Combining retinoic acid and calcitriol delivery for the recovery of mature oligodendrocytes in a cuprizone model.

Prof. Anne des Rieux

UCLouvain

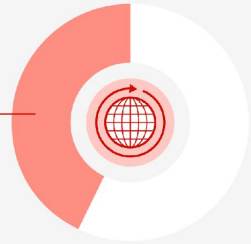
Advanced Drug Delivery and Biomaterials

Why the CNS?

Global burden of conditions affecting the nervous system

Neurological conditions are the number-one leading cause of disease burden worldwide.

In 2021, around **3·40 billion individuals** had conditions affecting the nervous system, equivalent to...



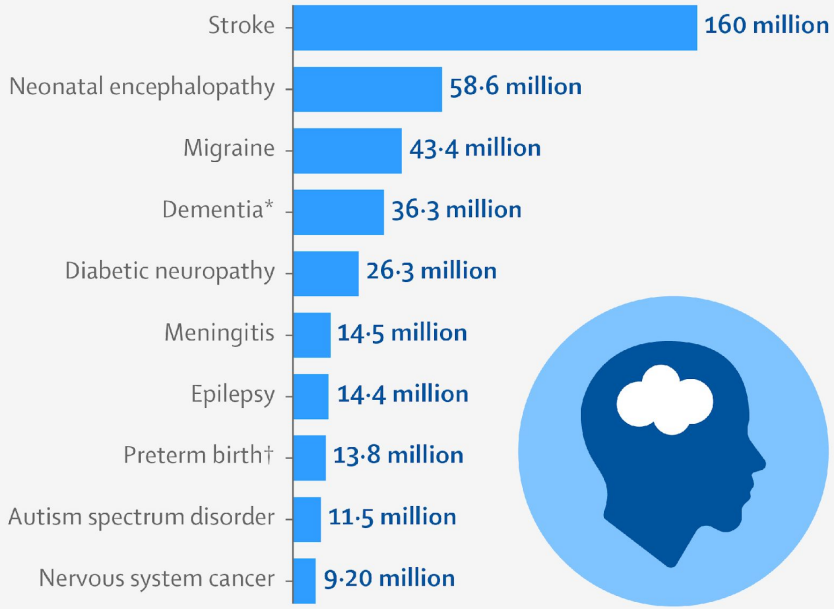
43% of the world population

These conditions contributed to...

443 million **Disability-adjusted life-years (DALYs)**

... making them the leading cause of disease burden worldwide.

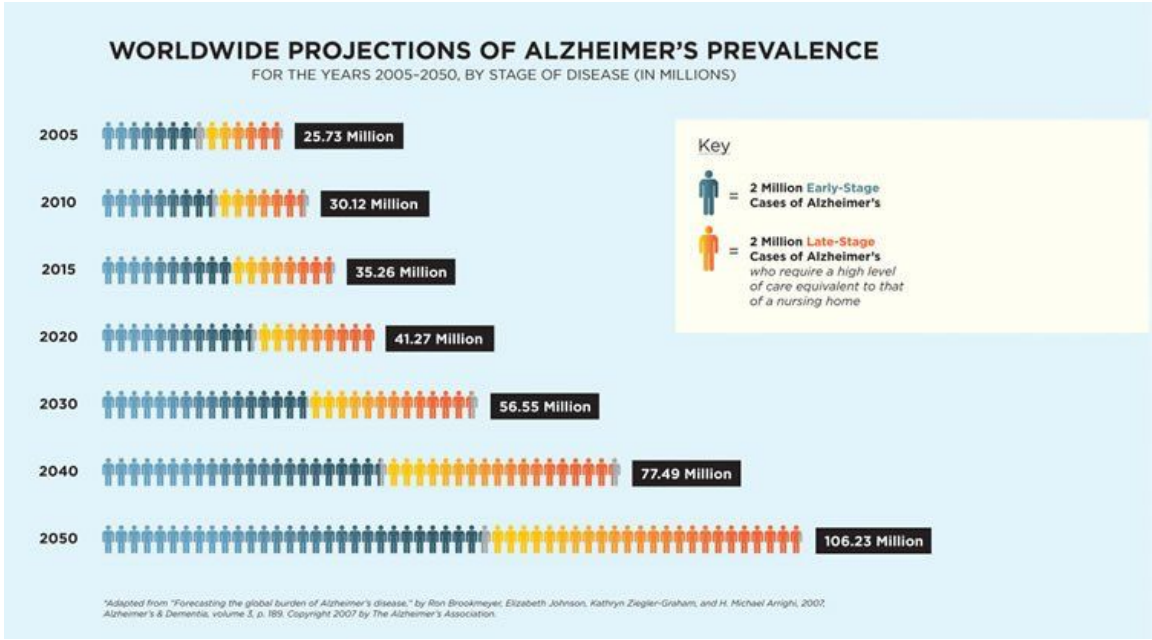
The ten neurological conditions that accounted for the greatest DALYs in 2021 were...



