



Nanoencapsulated CC-resynchronizing molecule for improved efficacy in Alzheimer's disease

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CRS2026
ANNUAL MEETING & EXPOSITION
LISBON
— PORTUGAL —

MULTISECTOR
INNOVATION
for ADVANCING
DELIVERY SCIENCE

JULY 6–9, 2026



Funded by
the European Union

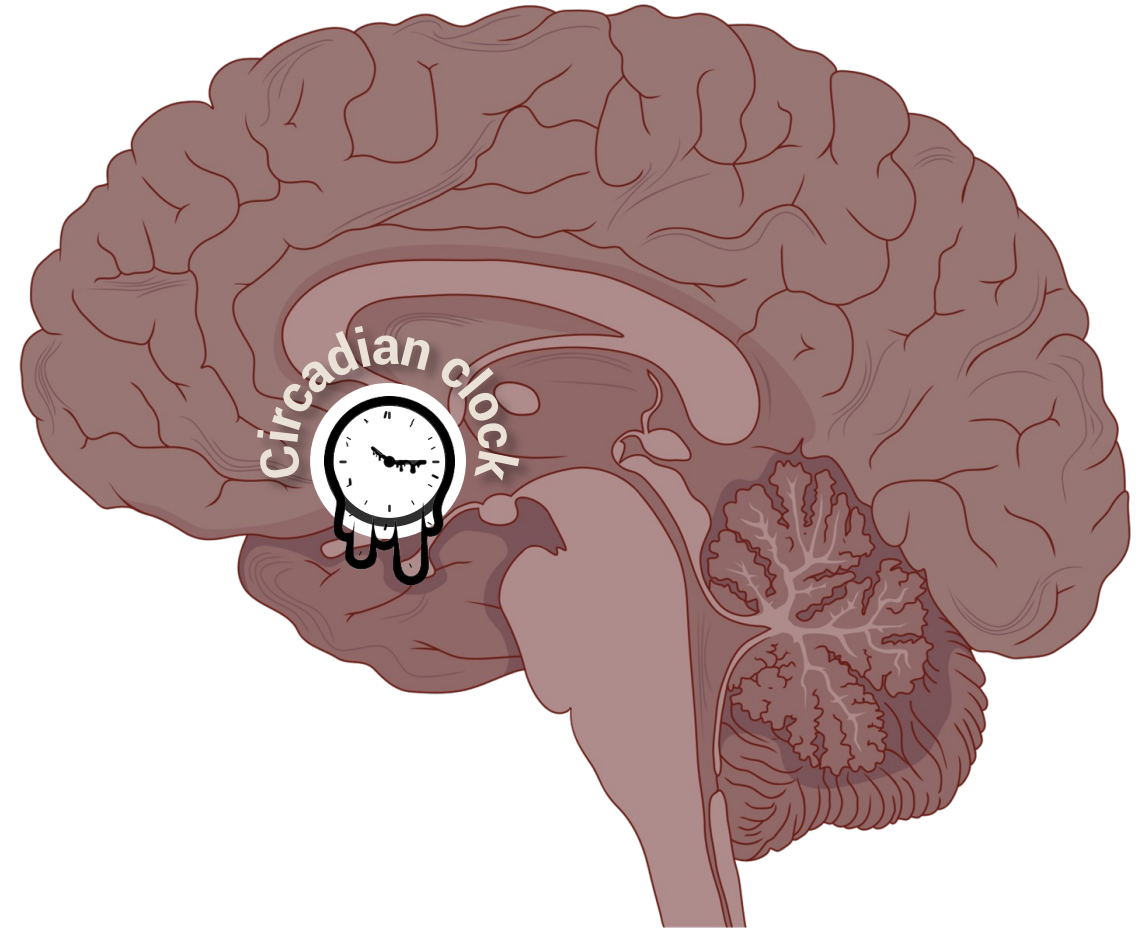
Time for new approaches

Alzheimer's disease

Accumulation of A β plaques and neurofibrillary tangles

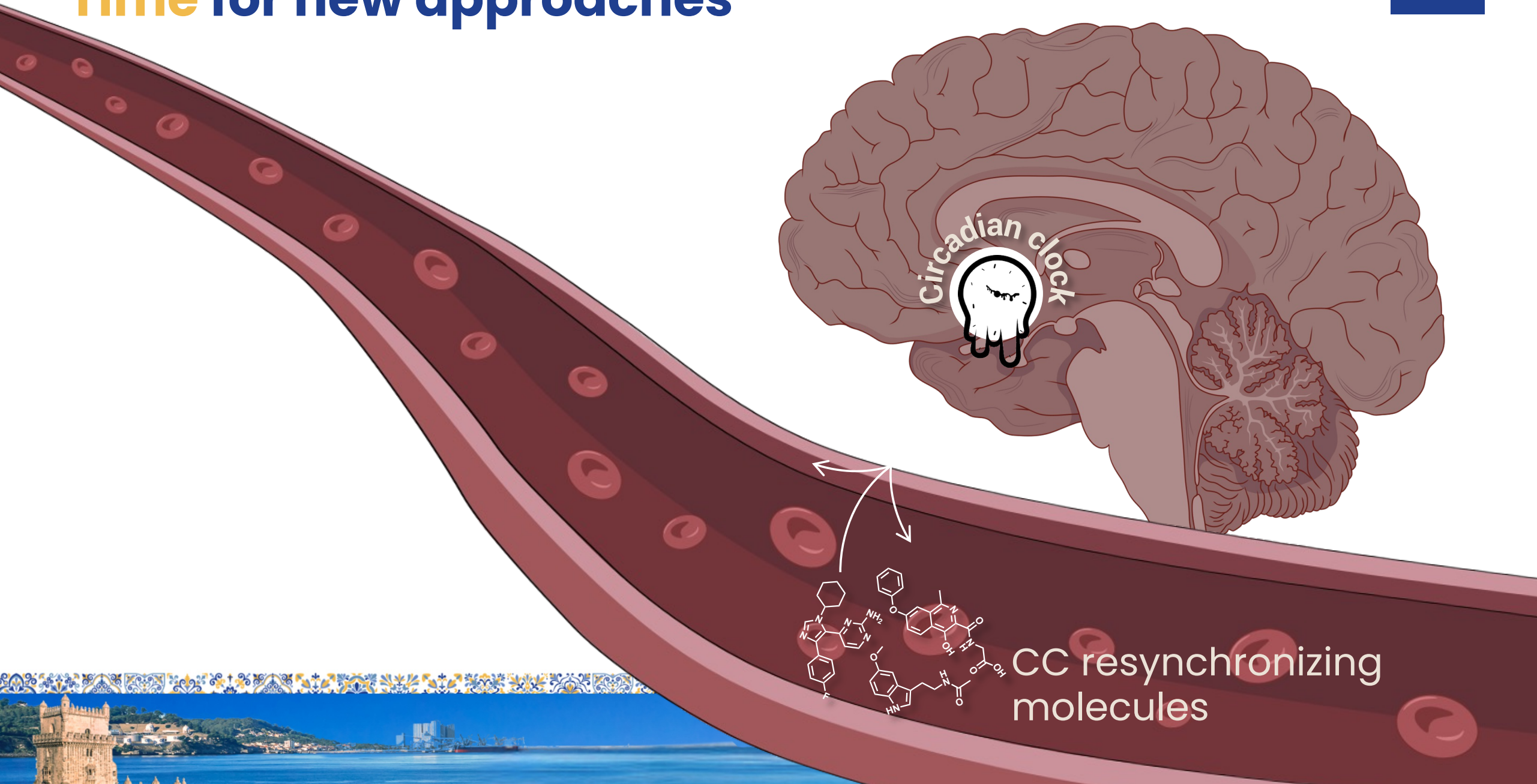
Multifactorial disease

Bidirectional relationship with circadian clock dysfunctions



