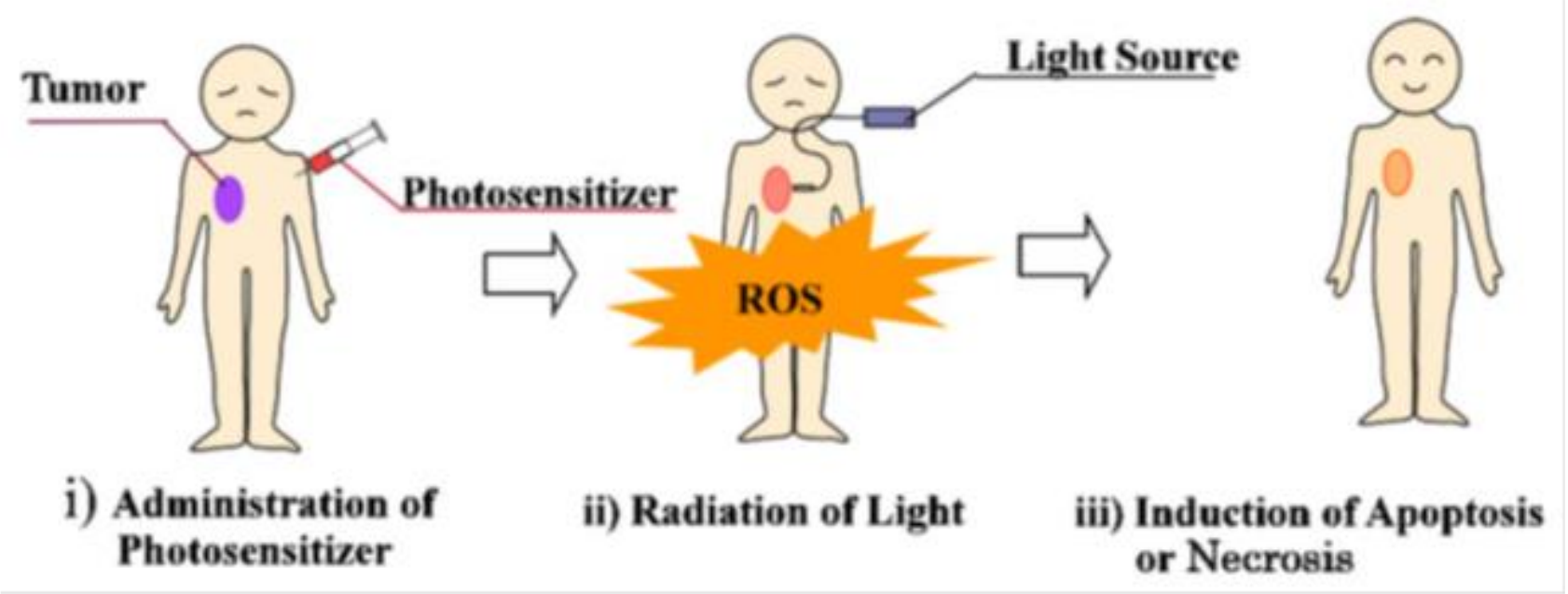
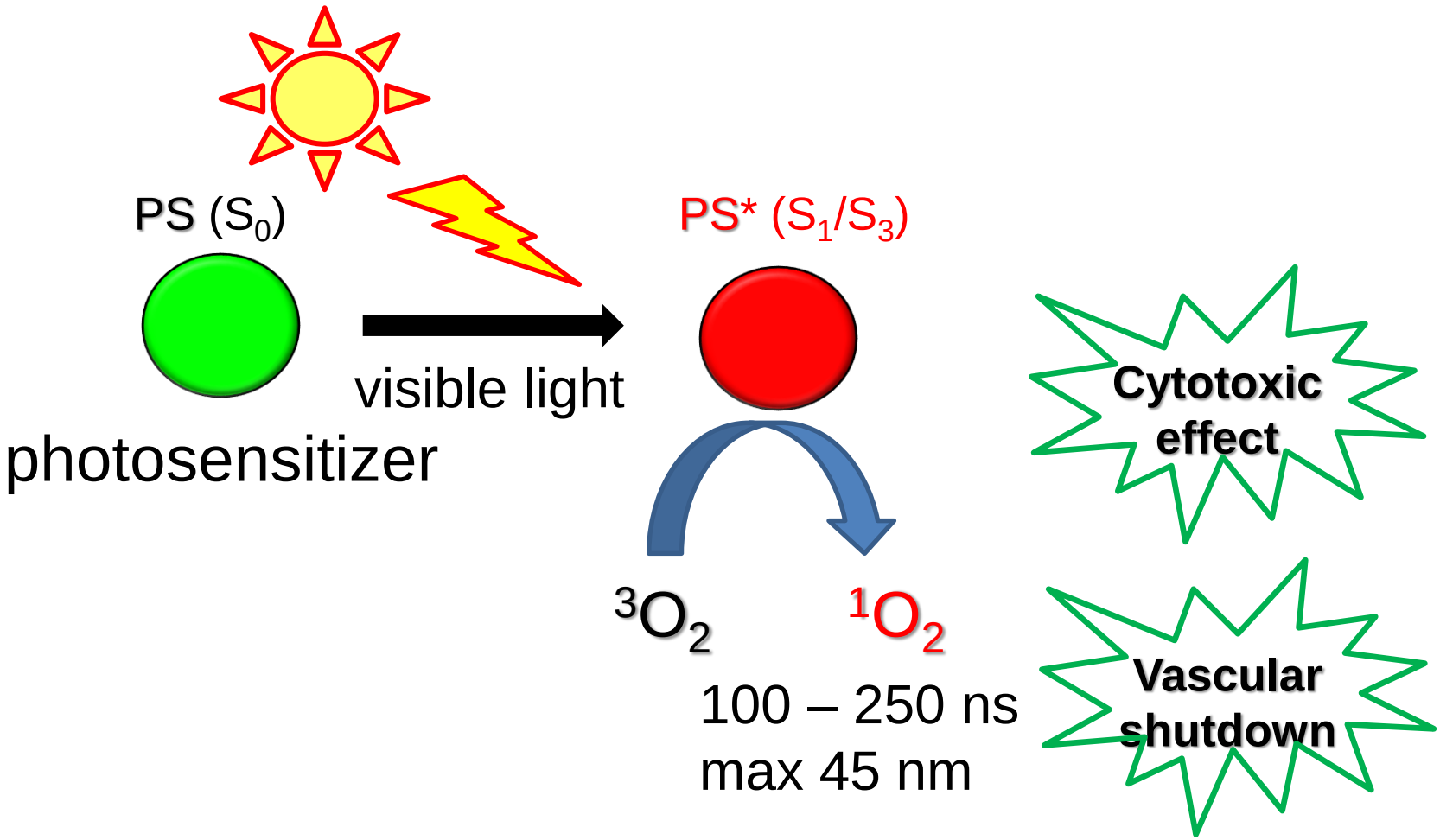
Photodynamic Therapy (PDT)

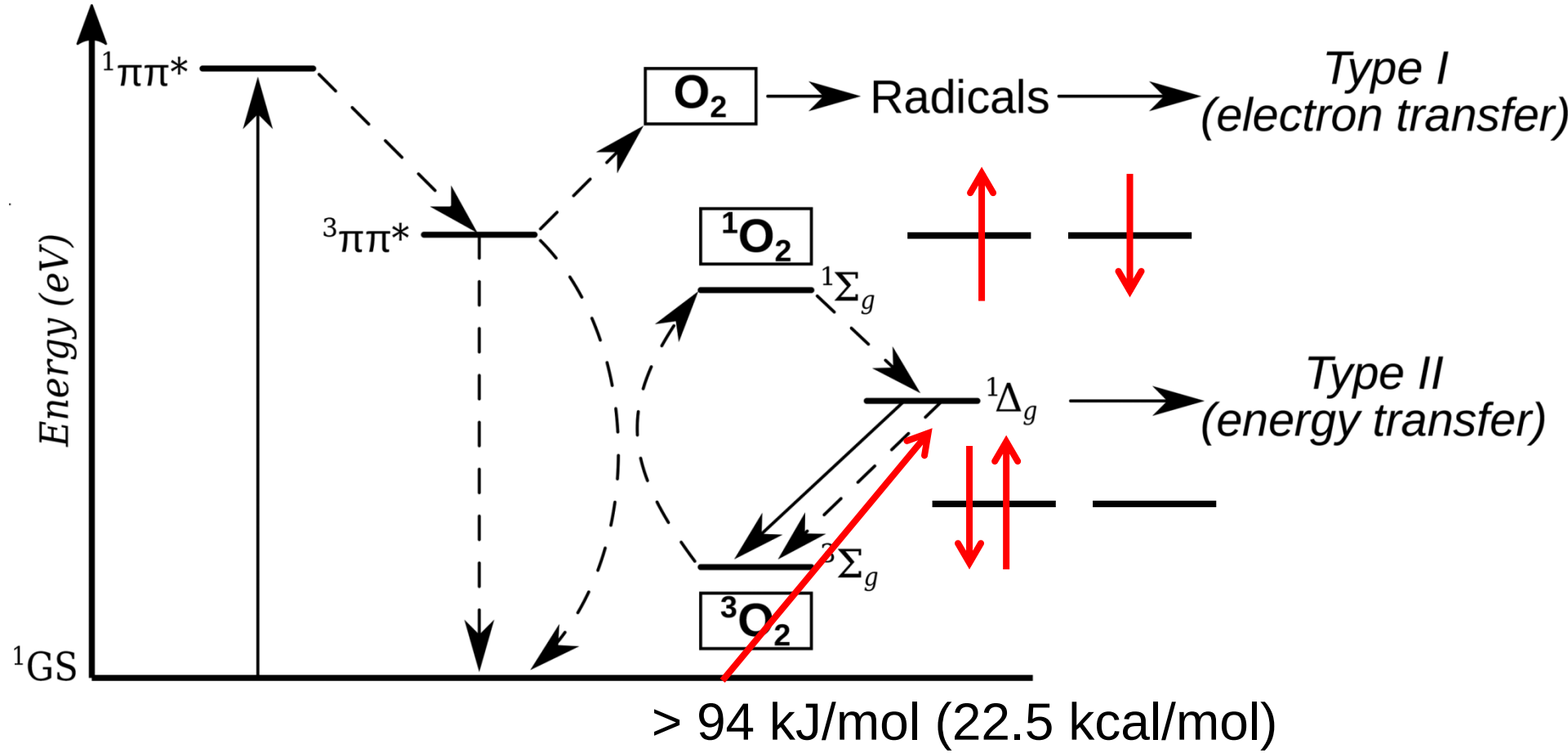
Localized and rather superficial solid tumors (mm deep)



