

Engineering Radiocatalytic Liposomes

with hydrophobic gold nanoclusters

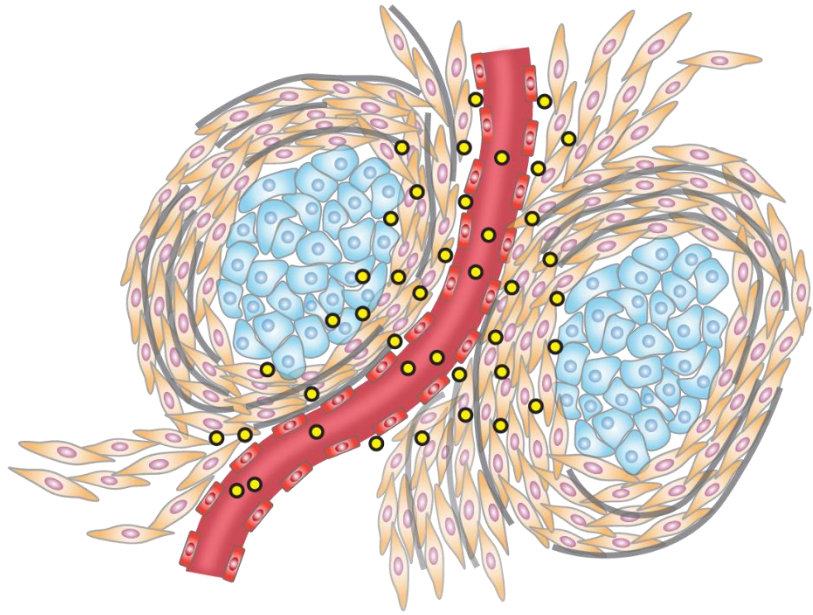
Mans Broekgaarden

Tenured Principal Investigator

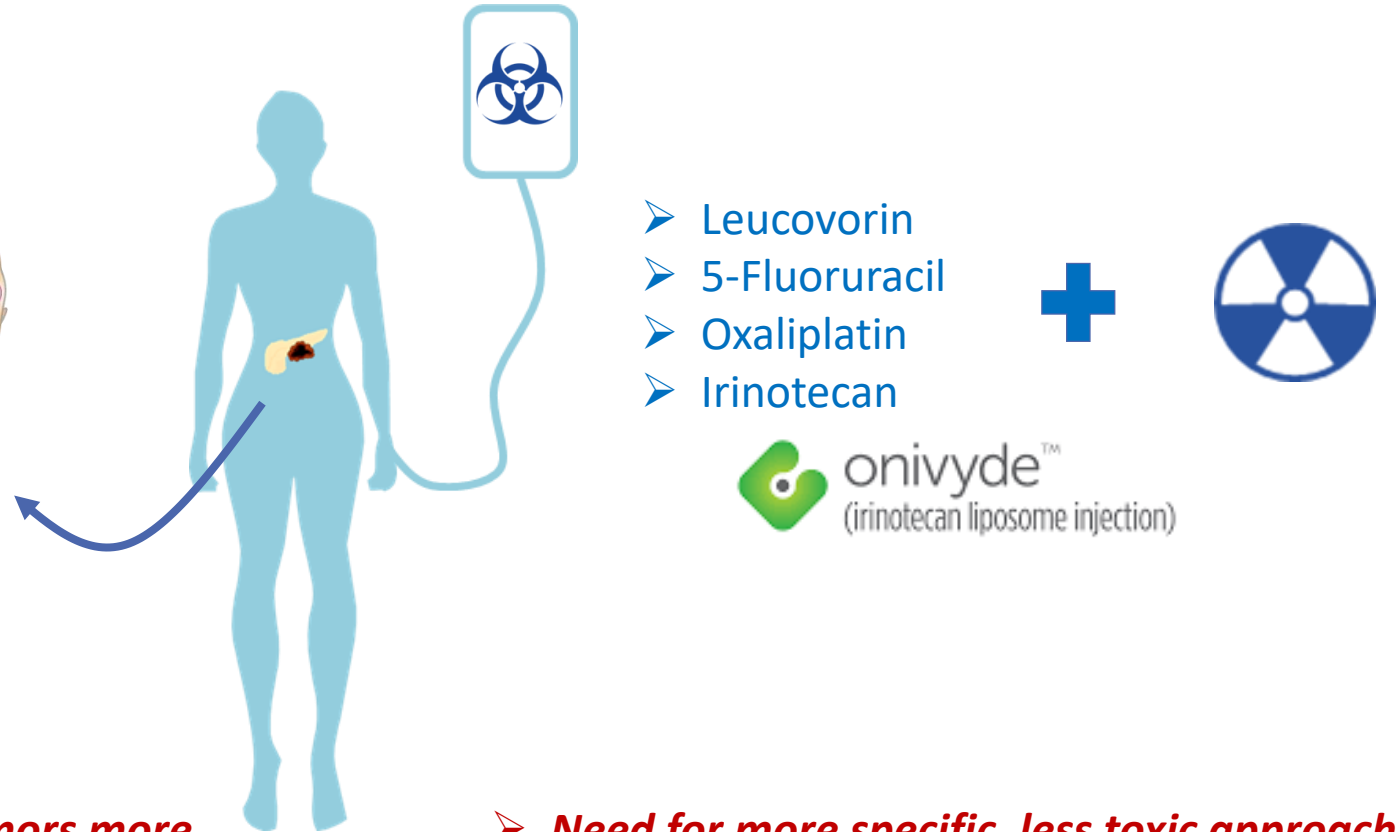
Board member Controlled Release Society: France & BeNeLux local chapter

