

5-ALA mediated PDT: History, Principles, and Clinical iPDT in Neurosurgery

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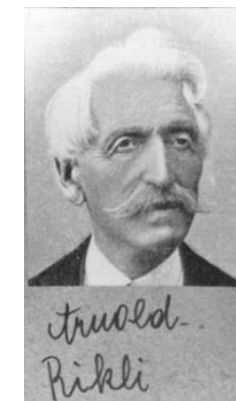
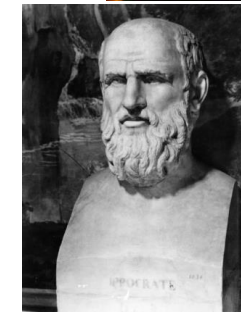
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GlioLighT Workshop

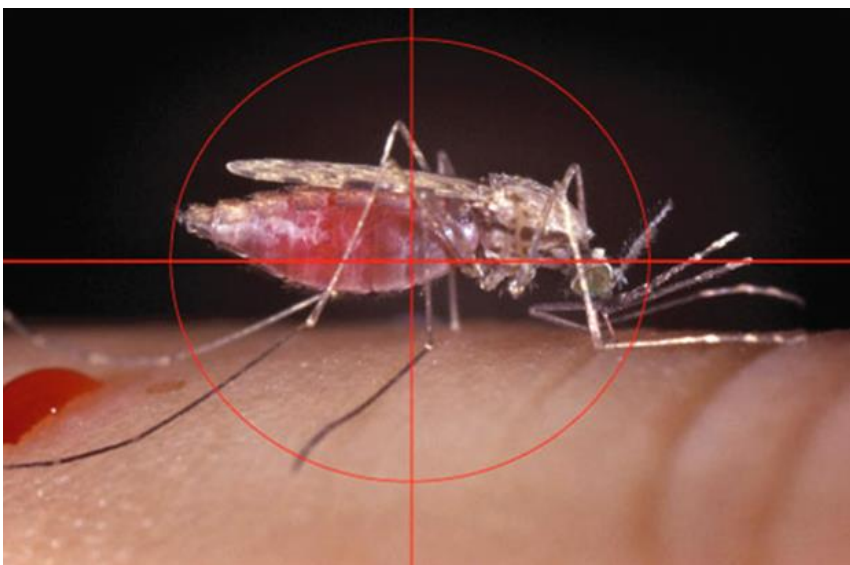
1st September 2026

History

- 3000 BC – Ancient Egypt & India; early reports about light therapy were used
- 1550 BC – Ebers Papyrus; phototherapy were utilized using plants to make a powder that was applied on depigmented lesions
- 1400 BC – India sacred books; patients suffering from vitiligo were given certain plant extracts and asked to stand in the sunlight for some times
- 200 BC - Greek; Hippocrates called it “Heliotherapy”, he recommended sunlight for restoration of health
- 100 BC – 300 AD - China; people consumed dyed paper which was exposed to sunlight to benefit from healing powers of the sun
- 1300 AD – Ibn El-bitar; “Terminologies of Pharmaceutics”
- 1855 AD – Arnold Rikli; pioneer of modern phototherapy, establishment of a National Medicine Institute, developed natural therapies (still valid today)
- 1893 AD – Niels Ryberg Finsen; sun garden in medical institutes, treatment of lupus vulgaris, Finsen lamp, Nobel Prize 1903



History

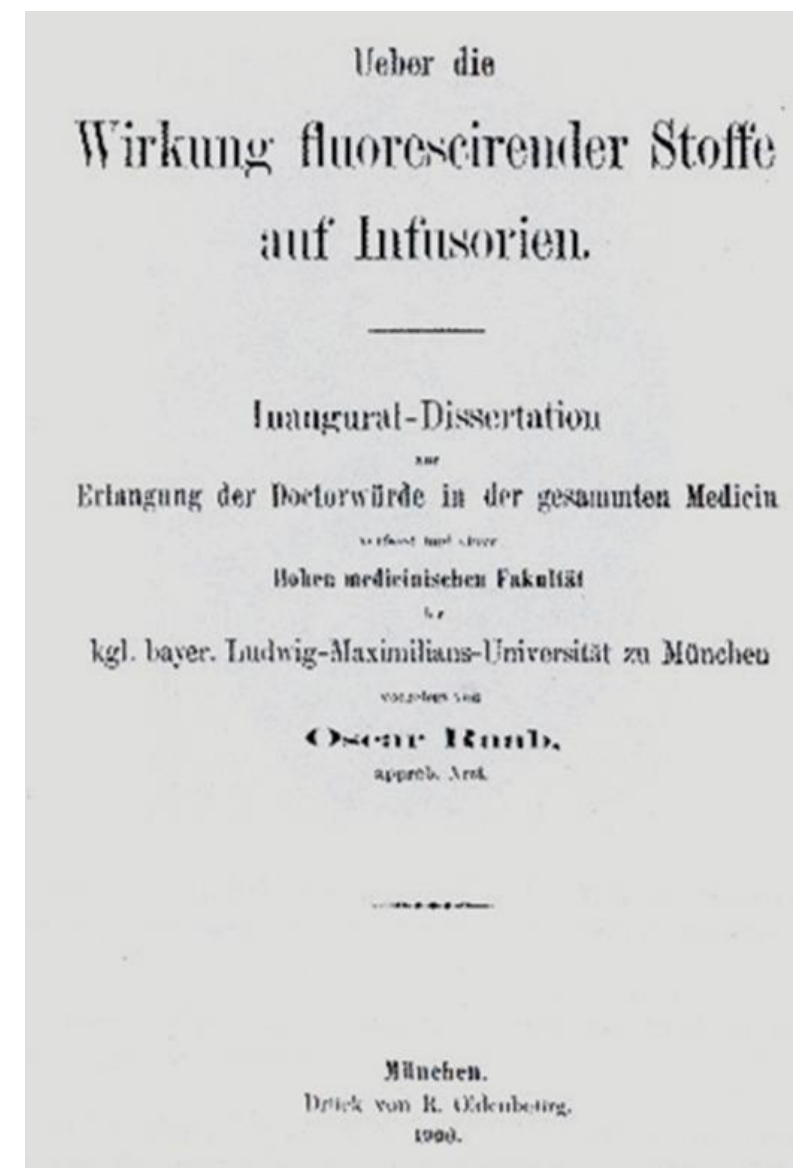


1897

Topic of the doctoral thesis for the Munich student Oscar Raab:

The relative toxicity of several drugs in discussion for malaria treatment

→ discovered phototoxicity



History



Hermann von Tappeiner,
1847-1927
Director of Pharmacological Institute



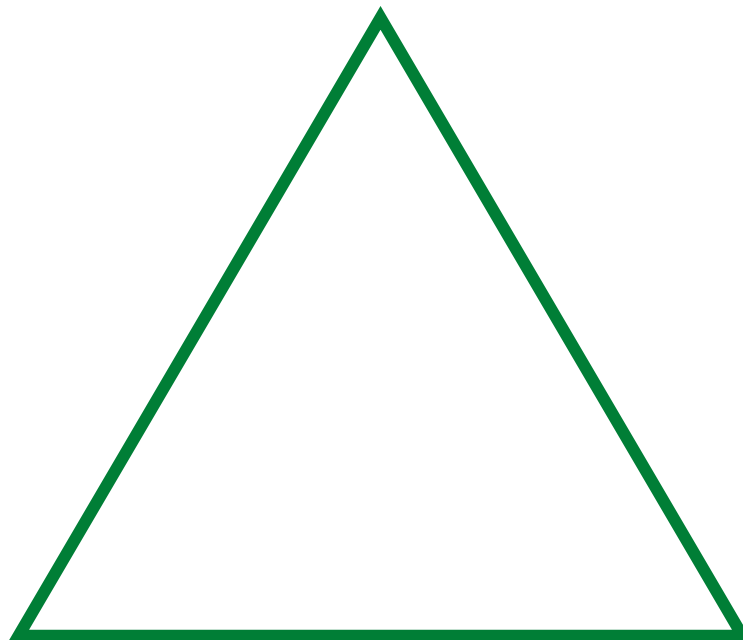
Albert Jesionek,
Dermatologist



„Photograms“ of the first documented patient treatment
70 years old daytaller's widow, multiple skin cancer
repetitive PDT with Eosin and sunlight / carbon arc lamp
10. September 1903 14. November 1903