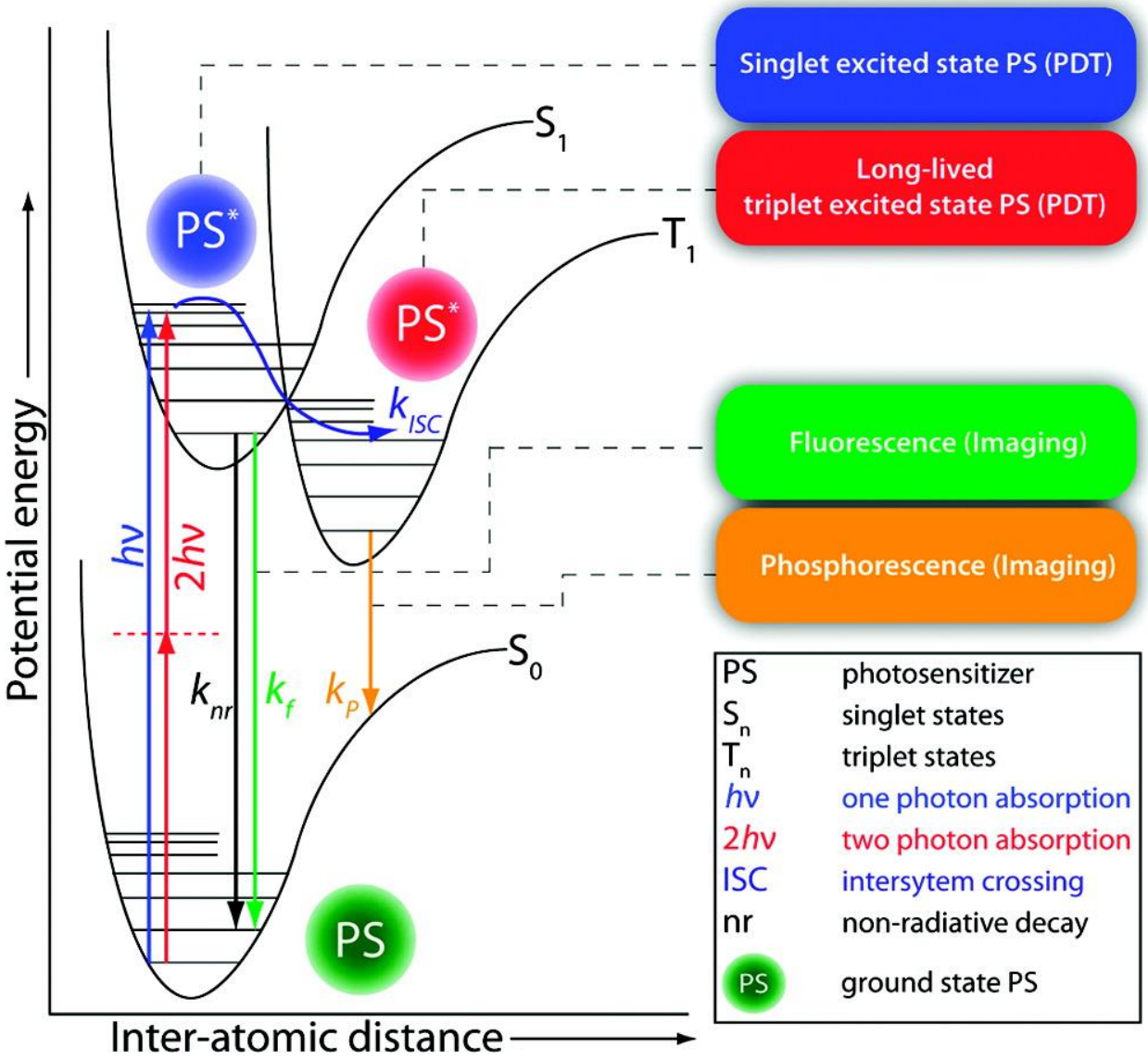
Spatio-temporal control on the active species

Ternary therapy: photosensitizer, light, oxygen

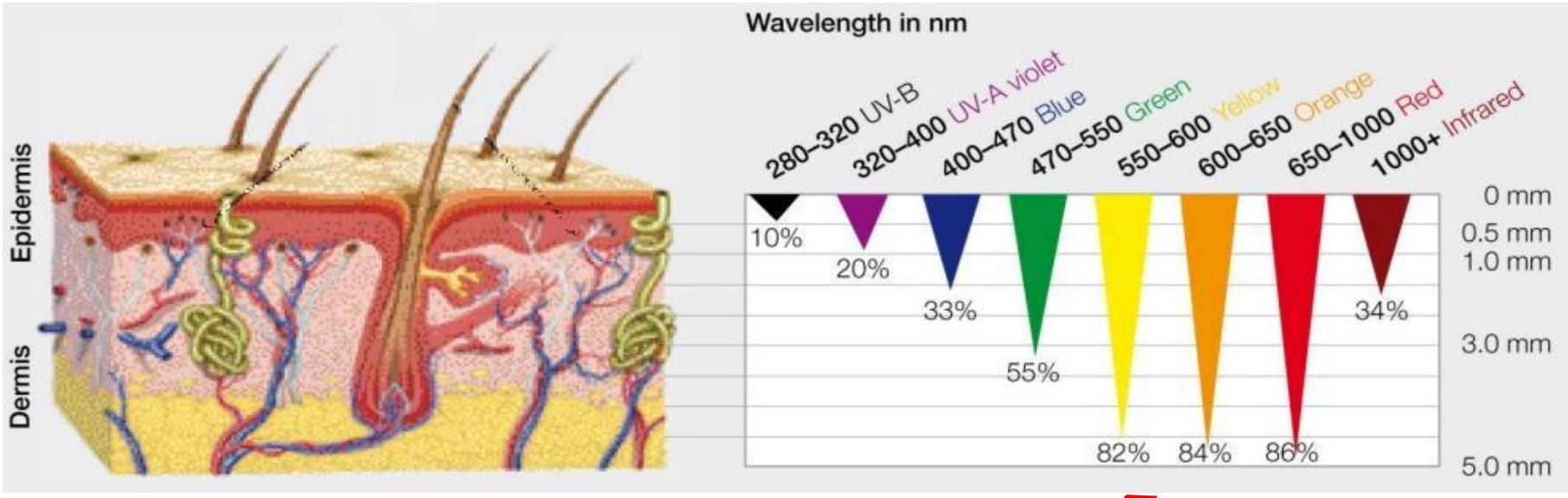




It is estimated that $^1O_2$ can diffuse for ca. 45 nm from the point where it is generated (lifetime: 100 – 250 ns).


Singlet excited state PS (PDT)
Long-lived
triplet excited state PS (PDT)
Fluorescence (Imaging)
Phosphorescence (Imaging)
Potential energy
Inter-atomic distance
S1
T1
S0
PS*
PS*
PS
kISC
hν
2hν
knr
kf
kP
PS photosensitizer
Sn singlet states
Tn triplet states
hν one photon absorption
2hν two photon absorption
ISC intersytem crossing
nr non-radiative decay
PS ground state PS

Tissue penetration of light



PDT window

ΔE between $^1O_2$ and $^3O_2$ = 94 kJ/mol

This energy gap is compatible with photosensitizers that have absorption maxima up to over 800 nm (their triplet excited state is still higher in energy than the ground state of $^3O_{2)}$.

The ideal photosensitizer

- Absorbs strongly in the PDT window (600 – 900 nm)
- Has a high $^1O_2$ quantum yield
- Is photostable (no photo-bleaching)
- Is non-toxic in the dark
- Localizes selectively in the diseased tissue
- Has a rapid clearance

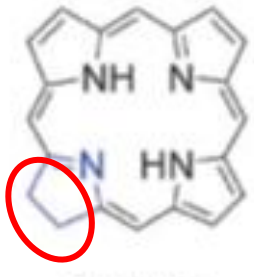
Tetrapyrrole macrocycles as photosensitizers

22π 600 – 650nm

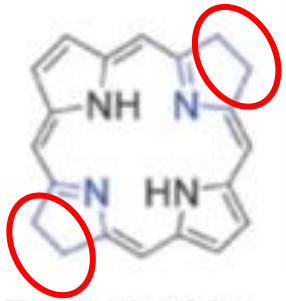
18π 700 – 800nm

20π 630 – 700nm

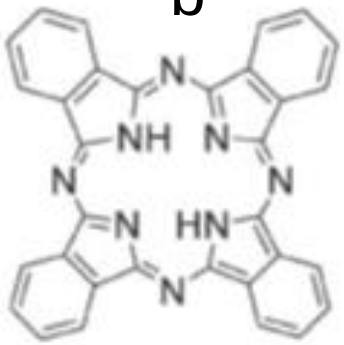
a



b

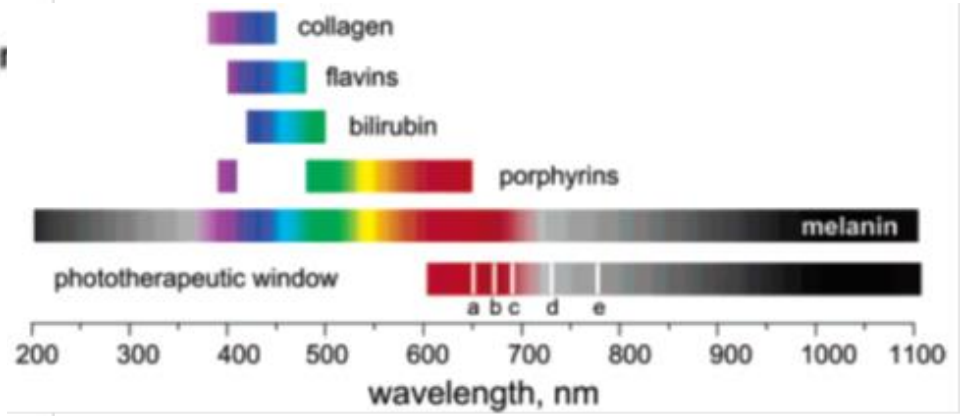


c



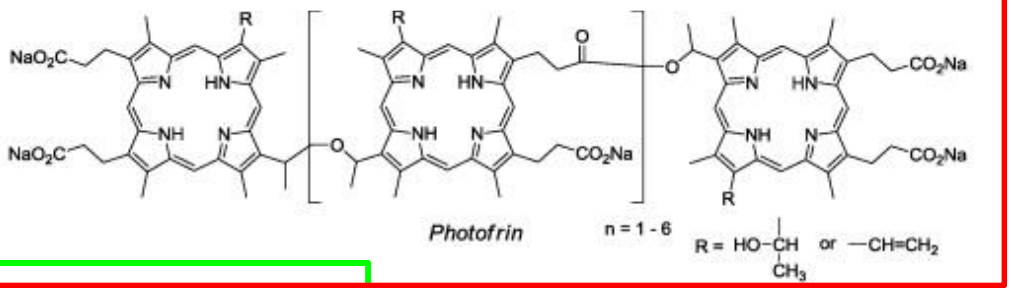
d

Phthalocyanine

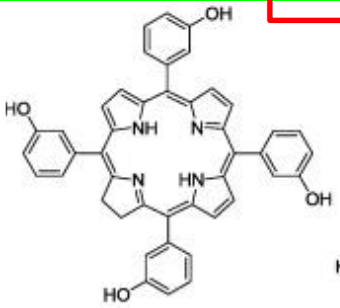


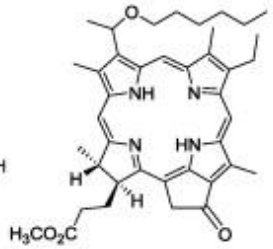
1st and 2nd generation photosensitizers for PDT

