Basic principles of Photodynamic therapy

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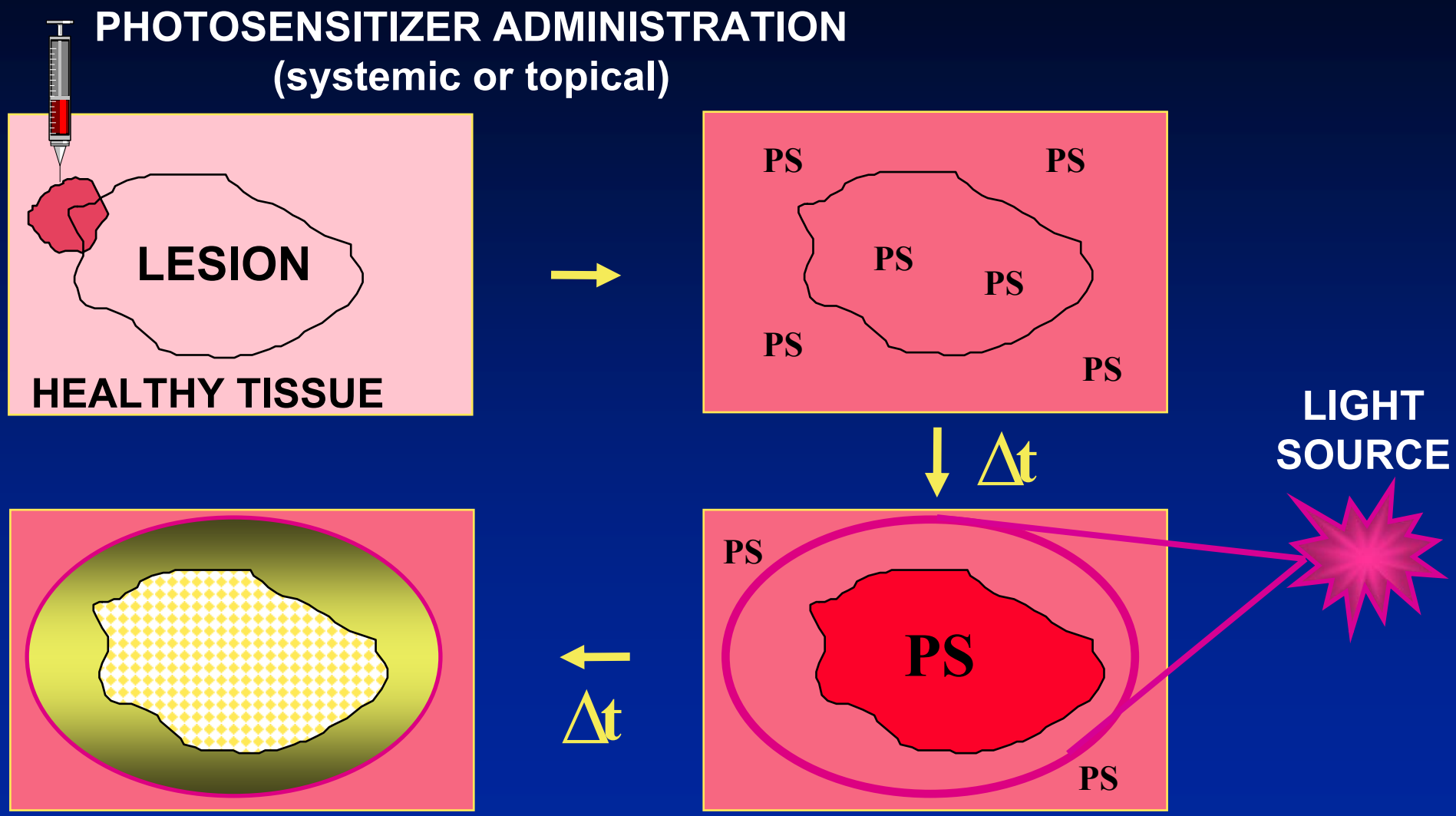
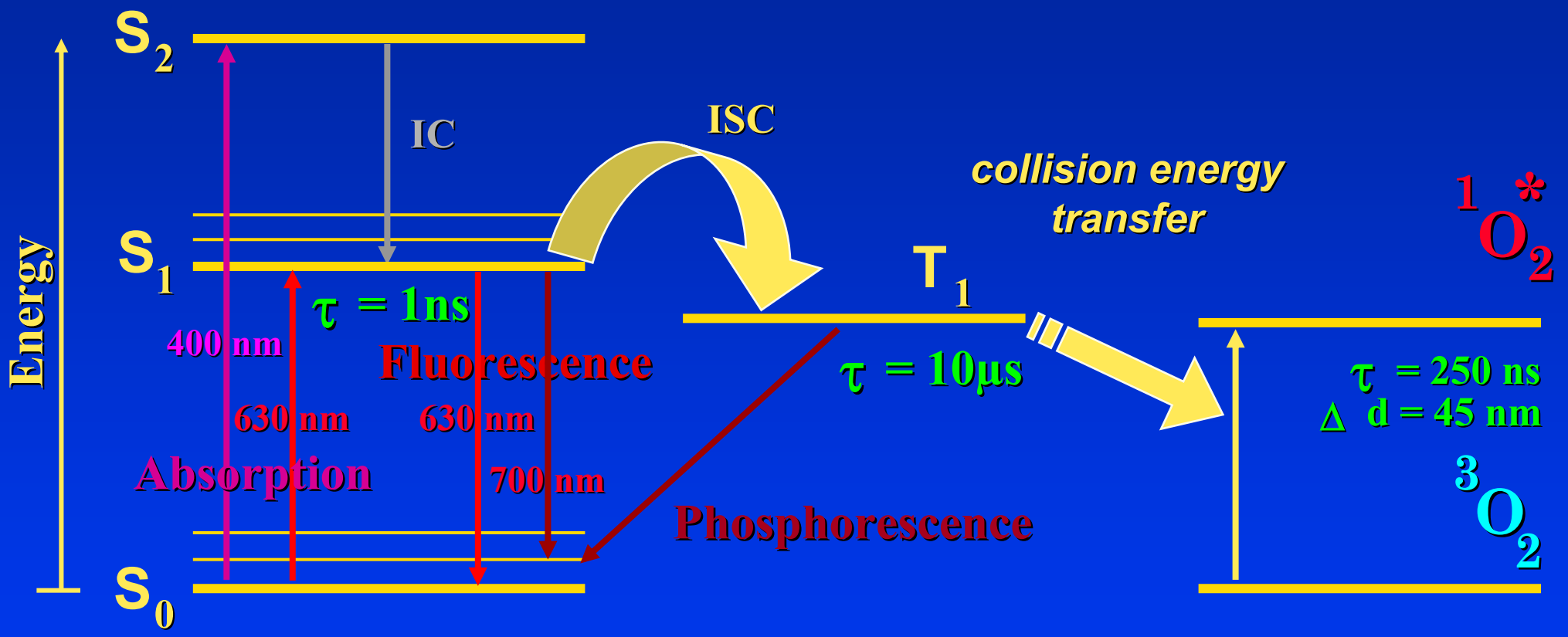
Principle of PDT



