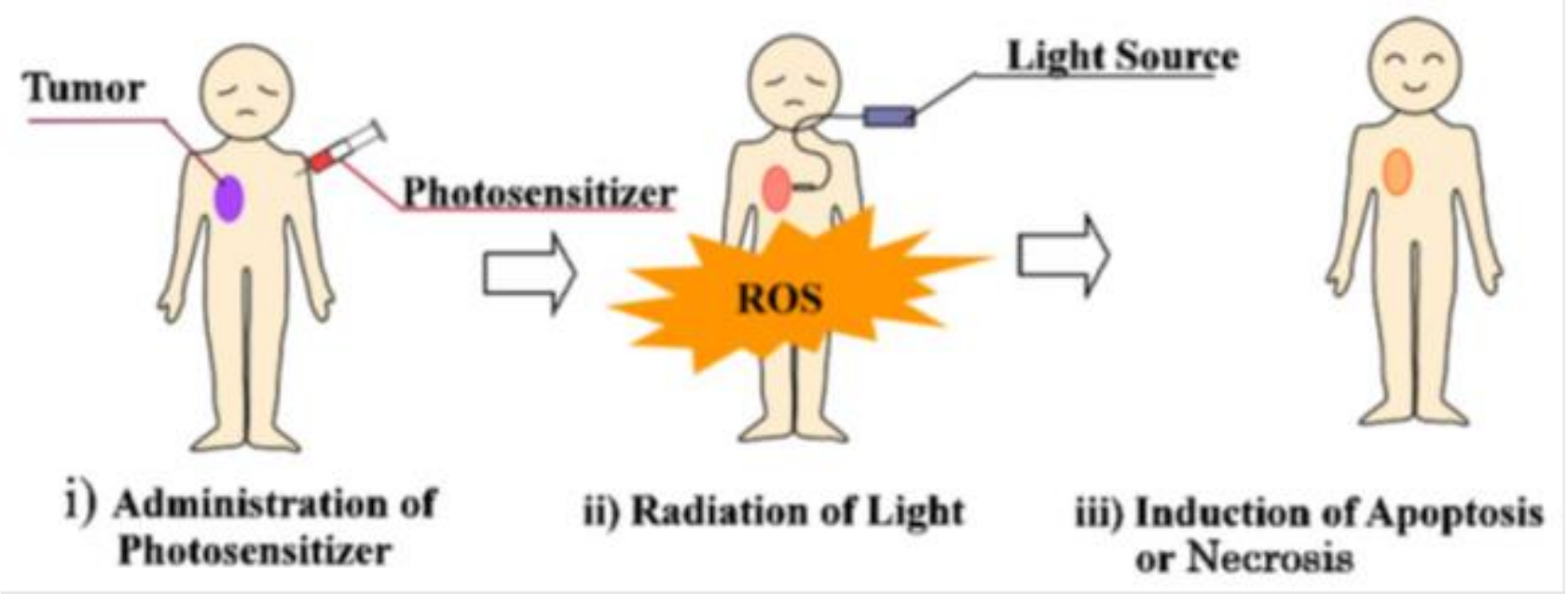
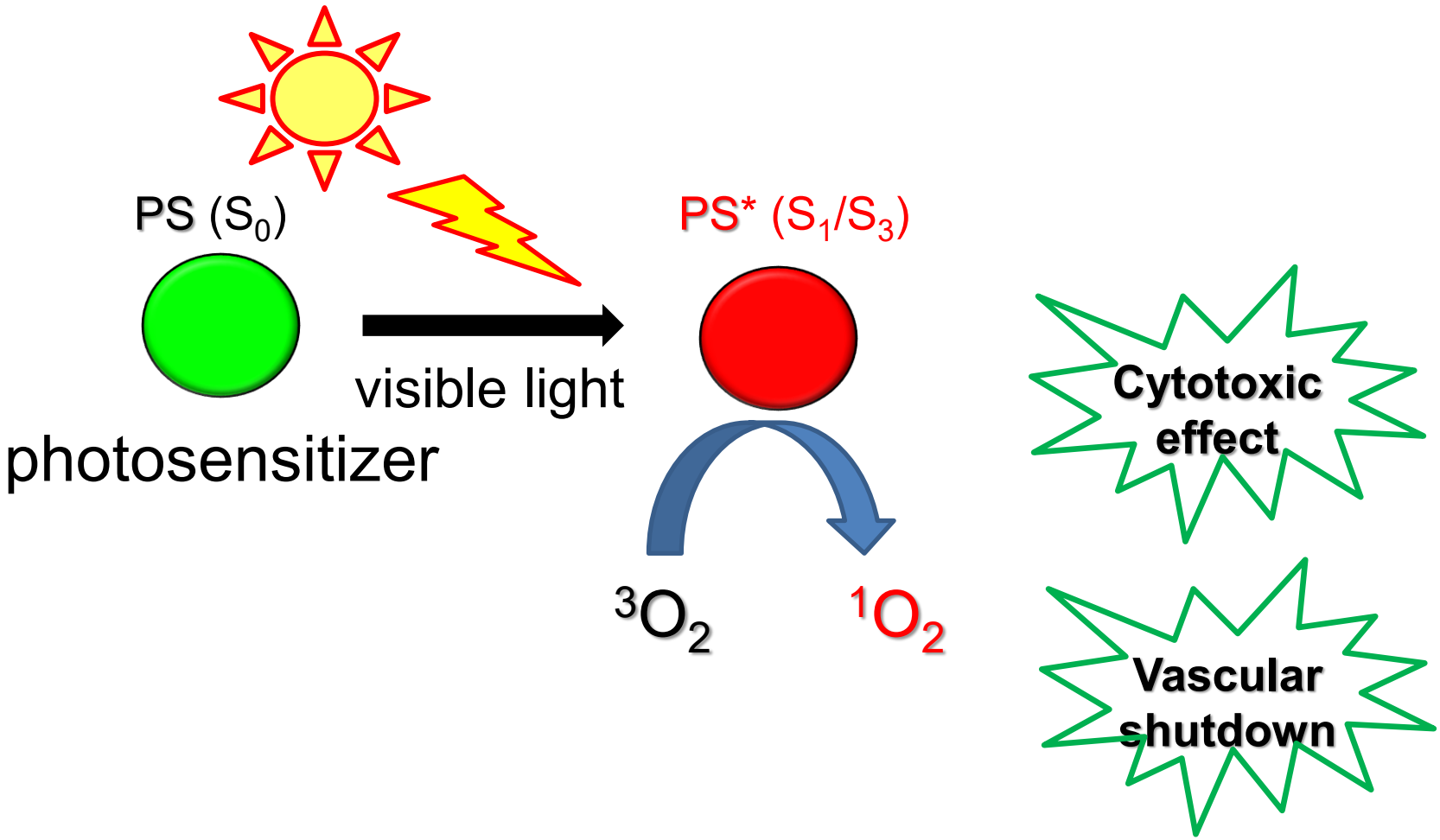
Photodynamic Therapy (PDT)

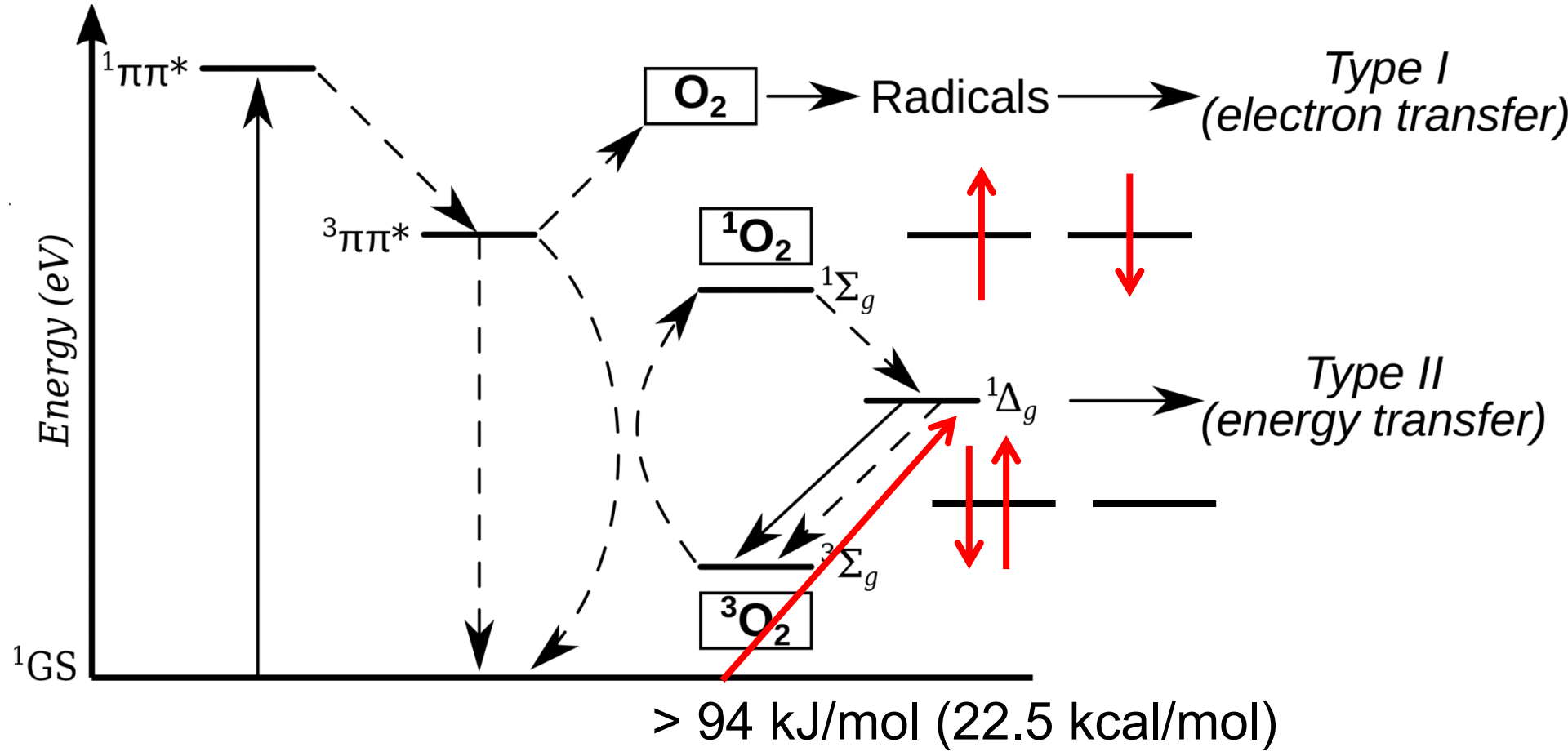
Localized and rather superficial solid tumors (mm deep)



