Institute for **Advanced Biosciences**

CENTRE DE RECHERCHE UGA – INSERM U 1209 – CNRS UMR 5309

Development of new radiotherapy modalities

Lucie Sancey

GDR MI2B – Ecully – Sept. 2021

iAB EPIGENETICS • ENVIRONMENT CELL PLASTICITY • CANCER

UGA Université Grenoble Alpes · Inserm La science pour la santé From science to health · cnrs · CHU Grenoble Alpes · EFS Établissement Français du Sang Du donneur aux patients

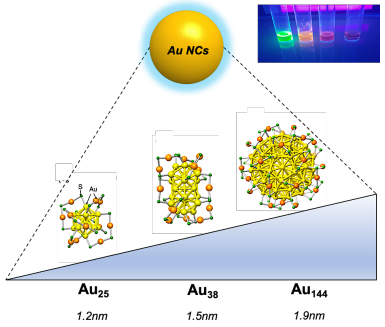
Development of new radiotherapy modalities

Radiotherapy

TUNABLE GOLD NANOCLUSTERS

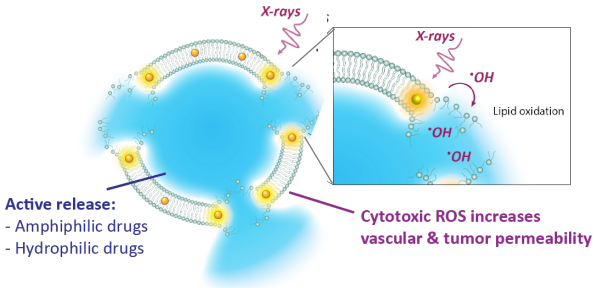
X. Le Guével

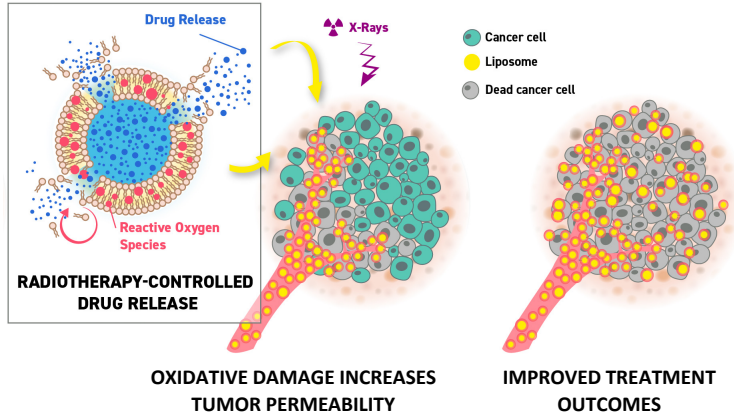
FLUORESCENCE MODULABLE
PHOTO/RADIO ACTIVABLE



LIPOSOMES FOR RADIOTHERAPY-TRIGGERED DRUG RELEASE IN PANCREATIC CANCER

M. Broekgaarden

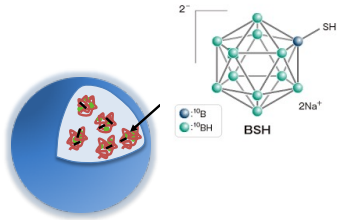


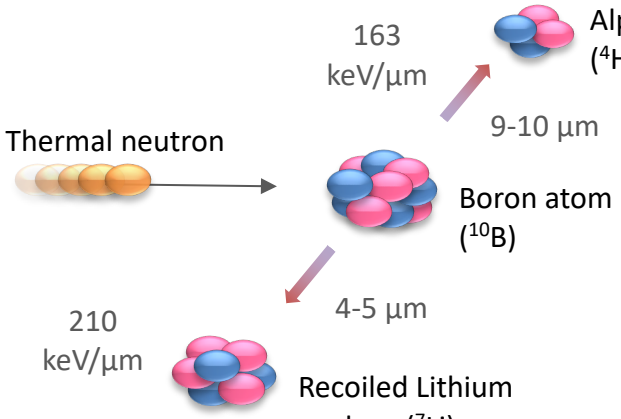


Neutrons therapy

L. Sancey

NANOPARTICLES
INNOVATIVE MOLECULES





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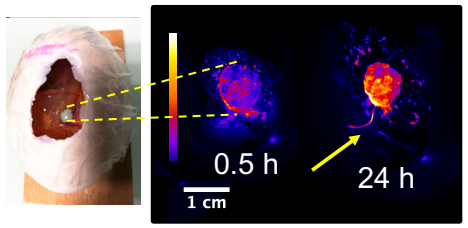
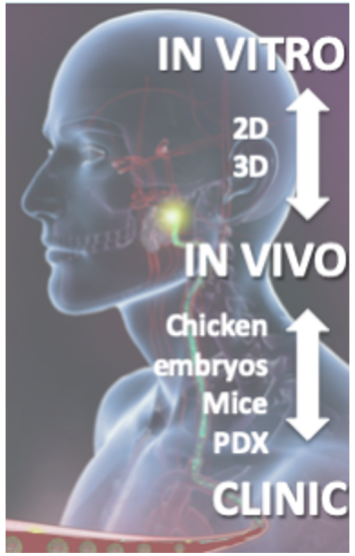


Optimal Grenoble



Lucie.sancey@univ-grenoble-alpes.fr Jean-luc.coll@univ-grenoble-alpes.fr

Development of new radiotherapy modalities

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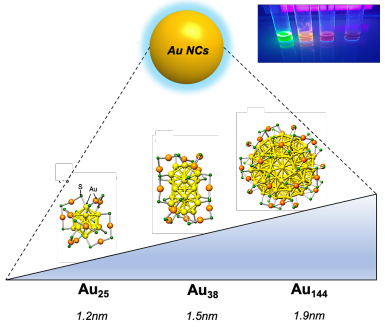
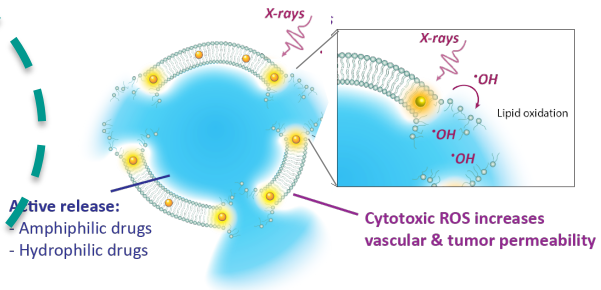
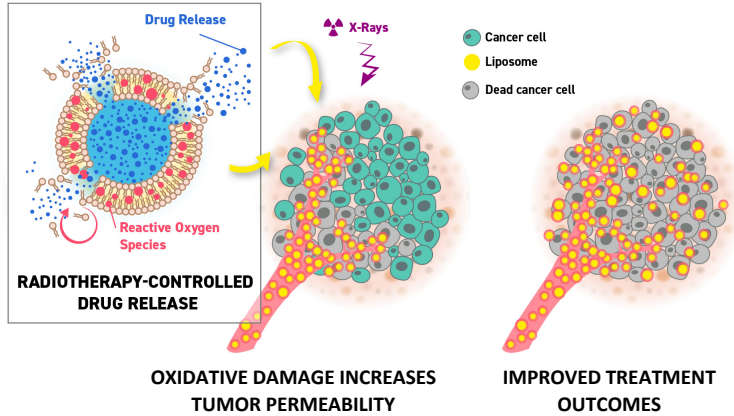


M. Broekgaarden

LIPOSOMES FOR RADIOTHERAPY-TRIGGERED DRUG RELEASE IN PANCREATIC CANCER





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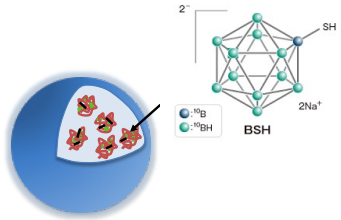

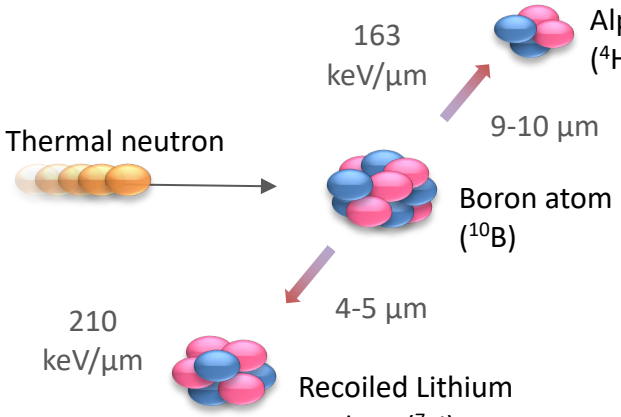

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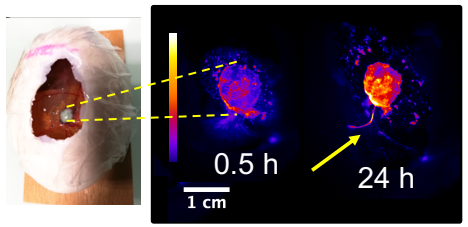

