

Recent Advances in the Use of Phospholipid Excipients

Workshop organized by the
Phospholipid Research Center Heidelberg/Germany



INTEGRATING
Delivery Science
ACROSS DISCIPLINES



Radiocontrolled Drug Delivery with High-Z Element-functionalized liposomes

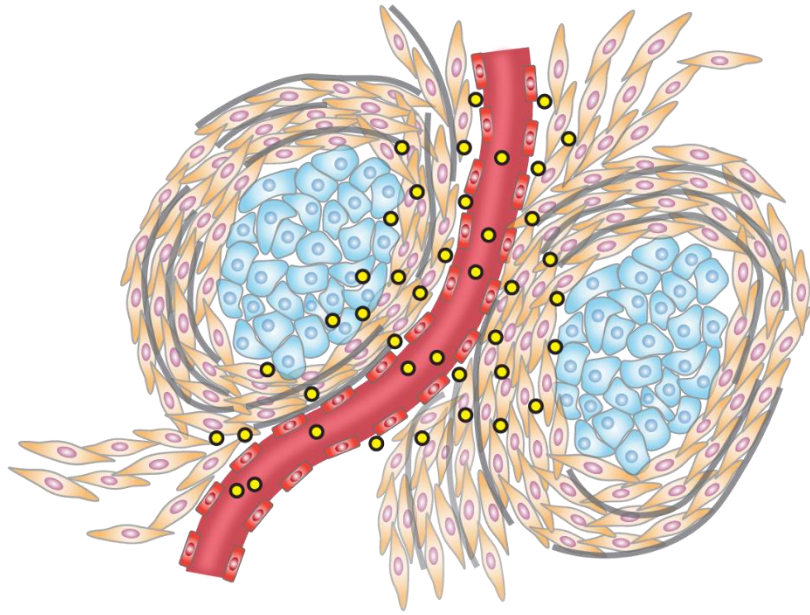
Mans Broekgaarden

Tenured Principal Investigator

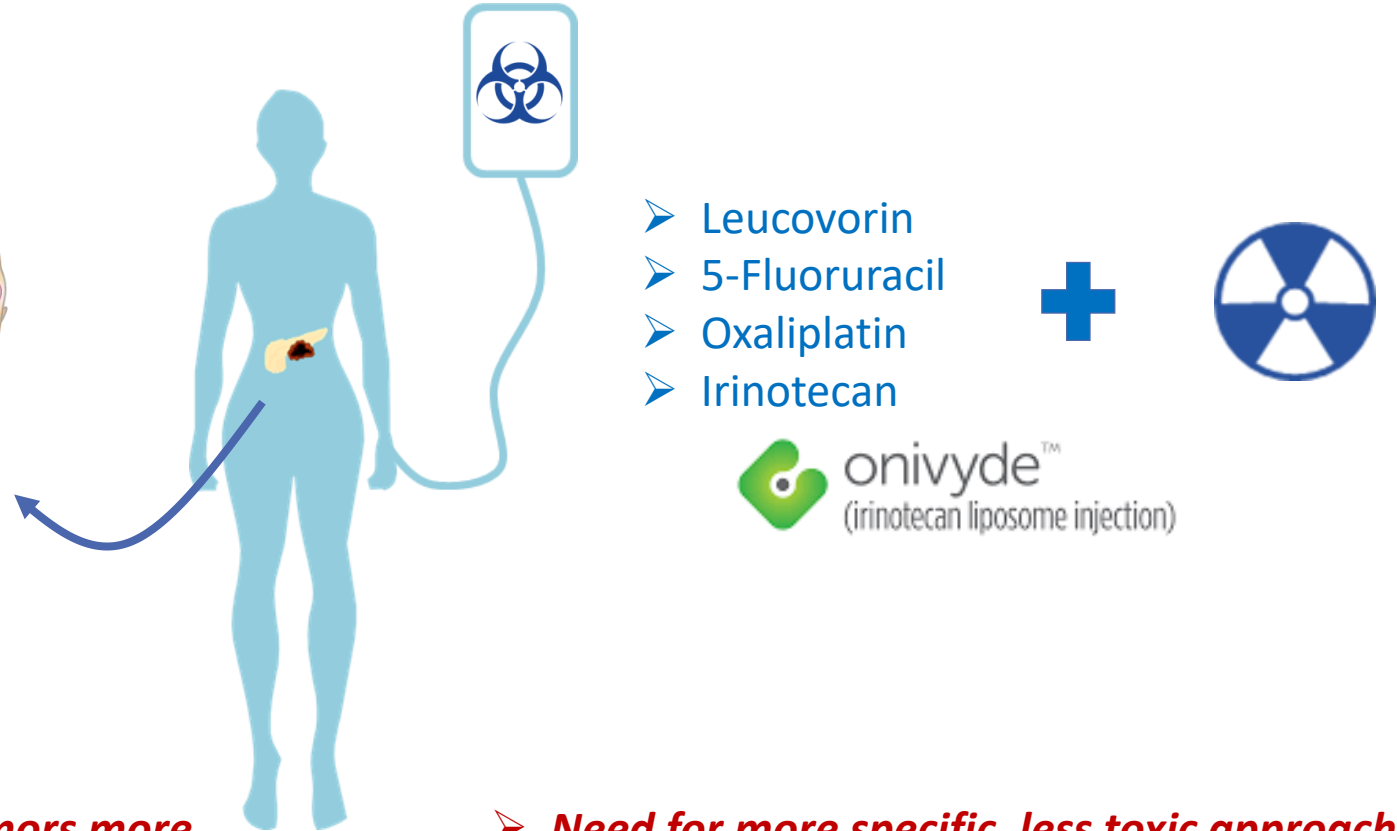
Board member Controlled Release Society: France & BeNeLux local chapter

THE PROTECTIVE CANCER STROMA

Nearly impenetrable stroma



High dose chemoradiotherapy



- Leucovorin
- 5-Fluoruracil
- Oxaliplatin
- Irinotecan

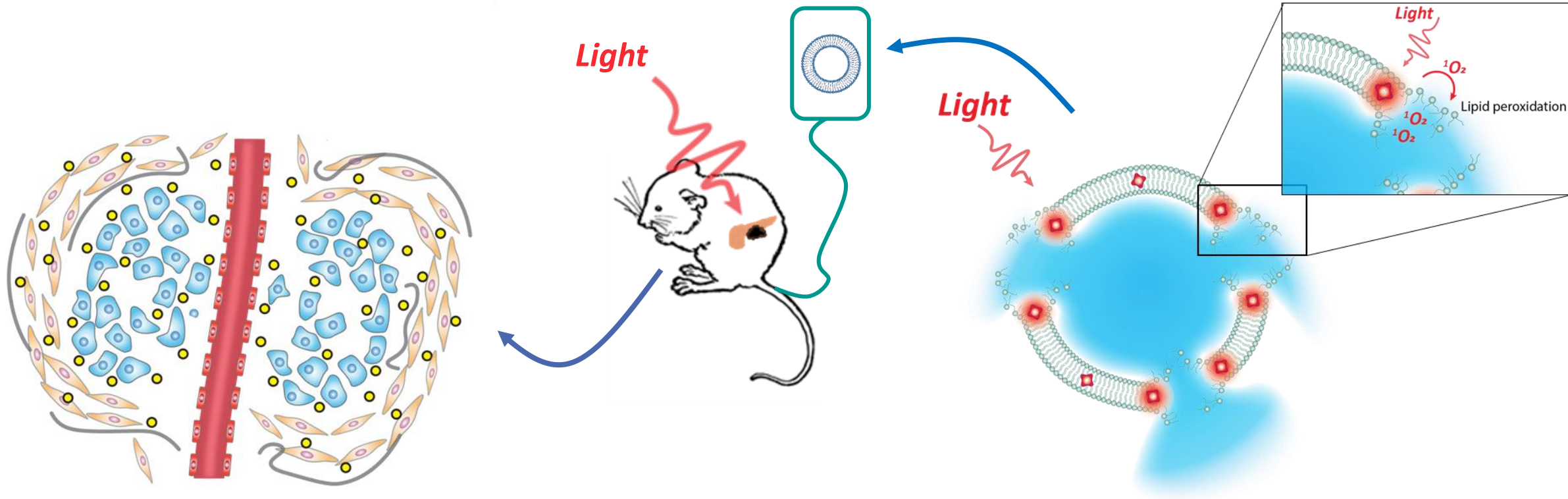
 **onivyde™**
(irinotecan liposome injection)

➤ ***Need for new approaches to make tumors more accessible to treatment***

➤ ***Need for more specific, less toxic approaches***

Adisheshaiah et al Nat Rev Clin Oncol 2016
Hosein et al., Nat Rev Gastroenterol Hepatol 2020