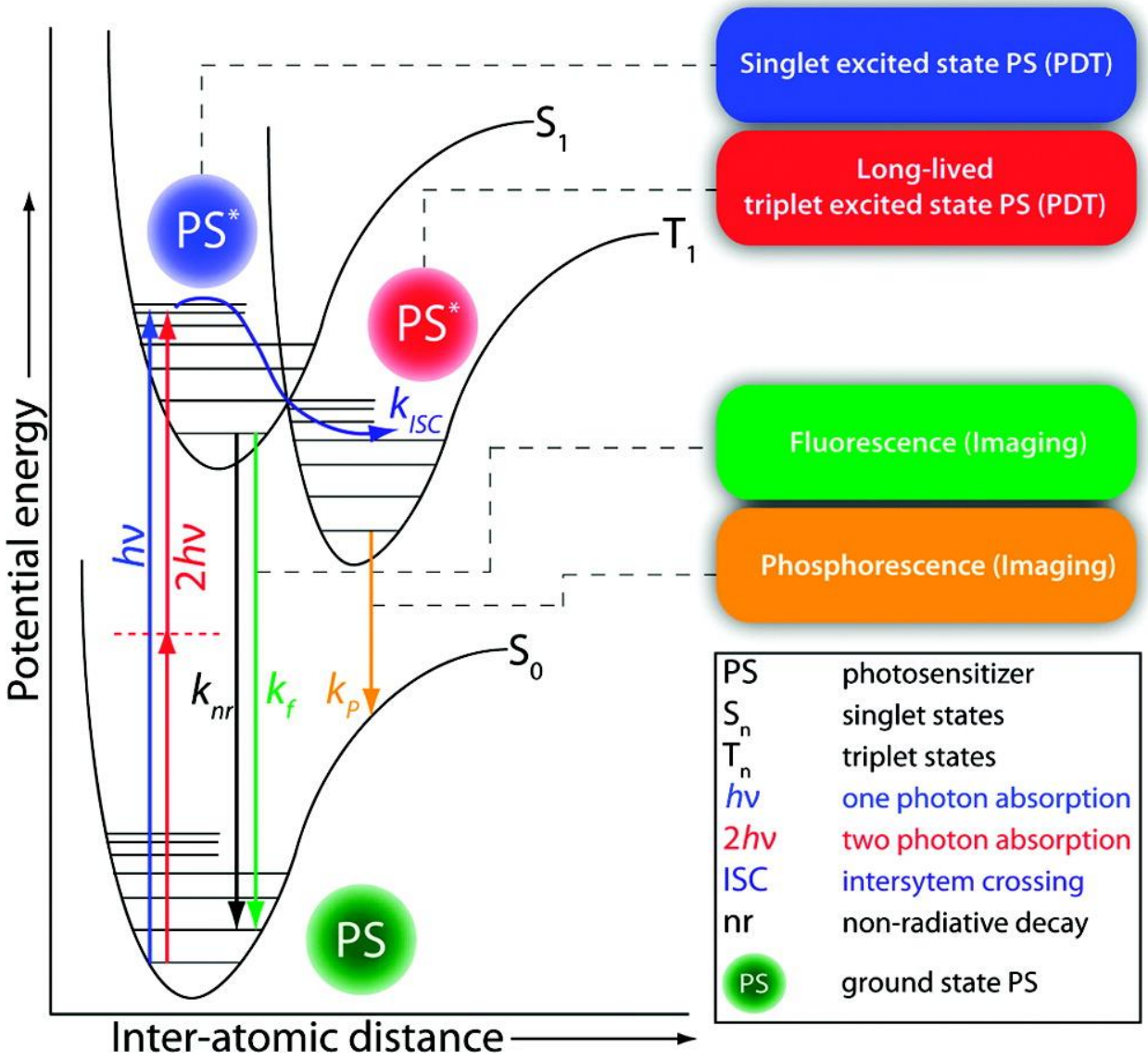
Spatio-temporal control on the active species

Ternary therapy: photosensitizer, light, oxygen

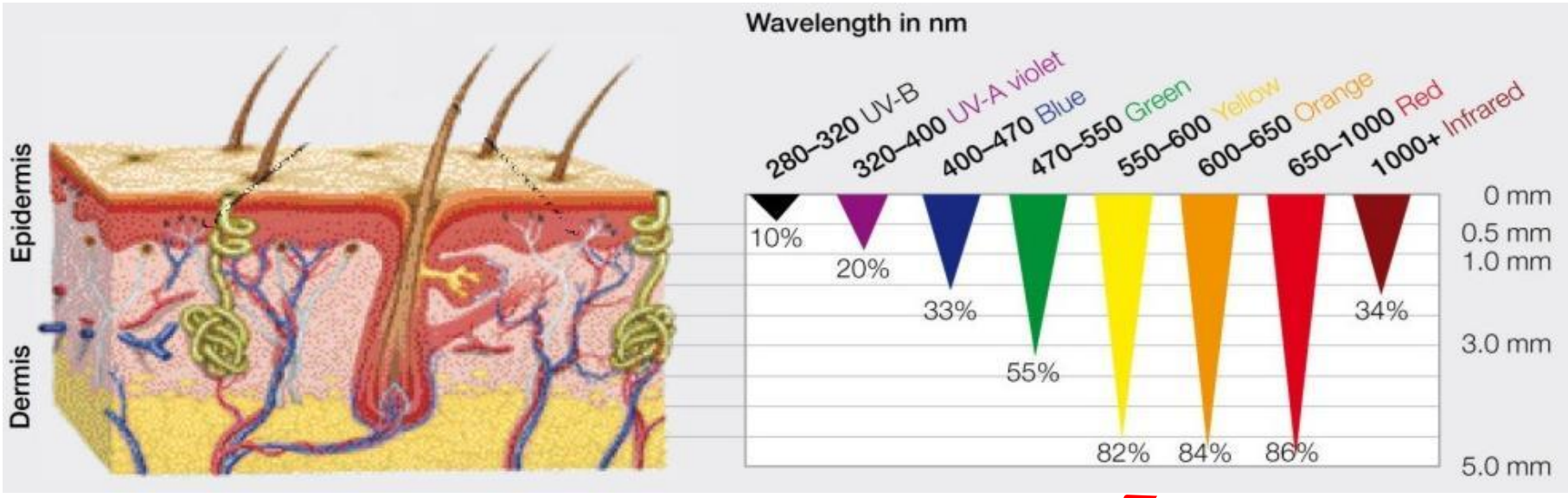




It is estimated that $^1O_2$ can diffuse for max ca. 45 nm (vs cell diameter 10 – 100 μm) from the point where it is generated (lifetime: 100 – 250 ns).


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

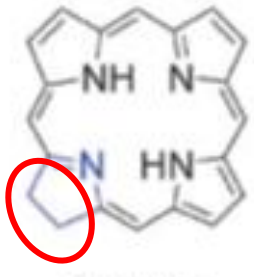
Tetrapyrrole macrocycles as photosensitizers

22π 600 – 650nm

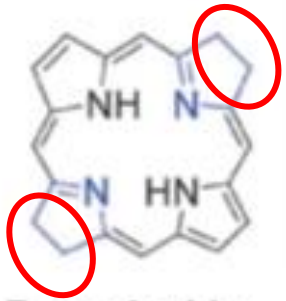
18π 700 – 800nm

20π 630 – 700nm

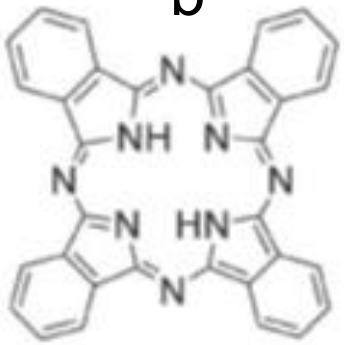
a



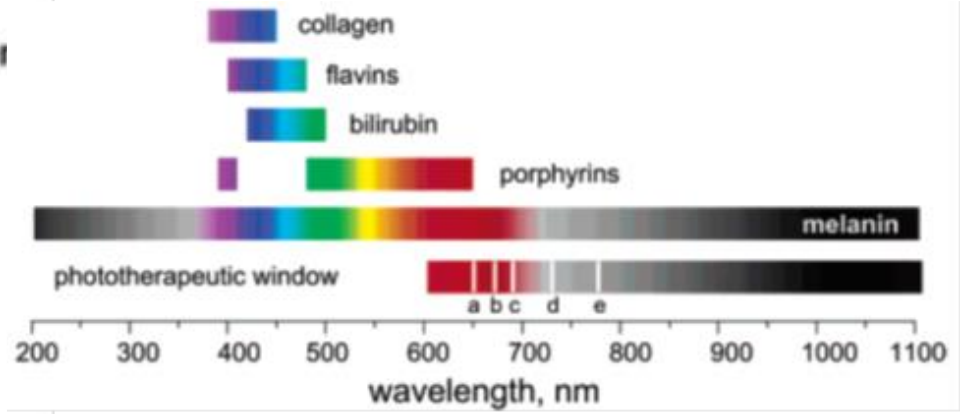
b



c



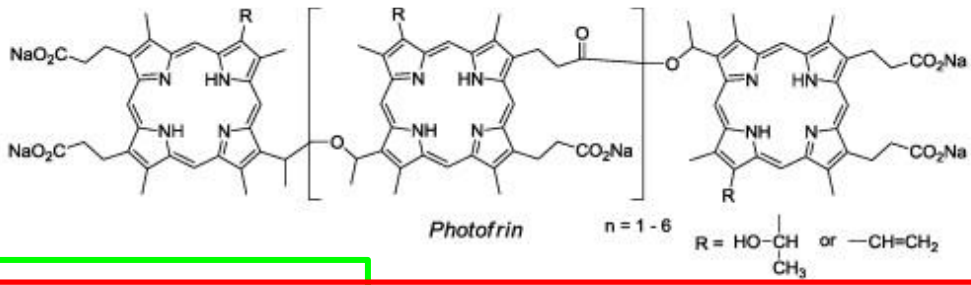
d

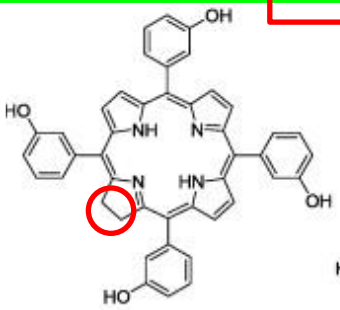


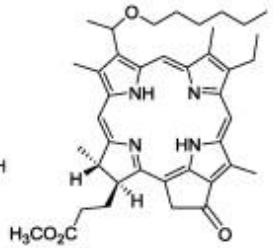
1st and 2nd generation photosensitizers for PDT

