Translation of a combination between a laser device and a medicinal agent, from bench to bedside

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Medical Device

ISO 13485:2016; Regulation (EU) 2017/745

Class I – non-invasive devices, unless…

They channel or store body fluids or cells, or liquids or gases : **Class IIa**
They are connected to Class IIa, IIb, or III : **Class IIb**

Class IIa – non-invasive devices intended for modifying the biological or chemical composition of the body

Includes active devices intended for diagnosis and monitoring

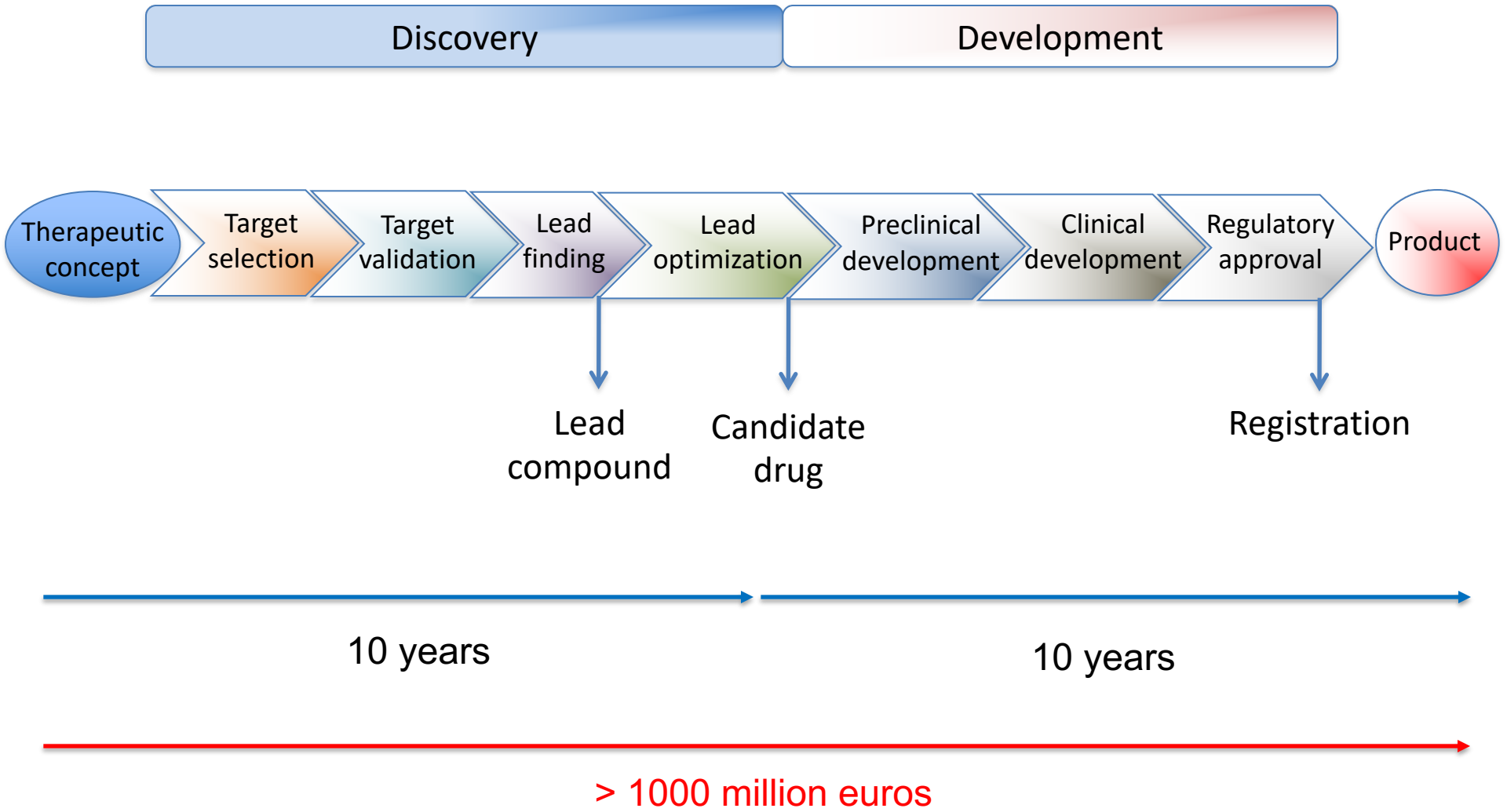
Class IIb – implantable devices and long-term surgical devices

Includes devices intended to emit ionizing radiation

Class III – active therapeutic devices with incorporated diagnostic function

Includes devices incorporating a medicinal product with an action ancillary to that of the device

Drug discovery and development



Combinations Products

Integral combination products

The device and the medicinal product form a single integrated product
pre-filled syringes, patches for transdermal drug delivery and pre-filled inhalers

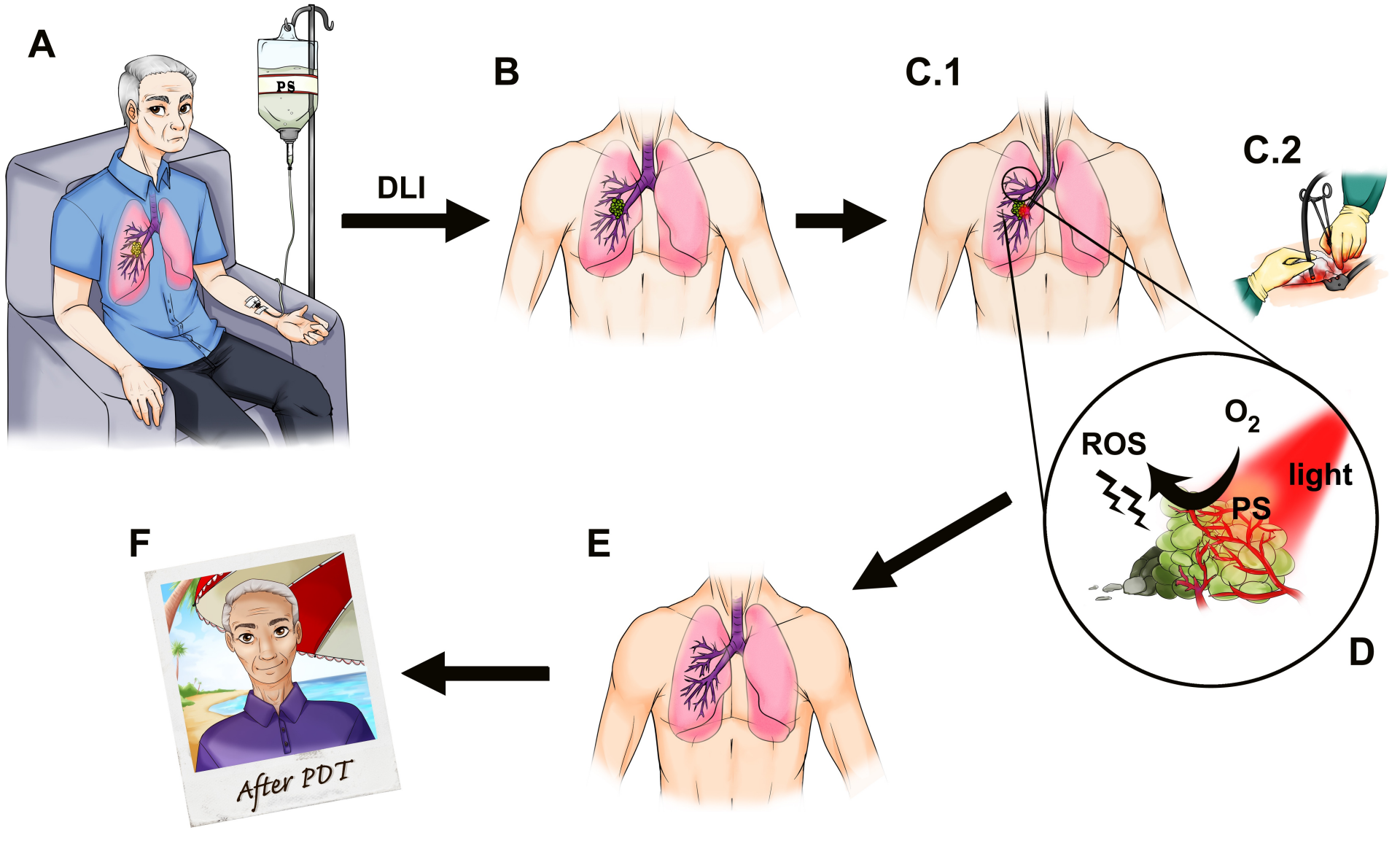
Co-packaged combination products

Device and medicinal products are separate items contained in the same pack
reusable pen for insulin cartridges, delivery system with controller for pain management

Medical device with ancillary medicinal substance

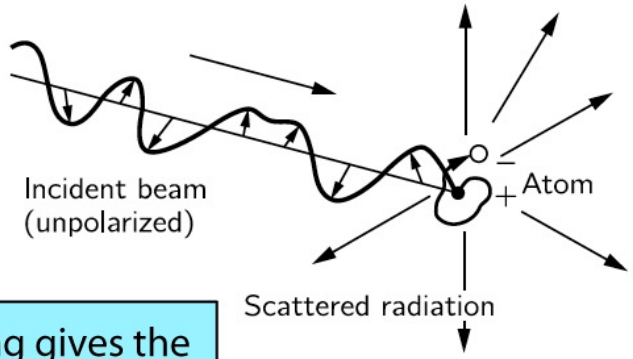
Device contains an ancillary medicinal substance to support is proper functioning
drug-eluting stents, catheters coated with antibiotic

PDT for solid tumors



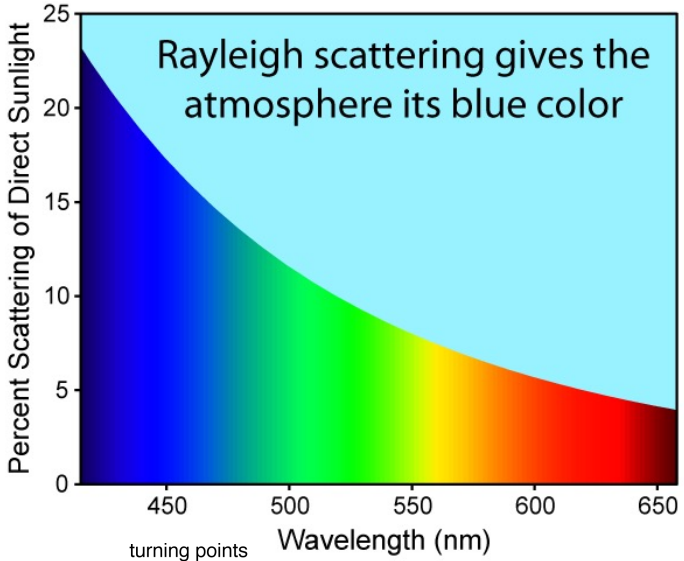
Light propagation in human tissues

Elastic scattering



Rayleigh
(very small particles)

$$I \propto \frac{1-\cos^2\theta}{\lambda^4} I_0$$

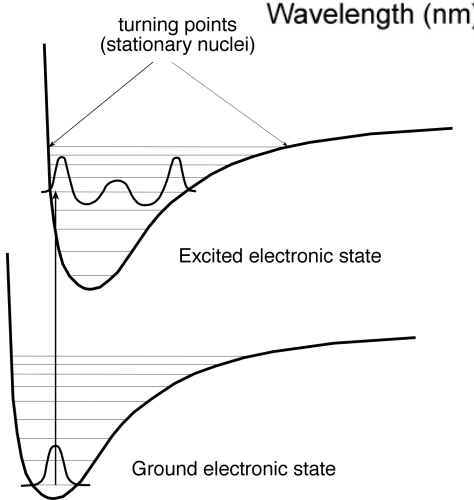


Mie
(particle size comparable with λ)

