

Optical Control of Neuronal Activities with Photoswitchable Nanovesicles

Hejian Xiong¹, Paul A. Slesinger^{2,}, Zhenpeng Qin^{1,3*}*

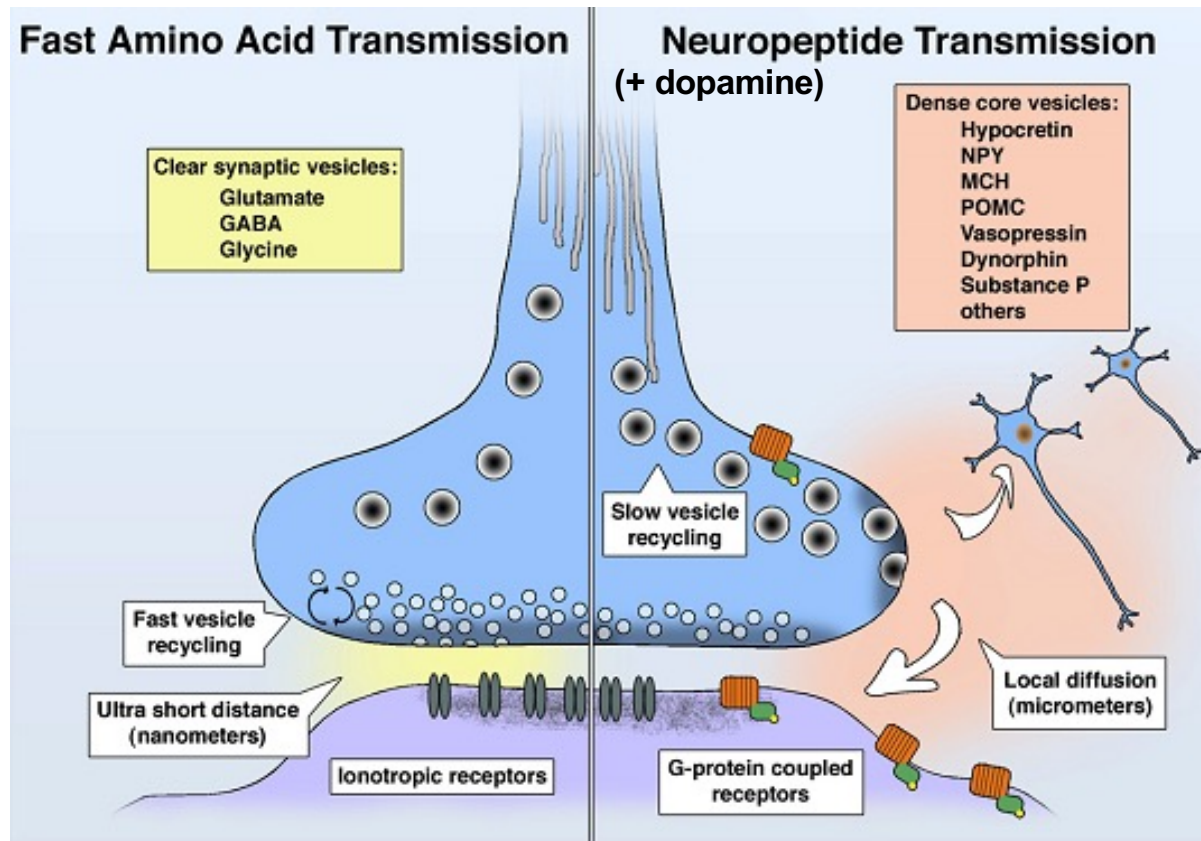
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²Icahn School of Medicine at Mount Sinai, New York, NY, USA

³ Department of Surgery, UT Southwestern Medical Center, Dallas, TX, USA

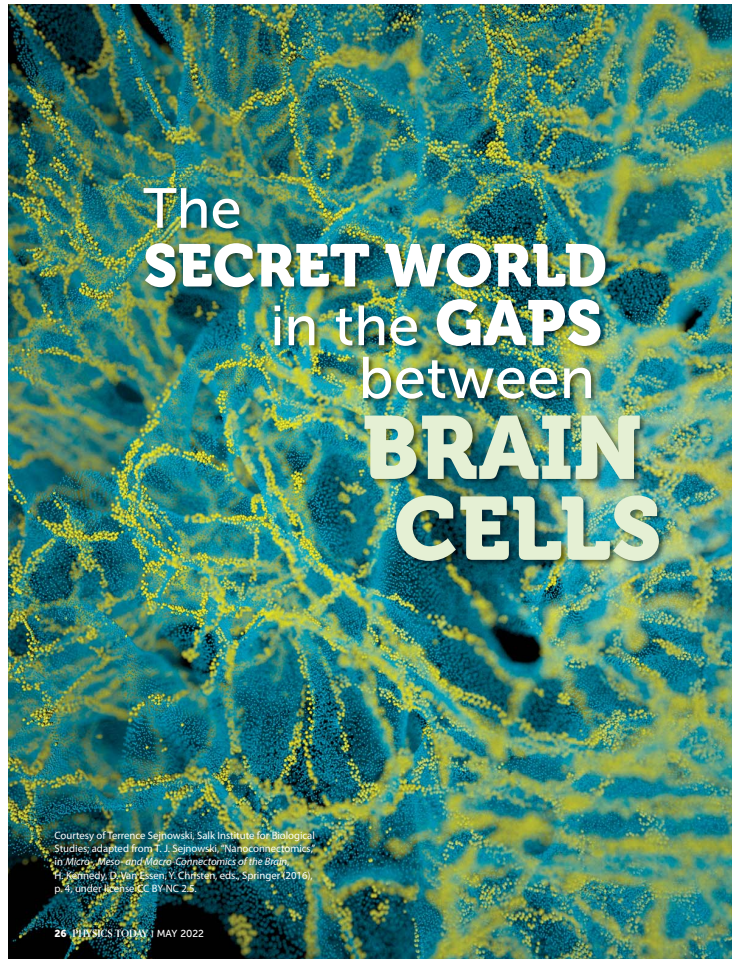
7th International Symposium on Phospholipids in Pharmaceutical Research
September 12, 2022

Two Types of Neurotransmissions



van den Pol. Neuron. 2012

Neuromodulator Diffuse Through the Extracellular Space

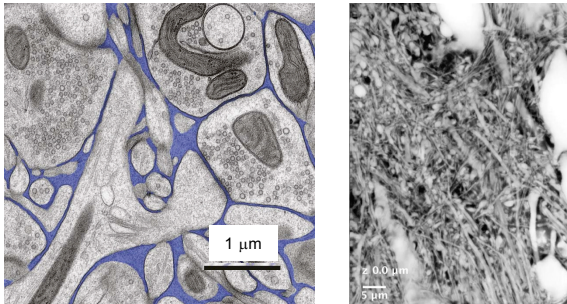


Charles Nicholson is an emeritus professor in the department of neuroscience and physiology at the New York University Grossman School of Medicine in New York City.