λ = 652
ε = 3×10⁴ M⁻¹cm⁻¹

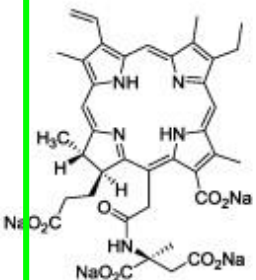


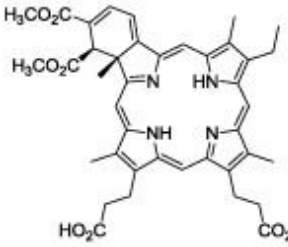
λ = 630
ε = 1170 M⁻¹cm⁻¹


Foscan

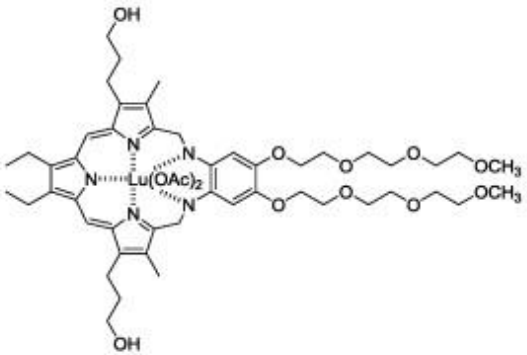

Photochlor

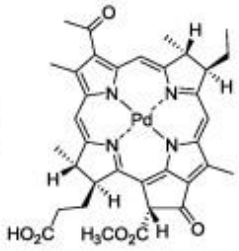
Tumor-avid

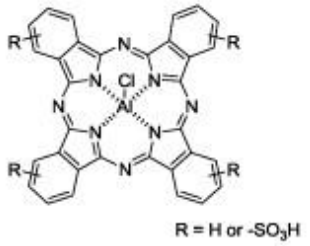

Talaporfin sodium


Visudyne

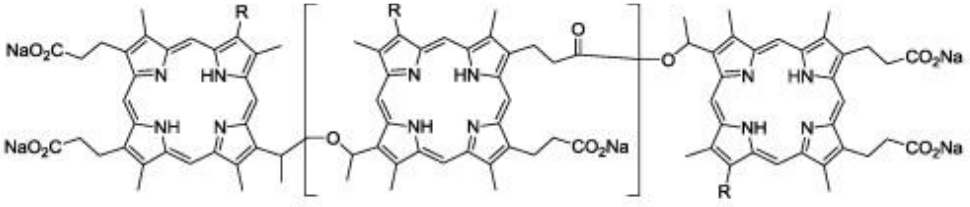

Purlytin

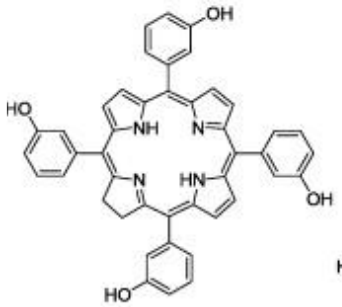

Lutrin

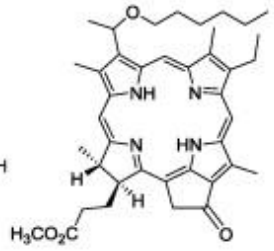

Tookad

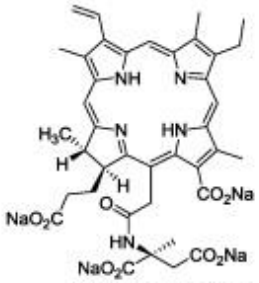

R = H or -SO3H

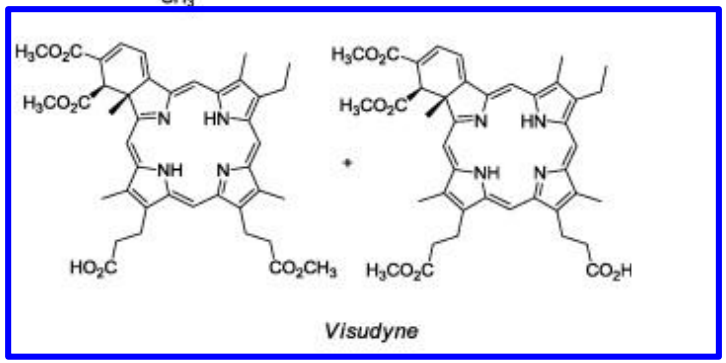
Photosens





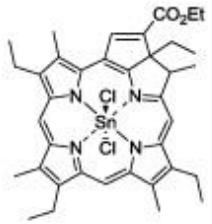


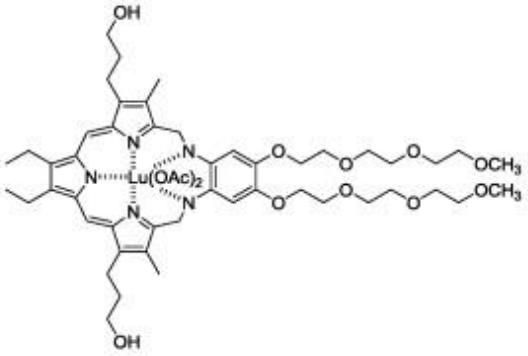


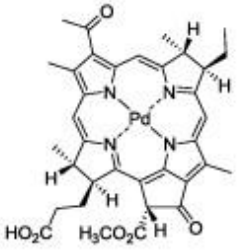


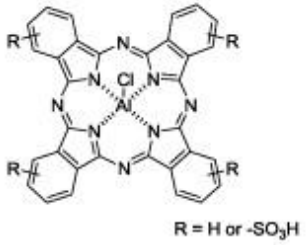
age-related macular degeneration (AMD)