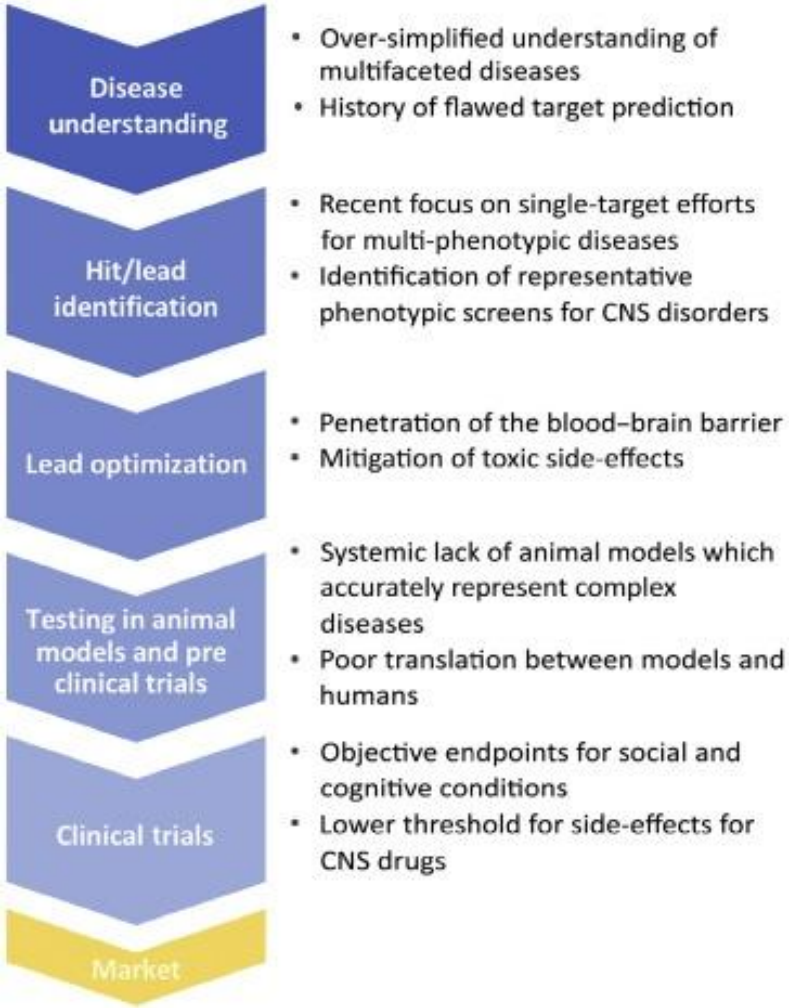
*Alzheimer's disease and other dementias; † Neurological complications associated with preterm birth

Read the full *Lancet Neurology* study at thelancet.com

GBD 2021 Nervous System Disorders Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurology* 2024; published online March 14. https://doi.org/10.1016/S1474-4422(24)00038-3.



Drug development for CNS pathologies



Trends in Chemistry

	CNS	Non-CNS
Chance of approval	8%	15%
Application-to-approval time (years)	1.9	1.2
Phase II + III development (years)	8.1	6.1
Chance of success in Phase III	46.00%	66.00%
Patient numbers in trials	300-500	10,000 – 60,000
Average cost of development	$1 billion - $5 billion	$600 million - $2 billion

Source: Tufts Center for the Study of Drug Development, 2012

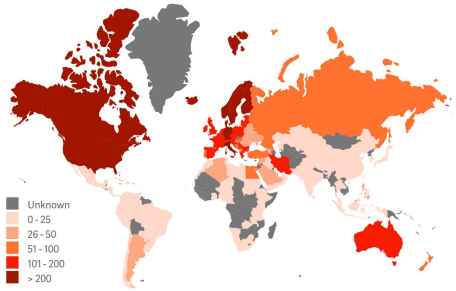
Table I

https://www.ddw-online.com/the-great-neuro-pipeline-brain-drain-why-big-pharma-hasnt-given-up-on-cns-disorders-909-201310/

Multiple sclerosis (MS)

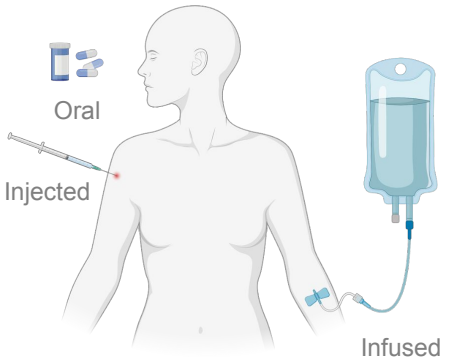
- Inflammatory autoimmune demyelinating disease

2.9 MILLION worldwide



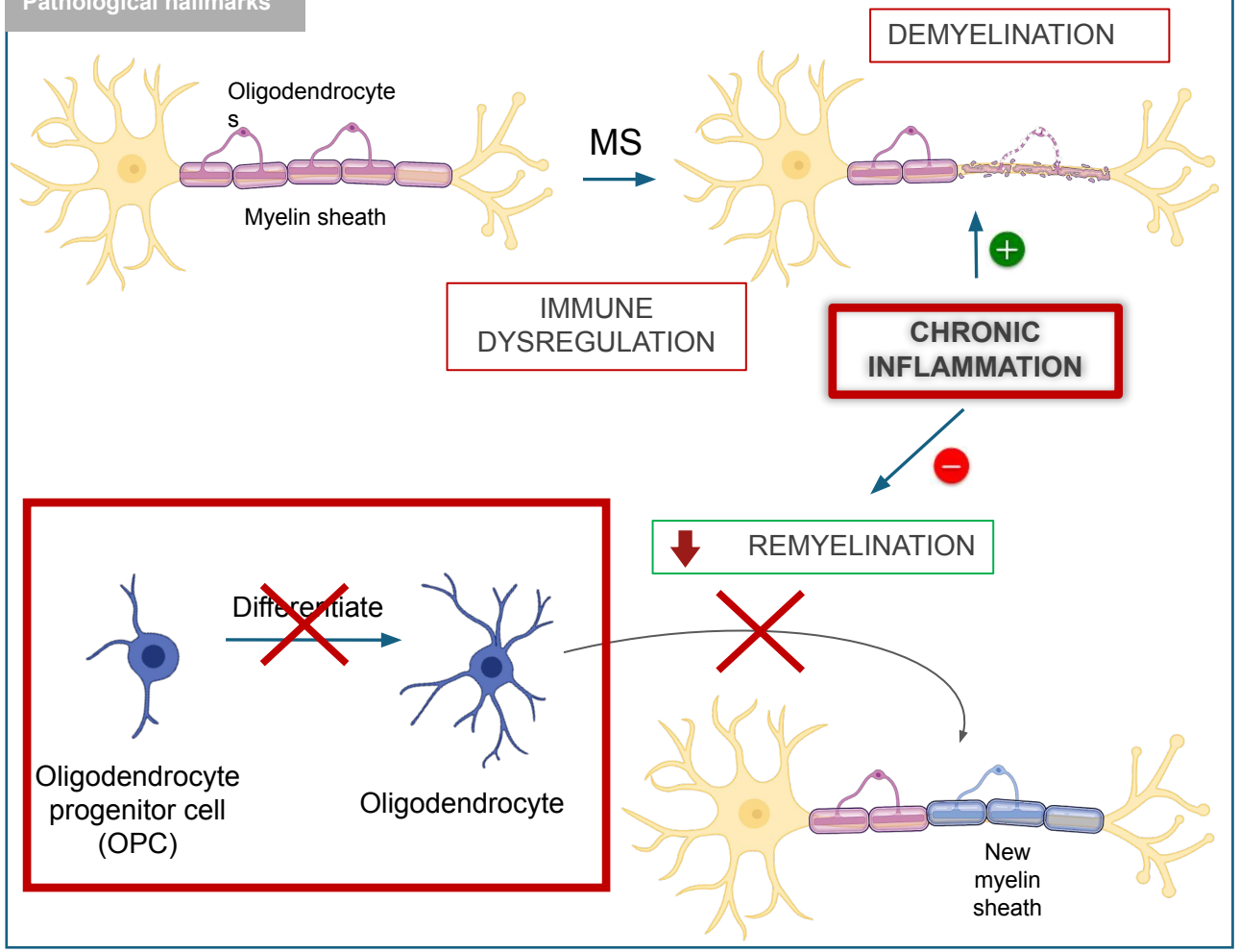
Number of people with MS Prevalence /100 000 people

