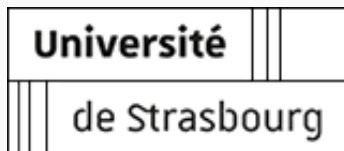




La thérapie photodynamique: vers le développement de photosensibilisateurs polyvalents et activables par pH pour le traitement des cancers ORL

Carlotta Figliola

Institut de Chimie et Procédés pour l'Énergie, l'Environnement et la Santé
« Chimie Moléculaire et Analytique », COMBO group
Université de Strasbourg - UMR CNRS 7515



Hierarchical & Functional
Materials for health,
environment & energy |
HiFunMat

Photodynamic therapy: introduction

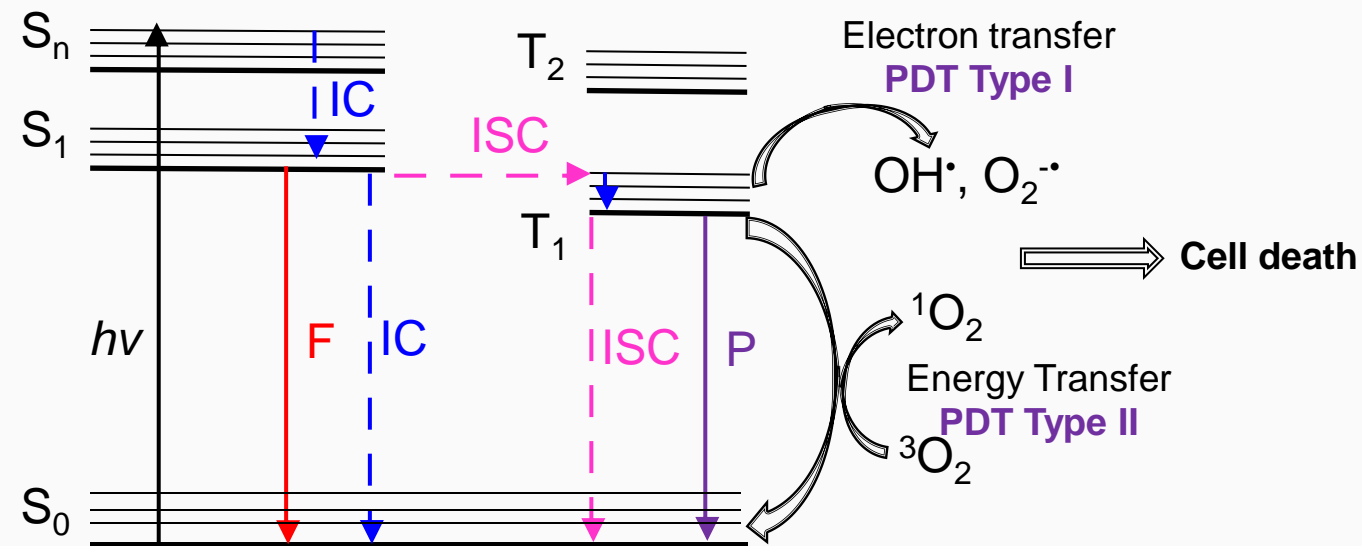
- ▶ Photochemistry-based therapy
- ▶ Oncology (breast, oral cavity, head, neck, skin, bladder), ophthalmology, urology, antimicrobial treatments
- ▶ Minimal invasiveness, low systemic toxicity, high tumor selectivity
- ▶ Combination with other treatments and repetitive treatment cycles



Dolmans, D. E. J. G. J.; Fukumura, D.; Jain, R. K. *Nat. Rev. Cancer* **2003**, 3 (5), 380; Monroe, S.; Colón, K. L.; Yin, H.; Roque, J.; Konda, P.; Gujar, S.; Thummel, R. P.; Lilge, L.; Cameron, C. G.; McFarland, S. A. *Chem. Rev.* **2019**, 119 (2), 797; Pham, T. C.; Nguyen, V.-N.; Choi, Y.; Lee, S.; Yoon, J. *Chem. Rev.* **2021**, 121 (21), 13454.

Photodynamic therapy: introduction

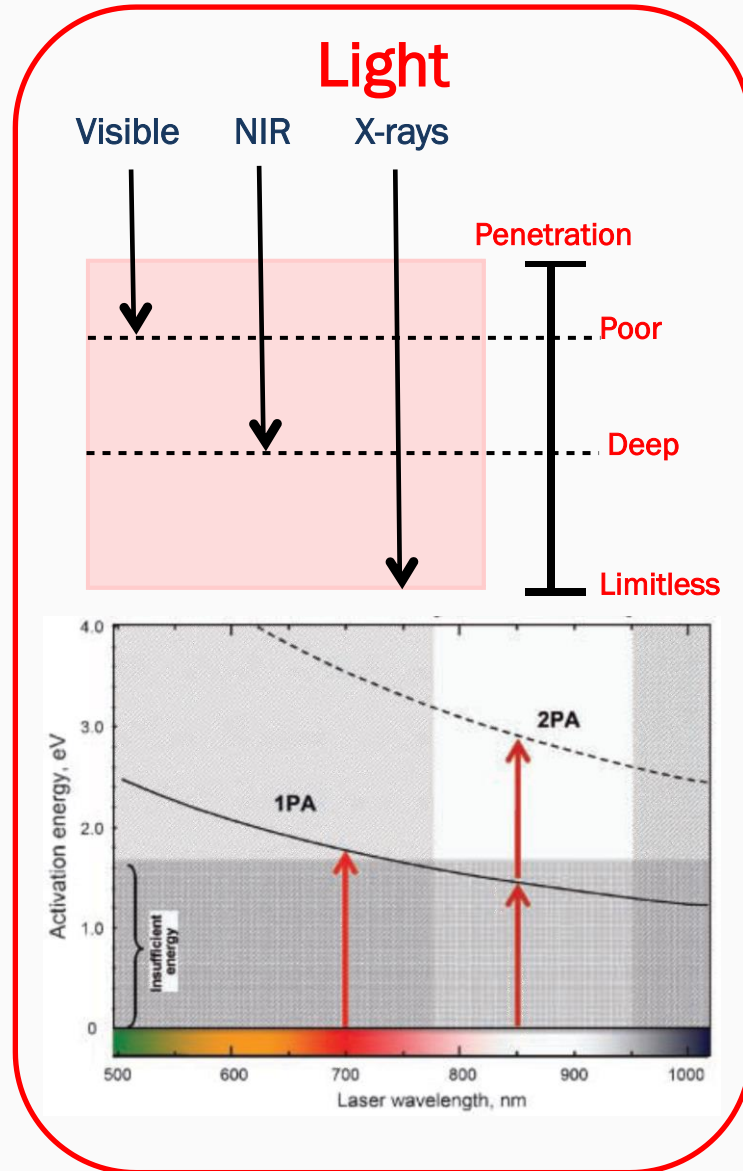
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- ▶ Combination of two non-toxic components, **photosensitizer (PS)** and **light**