LIGHT-CONTROLLED DRUG RELEASE



Increased tumor permeability

Spring... Hasan, Nat Nanotechnol 2016

Huang...Hasan, Cancer Res 2018

Obaid...Broekgaarden...Hasan, Nano Lett 2019

Drug delivery at the right place

Lovell et al., Nat Mat 2011

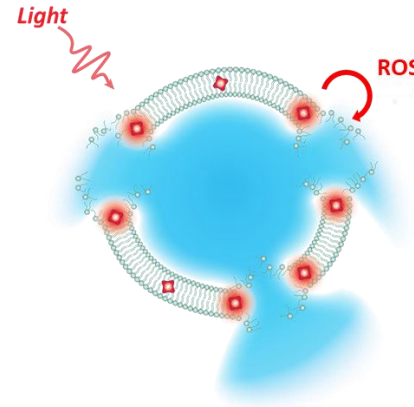
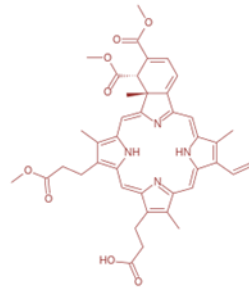
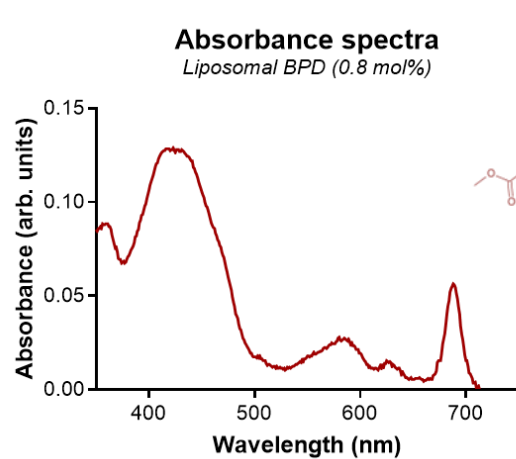
Broekgaarden et al., Curr Med Chem 2014

Luo...Lovell Small & Biomaterials 2017

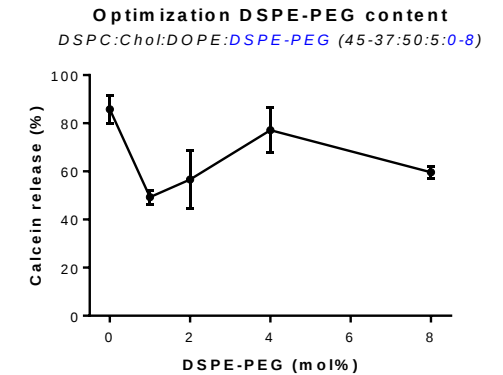
Engineering oxidation-responsive liposomes (OXILs)



Dr. Tristan
LE CLAINCHE

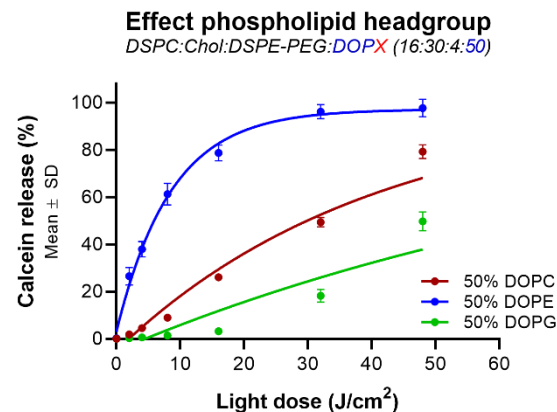


>40 formulations tested

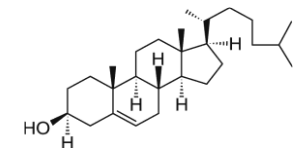
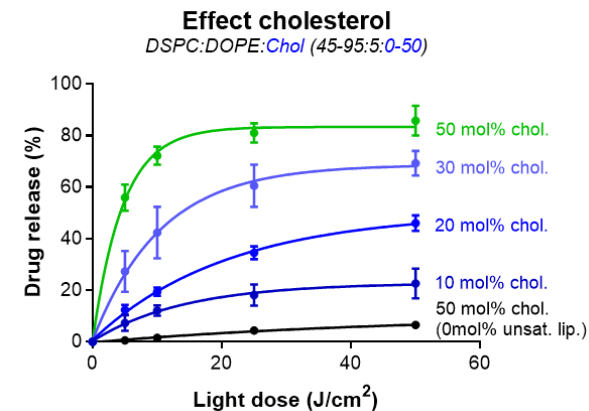


✓ Optimal release using 4mol% DSPE-PEG

✓ BPD included at 0.8 mol%
(Quenching at higher concentrations)



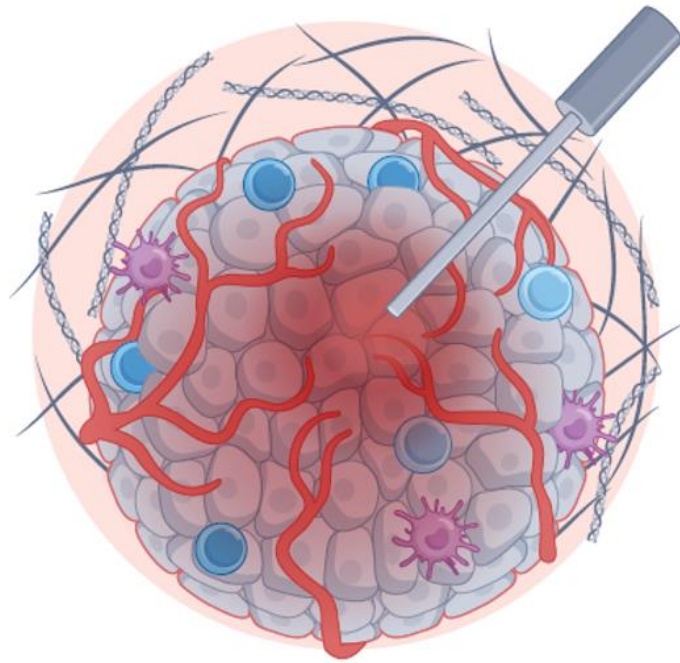
✓ Strong influence phospholipid headgroup
Less is better: 5 mol% suffices



✓ Essential role for cholesterol
Similar membrane insertion as BPD

Increasing tumor permeability

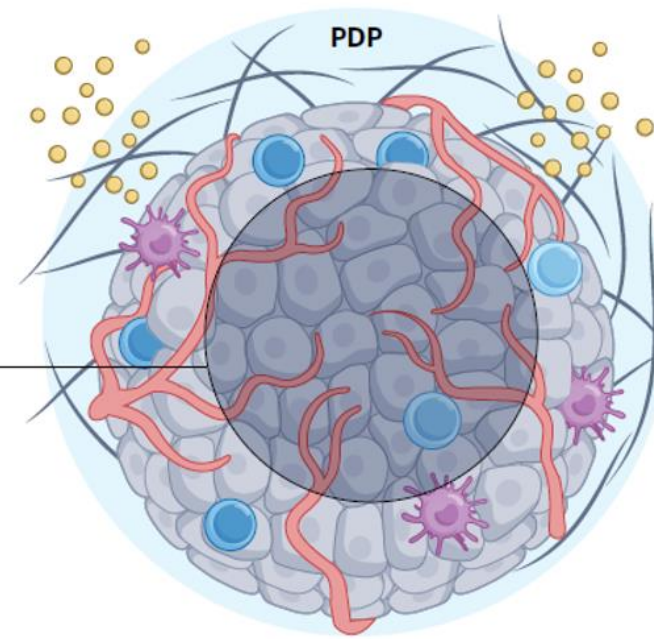
“Photodynamic Priming”



PDT

Light fluence reduces exponentially with depth, creating an acute death zone (up to 15–20 mm in diameter)

- Tumour cell death
- Vascular damage



PDP (a finite priming volume that extends beyond the PDT death zone)

- Vascular permeabilization
- Stroma loosening
- Drug transporter inhibition
- Chemoresistance mitigation
- Cytokine release
- Increase in DAMPs
- Fibroblast-associated cytokine suppression

Combine with adjuvant treatment(s) (e.g., chemotherapy, RTKi, ICI)