Cell diameter	40 λ
Mitochondria length	λ
Ribosome width	λ/20

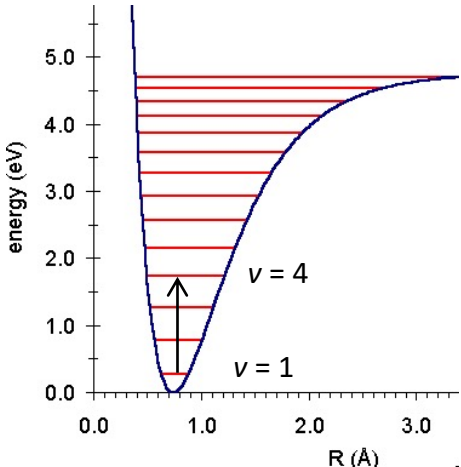
Absorption

Electronic excitation

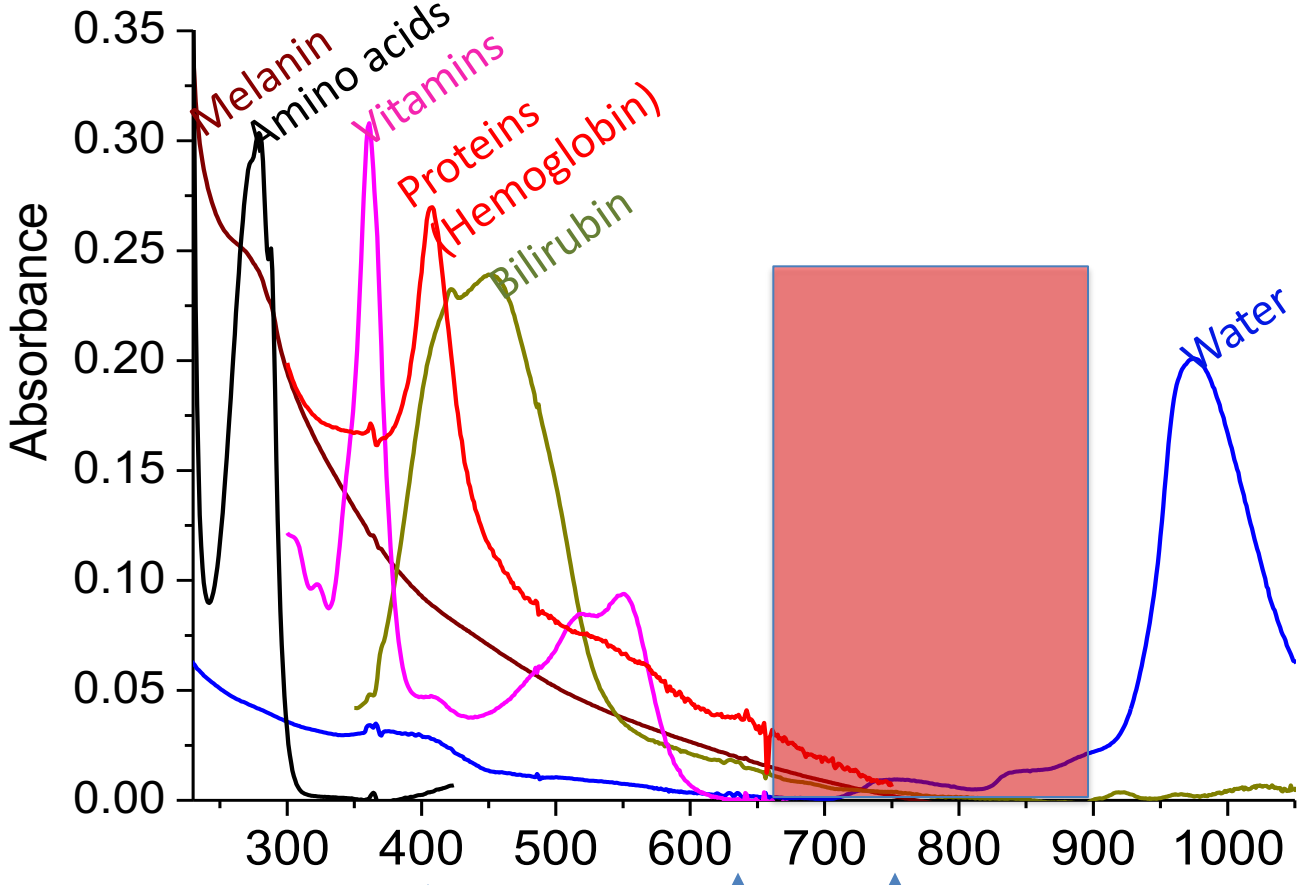


Vibration overtones

For λ=700 nm



Endogenous chromophores and the phototherapeutic window



δ – optical penetration depth

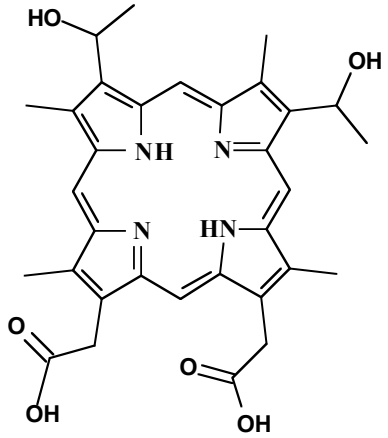
3δ ≈ 95% light attenuation

0.8 mm

5.4 mm

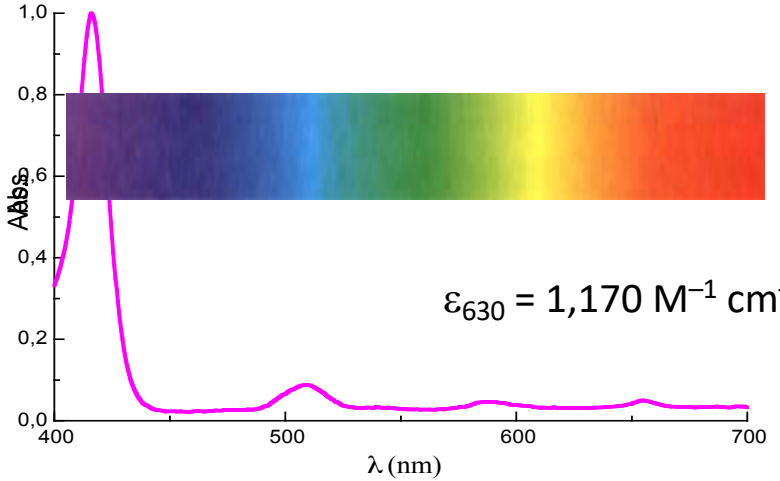
6.9 mm

J. M. Dabrowski, L. G. Arnaut, *Photochem. Photobiol. Sci.*, 14 (2015) 1765-1780

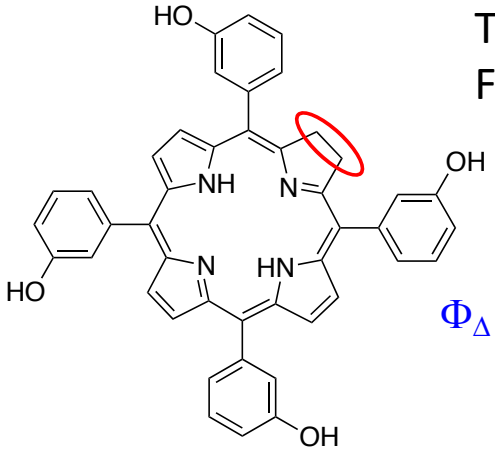


Porfimer sodium
Photofrin®

Φ_Δ = 0.36 in PBS

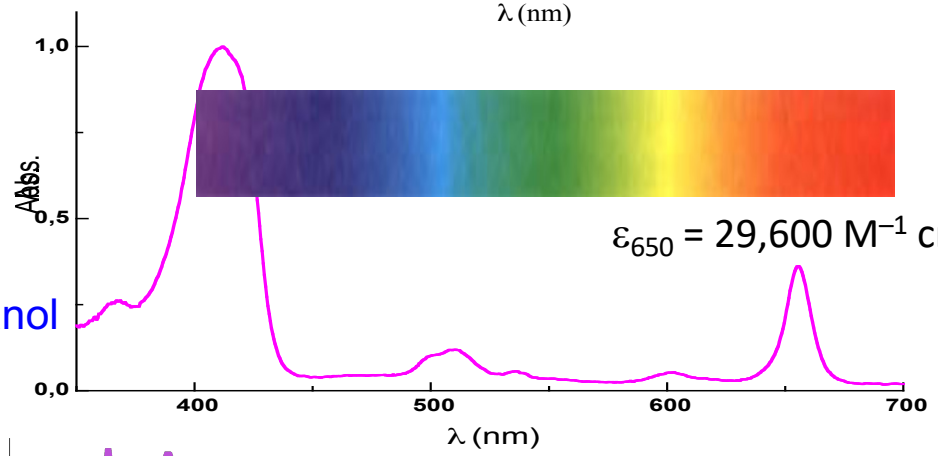


ε_{630} = 1,170 M^{-1} cm^{-1}

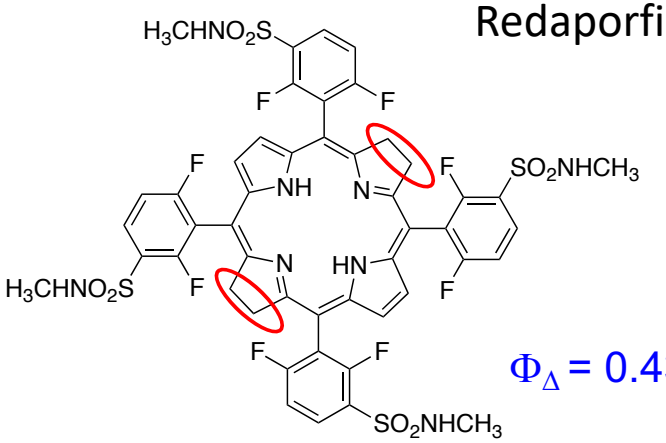


Temoporfin
Foscan®

Φ_Δ = 0.43 in methanol

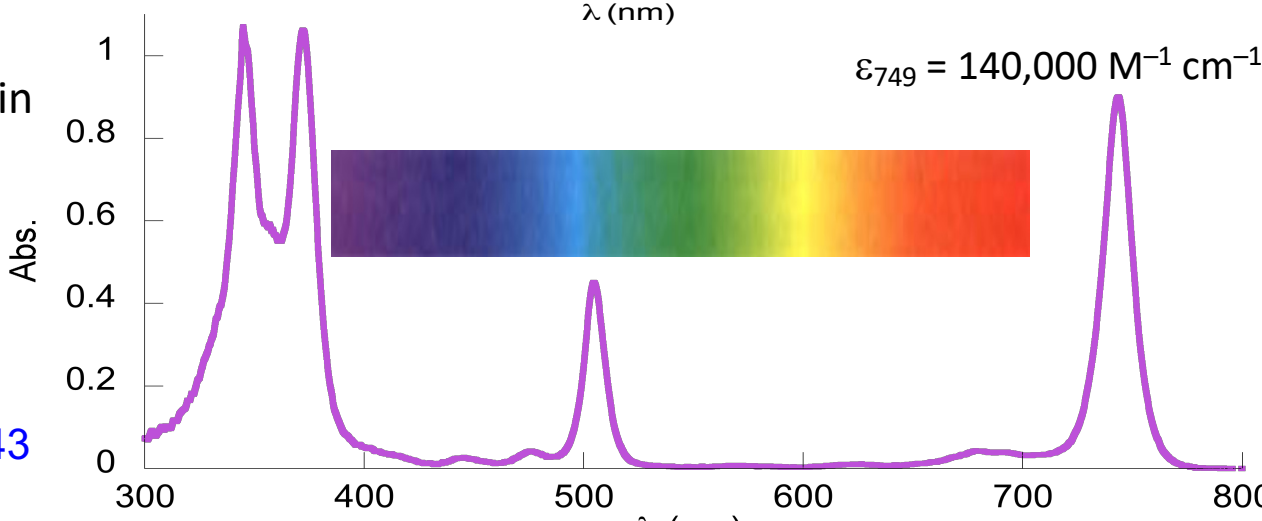


ε_{650} = 29,600 M^{-1} cm^{-1}



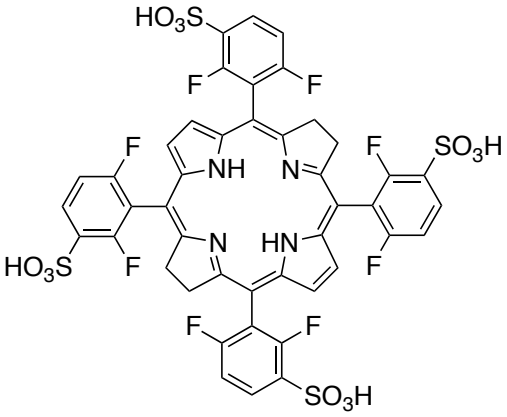
Redaporfin

Φ_Δ = 0.43