No CURATIVE treatment

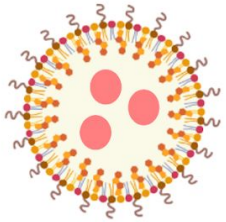


Bioavailability in the CNS ✗

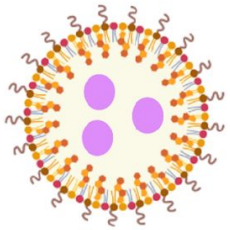
Pathological hallmarks



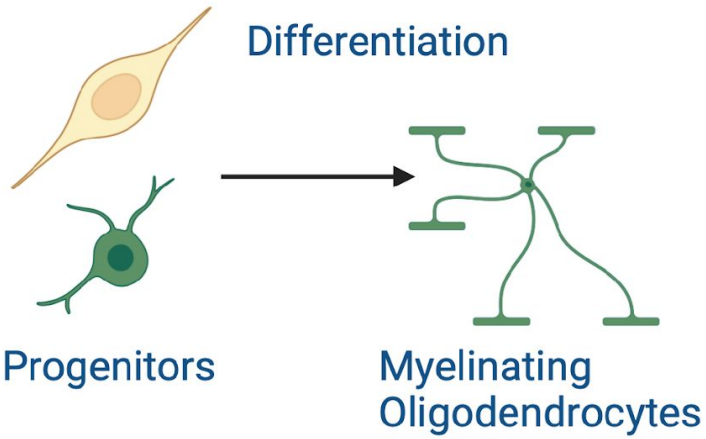
Dr. Yasmine Labrak



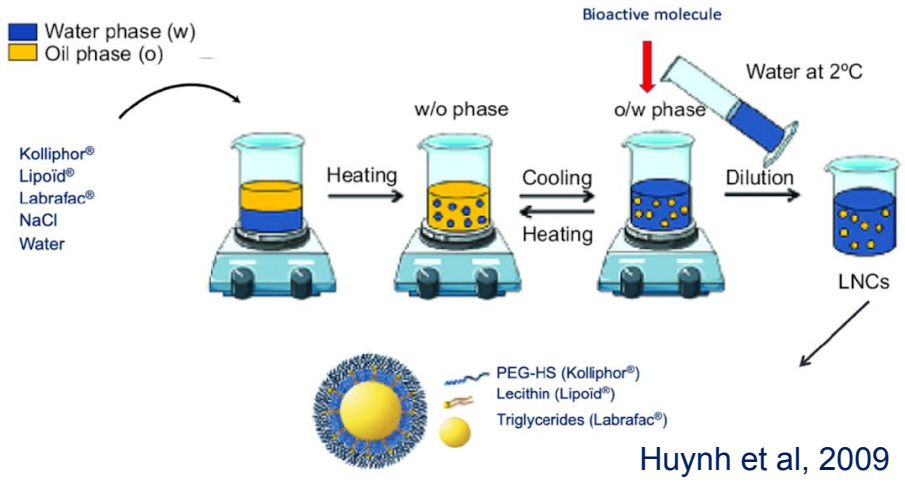
Calcitriol loaded-LNC



Retinoic acid loaded-LNC



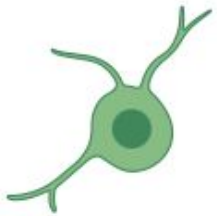
Easy, scalable
High EE of lipophilic molecules



Huynh et al, 2009

Created with biorender

Does the combined administration of LNC-encapsulated retinoic acid and calcitriol stimulates oligodendrocyte progenitor cell differentiation ?



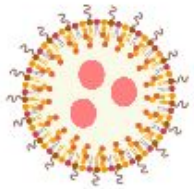
CG4-cells
or OPC in a mixed glial cells culture

