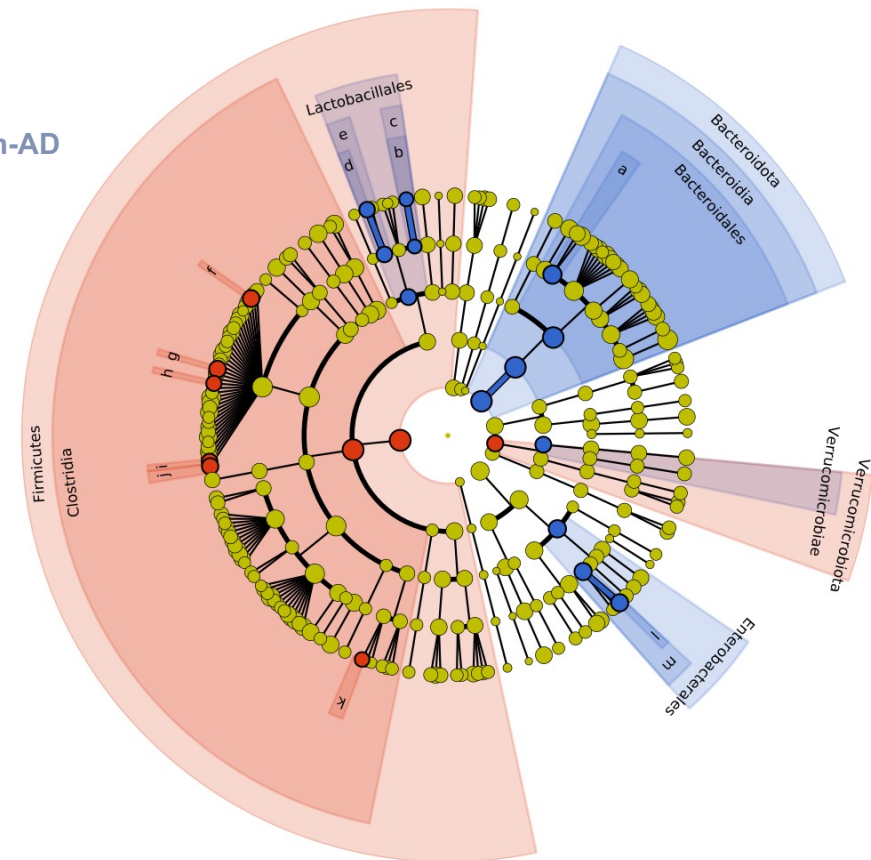
Preliminary results: fecal metagenomics (16S)



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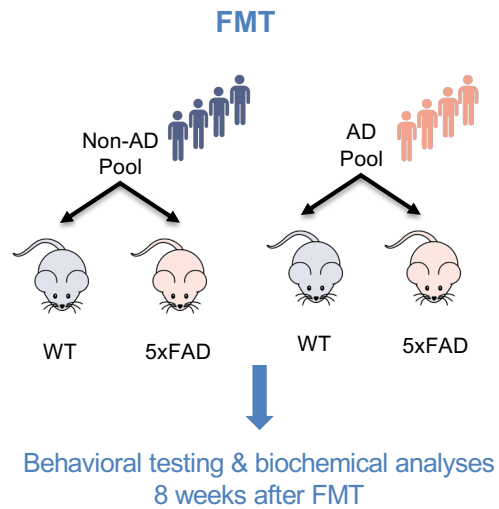


48 AD
46 Non-AD

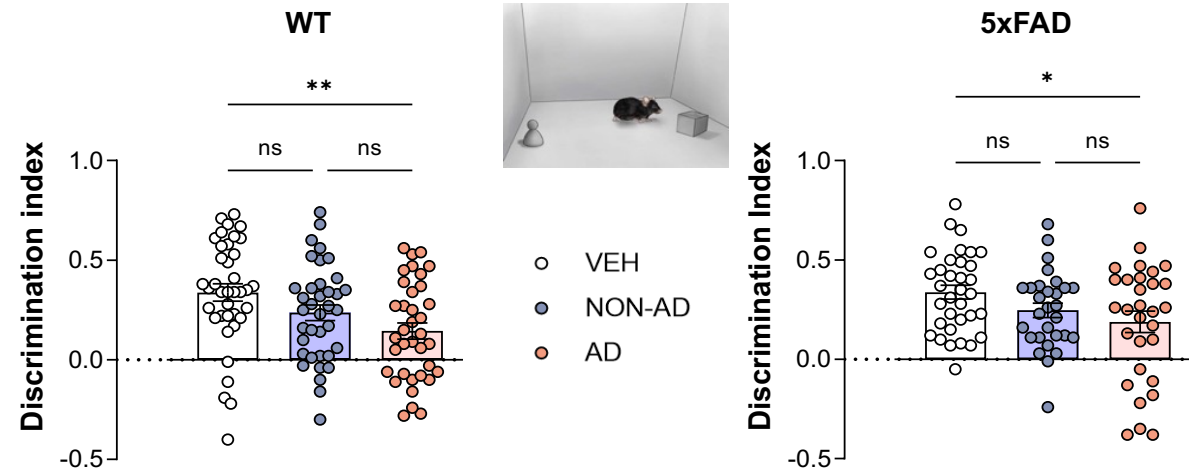


Cladogram : LEfSe, Linear discriminant analysis Effect Size: taxa significantly more abundant in AD or Non-AD groups