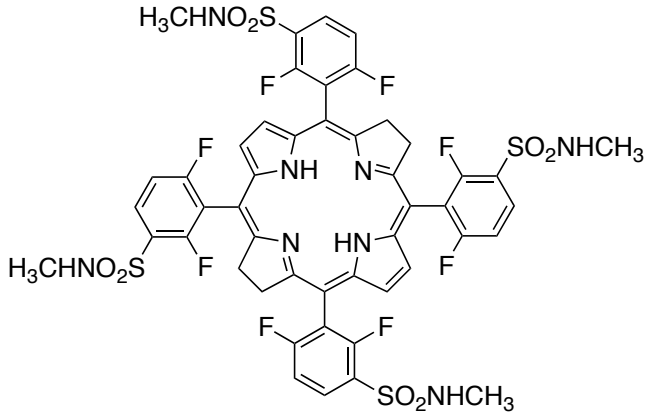


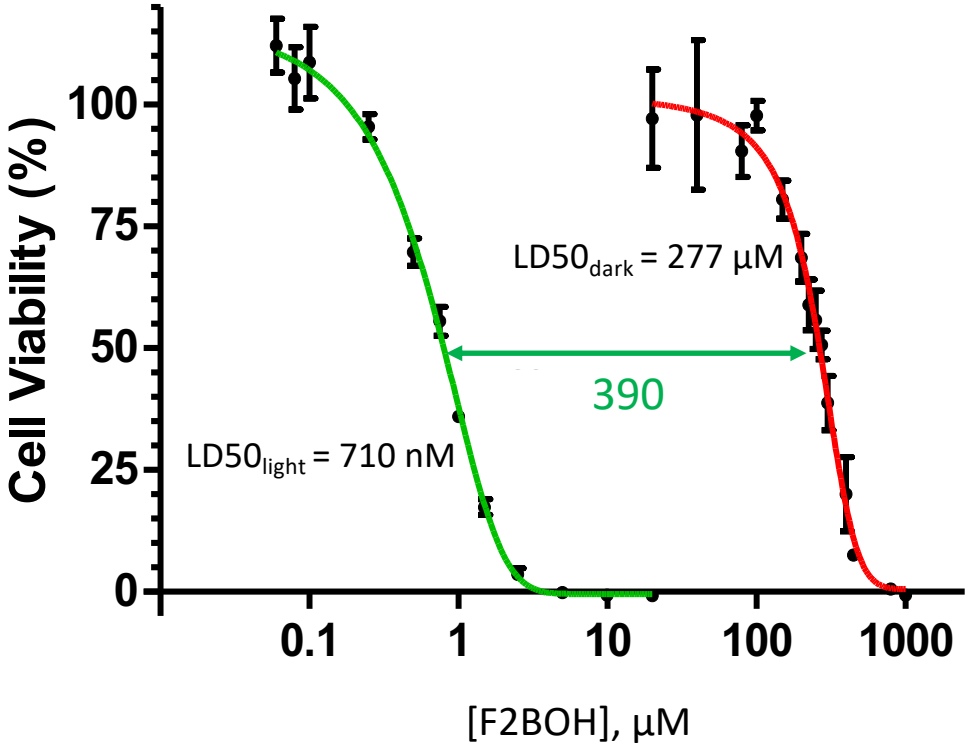
ε_{749} = 140,000 M^{-1} cm^{-1}

Toxicity and phototoxicity

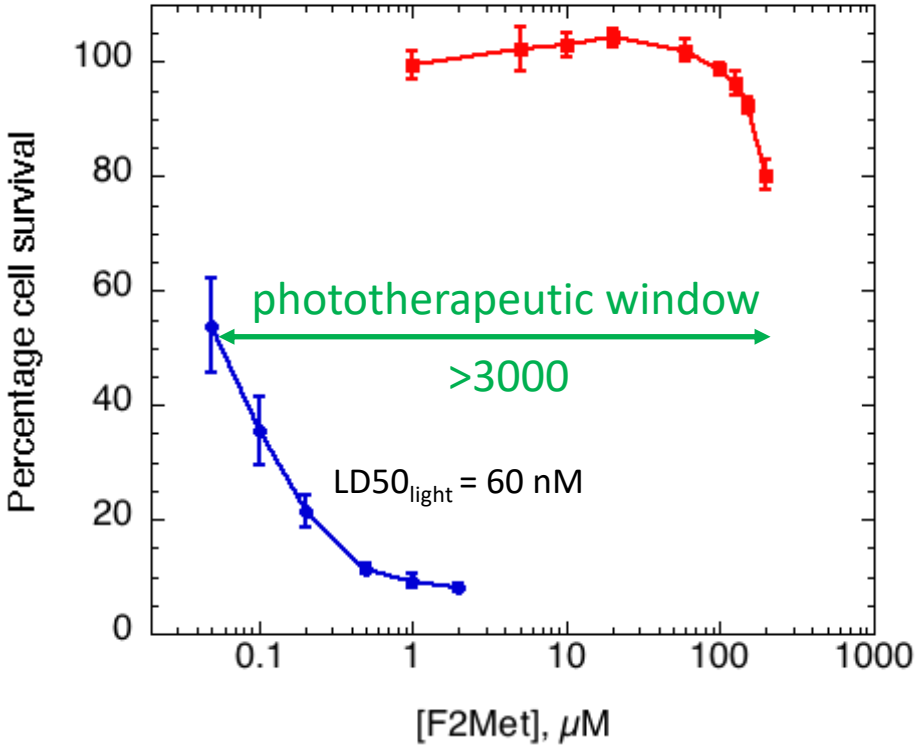


In vitro CT26 cell line
6 J/cm^2





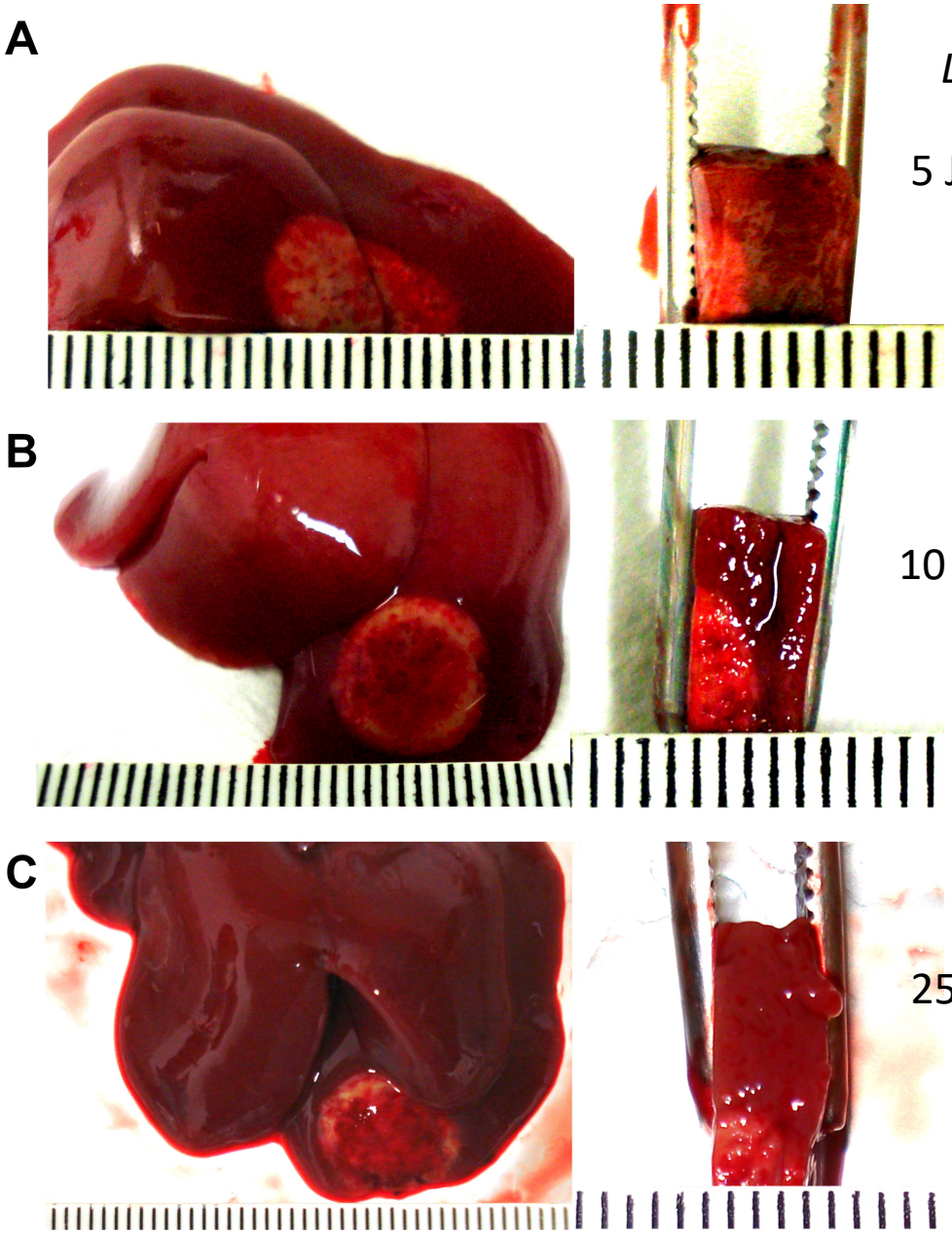
Hydrophilic bacteriochlorin



Amphiphilic bacteriochlorin

Depth of necrosis – Frontal illumination, 1 cm diameter spot

Rat liver, 0.75 mg/kg redaporfin , DLI =15 min, λ= 750 nm, *P*=130 mW/cm²

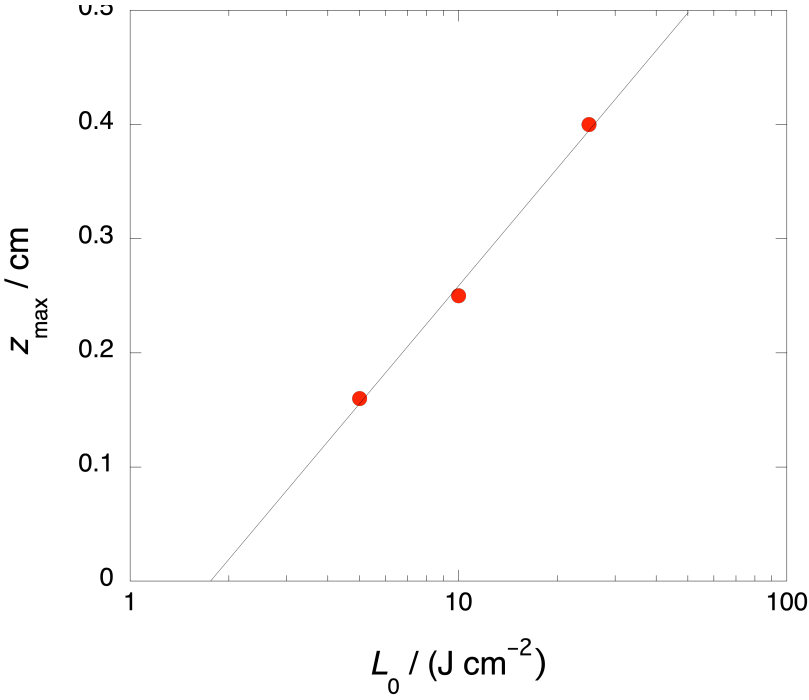


L_0 =

5 J/cm²

10 J/cm²

25 J/cm²



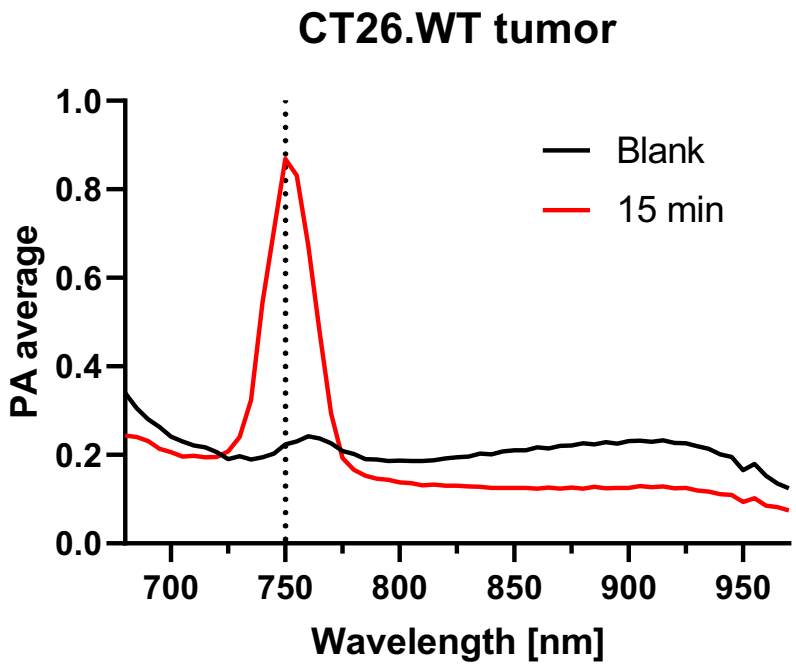
Photodynamic threshold dose

$$T = 2.3\,\varepsilon C_{\mathrm{loc}} L_{\mathrm{th}}$$

≈ 11 mM

Rocha, et al, Photochem. Photobiol. 96 (2020) 692

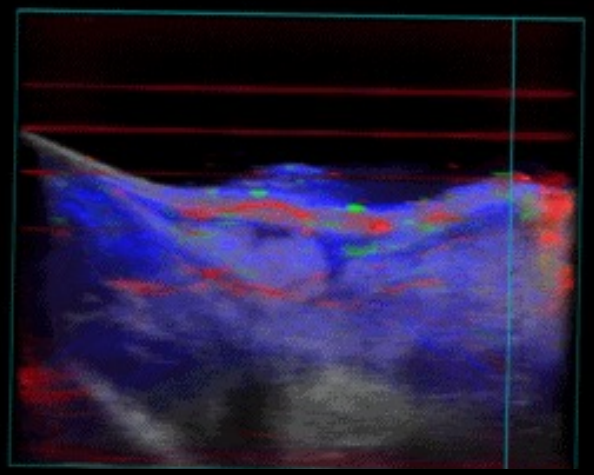
Redaporfin tumor accumulation by Photoacoustic Tomography



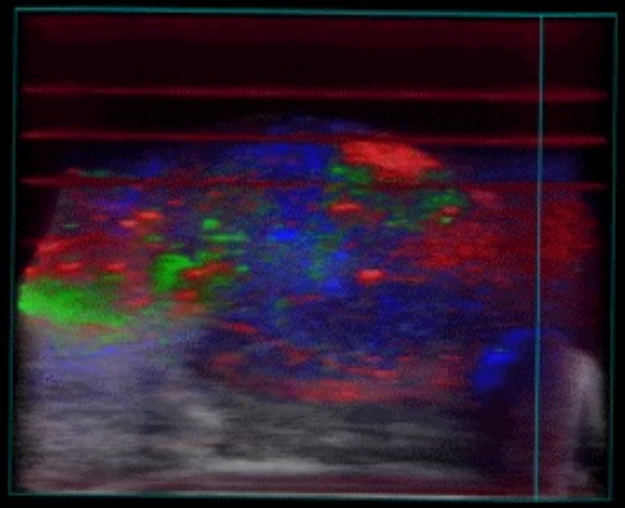
Photoacoustic tomography of tumors after administration of redaporfin