First line treatment

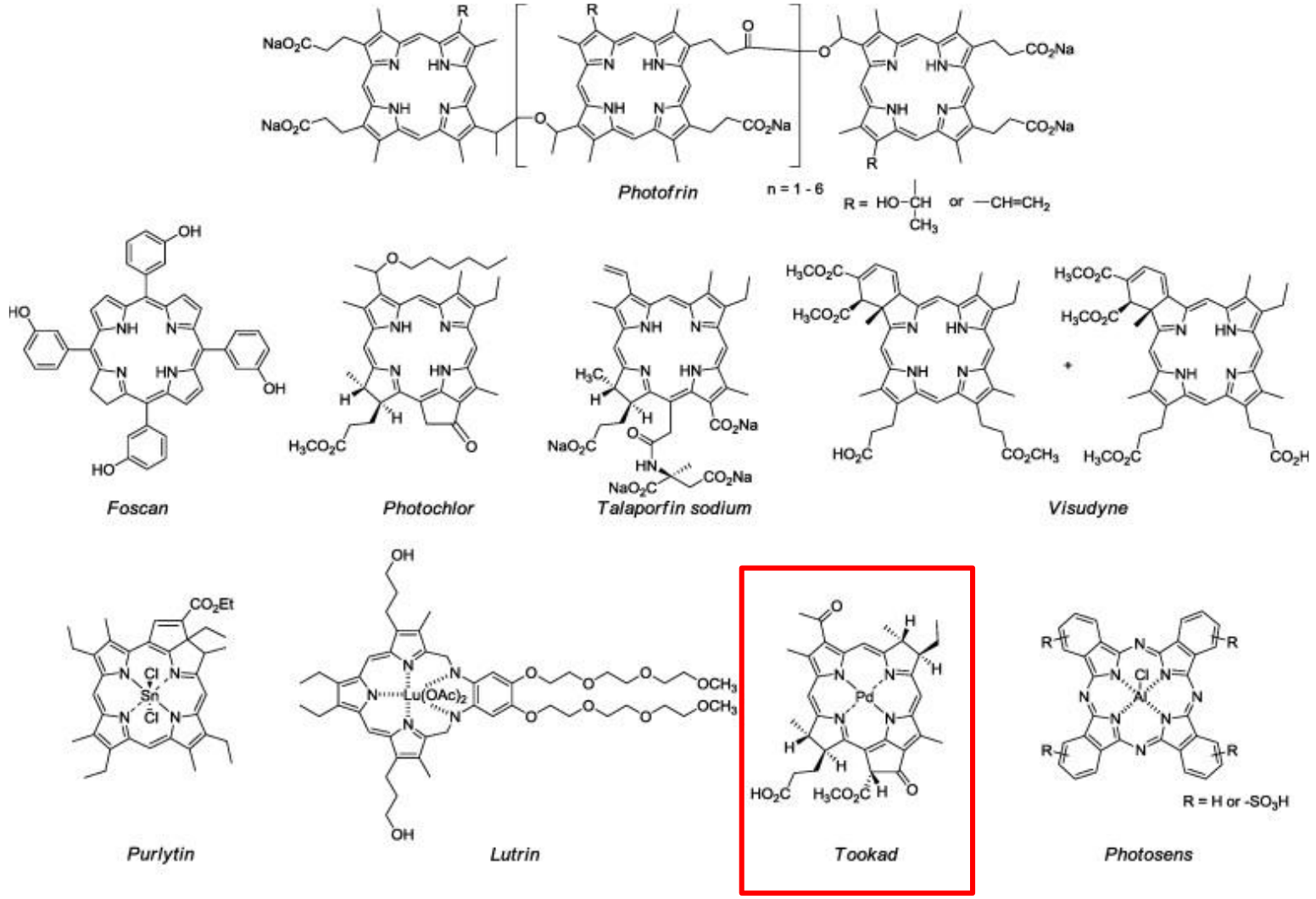




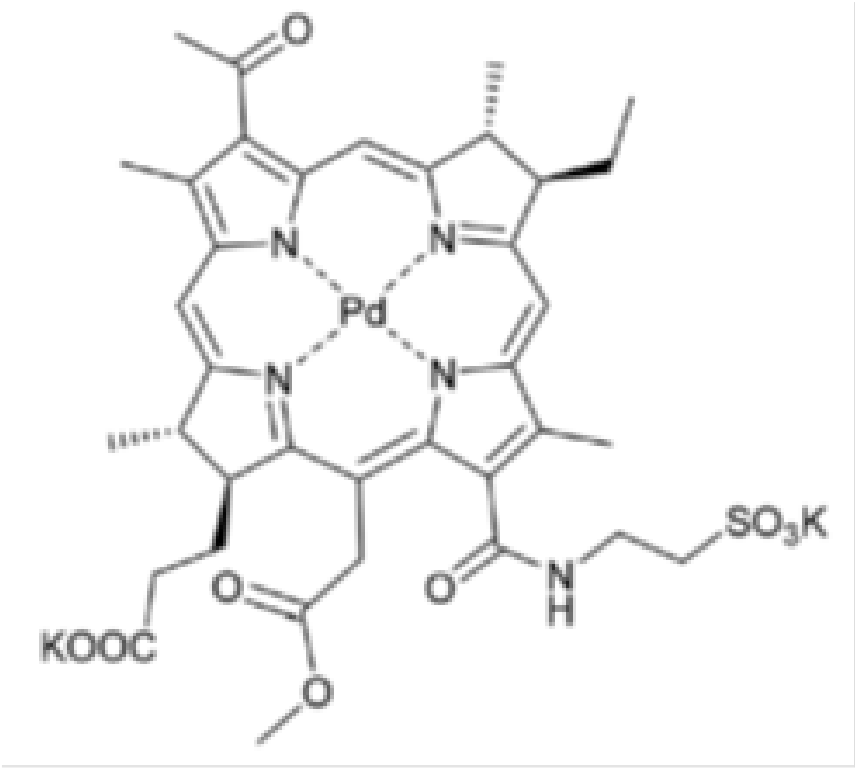




Currently AMD is the most important application of PDT, with millions of patients treated.



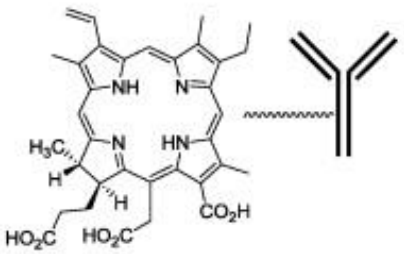
Pd favors intersystem crossing to the triplet state of the excited PS



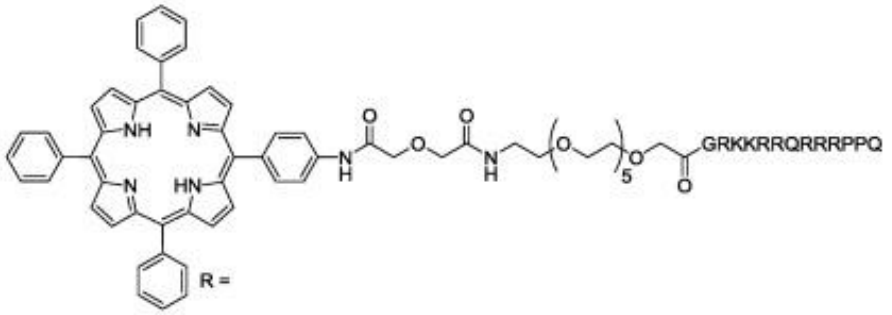
Soluble-TOOKAD

(palladium-bacteriopheophorbide)

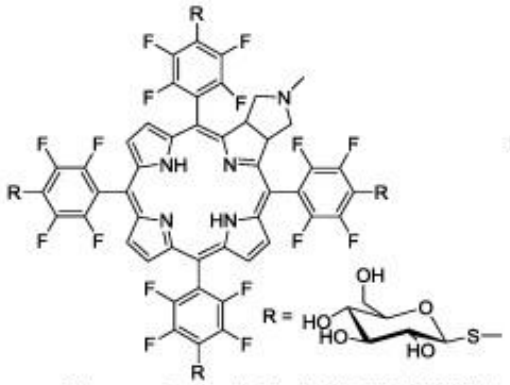
3rd generation photosensitizers for PDT (*targeted*)



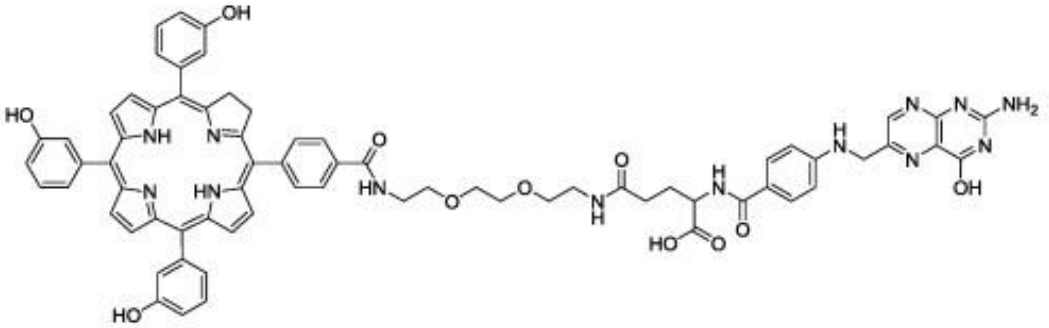
IgG conjugated chlorin



HIV-1 Tat peptide conjugated porphyrin

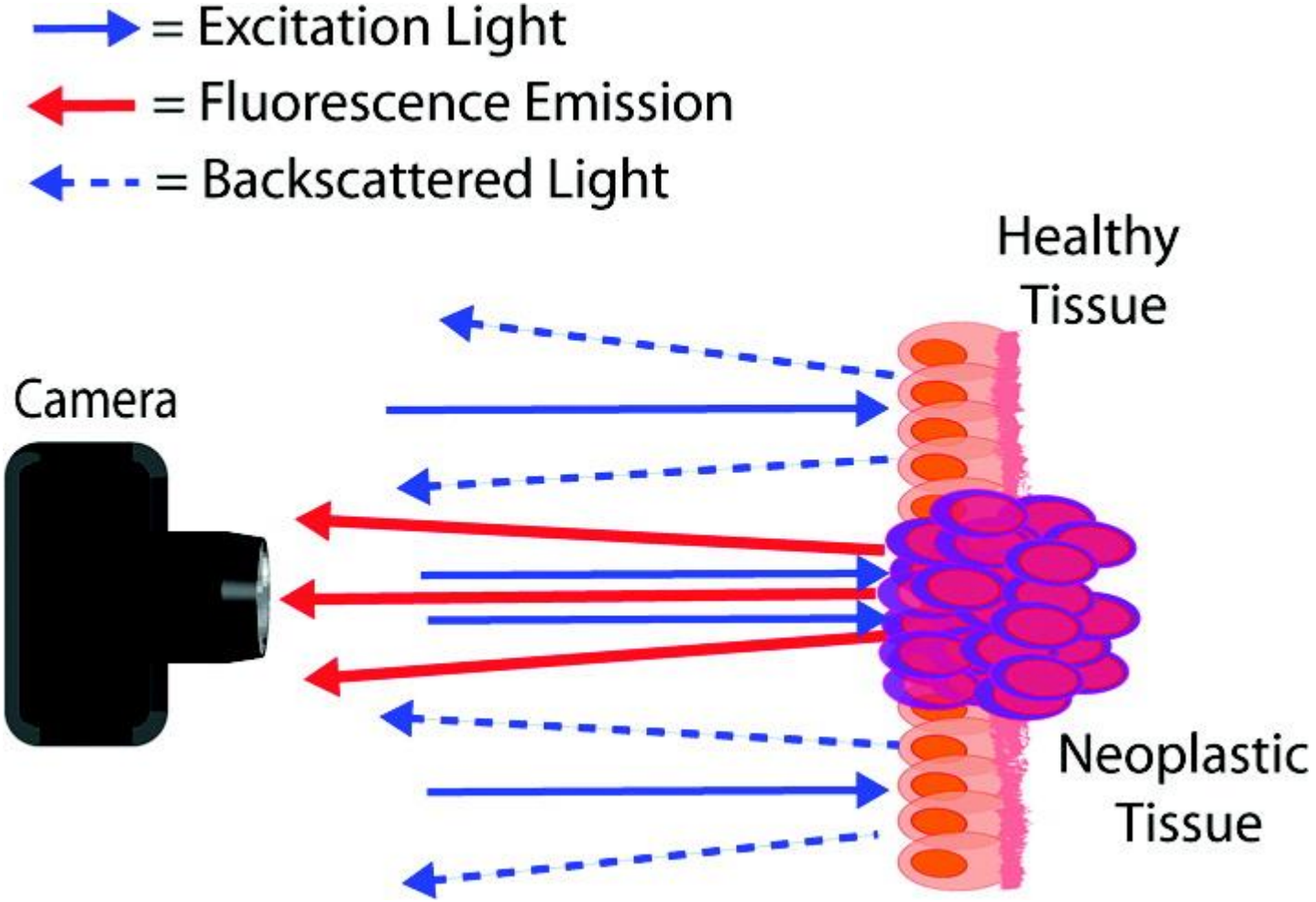


Glycoconjugated chlorin (H_2TFPC-SGlc)