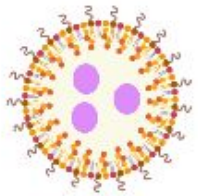
In vitro

In vivo

Cell treatment

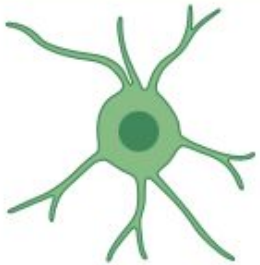
Treatments



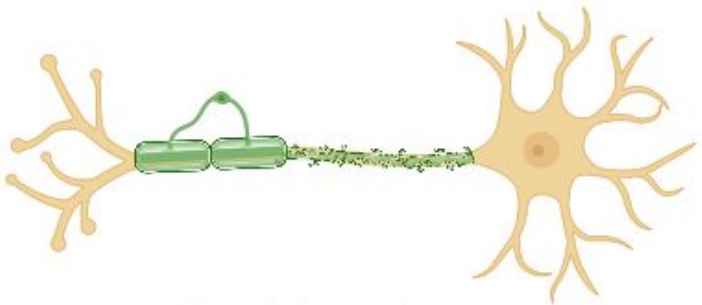


Retinoic acid loaded-LNC

Calcitriol loaded-LNC

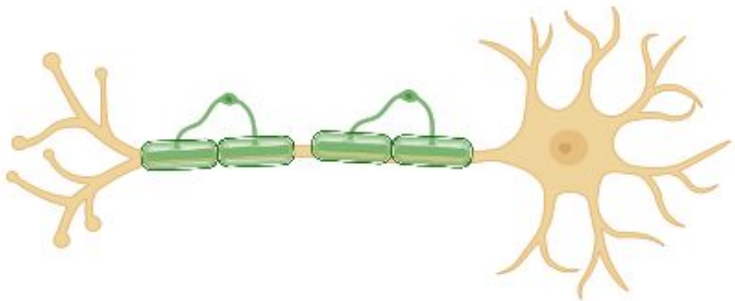


Impact on the expression of differenciation markers by RT-qPCR



Cuprizone induced demyelination in C57BL/6 mice

Intranasal administration in mice



Impact on the expression of differenciation markers by immunofluoresence in brain slices

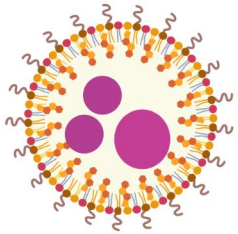
LNC: Lipid NanoCapsules, OPC: Oligodendrocyte progenitor cells, CG-4: rat OPC cell line

Created with biorender

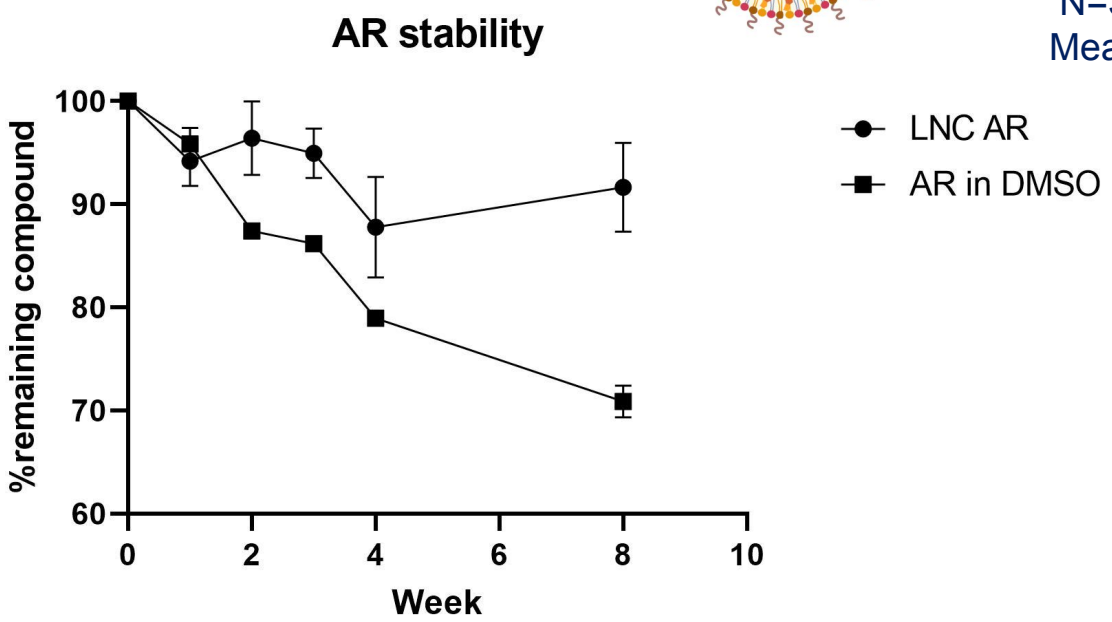
Solubilization and Stabilization with LNC

Retinoic acid (AR)
Calcitriol (Cal)

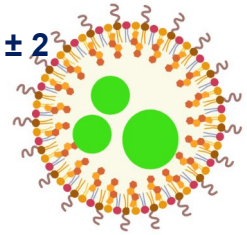
Encapsulation efficiency : 83 % ± 10
Size : 67 nm ± 4
PDI: 0,01 ±0,01
ζ potential: -3,5 ± 0,04 mV

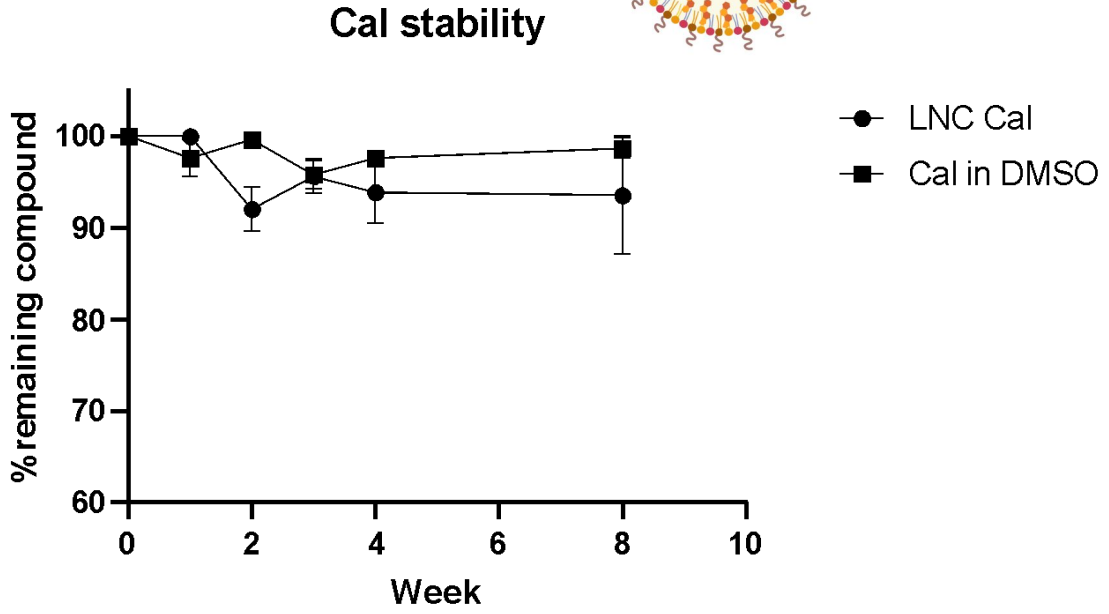


N=3
Mean+/- SD



Encapsulation efficiency : 86 % ± 2
Size : 57 nm ±6
PDI: 0,07 ±0,02
ζ potential: -2,7 ± 0,35 mV