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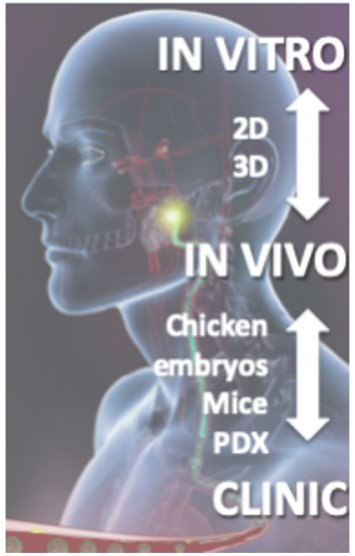

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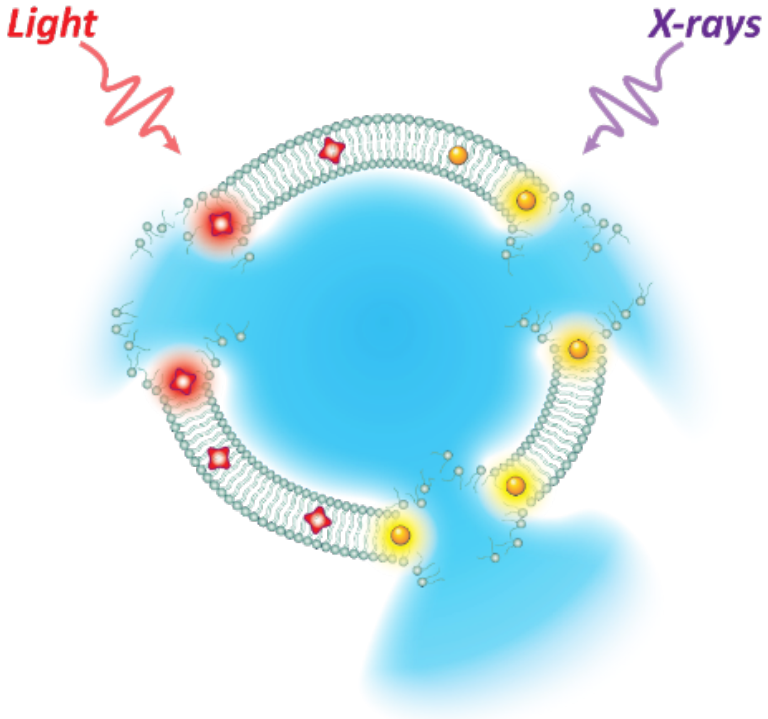

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Light- and Radiation-controlled drug delivery

Mans Broekgaarden

M. Broekgaarden

PANCREATIC CANCER

A need for improved treatment safety & efficacy

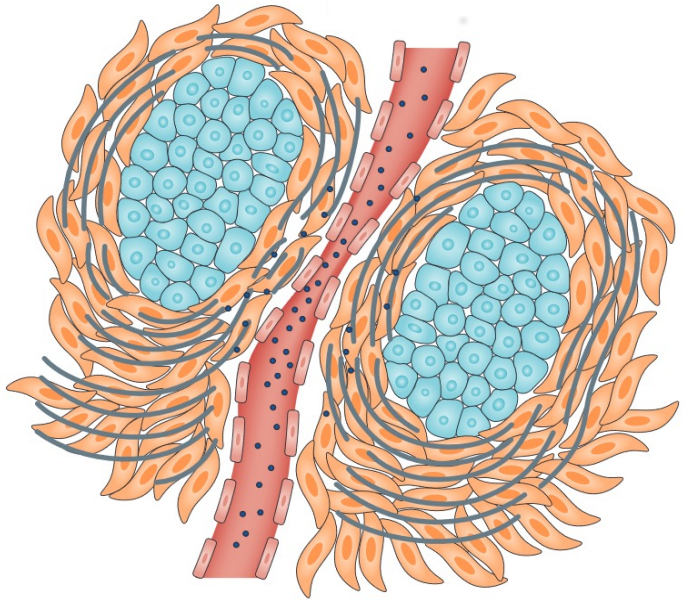
85% of patients not eligible for surgery

Median survival 6 months

Radiotherapy + chemotherapy

Median survival 15 months

Intolerable chemotherapy doses required



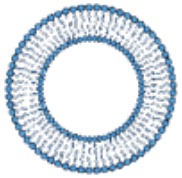
Adiseshaiah et al., Nat Rev Clinical Oncol 2016

Liposomal chemotherapeutics

+ Specific accumulation in tumor

+ Improved safety

- Uncontrolled drug release



Challenges

Spatiotemporal controlled drug release

At the right place & right time

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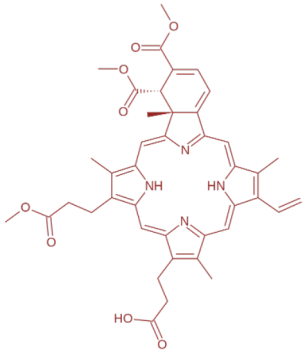
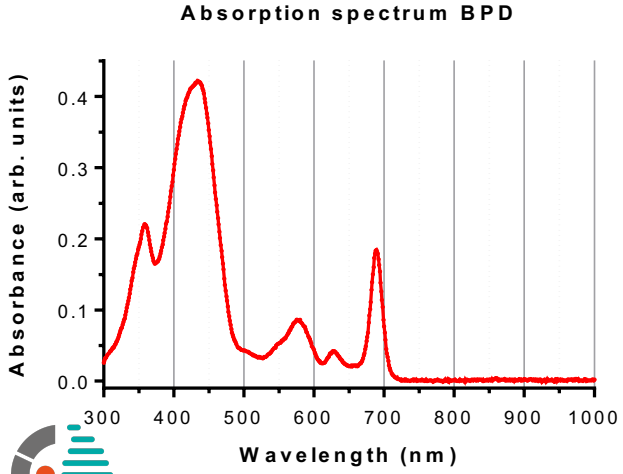
Controlled drug release by light and radiation

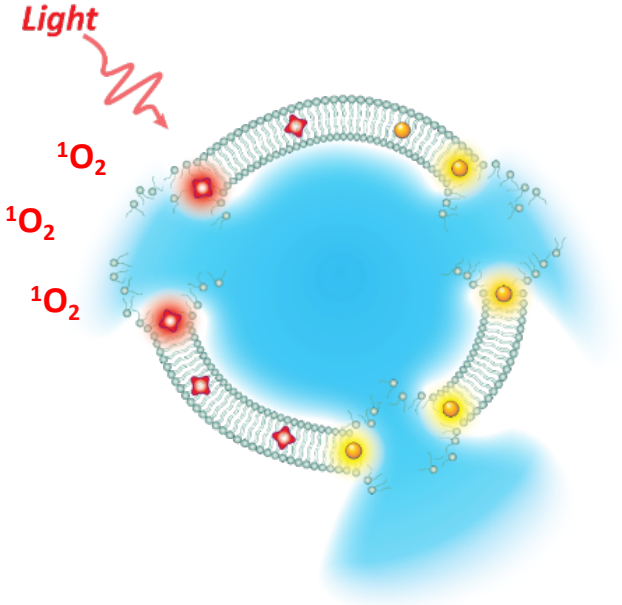
M. Broekgaarden

PHOTODYNAMIC THERAPY

Benzoporphyrin derivative (BPD)







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Controlled drug release by light and radiation

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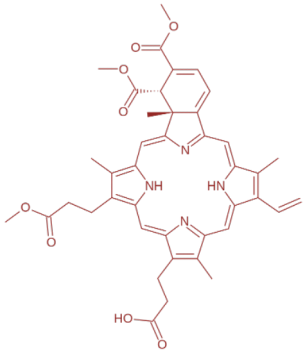
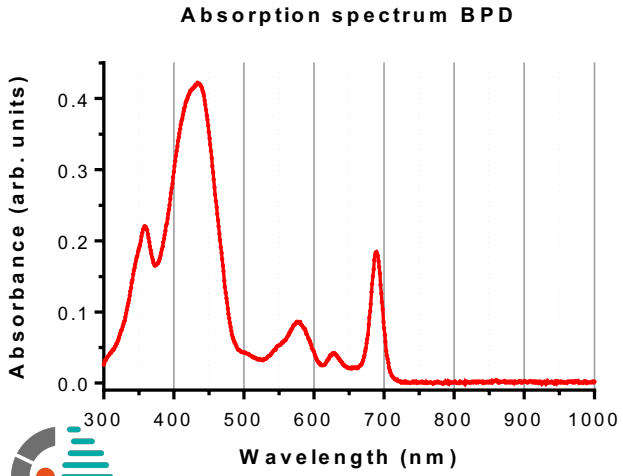
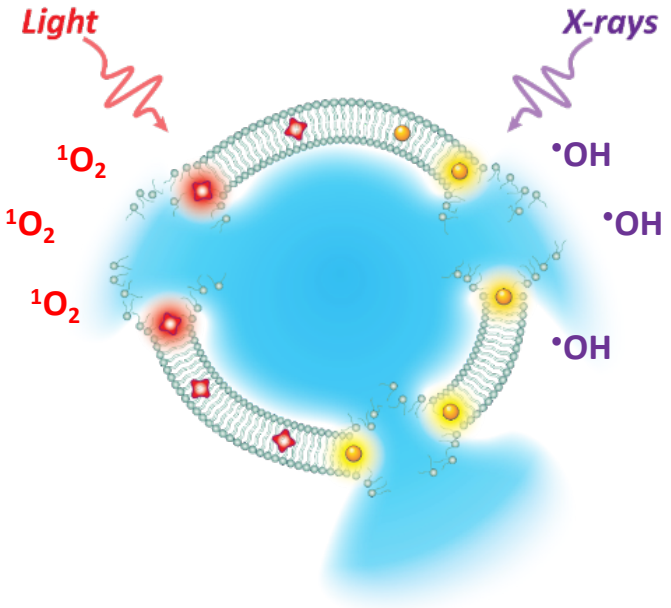
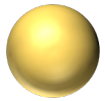