Neuromodulator Diffuse Through the Extracellular Space

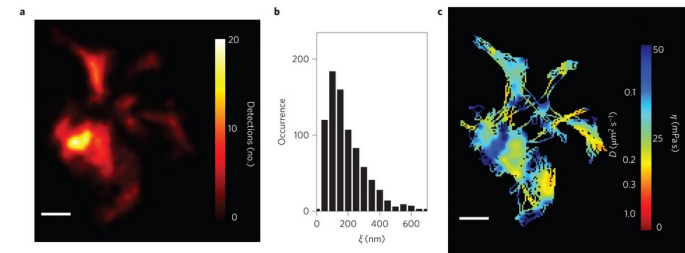
Ultrastructure Imaging



Korogod et al. *eLife*, 2015: cryoEM

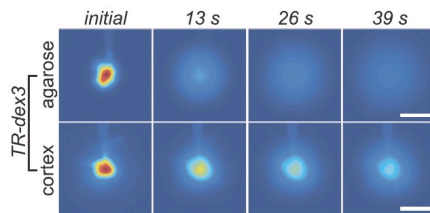
Nagerl et al. *Cell* 2018: SUSHI

Nanoparticle Tracking

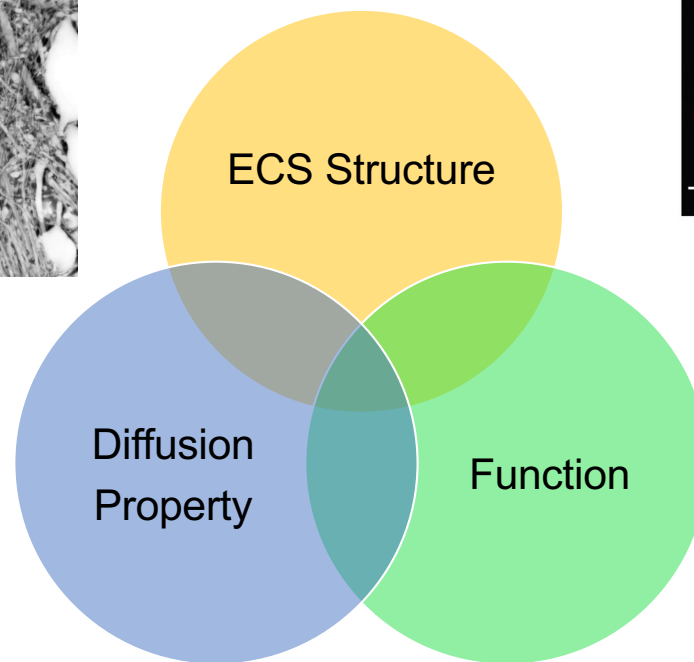


Cognet et al. *Nat Nanotechnol.* 2017

Dye Diffusion Measurement



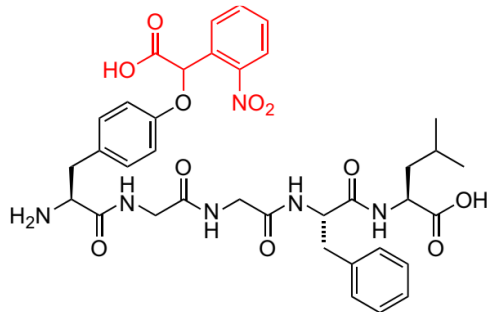
Nicholson et al. *PNAS* 2006



Question 1:
How far and fast do neuromodulators
send the signal in the brain?

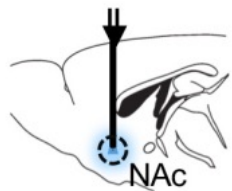
State-of-the-art

Caged compound



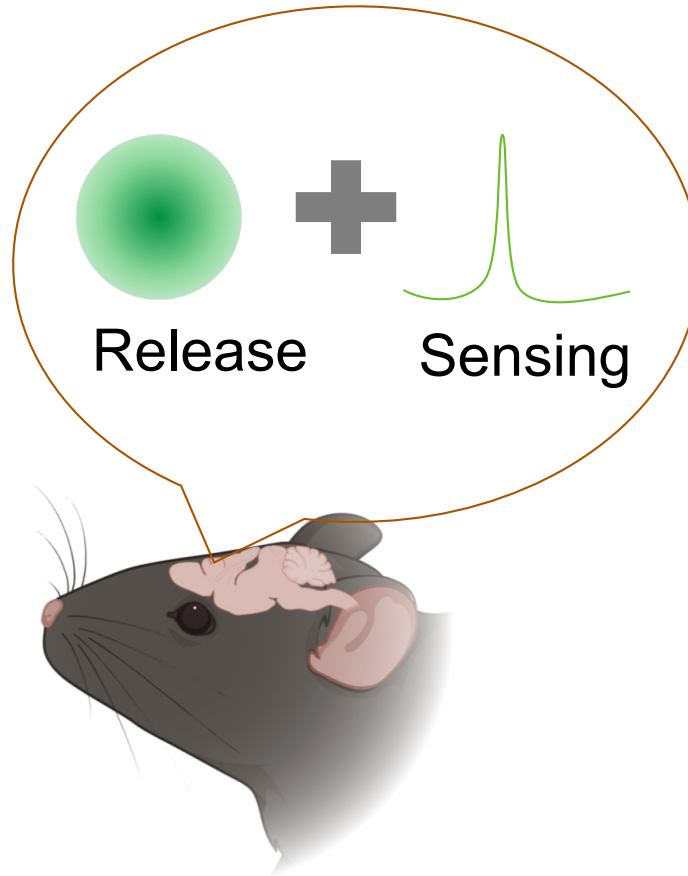
Banghart et al, *Neuron*, 2012

Optogenetic

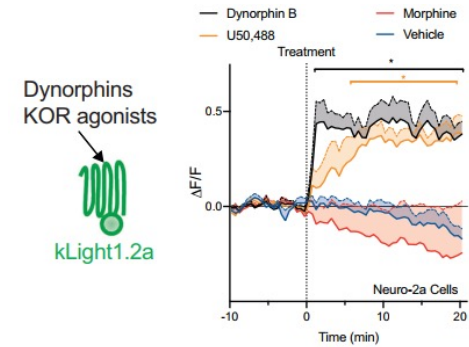


Opto-dialysis probe
Implant

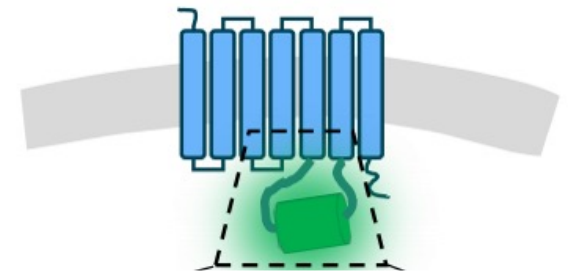
Al-Hasani et al, *eLife* 2018



Genetically encoded sensors

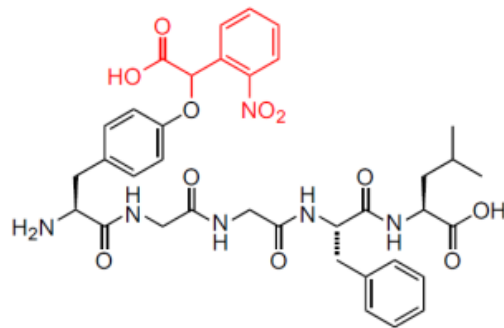


Abraham et al, *Neuropsychopharmacology* 2021

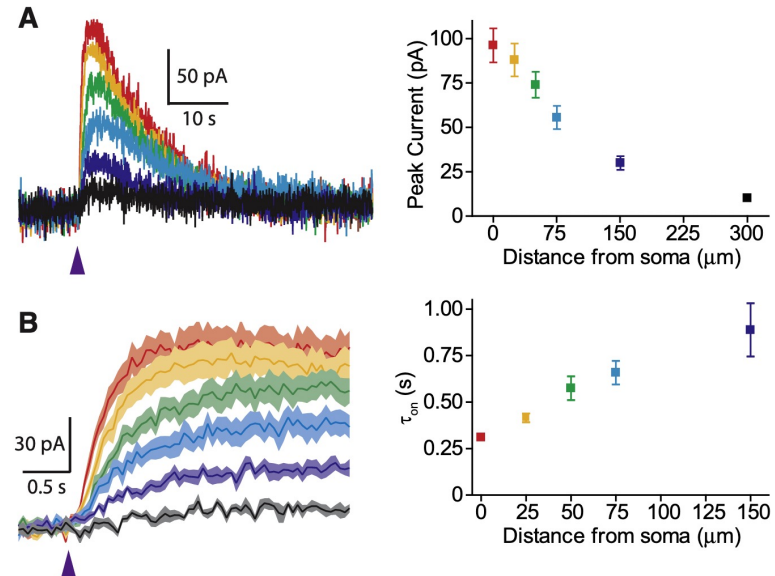


Wang et al, *BioRxiv* 2022

State-of-the-art: Caged Compounds



[Leu⁵]-enkephalin (LE)