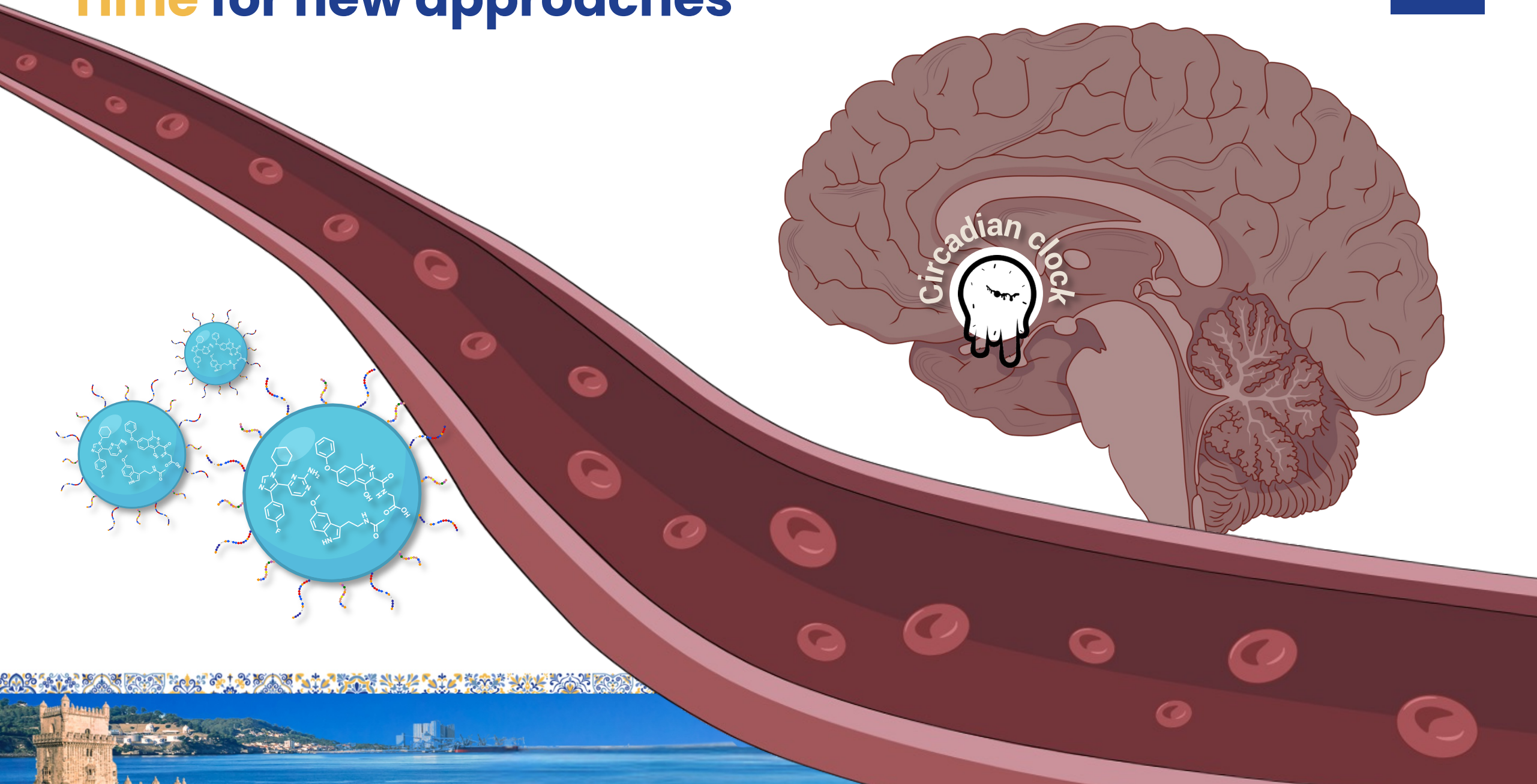
Time for new approaches

1



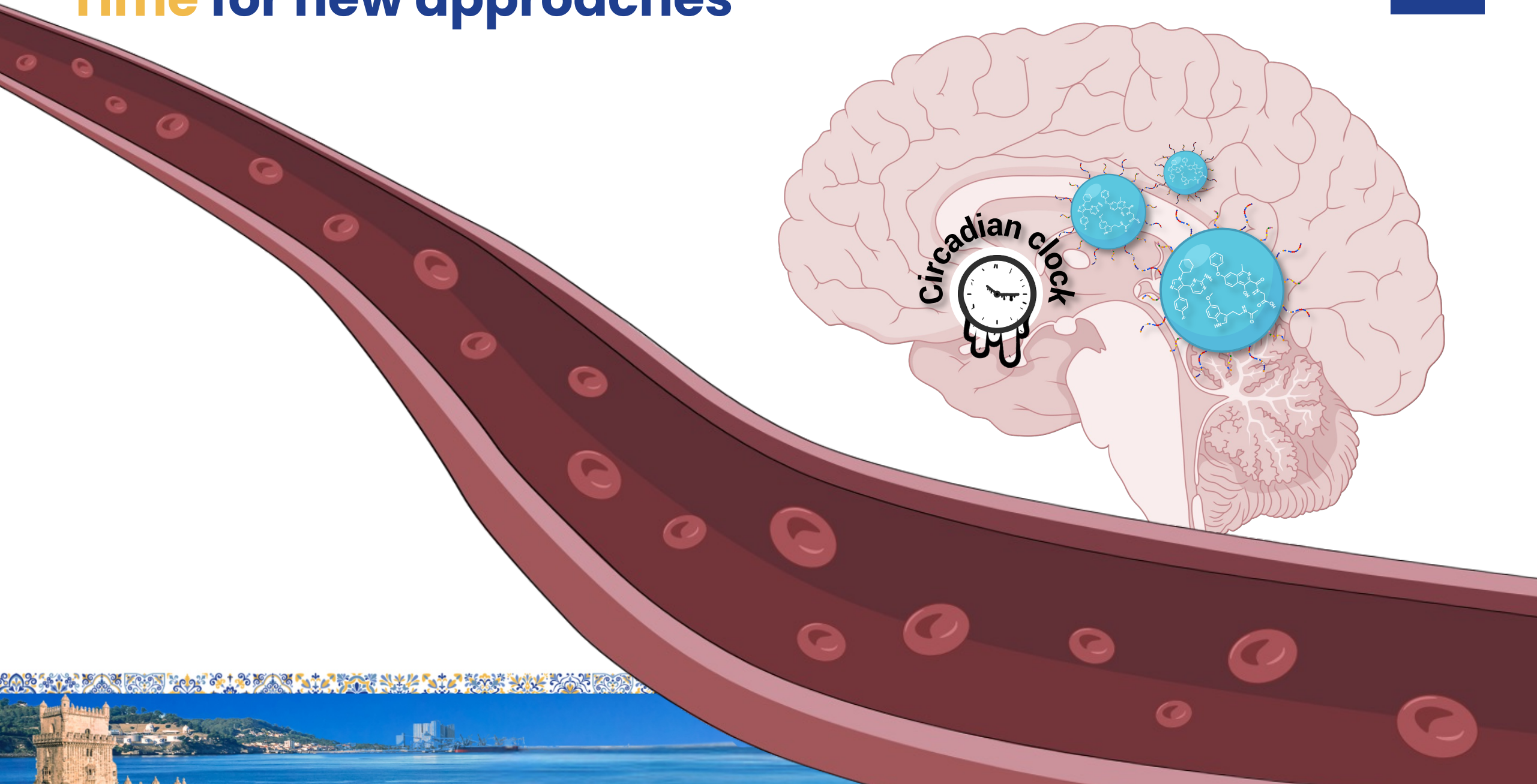
Time for new approaches

1

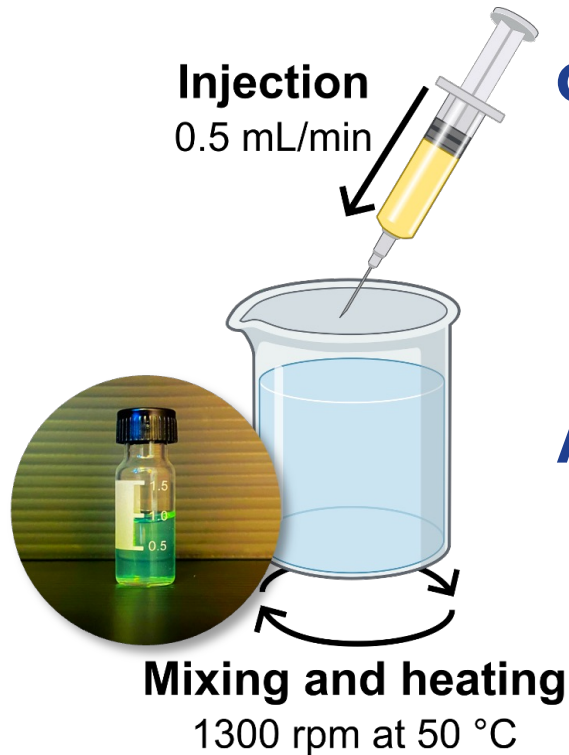


Time for new approaches

1



Nanoparticle preparation



Organic phase

- PLGA
- PLGA-PEG
- Cargo
- PLGA-Cy5

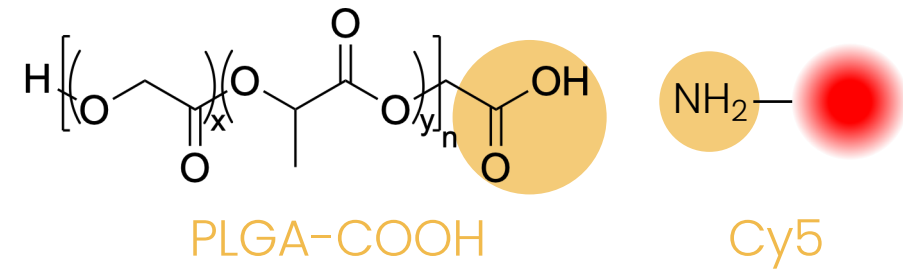
Aqueous phase

- P407 1%
- PVA 1%

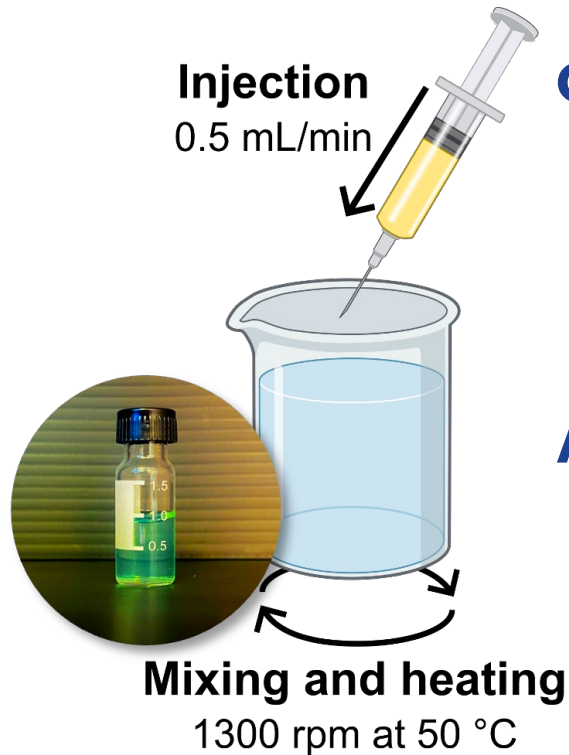
Fluorescence labeling

Encapsulation of DiO

Covalent binding of Cy5



Nanoparticle preparation



Organic phase

- PLGA
- PLGA-PEG