Blue = deoxyhemoglobin Red = oxyhemoglobin Green = redaporfin

4T1@48h



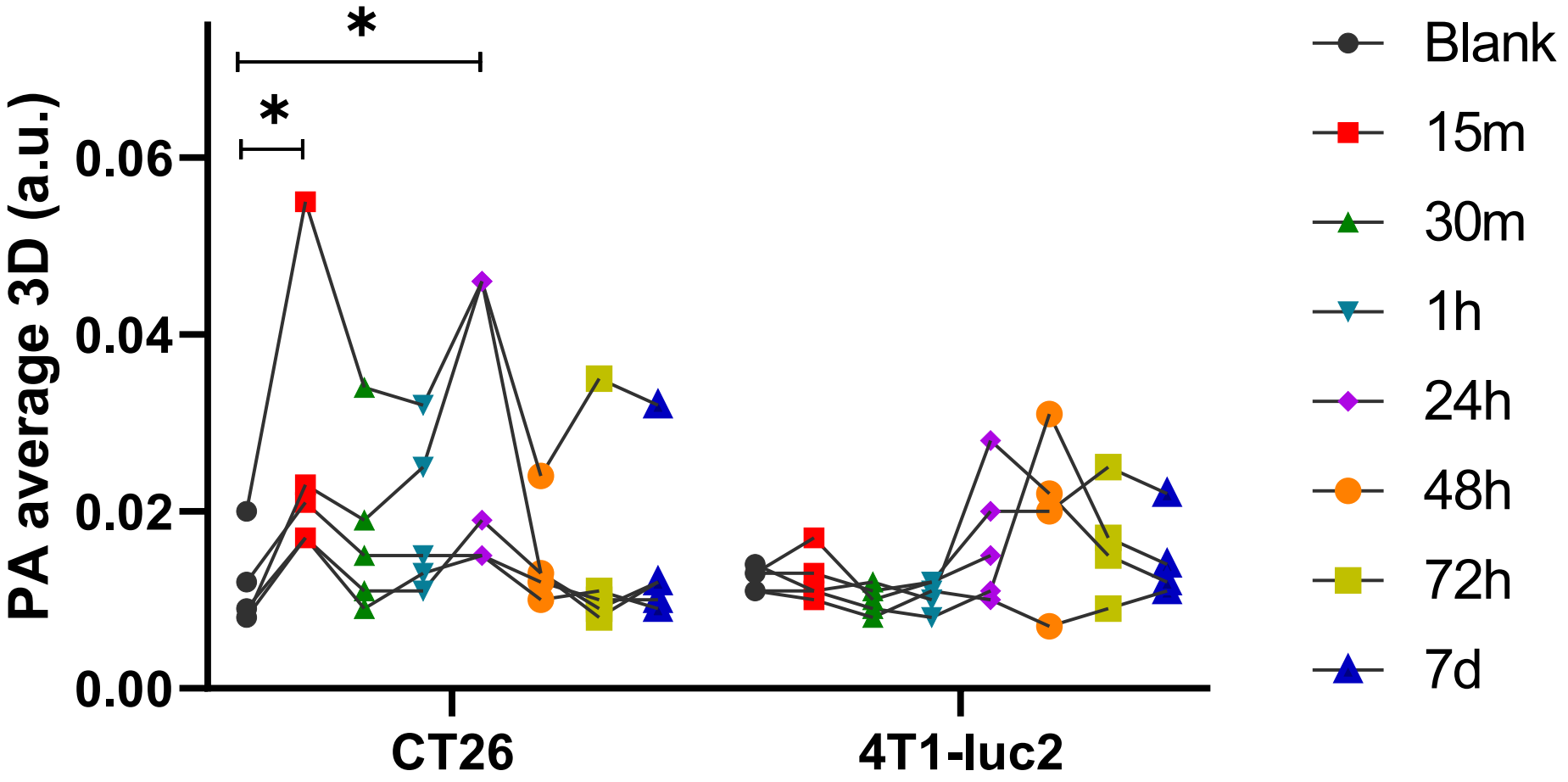
CT26@15min



Vevo LAZR-X Multimodal Imaging

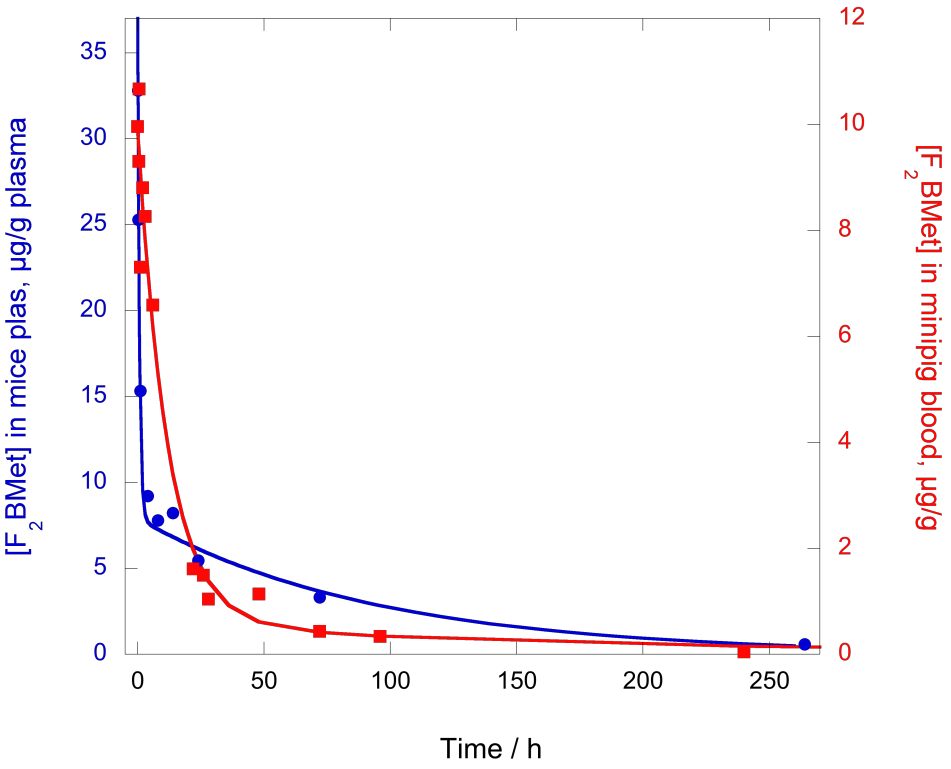
Profile of redaporfin accumulation in the tumor followed by photoacoustic tomography

redaporfin 1.65 mg/kg



Pharmacokinetics in BALB/c mice and minipigs

(i.v. administration of 1.5 mg/kg)



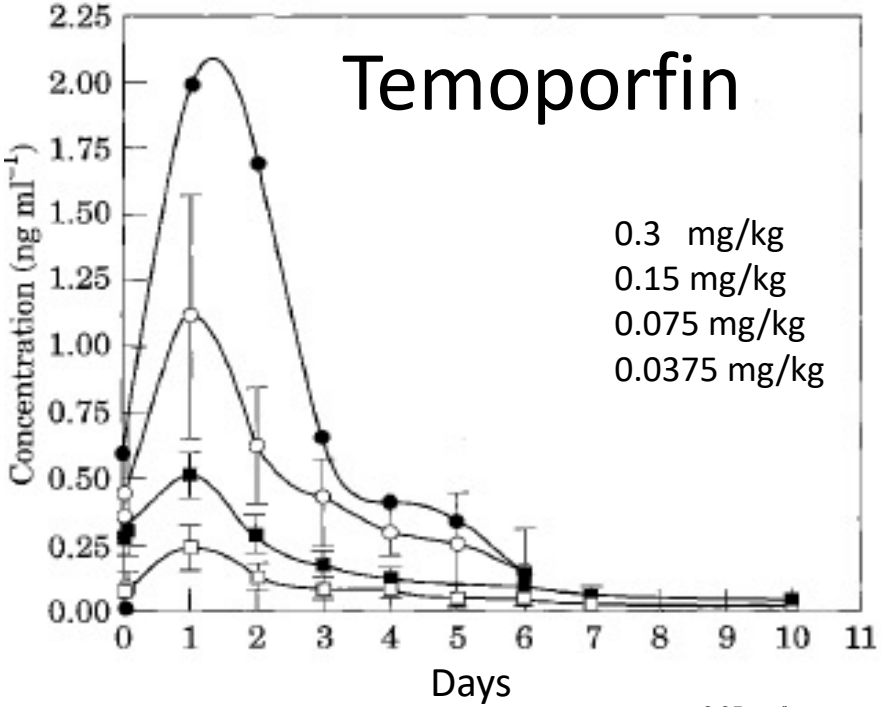
PK parameter	BALB/c mice	Minipigs
i.v. dose (mg/kg)	2	2
C_{max} (µg/mL)	39	9.9
V_D (mL/kg)	52	202
$t_{1/2}$ (α) (h)	0.5	8.2
$t_{1/2}$ (β) (h)	65	121
AUC_∞ (µg h/mL)	763	213
CL (mL/kg/h)	2.6	9.4

- The PK of redaporfin in plasma of mice follows a 2 compartment model
- 90% of redaporfin is cleared from the plasma in 3 days

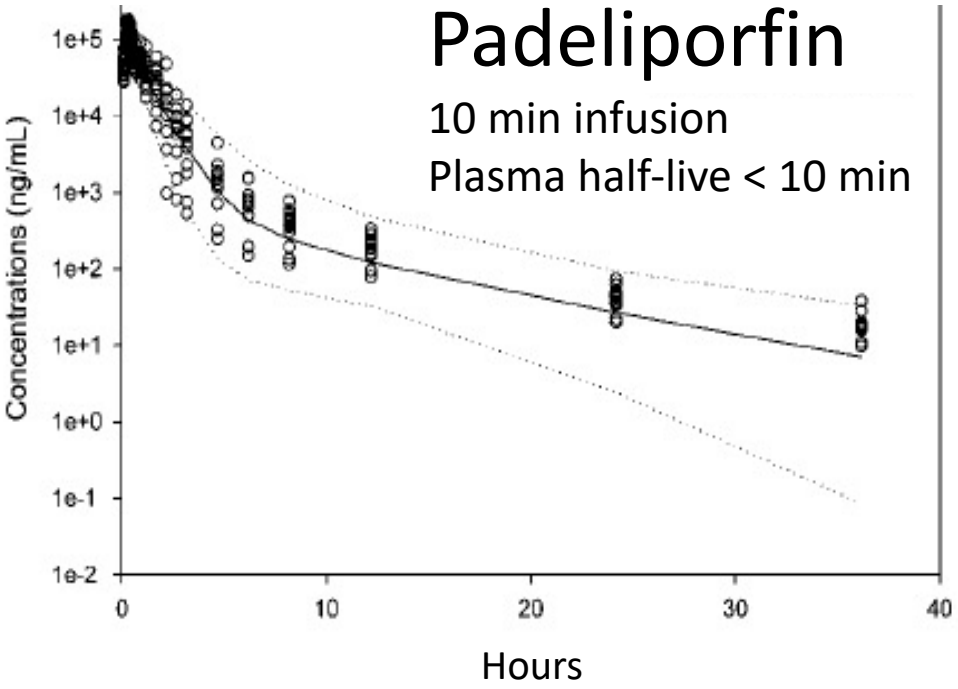
R. Saavedra, L: B. Rocha, J. D. Dabrowski, L. G. Arnaut. ChemMedChem 9 (2014) 390