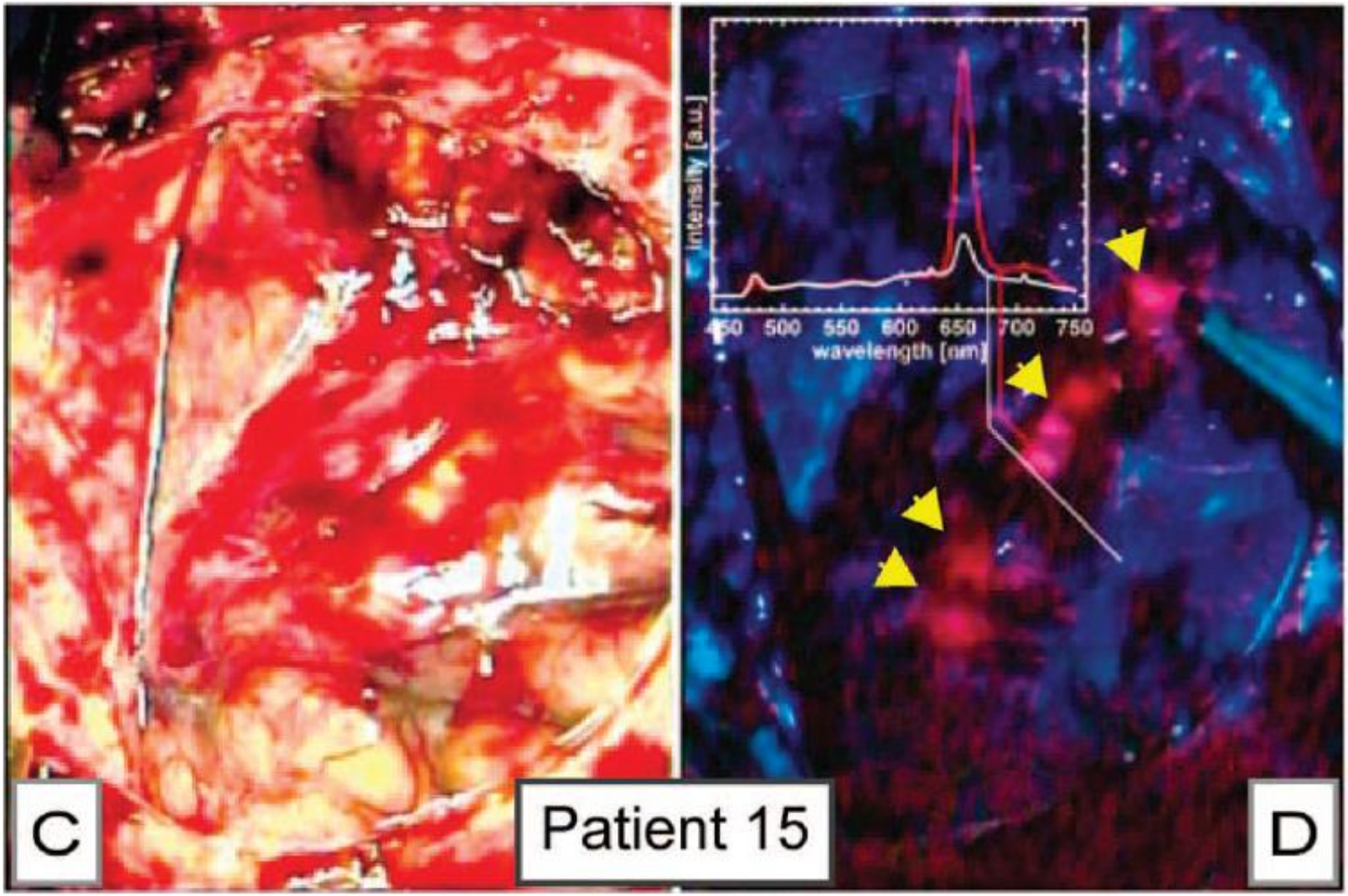


Folate conjugated temoporfin

Tumor margin resection with *tumor avid* PS's

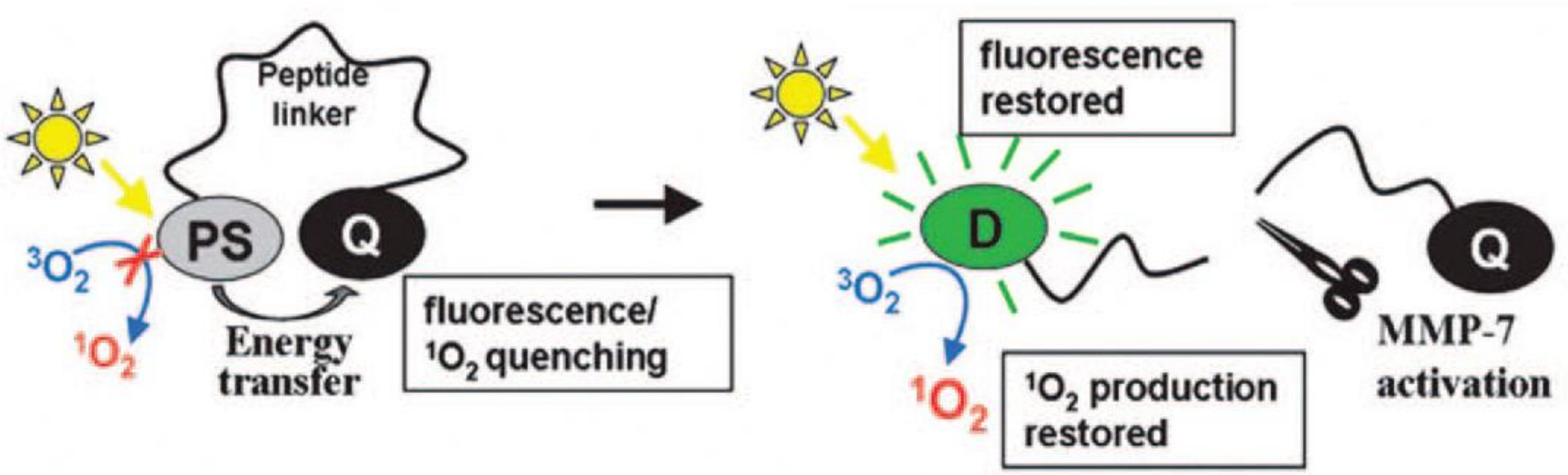


Brain tumor, patient treated with Foscan



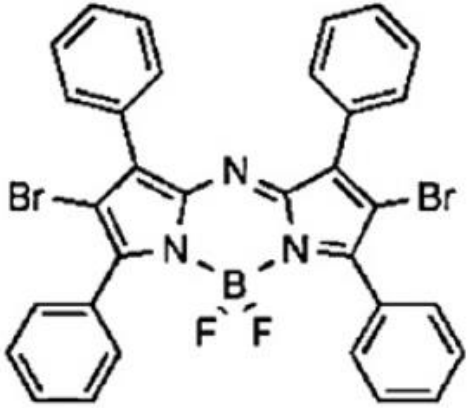
Blue light

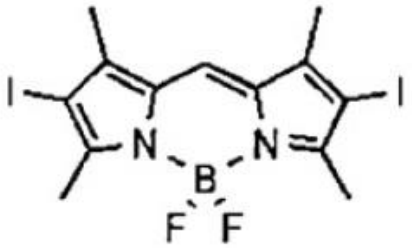
Site-activated constructs

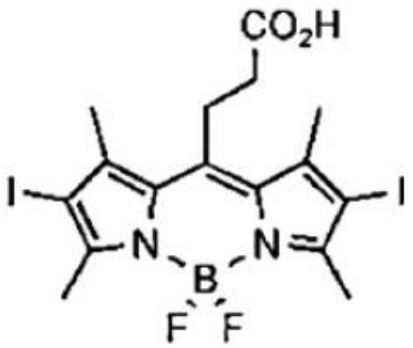


The activating enzyme might be overexpressed in the tumor cells, or be expressed by bacteria and not by cells…

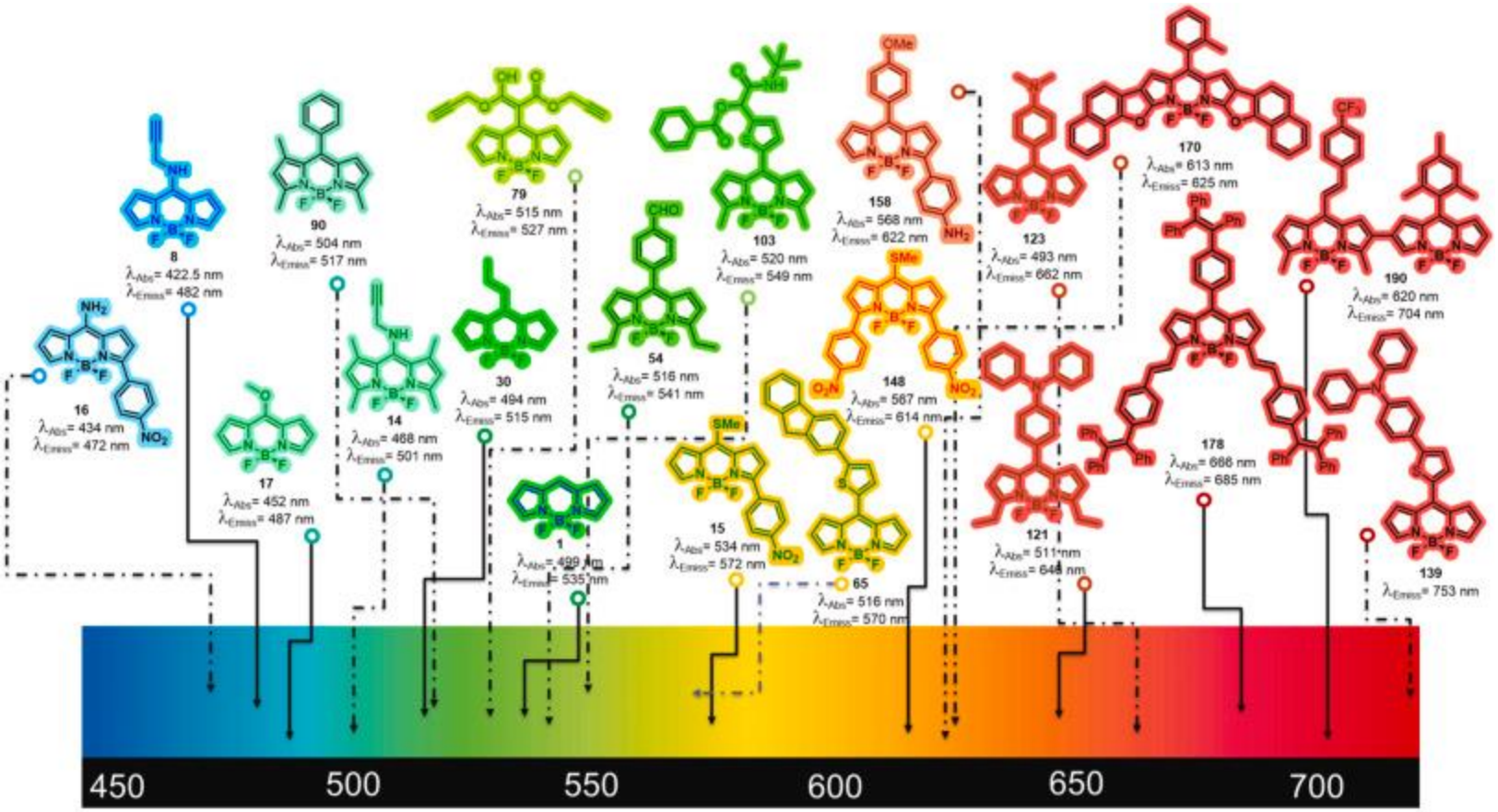
Derivati del BODIPY (*boron-dipyrromethene)*