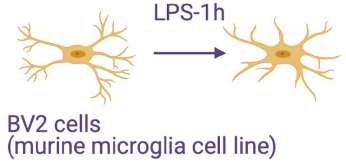


LNCs and DMSO solution stored at 4°C and protected from light
Quantification by HPLC-UV

For LNC N=3
For free drugs n=3
Mean+/- SEM

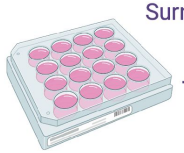
Labrak et al., Int. J. Pharm, 2024

RA



LPS + Treatments-8h

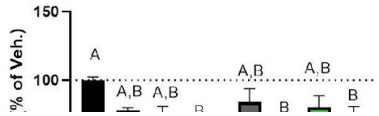
0.03 µM to 10 µM
Retinoic acid (RA)
Calcitriol (CA)
Combination (CARA)

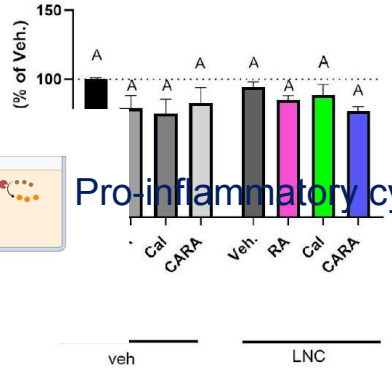


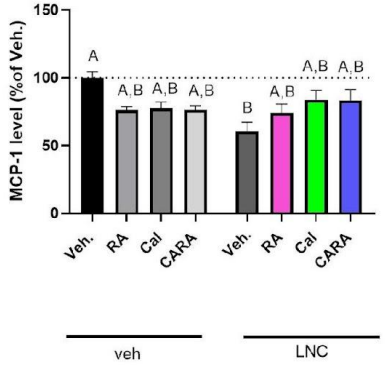