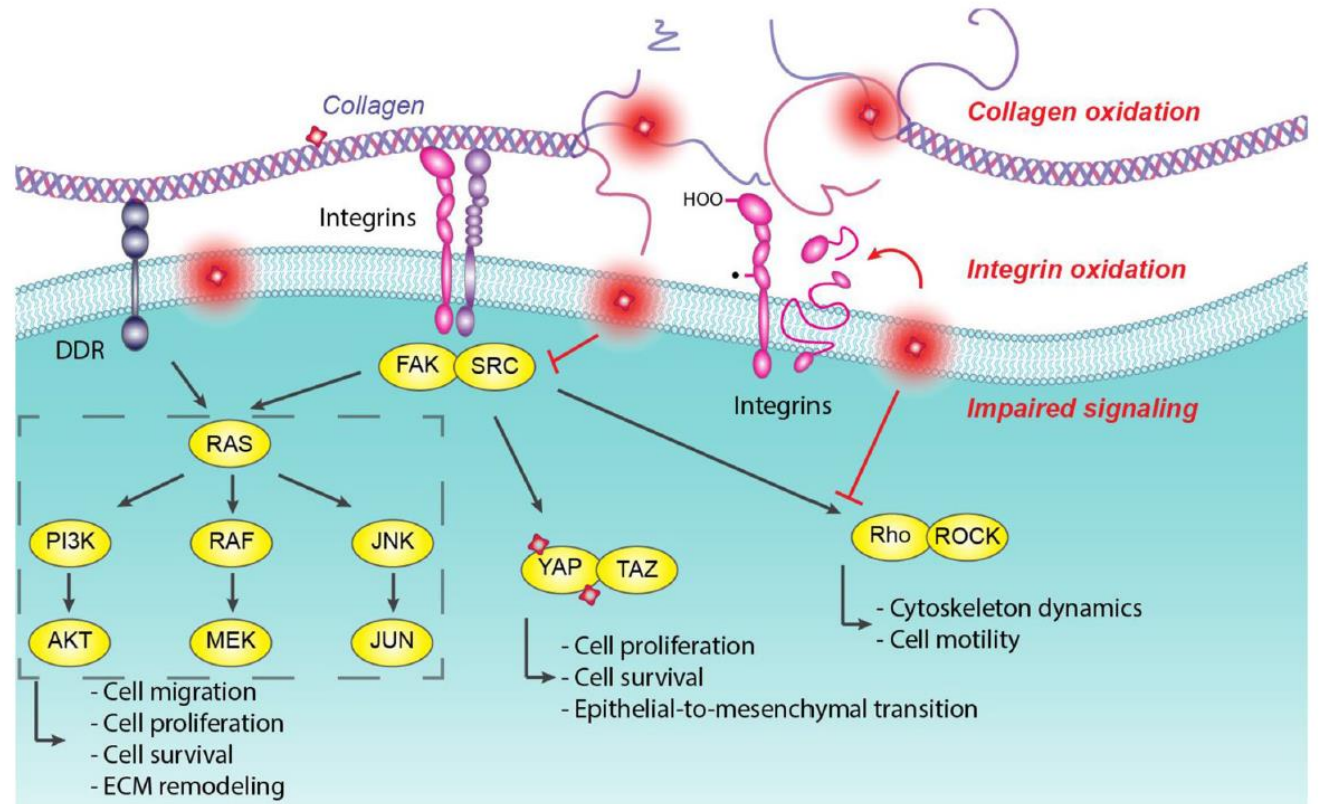
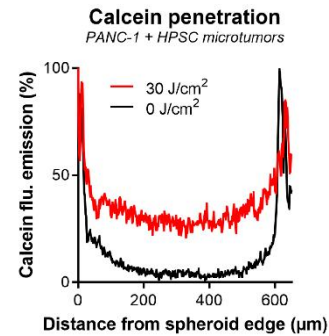
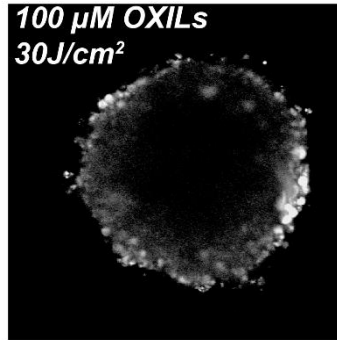
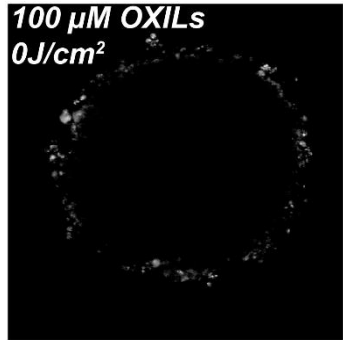
- Local tumour destruction
- Anti-metastatic effects

Obaid G., Broekgaarden M., Hasan T. *Nano Lett* 2019

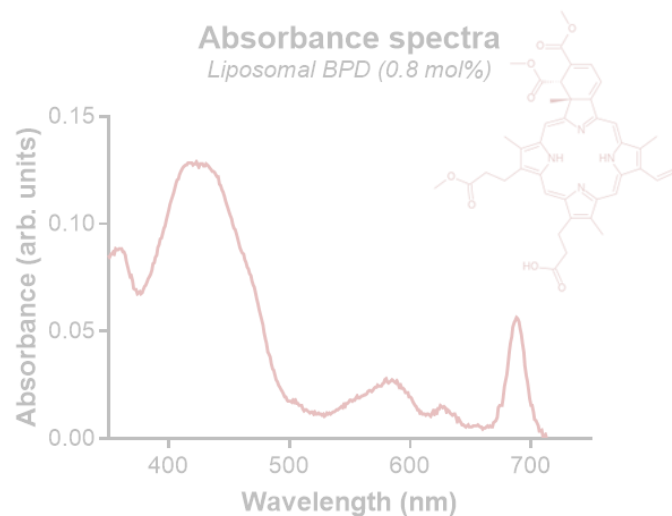
Obaid G, Celli JP, Broekgaarden M, Bulin AL, Uusimaa P, Pogue B, Hasan T, Huang HC. *Nat Rev Bioeng* 2024

Increasing tumor permeability

“Photodynamic Priming”



FROM LIGHT TO X-RAYS

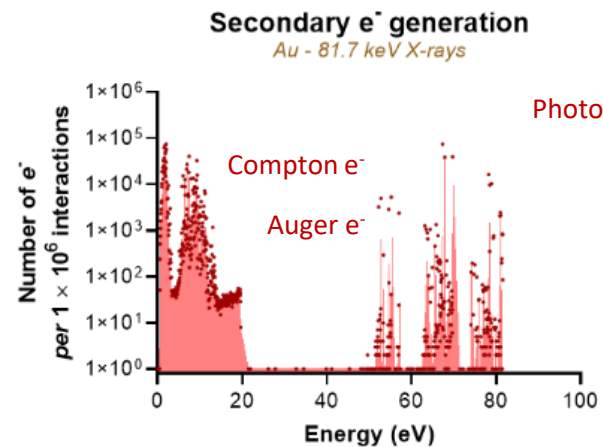
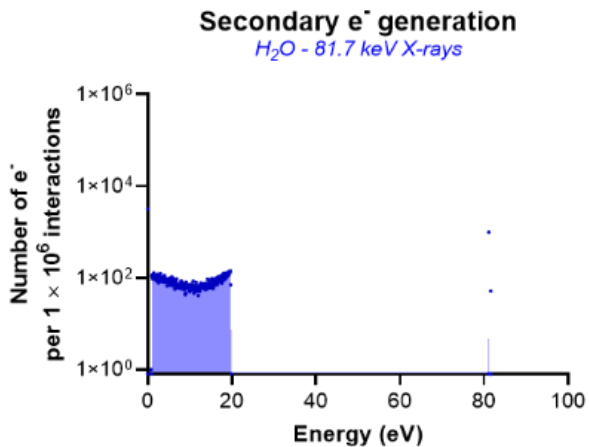
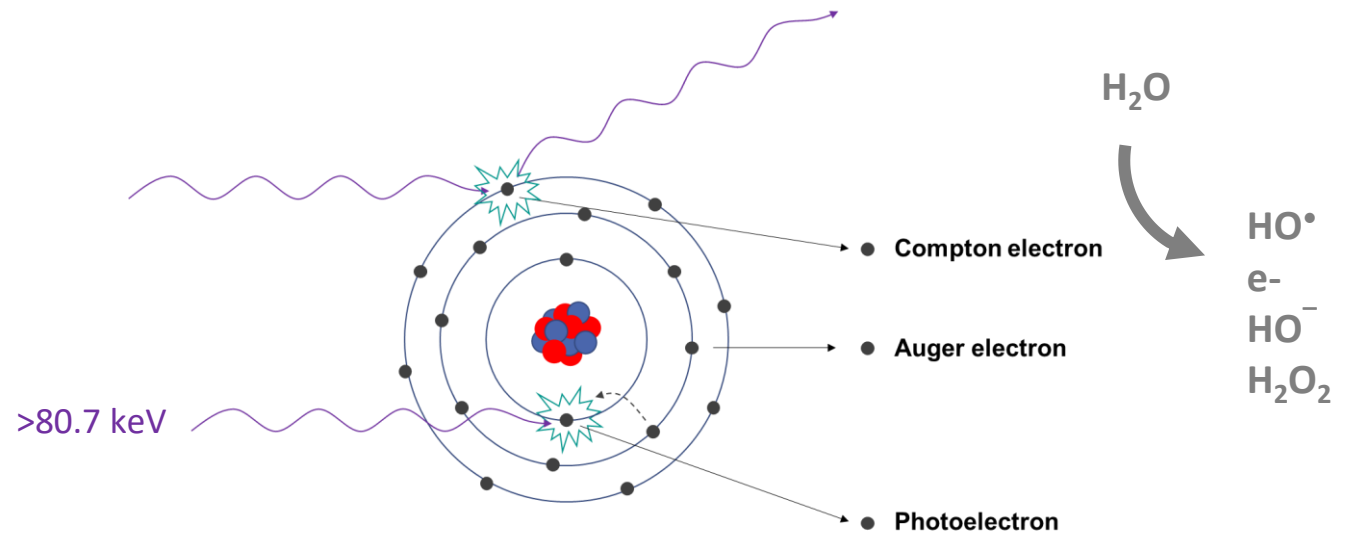
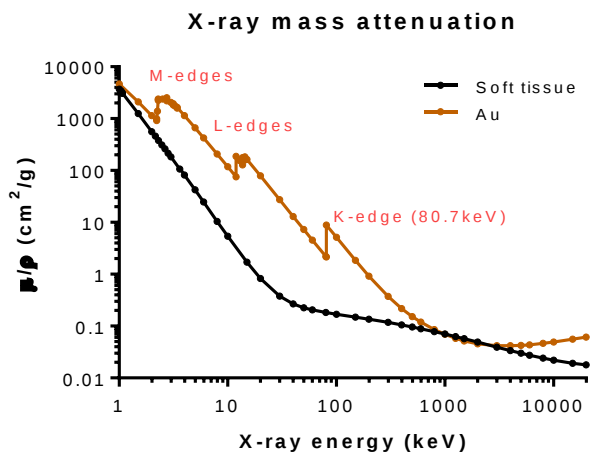