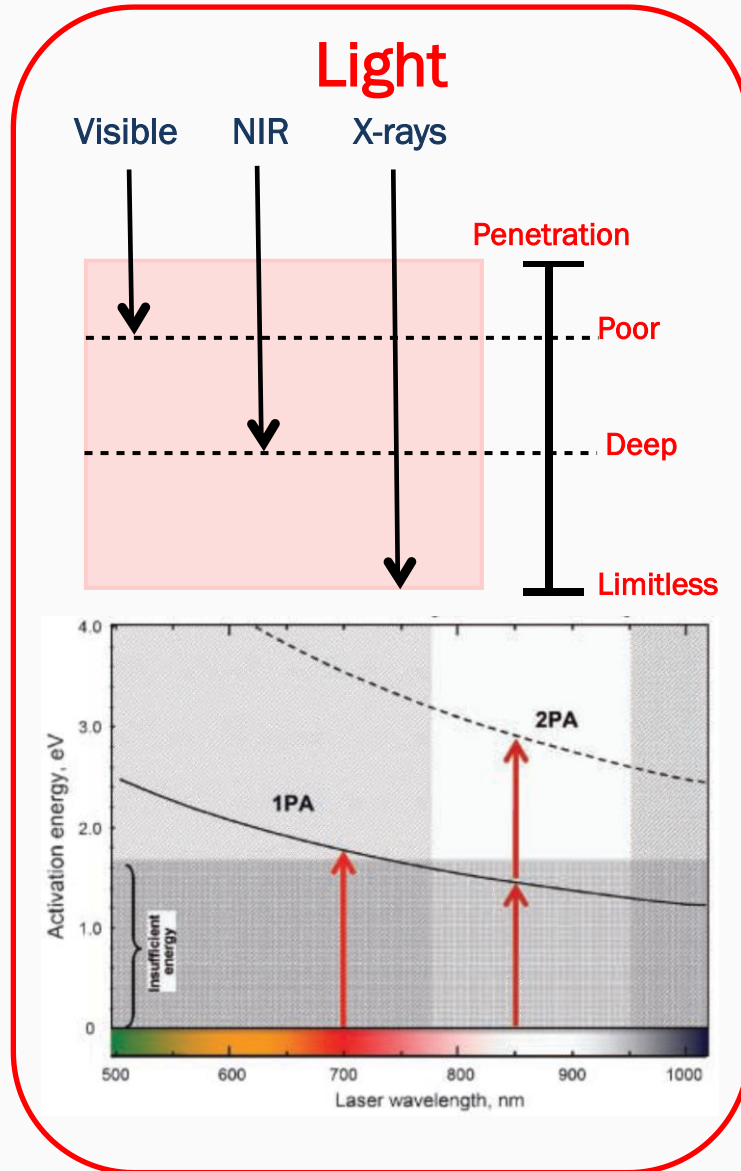
Dolmans, D. E. J. G. J.; Fukumura, D.; Jain, R. K. *Nat. Rev. Cancer* **2003**, 3 (5), 380; Monroe, S.; Colón, K. L.; Yin, H.; Roque, J.; Konda, P.; Gujar, S.; Thummel, R. P.; Lilge, L.; Cameron, C. G.; McFarland, S. A. *Chem. Rev.* **2019**, 119 (2), 797; Pham, T. C.; Nguyen, V.-N.; Choi, Y.; Lee, S.; Yoon, J. *Chem. Rev.* **2021**, 121 (21), 13454.