Surnageants-ELISA

Pro-inflammatory cytokines

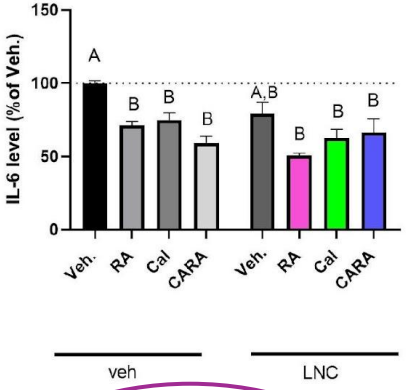
0,03µM

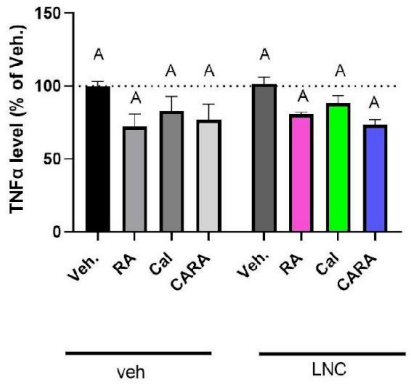


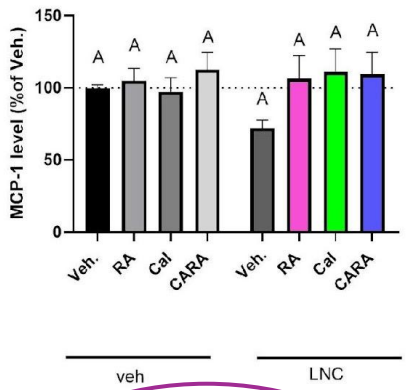




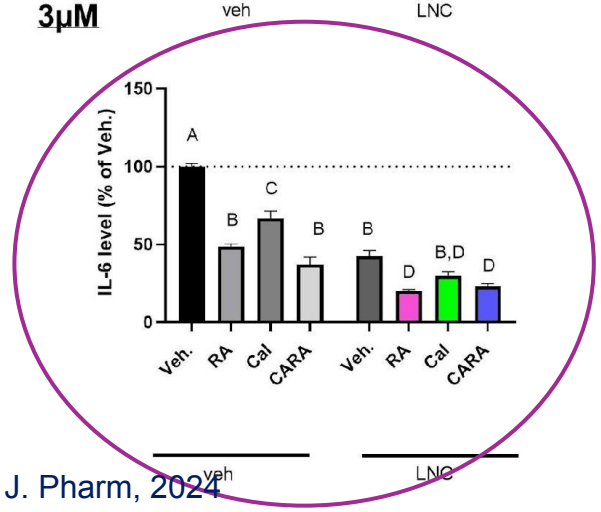
0,3µM

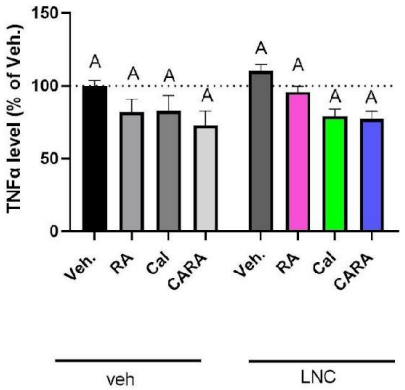


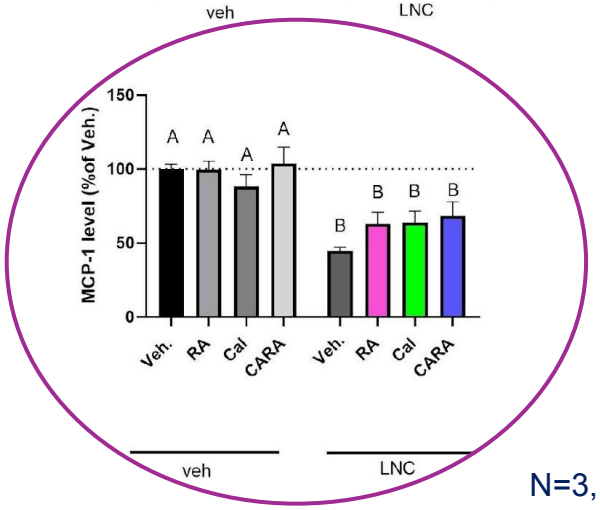




3µM







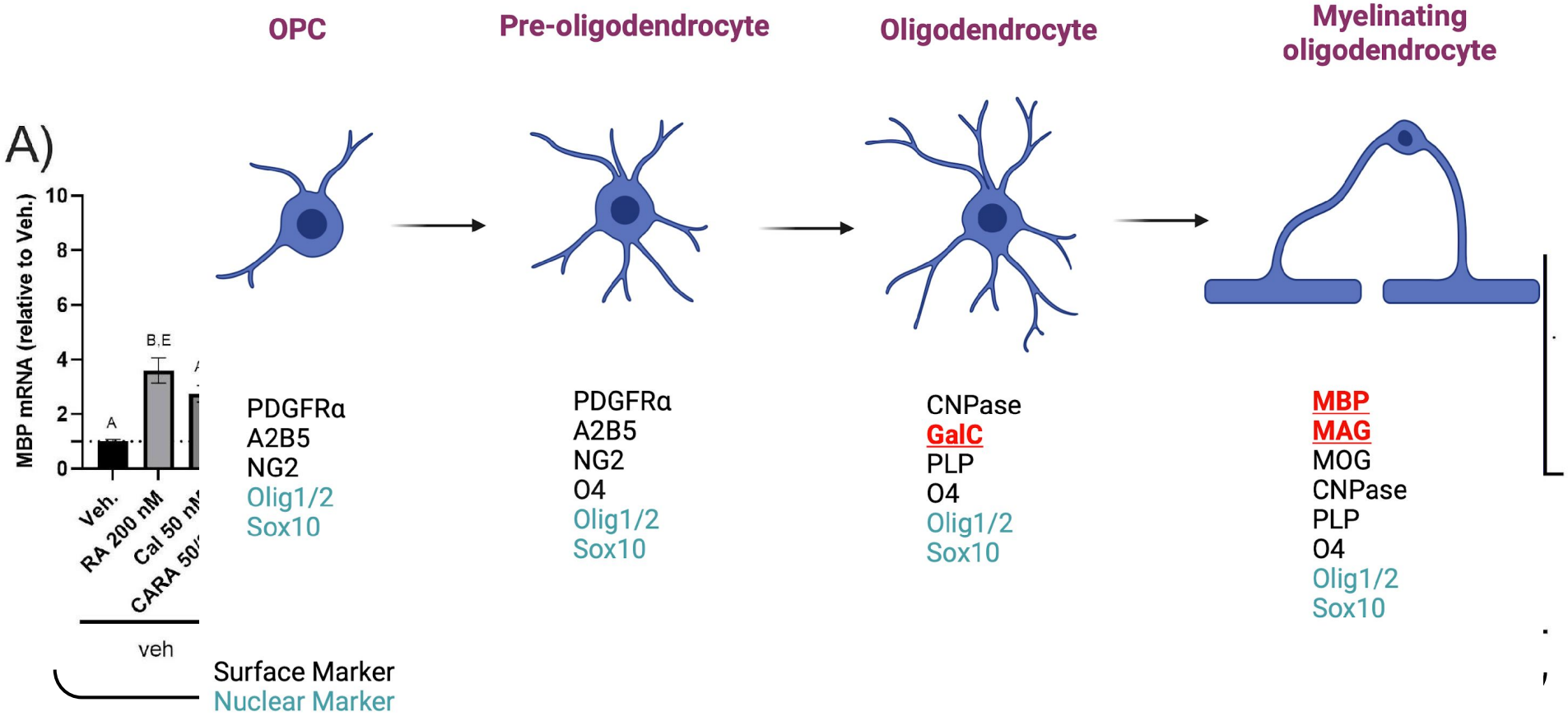
RA: Retinoic acid
Cal: calcitriol
CARA: combination of RA&Cal (1:1)