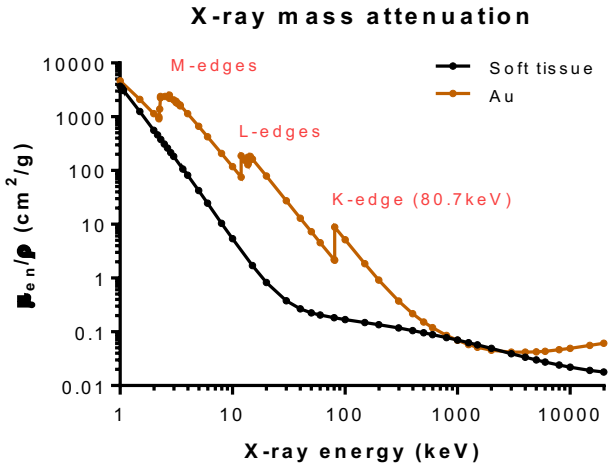


RADIATION THERAPY



Gold nanoclusters 3-nm

- *Dodecanethiol-stabilized (hydrophobic)*



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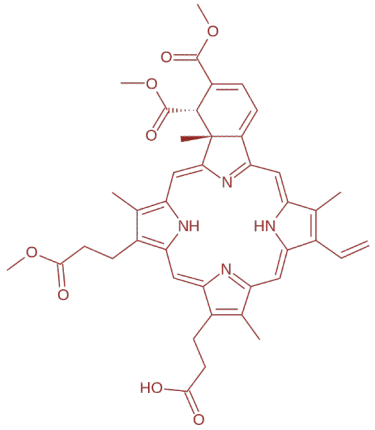
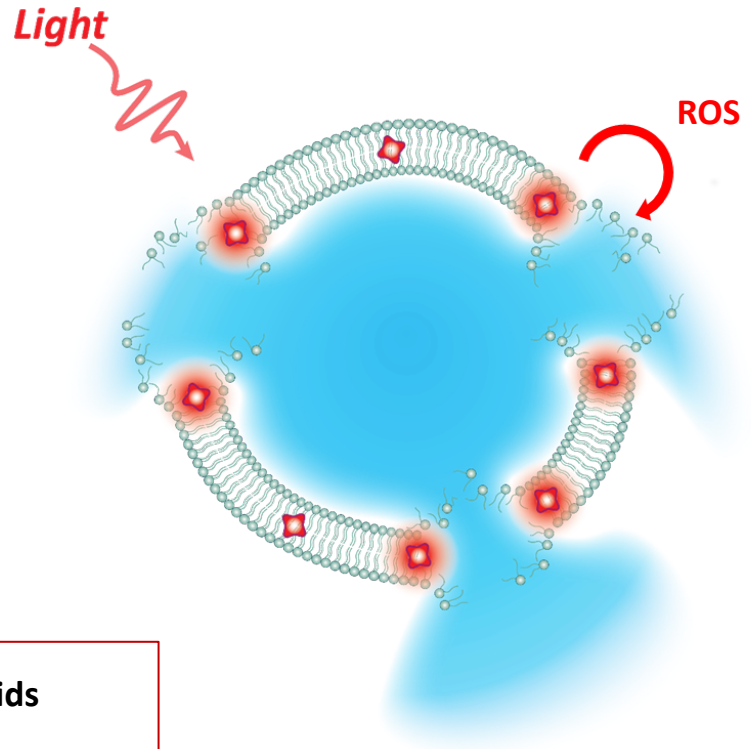
Light-triggered release with oxidation-responsive liposomes

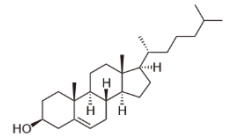
I. Photosensitizer (BPD)





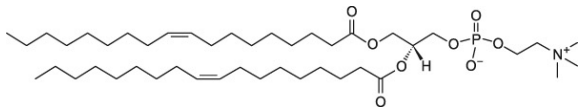
III. Membrane fluidity

Cholesterol



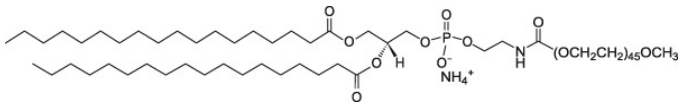
II. Oxidation-susceptible lipids

Unsaturated lipids



IV. Stabilisation lipids

PEG-conjugated lipids



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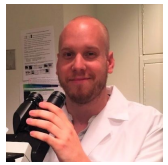

Cholesterol greatly impacts release efficiency

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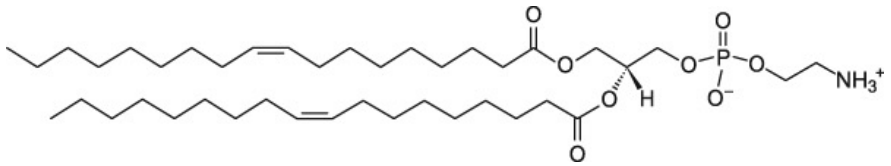
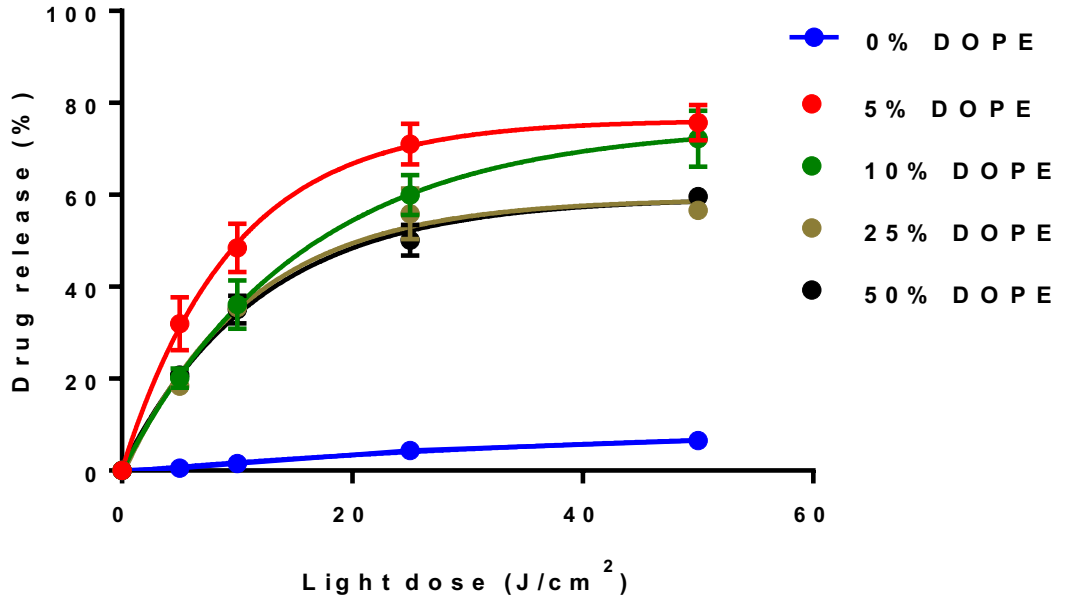
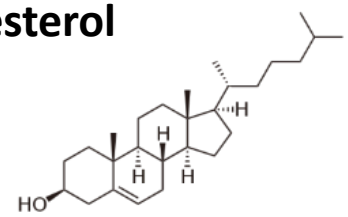
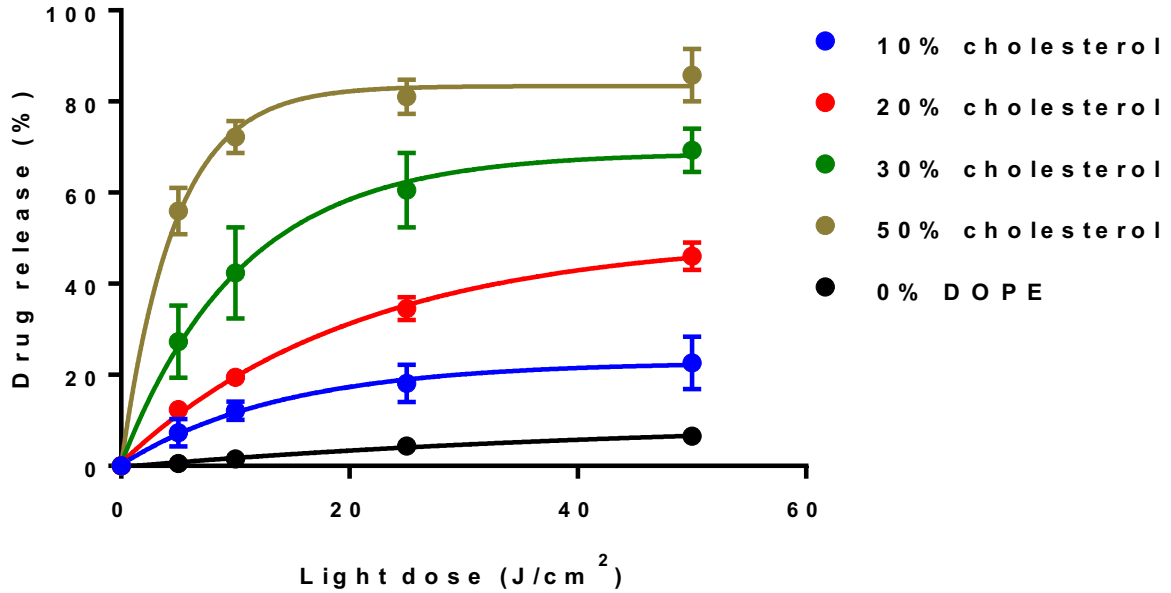
Impact of Di-oleoyl-phosphoethanolamine (DOPE)