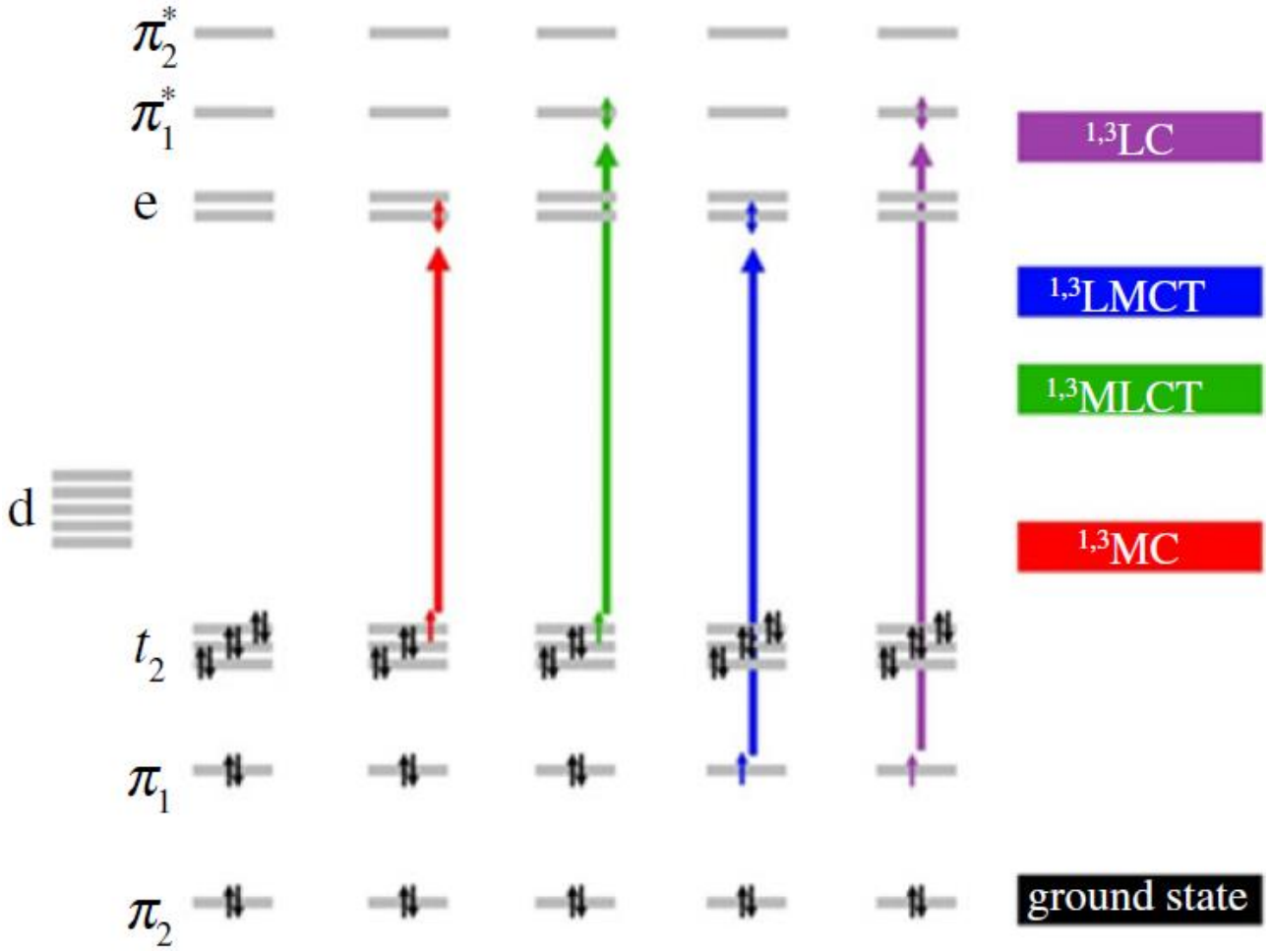




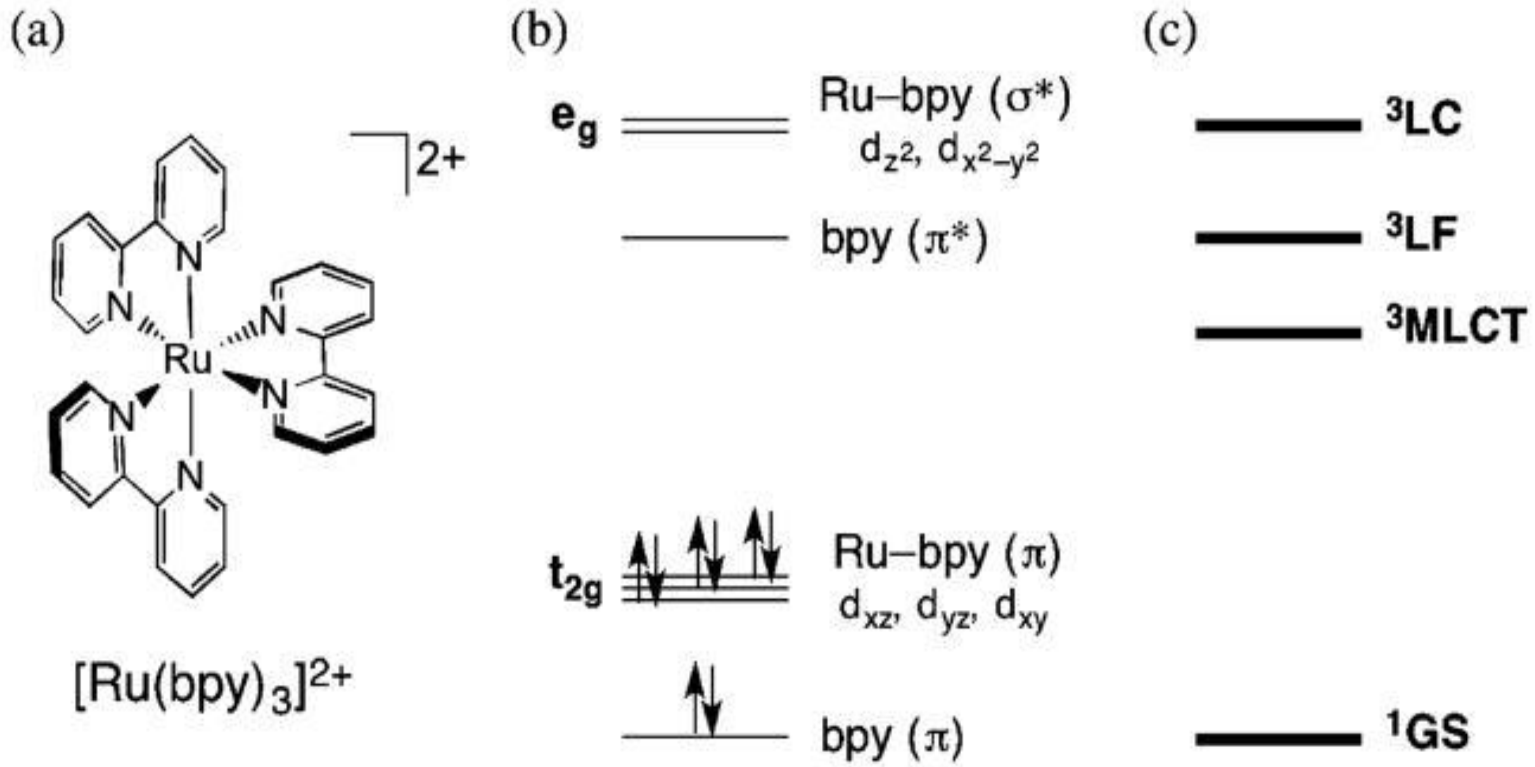
Tuning the absorption of BODIPY



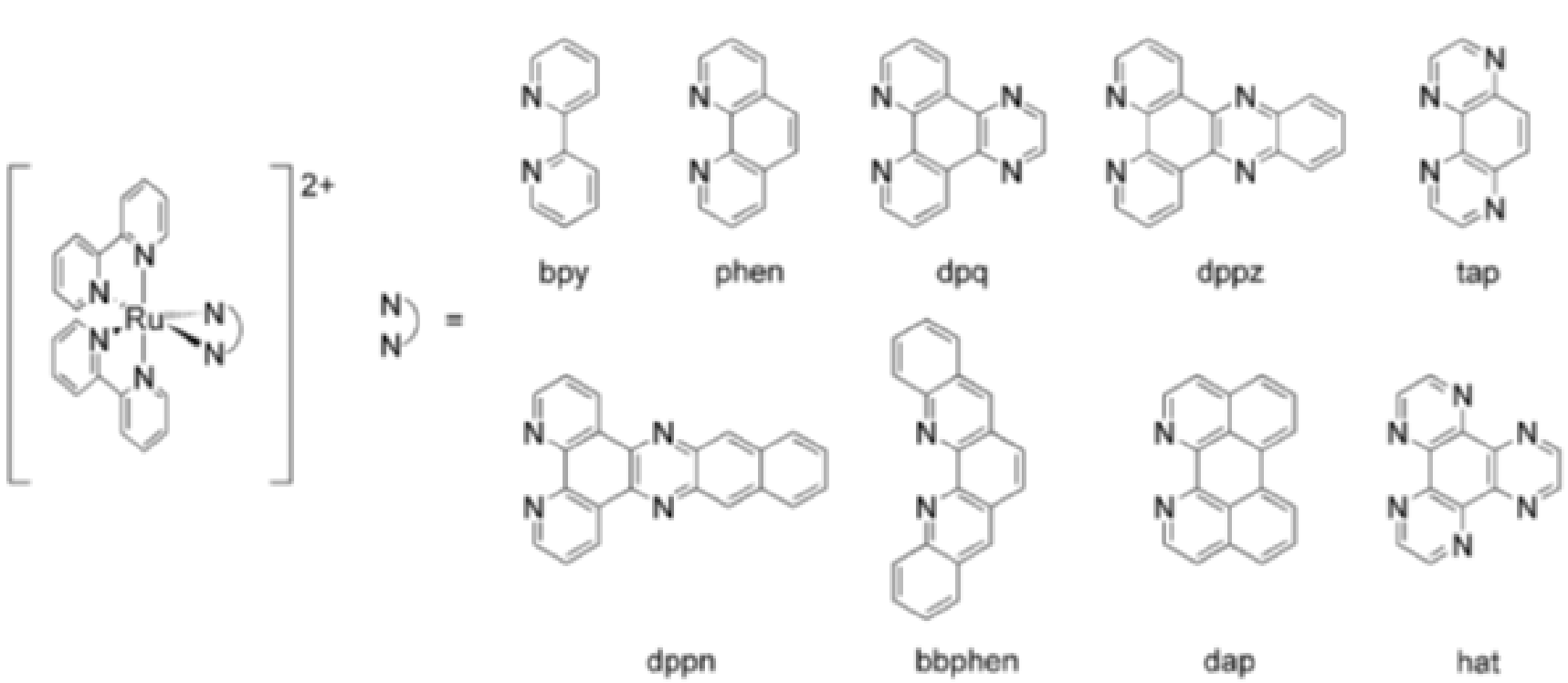
Photoactivatable metal compounds



Diagrammi semplificati degli MO di frontiera e degli stati di $[Ru(bpy)_3]^{2+}$

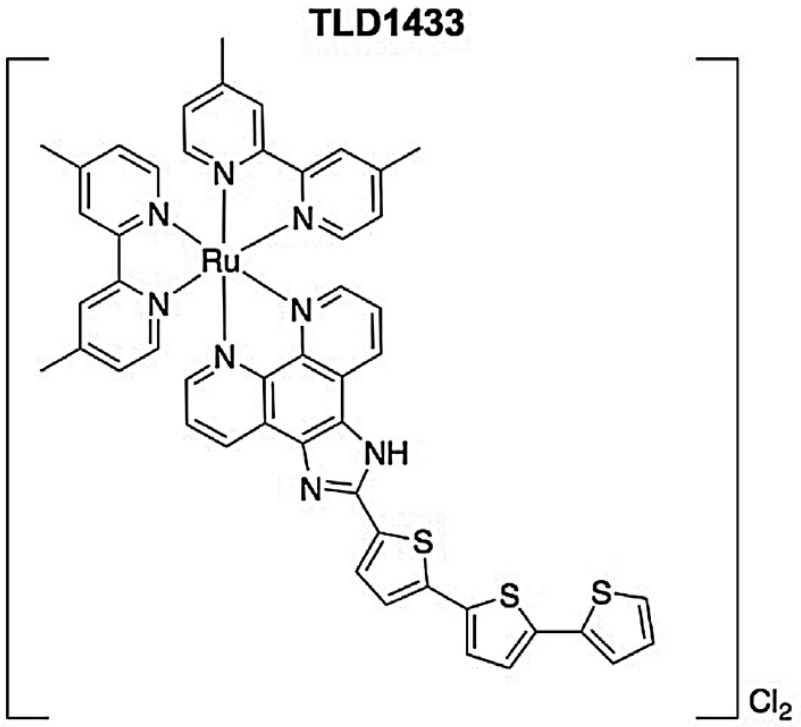


Metal complexes for PDT

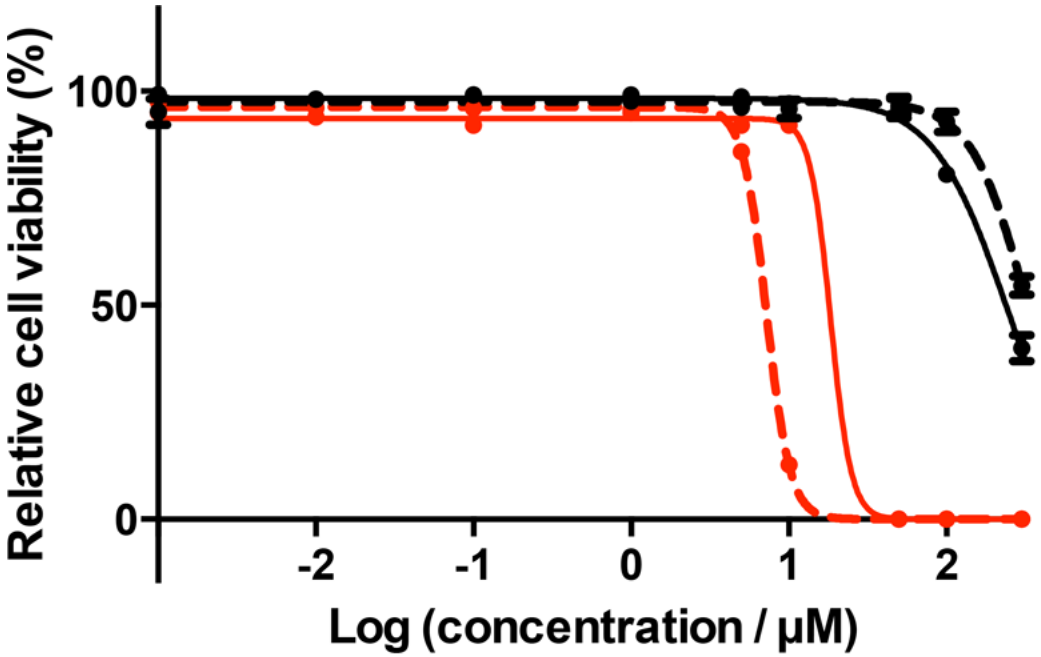


Health Canada Approves Clinical Trial Application for Anti-Cancer Drug

Toronto, Ontario – December 17, 2015, Theralase Technologies Inc. ("Theralase" or the "Company") (TLT:TSXV) (TLTFF:OTC), a leading