λ = 652
ε = 3×10⁴ M⁻¹cm⁻¹

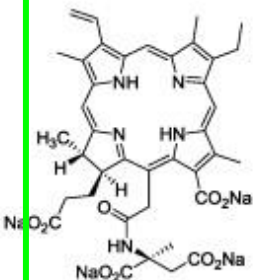
λ = 630
ε = 1170 M⁻¹cm⁻¹

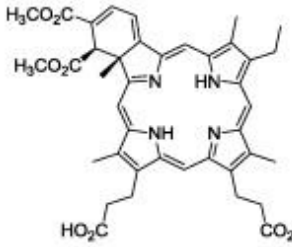


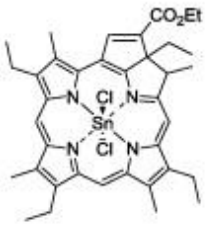

Foscan

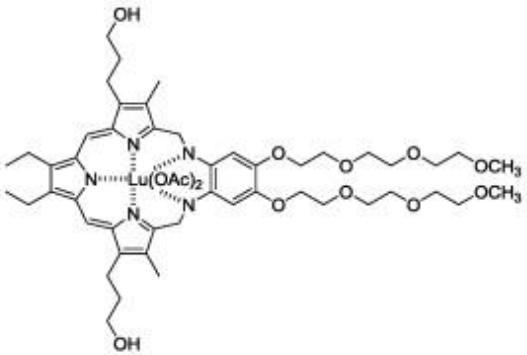

Photochlor

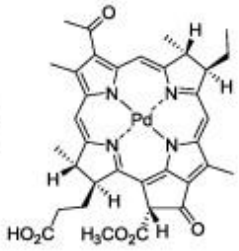
Tumor-avid

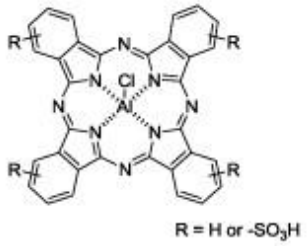

Talaporfin sodium


Visudyne

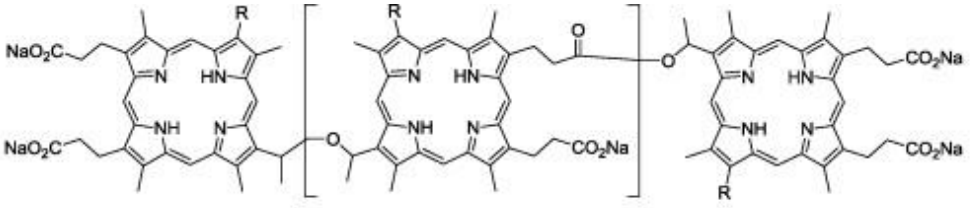

Purlytin

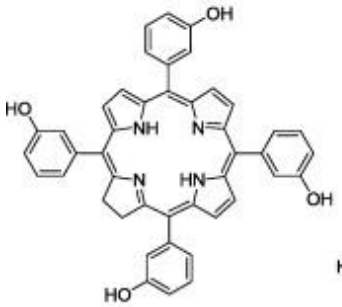

Lutrin

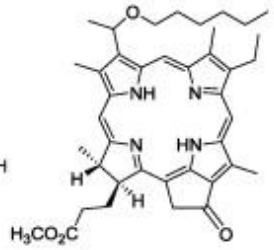

Tookad

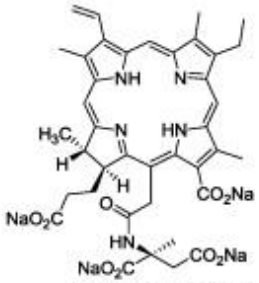


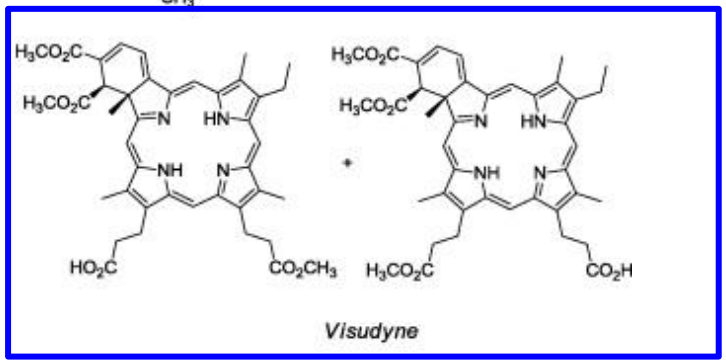
Photosens




Foscan

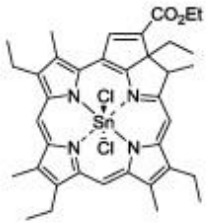

Photochlor

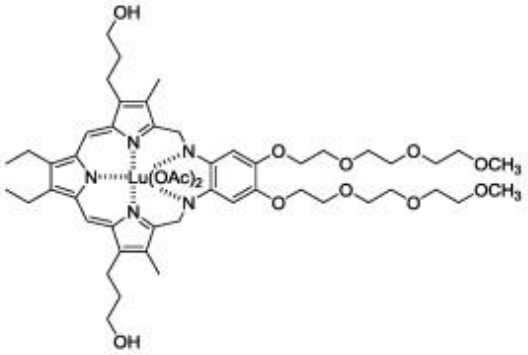

Talaporfin sodium

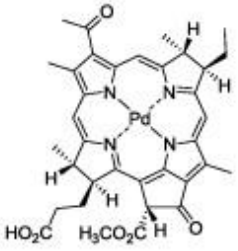

Visudyne

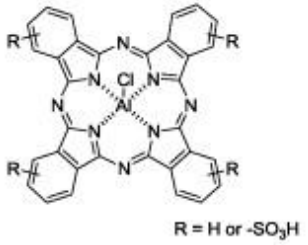
age-related macular degeneration (AMD)

