A new technology at chemistry-biology interface for photocontrolled release of bioactive molecules in the brain

Camille Ruffier[1], Emmanuel Ibarboure[2], Jean-Christophe Helbling[1], Maria-Florencia Angelo[1], Sébastien Marais[4], Rémi Kinet[5], Noel Pairault[3], Benjamin Dehay[5], Pierre Trifilieff[1], Nathan D. McClenaghan[3], Sébastien Lecommandoux[2], Clémentine Bosch-Bouju[1]

[1] Univ. Bordeaux, INRAE, Bordeaux INP, Nutrineuro, UMR1286, FR-33000, Bordeaux, France
[2] Univ. Bordeaux, CNRS, Bordeaux INP, LCPO, ENSMAC, UMR5629, FR-33000, Bordeaux, France
[3] Univ. Bordeaux, CNRS, Bordeaux INP, ISM, UMR5255, F-33000, Bordeaux, France
[4] Univ. Bordeaux, CNRS, INSERM, INRAE, BIC, UAR3420, US4, FR-33000, Bordeaux, France
[5] Univ. Bordeaux, CNRS, IMN, UMR5293, FR-33000, Bordeaux, France

CONTEXT

- **Brain disorders** affect 1 in 3 people worldwide.
- **The blood-brain barrier** (BBB) limits drug delivery to the brain.
- **Light-based tools** (e.g., optogenetics) allow precise brain control but lack clinical use.
- **Polymersomes** offer stable, efficient drug delivery.

OBJECTIVE

To develop photosensitive polymersomes that enable **local delivery of biomolecules to the brain** through **light activation**, precisely controlled in **time**, **space** and **concentration**.

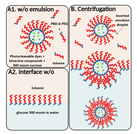
What's Innovative?
- Light-triggered delivery system for specific drug delivery to the brain.
- Combines polymersomes with stimulation precision.

PRINCIPLE OF THE NEUROTECHNOLOGY

DRUG DELIVERY SYSTEM

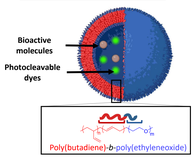
To control the concentration of encapsulated molecules

Inverse Emulsion-Centrifugation[1]



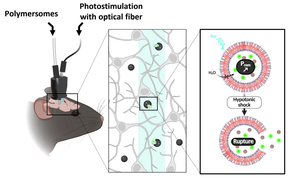
[1]Peyret, A., (2017), *Angewandte Chemie*, PMID: 27981689

Photosensitive polymersomes



NEUROSTIMULATION

To control the release of molecules **in time** and **space** using an **optical fiber**

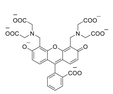


Key Features:
Stimuli:
Light by optical fiber
Target:
Deep brain structures
System:
Photosensitive biocompatible polymersomes
Precision:
Time and space
Therapeutic scope:
Targets multiple brain diseases, including glioblastoma

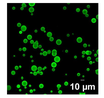
RESULTS

1-PHOTOSENSITIVE POLYMERSOMES DESIGN

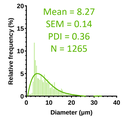
Calcein
λ_{exc} = 488 nm



Calcein-loaded polymersomes



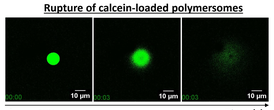
Size distributions



✔Physiological osmolarity ✔No toxic solvents ✔Small size

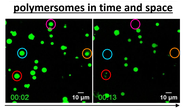
2-PHOTORELEASE OF POLYMERSOMES' CONTENTS IN SOLUTION

Rupture of calcein-loaded polymersomes



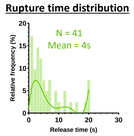
λ_{exc} = 488 nm **Time (s)**

Selective rupture of calcein-loaded polymersomes in time and space



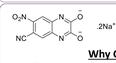
λ_{exc} = 488 nm **Time (s)**

Rupture time distribution



✔Controlled release

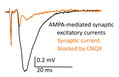
3-ENCAPSULATION OF CNQX (100 µM) IN POLYMERSOMES

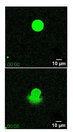


CNQX = A blocker of neuronal transmission (glutamate AMPA receptor antagonist)

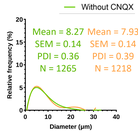
Why CNQX?
- To **monitor** and **validate** polymersome release by electrophysiology.
- To **counteract** invasion of neuronal networks by glioblastoma cells.[2]

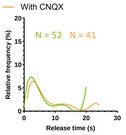
[2] Venkataramani, V., et al., (2022), Cell, PMID: 35914528





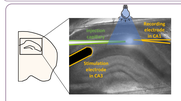
Without CNQX — With CNQX



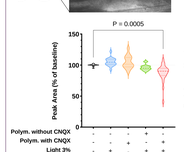


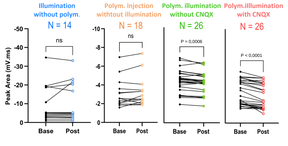
✔No impact on photoactivation properties

4-PHOTOSTIMULATION OF POLYMERSOMES IN BRAIN SLICES

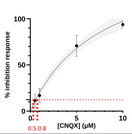


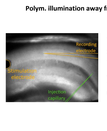
✔Only photostimulation of CNQX-loaded polymersomes leads to CNQX release and suppression of excitatory potentials

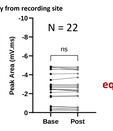




Is the released CNQX concentration equivalent to the initially loaded dose?



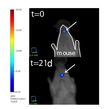


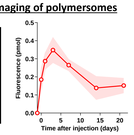


✔10 µM in bath: complete block
✔100 µM local: equiv. 0.5-0.8 µM in bath

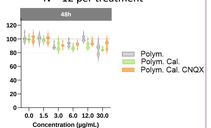
5-ASSESSMENT OF BIOAVAILABILITY AND BIOSAFETY OF POLYMERSOMES

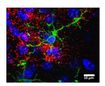
***In Vivo* imaging of polymersomes**

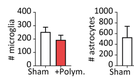




MTT viability test
BE(2)-M17 human cell lines.
N = 12 per treatment







✔No strong effect on cell viability

✔Good bioavailability ✔Persistent fluorescence at 21d

KEY MESSAGE & NEXT STEPS

Feature	Traditionnal Approach	Our Neurotechnology
Brain targeting	Systemic/Diffuse	Highly Precise
Temporal Control	None	On-demand
BBB Bypass	Partial	Targeted/Localized

Next step: Implementation in a glioblastoma model

Figures created using Biorender and ChemDraw

FUNDING

anr Grand Programme de Recherche BRAIN_2030 — université de BORDEAUX — FONDATION MEDISITE — BORDEAUX INP