PDT Fundamental

Photosensitizer

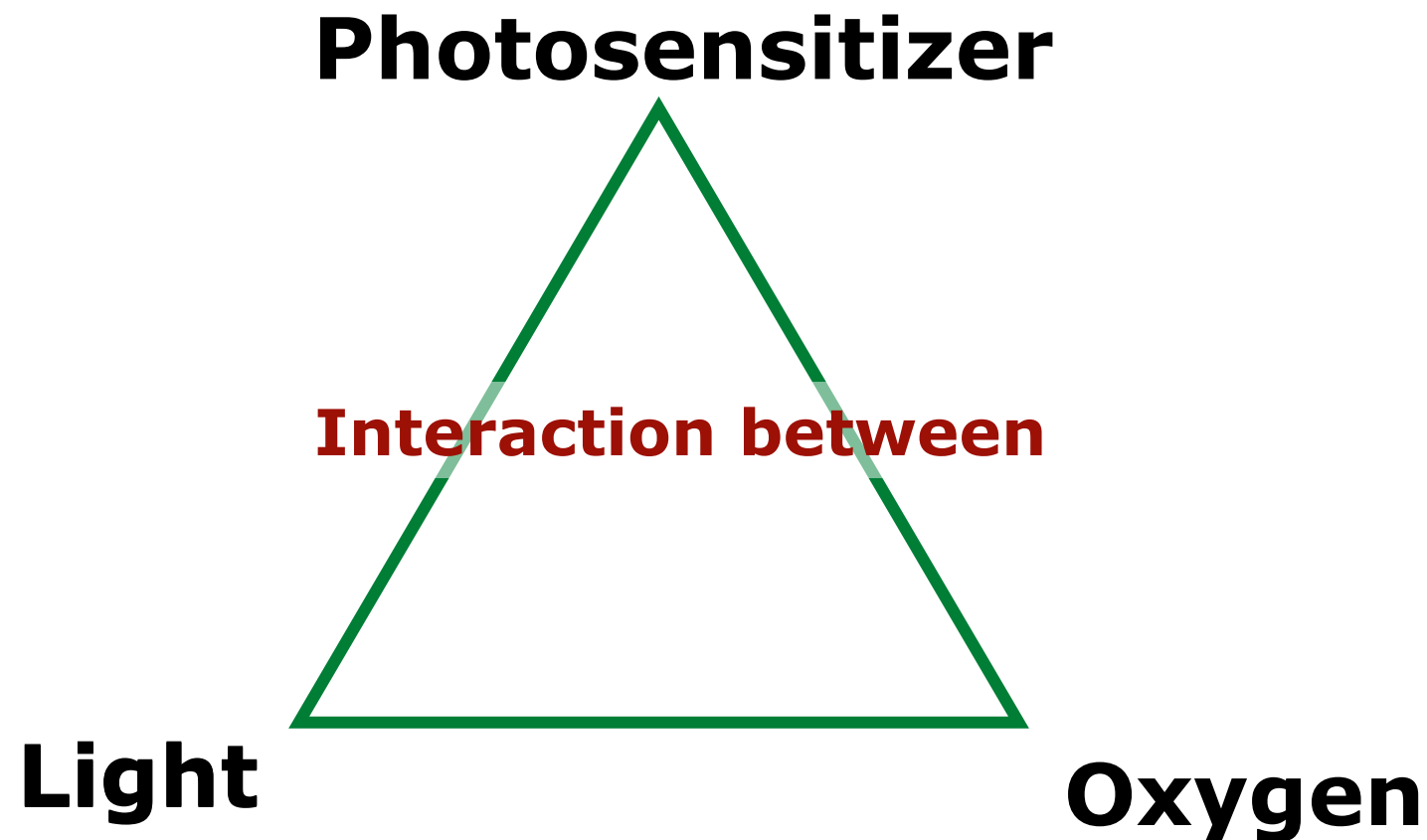


Light

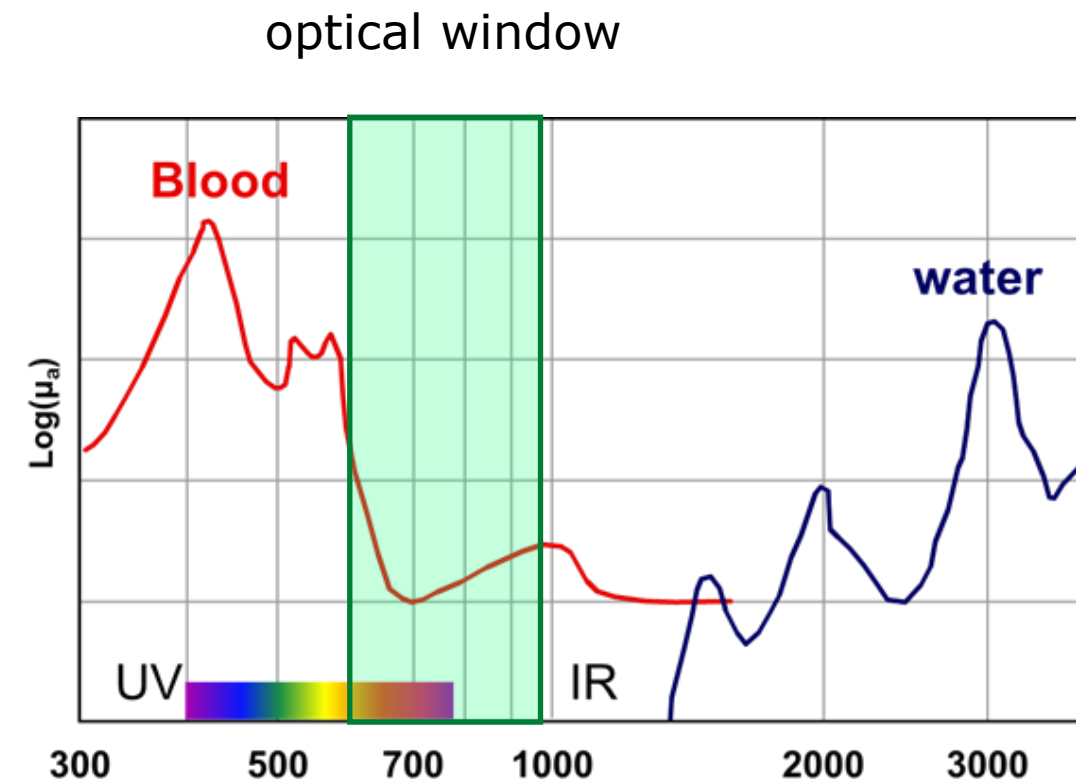
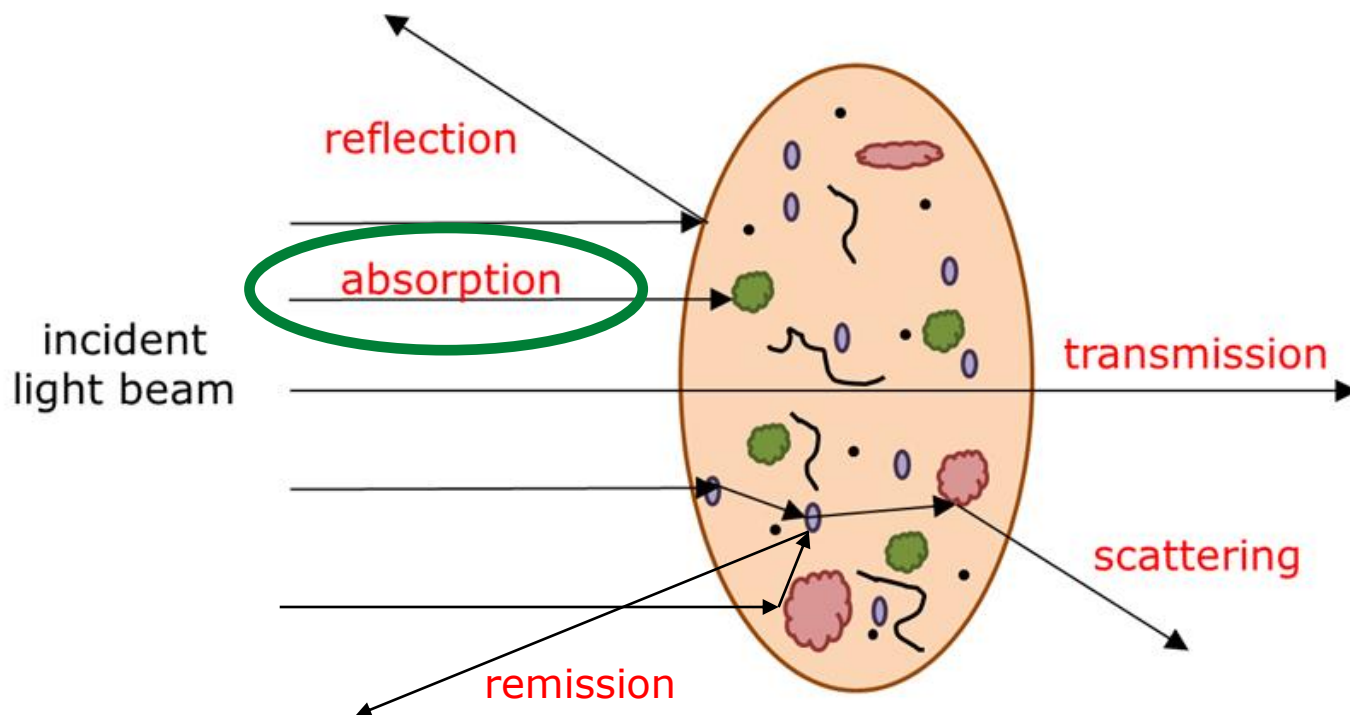
Oxygen



PDT Fundamental



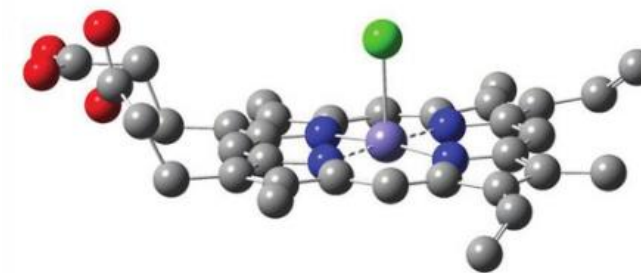
Light and Tissue Optics



For deep light penetration to avoid main tissue absorbance wavelength within optical window best