- Cargo
- PLGA-Cy5
- PLGA-PEG-peptide

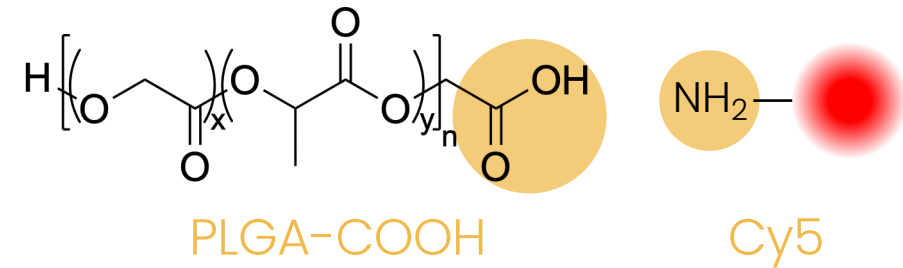
Aqueous phase

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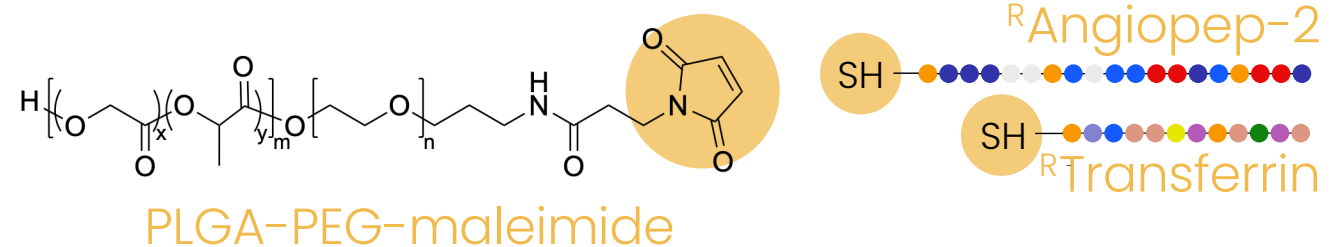
Fluorescence labeling

Encapsulation of DiO

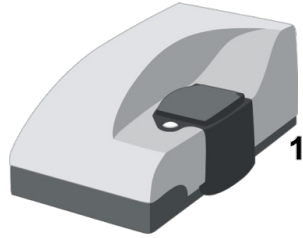
Covalent binding of Cy5



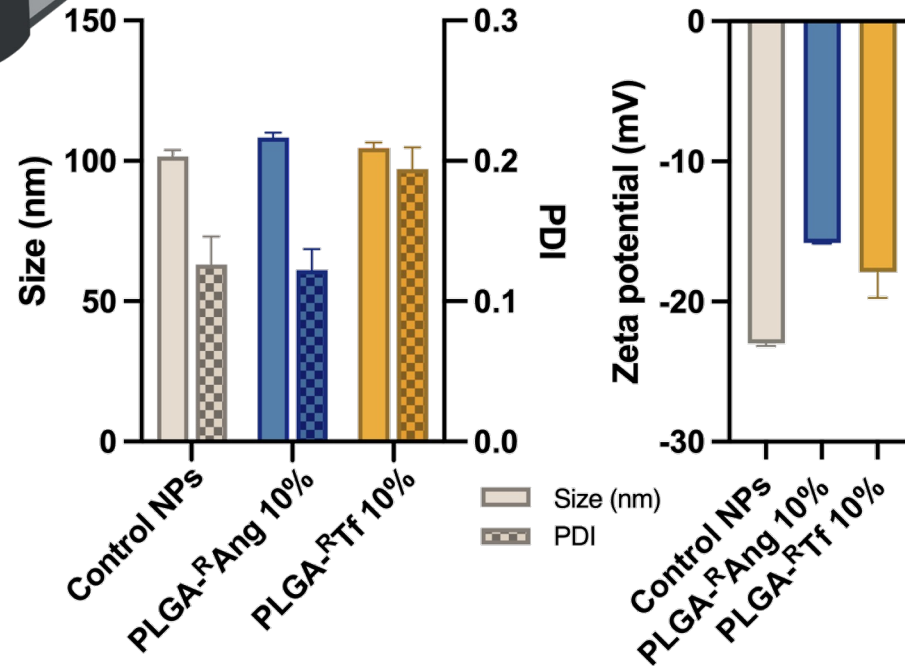
Functionalization



Nanoparticle characterization



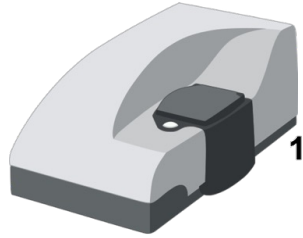
DLS and ELS



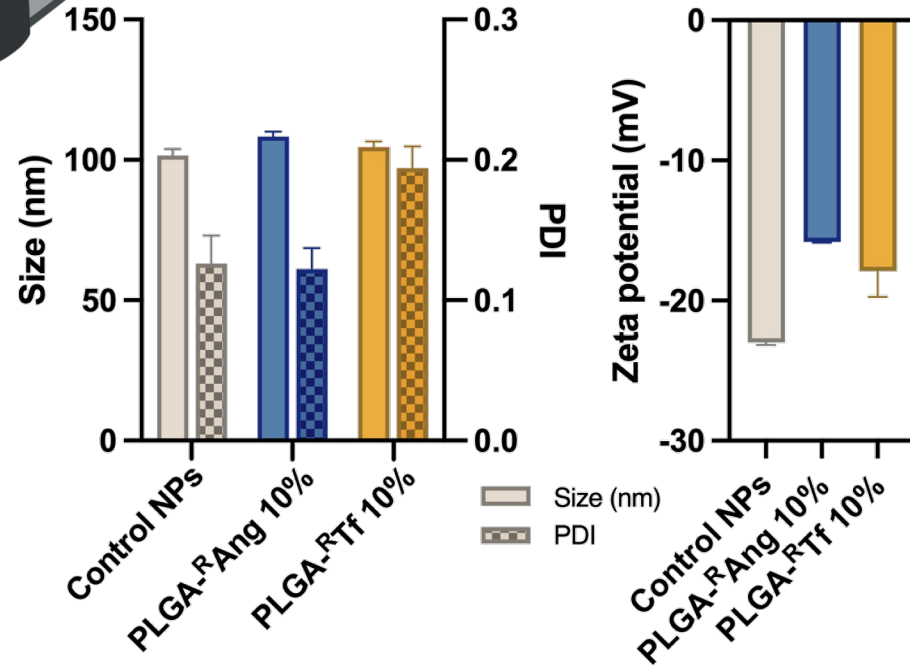
Size around 100 nm
PDI below 0.3
Surface charge slightly negative