Impact of Cholesterol





Presence of unsaturated lipids such as DOPE is essential !

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From light to radiation

Light-controlled drug release

- Efficient and proven concept

- Photodynamic therapy still experimental
- Shallow tissue penetration (1 cm)

X-ray-controlled drug release

- Largely unexplored

- >60% of cancer patients receive radiotherapy
- Deep tissue penetration

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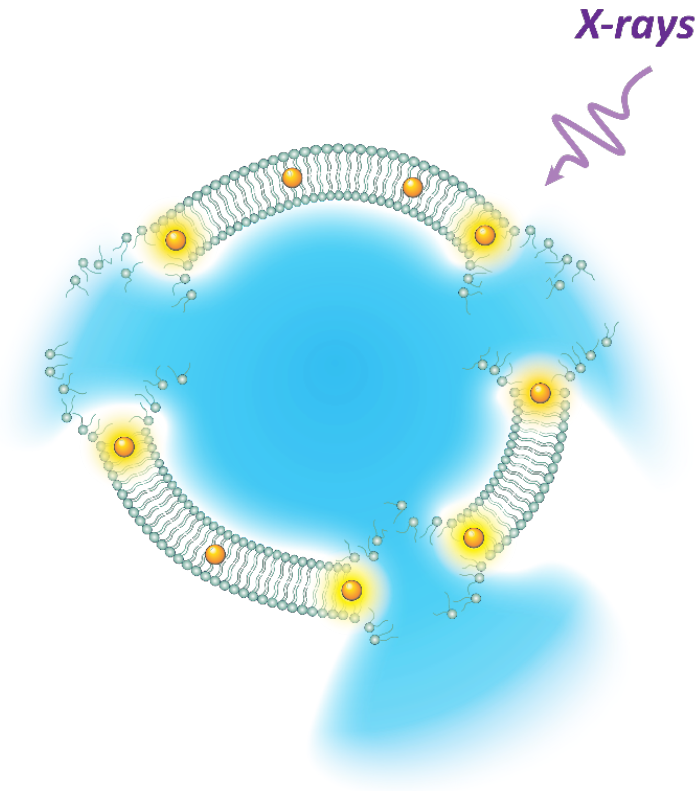
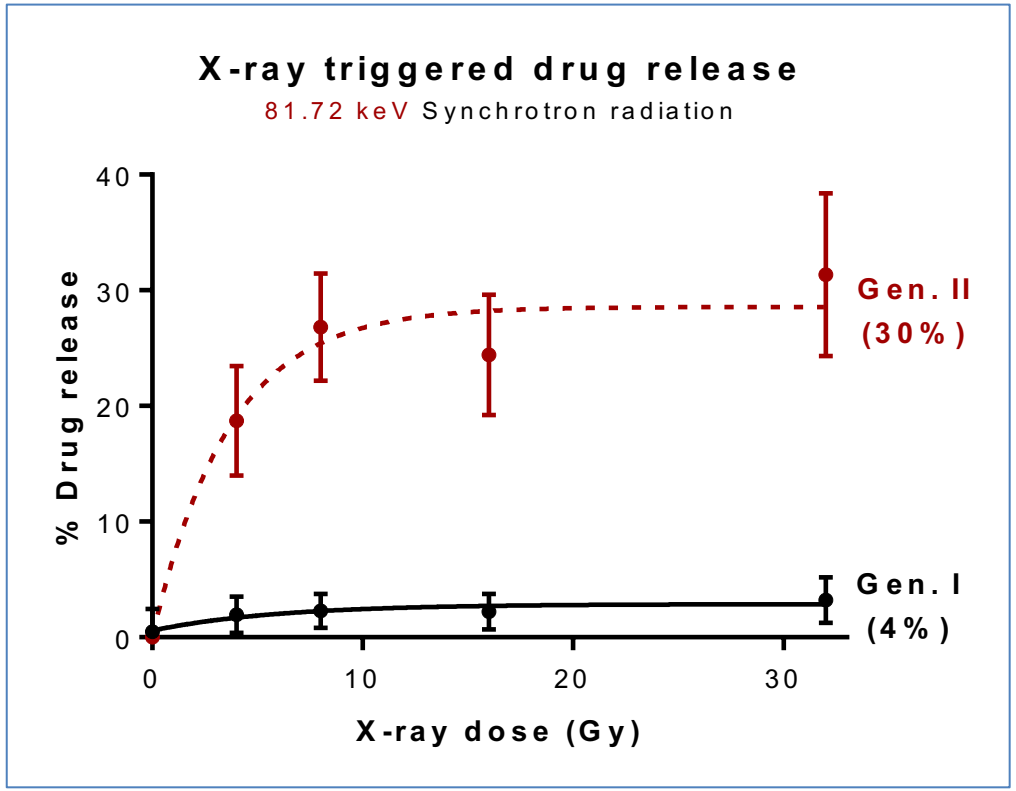
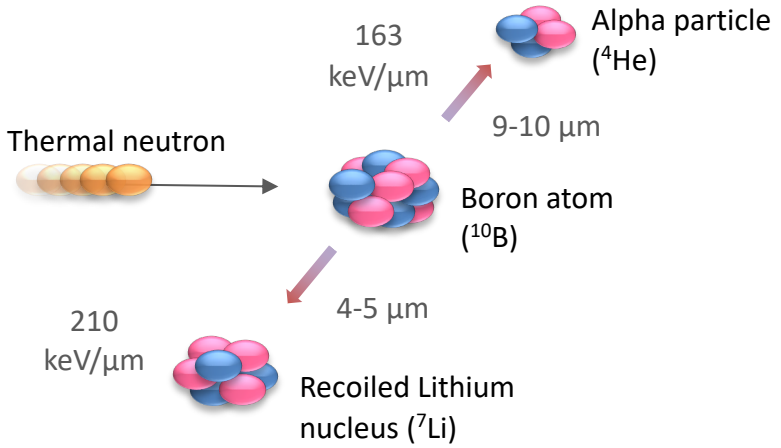
X-ray controlled drug release