First line treatment


Purlytin

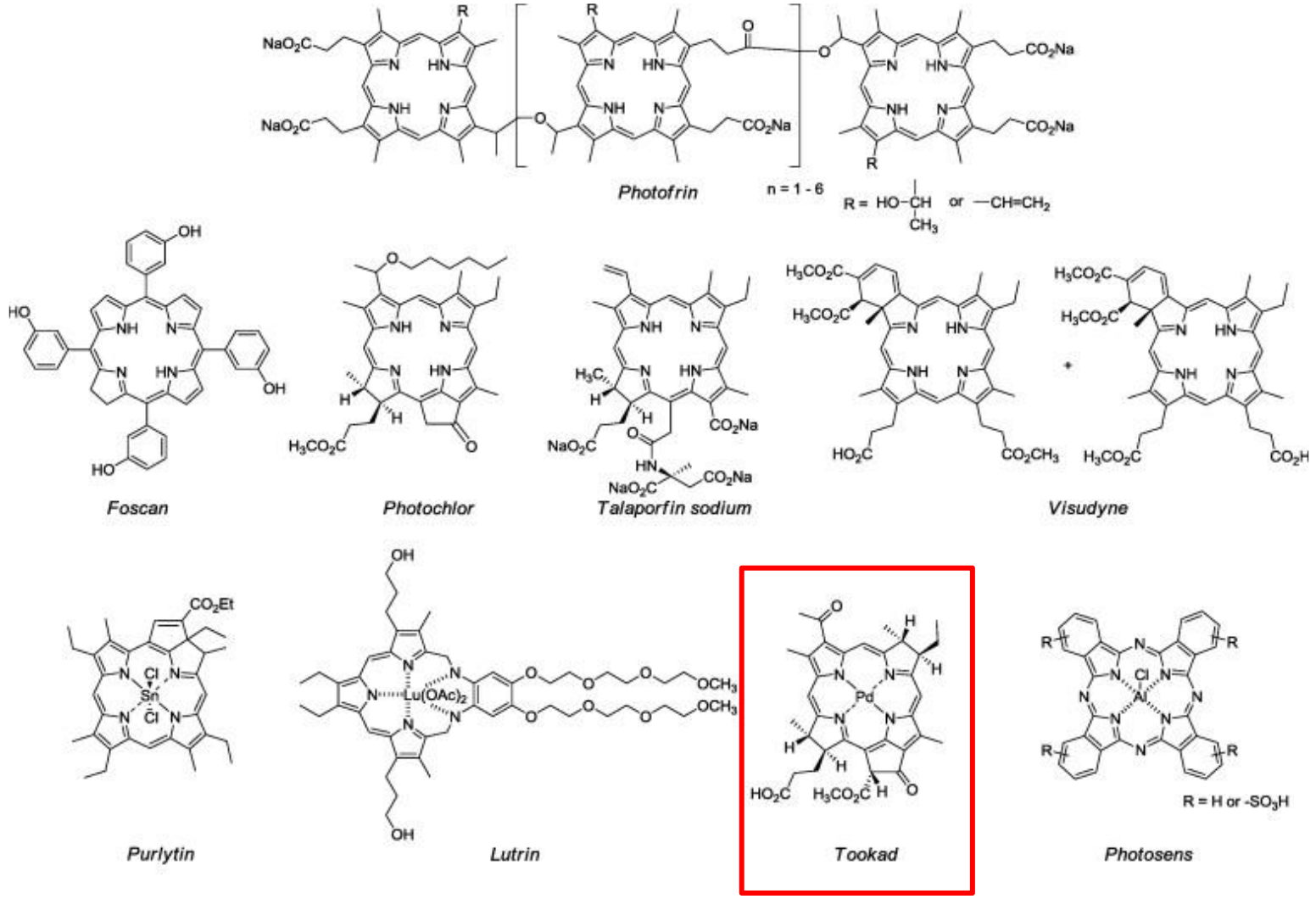

Lutrin


Tookad

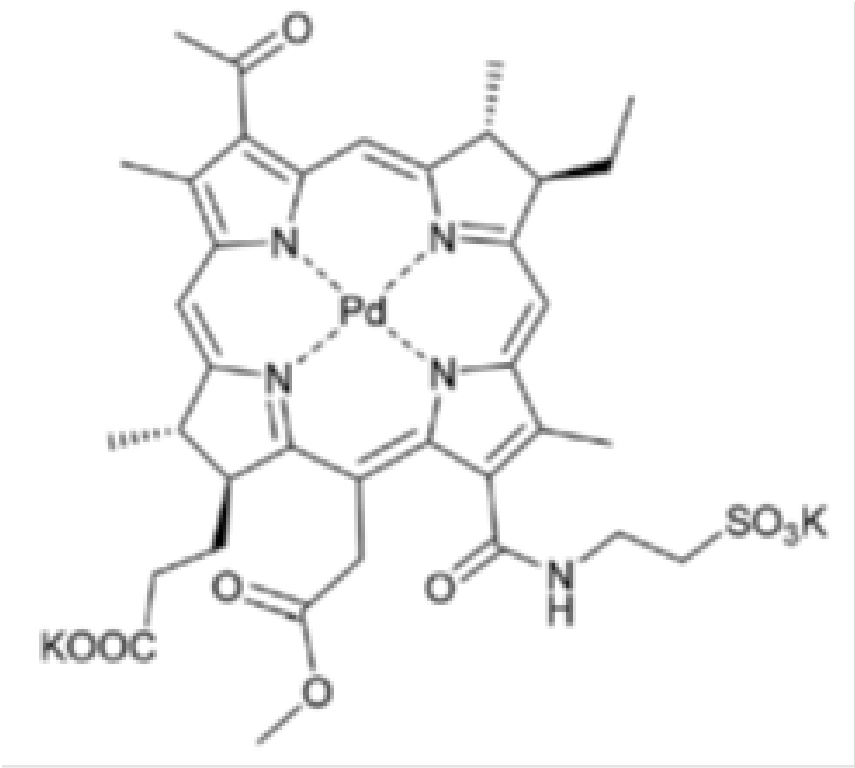


Photosens

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



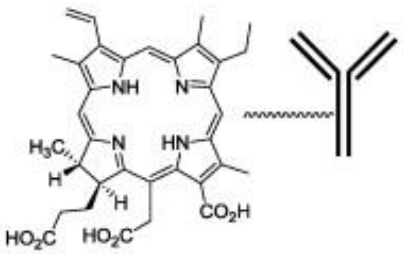
Pd favors intersystem crossing to the triplet state of the excited PS



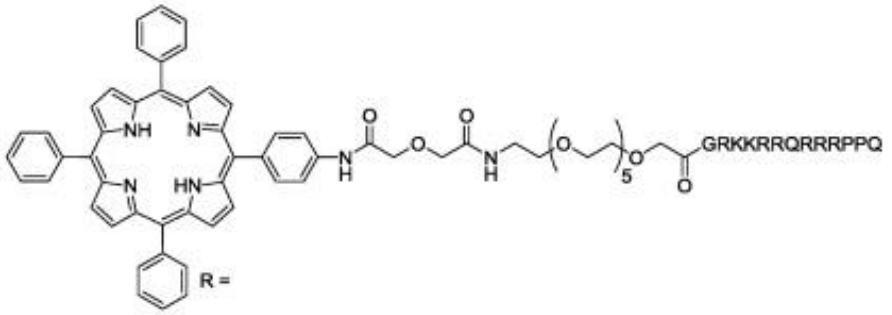
Soluble-TOOKAD

(palladium-bacteriopheophorbide)

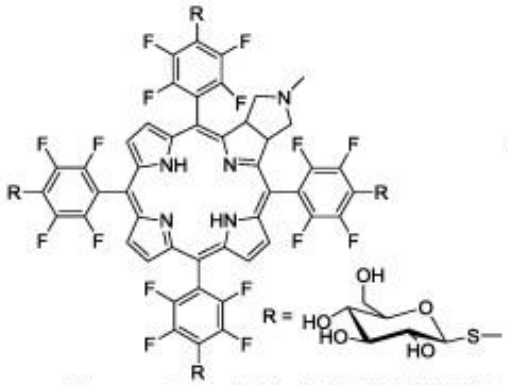
3rd generation photosensitizers for PDT (*targeted*)



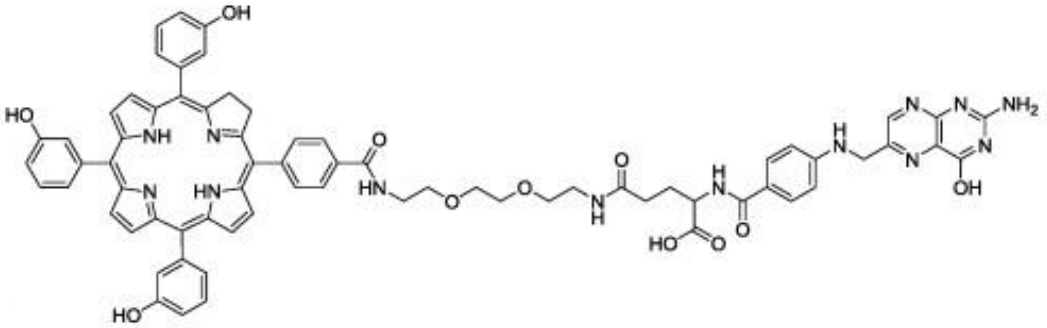
IgG conjugated chlorin



HIV-1 Tat peptide conjugated porphyrin

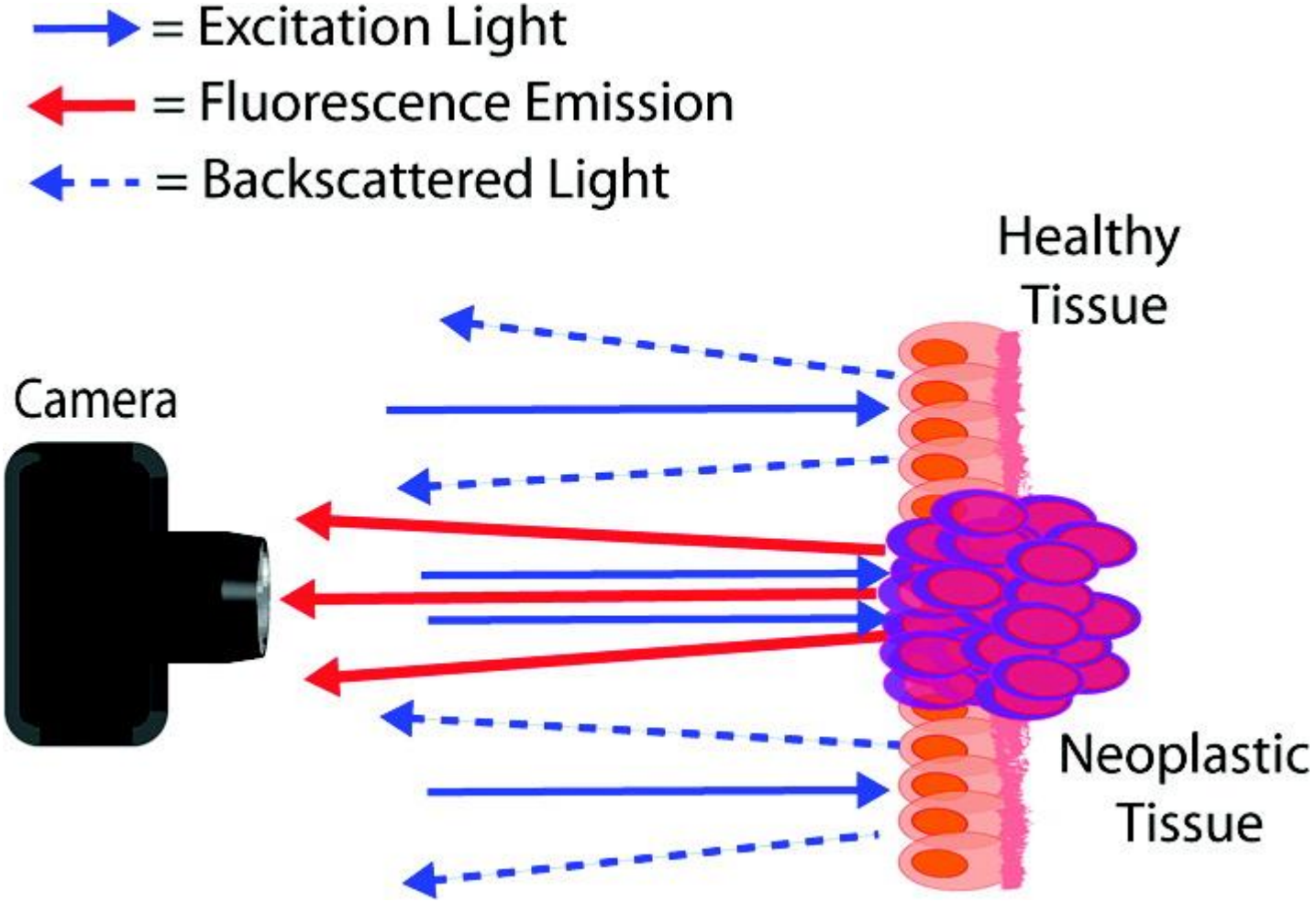


Glycoconjugated chlorin (H_2TFPC-SGlc)