Photodynamic therapy: current challenges

Photodynamic therapy: current challenges



Photodynamic therapy: current challenges

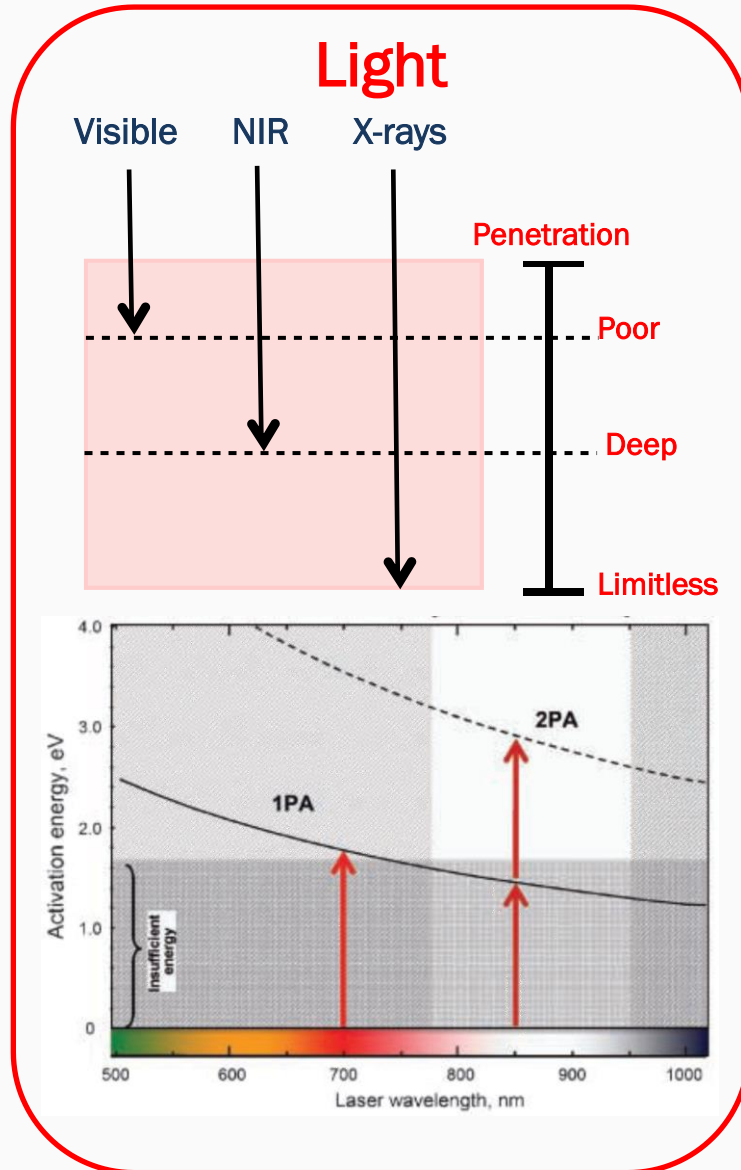


Photosensitizer

- ▶ Absorption in the therapeutic window
- ▶ Selective
- ▶ Good accumulation in tissues
- ▶ High body clearance
- ▶ Good ratio water soluble/lipophilicity

generic name	chemical name	structure	λ_{ex} (nm)	ϵ_{max} ($M^{-1}\cdot cm^{-1}$)	cancer types	
porfimer sodium ^a	Photofrin	porphyrin	630	3000	high-grade dysplasia in Barrett's esophagus, obstructive esophageal cancer, lung cancer; bladder cancer (only in Canada)	
5-aminolevulinic acid (5-ALA) ^b	Ameluz; Levulan	porphyrin precursor	632 ^c	5000 ^c	basal cell carcinoma, squamous cell carcinoma	
methyl 5-aminolevulinate (MAL) ^b	Metvix; Metvixia	porphyrin precursor	635 ^c	NR ^d	basal cell carcinoma	
verteporfin (BPD-MA)	Visudyne	worldwide	chlorin	689	34 000	age-related macular degeneration

Photodynamic therapy: current challenges



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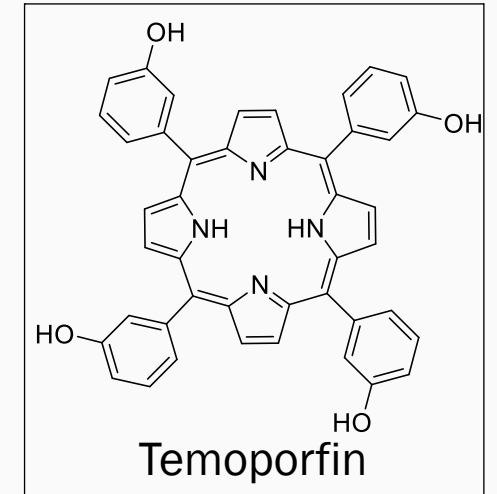
Oxygen

Hypoxia (solid tumors)

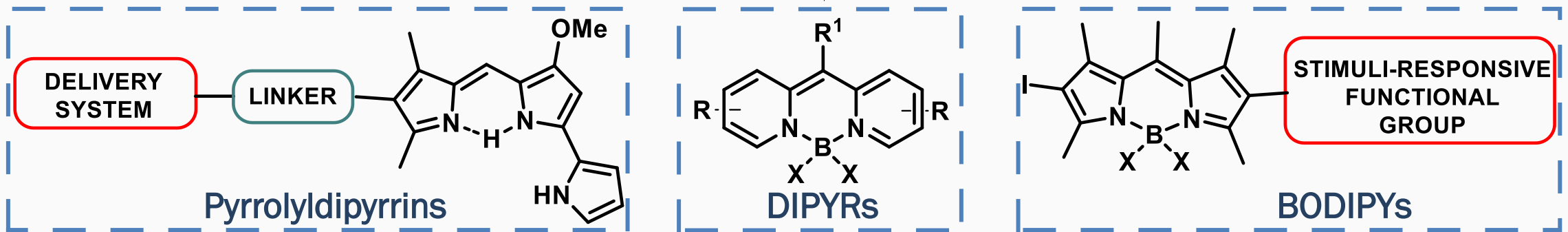
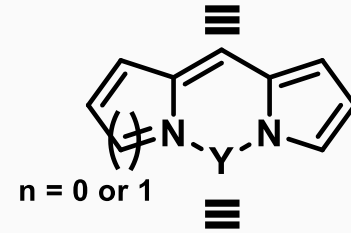
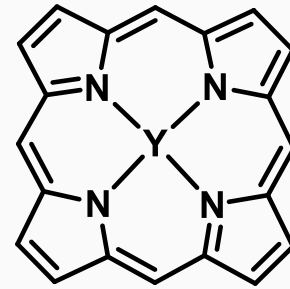
Van Straten, D.; Mashayekhi, V.; De Bruijn, S. H.; Oliveira, S.; Robinson, J. D. *Cancers* **2017**, *9* (2), 19; Monroe, S.; Colón, K. L.; Yin, H.; Roque, J.; Konda, P.; Gujar, S.; Thummel, R. P.; Lilge, L.; Cameron, C. G.; McFarland, S. A. *Chem. Rev.* **2019**, *119* (2), 797; Pham, T. C.; Nguyen, V.-N.; Choi, Y.; Lee, S.; Yoon, J. *Chem. Rev.* **2021**, *121* (21), 13454.