PDT Fundamental

Photosensitizer



Light

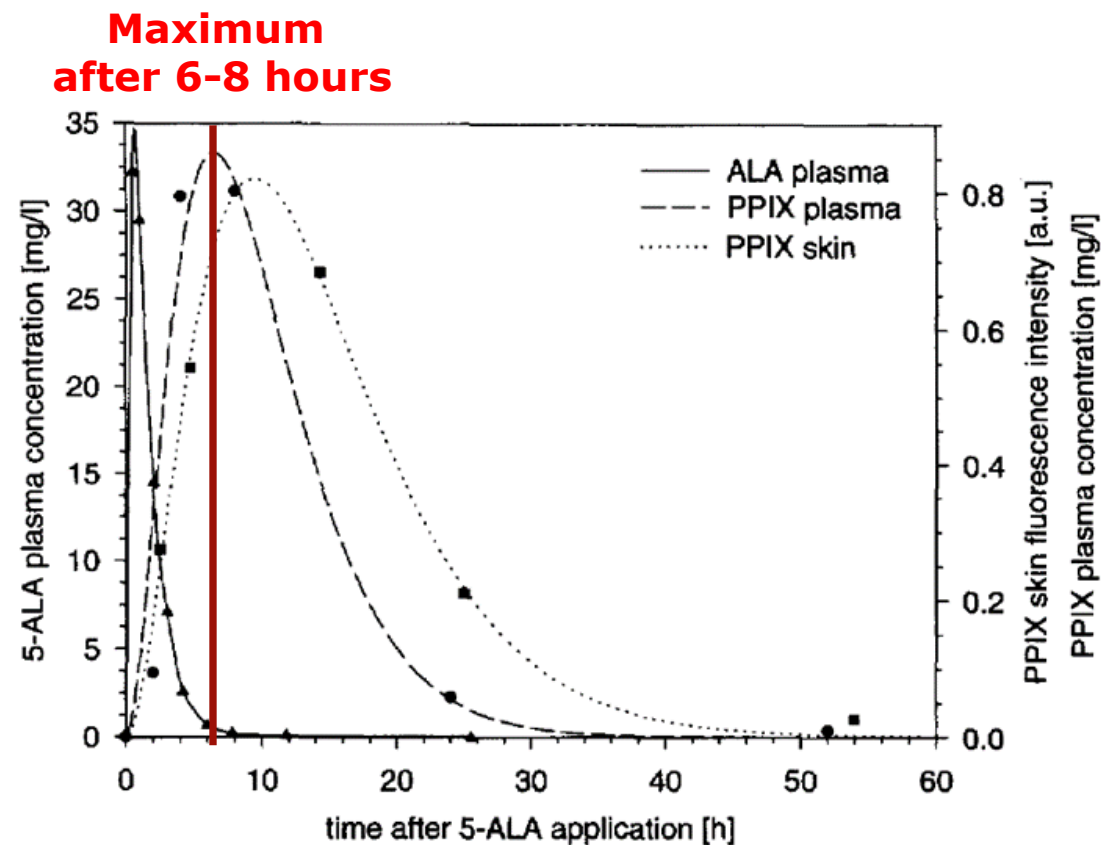
Oxygen

The “Ideal” Photosensitizer

- No dark toxicity
- Selective targeting
- High quantum yield
- Long wavelength excitation (strong absorption, high extinction coefficient)
- Present clearance from the body
- Short drug-light interval
- Photobleaching (yes or no?)
- No interference with radio- or chemotherapy
- Have a simple and stable drug formulation

Pharmacokinetics

- Pharmacokinetics (ADME)
 - **A**bsorption – entering blood circulation
 - **D**istribution – dispersion of substances throughout of fluids and tissue of human body
 - **M**etabolism – recognition by the organism
 - **E**xcretion – removal of the substance from the human body



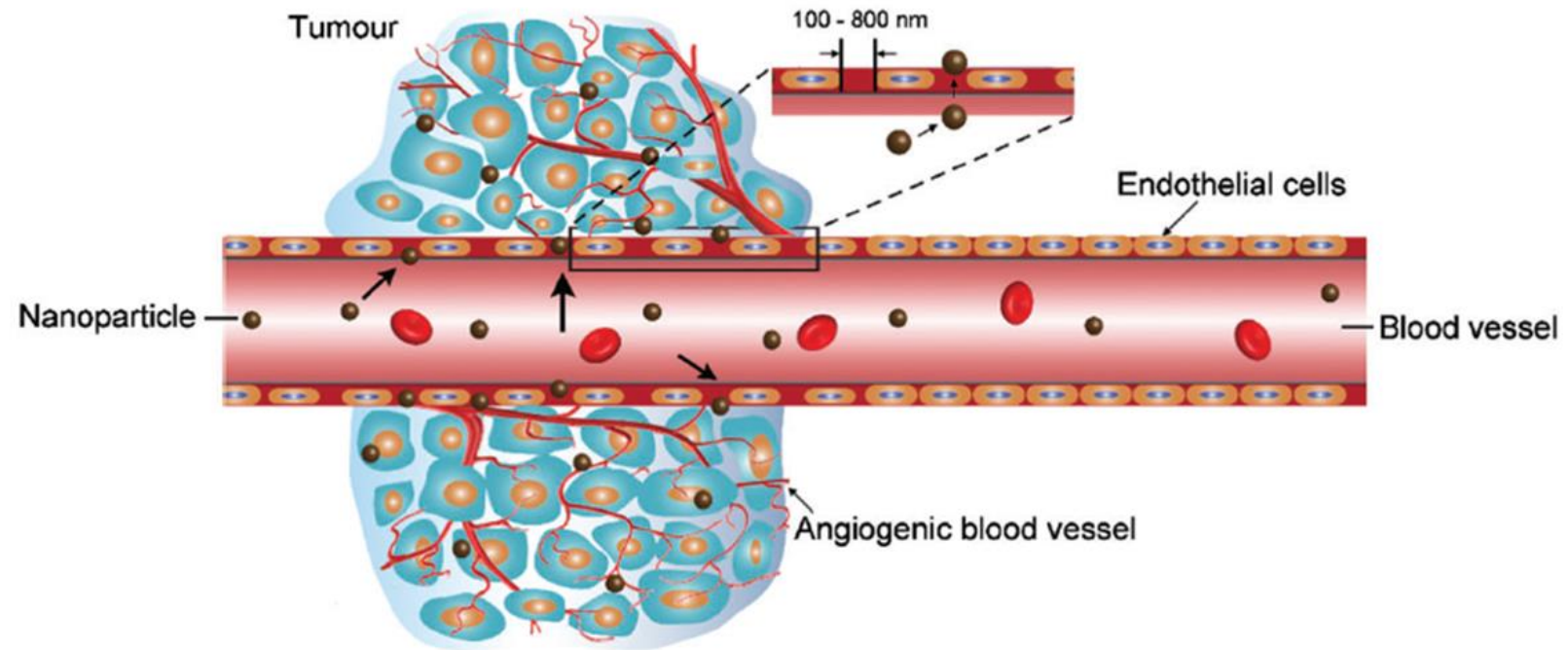
e.g. 20 mg/kg oral ALA

Gossner 1998, Gastro

Photosensitizer Selectivity

Enhanced permeability and retention (**EPR**-effect)
(→ e.g. nanocarrier)

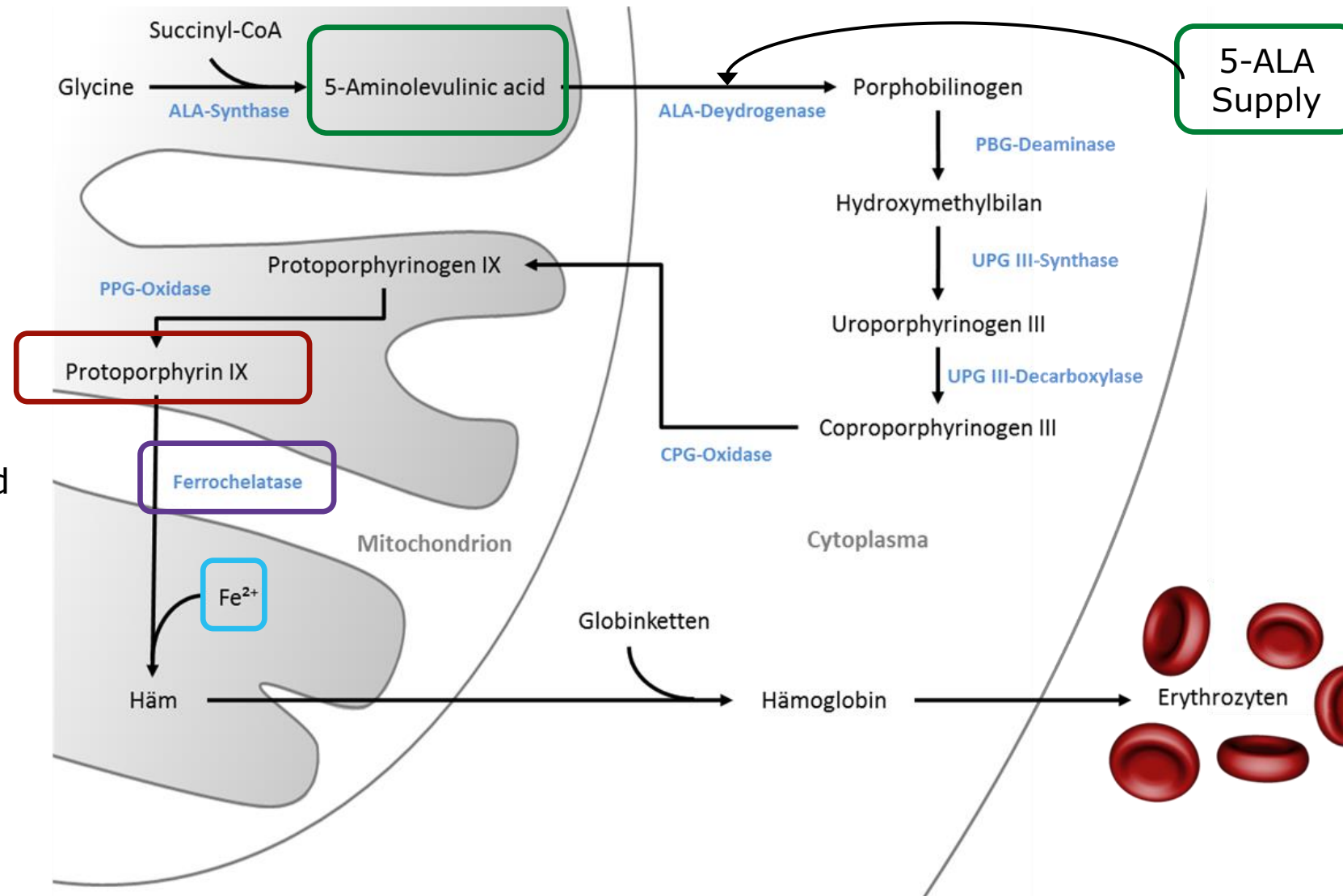
- High generation of new blood vessels in malignant tumor tissue (angiogenesis)
- Discontinued endothelium
- Inhibited or poor lymphatic system



Jobayer Sonju 2021, J. Contr. Rel.