Under investigation from cells to mice

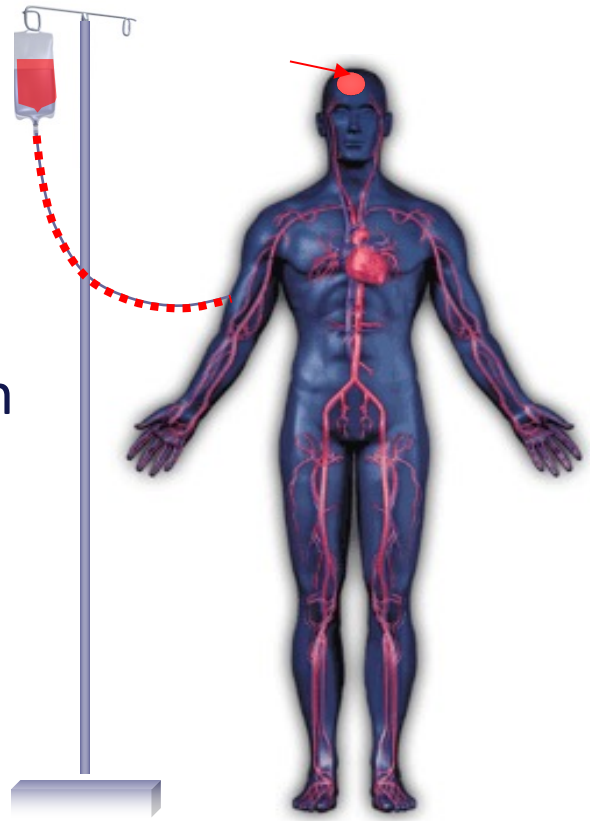


Theranostic compounds for Boron Neutron Capture Therapy

Boron Neutron Capture Therapy: Principle

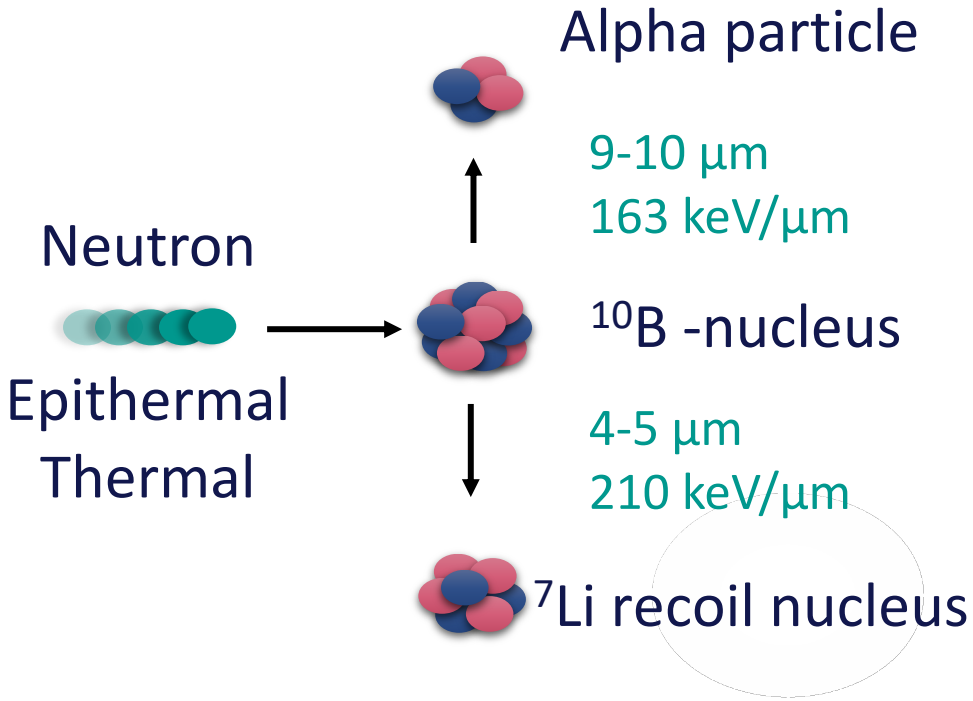
1) Boron-10 vectorization in tumor

Boron accumulation
in the tumor



IV
infusion

2) Neutron exposition



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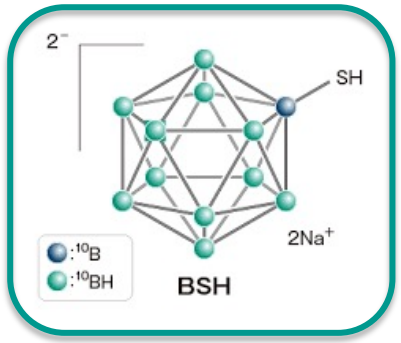
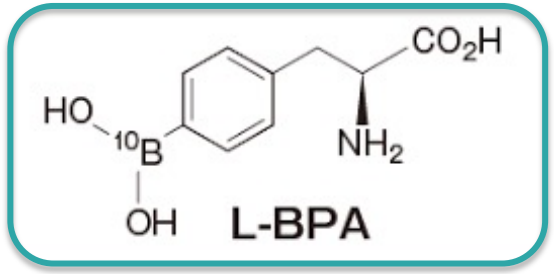
Current limitations the FDA-approved boron-based compounds



+ 12 boron atoms
- Weak tumor accumulation



+ Tumor-specific
- Poor number of Boron-atom

- Objectives: **To develop innovative theranostic boron-containing compounds**

  To evaluate their tumor accumulation

  To evaluate their BNCT efficacy in relevant biological models

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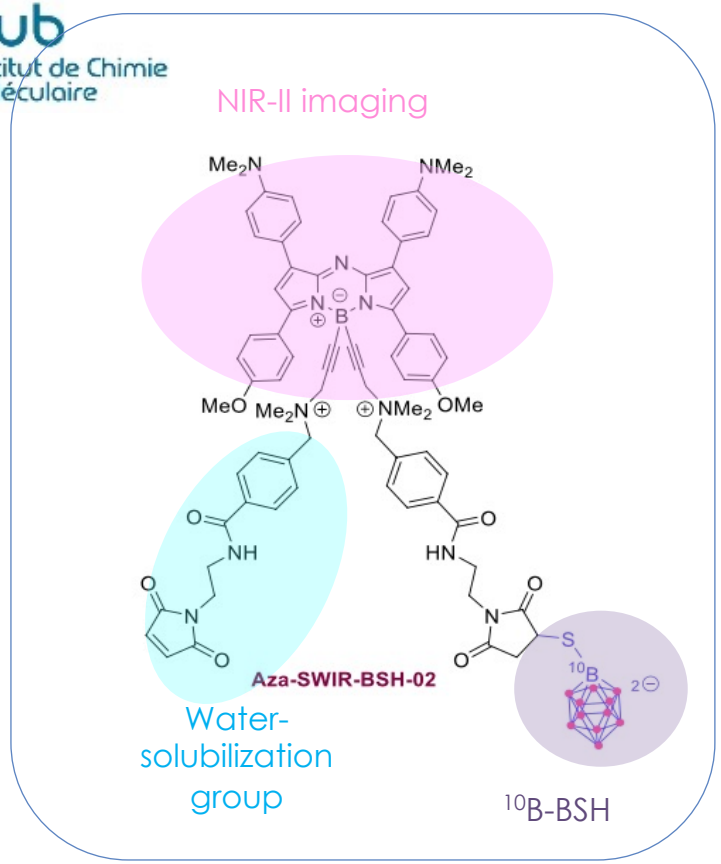
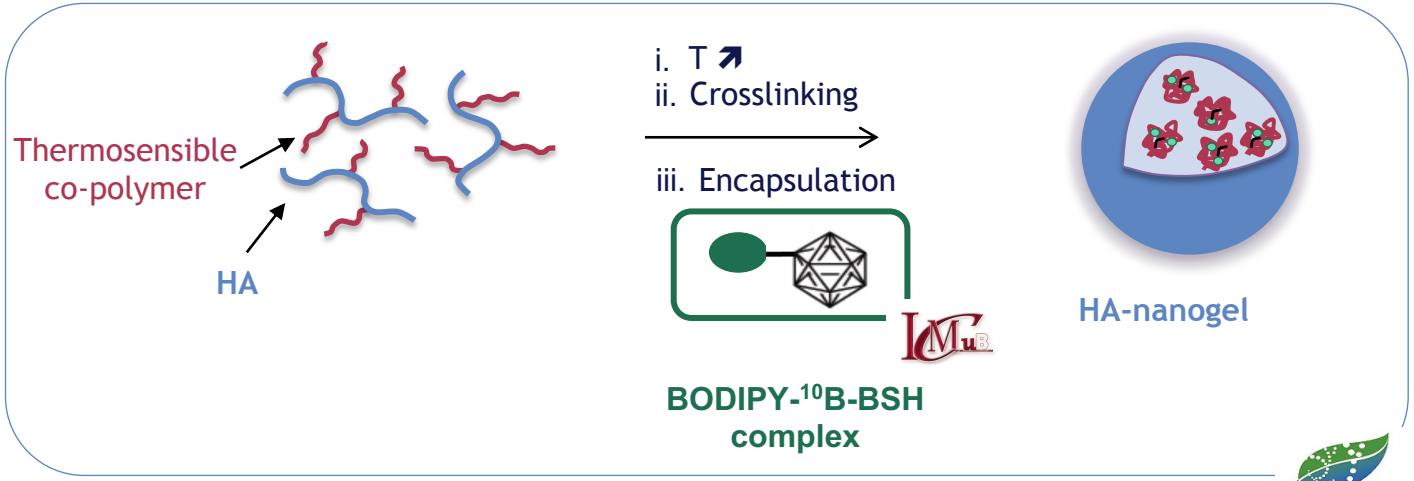
Theranostic vectors of boron-10