Photodynamic therapy against HNC

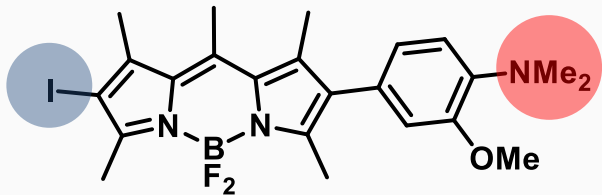
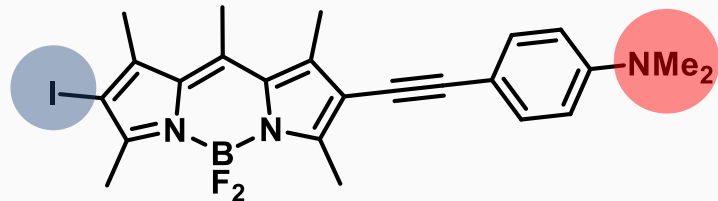
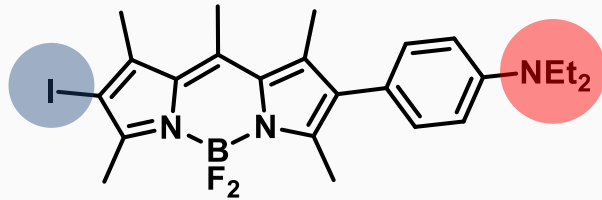
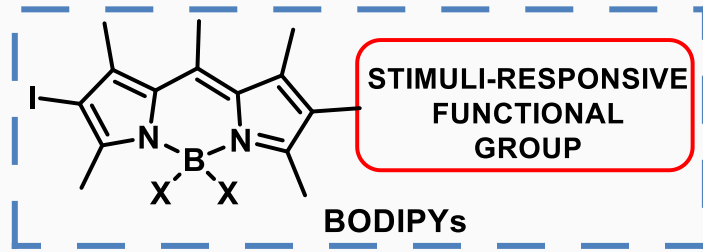
- ▶ *meta*-tetrahydroxyphenylchlorin (*m*THPC or Temoporfin) is a second-generation PS.
- ▶ approved only in European countries for treatment of HNC.
- ▶ In case of early stage HNC and smaller lesions of ≤ 5 mm of thickness, PDT treatment is as effective as surgery because of its low light penetration in tissues (excitation wavelength of 652 nm),
- ▶ In case of advanced HNC, a palliative PDT treatment is preferred over standard care.
- ▶ PDT is a valuable treatment option in patients with oral and/or oropharyngeal inoperable HNC and it can induce durable local control in an important fraction of treated patients, with an acceptable toxicity profile. Different formulations of Temoporfin altering the solubility and tumour distribution have been commercialized and few chemical alterations of the structure reported without significant advances in preclinical and clinical trials, to the best of our knowledge.
- ▶ Despite its numerous side effects, Temoporfin is considered the main PS reference for PDT treatment because of the extensive scientific knowledge.