PpIX Accumulation – Heme Biosynthesis

- Administration of 5-Aminolevulinic Acid (5-ALA)
- Metabolization to Protoporphyrin IX (PpIX, photoactive)
- Tumor:
Reduced Ferrochelatase activity and Fe^{2+} availability



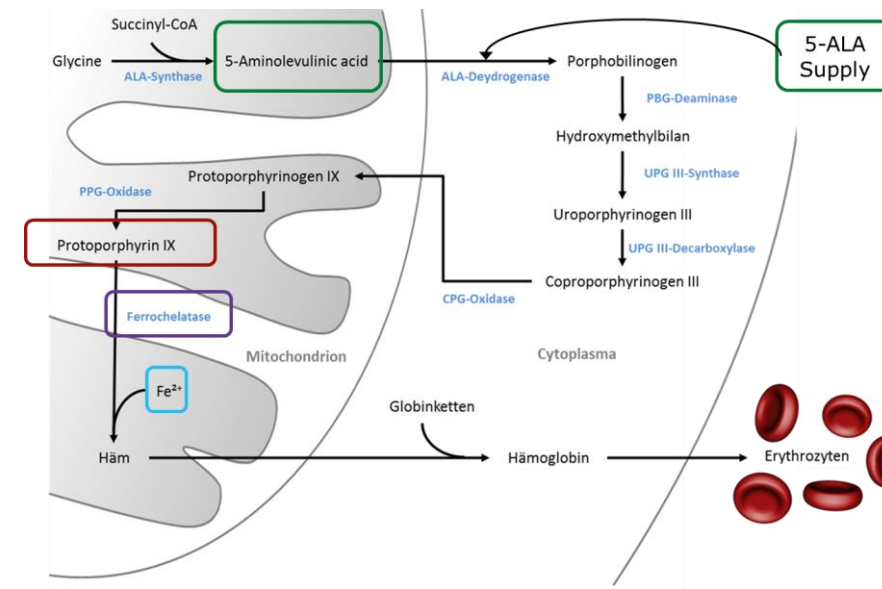
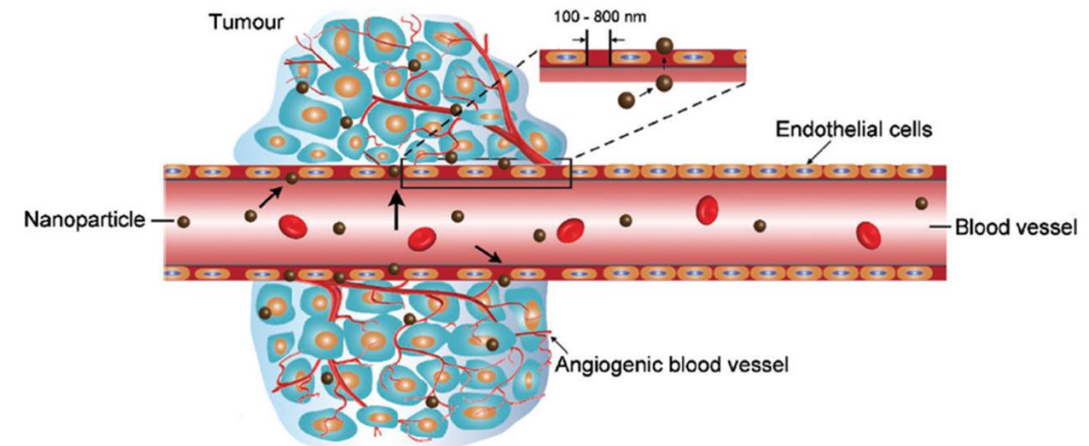
L Lilge, J Clinical Laser Med Surg, 1998
 S Collaud, CurrMedChemAntiCancerAgents, 2004
 H Stepp, Las Surg Med 2018

PpIX Accumulation – Selectivity

- Combination of EPR effect and heme biosynthesis conditions

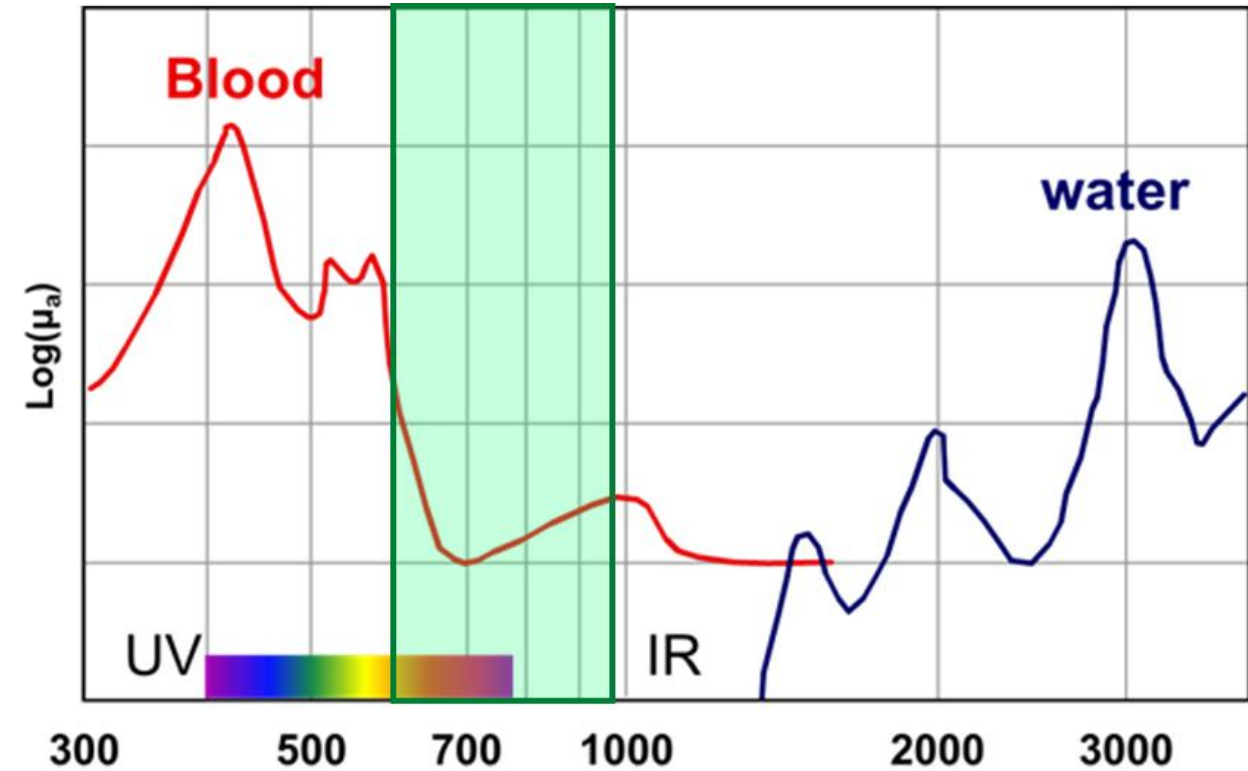
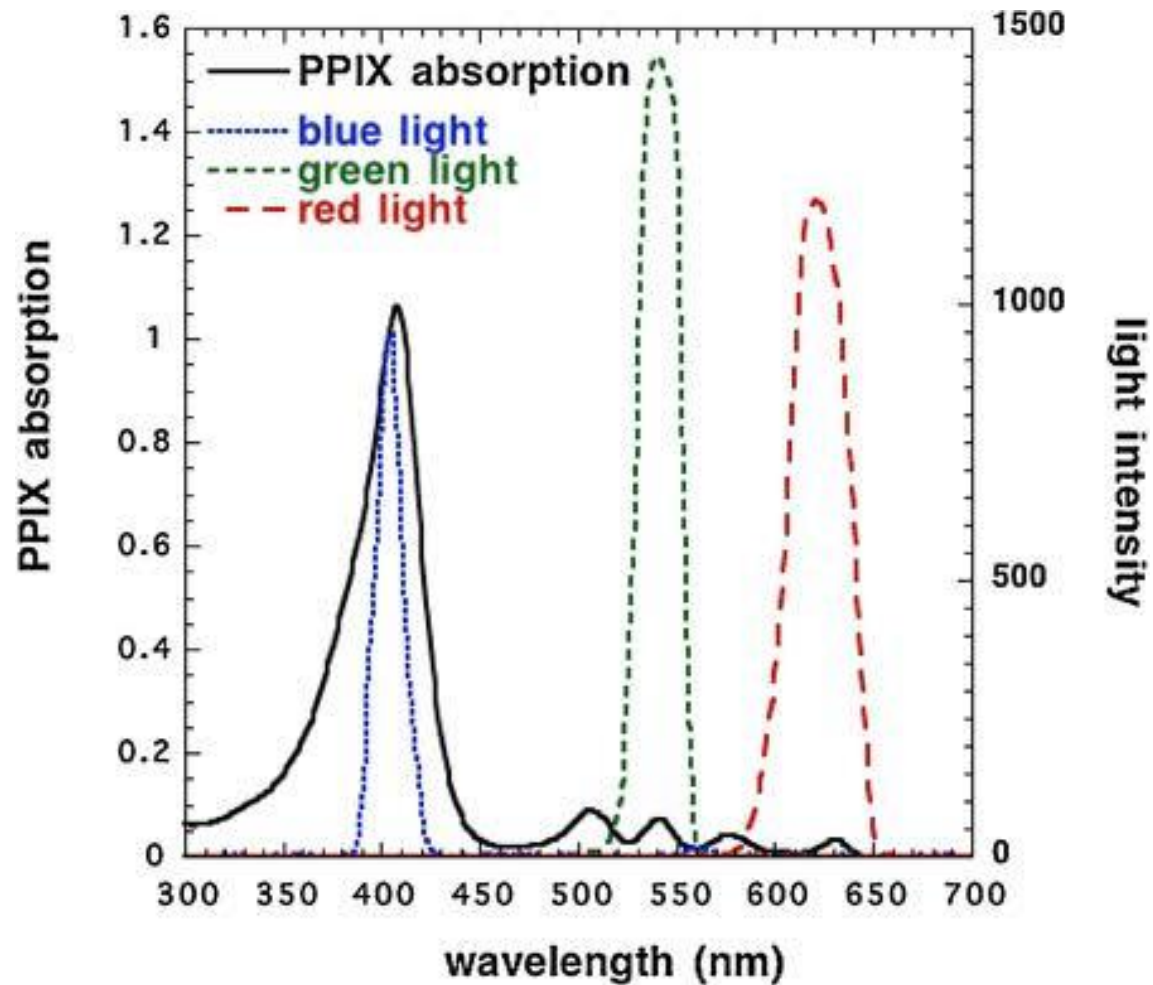
- Uptake Ratio:

Tumor/WM: 95/1 (20mg/kg ALA, 6h)



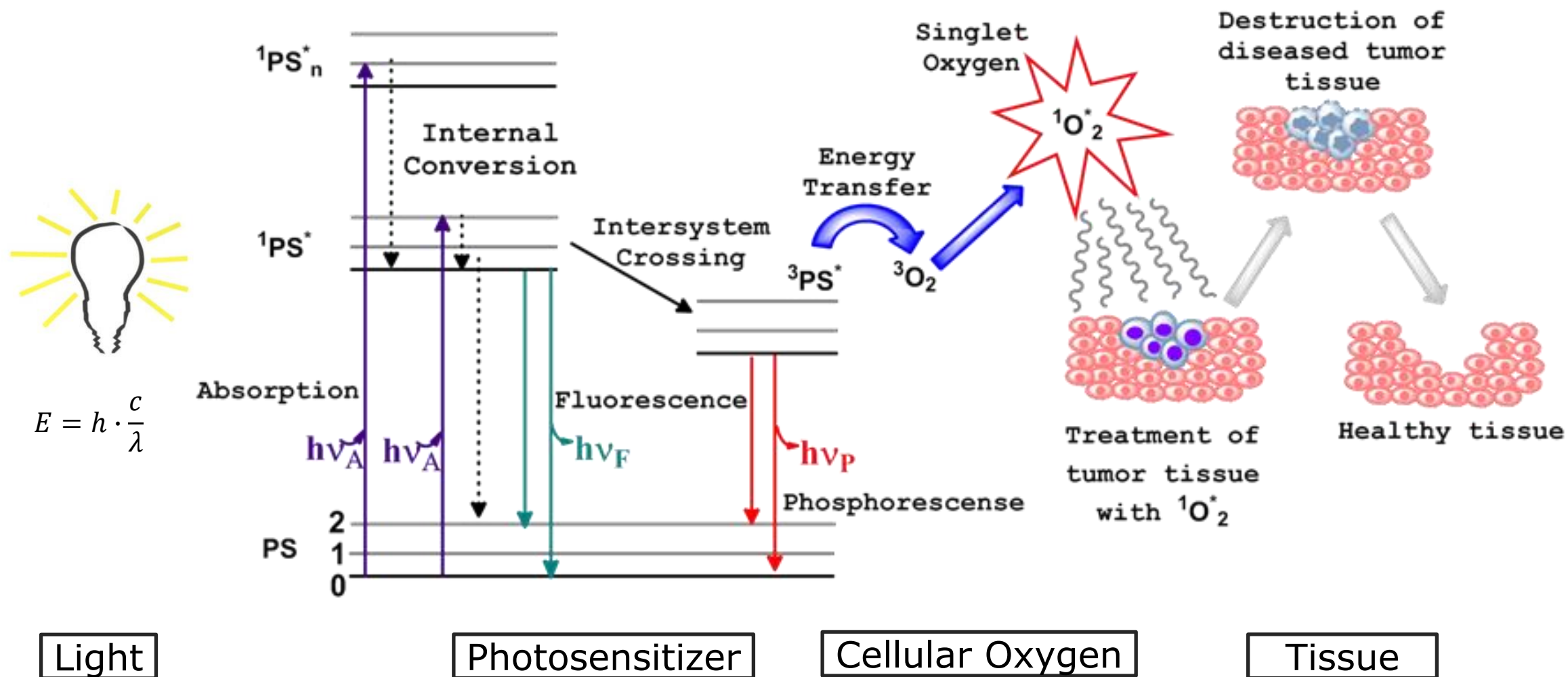
L Lilge, J Clinical Laser Med Surg, 1998
S Collaud, CurrMedChemAntiCancerAgents, 2004
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Light Absorption by Photosensitizer



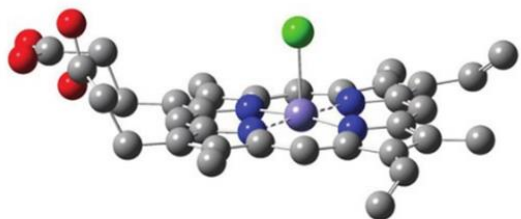
Hamblin 2019 PD&PDT

Physics – Jablonski Diagram



Rostami 2016 Pharma. Sc.

PDT Fundamental



Tumorselectivity
Photosensitizer

Photosensitizer
Fluorescence
Detection (PFD)

Drug – Light
interval



Optical
tissue
parameters

Light
Dosimetry

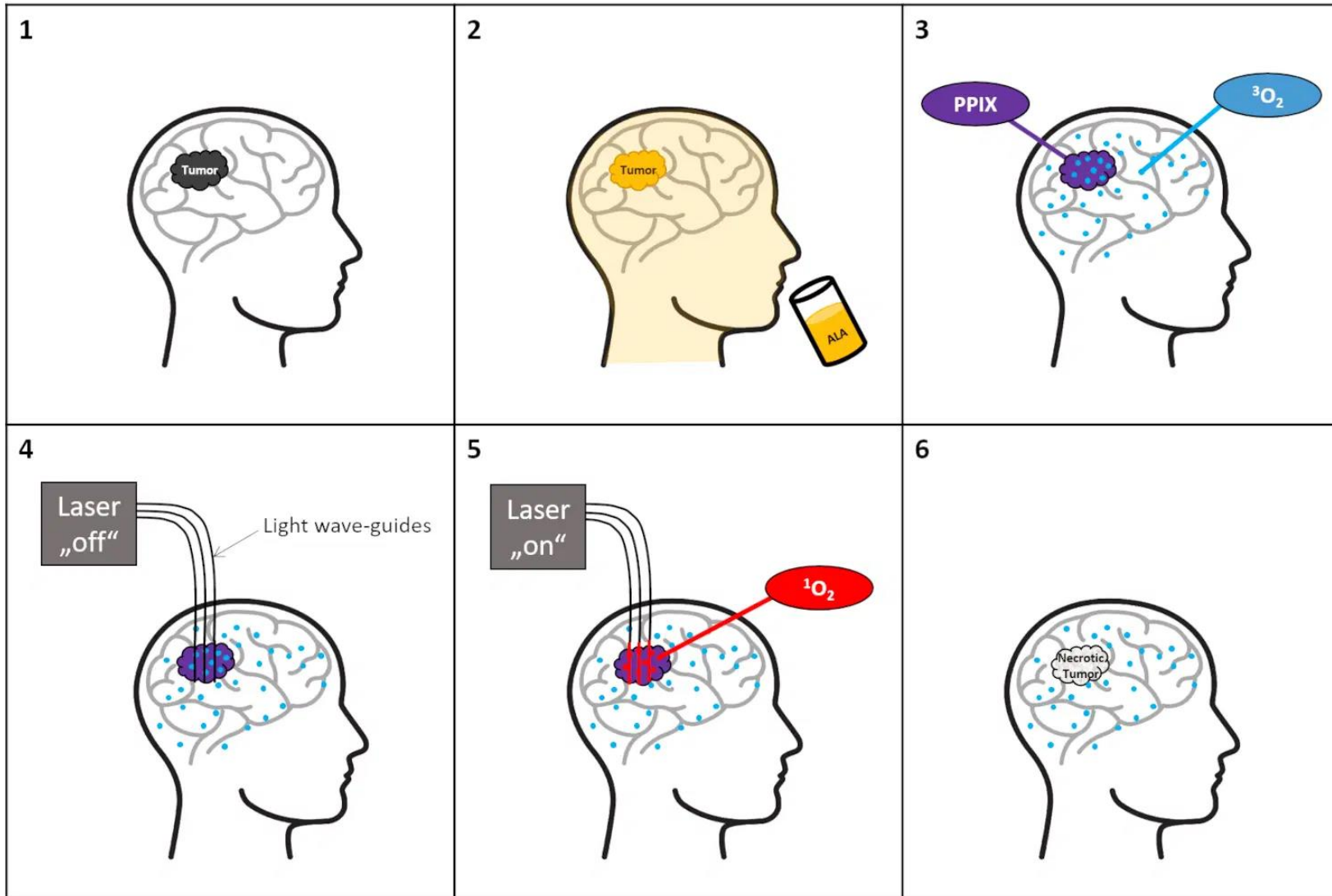
Type I: superoxide ion hydroxyl radical
Type II: singlet oxygen
Type III: direct destruction