Banghart et al. *Neuron*, 2012

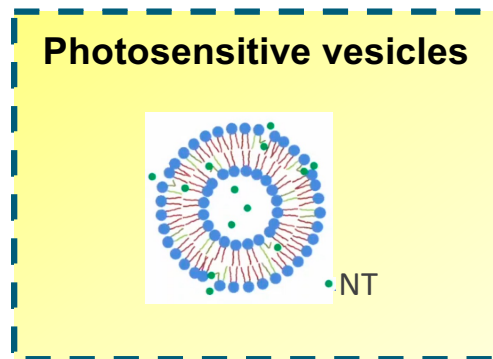
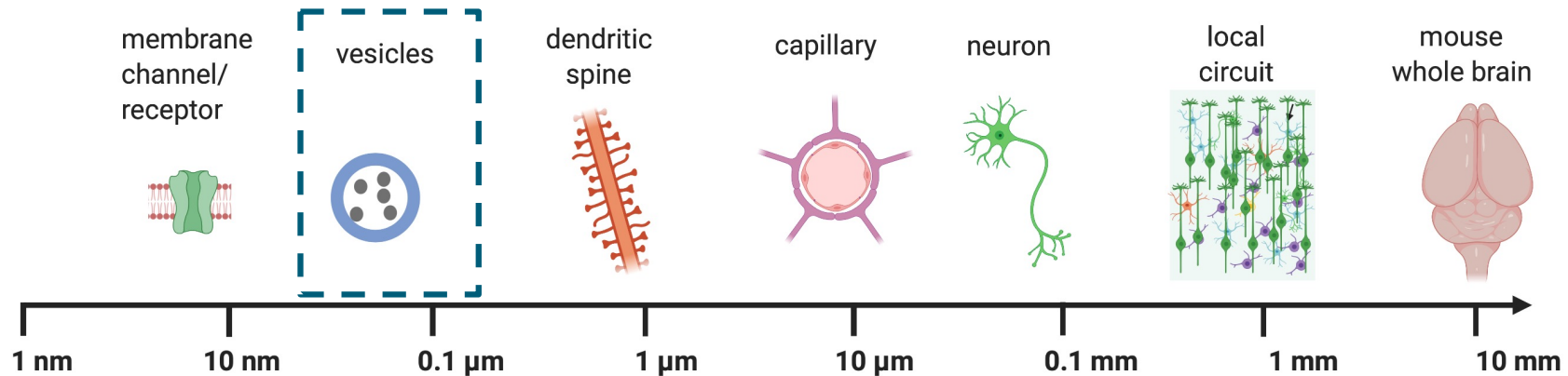
Challenges in caging molecules:

- Make one caged molecule at a time
- Peptides: proteolytic degradation
- UV excitation

Need

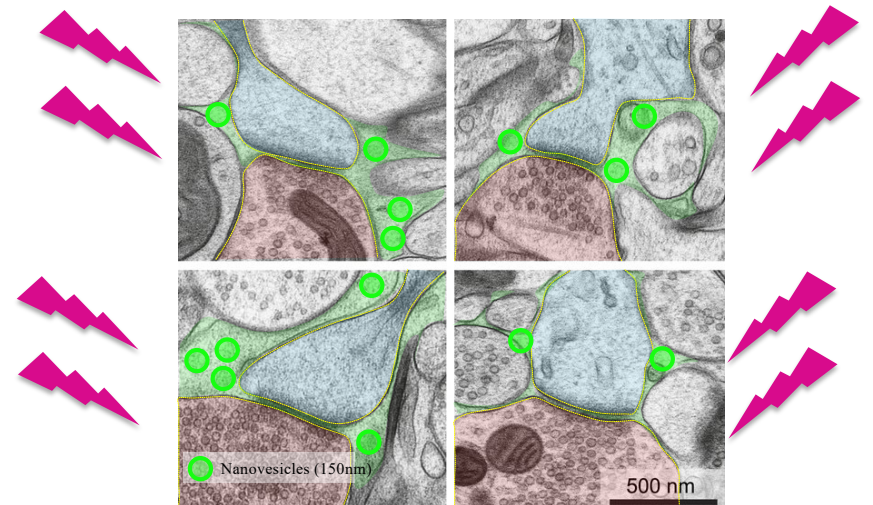
- Adaptable for many molecules
- Stable *in vivo*
- Near infrared, deep penetration

Concept: Develop photosensitive nanovesicles



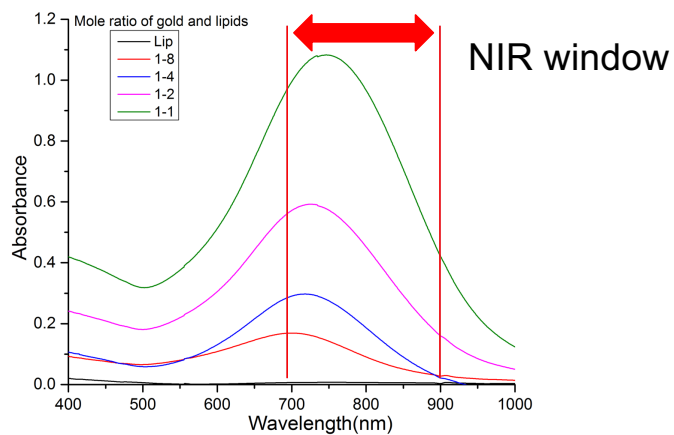
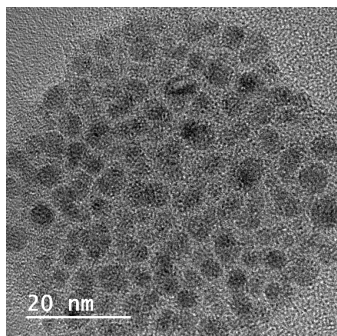
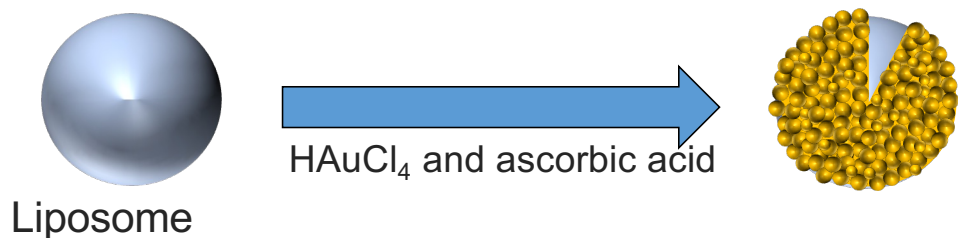
Matter. 2021

Mascaro et al. *J. Biomedical Optics* 2015, with modification
 Hong & Lieber, *Nat. Rev. Neuroscience* 2019

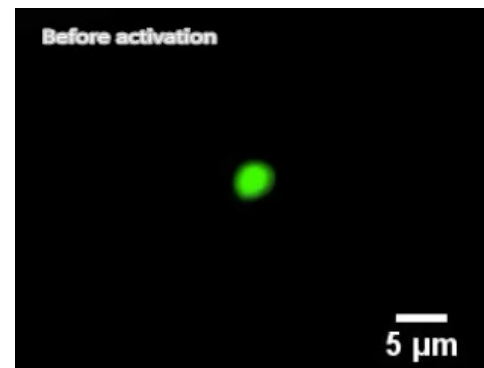
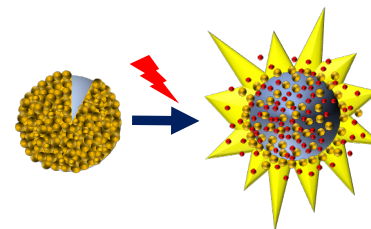


Gold-coated Nanovesicles Allows Rapid Release

Preparation and Near-Infrared Absorption



Millisecond photorelease
 10^3 faster than other systems (seconds)

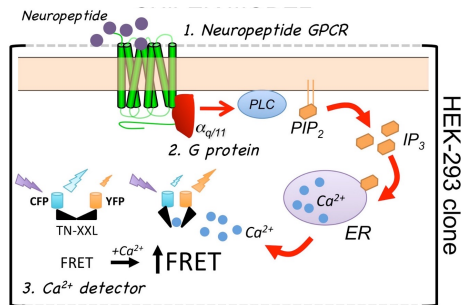


Xiuying Li

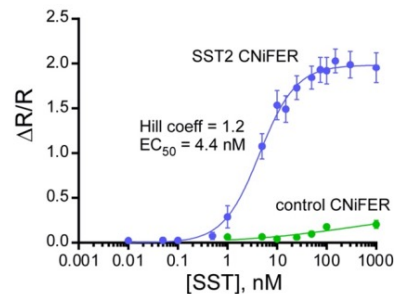
Neuropeptide Sensor: CNiFERs

CNiFERs (Cell-based Neurotransmitter Fluorescent Engineered Reporters)