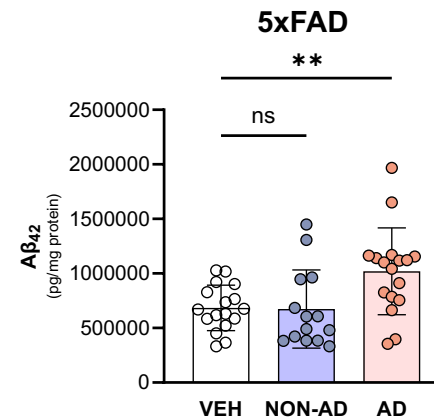
Preliminary results : human to mouse FMT



Novel Object Recognition

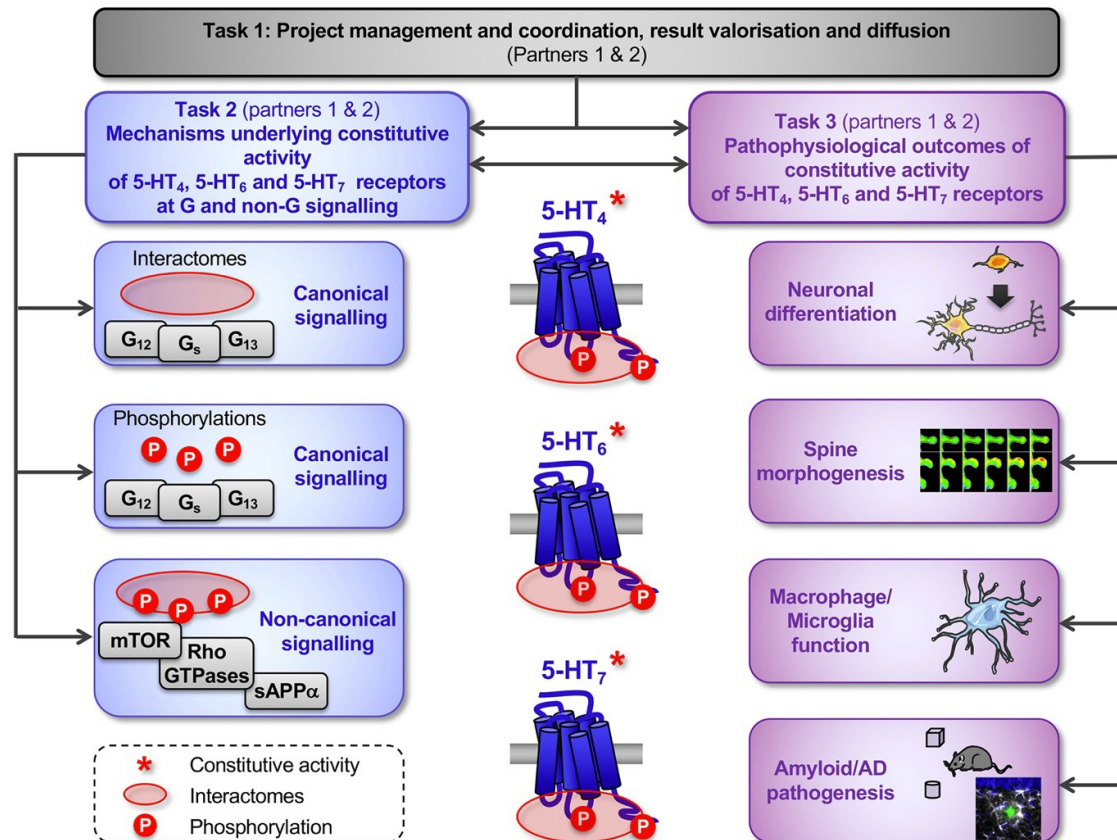


Human A β_{42} in cortex (ELISA)



Constitutive activity of Gs-coupled serotonin receptors: from underlying mechanisms to pathophysiological outcomes