Labrak et al., Int. J. Pharm, 2024

N=3, n=4 ; Mean+/- SEM

LNC-Cal and LNC-CARA increased OPC differentiation

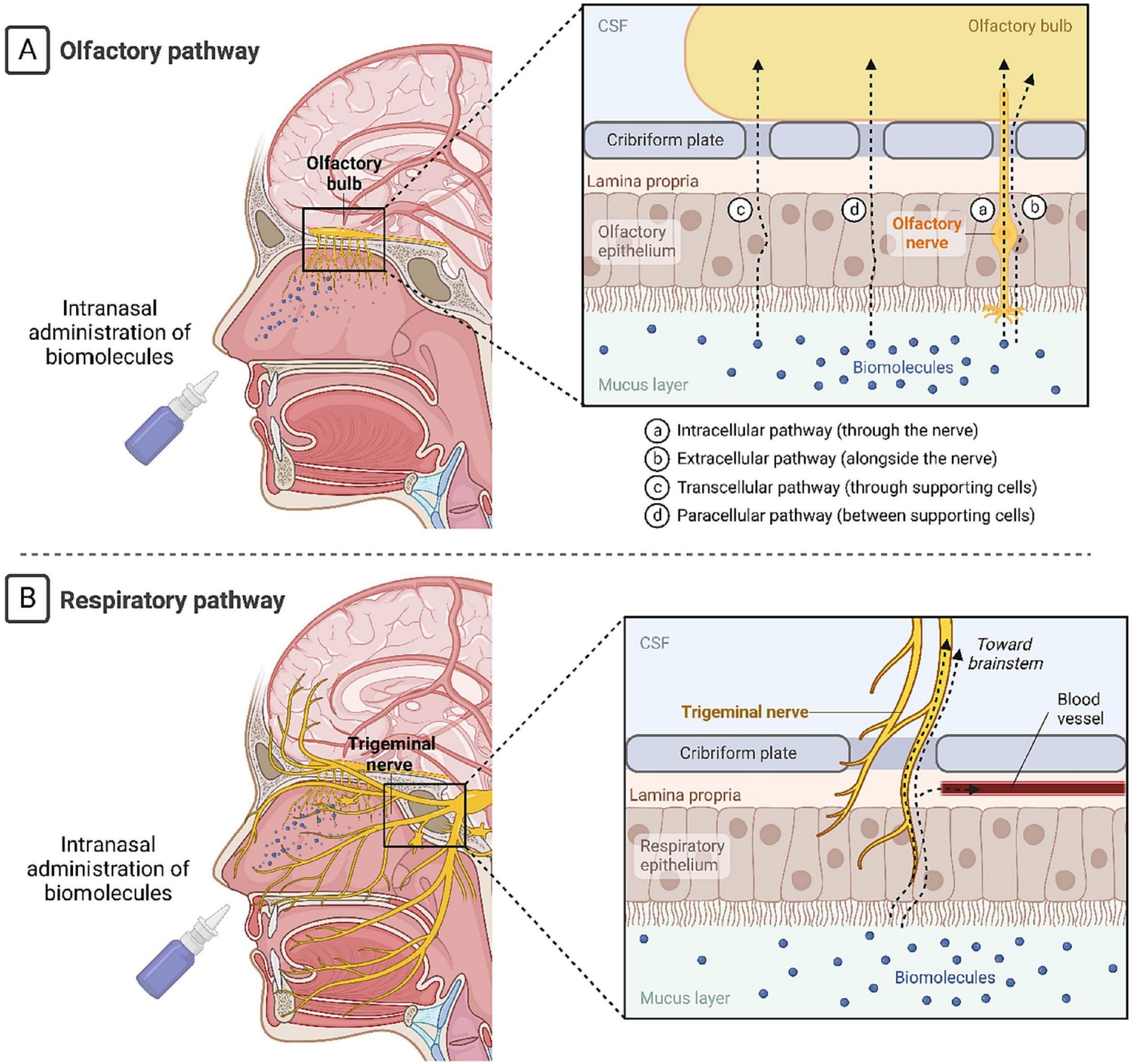
MBP



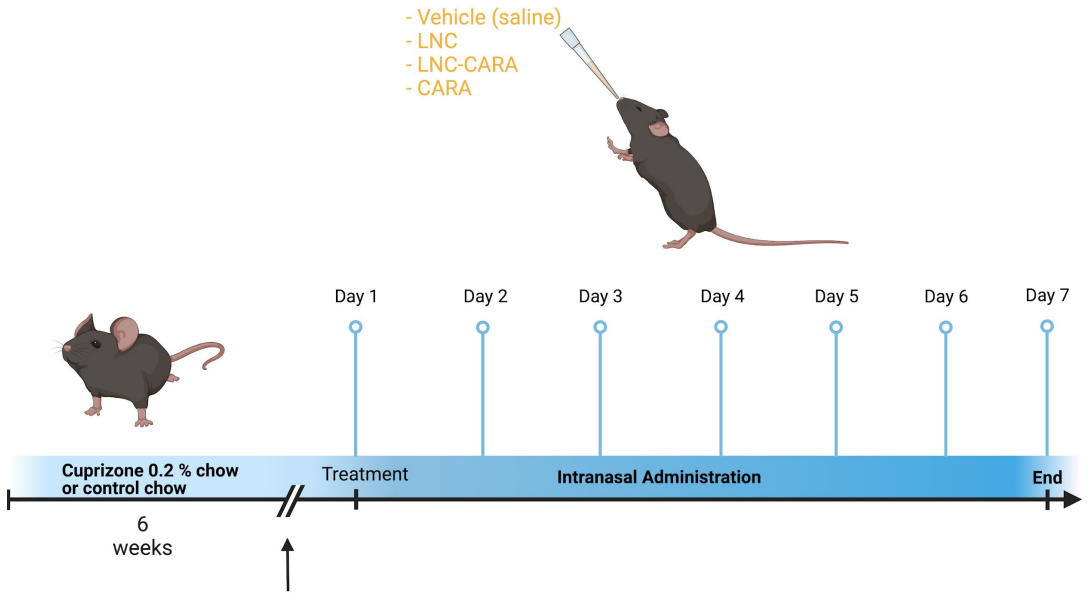
OPC: Oligodendrocyte progenitor cells
MBP: Myelin Basic Protein
MAG: Myelin associated glycoprotein