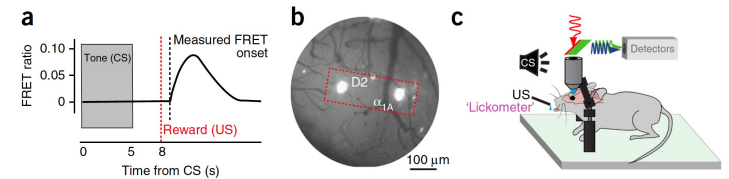
Cell-based sensor



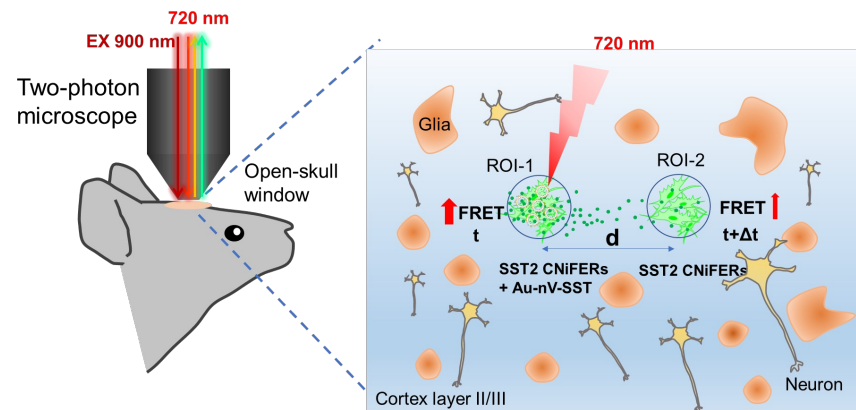
Nanomolar sensitivity



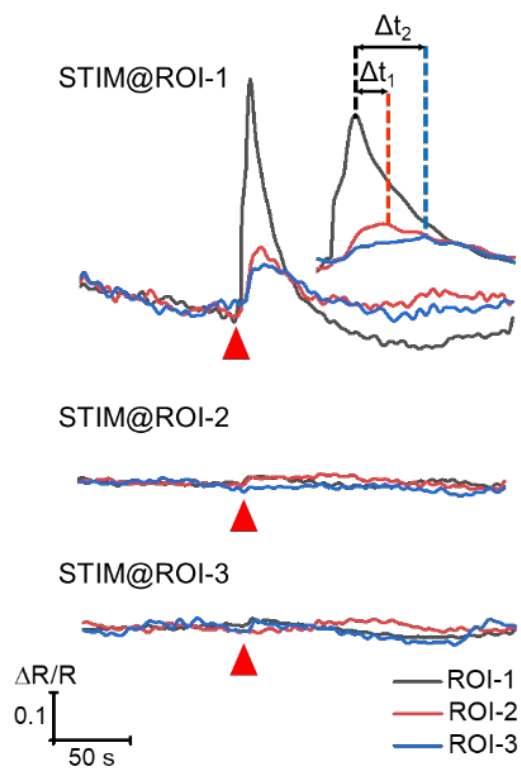
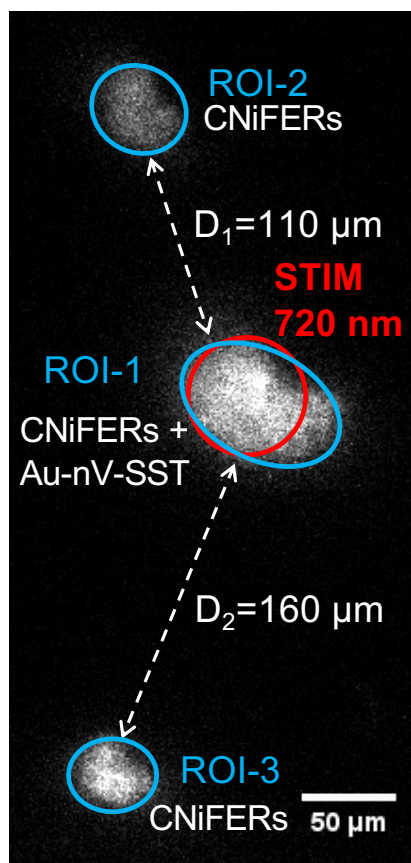
Detection of neurotransmitters in vivo



Monitoring neuropeptide diffusion *in vivo*

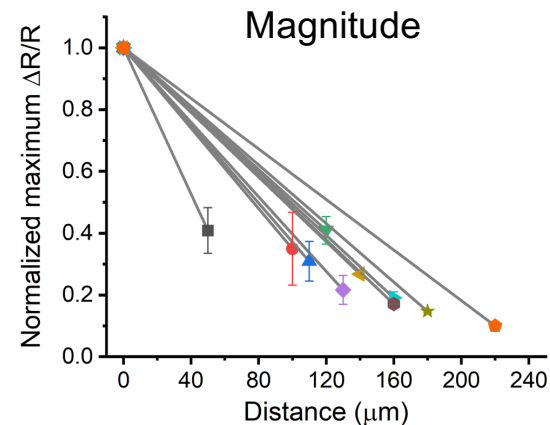
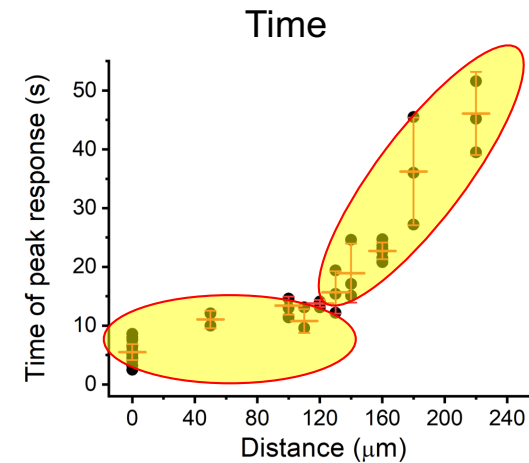
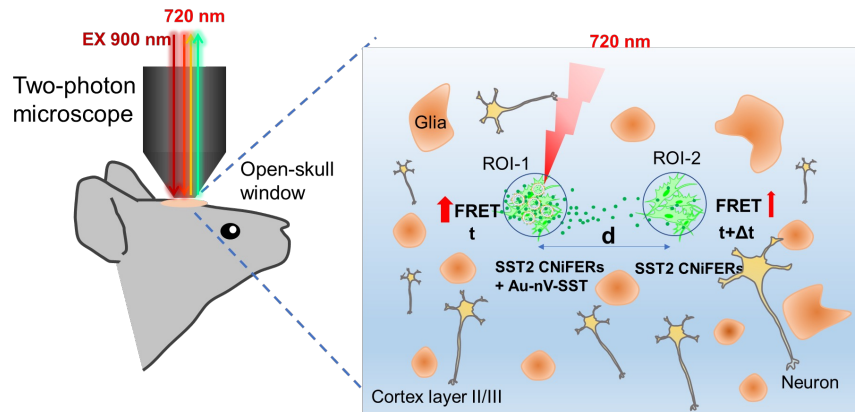


Monitoring neuropeptide diffusion *in vivo*



H. Xiong, ... P. A. Slesinger, Z. Qin, Probing Neuropeptide Volume Transmission In Vivo by Simultaneous Near-Infrared Light-Triggered Release and Optical Sensing. *Angewandte Chemie Int Ed.* 61, e202206122 (2022).