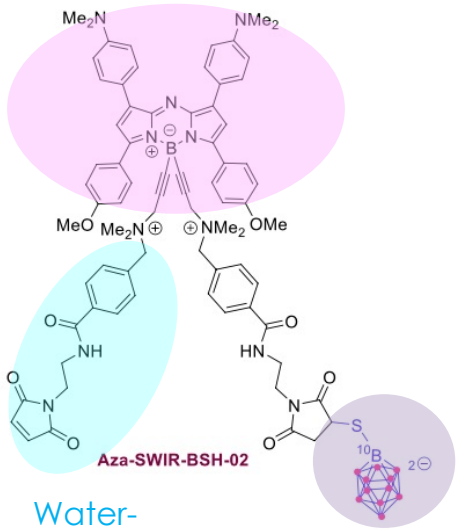
aza-BODIPY as theranostic BSH vector



Hyaluronic acid based nanogel

aza-BODIDY as ^{10}B-BSH vector: distribution

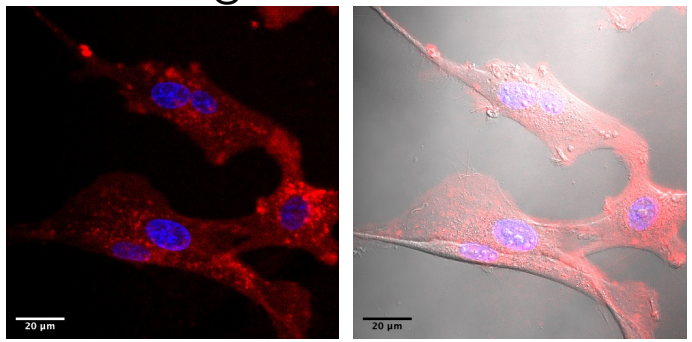
SWIR imaging



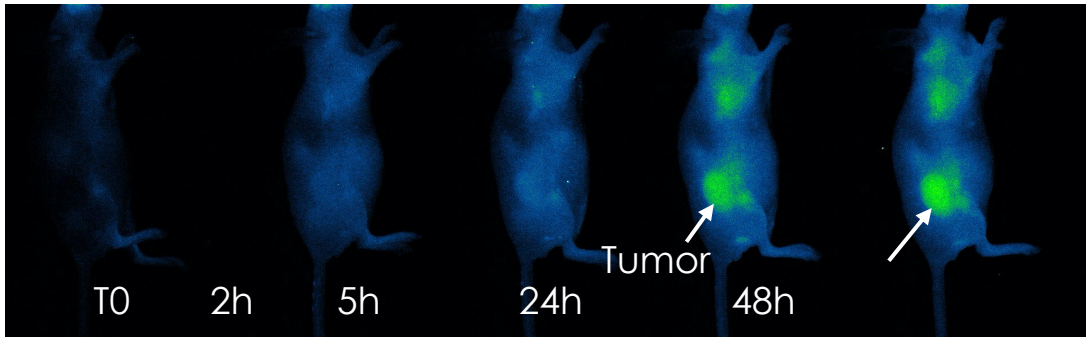
Water-solubilization group

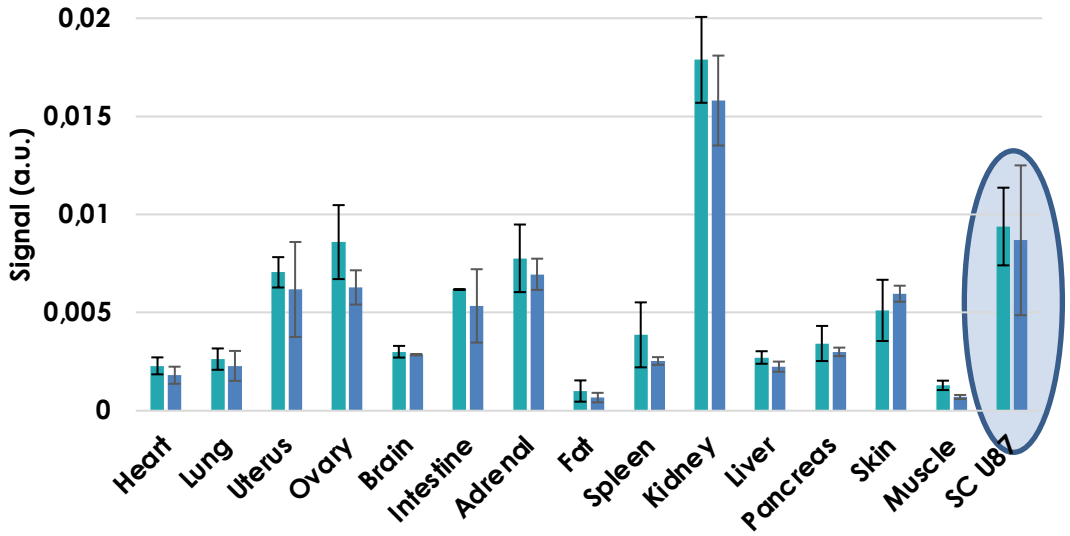
^{10}B-BSH

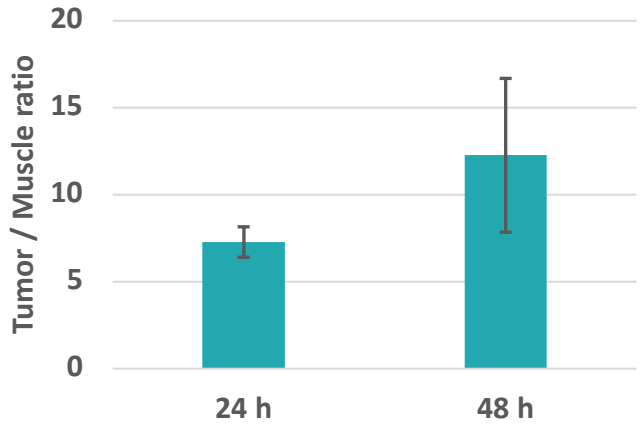
U87-MG glioblastoma cells



Mouse-bearing U87-MG sub-cutaneous tumor







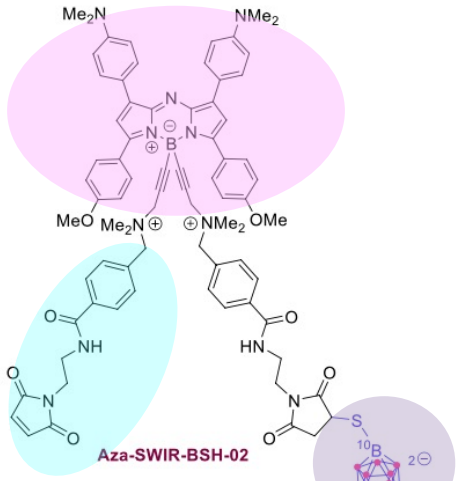
Ex-vivo Tumor / Muscle ratio
> 5 at 24 h and 48 h

Godard et al, Bioconjugate Chem 2020

Kalot et al, Cells 2020

aza-BODIDY as ^{10}B-BSH vector: distribution

SWIR imaging



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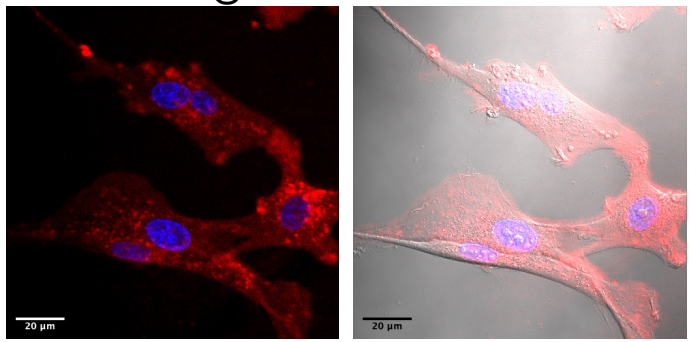
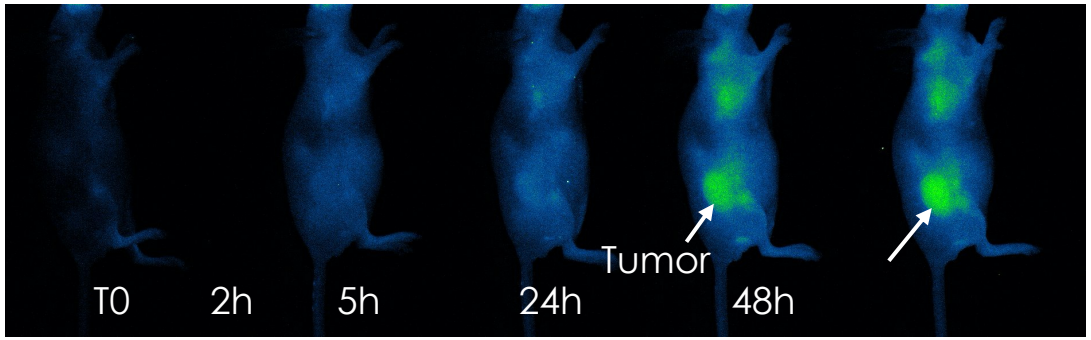
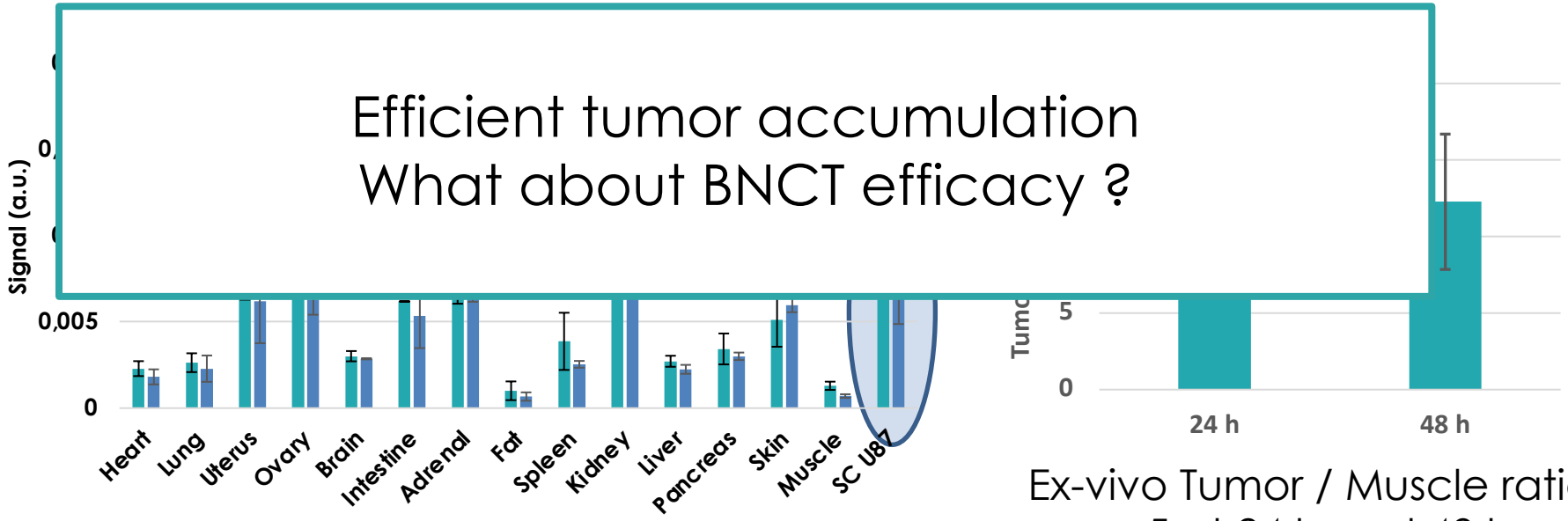