Oxygen
Supply

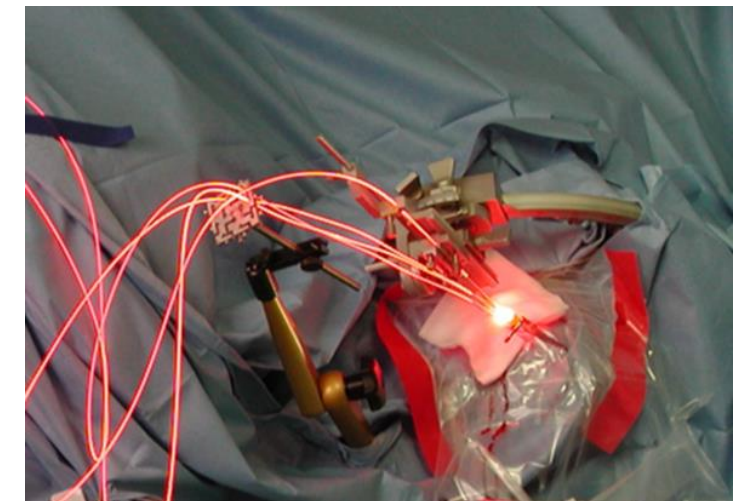


Treatment
monitoring

Principle of Clinical 5-ALA iPDT



Cylindrical Diffuser Fiber (CDF)



T Beck, Las Surg Med, 2008
S Lietke, Cancers, 2021

Clinical Approach - Malignant Gliomas

- 6/100'000 glioma cases per year, 2-3% of cancer deaths
- Most common primary brain tumors
- 2/3 of all gliomas are malignant (WHO 3/4)
- Prognosis:
 - WHO 3: Overall Survival (OS) 2 years
 - WHO 4:(glioblastoma multiforme; GBM): OS 19 months (2-year survival rate 27% 5 year survival rate <5%)



J-C Tonn, Oncology of CNS Tumors, Springer 2010
D Louis, NeuOnc 2021

<https://www.dgnc.de/gesellschaft/fuer-patienten/intrakranielle-gliome/>

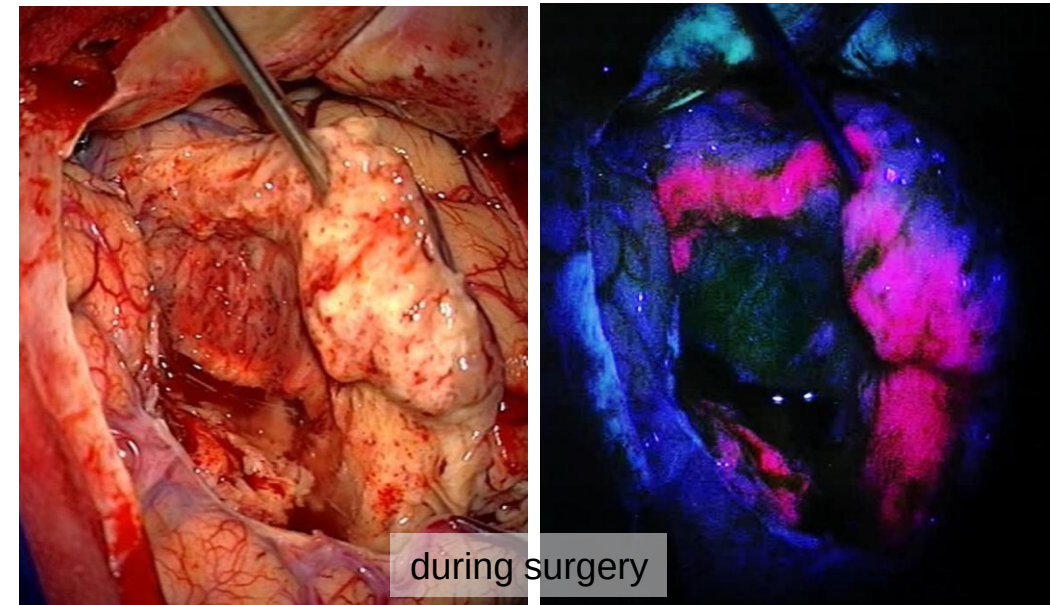
Clinical Approach - Malignant Glioma SOC

- Criterion-Standard Therapy:
Fluorescence Guided Resection (**FGR**)
followed by Radiochemotherapy and Tumor-Treating-Fields
- Challenges:
 - Infiltrative Growth of tumor
 - Resection with safety margin not possible
 - Not applicable in eloquent brain areas

No 100% curing treatment

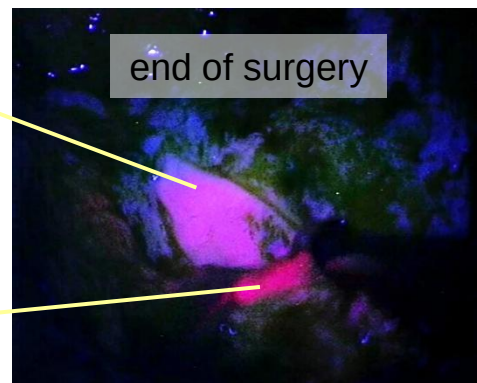
→ **Treatment Approach:**

Interstitial Photodynamic Therapy using 5-ALA



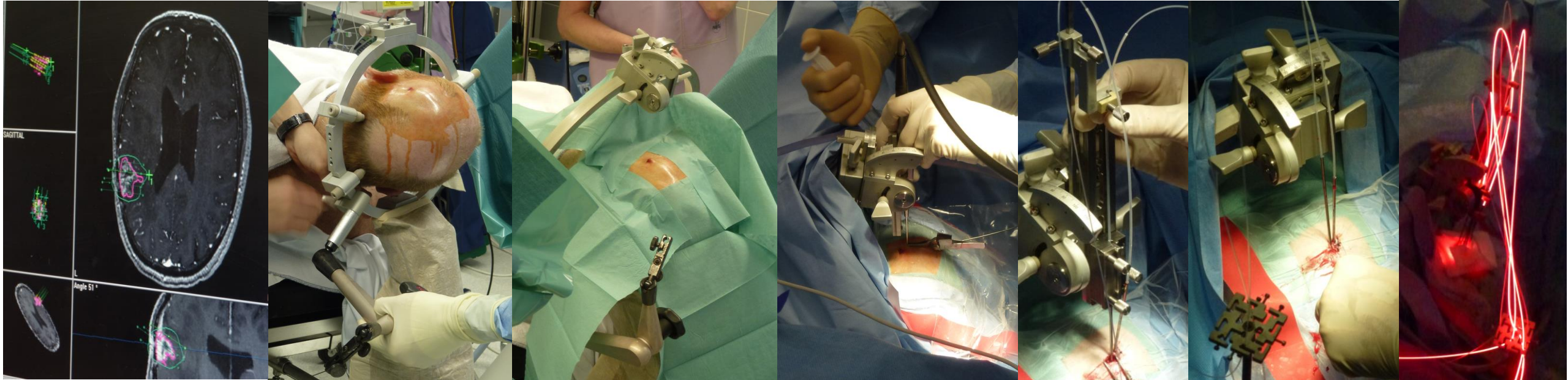
Unspecific fluorescence at wall of ventricle

Residual tumor



W Stummer, Neurosurgery 2014
Stepp and Stummer, Optical Methods and Instrumentation in Brain Imaging and Therapy, Springer 2008
EANO guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas; Lancet Oncol 2017