Monitoring neuropeptide diffusion *in vivo*

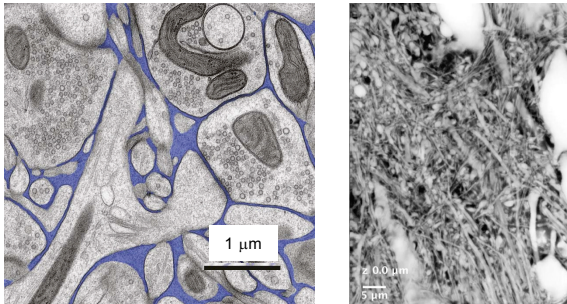


- Max transmission: 240 μm
- < 130 μm: reduced but synchronized SST transmission
- Longer distances: smaller and delayed transmission

H. Xiong, ... P. A. Slesinger, Z. Qin, Probing Neuropeptide Volume Transmission In Vivo by Simultaneous Near-Infrared Light-Triggered Release and Optical Sensing. *Angewandte Chemie Int Ed.* 61, e202206122 (2022).

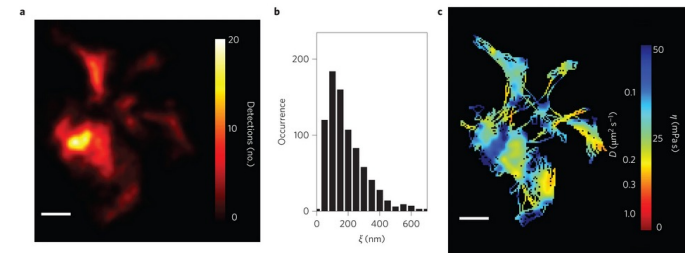
Neuromodulator Diffuse Through the Extracellular Space

Ultrastructure Imaging



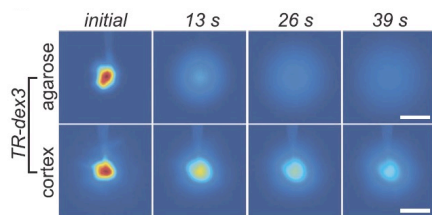
Korogod et al. *eLife*, 2015;
Nagerl et al. *Cell* 2018

Nanoparticle Tracking

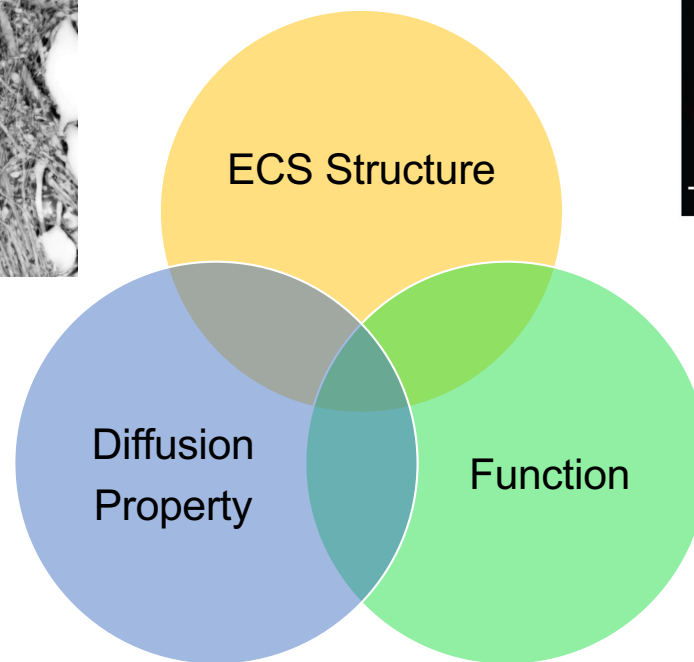


Cognet et al. *Nat Nanotechnol.* 2017

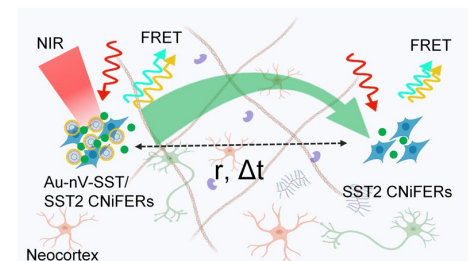
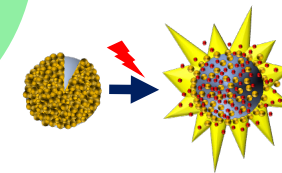
Dye Diffusion Measurement



Thorne et al. *PNAS* 2006



Distance and Time for Neuromodulation



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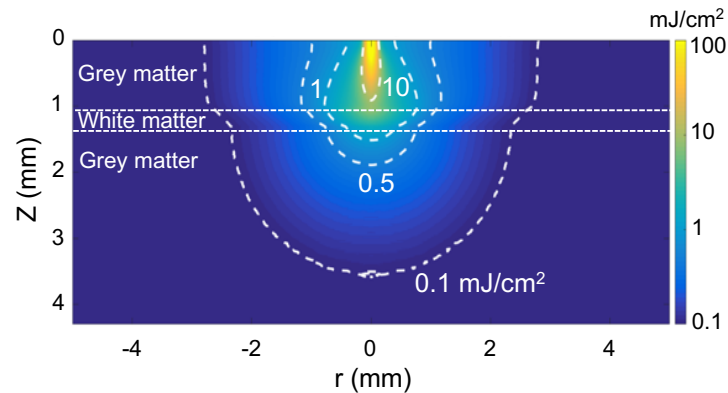
Reach Deep Brain Regions



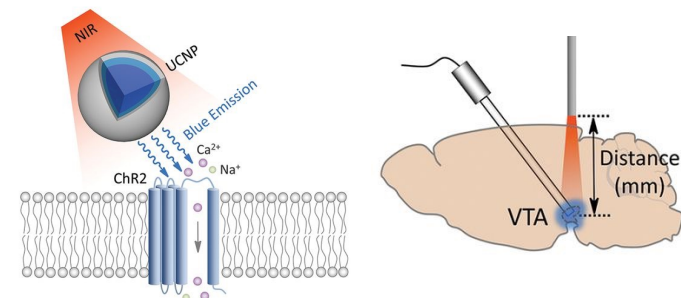
Hejian Xiong



Light attenuation in tissue



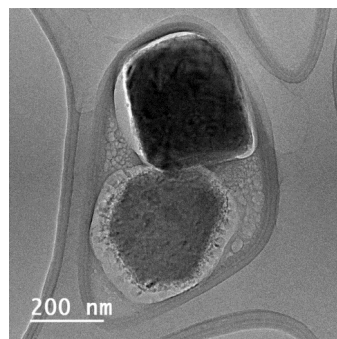
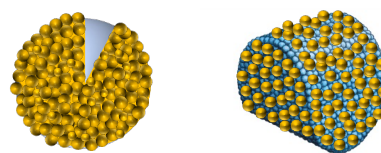
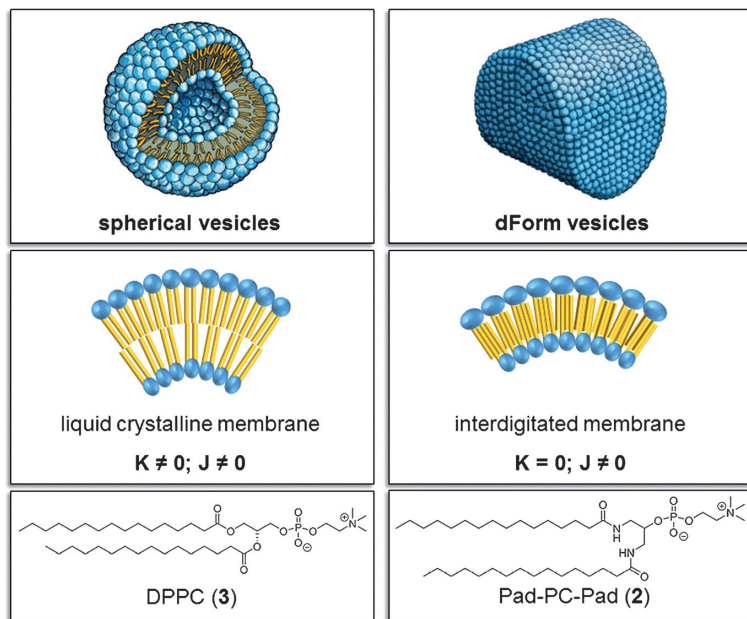
Upconversion nanoparticle mediated optogenetics



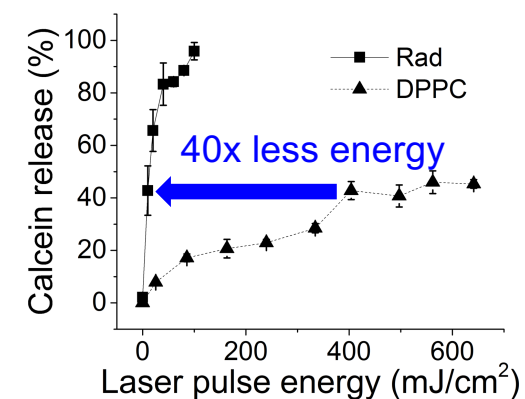
Chen et al. Science 2018

Question 2: engineer materials with high photosensitivity to reach deeper brain regions?