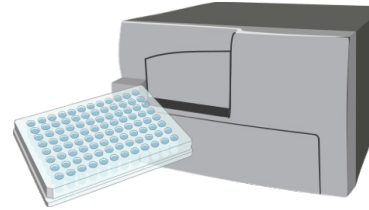
Nanoparticle characterization



DLS and ELS

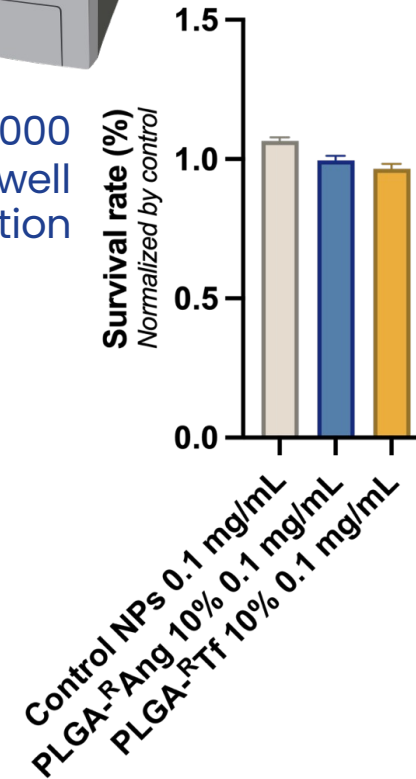


Size around 100 nm
PDI below 0.3
Surface charge slightly negative



MTT assay

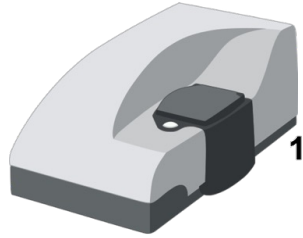
SH-SY5Y 10 000 cells/well
24 h incubation



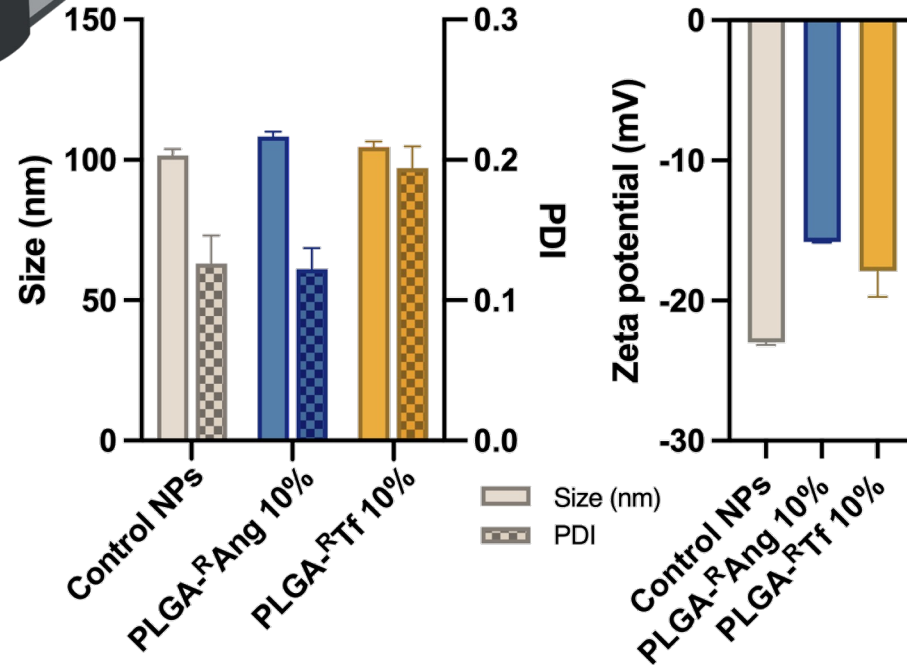
No toxicity of the targeting peptide



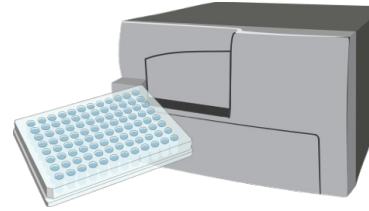
Nanoparticle characterization



DLS and ELS

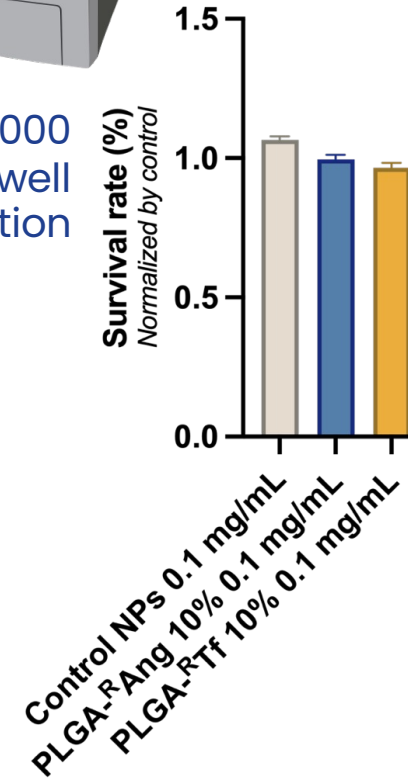


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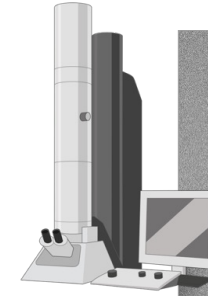


MTT assay

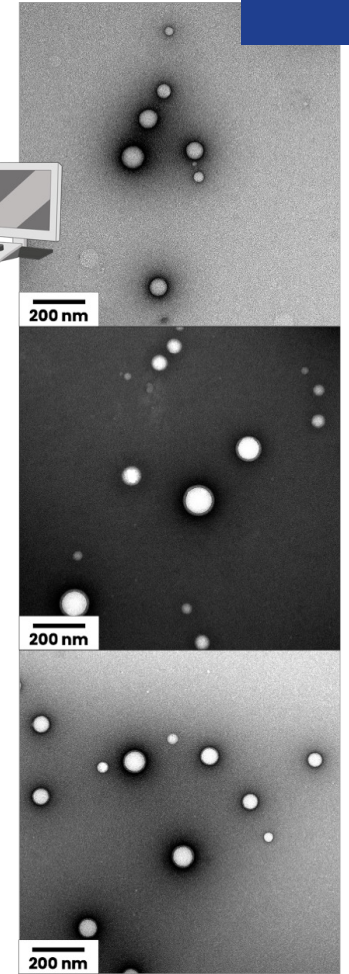
SH-SY5Y 10 000 cells/well
24 h incubation