THE PROTECTIVE CANCER STROMA

Nearly impenetrable stroma



High dose chemoradiotherapy

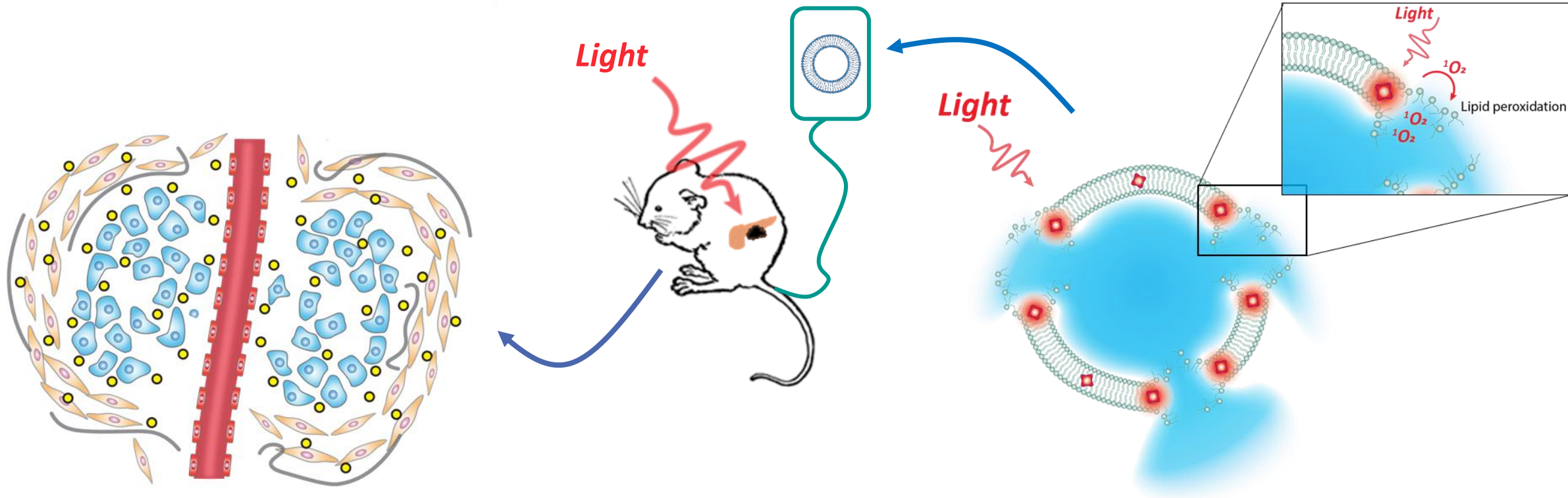


➤ ***Need for new approaches to make tumors more accessible to treatment***

➤ ***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

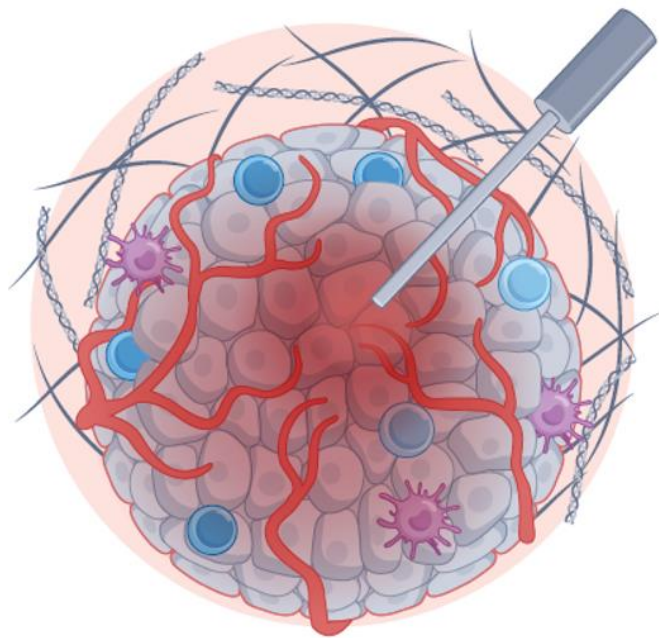
Lovell et al., Nat Mat 2011

Broekgaarden et al., Curr Med Chem 2014

Luo...Lovell Small & Biomaterials 2017

Increasing tumor permeability

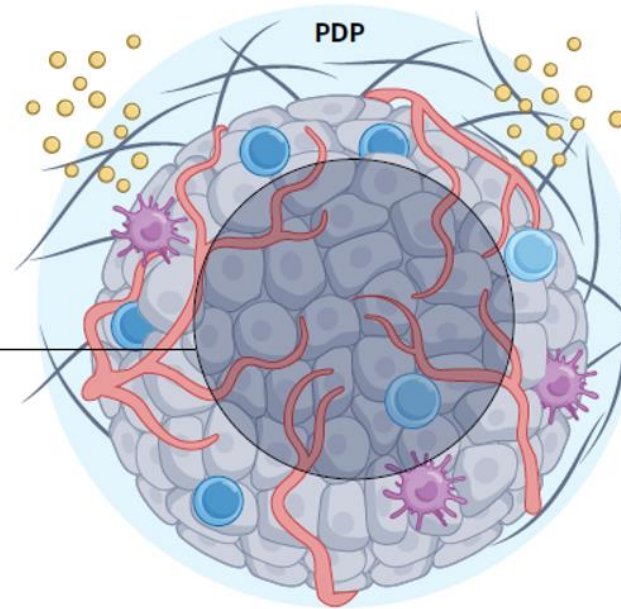
“Photodynamic Priming”



PDT

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

- Tumour cell death
- Vascular damage



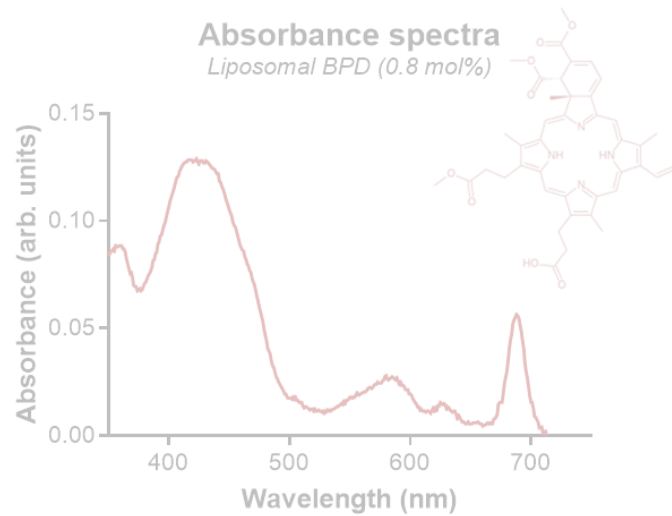
PDP (a finite priming volume that extends beyond the PDT death zone)