Mechanoresponsive Nanovesicles (m-nV)



High photosensitivity

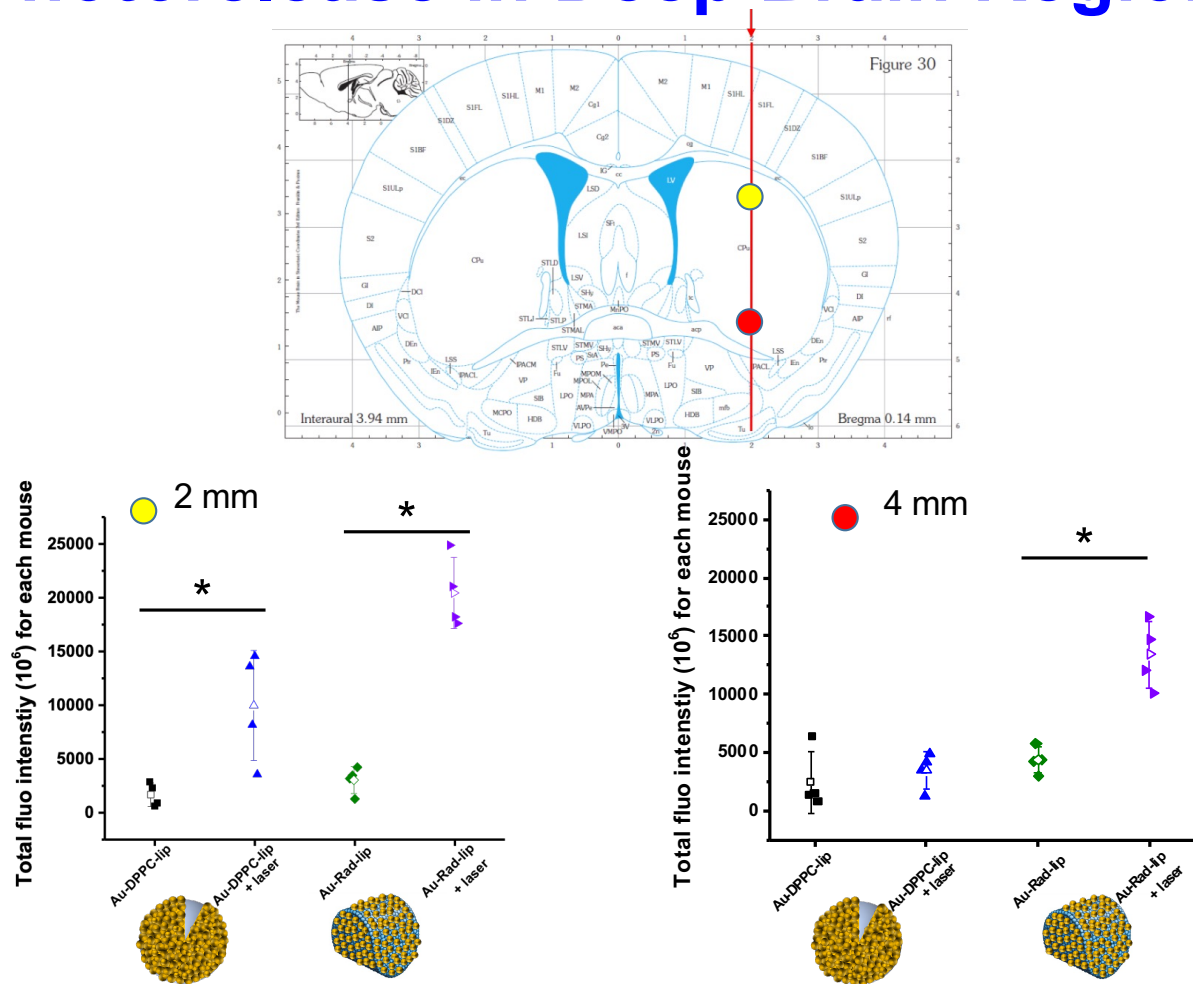


Zumbuehl group
Nat. Nanotechnol. 2012;
Angew. Chem. 2017

acthera

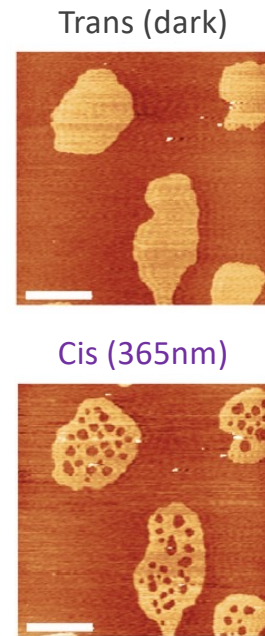
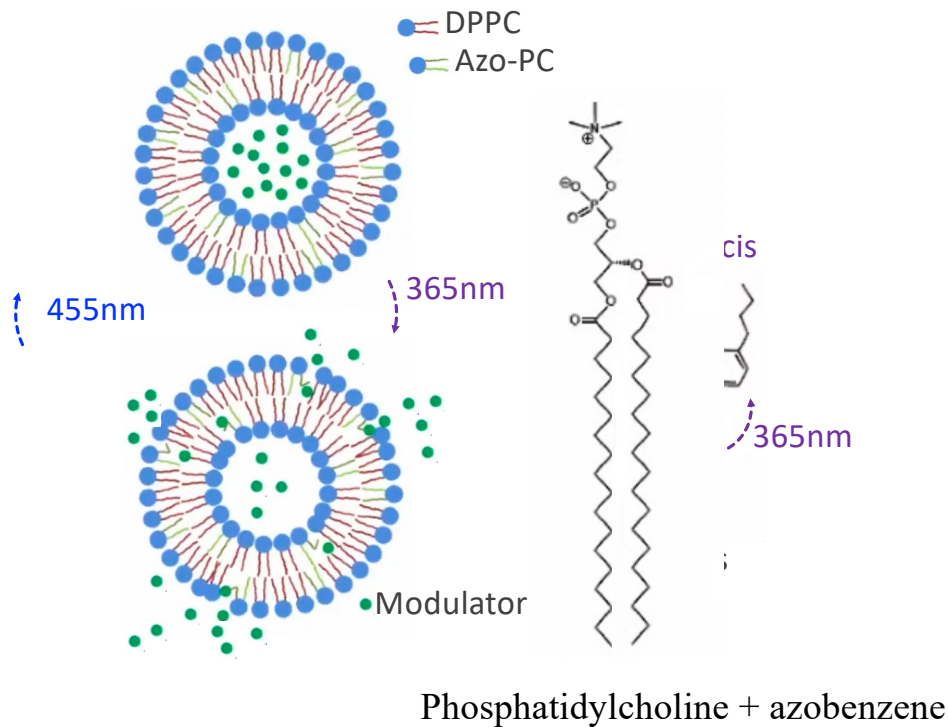
[H. Xiong, X. Li], ..., P. A. Slesinger, A. Zumbuehl, Z. Qin, Near-Infrared Light Triggered-Release in Deep Brain Regions Using Ultra-photosensitive Nanovesicles. *Angewandte Chemie Int Ed.* **59**, 8608–8615 (2020).

Photorelease in Deep Brain Regions



[H. Xiong, X. Li], ..., P. A. Slesinger, A. Zumbuehl, Z. Qin, Near-Infrared Light Triggered-Release in Deep Brain Regions Using Ultra-photosensitive Nanovesicles. **Angewandte Chemie Int Ed.** **59**, 8608–8615 (2020).