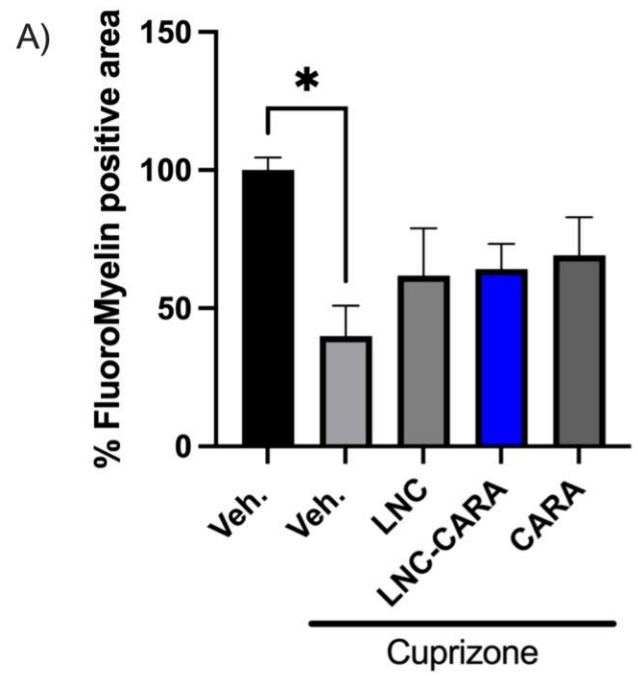
N=2, n=4, Mean +/- SEM

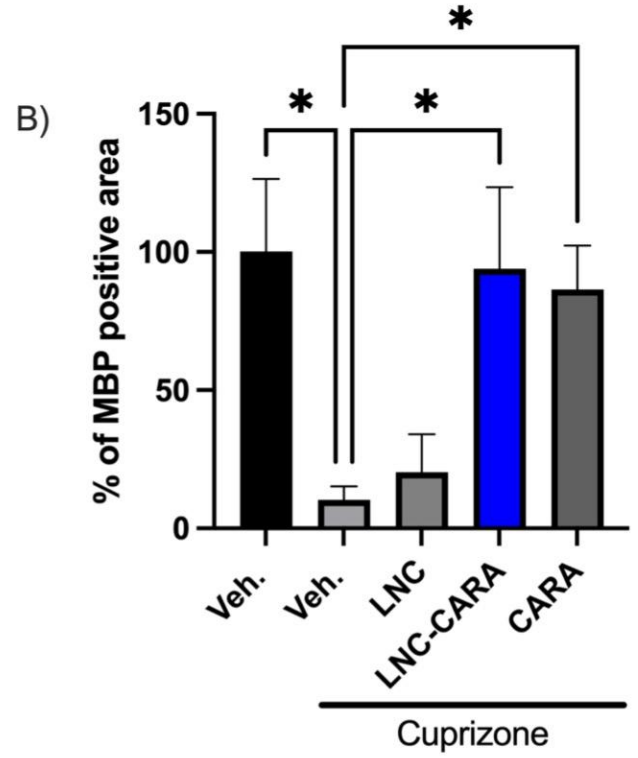
Collaboration with Dr M.Al Houayek (BPBL) and Dr L.D'Auria (IoNS)


A Olfactory pathway
Olfactory bulb
Intranasal administration of biomolecules
CSF
Olfactory bulb
Cribriform plate
Lamina propria
Olfactory epithelium
Olfactory nerve
Biomolecules
Mucus layer
a Intracellular pathway (through the nerve)
b Extracellular pathway (alongside the nerve)
c Transcellular pathway (through supporting cells)
d Paracellular pathway (between supporting cells)
B Respiratory pathway
Trigeminal nerve
Intranasal administration of biomolecules
CSF
Toward brainstem
Trigeminal nerve
Blood vessel
Cribriform plate
Lamina propria
Respiratory epithelium
Biomolecules
Mucus layer

LNC CARA increased mature oligodendrocyte population in a demyelination model



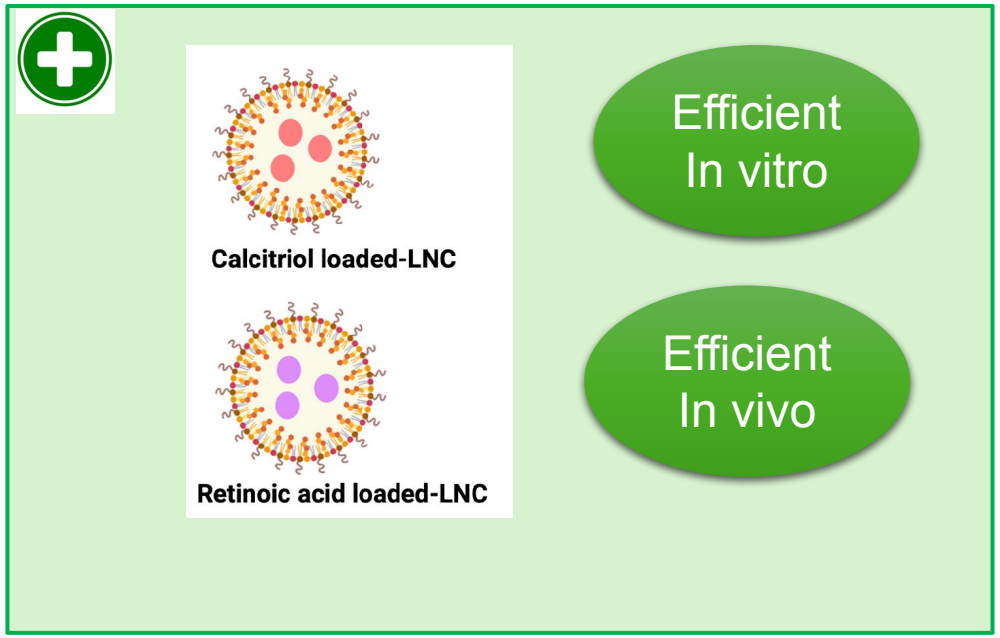




Labrak et al., Int. J. Pharm, 2024

N=3, n=3, Mean +/- SEM

Conclusions on combined treatment with RA and Cal



Combination with an anti-inflammatory nanomedicine

Take home message

- LNC are great carriers for CNS delivery of lipophilic drugs
- Intranasal best non-invasive delivery route
- Combination of drugs to tackle complicated diseases
- But limited by drug systemic toxicity and accumulation in CNS

- Increase residence time at olfactory mucosa and penetration into the brain
- Balance toxicity and efficacy (new molecules/new combinations)

Acknowledgments

- Prof. Muccioli (BPBL)
- Prof. van Pesch (IoNS)
- Members of ADDB and BPBL's lab
- Collaborators

FONDATION CHARCOT STICHTING

Vaincre la sclérose en plaques
Multiple sclerose overwinnen

Nanomedicines
Tissue engineering
Nucelic acid delivery
Cancers
M cells
Spinal cord
Hydrogel
Transdermal
Biomaterials
DNA - siRNA
Polymers
Formulations
Dental resine
Vaccines
Macrophages
In vitro and preclinical evaluation studies
Regenerative medicine
Nanotheranostic
Pulmonary drug delivery
Oral administration
Nanoparticles
Chemotherapy
Drug delivery
Gene silencing
DDB
Advanced Drug Delivery and Biomaterials

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