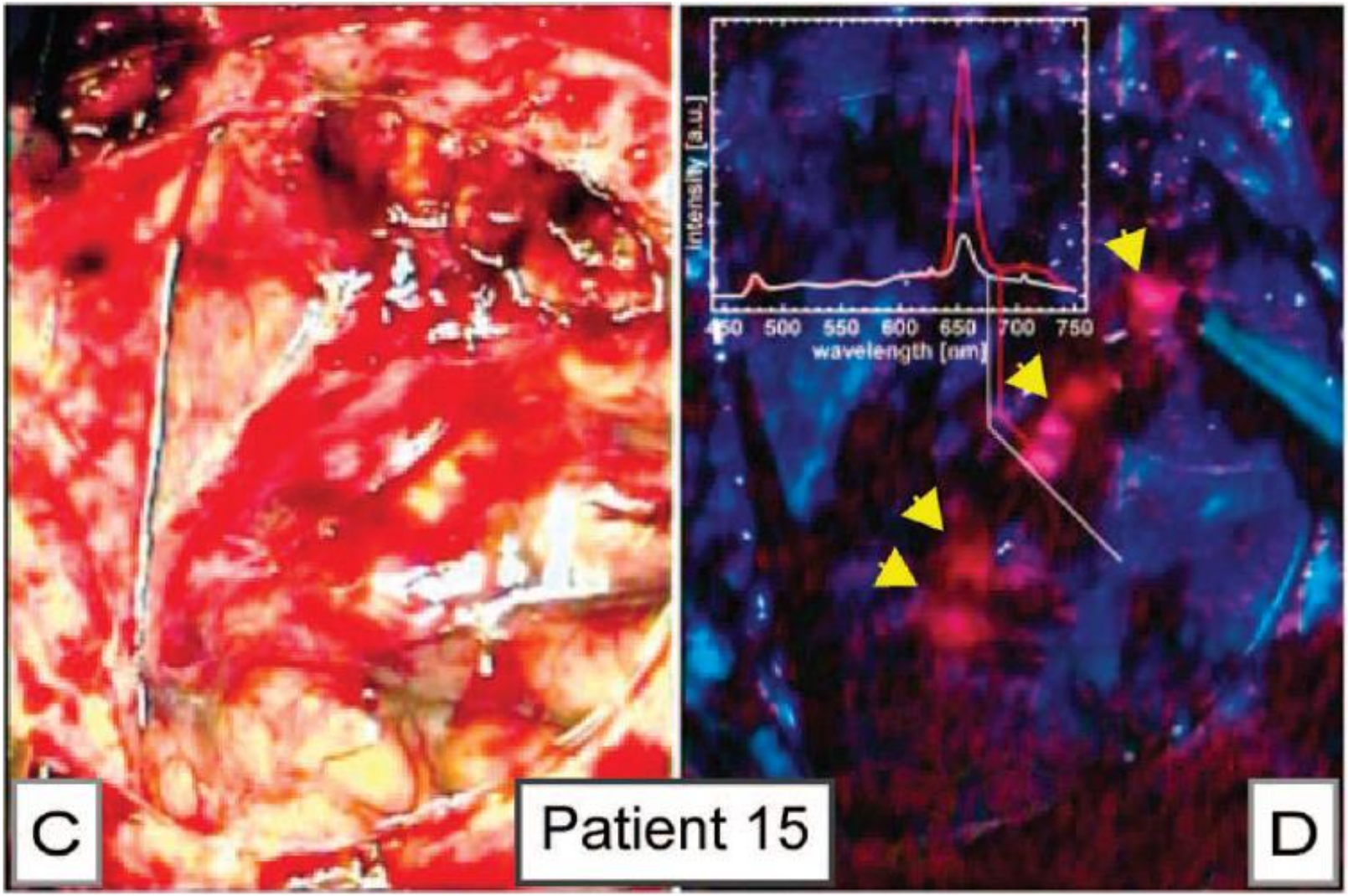


Folate conjugated temoporfin

Tumor margin resection with *tumor avid* PS's

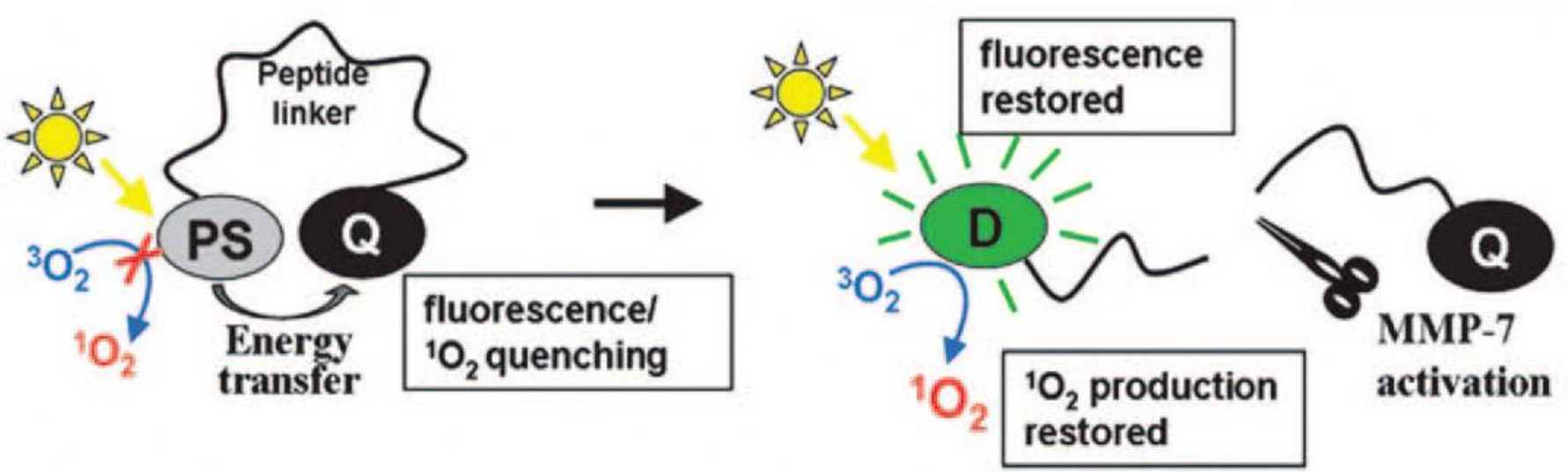


Brain tumor, patient treated with Foscan



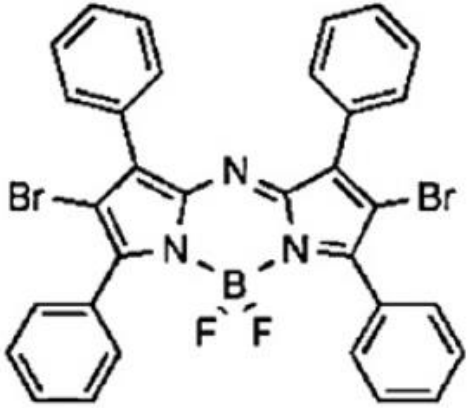
Blue light

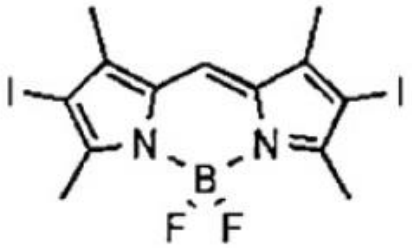
Site-activated constructs

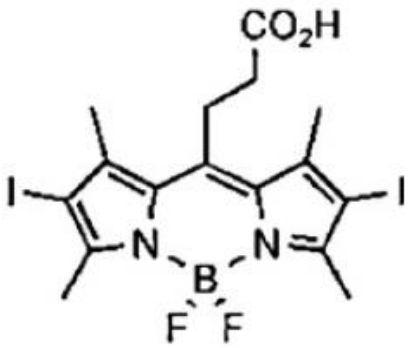


The activating enzyme might be overexpressed in the tumor cells, or be expressed by bacteria and not by cells…

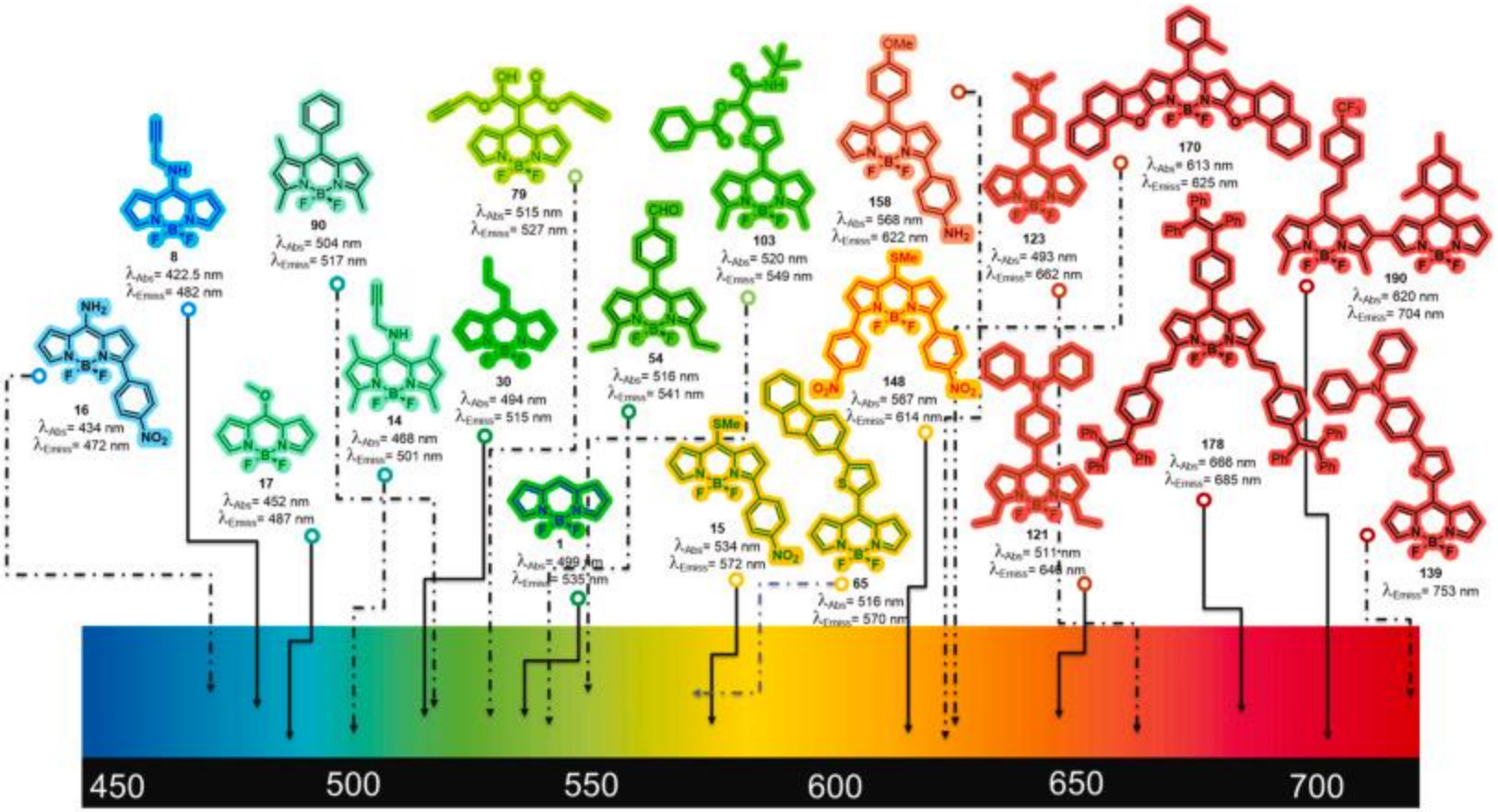
Derivati del BODIPY (*boron-dipyrromethene)*