Azo-PC: Photo-switchable lipids



Kol et al., 2019



Prof. Dirk Trauner
(Penn)

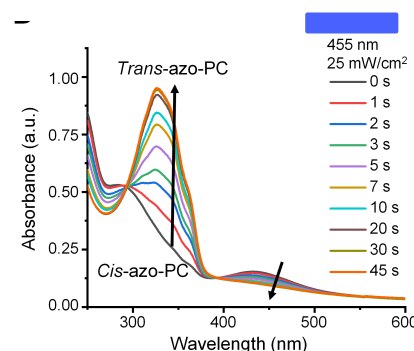
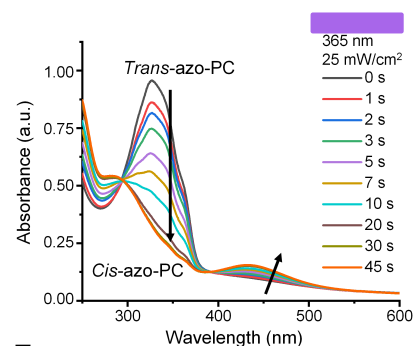
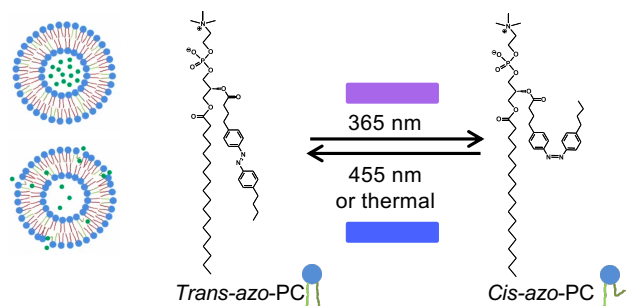


Johannes Morstein

- Protected contents

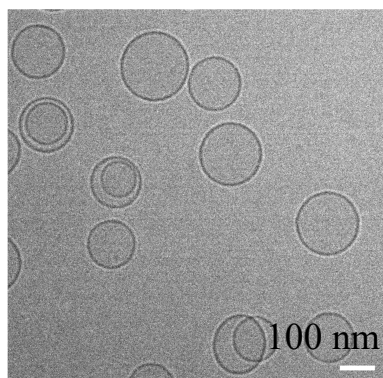
- Released contents

Properties of azo-PC vesicles

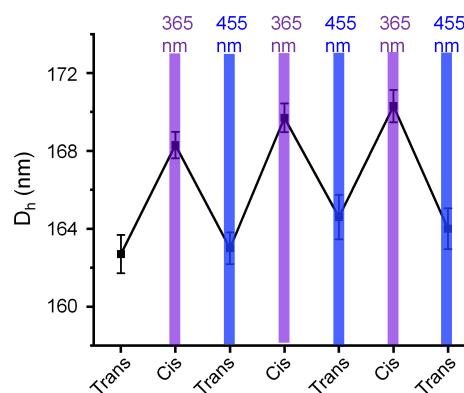


EM

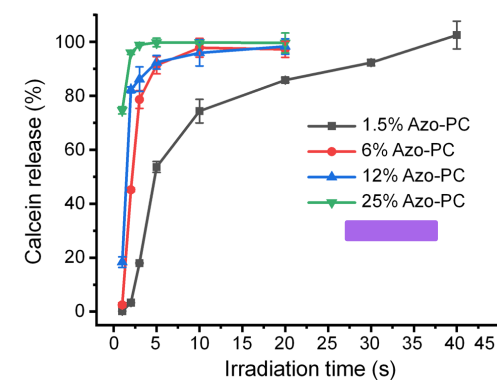
- Switchable / reversible
- ~150 nm size
- Change in volume
- [Azo-PC]