- 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

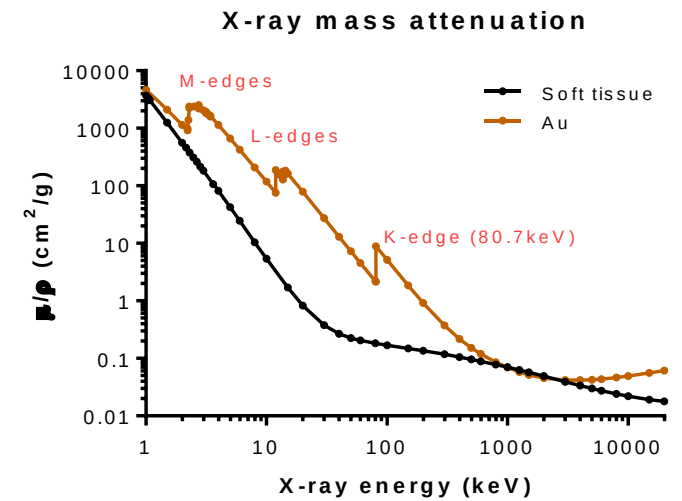
FROM LIGHT TO X-RAYS



Penetration in tissue 1-2cm
Challenging clinical translation



Penetration in tissue >10cm
Standard-of-care for 60% of all cancer patients



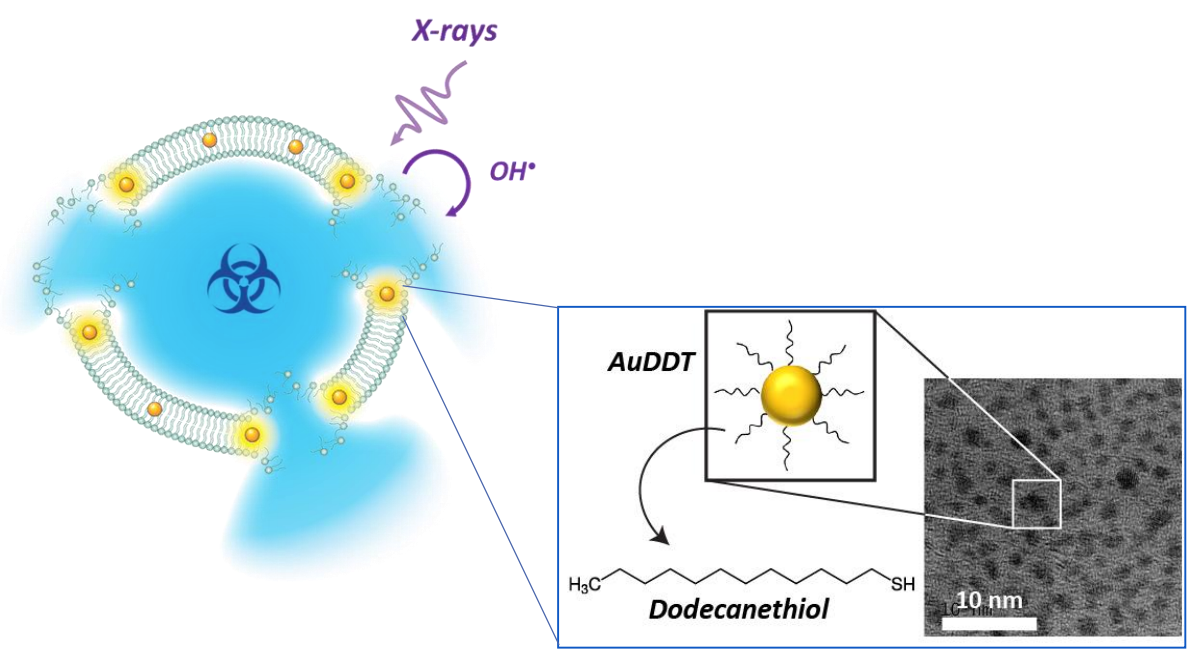
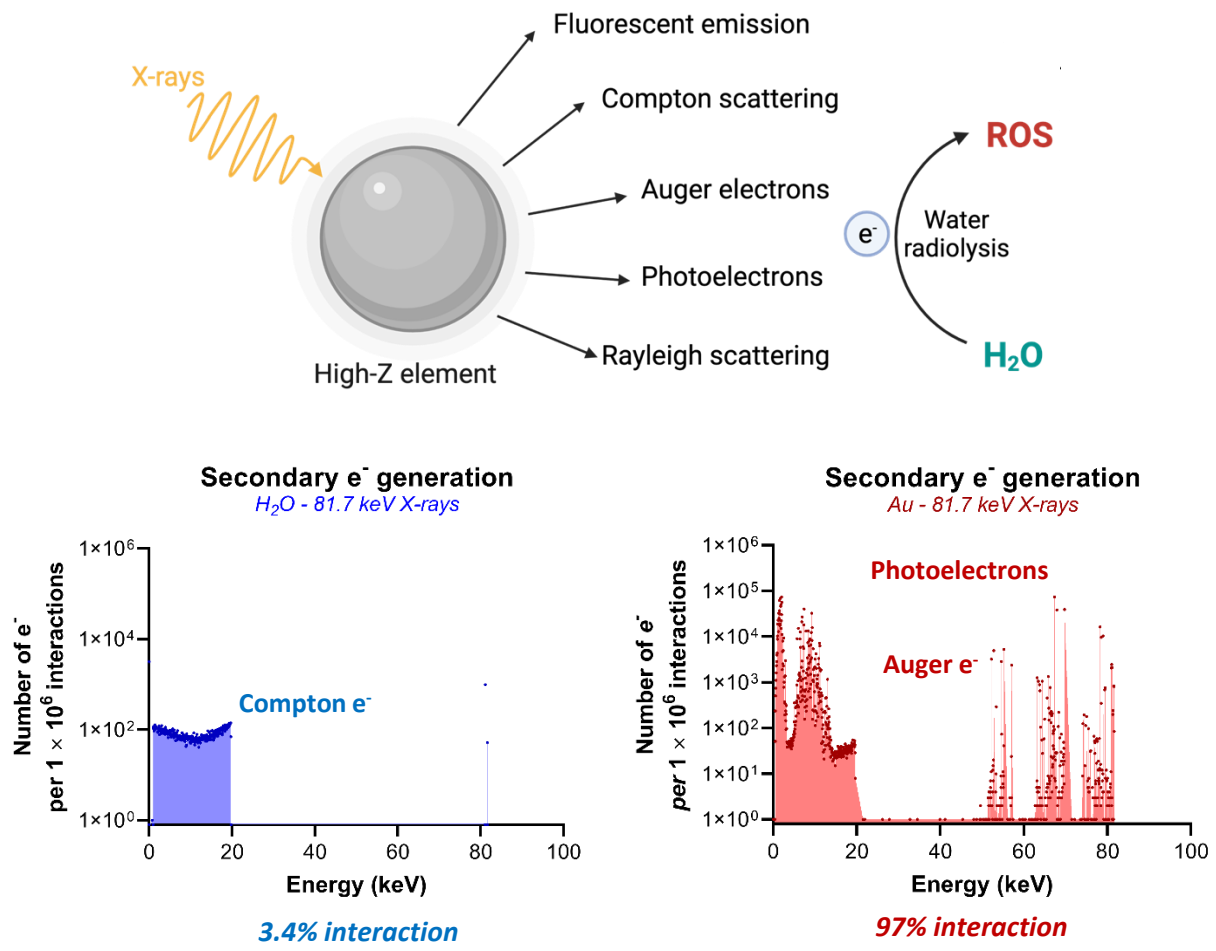