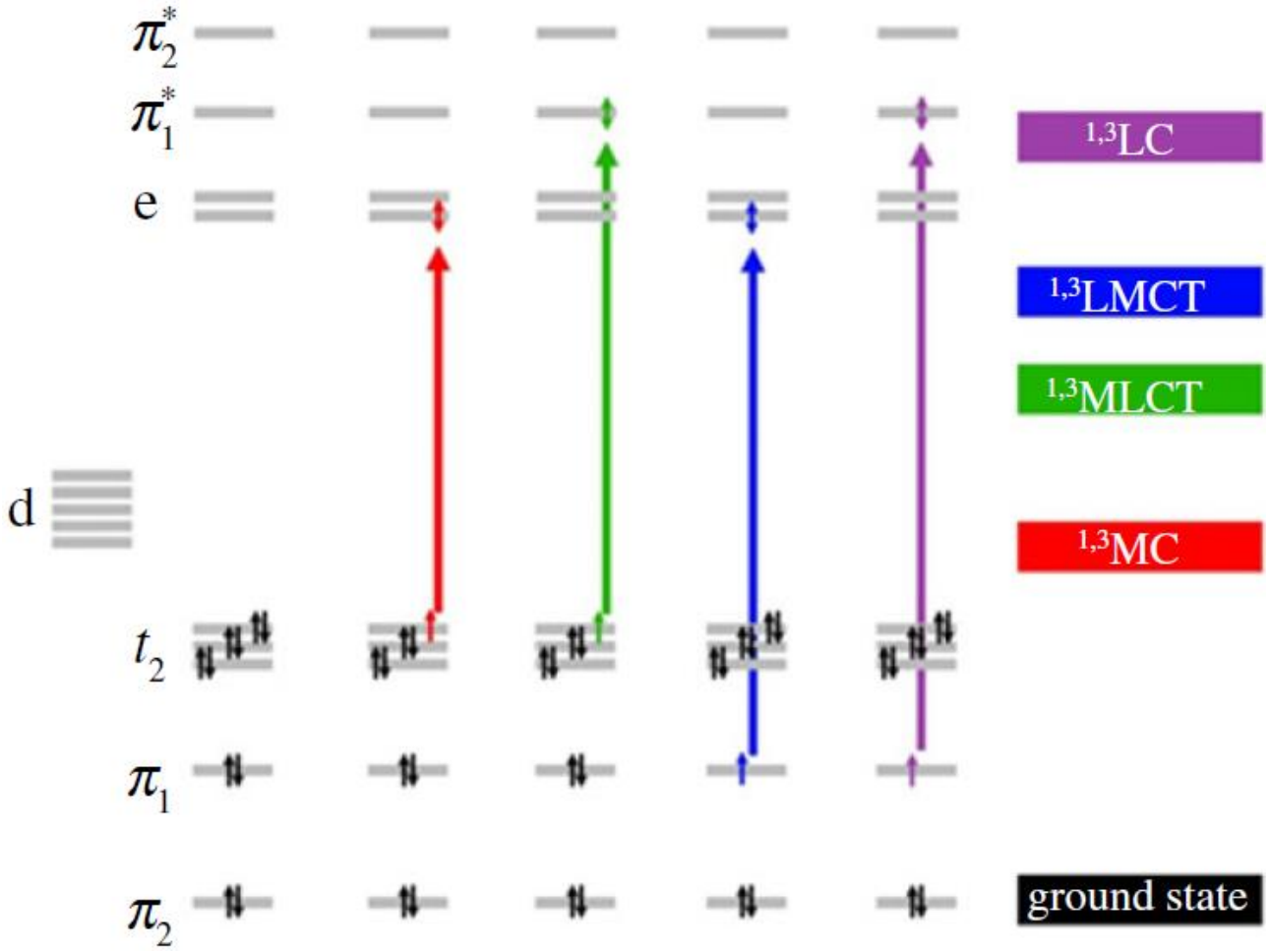




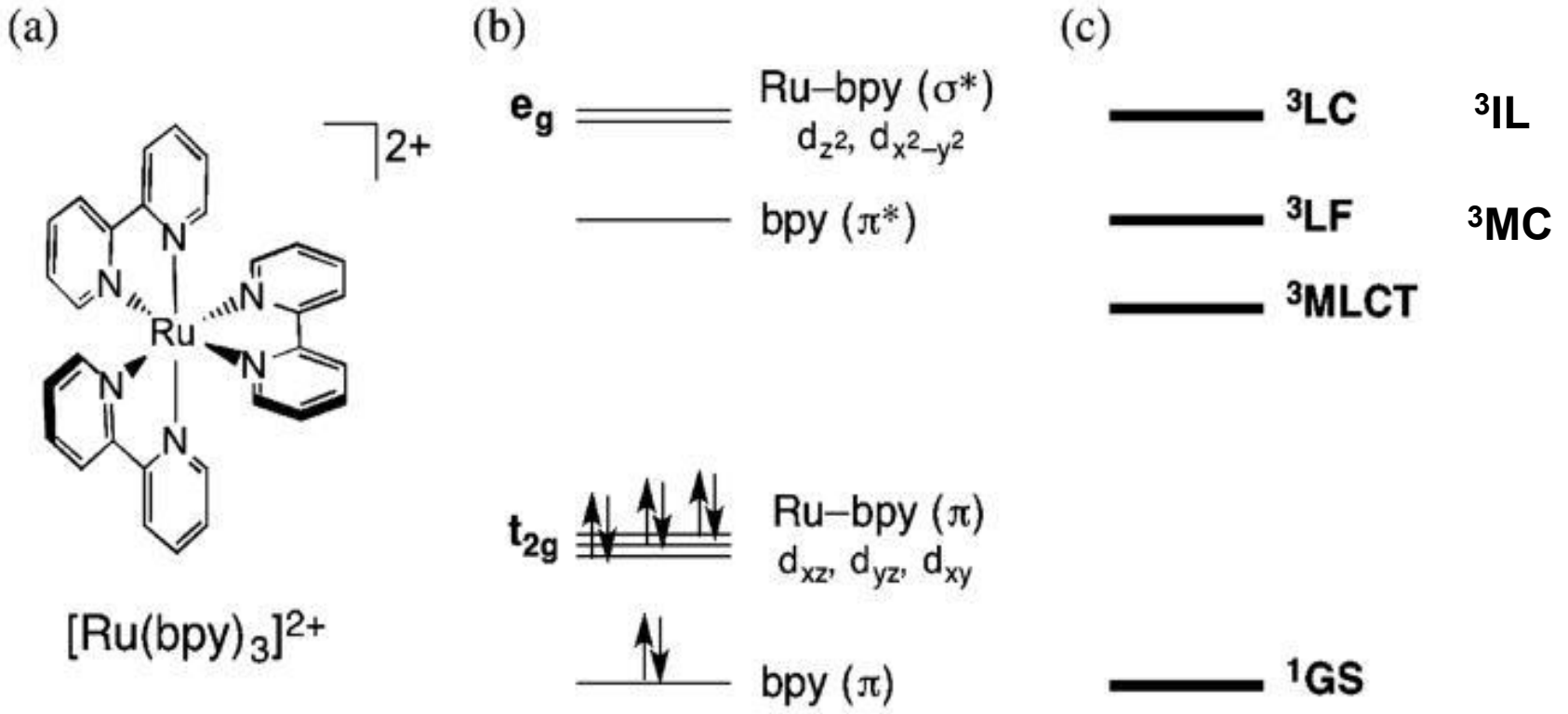
Tuning the absorption of BODIPY



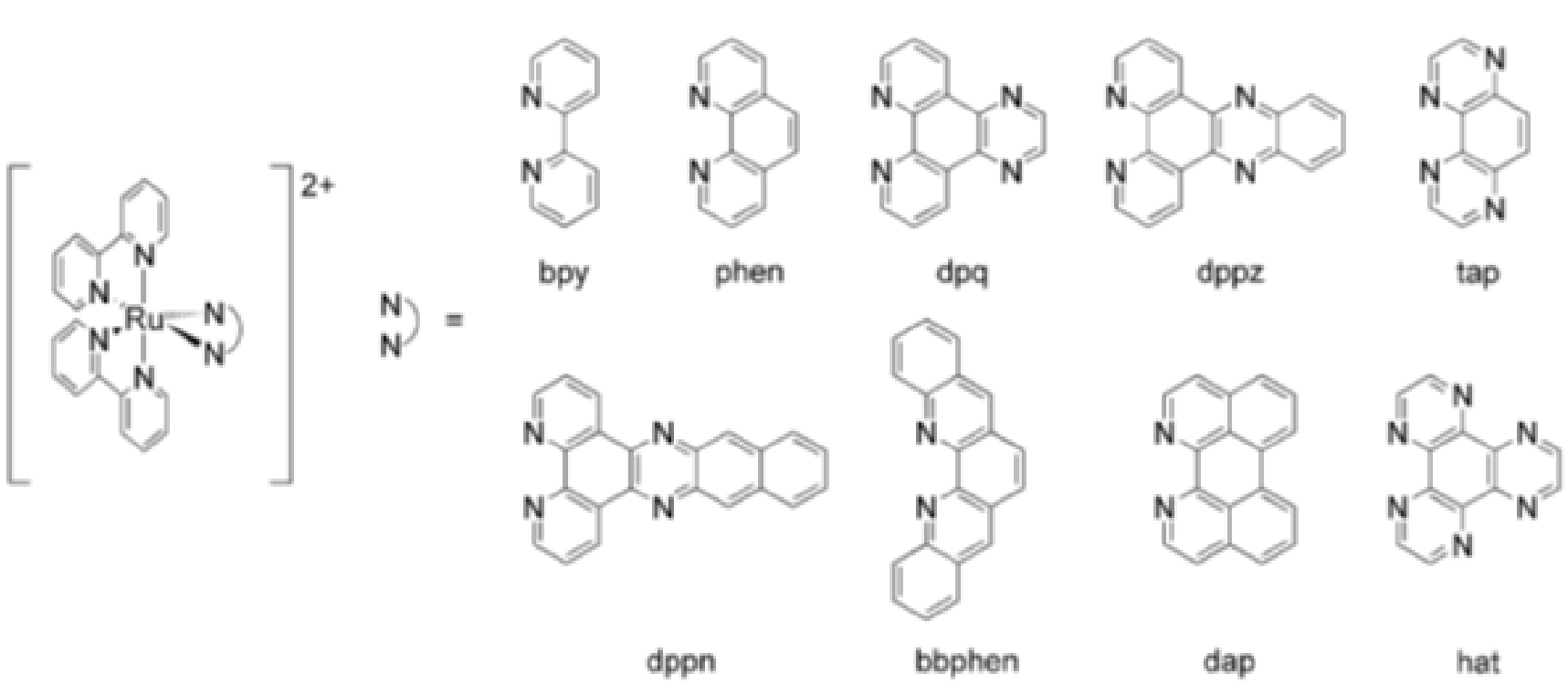
Photoactivatable metal compounds



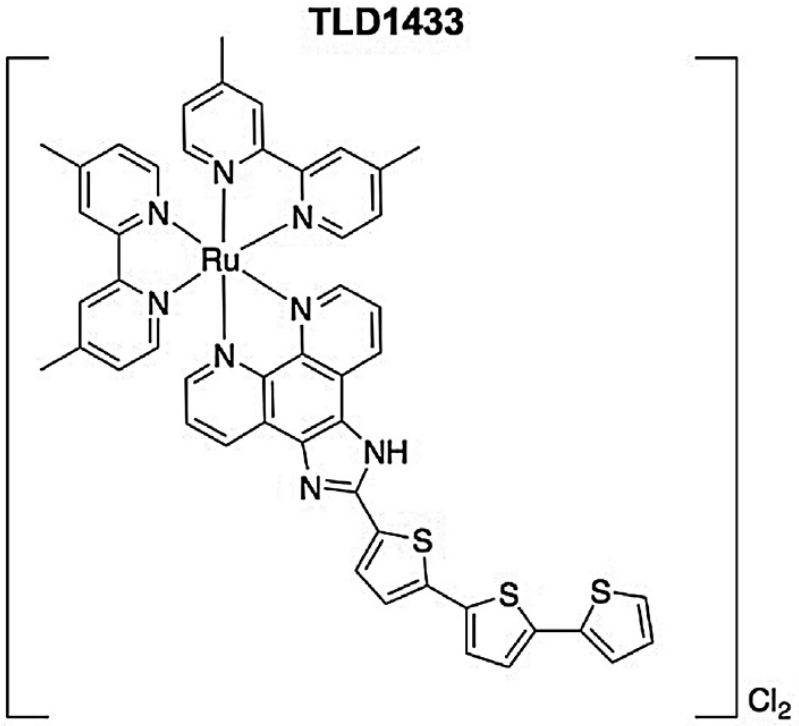
Simplified diagrams for the frontier MOs and states of $[Ru(bpy)_3]^{2+}$



Metal complexes for PDT



First inorganic compound to reach a clinical phase as PDT agent



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").

Ongoing phase 2 clinical trial of TLD-1433

Key Clinical Trial Details for TLD-1433 (NCT03945162)

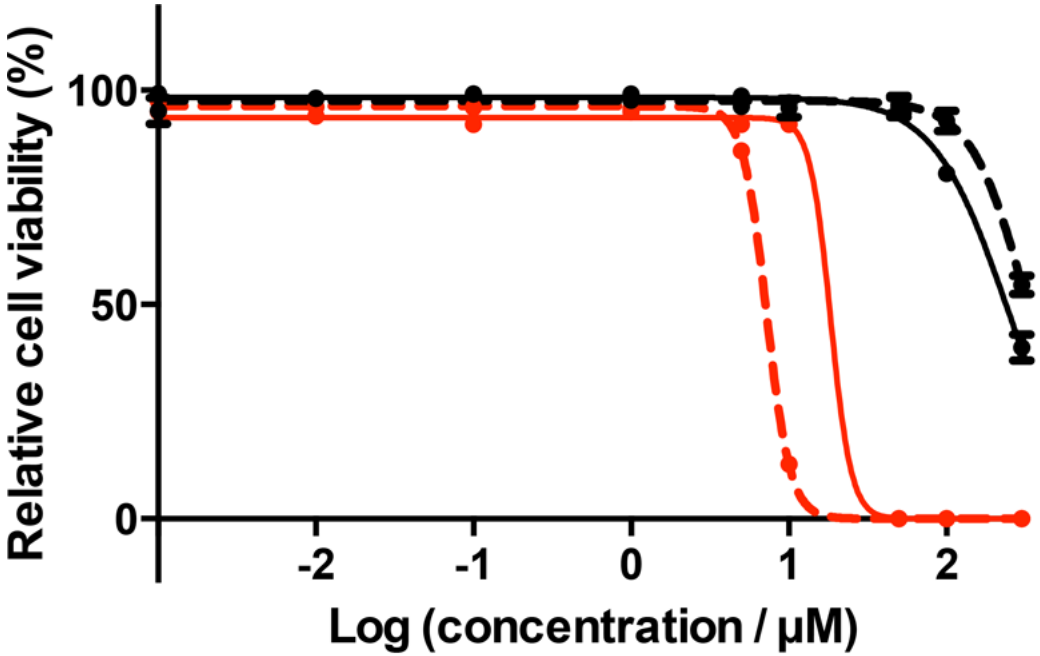
- **Indication:** BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) carcinoma in situ (CIS), with or without papillary disease.
- **Procedure:** Patients receive an intravesical instillation of TLD-1433, followed by activation with a 520 nm laser (photodynamic therapy).
- **Efficacy:** Interim phase 2 data showed a 64.4% complete response (CR) rate. Durable response (sustained CR) was observed in 40.4% to 42.6% of patients at 450 days, with some responses lasting up to 1080 days (approx. 3 years).
- **Safety:** The therapy is well-tolerated with no severe systemic toxicity or light sensitivity reactions. The most common adverse event is moderate bladder irritability, which typically resolves within weeks.
- **Status:** The phase 2 study is ongoing (active, not recruiting/enrolling) and was initiated by Theralase Technologies Inc..
- **Future Outlook:** Data completion is expected in 2026, with potential for regulatory approval filings with the FDA and Health Canada in 2026 or 2027. ClinicalTrials.gov +7

Background and Purpose

TLD-1433 aims to provide a bladder-sparing option for patients who have failed standard Bacillus Calmette-Guérin (BCG) therapy and are not candidates for or refuse radical cystectomy (bladder removal). The treatment works by destroying cancer cells through activated light while being rapidly cleared from the body (24 hours in urine, 72 hours in plasma). CancerNetwork +3