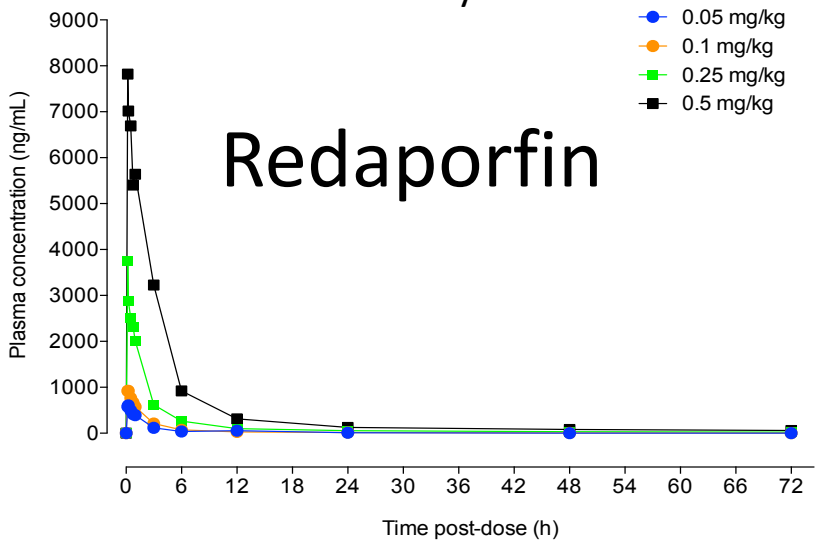
Clinical pharmacokinetics

Ronn, A. M. et al Laser Med. Sci. 11 (1996) 267



M.-A. Fabre et al J. Pharm. Sci. 96 (2007) 3444



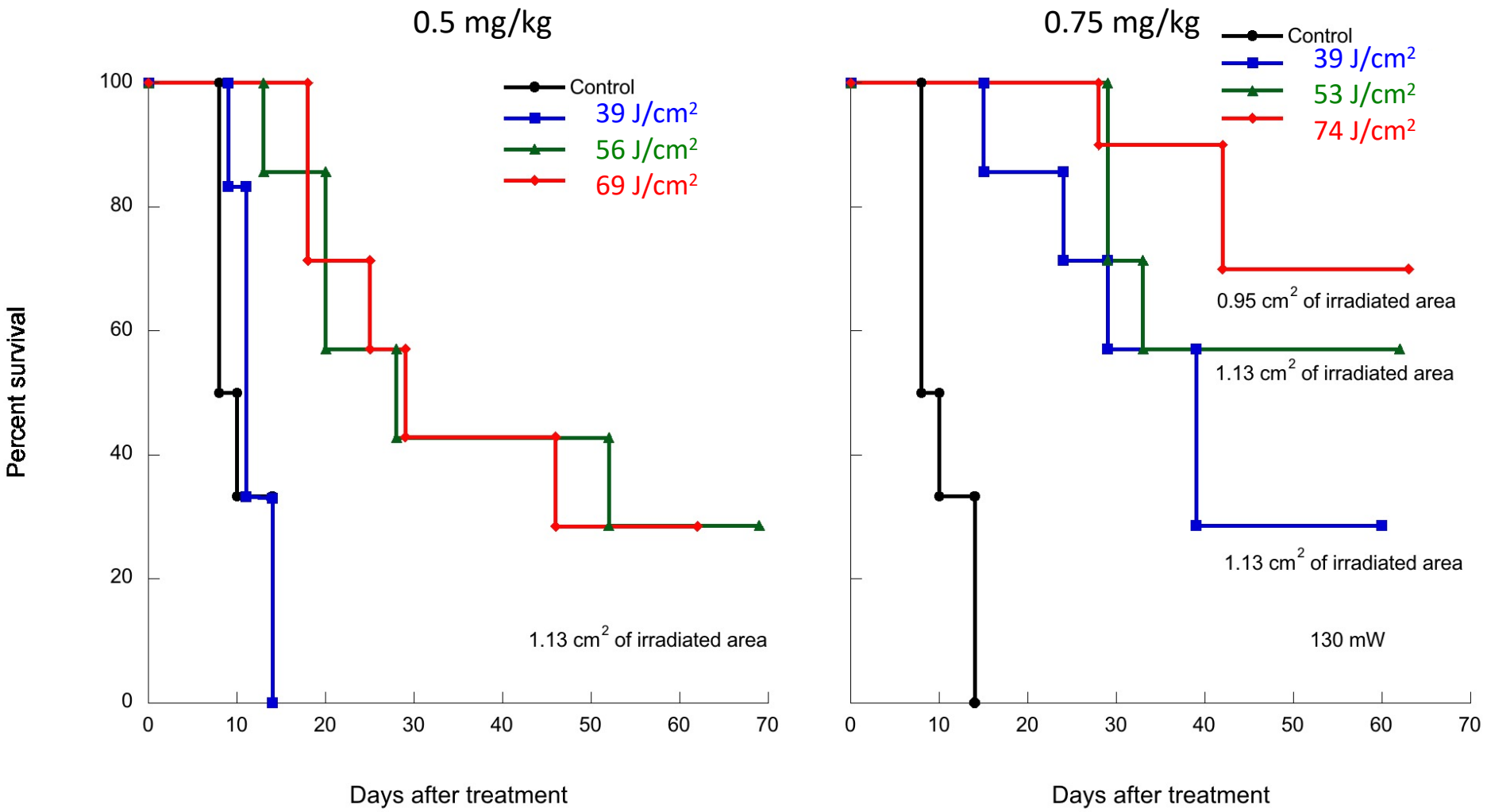


PK parameter	Clinical
i.v. dose (mg/kg)	0.1
C_{max} (µg/mL)	1
V_D (mL/kg)	1380
$t_{1/2}$ (α) (h)	0.8
$t_{1/2}$ (β) (h)	26
CL (mL/kg/h)	40

Escalating drug and light doses

CT26 colo tumors in BALB/c mice

drug-to-light interval = 15 min



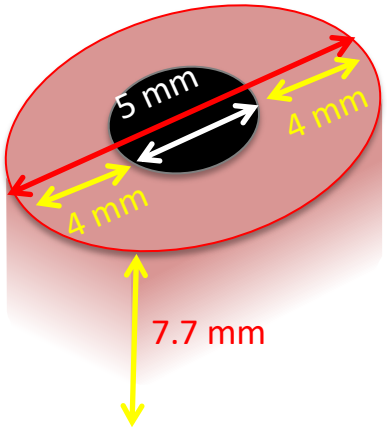
L. B. Rocha, *Eur. J. Cancer*, 51 (2015) 1822