No toxicity of the targeting peptide



TEM

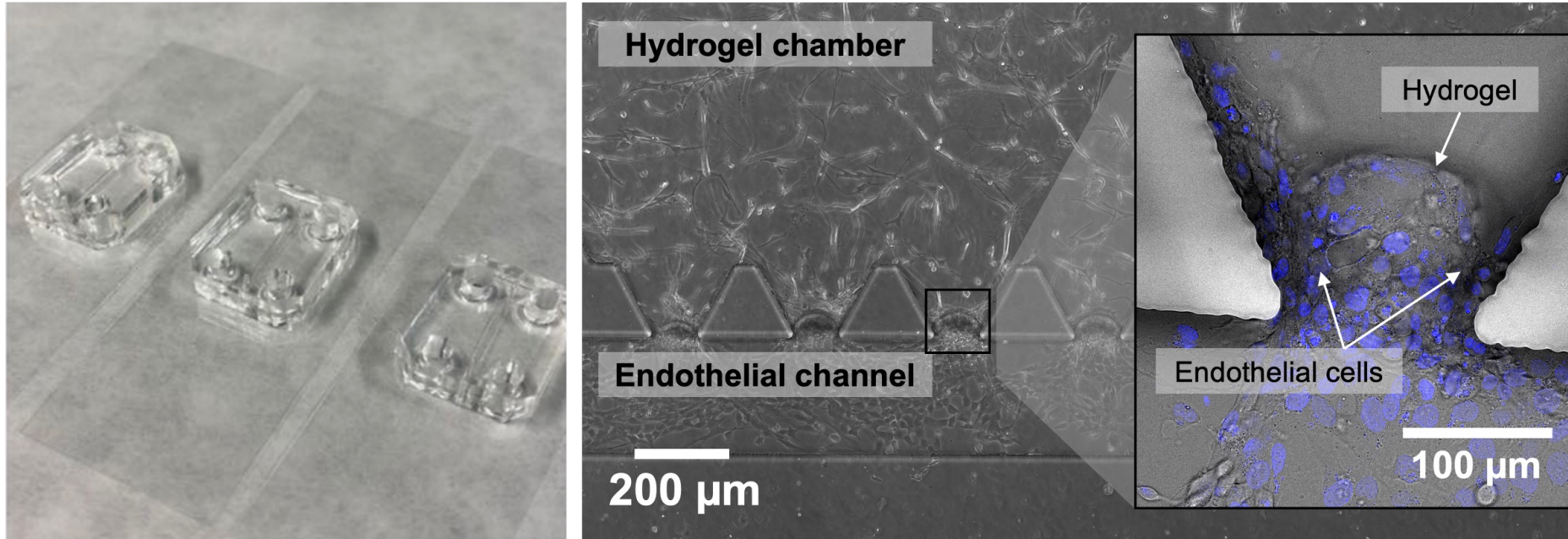


No aggregation



BBB crossing evaluation

BBB-on-a-chip



Coculture human brain endothelial cells, astrocytes and pericytes

30 min incubation

Fluorescence imaging

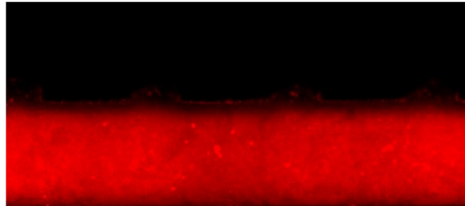
BBB crossing evaluation

BBB-on-a-chip

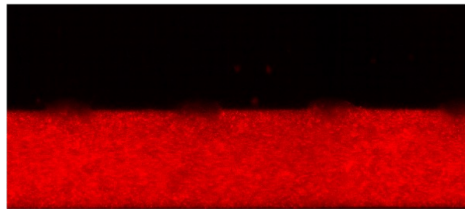
Injection

30 min

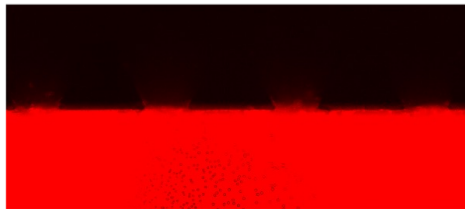
Control



PLGA-RAng
10%



PLGA-RTf
10%



PLGA-RTf
30%



BBB crossing evaluation

BBB-on-a-chip

Injection

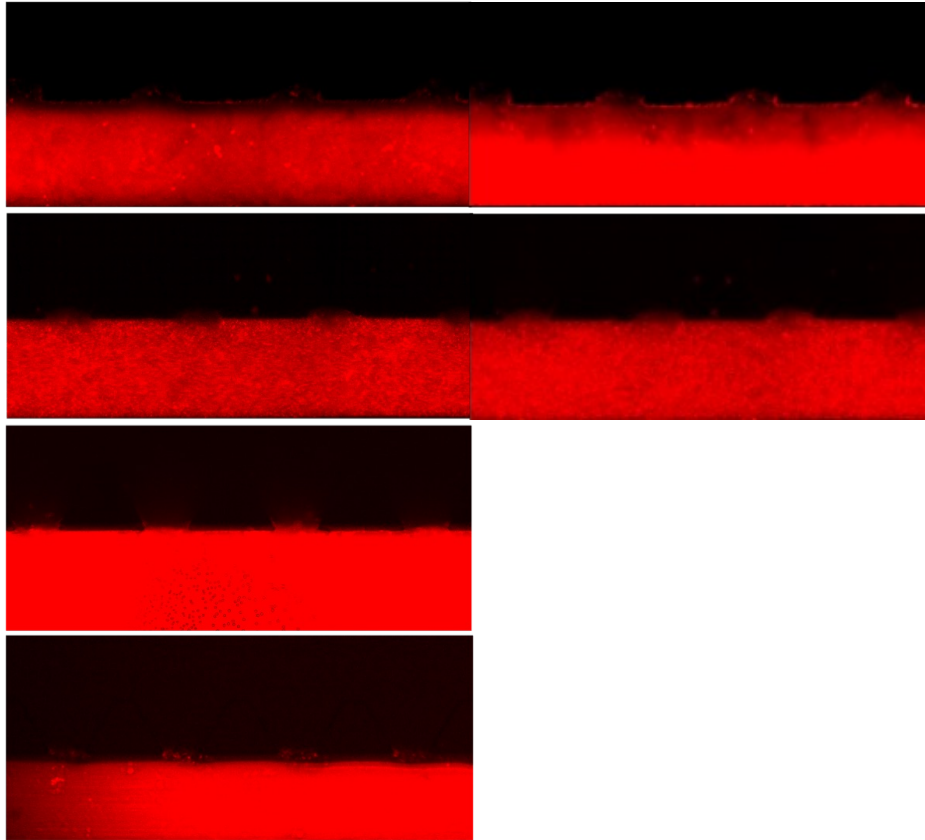
30 min

Control

PLGA-RAng
10%

PLGA-RTf
10%

PLGA-RTf
30%

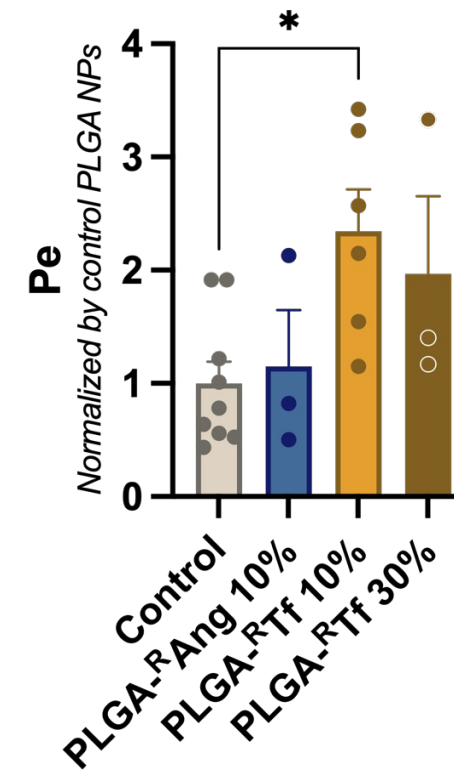
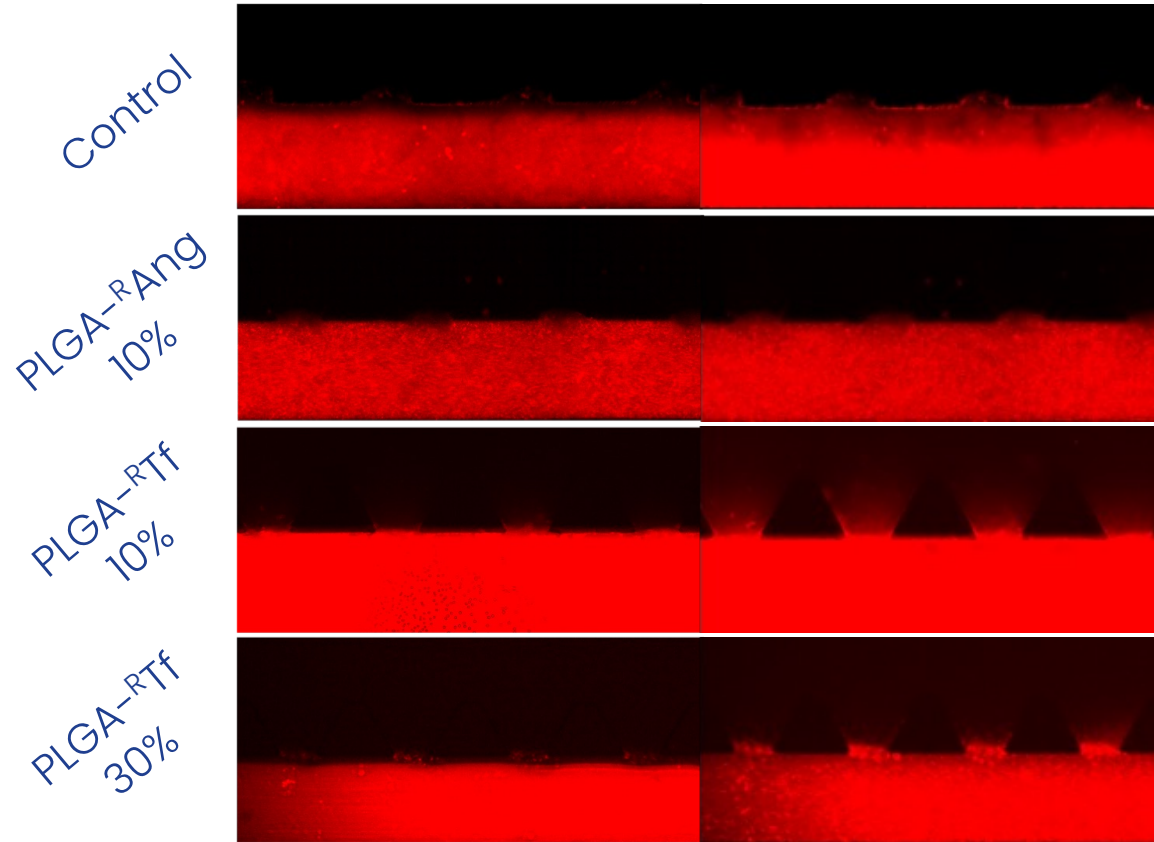