Δ volume



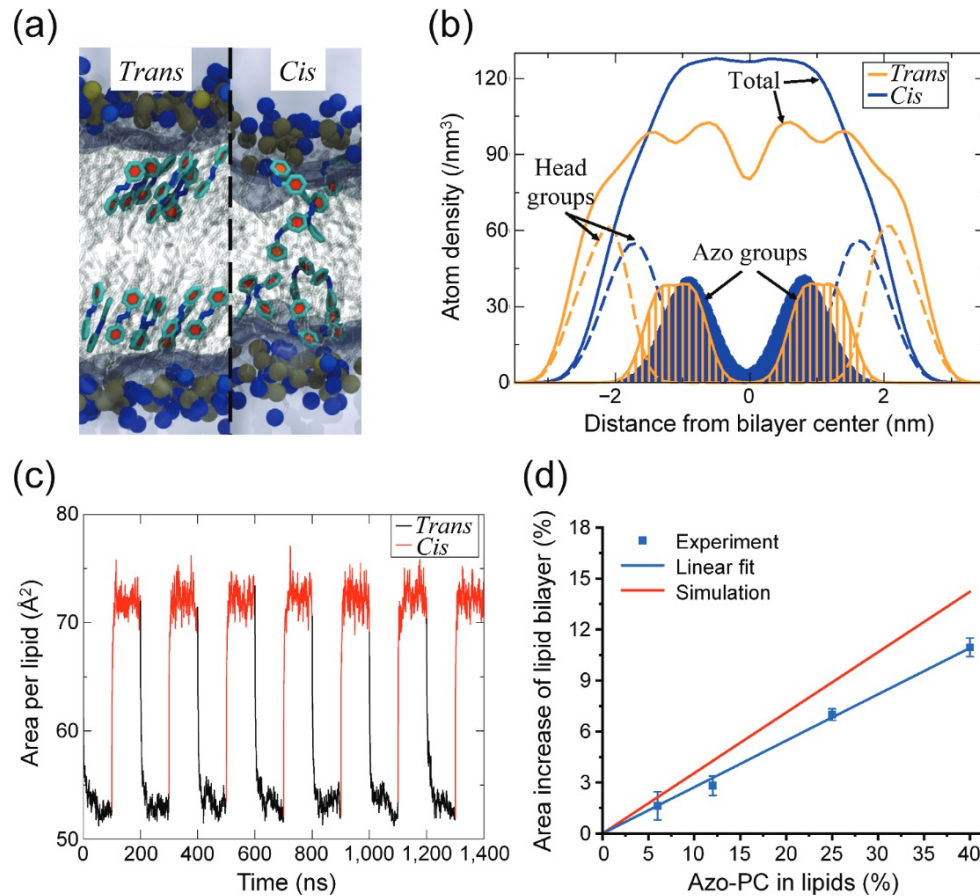
Δ Composition



Courtesy of Dr. Paul Slesinger

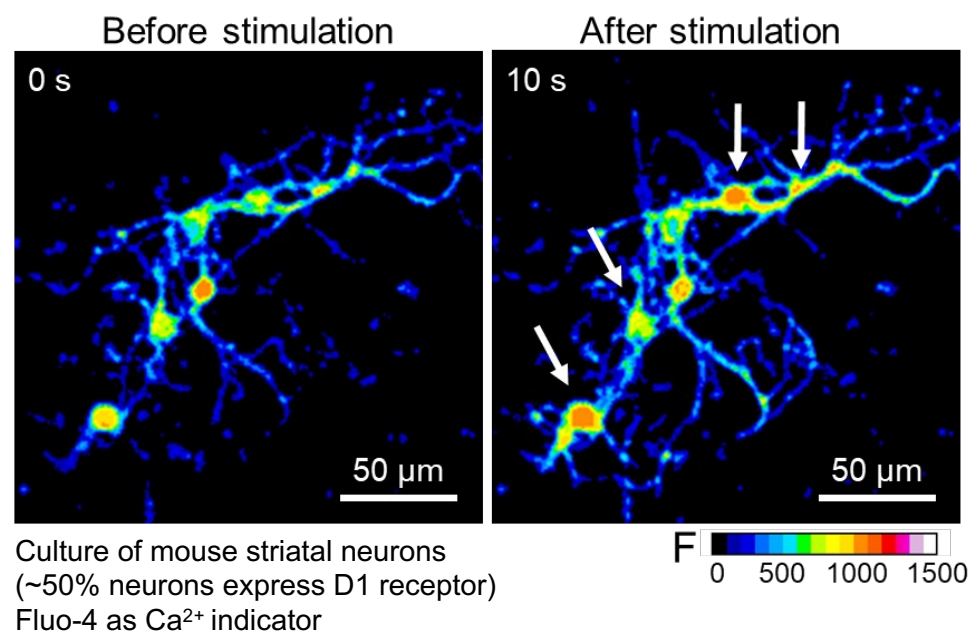
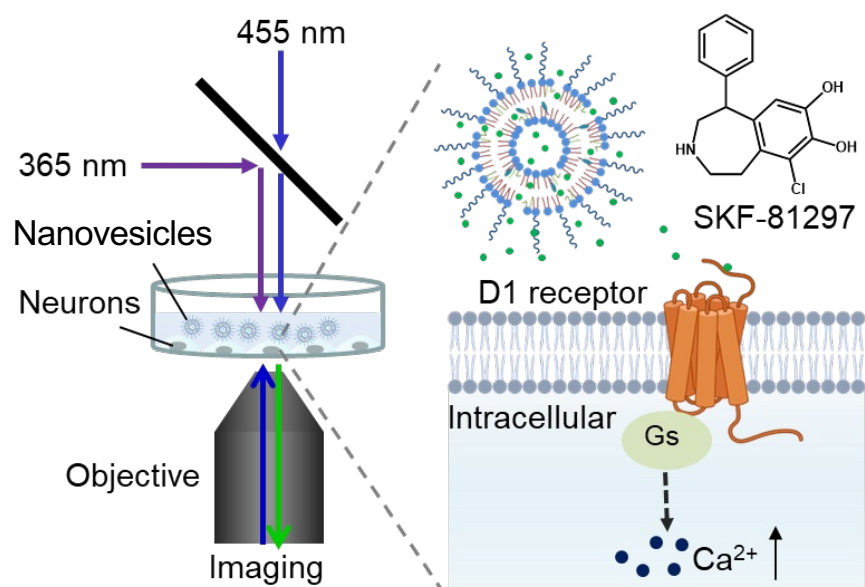
H. Xiong, K. A. Alberto, J. Youn, J. Taura, J. Morstein, X. Li, Y. Wang, D. Trauner, P. A. Slesinger, S. O. Nielsen, Z. Qin, Optical control of neuronal activities with photoswitchable nanovesicles. **Nano Res**, 1–9 (2022).

Photoswitchable Release: Bilayer Thickness Changes



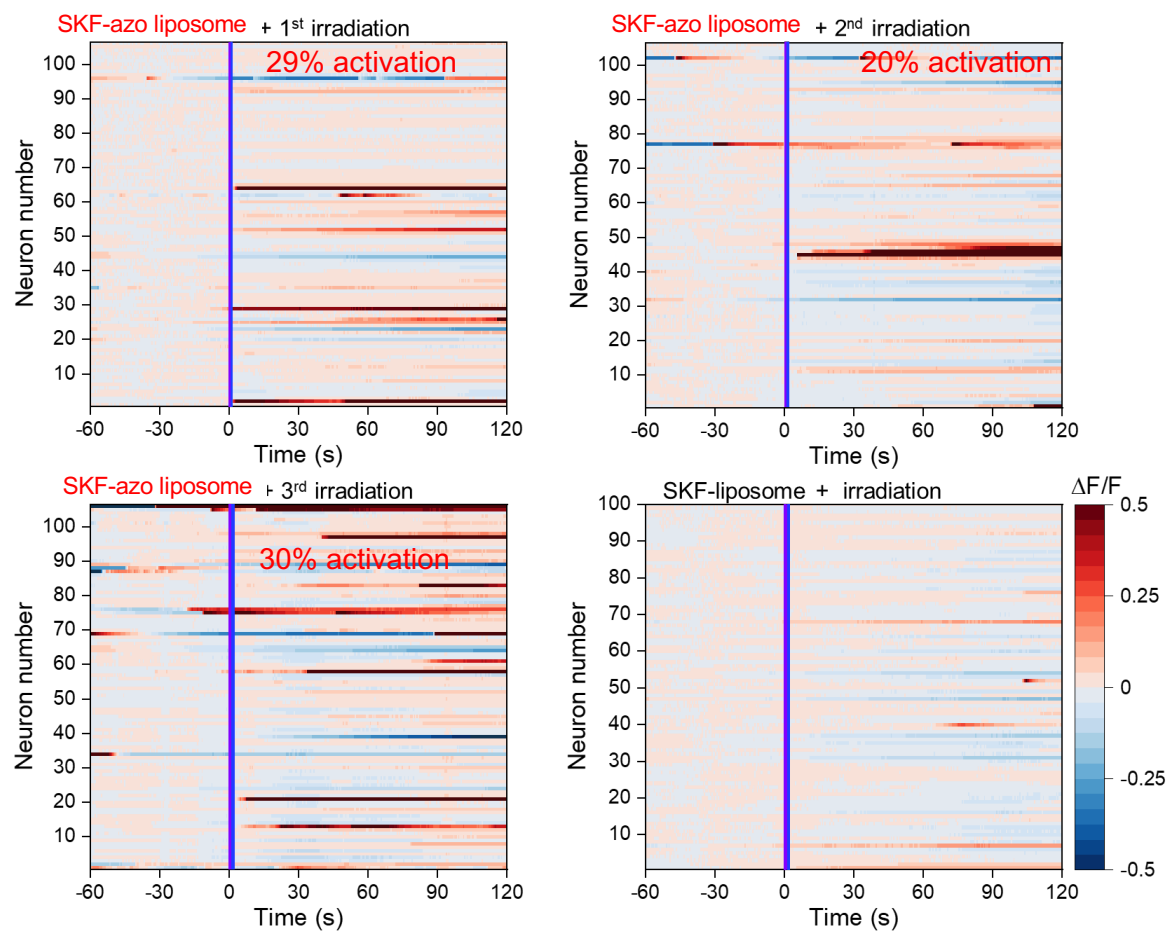
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In vitro neuromodulation



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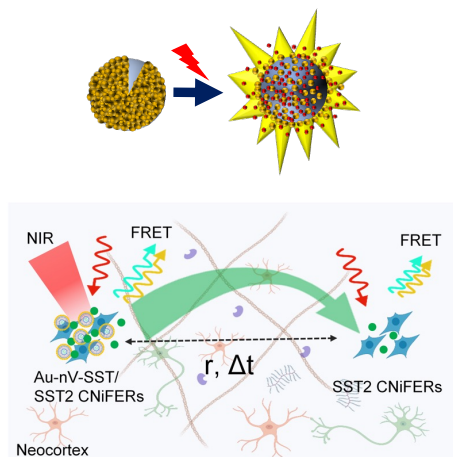
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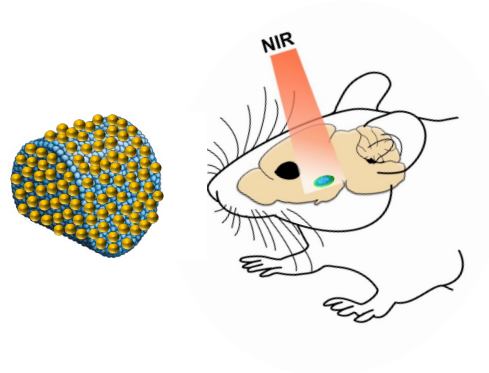
Take home messages

Distance and Time for Neuromodulation



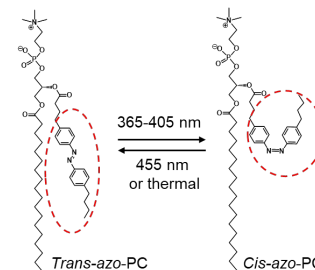
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Reach deep brain regions



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Photoswitchable vesicles



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Acknowledgement



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Hejian Xiong



NanoBrain Lab

Collaborators:



Prof. Paul A. Slesinger
(Mt Sinai)



Prof. Dirk Trauner
(Penn)



Dr. Andreas Zumbuehl
(Acthera Therapeutics)



Phospholipid Research Center