Mouse-bearing U87-MG sub-cutaneous tumor



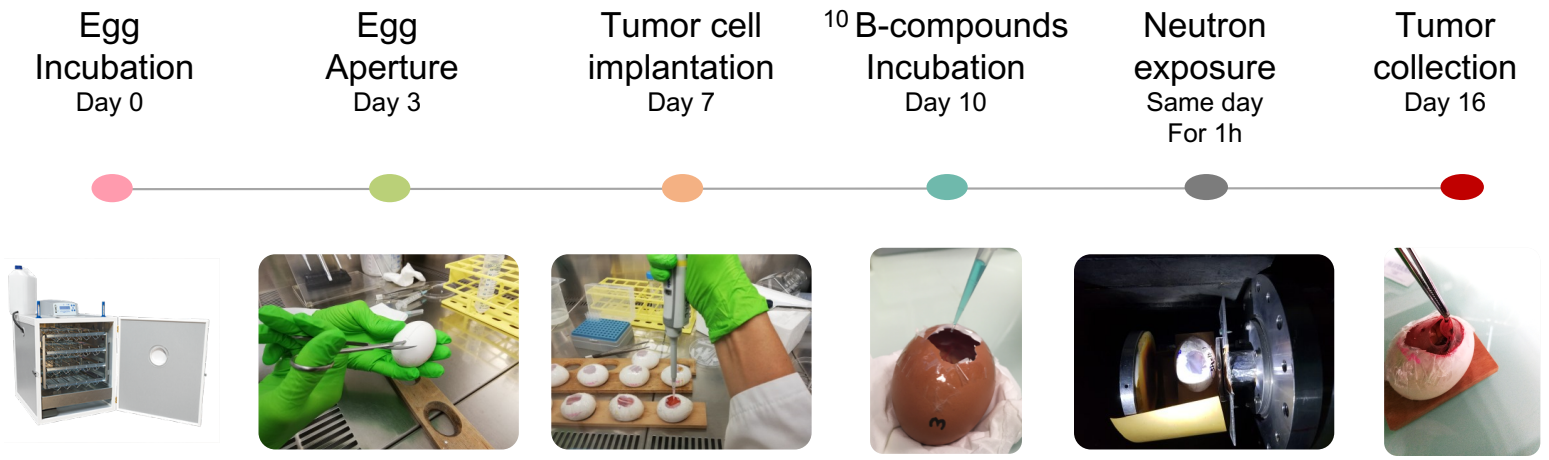
Efficient tumor accumulation
What about BNCT efficacy ?



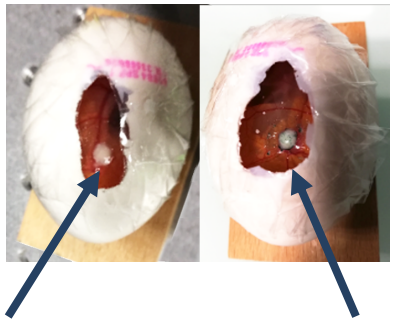
Ex-vivo Tumor / Muscle ratio
> 5 at 24 h and 48 h

aza-BODIDY as ^{10}B-BSH vector: BNCT efficacy

- In ovo model of tumor



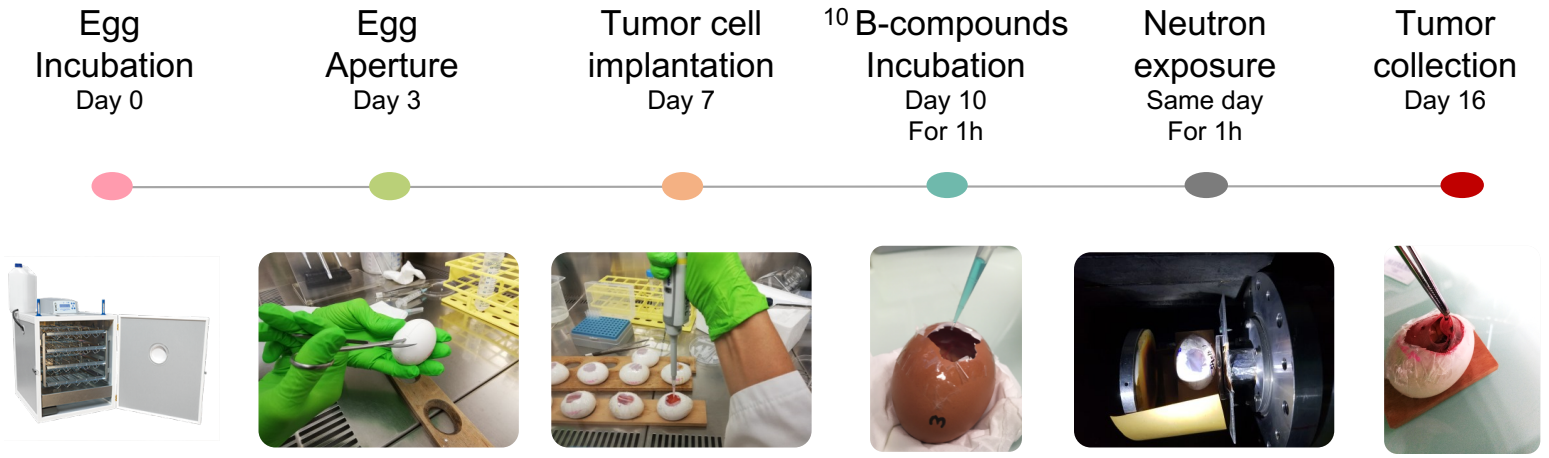
- Representative eggs after BSH or aza-BODIPY-BSH incubation (day 10)



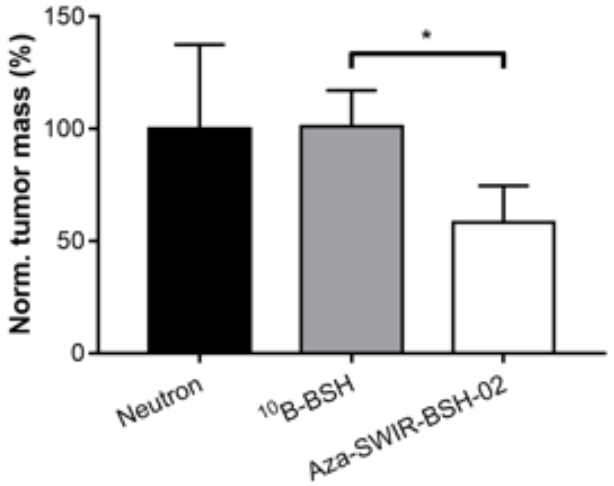
The "blue" aza-BODIPY is accumulated inside the tumor mass.