BBB crossing evaluation

BBB-on-a-chip

Injection

30 min

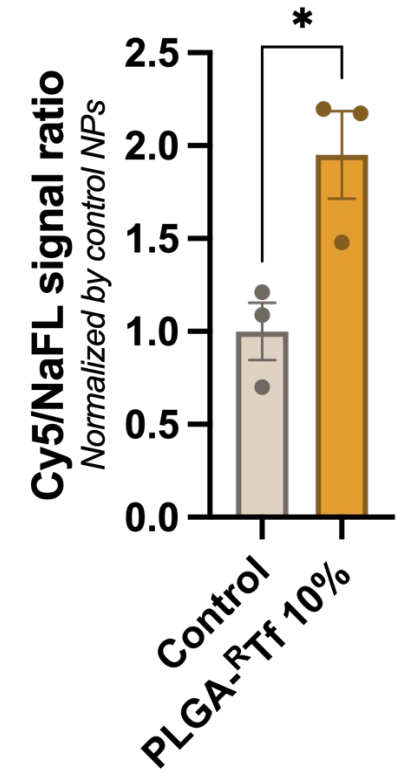
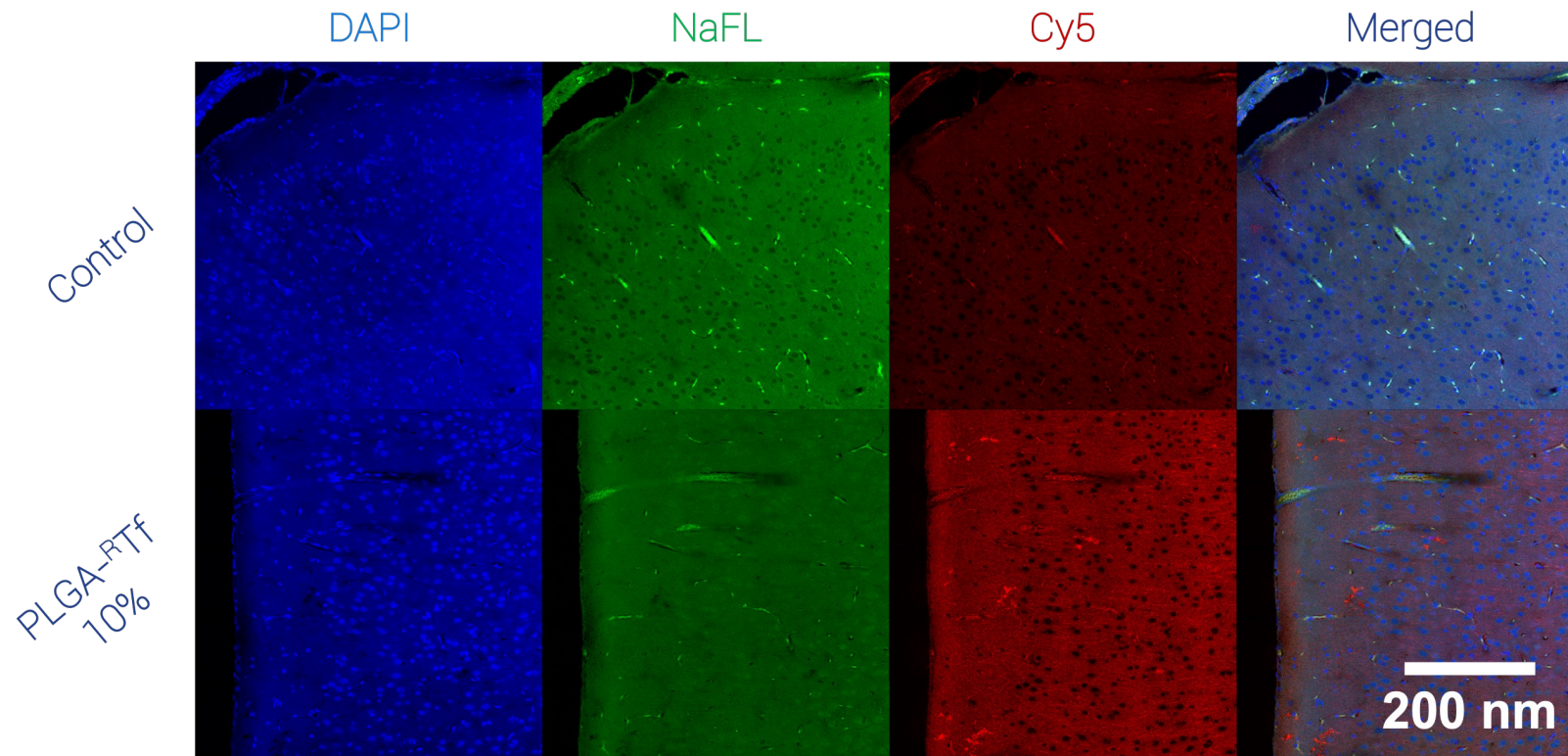