Contact_5-HT project



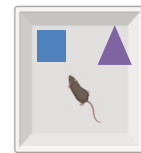
Dr. Evgeni Ponimaskin

Preliminary results: impact of 5-HT₆ and 5-HT₄ receptor deletion in 5XFAD mice

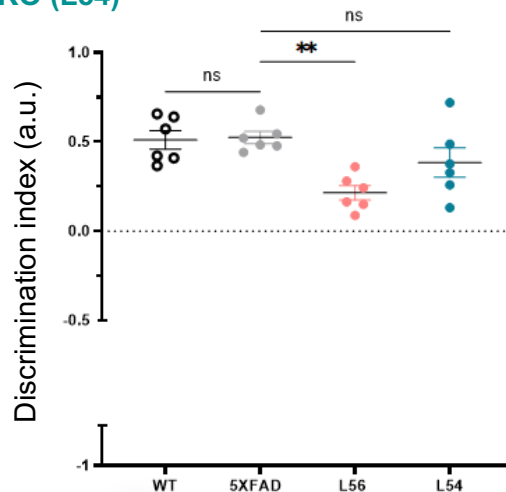
Four groups

- WT
- 5XFAD
- 5XFAD 5-HT₆R KO (L56)
- 5XFAD 5-HT₄R KO (L54)

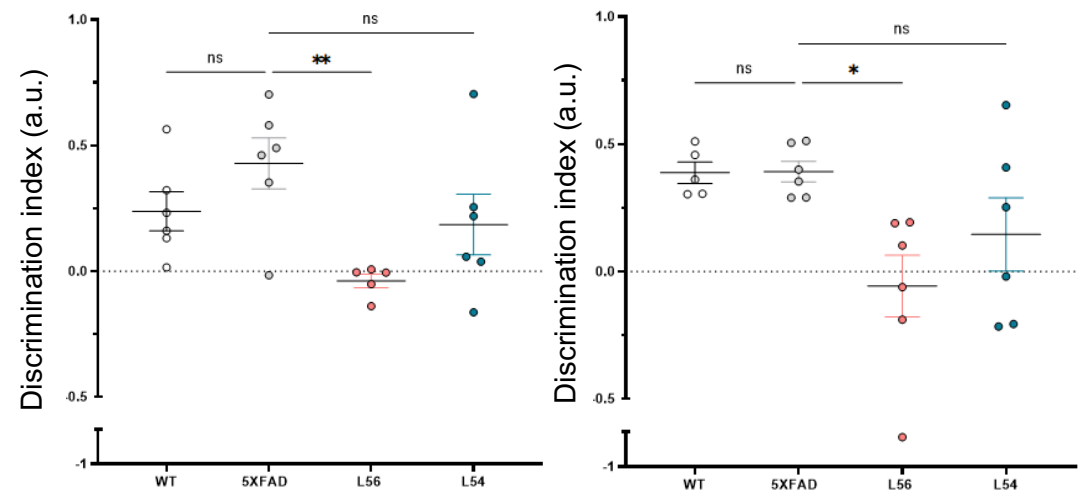
Novel object recognition test



24 h retention



Three chamber test (Crawley test)



- Female 5XFAD 5-HT₆R KO mice exhibit a strong episodic and social memory impairment
- No impact of 5-HT₆R deletion in male 5XFAD mice
- No impact of 5-HT₄R deletion in male and female 5XFAD mice

What can we bring ?

MHH
Medizinische Hochschule
Hannover



E PONIMASKIN



P MARIN - S CLAEYSEN



Yun Kyung KIM

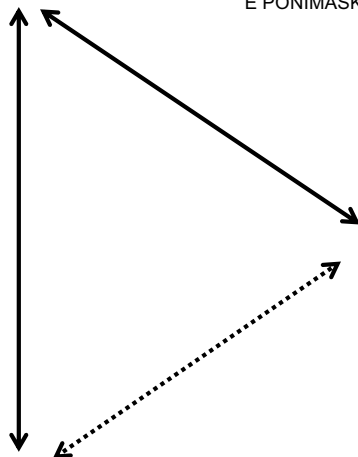
What can we bring ?

MHH

Medizinische Hochschule
Hannover



E PONIMASKIN



IGF
INSTITUT DE GÉNOMIQUE FONCTIONNELLE



P MARIN - S CLAEYSEN



Yun Kyung KIM

- Expertise in GPCR signalling
- Quantitative (phospho-)proteomics
- Single-cell proteomics (under development)
- Electrophysiology
- Microbiota studies
- Animal models
 - ✓ Amyloid pathology
 - ✓ Depression
 - ✓ Schizophrenia
- Patient cohorts (collaboration with Montpellier University Hospital)

Thank you for your attention!



Evgeni Ponimaskin



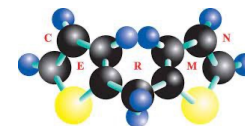
Frédéric Lamaty
Xavier Bantreil



Audrey Gabelle
Karim Bennys



Pawel Zajdel
Katarzyna Grychowska



Patrick Dallemagne
Christophe Rochais



Michel Boulouard
Thomas Fréret

SMEs



VAIOMER – Labège
Benjamin Lellouvier



NBX Biosciences
Damien Rei



MaaT Pharma
Hervé Affagard

Financial supports



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