Collab. Anne-Laure BULIN



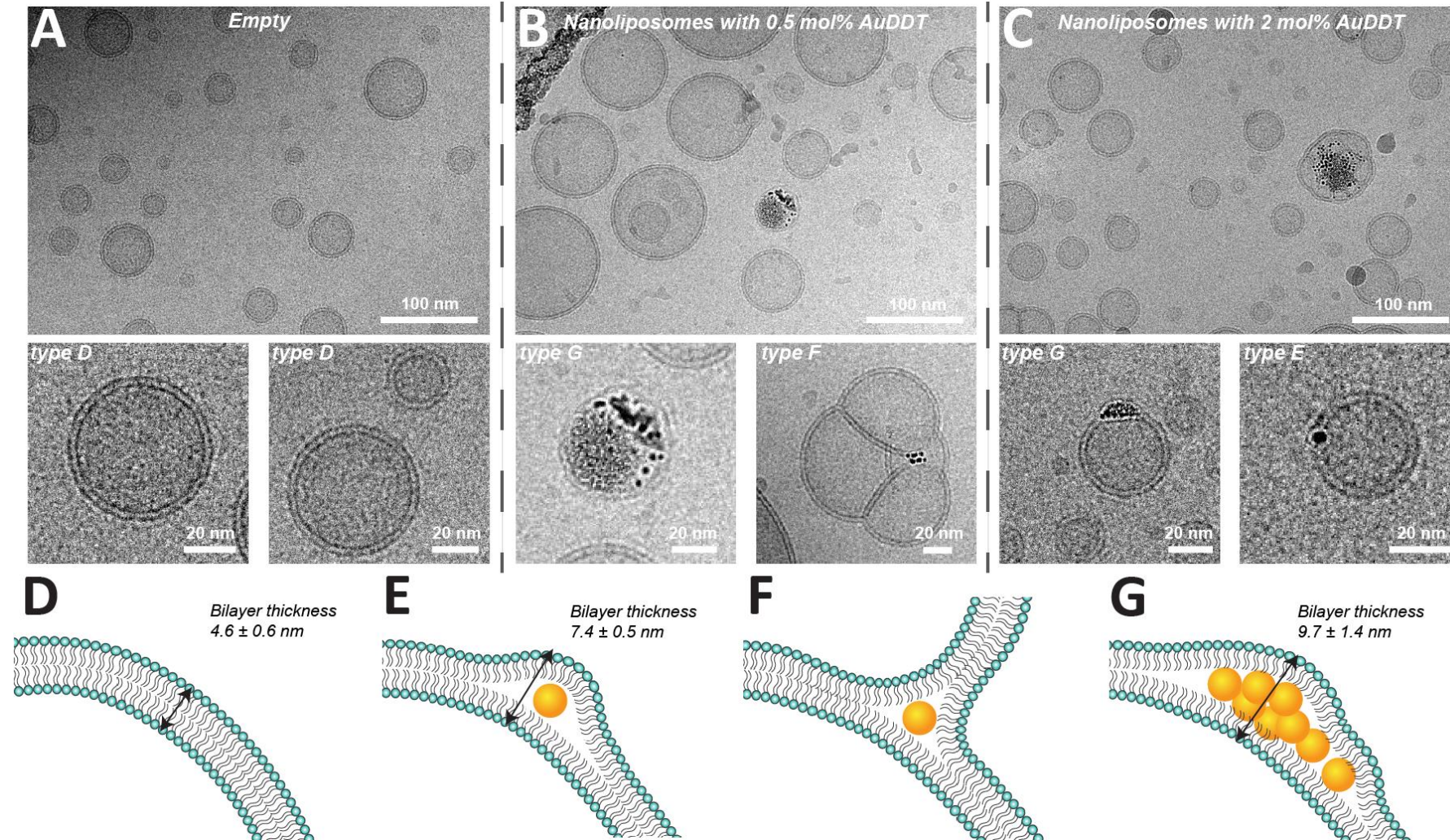
Collab. Xavier LE GUEVEL

RADIOTHERAPY-RESPONSIVE LIPOSOMES



Carigga-Gutierrez NM, Le Clainche T, Broekgaarden M. In resubmission (Adv Materials)