2.35-fold brain permeation increase



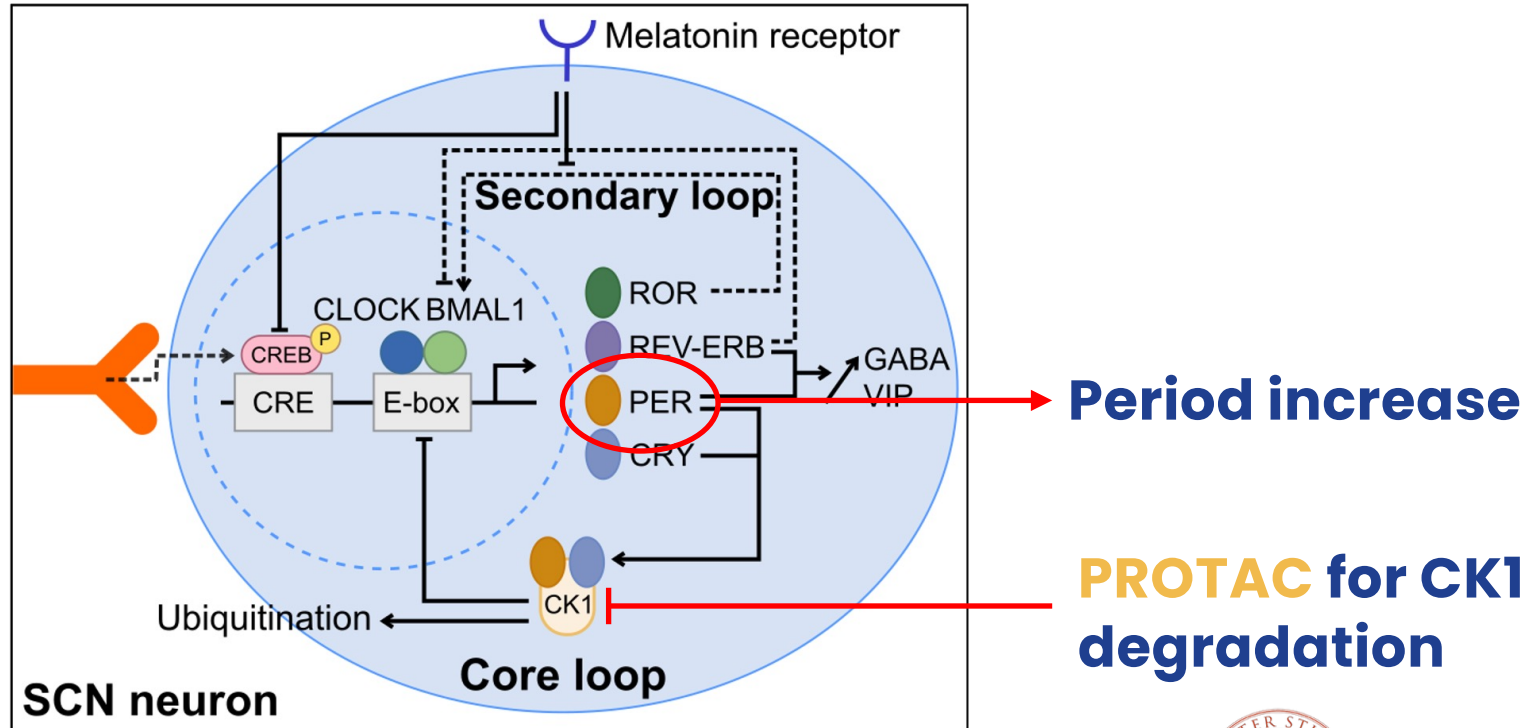
BBB crossing evaluation

In vivo brain penetration



1.95-fold brain
permeation increase

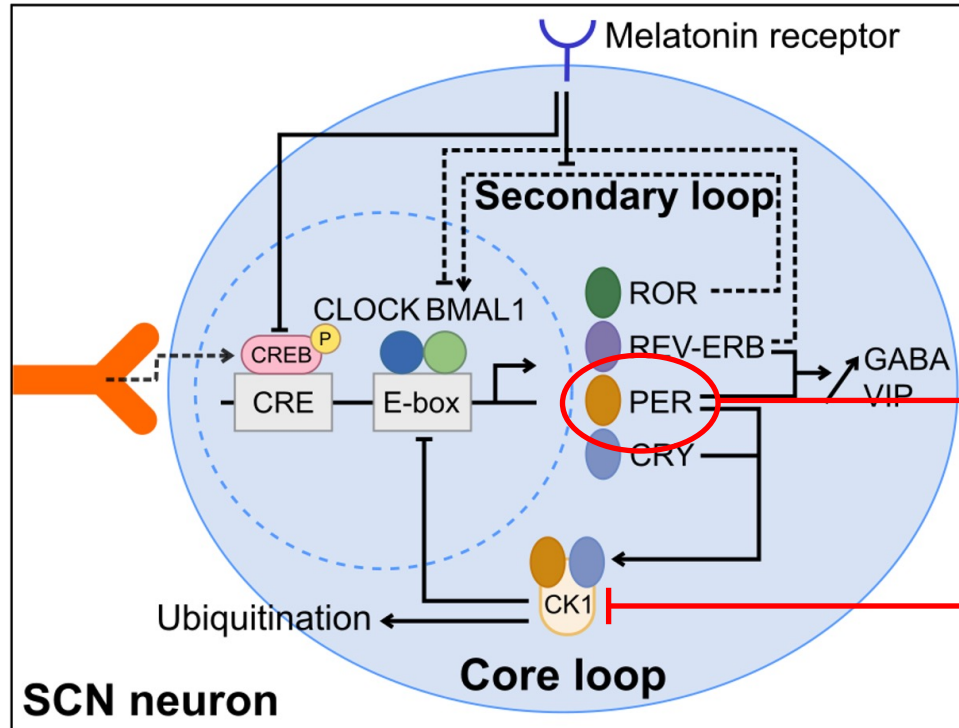
Circadian clock modulation



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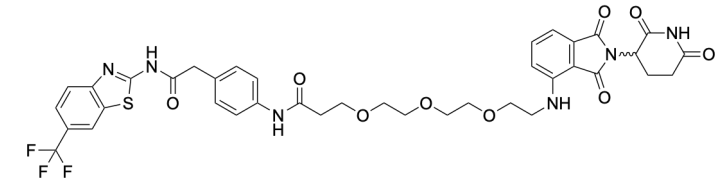