Clinical Approach – 5-ALA iPDT



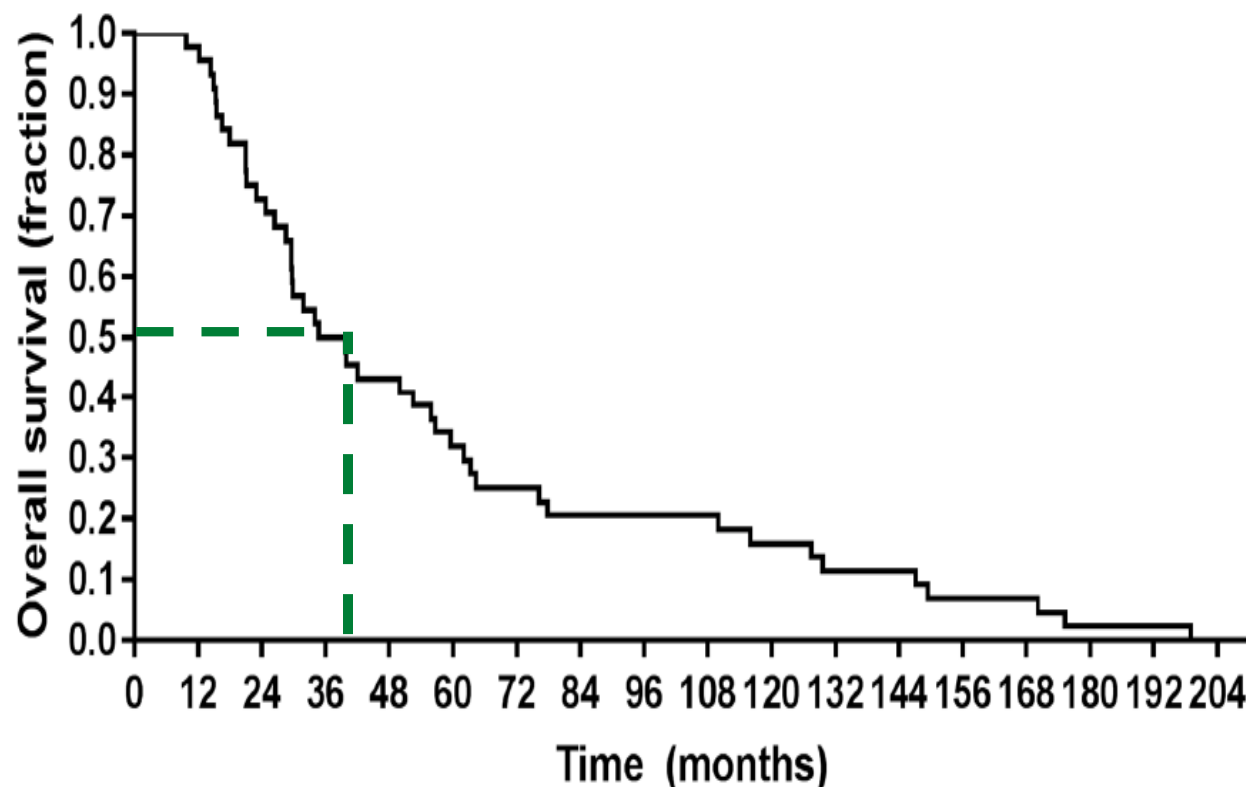
- 20 mg/kg 5-ALA, orally/systemically 4...6 hours prior to PDT
- 3D-planning
- Stereotactic positioning of cylindrical light diffusers (20-40 mm diffuser length)
- Irradiation: 635nm, 200 mW/cm, 60min, 720J/cm



Clinical Outcome

Malignant glioma recurrences

- Retrospective analysis of 47 iPDT healing trials on malignant gliomas
- 44 / 47 full clinical data set
 - 37 WHO-IV; GBM
 - 7 WHO-III; Astrocytoma
- PFS = 7,1 months (0,6–93,9 months)
- PRS = 13,0 months (4,7–105,6 months)
- **Median OS (t_0 = initial diagnosis) = 39,7 months (9,8–199,0 months)**



C Fernandes, Codon Pub., 2017
S Lietke, 71 Jahrestagung der DGNC, 2020
S Lietke, Cancers, 2021

Clinical outcome

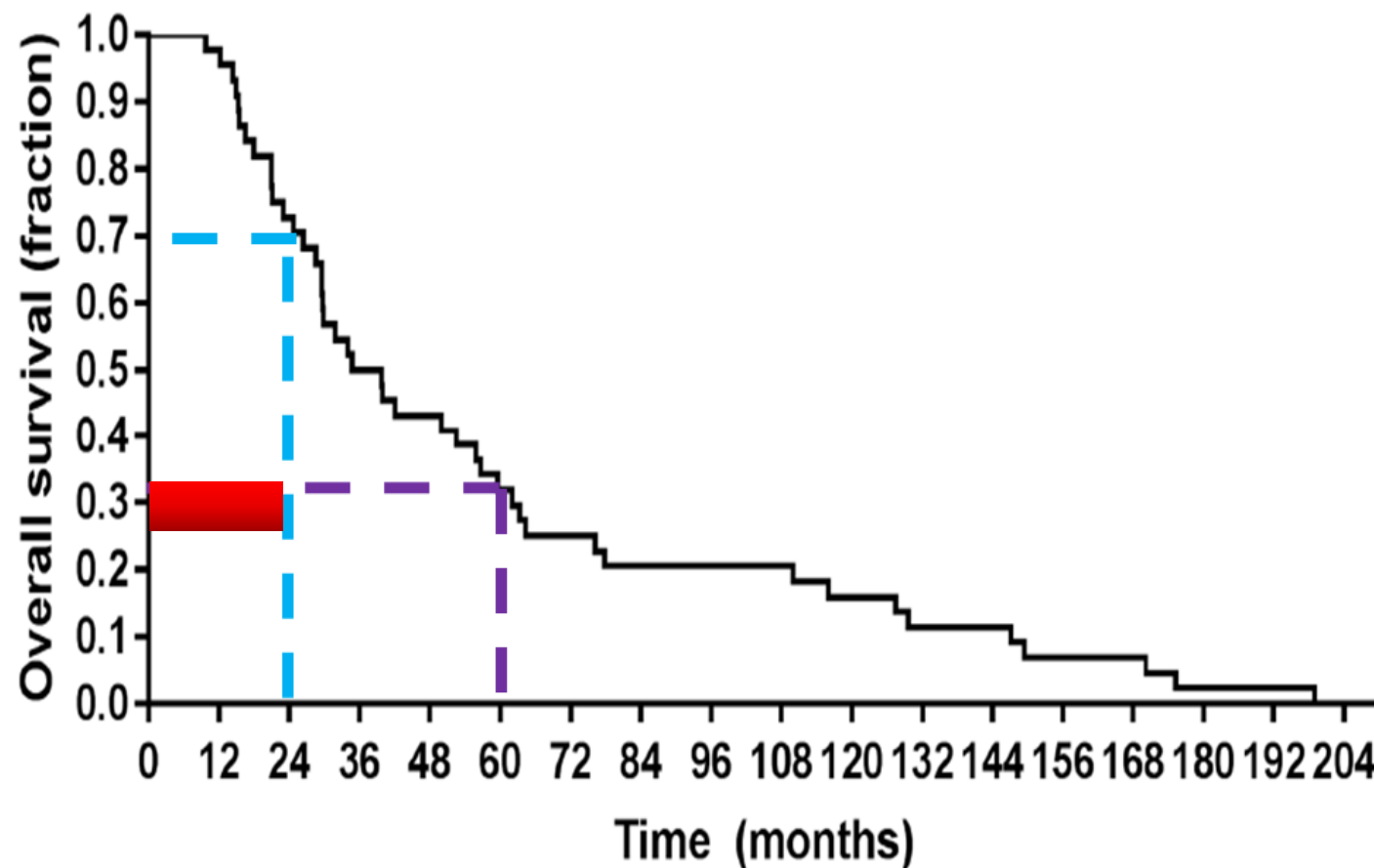
Malignant glioma recurrences

iPDT:

- 2 year - OS 70%
- 5 year - OS 33%

Standard therapy:

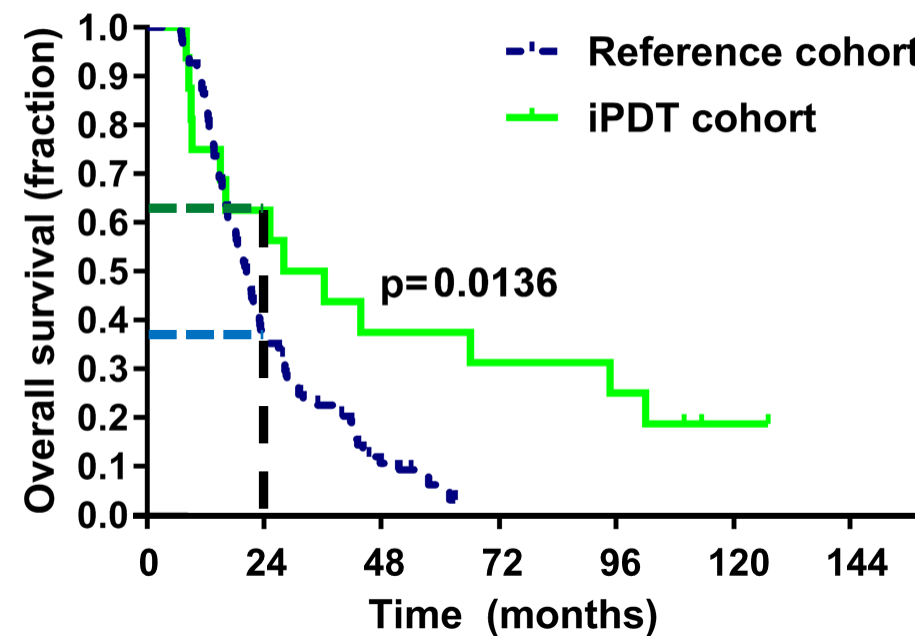
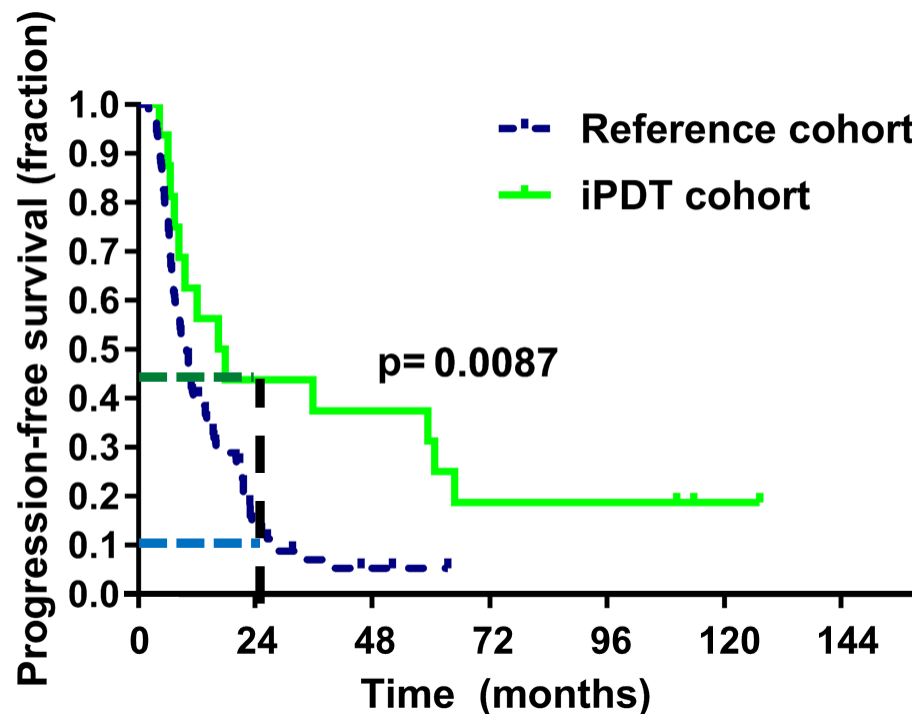
2 year - OS 26-33%