Liposomes containing hydrophobic gold nanoclusters





Collab. Helene
ELLEAUME



Collab. Anne-
Laure BULIN

RADIOCATALYTIC EFFECTS

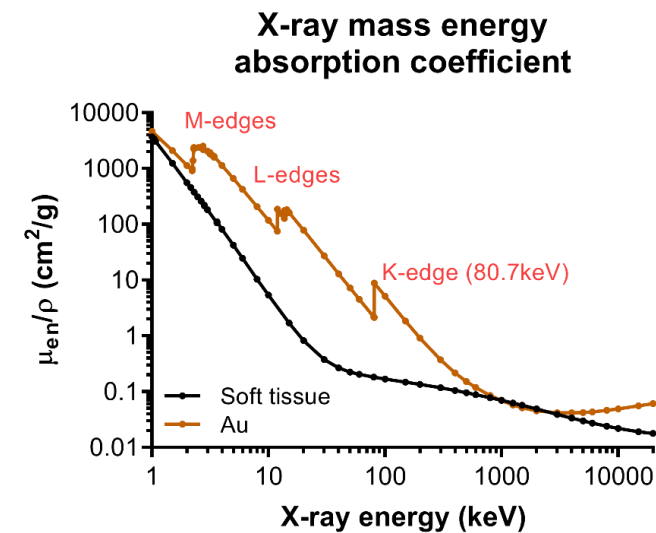
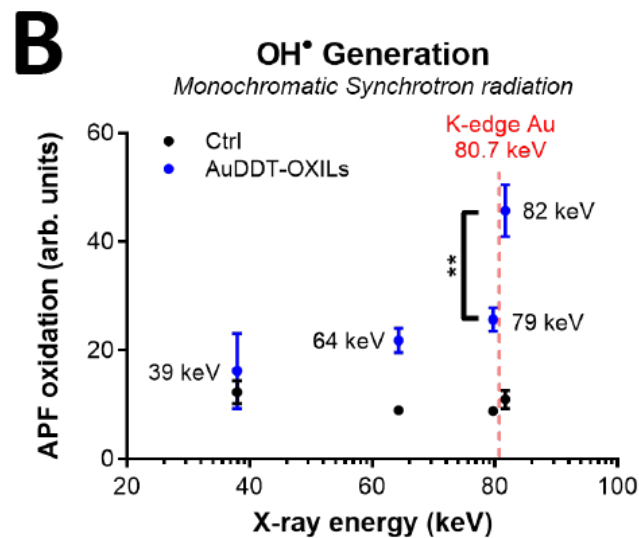
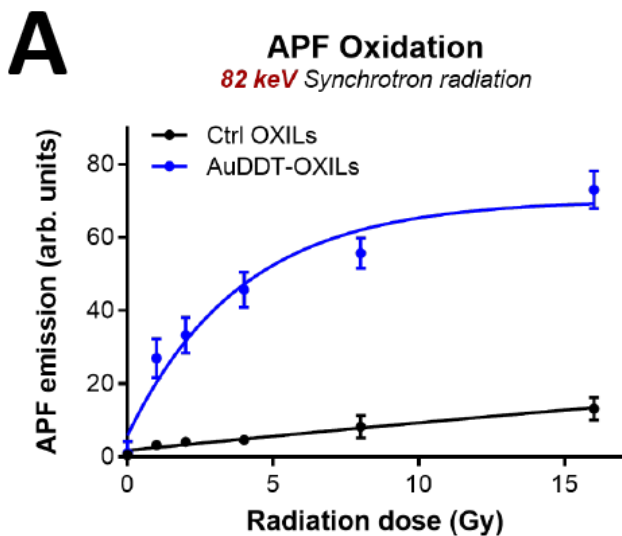
Oxidation-responsive liposomes (OXILs)



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Nazareth
CARIGGA



- ✓ Increased ROS generation
- ✓ Au-dependent process

- Above K-edge:
- ✓ Higher chance of interaction
 - ✓ Low-energy photoelectrons (1keV)
 - ✓ High-energy Auger electrons (50keV)

RADIOCONTROLLED CARGO RELEASE

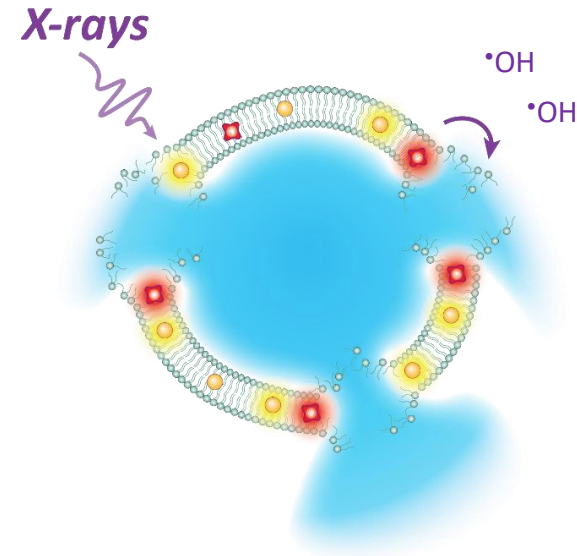
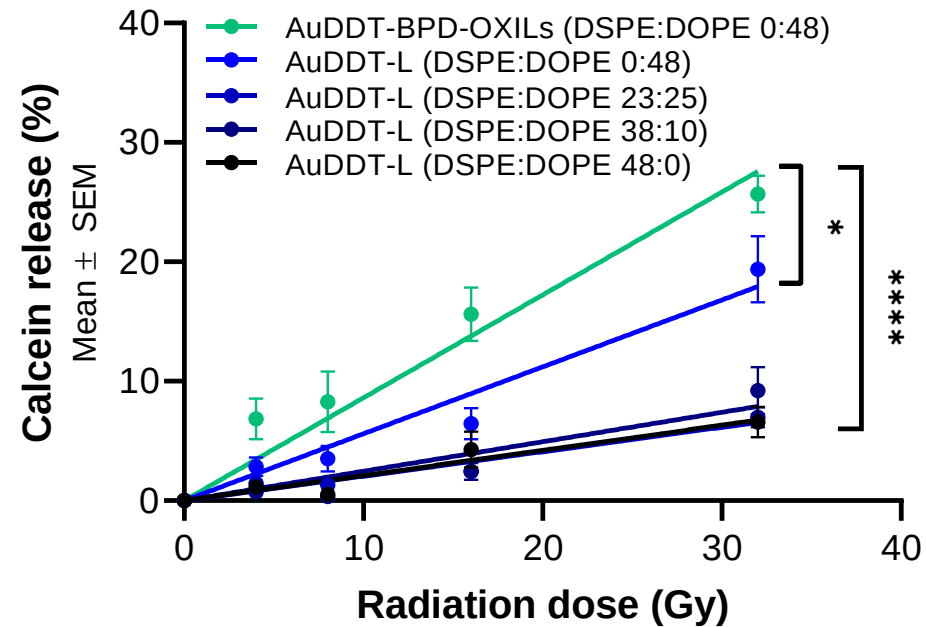
Depends on unsaturated lipid content