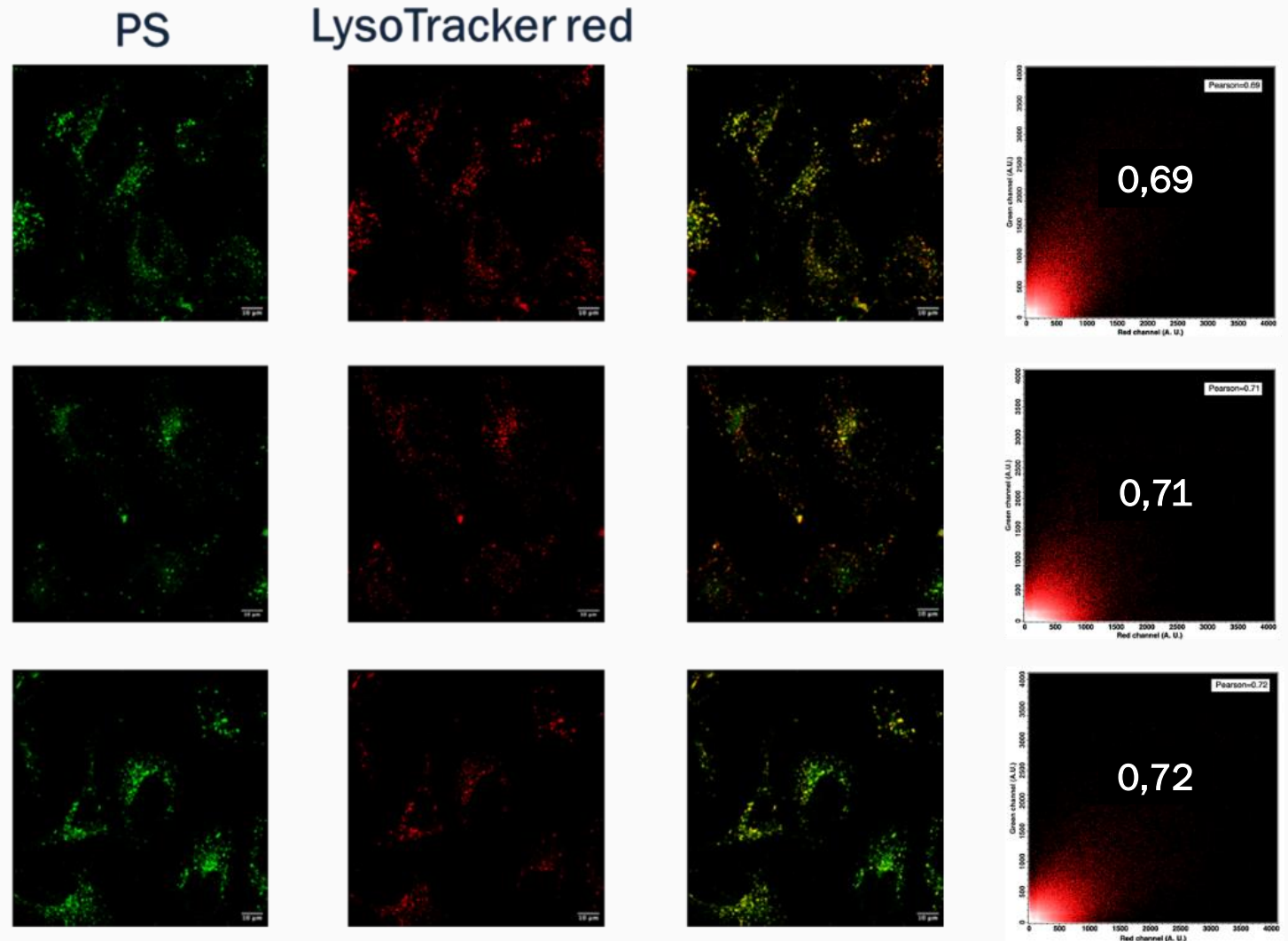
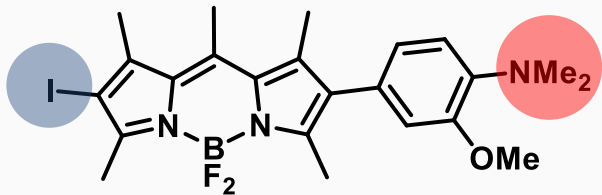
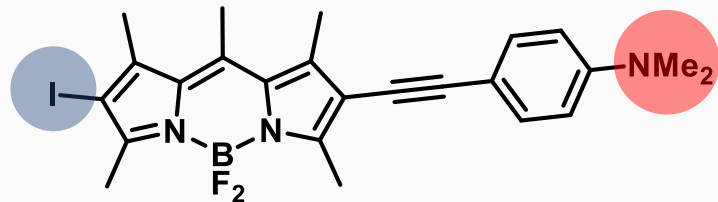
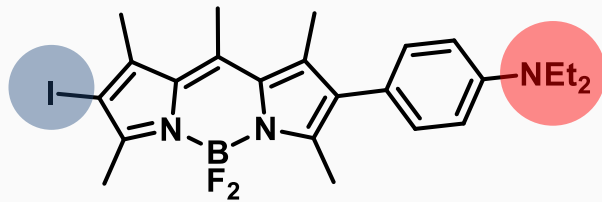
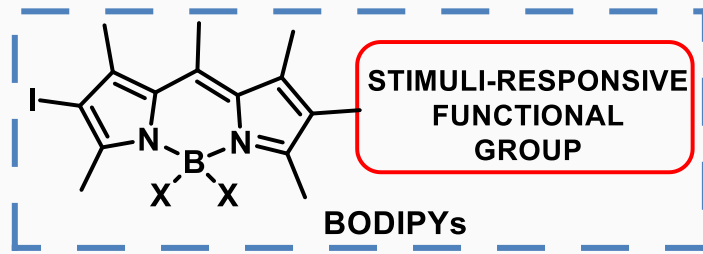
Photosensitizing platforms



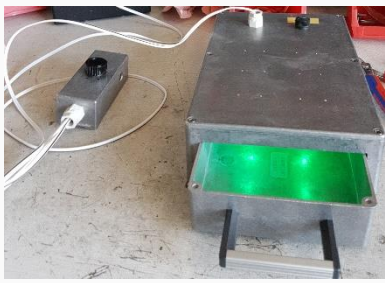
Current work on BODIPYs



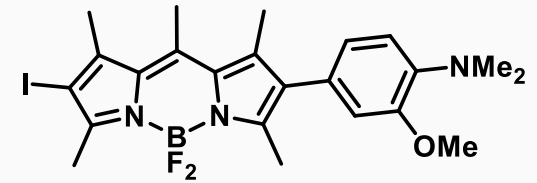
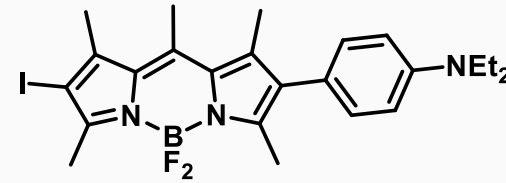
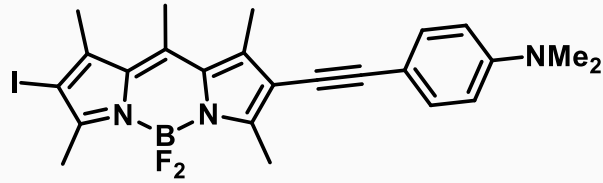
Current work on BODIPYs