Collab. Anne-Laure BULIN

The Radiation Dose-Enhancement effect

by high-Z elements





Collab. Xavier
LE GUEVEL

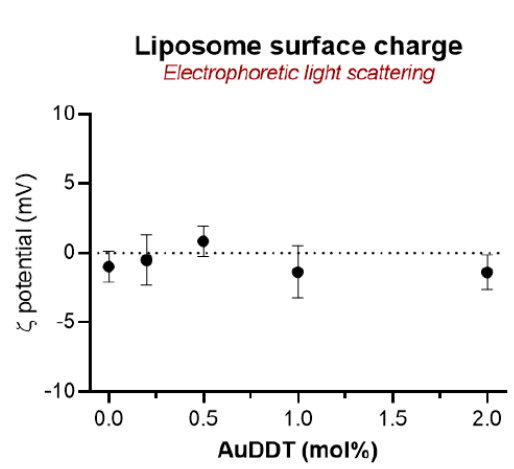
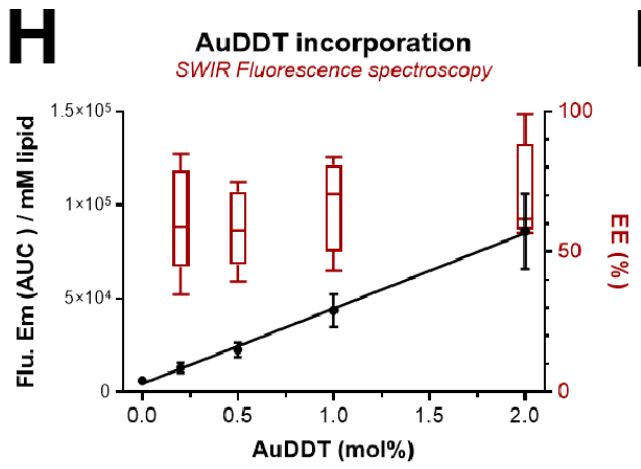
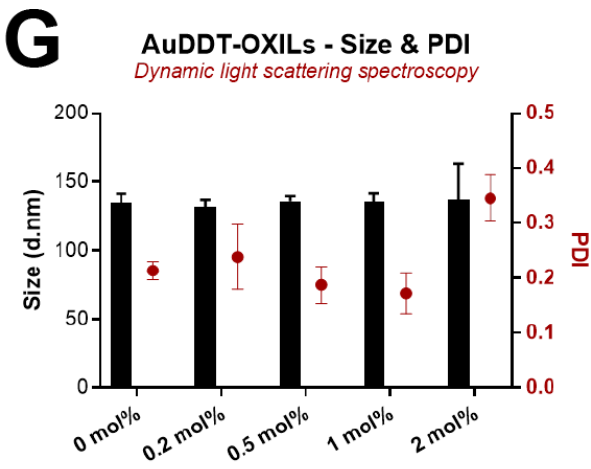
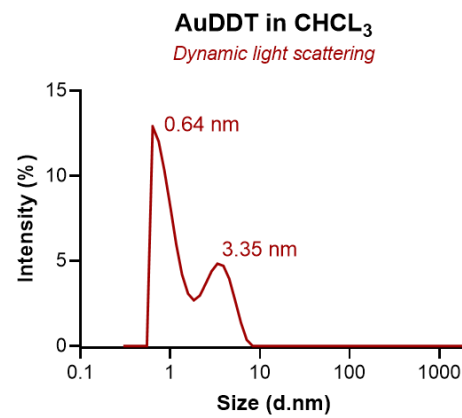
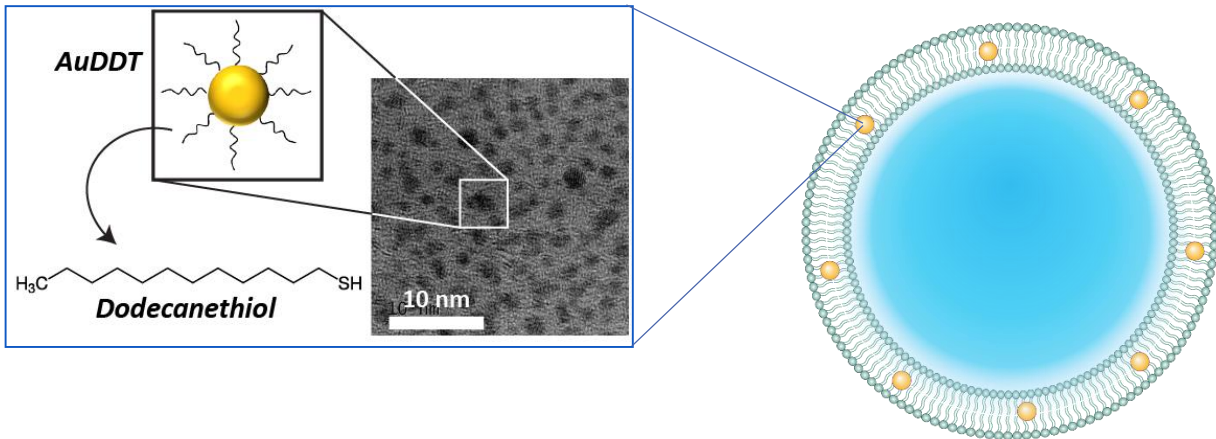
Functionalizing OXILs with high-Z elements



Dr. Tristan
LE CLAINCHE



Nazareth
CARIGGA



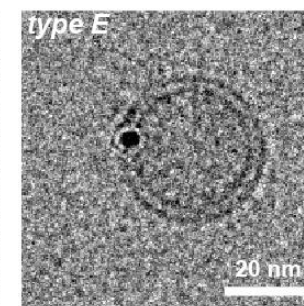
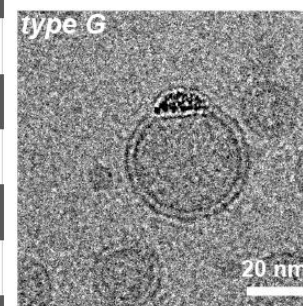
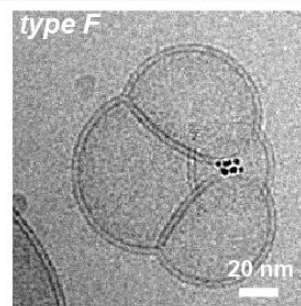
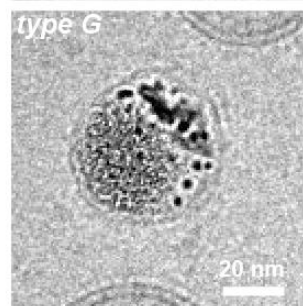
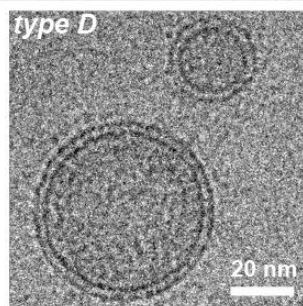
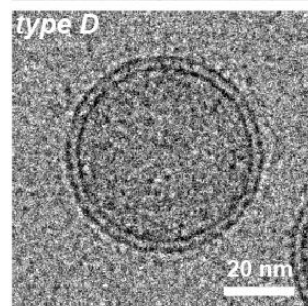
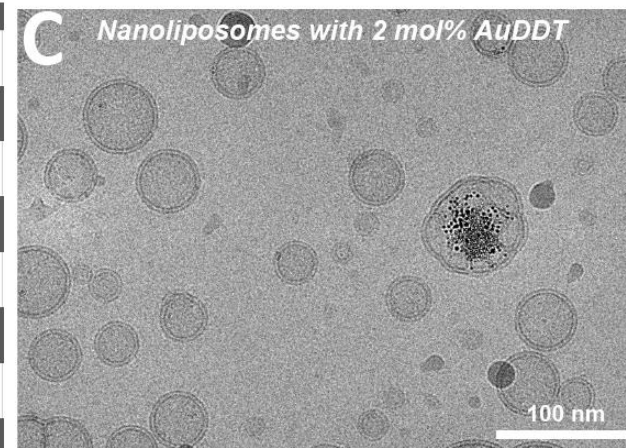
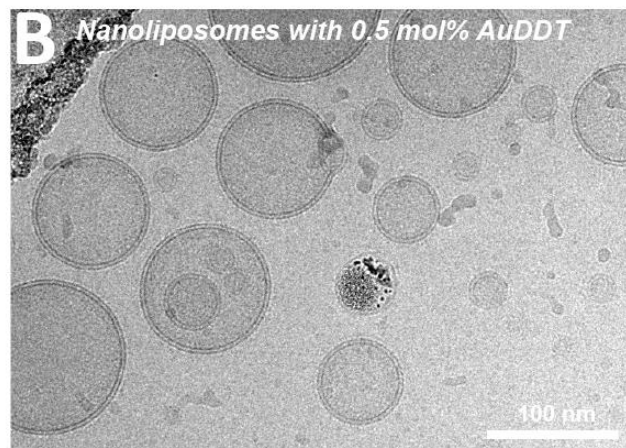
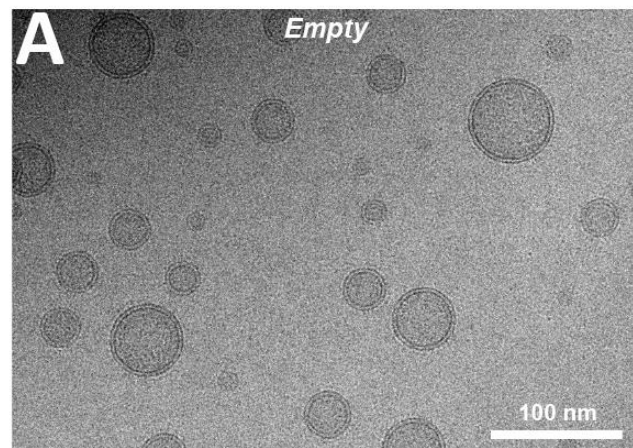
Cryo-TEM