biotechnology manufacturer focused on commercializing medical technologies to eliminate pain and destroy cancer, announced today that Health Canada has approved its next generation anti-cancer drug, TLD-1433, under Clinical Trial Application ("CTA") for evaluation in a Phase Ib clinical trial for patients inflicted with Non-Muscle Invasive Bladder Cancer ("NMIBC").



In vitro studies



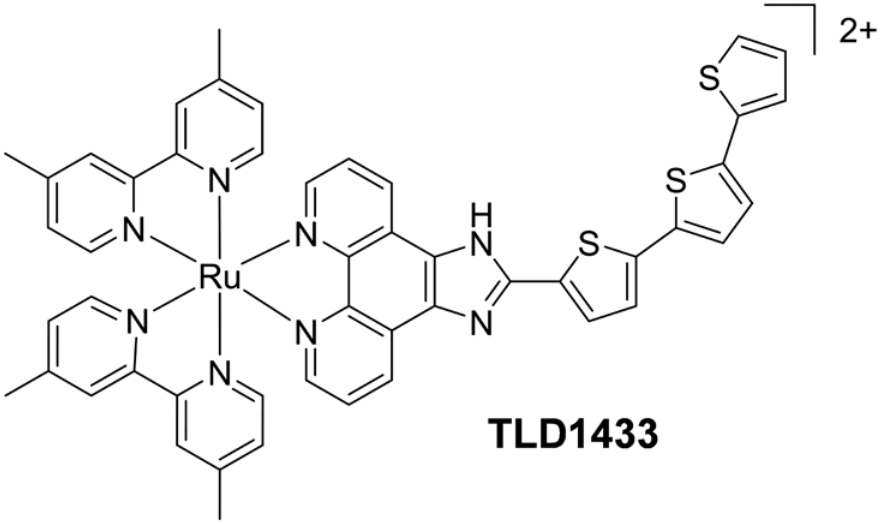
TLD1433, Dark EC_{50} > 300 µM

TLD1433, Red EC_{50} = 7.20 ± 1.10 µM

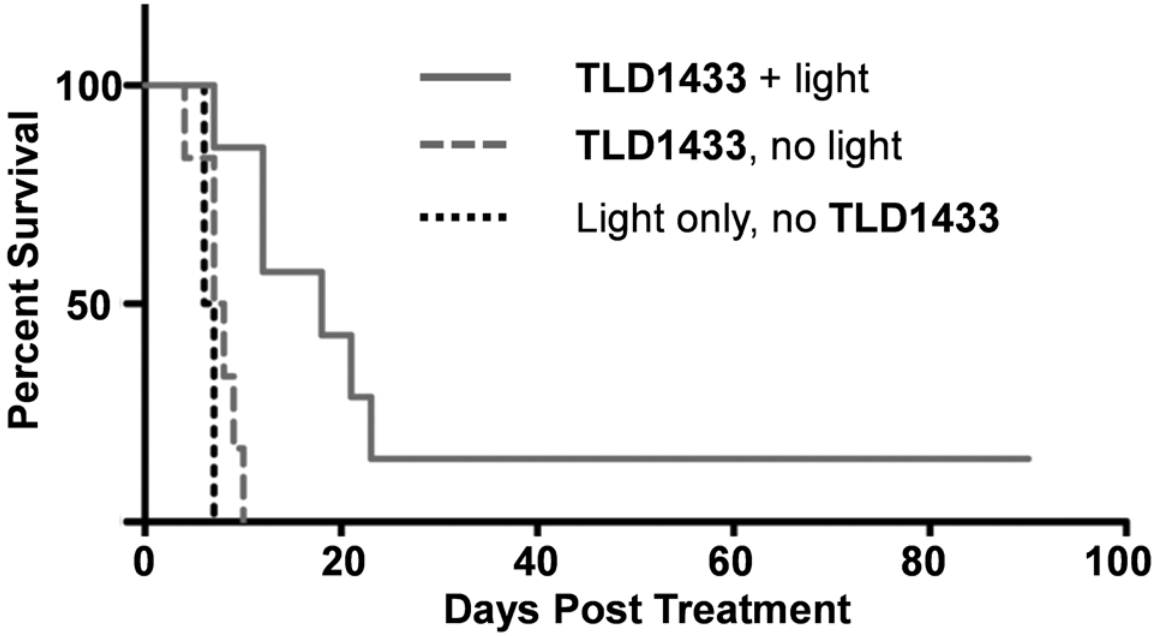
$[Os(dmb)_2(IP\text{-}3T)]Cl_2$, Dark EC_{50} = 242 ± 3 µM