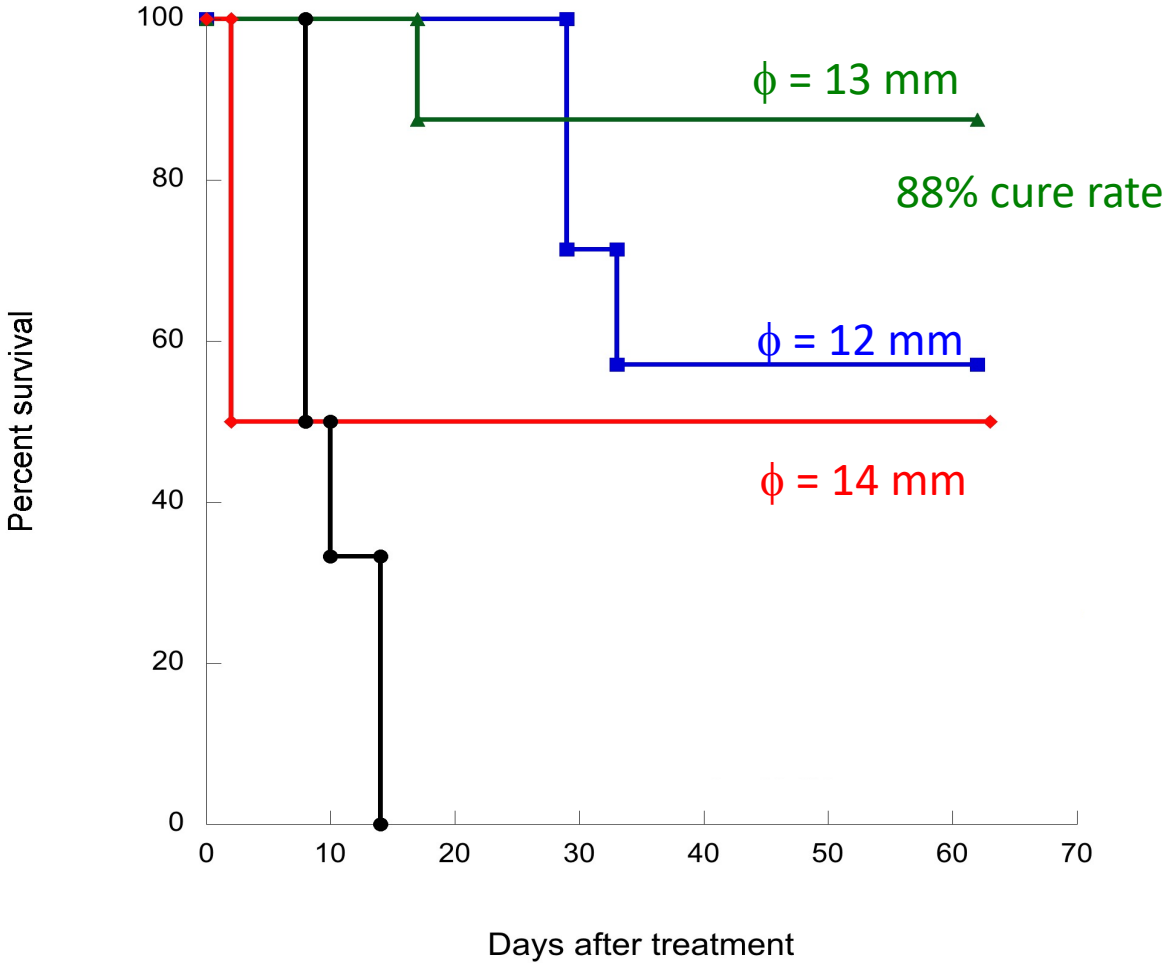
Optimizing tumor margins

CT26 colo tumors in BALB/c mice

drug-to-light interval = **15 min**

0.75 mg/kg **51±2 J/cm²**

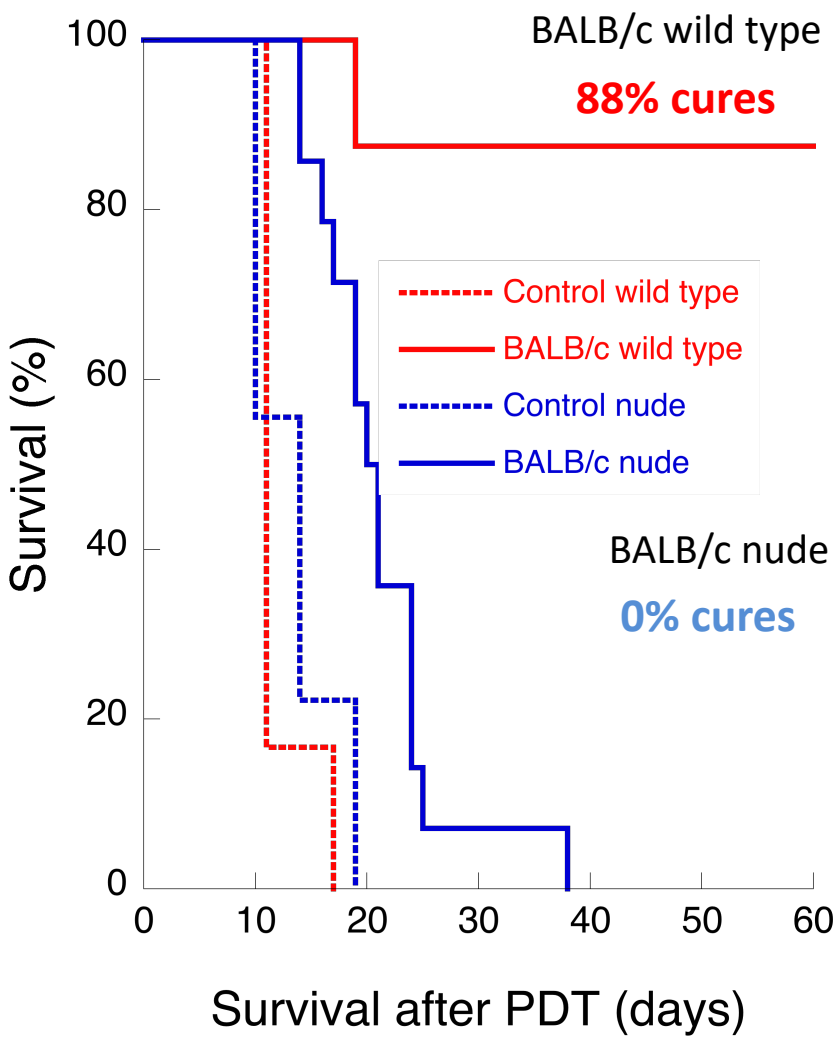


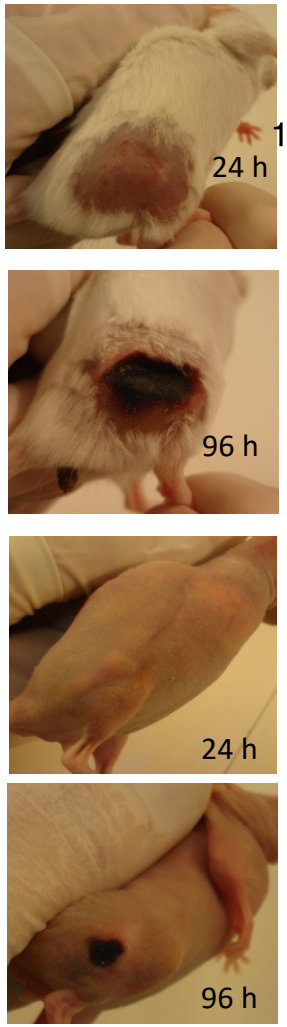


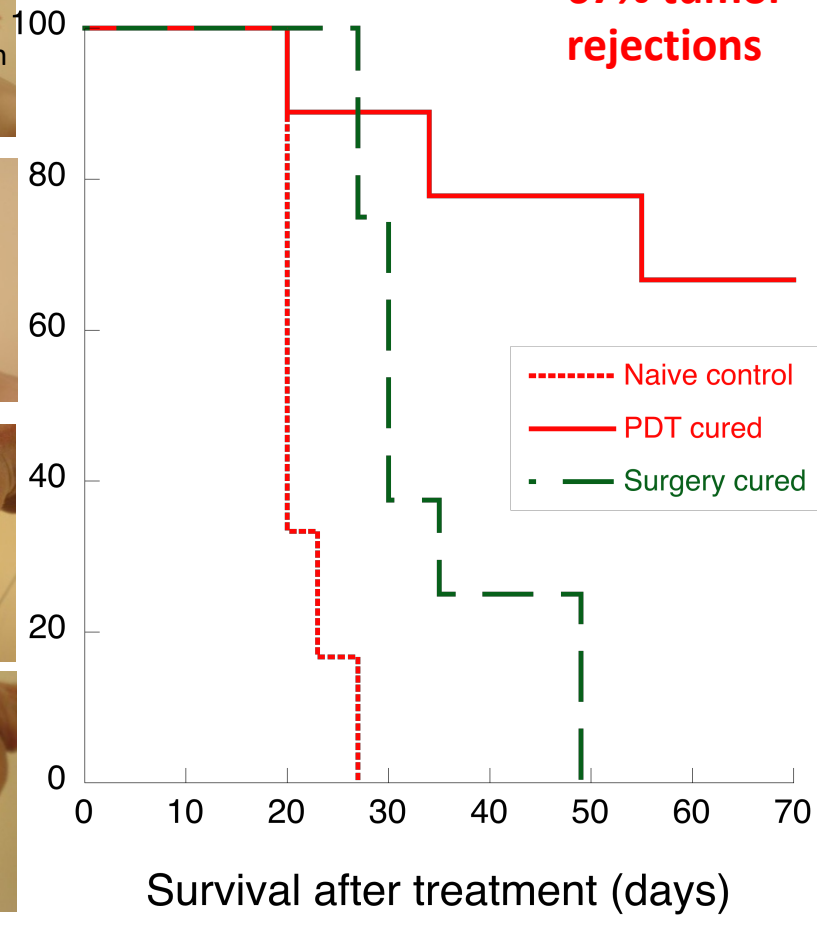
L. B. Rocha, *Eur. J. Cancer*, 51 (2015) 1822

PDT triggers systemic anti-tumor immunity

PDT of BALB/C mice with CT26 colon carcinoma, 0.75mg/kg, 50 J/cm^2







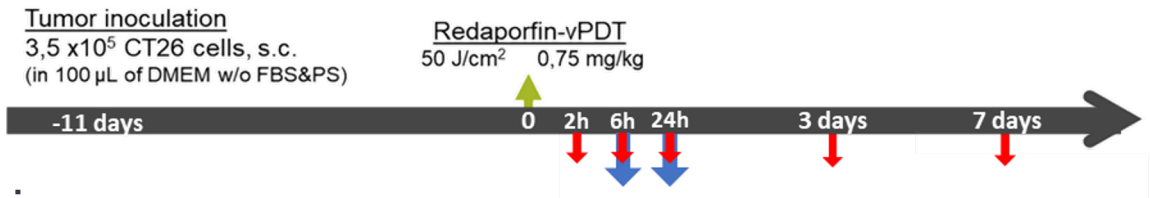
Immune competent mice respond strongly to redaporfin-PDT, with unprecedented cure rates

Cured mice acquires immune memory that rejects tumor cells more than 6 months after