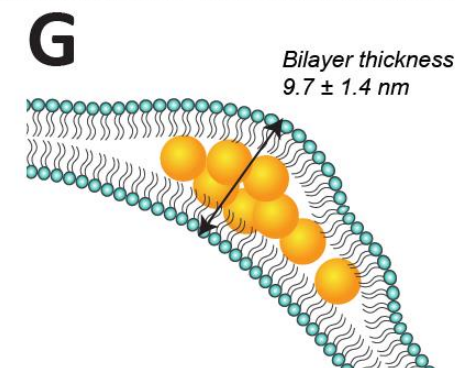
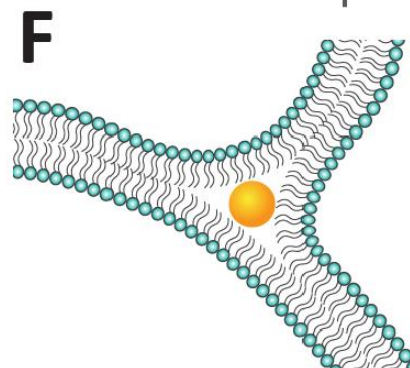
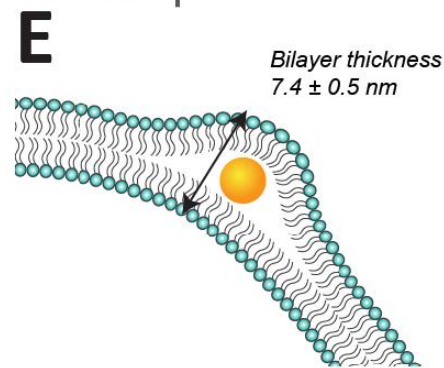
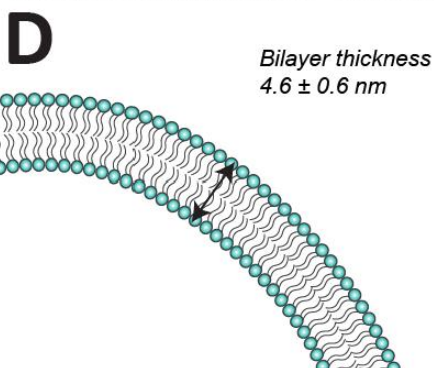
Collab. Isai
KANDIAH ESRF



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- ✓ AuDDT in lipid bilayer
- ✓ Aggregations
- × Liposome instability >0.5 mol%





Collab. Helene
ELLEAUME



Collab. Anne-
Laure BULIN

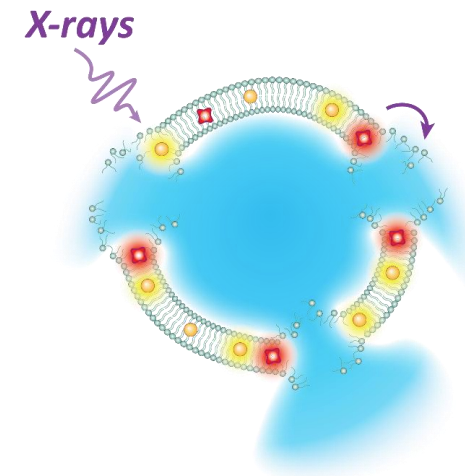
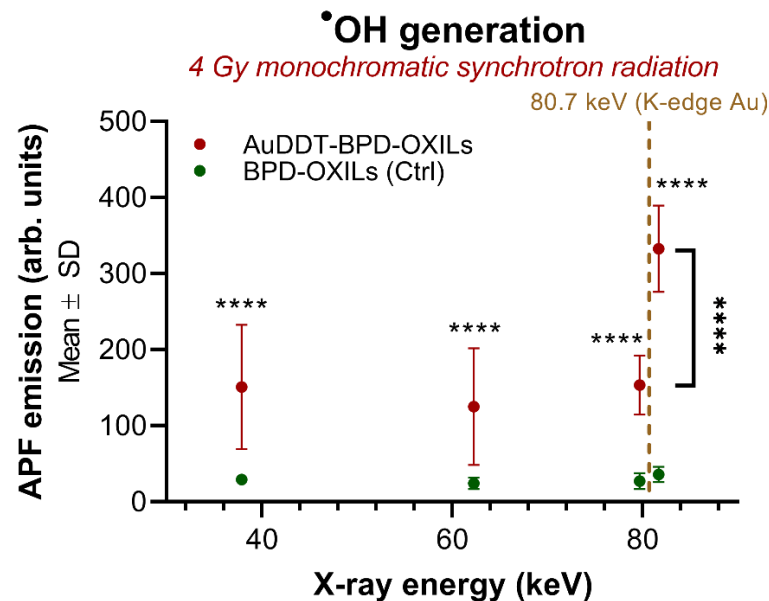
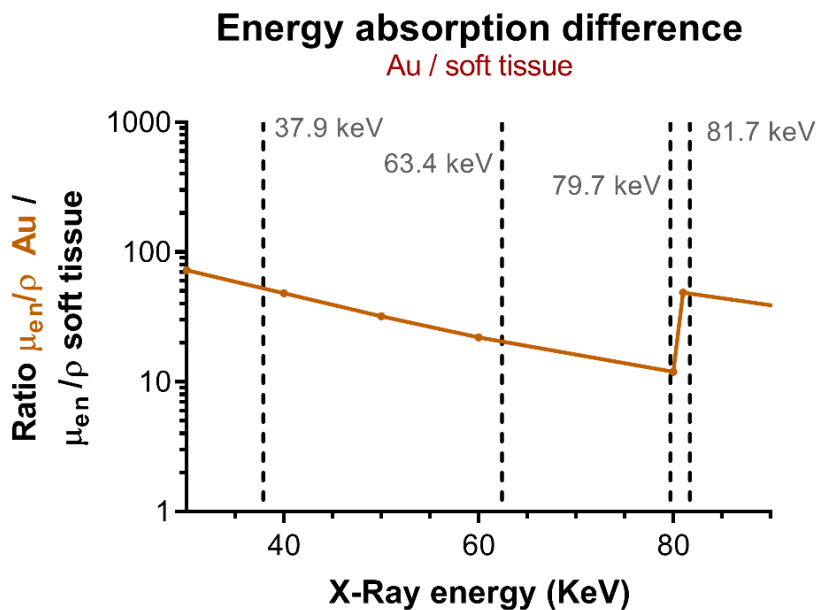
Radiocatalytic effects of AuDDT-OXILs



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- ✓ Elevated ROS production
- ✓ Gold-dependent process

- ✓ Effect amplified in presence BPD

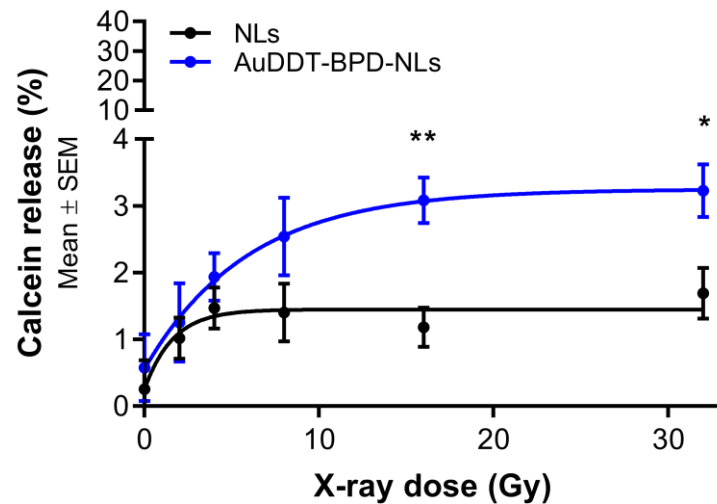


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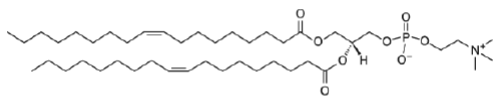
Radiocontrolled drug release

X-ray triggered cargo release

DOPE:DSPE-PEG (98:2)