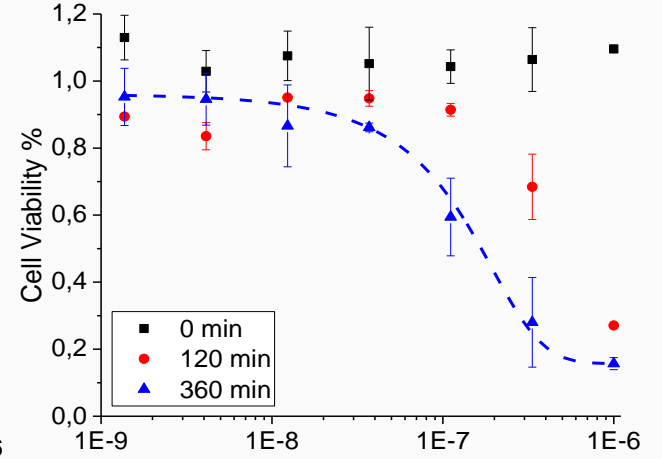
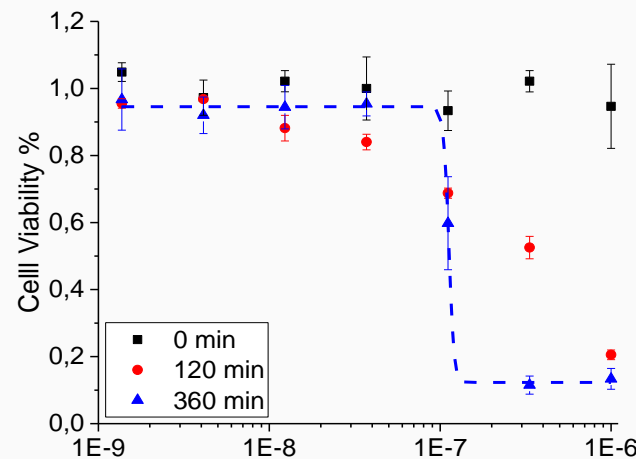
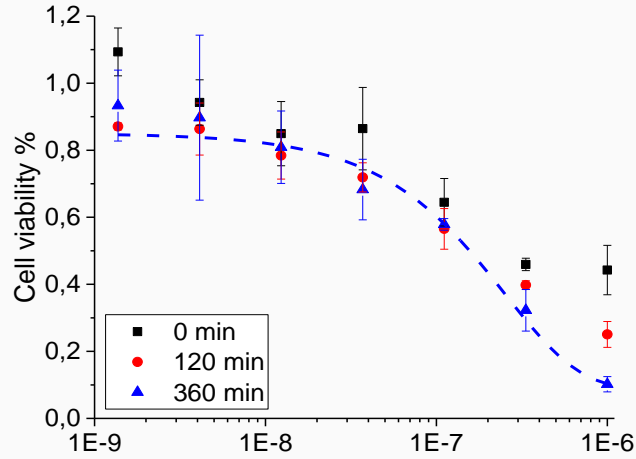
Co-localization and photodynamic cytotoxic tests are in collaboration with Pr. Pascal Didier and Dr. Halina Anton (Laboratoire de bioimagerie et pathologies – LBP, UMR7021)



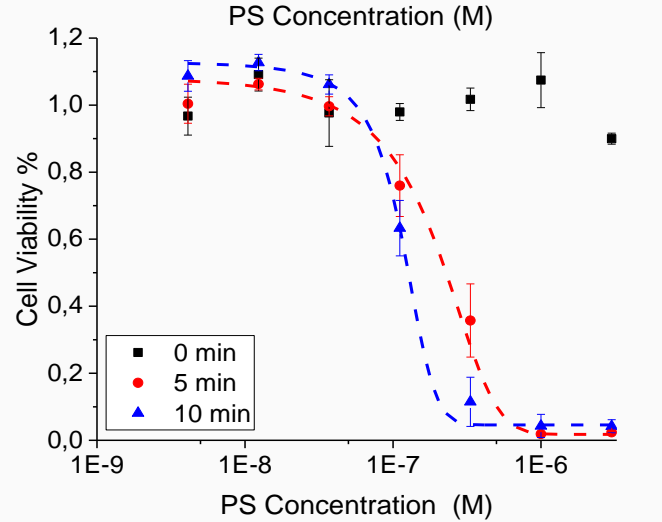
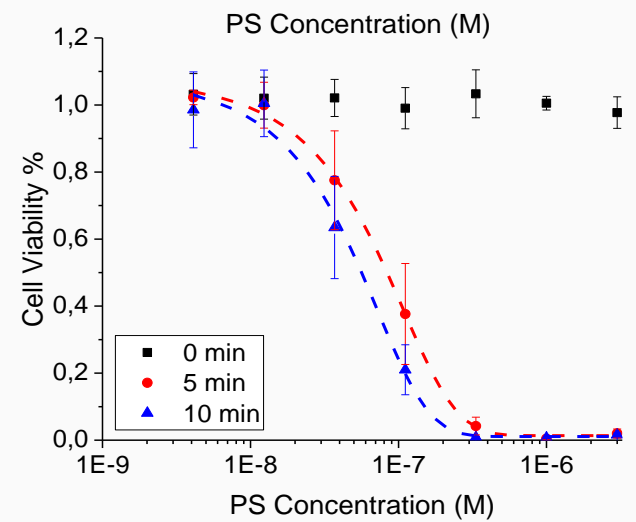
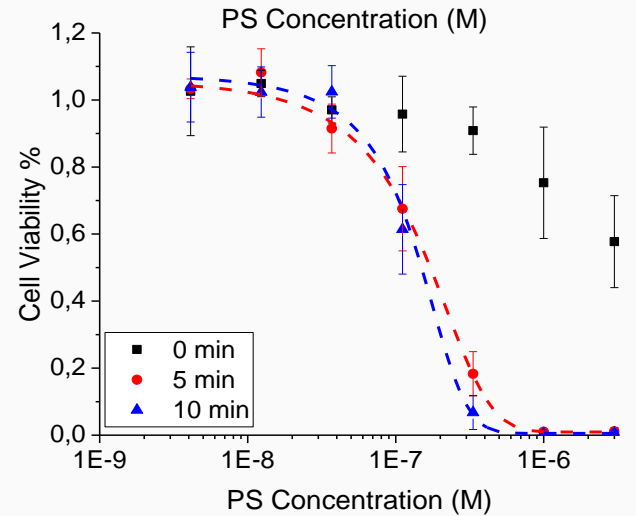
Current work on BODIPYs