2025

In vitro studies



Phototoxicity Index, PI

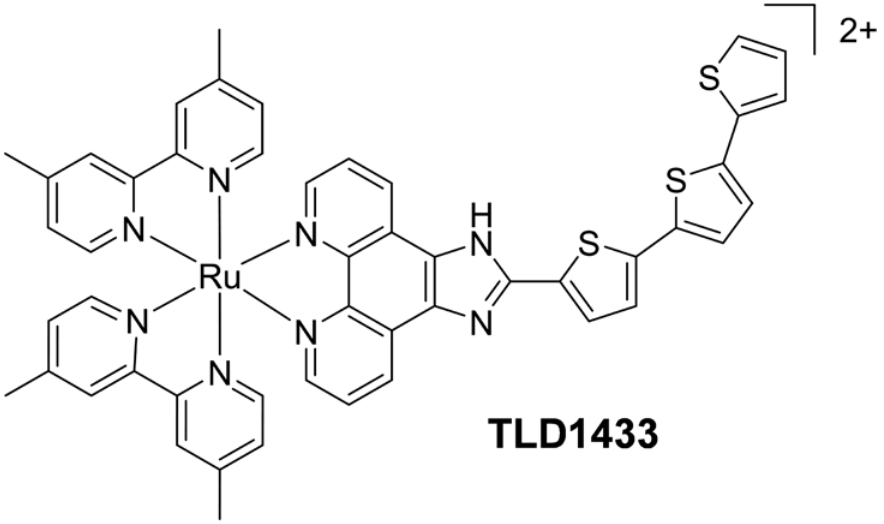
TLD1433, Dark EC_{50} > 300 µM

TLD1433, Red EC_{50} = 7.20 ± 1.10 µM

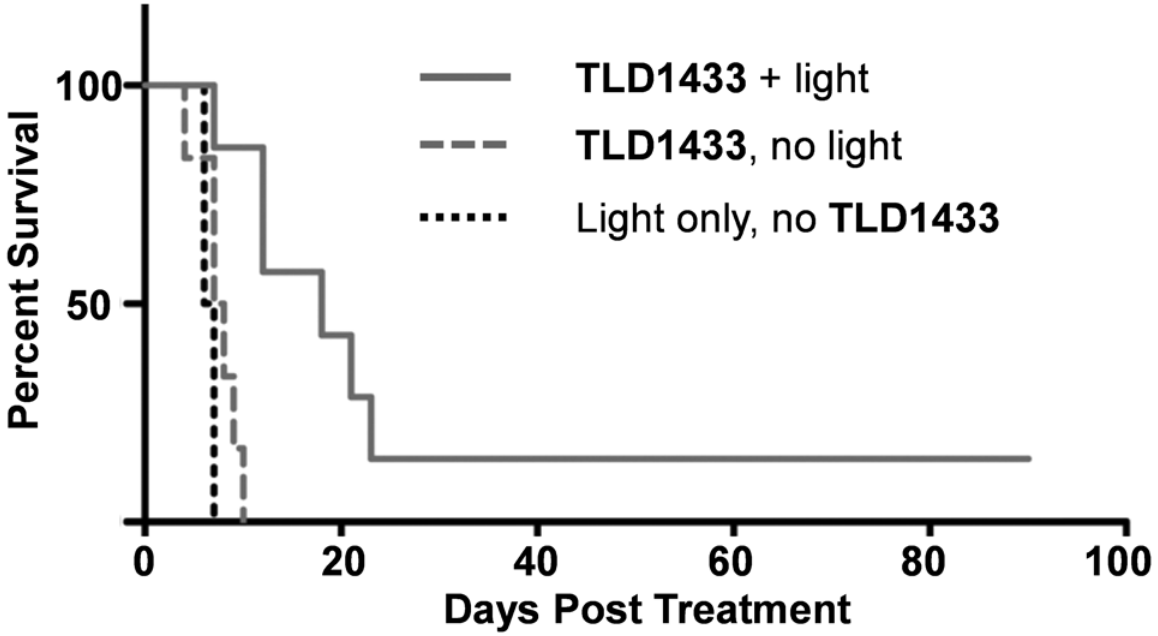
$[Os(dmb)_2(IP\text{-}3T)]Cl_2$, Dark EC_{50} = 242 ± 3 µM

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

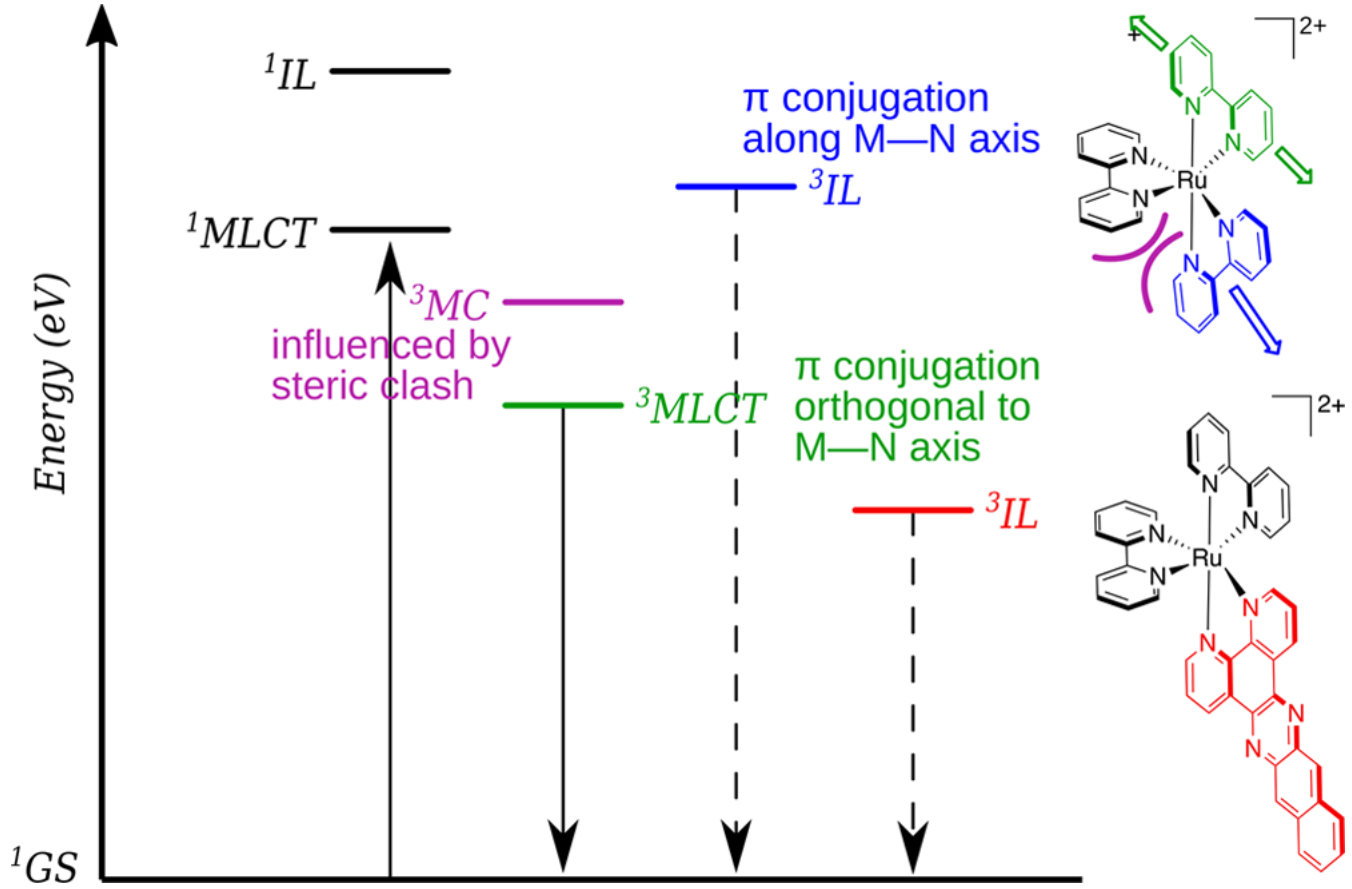
In vivo studies



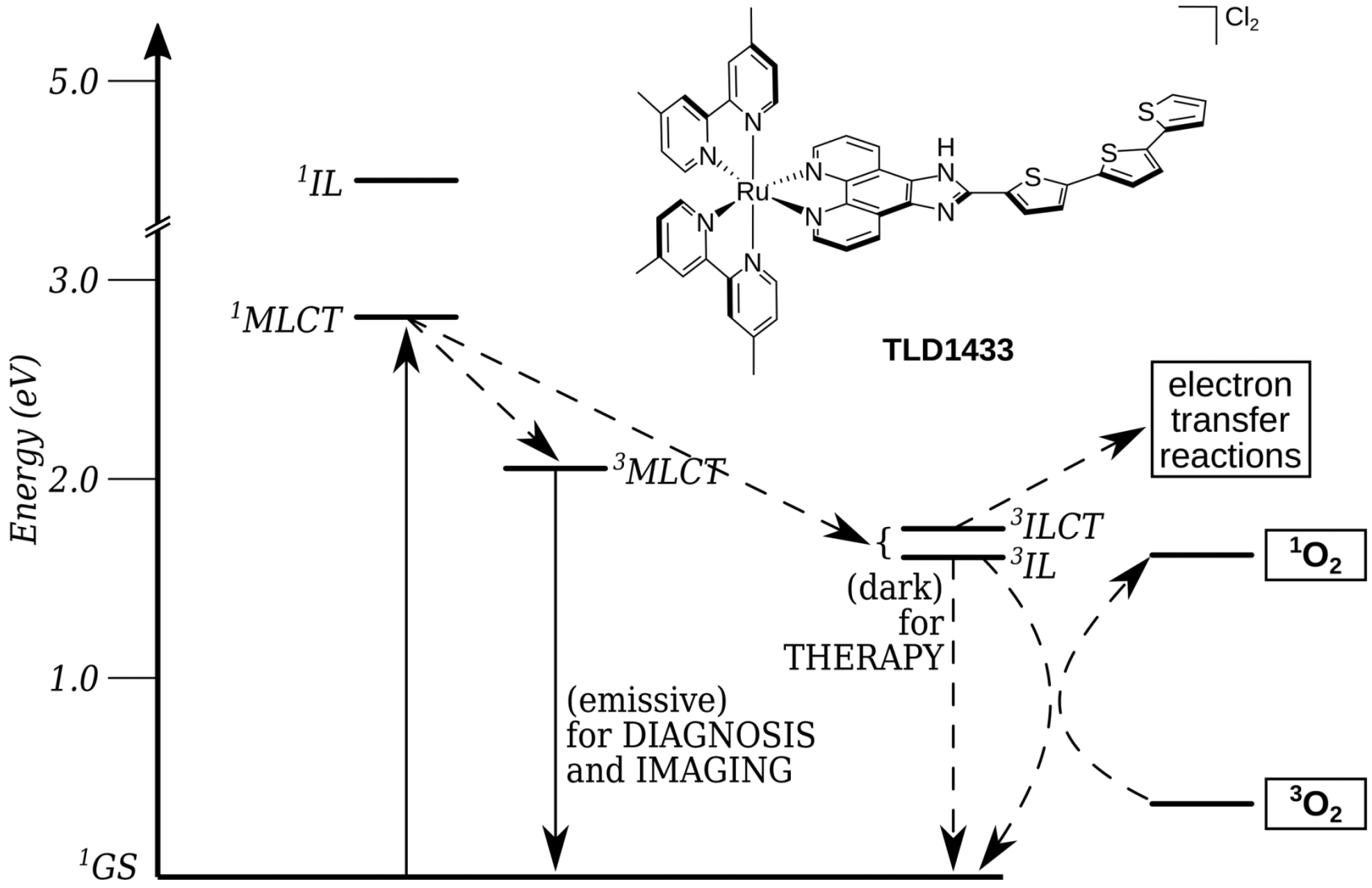
TLD1433



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

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.