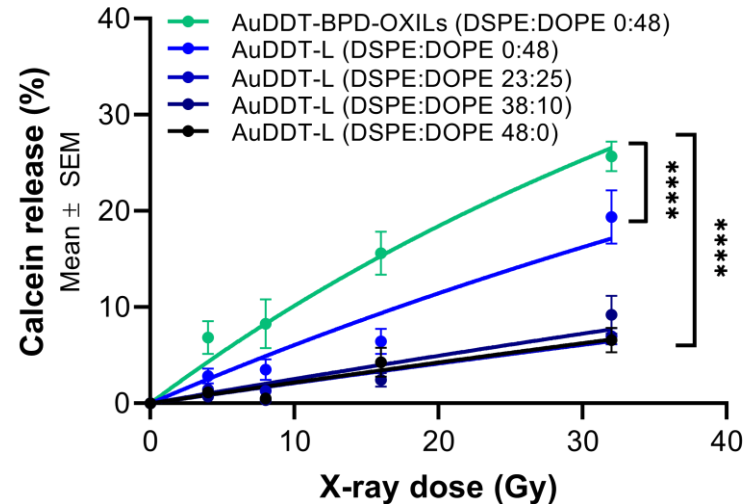
Main oxidation-responsive lipid:



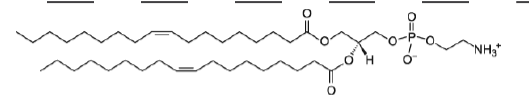
18:1 ($\Delta 9$ -cis) dioleoyl-phosphatidylcholine (DOPC)

X-Ray triggered cargo release

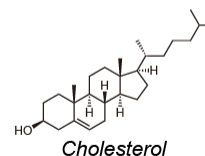
DSPC:DOPE:Chol:DSPE-PEG (48-0:0-48:48:4)



Main oxidation-responsive lipids:



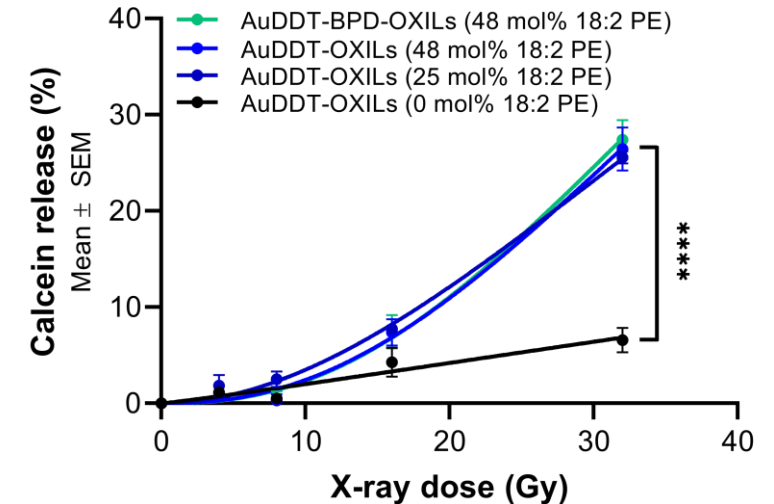
18:1 ($\Delta 9$ -cis) dioleoyl-phosphatidylethanolamine (DOPE)



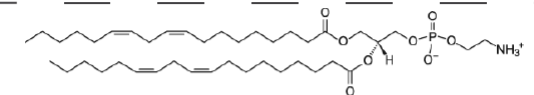
Cholesterol

X-Ray triggered cargo release

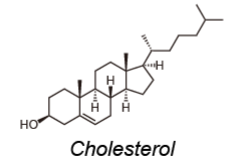
DSPC:DLinPE:Chol:DSPE-PEG (48-0:0-48:48:4)



Main oxidation-responsive lipids:



18:2 dilinoleoyl-phosphatidylethanolamine (DLinPE)



Cholesterol

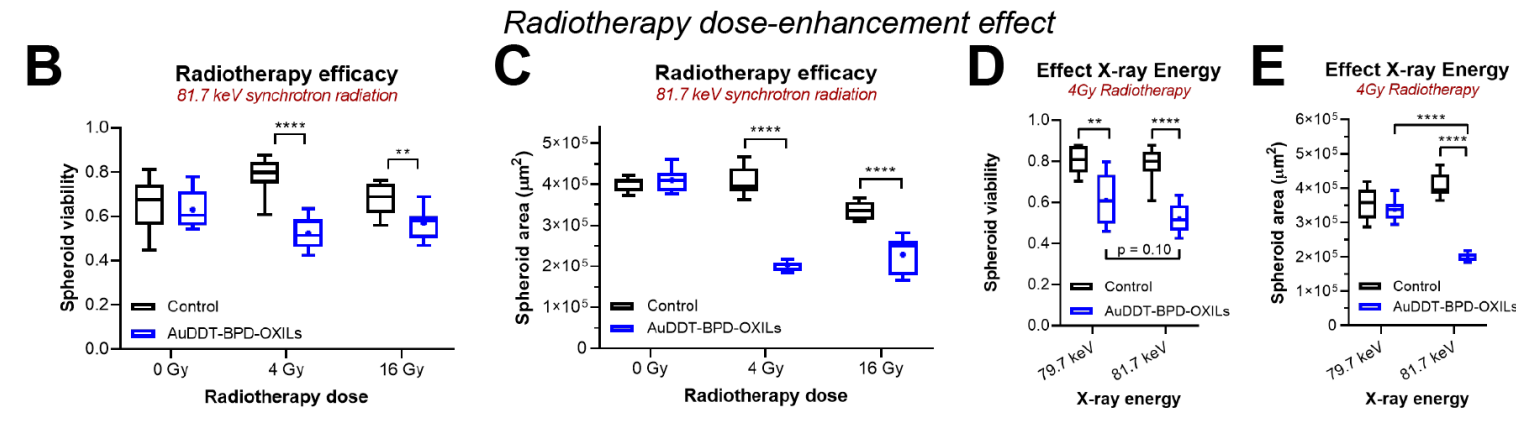
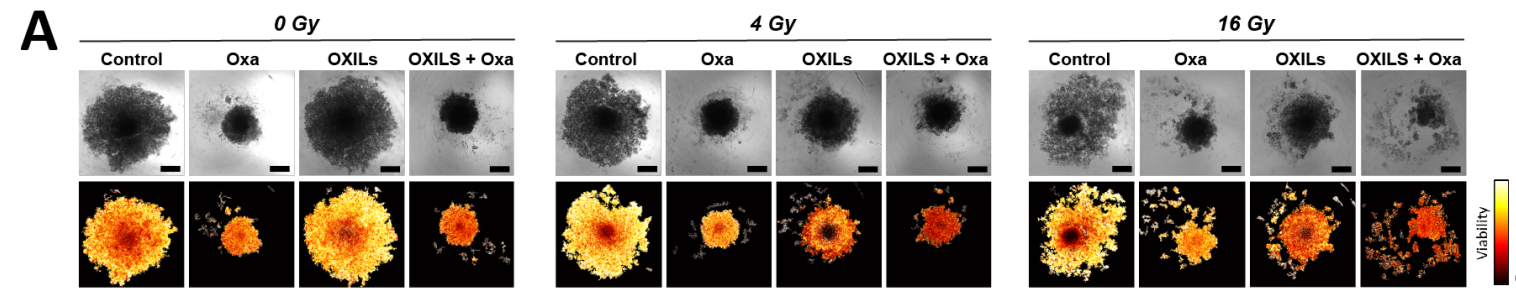
Radio-chemotherapy enhancement



Malika
KADRI



Dr. Tristan
LE
CLAINCHE



- ✓ AuDDT-OXILs enhance radiotherapy
- ✓ Smaller and less viable microtumors

Synergy with oxaliplatin

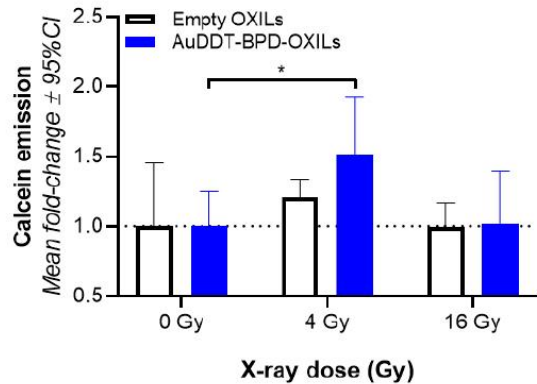
- ✓ In MIA PaCa-2 microtumors
- × In PANC-1 microtumors (not shown)

Radiotherapy increases tumor permeability

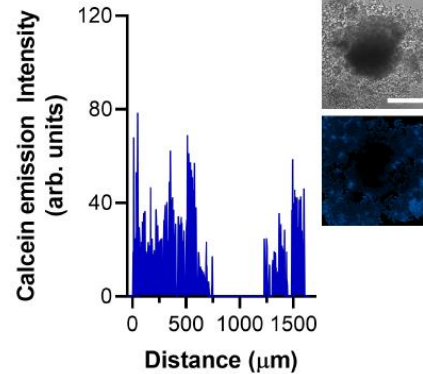


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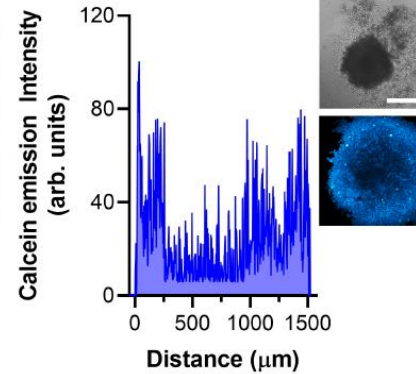
A MIA PaCa-2 microtumor permeability
81.7 keV Synchrotron radiation