L. B. Rocha, L. C. Gomes-da-Silva, J. M. Dabrowski, L. G. Arnaut, *Eur. J. Cancer*, 51 (2015) 1822-1830

Immune responses after vascular-PDT with redaporfin

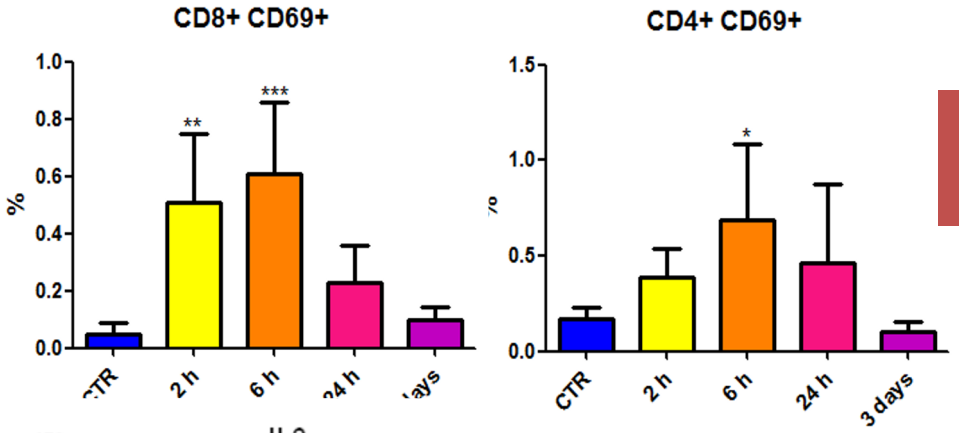
BALB/c Animal Model
CT26WT cell line



Blood analysis:

CD69⁺ T cells

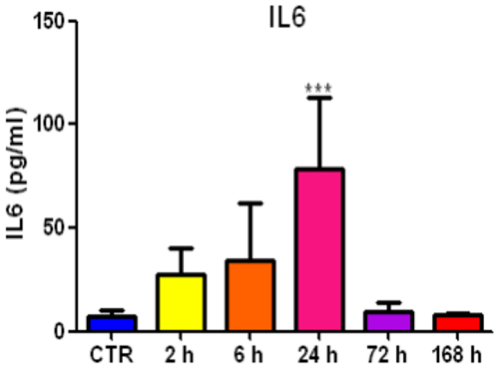
One-way ANOVA, n=5



↑ of activated T cells 6h post PDT

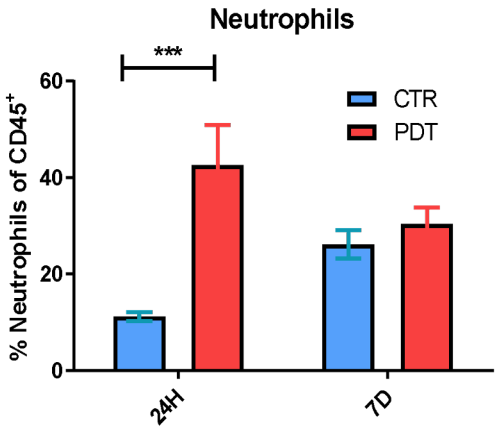
IL- 6 Cytokine

One-way ANOVA, n=5



Neutrophilia

Induced 24h post-PDT

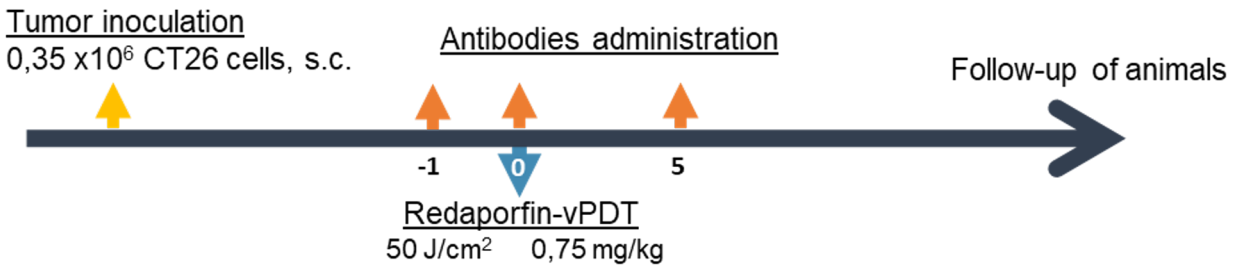


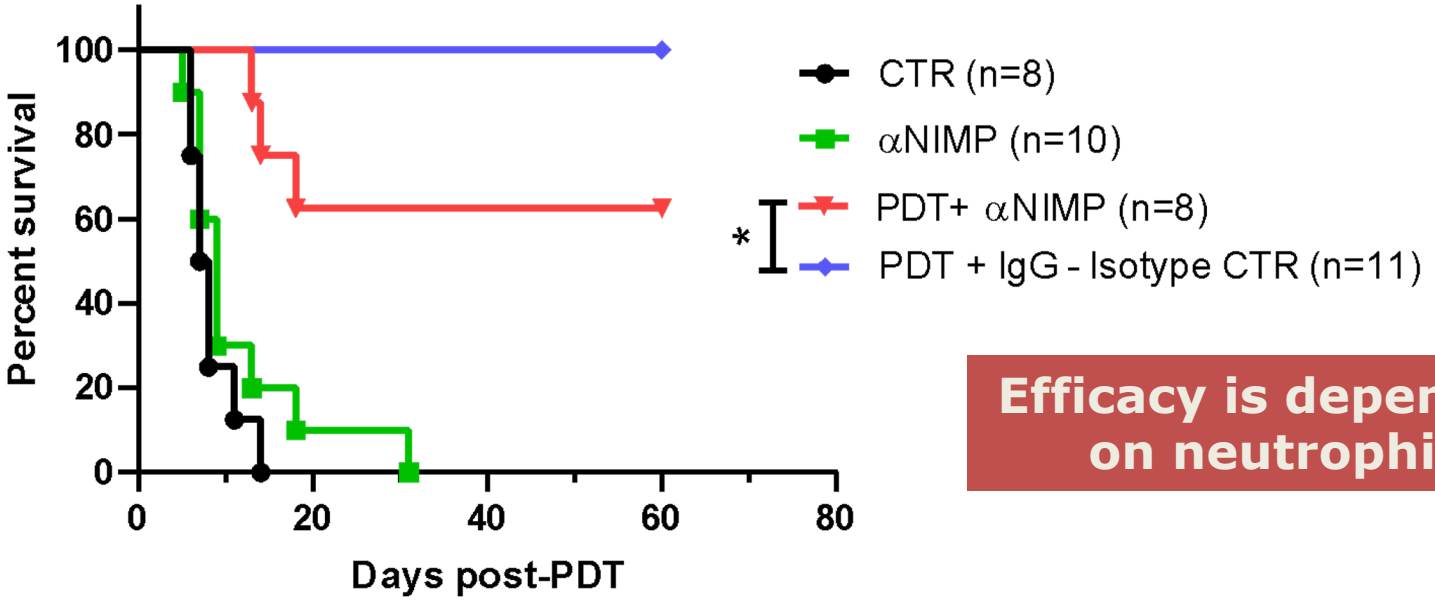
Lobo,… Arnaut, J. Clin. Med., 9 (2020) 104

Immune responses after vascular-PDT with redaporfin

BALB/c Animal Model
CT26WT cell line

Selective Depletion of Neutrophils (mAb NIMP-R14)