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X-Ray triggered calcein release

81.7 keV synchrotron irradiation



✓ ~30% release

*In presence of benzoporphyrin derivative (BPD)
Perturbed lipid packing?*

Aim 2

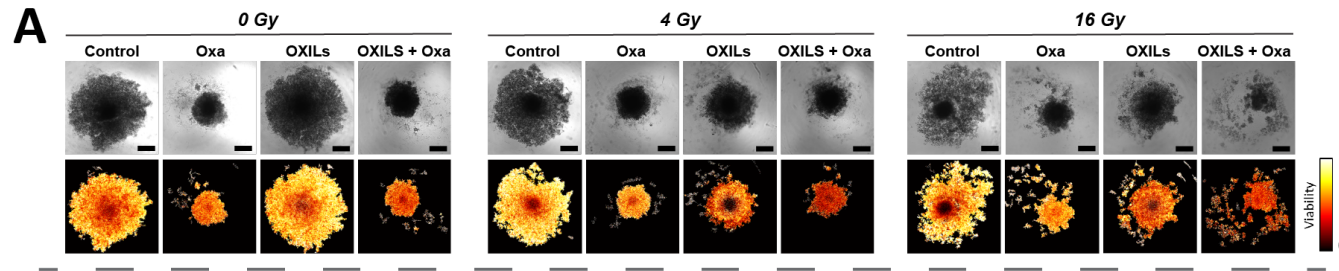
Radiotherapy enhancement



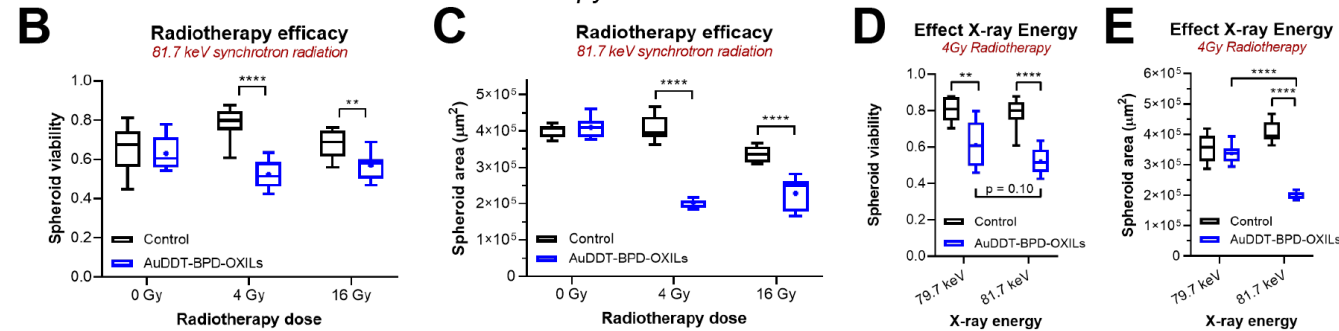
Malika
KADRI



Dr. Tristan
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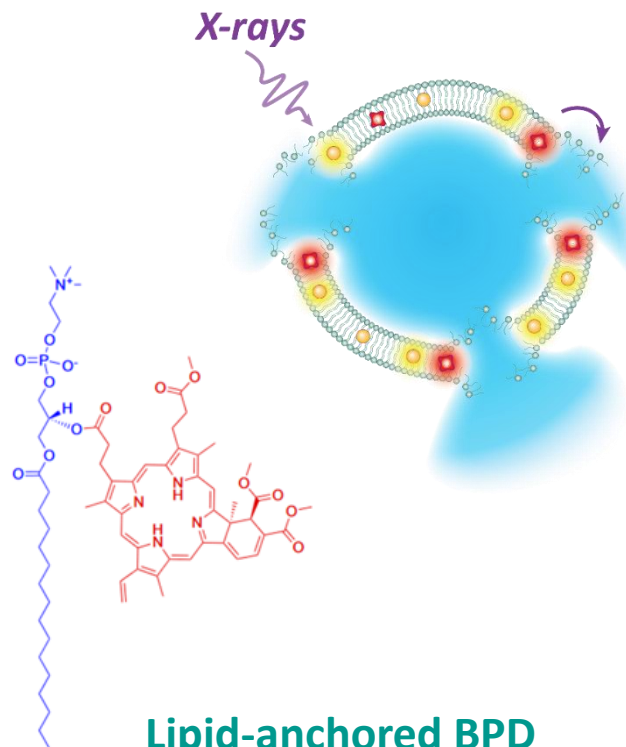
Radiotherapy dose-enhancement effect