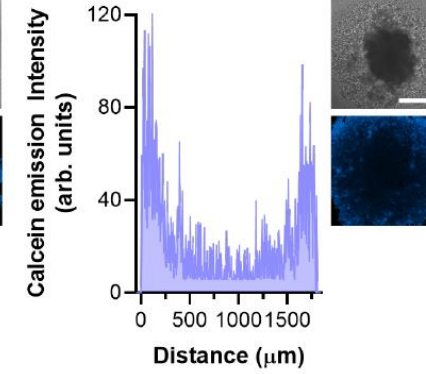
B Calcein penetration
AuDDT-BPD-OXILs 0 Gy



Calcein penetration
AuDDT-BPD-OXILs 4 Gy

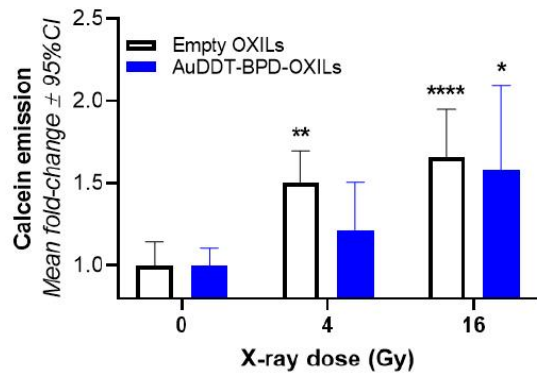


Calcein penetration
AuDDT-BPD-OXILs 16 Gy

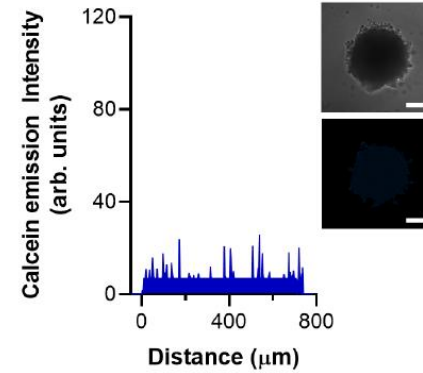


- ✓ Radiotherapy enhances tumor permeability (after 24h)
 - ✓ Mostly in tumor periphery

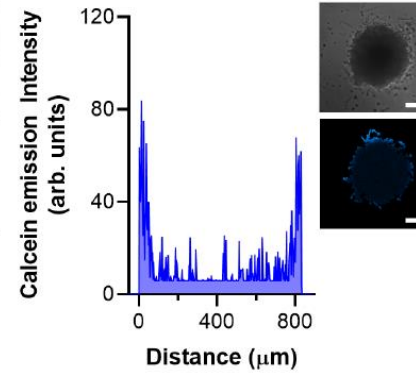
C PANC-1 microtumor permeability
81.7 keV Synchrotron radiation



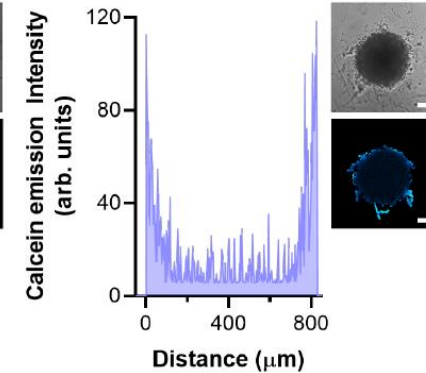
D Calcein penetration
AuDDT-BPD-OXILs 0 Gy



Calcein penetration
AuDDT-BPD-OXILs 4 Gy



Calcein penetration
AuDDT-BPD-OXILs 16 Gy



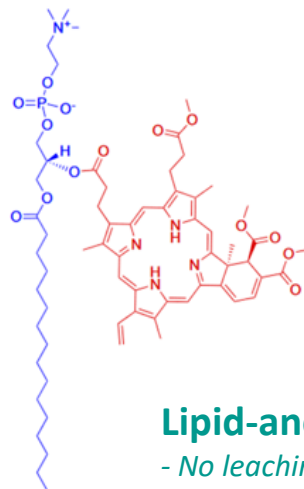
- ✗ No enhancement by AuDDT-OXILs



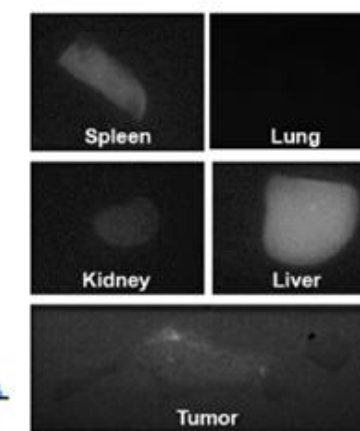
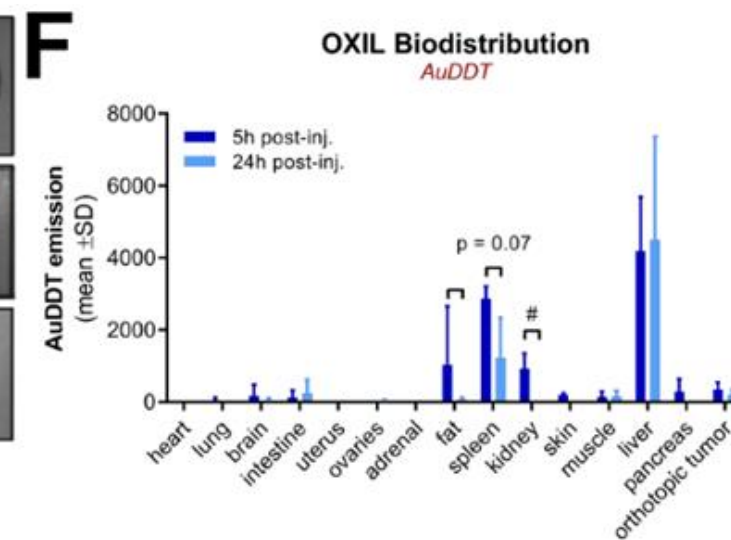
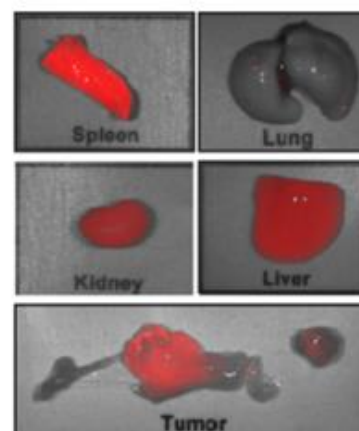
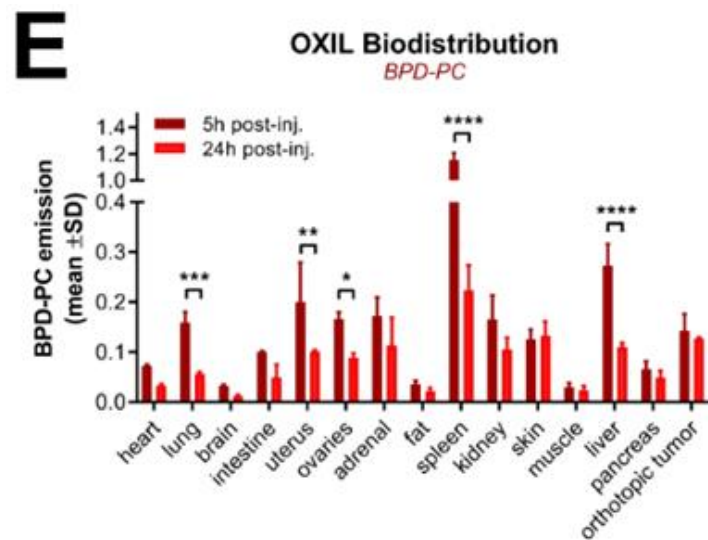
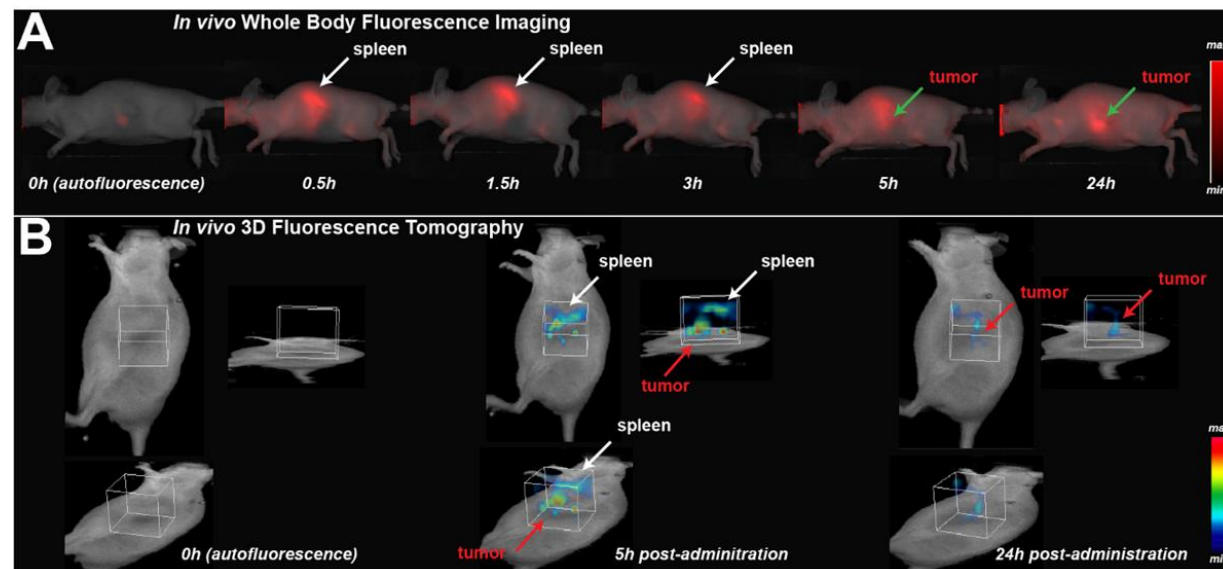
Efficient tumor accumulation of OXILs

But what about AuDDT?