aza-BODIDY as ^{10}B-BSH vector: BNCT efficacy

- In ovo model of tumor



- Tumor masses collected 6 days after neutron exposure



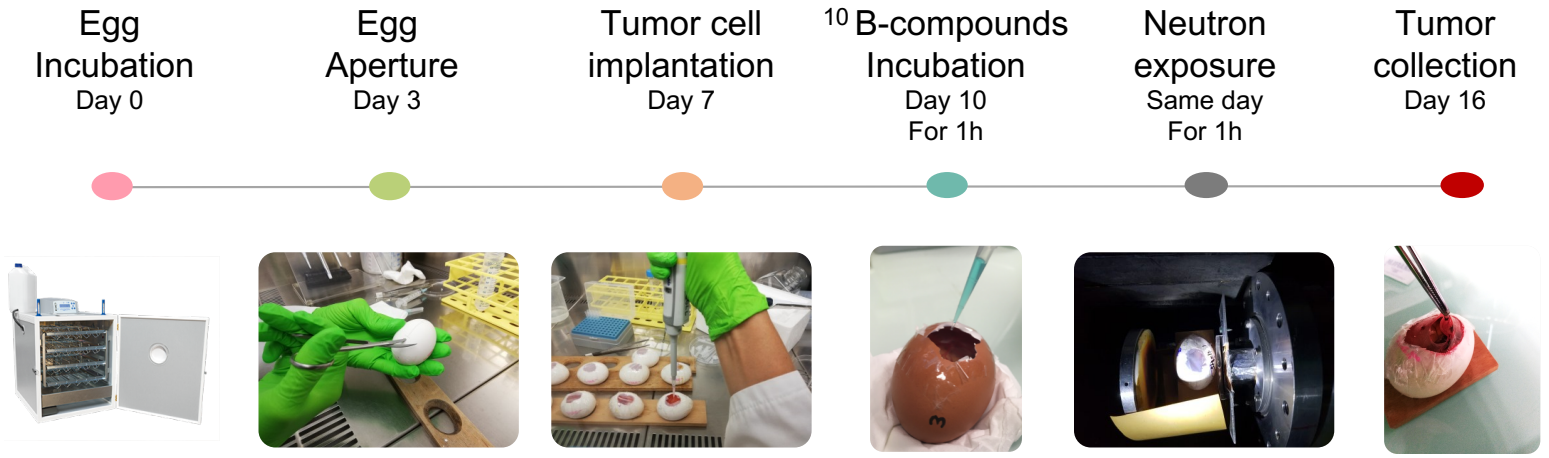
aza-BODIPY-BSH was able to significantly reduce tumor mass (-40%) while BSH did not.

Kalot et al, Cells 2020

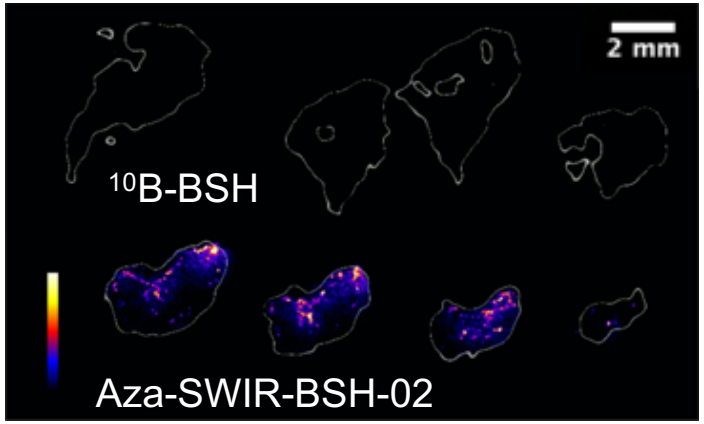
Sauerwein et al, Life 2021

aza-BODIDY as ^{10}B-BSH vector: BNCT efficacy

- In ovo model of tumor



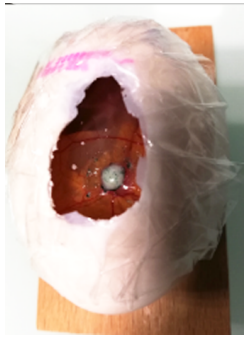
- Boron was still present in the tumor 6 days after neutron exposure after aza-BODIPY vectorization

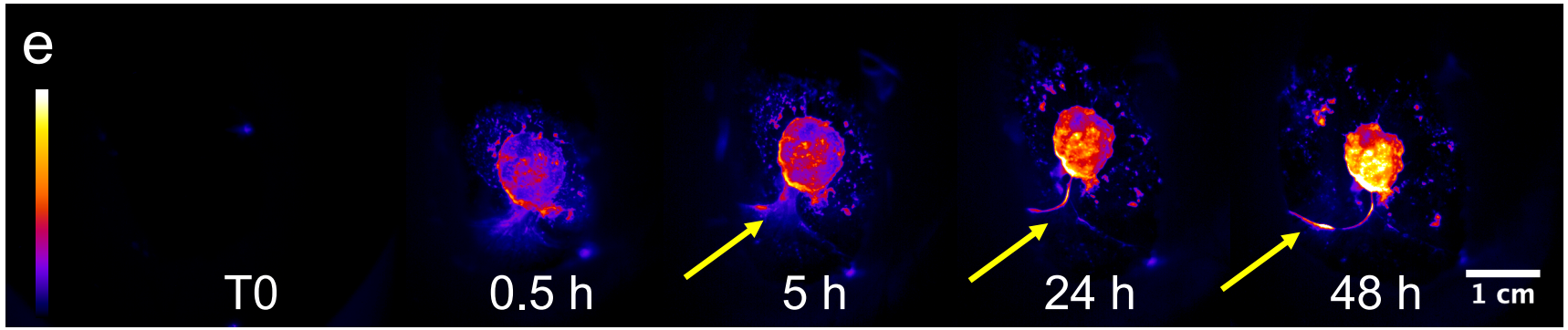


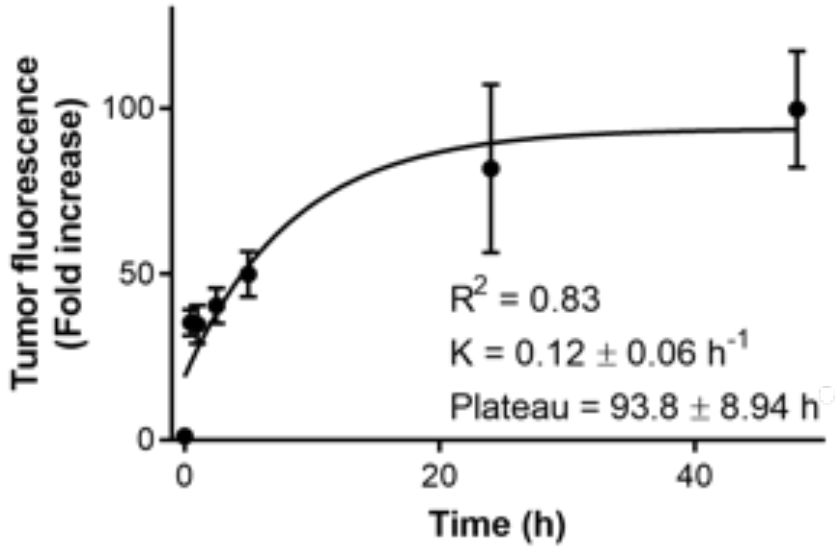
Boron was detected on tumor sections using LIBS elemental imaging after aza-BODIPY-BSH incubation

Kinetic of tumor uptake

- In ovo distribution of aza-BODIPY-BSH using fluorescent optical imaging







- In ovo distribution evidences a maximum tumor uptake after 24-48 h

➔ BNCT efficacy might be optimal if the compound is incubated for >24 h

Take home message

- Development of new radiotherapy modalities for a better tumor control and a limitation of the side effects
- Drug formulation optimization for a better efficacy (drug release/tumor targeting)
- Theranostic compounds for BNCT
- PoC:
  - Synchrotron → 6MV clinical irradiator
  - BNCT for Rodents-bearing tumors

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EPIGENETICS • ENVIRONMENT
CELL PLASTICITY • CANCER

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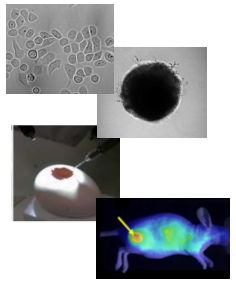
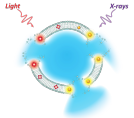
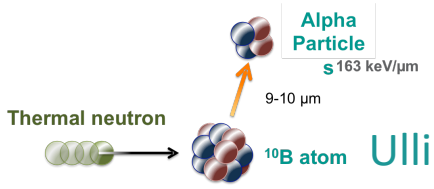


Mans BROEKGAARDEN

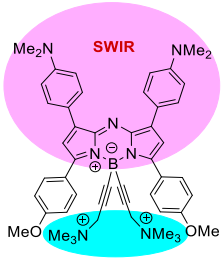


Xavier LE GUEVEL



Ulli KÖSTER

Christine GOZE
Amélie GODARD
Ewen BODIO



Wolfgang SAUERWEIN