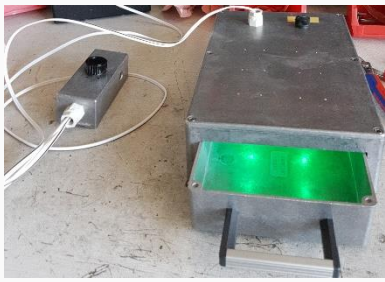


**Power density
=0.45 mW/cm²**

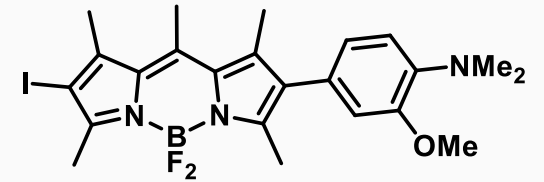
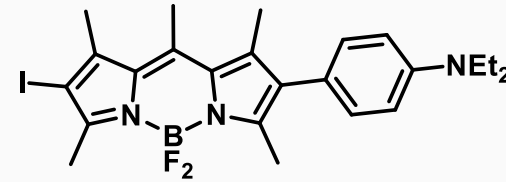
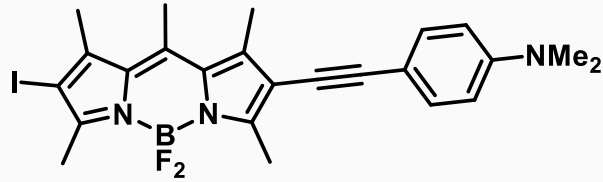


**Power density
=7.1 mW/cm²**

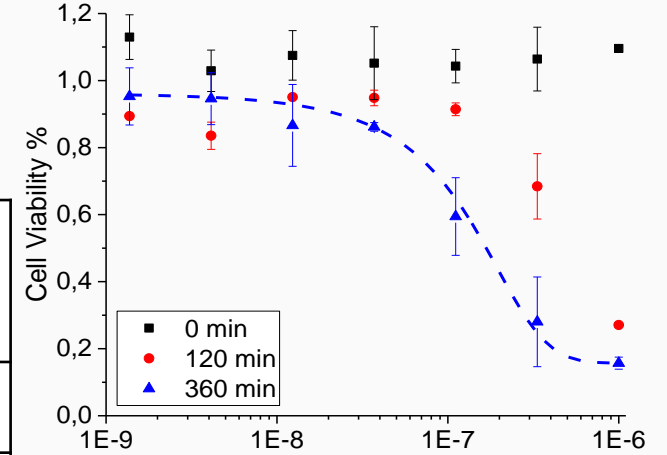
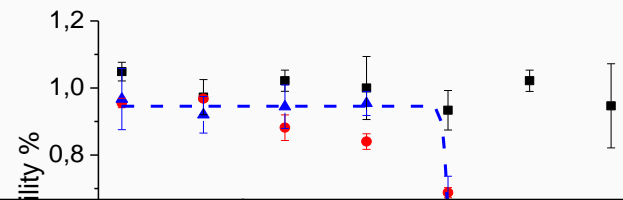
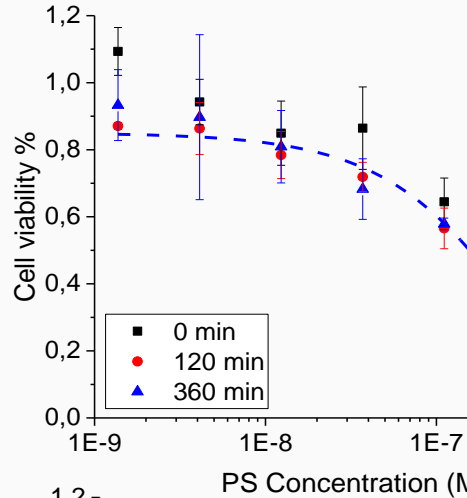