Collab Dr.
Girgis OBAID



Lipid-anchored BPD
- No leaching from liposomes



Looking back

Liposomes with hydrophobic High-Z clusters

- Synthesis optimized
- Validated encapsulation

Radiocatalytic effects

- High-flux monochromatic radiation
- Gold-dependent, but enhanced by porphyrins
- Radiotherapy-controlled drug release (30%)

Radiosensitizing properties

- Smaller & less viable microtumors after radiotherapy
- Model-dependent synergy with oxaliplatin
- Little effect on tumor permeability

Looking forward

Challenges with hydrophobic High-Z clusters

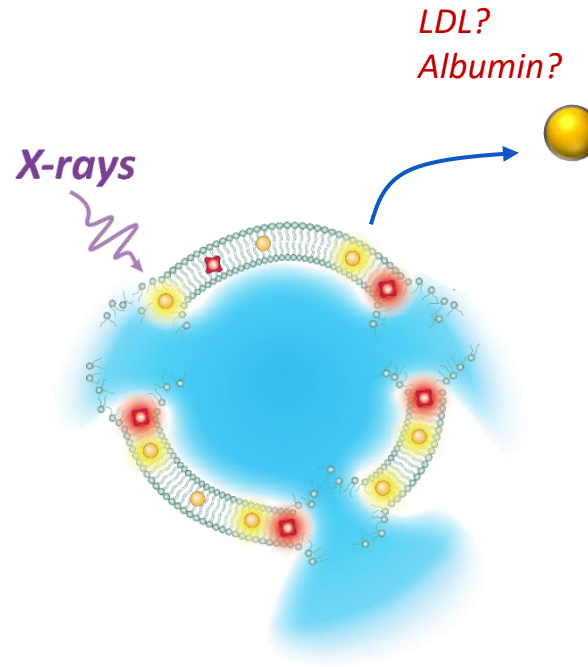
- Limited loading possibility <1 mol%
- Leaching in biological media?

Translatability of Radiocatalytic effects

- Low-flux polychromatic X-rays?
- Beyond 30% release with fractionated radiotherapy?
- Oxaliplatin suitable cargo

Radiosensitizing mechanisms?

- Immunogenic cell death?
- Effect on mechanobiology?
- In vivo efficacy?



Translatability of Radiocatalytic effects



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Synchrotron radiation

Monochromatic, >50Gy/min

Broad-spectrum X-ray irradiator

Polychromatic, 3Gy/min

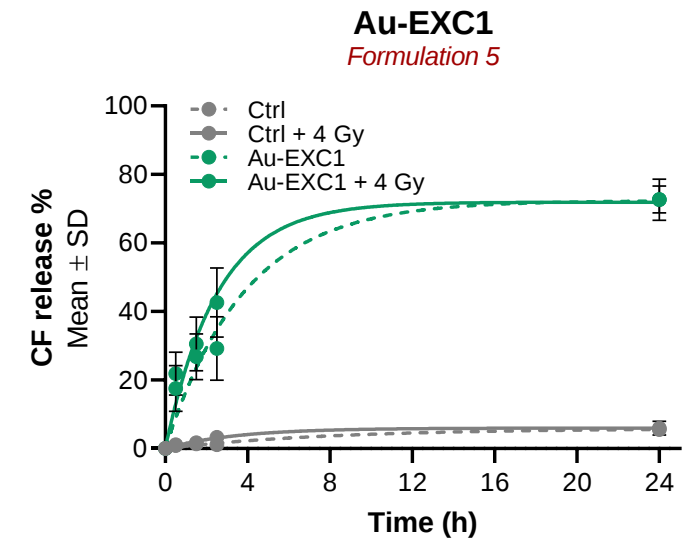
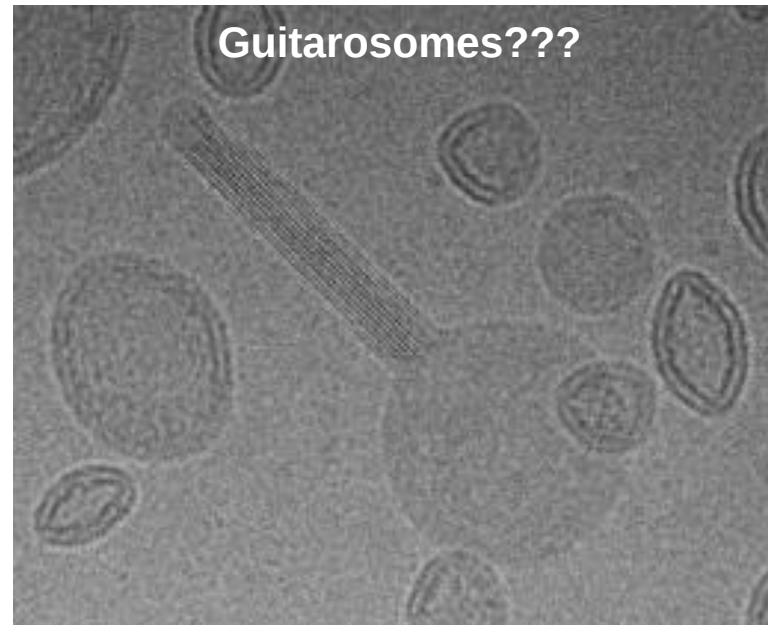
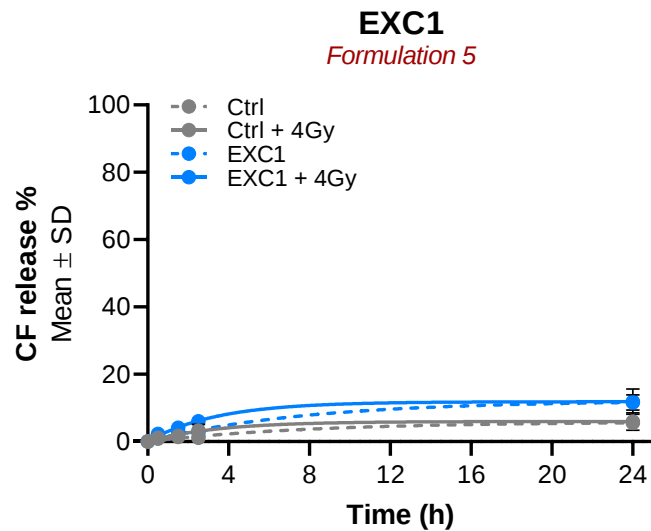
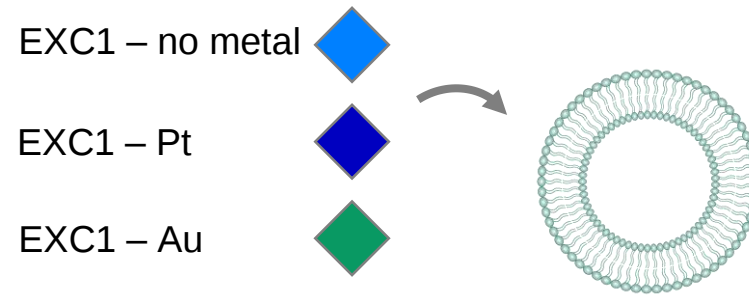




Sofia
LEO

Challenges with hydrophobic High-Z clusters

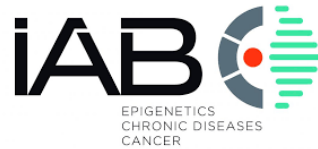
Alternative compounds under evaluation



Acknowledgements

Institute for Advanced Biosciences

Jean-Luc COLL
Anne-Laure BULIN
Xavier Le GUEVEL
Benoit BUSSE
Lucie SANCEY
Amandine HURBIN



**Nazareth
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**Sofia
LEO**



**Malika
KADRI**



**Dr. Tristan
LE CLAINCHE**



**Matilde
TUBERTINI**
Collab ISOF, Bologna



**Elena
MURILLA-VILELLO**



**Dr. Ahmed
ABDELHAMID**



**N ria
PUJOL-SOL **

University of Texas at Dallas

Girgis OBAID
Chanda BHANDARI



Synchrotron Radiation for Biomedicine

H l ne ELLEAUME
Sarvenaz KESHMIRI



Eur. Synchrotron Radiation Facility

Eaazhisai KANDIAH
Marc-Andr  HOGRAINDLEUR



CRS ISOF Bologna

Greta VARCHI
Claudia FERRONI

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