C Fernandes, Codon Pub., 2017
S Lietke, 71 Jahrestagung der DGNC, 2020
S Lietke, Cancers, 2021

Clinical Outcome

De-novo GBM

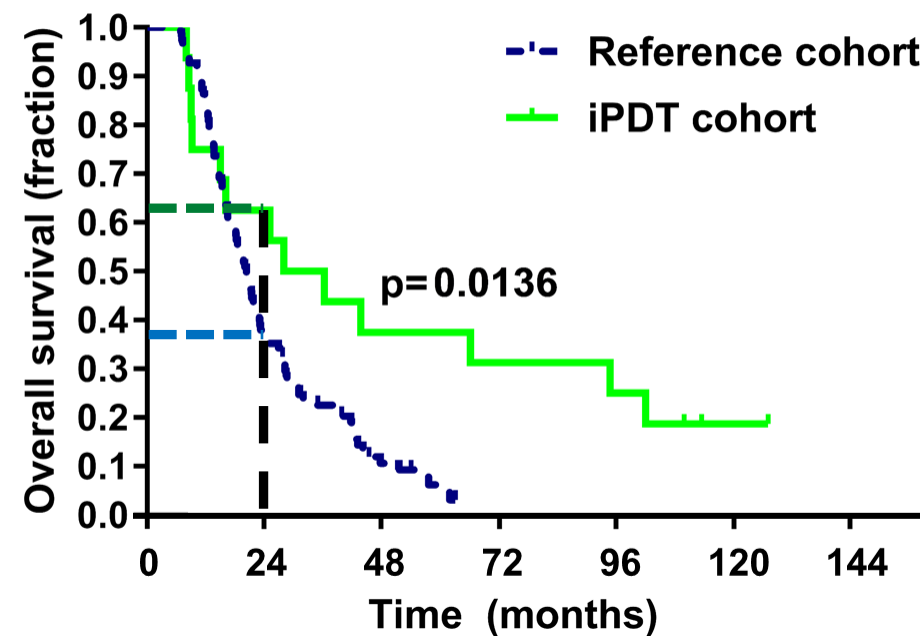
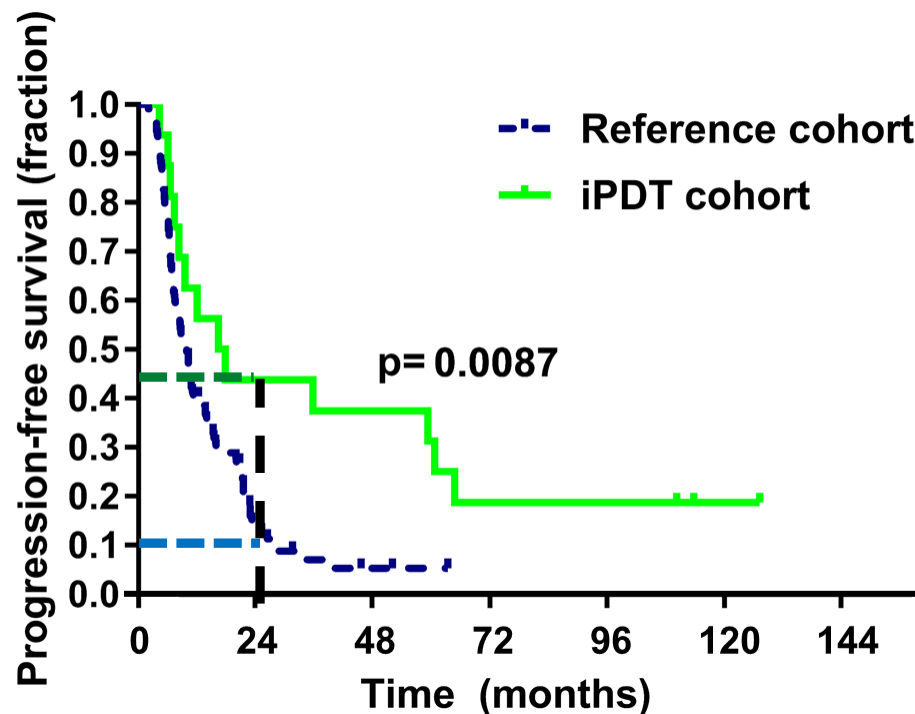


iPDT on de-novo GBM vs. tumor resection

- median PFS **16.4** months vs. *9.9 months*
- median OS **28** months [CI-95%: 6.0 - 50] vs. 20.4 months [17.9 - 22.9]

Clinical Outcome

De-novo GBM



iPDT on de-novo GBM vs. tumor resection

- 2-year PFS **45%** vs. **15%**
- 2-year OS **62.5%** vs. **37%**

Last evaluation (2025):
Still 3 Patients without recurrence (PFS > 120 months)

Clinical Studies - PDT for GBM

Germany:

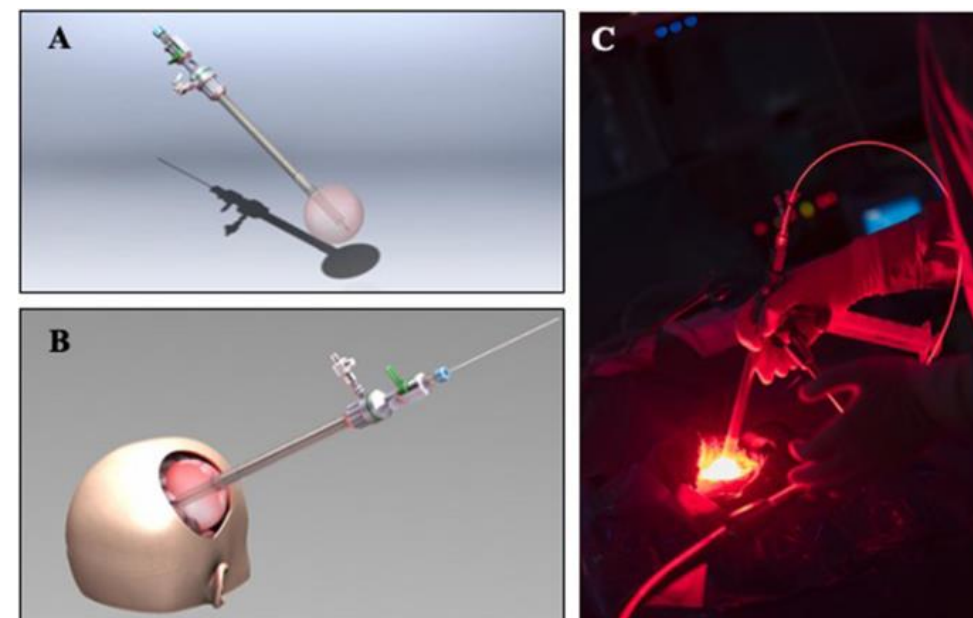
2 clinical trials (de-nove and recurrences), recruitment ended, data under analysis

France:

INDYGO – Resection cavity iPDT.
median overall survival (OS) of 23.4 months
12-month progression-free survival (PFS) rate of 60%
Follow Up Trail DOSINDYGO in preparation

Japan:

Resection Cavity – Talaporphirin Sodium mediated PDT
clinically approved since 2013
Median OS: 26 months



Thanks to:



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Prof. Dr. Alexander Buchner



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Dr. Stefanie Quach



PD Dr. Adrian Rühm



Dr. Marco Foglar



Mohamed El Fahim



Prof. Dr. Katja Parodi



Prof. Dr. Dr. Olaf Dietrich



Prof. Dr. Birgit Ertl-Wagner



Prof. Dr. Lothar Lilge



Dr. Maximilain Eisel



and many more:

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Prof. Dr. em. Wolfgang Zimmermann

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Jonathan Weller; Cristoph Barth; Mathias Hübner

Uniklinik Salzburg:

PD Dr. Christoph Schwartz

University of Toronto/ UHN-Toronto:

Prof. Dr. Vaughn Betz; Dr. Fynn Swiegelshohn; Chris McFadden; Tanner Young-Schultz



6th PDT-PDD Symposium

Nancy, France, October 26th – 30th 2026

Photodynamic Therapy and Photodiagnosis Update 2026



Thank you very much.
Questions?

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