$[Os(dmb)_2(IP\text{-}3T)]Cl_2$, Red EC_{50} = 18.4 ± 0.1 µM

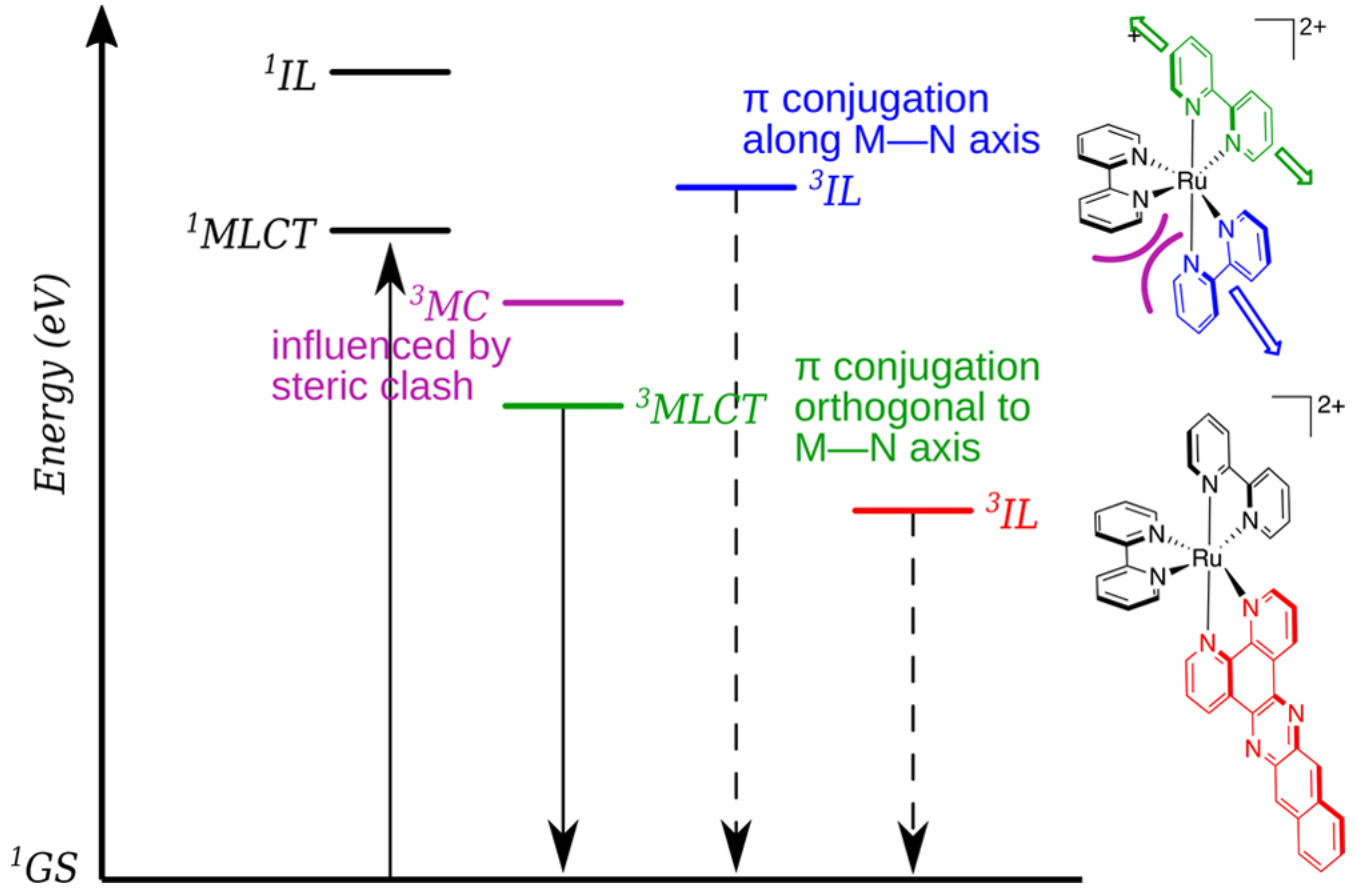
In vivo studies



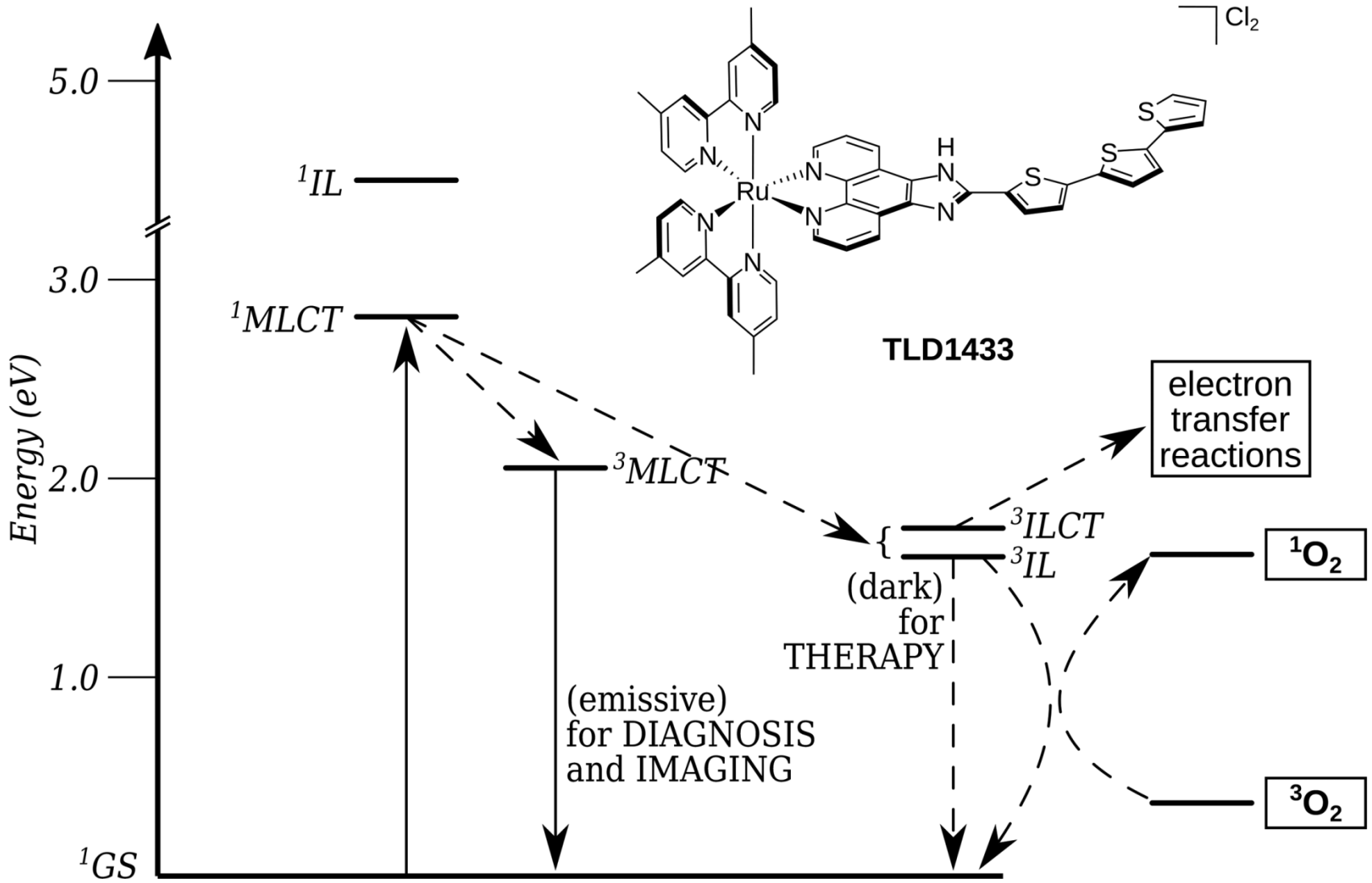
TLD1433



Molecular design



Increasing the π-conjugation of a diimine ligand decreases the energy of the excited state ^{3}IL (*intraligand*), resulting in an increase in its lifetime and greater production of $^1O_2$.


5.0
3.0
2.0
1.0
Energy (eV)
^1GS
^1IL
^1MLCT
^3MLCT
^3ILCT
^3IL
(dark)
for
THERAPY
(emissive)
for DIAGNOSIS
and IMAGING
electron
transfer
reactions
$^1O_2$
$^3O_2$
Cl2
Ru
N
H
S
TLD1433

Data 2020

Table 1. PDT agents in clinical use or in clinical trials[a].

Class	PDT agent	Metal	Stage	Excitation (nm)	Area	Cancer type
Protoporphyrin IX precursor	5-Aminolevulinic acid (Levulan®)		FDA approved	635	Global	Skin, brain, oesophagus
	Methyl aminolevulinate (Metvix®)		FDA approved	635		Skin
	Hexyl 5-aminolevulinate (Hexvix®)		FDA approved	380–450 (diagnosis)		Bladder
Porphyrin derivatives	Porfimer sodium (Photofrin®)		FDA approved	630	Global	Lung, bladder, oesophagus, bile duct, brain
	Photogem		MHRF approved	660	Russia	Respiratory and digestive tracts, urogenital
Chlorin derivatives	Temoporfin (Foscan®)		EMA approved	652	EU	Head and neck, bile duct, lung
	Ce6-PVP (Fotolon®)		Phase 2	660–670	Germany	Lung
	Radachlorin®		MHRF approved	662	Russia	Skin
	Talaporfin sodium (Laserphyrin®)		MHLW approved	664	Japan	Lung, brain
	HPPH (Photochlor®)		Phase 2	665	USA	Lung, oral cavity, oesophagus
Bacteriochlorin derivatives	Redaporfin		Phase 2	749	Portugal	Head and neck
Phthalocyanine derivatives	Silicon phthalocyanine (Pc4)		Phase 1	672	USA	Skin
Metal complex	Padoporfin (TOOKAD®)	Pd	Terminated	763	EU	Prostate
	Padeliporfin potassium (TOOKAD® Soluble)	Pd	EMA approved	753	EU	Prostate
	TLD-1433	Ru	Phase 2	520	Canada	Bladder, brain
	Motexafin lutetium (Antrin®)	Lu	Terminated	732	USA	Breast, prostate
	Rostaporfin (Purlytin®)	Sn	Phase 2/3	664	USA	Breast, bile duct, ovarian, colon

[a]Data from clinicaltrials.gov.