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

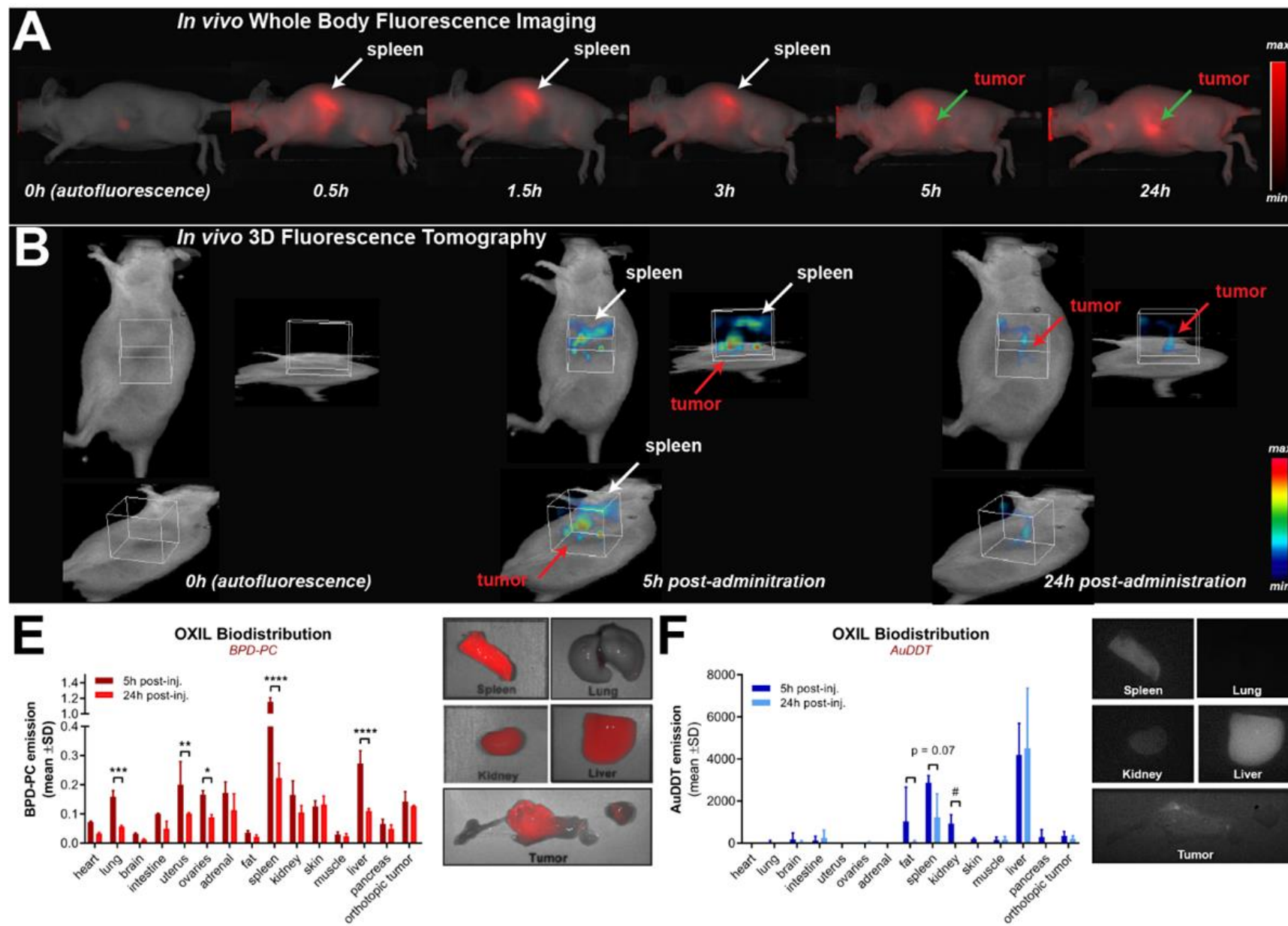


Biodistribution



Lipid-anchored BPD

- No leaching from liposomes



Take home messages

Looking back

High-Z metallated liposomes

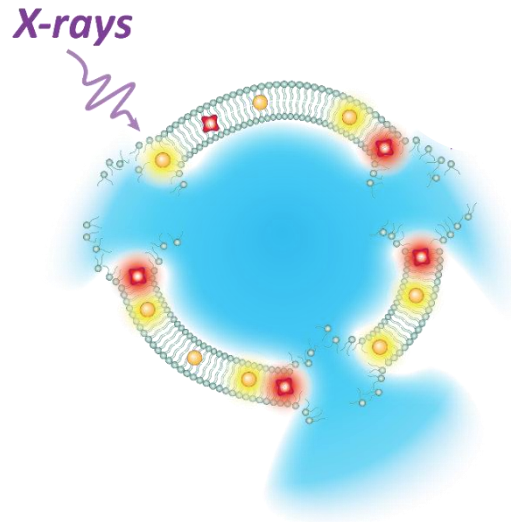
- ✓ Synthesis optimized
- ✓ Validated encapsulation

Radiocatalytic effects

- ✓ 5-fold increase with Synchrotron 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

Improving biodistribution

- Excellent biodistribution of liposomes
- AuDDT retained in liposomes?
- Higher dose studies underway
- Elemental quantification underway



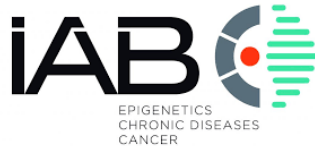
What about broad-spectrum X-rays?

- ✓ Radiocatalytic effects
- Mechanistic studies underway
- In vivo studies underway

Acknowledgements

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