Current work on BODIPYs

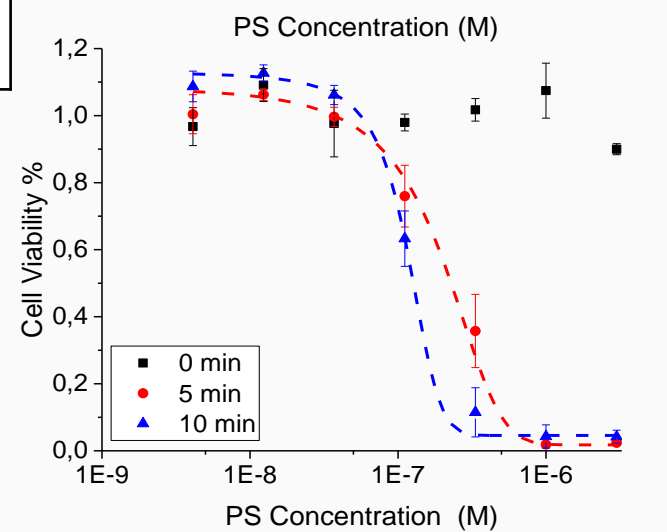
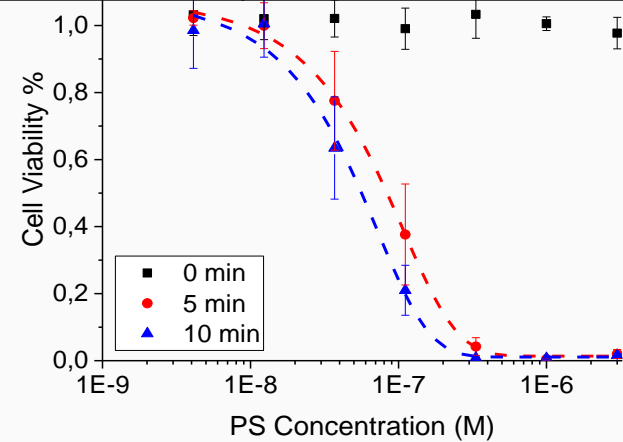
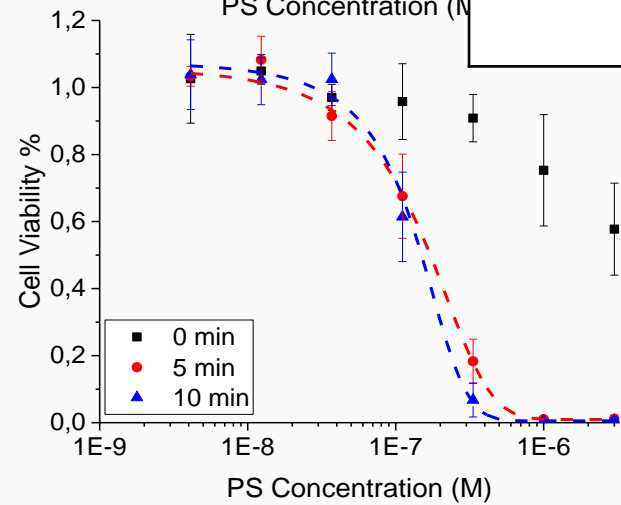


**Power density
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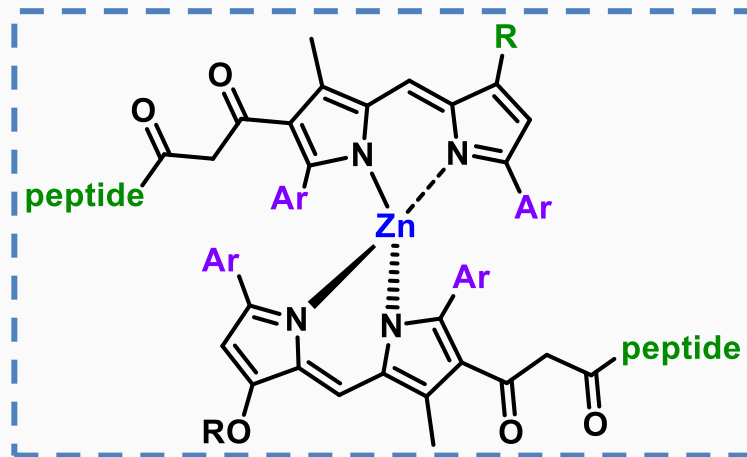
	IC ₅₀ after 10 min, PD = 7.1mW/cm ²
2	0.06 μM
3	0.12 μM

**Power density
=7.1 mW/cm²**



Current work on BODIPYs

Project **TABATA** in collaboration with Dr. Halina Anton, Dr. Sophie Martin and Pr. Pascal Didier
(Laboratoire de bioimagerie et pathologies – LBP, UMR7021)

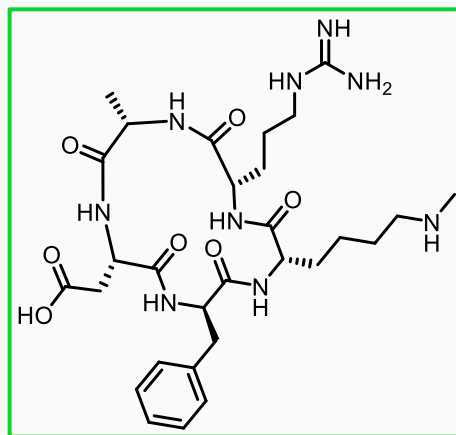


pH-responding
functional groups

Extended
 π -conjugation

High binding-affinity
ligand

Singlet oxygen
production



= Arg-Gly-Asp tripeptide (or RGD motif) => $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins*

*A. C. Jung, A.-M. Ray, L. Ramolu, C. Macabre, F. Simon, F. Noulet, A.-F. Blandin, G. Renner, M. Lehmann, L. Choulier, H. Kessler, J. Abecassis, M. Dontenwill and S. Martin, *Oncotarget*, 2015, **6**, 41884-47901; H. You, H.-E. Yoon, P.-H. Jeong, H. Ko, J.-H. Yoon and Y.-C. Kim, *Bioorg. Med. Chem.*, 2015, **23**, 1453-1462; T. Zhu, J. Xiong, Z. Xue, Y. Su, F. Sun, R. Chai, J. Xu, Y. Feng and S. Meng, *RSC Adv.*, 2018, **8**, 20087-20094.

Acknowledgments



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Pascal Didier
Halina Anton
Sophie Martin
Pascal Retailleau