Circadian clock modulation



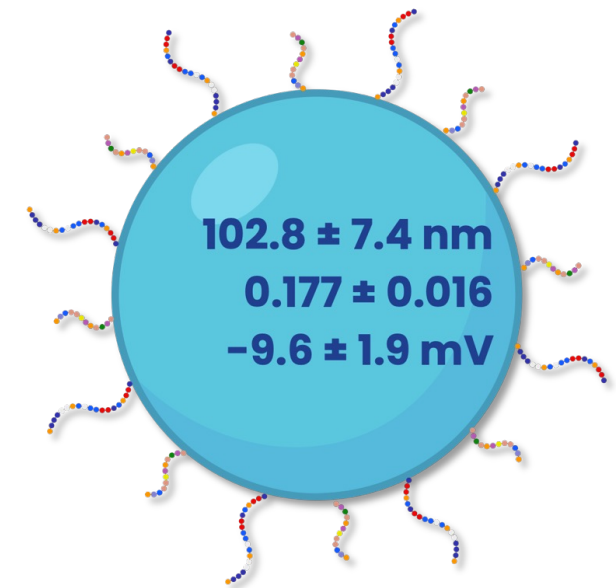
Period increase

PROTAC for CK1 degradation

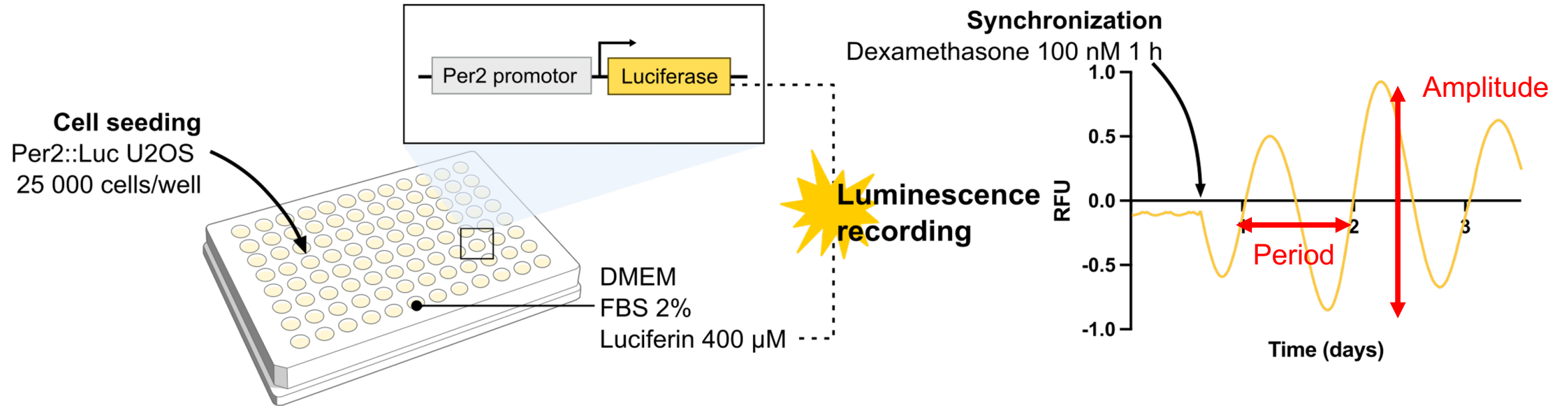


Practically insoluble in water

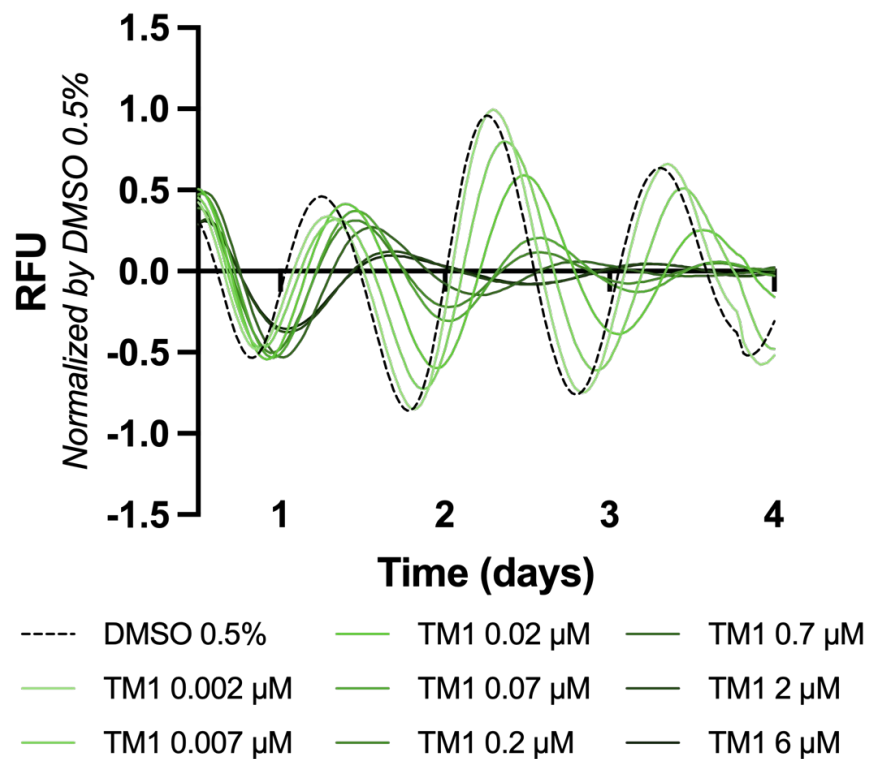
Not BBB permeable

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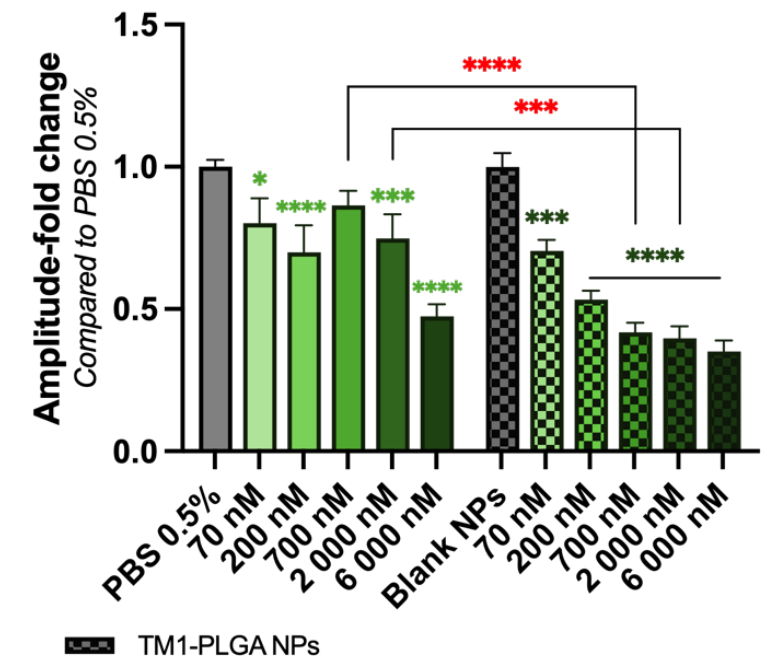
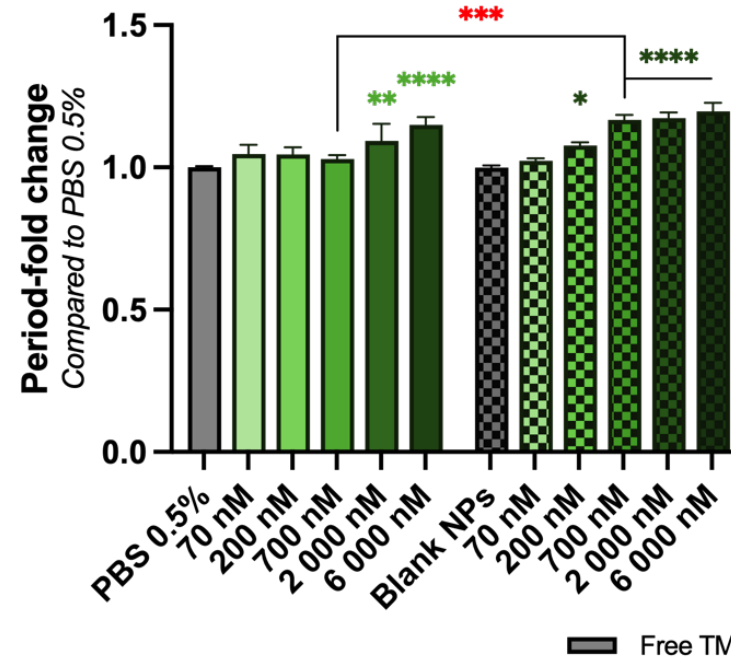
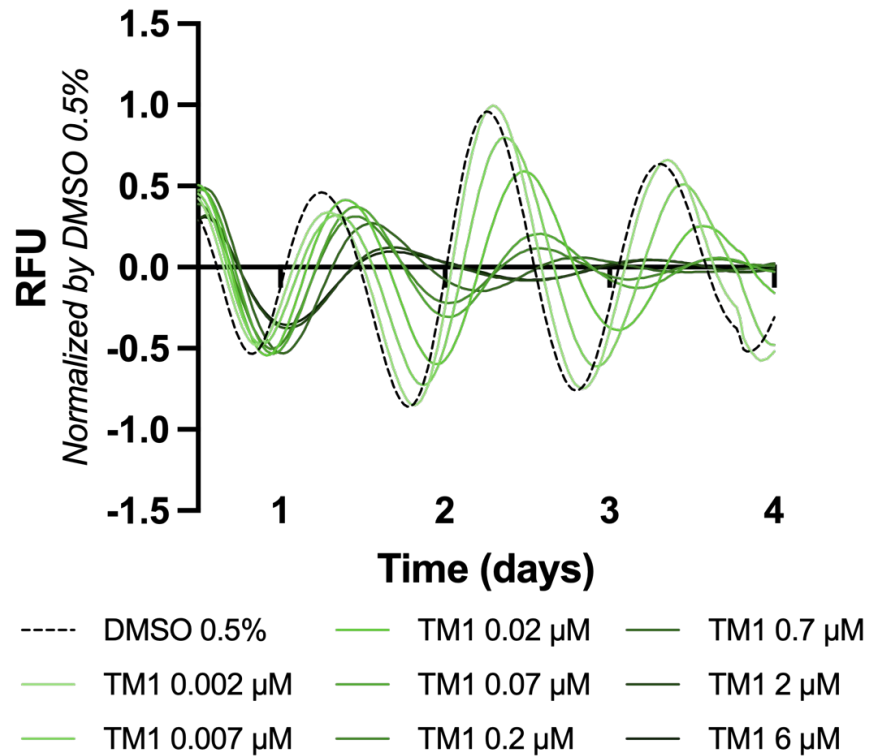
Circadian clock modulation



Circadian clock modulation



Circadian clock modulation



Period increase up to 27.6 h with free TM1 and 28.6 h when encapsulated

Amplitude decrease by 53 % with free TM1 and 65% when encapsulated



Conclusions



PLGA-^RTransferrin 10% showed a 2-fold increase in BBB crossing ability in vitro and in vivo

Retroenantomers can be used for organ targeting



Conclusions



PLGA-^RTransferrin 10% showed a 2-fold increase in BBB crossing ability in vitro and in vivo

Retroenantomers can be used for organ targeting



NPs increased the efficacy of a new PROTAC to modulate the CC



Conclusions

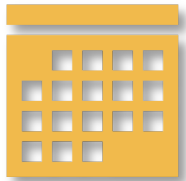


PLGA-^RTransferrin 10% showed a 2-fold increase in BBB crossing ability in vitro and in vivo

Retroenantiomers can be used for organ targeting



NPs increased the efficacy of a new PROTAC to modulate the CC



Full body biodistribution study is currently being performed
System evaluation in an AD model needs to be organized



Acknowledgements

Supervision

IMDEA Nanoscience “Biosensors in Neuroscience” group (**Madrid, Spain**): Valle Palomo

University of Bologna (**Bologna, Italy**): Paolo Blasi

Circadian Therapeutics (**Oxford, UK**): Sridhar Vasudevan

Collaborators

IBEC “Nanobioengineering” group (**Barcelona, Spain**): Andrés Crespo, Sujey Palma-Florez, Anna Lagunas, Mònica Mir

University Milano-Bicocca (**Monza, Italy**): Giulia Terribile, Giulio Sancini

Financial support



TClock4AD MSCA consortium

SPLC-CRS travel grant





Thank you for your attention!

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