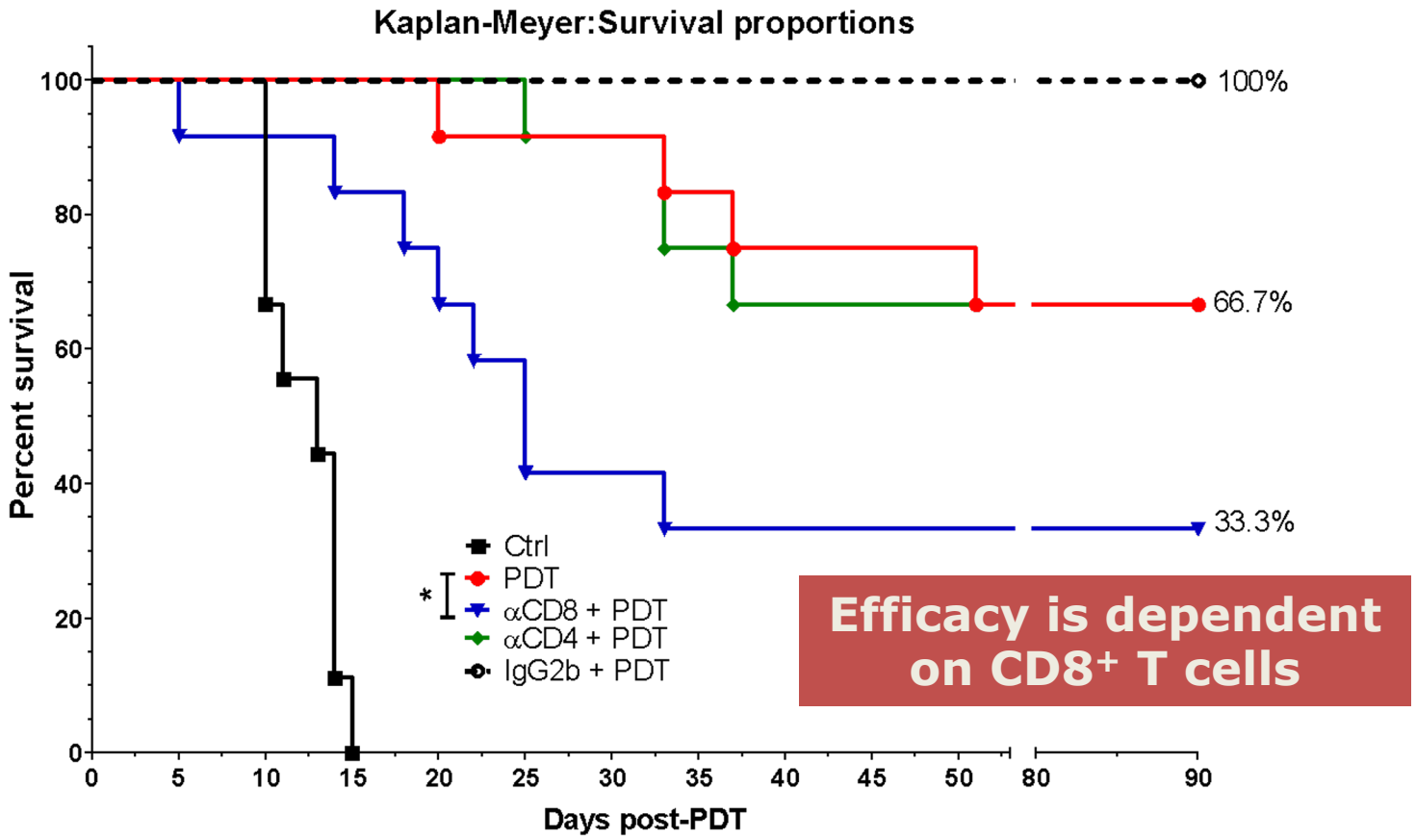
Efficacy is dependent on neutrophils

Lobo,… Arnaut, J. Clin. Med., 9 (2020) 104

Immune responses after vascular-PDT with redaporfin

BALB/c Animal Model
CT26WT cell line

Selective depletion of **CD8+** or **CD4+** T cell populations



Efficacy is dependent on CD8⁺ T cells

Lobo,… Arnaut, J. Clin. Med., 9 (2020) 104

Redaporfin PDT Clinical Trial

Clinical Trial: NCT02070432

Luzitin

Your wellness matters

- Luzitin code:
- LUZ11-CDU-001

- ClinicalTrials.gov Identifier:
- NCT02070432

- EudraCT Number:
- 2013-003133-14

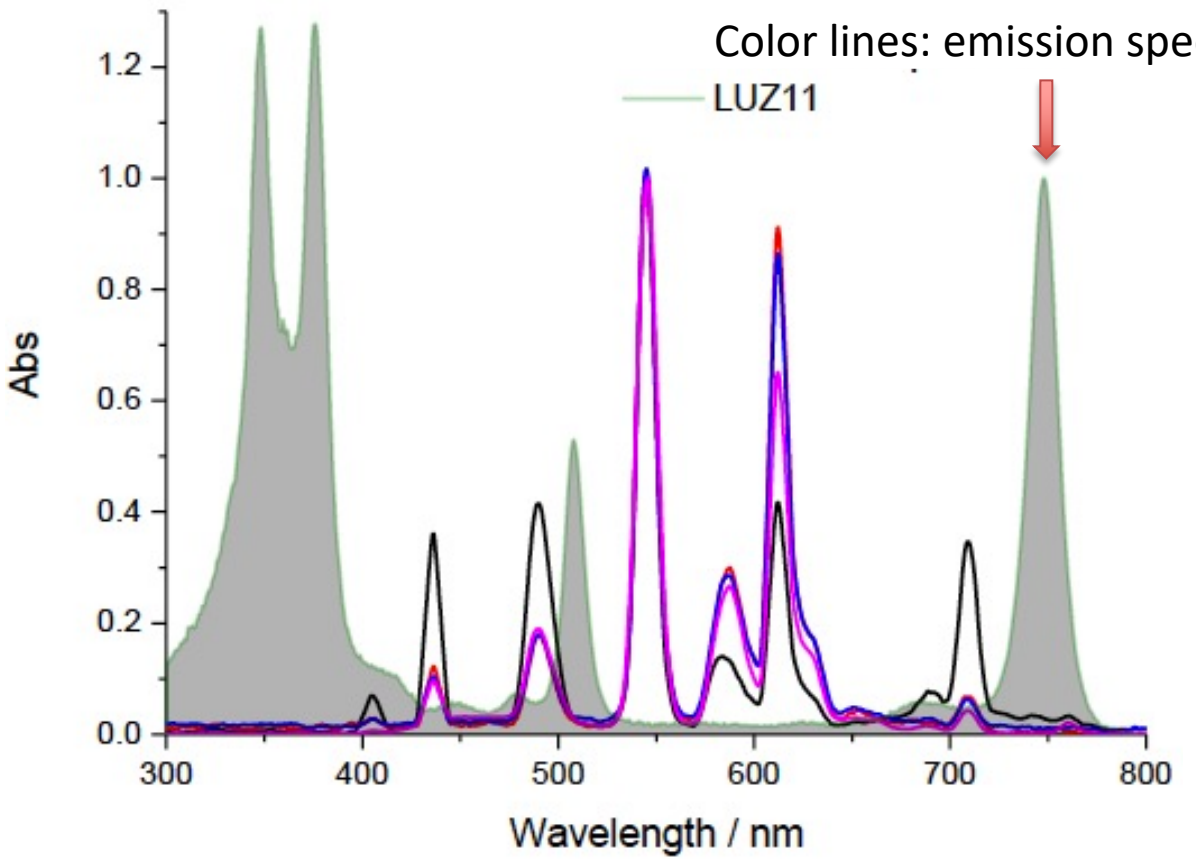
- Study team
- Clinical staff of the Portuguese Institute of Oncology – Porto operating at the Hospital CUF Porto's facilities
- PI: Lucio Lara-Santos, MD, PhD

Study title

An open-label study to investigate the tolerability, pharmacokinetics and antitumor effect following photodynamic therapy (PDT) with single-ascending doses of LUZ11 in patients with advanced head and neck cancer

Light

Shaded area: absorption spectrum of redaporfin
Color lines: emission spectra of LED lights in different rooms



Diode laser
749 nm, 1.5 W
Calibration port for microlens fiber
and for cylindrical diffuser

Redaporfin in Head & Neck Advanced Cancer

Clinical case: Man, 63 years, diagnosed JAN2012 with squamous cell carcinoma of the mouth floor
After chemotherapy, radiotherapy and surgery, proposed to palliative care APR2016
Referred to clinical trial, met inclusion criteria (Karnofsky performance status ≥ 60%)

Intravenous infusion of 0.75 mg/kg redaporfin
Sequential illumination of 4 areas
1st area illuminated 5 min after infusion for 6.4 min, then on to the 2nd area, and so on
Light dose 50 J/cm^2
Total time for the procedure ≈ 1 h

Reda porfin

0.75 mg/kg

DLI = 5 – 40 min

Frontal illumination

50 J/cm^2

Redaporfin-PDT + nivolumab-immunotherapy

Patient re-started palliative chemotherapy

Failing to respond to chemotherapy, the patient started immunotherapy with nivolumab

September 2016

June 2017

One cycle of redaporfin-PDT + 3 cycles of nivolumab

Nivolumab: anti-PD1 monoclonal antibody (checkpoint inhibitor)

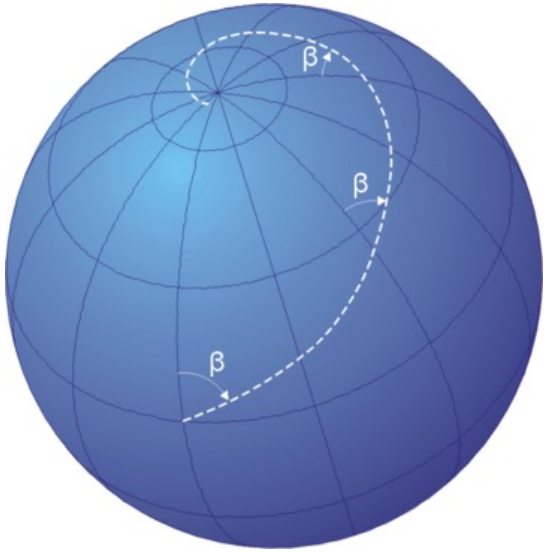
L. L. Santos, *Case Rep. Oncol.*, 11 (2018) 769

Pedro Nunes (Petrus Nonius)

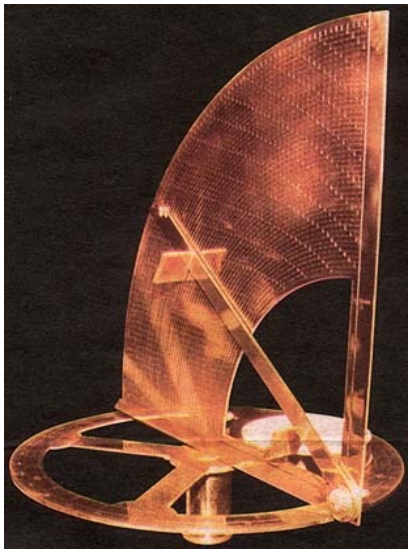
1502 - 1578

1525 – Medical Doctor
1544 – Professor of Mathematics
1547 – Chief Cosmographer of the Kingdom

1537 – Treaty of the Sphere
Loxodrome



1542 – De Crepusculis
Nonius



"Manifesto he que **estes descobrimentos** de costas: ylhas e terras firmes: **não se fizeram indo a acertar** mas **partiam os nossos mareantes muy ensinados e providos de estromentos e regras de astrologia e geometria**, que sam as cousas de que os Cosmographos ham –de andar apercebidos"

… These discoveries … were not made by trial–and–error ... Our sailors sailed well instructed and equipped, knowledgeable of the dictates of astronomy and geometry

· U C ·

UNIVERSIDADE DE COIMBRA

FCT

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