Photophysical Processes in:

Fluorescence detection

Photodynamic Therapy



Porphyrins spectroscopy

Singlet Oxygen production

Historical

Over 30 centuries ago, plant extracts containing psoralens (Furocoumarin) were used with subsequent exposure to sunlight to treat psoriasis and vitiligo (Leukoderma) in India, Egypt and China.

1900 O. RAAB - Uses acridine + light to kill paramecium (Z. Biol. 39, 524, 1900).

1903 H.V. TAPPEINER + A. JESIONEK - Use eosin + light for skin diseases (Herpes, Psoriasis and skin cancer). (Münch. Med. Wochenschr., 50, 2042, 1903).

Historical Cont.

1976 J. F. KELLY + M. E. SNELL - First clinical PDT of a bladder carcinoma with HPD. (J. Urol., 115, 150, 1976).

1978 T. J. DOUGHERTY et al.- Clinical assessment of PDT (Cancer Res., 38, 2628, 1978).

! LASERS + OPTICAL FIBERS !

1993 First approval (by the canadian health agency) of PDT with Photofrin® for the prophylactic treatment of bladder cancer.

Approved Indications for Photofrin® - PDT
(Porfimer sodium; QLT / Axcan)

Indication	States
Esophageal Cancer	USA (A), The Netherlands (A+E) , France (A), U.K. (A) , Canada (A), Japan (E), Finland (A), Sweden (A), Italy (A), Ireland (A), Portugal (A).
Lung Cancer	USA (E+A), Japan (E), France (A) , The Netherlands (E+A) , Germany (E+A), Finland (A), UK (A), Sweden (A), Italy (A), Ireland (A).
Bladder Cancer	Canada (A)
Gastric Cancer	Japan (E)
Cervical Cancer / Dysplasia	Japan (E)

(A): Advanced Stage Tumors; (E): Early Stage Tumors. In July 2000

Approved Indications for Visudyne™- PDT
(BPD-MA; QLT / Ciba-vision)

Indication	States
Age-related macular degeneration in patients with predominantly classic subfoveal choroidal Neovascularization	USA, Canada, Switzerland Argentina, Australia, Brazil Colombia, Malta, Korea Norway and EU.

In October 2000

Approved Indications for Levulan® - PDT
(ALA; DUSA / Berlex / Schering)

Indication	State
Non-hyperkeratotic actinic keratoses of the face and scalp.	USA

In September 2000

Photosensitizers

First generation

- Hematoporphyrin Derivative (HPD)
- Dihematoporphyrin ester/ether (Photofrin®)

Second generation

- mTHPC (Foscan®)
- Benzoporphyrin derivative (Visudyne™, Verteporfin™)
- ALA / PpIX (Levulan®)
- ALA-esters / PpIX (Metvix®, Hexvix™)
- N - Aspartyl Chlorin e6 (NPe6)
- Tin Etiopurpurin, SnET2 (Purlytin™)
- Lutetium Texaphyrin (Optrin™, Lutrin™, Antrin™)
- Phthalocyanines (AlPcTS, Pc 4, ...)
- Porphines (TPPS4)
- …

PDT with first generation PS

Photofrin®

Drawbacks and side effects

- Poorly defined mixture
- Poor tumor selectivity
- Absorption at 630 nm
- Moderate phototoxicity
- Long-term skin photosensitization
- Long drug / Light interval
- Long lifetime in the body
- Not for topical administration

PDT with second generation PS

PS	Dose (mg/kg)	D / L (hours)	WL (nm)	Light dose (J/cm2)
mTHPC	0.075 - 0.15	96	652 514	5 - 20 75 - 120
ALA-PpIX	60 Topical 20%	4 - 6	635 BLUE	10 - 200
BPD-MA	0.3	1 - 2	690	50 - 150
NPe6	0.5 - 1	4 - 8	664	50 - 100
Lu-Tex	0.6 - 7	3	732	150
SnET2	1.2	24	660	200

PDT with second generation PS

5 - ALA / PpIX

- Absorption at 635 nm (Blue light also used)
- Dose 30 - 60 mg/kg orally (20% for topical administrations)
- D / L interval 4 - 18 h
- Light dose 10 - 150 J/cm2
- Skin photosensitization 24 - 48 h

PDT with second generation PS

5 - ALA / PpIX

- Used to treat a large variety of superficial lesions:

  - Dermatology: - BCC superficial: (87% CR, 5% PR, 8% NR)
    - BCC nodular: (53% CR, 35% PR, 12% NR)

      Peng et al., Cancer, 79, 2282, 1997.

    - Actinic Keratoses (86% lesions cleared)

      Phase III trials reported by DUSA Inc.

    - SCC, Bowen's disease, mycosis fungoides, psoriasis, etc.

      Kennedy, J. Clin. Laser Med.&Surg., 14, 289, 1996.

PDT in Dermatology

Used to treat precanceroses and malignant tumors

Kulka et al., J. Am. Acad. Dermatol, 42(3), 389, 2000.
Fritsch et al., Arch. Dermatol., 134, 207, 1998.

- BCC (superficial and nodular)
- Actinic keratoses
- Actinic cheilitis
- SCC
- Bowen's disease.
- Kaposi 's sarcoma
- Malignant melanoma
- Skin metastases
- Mycosis fungoides
- ...

PDT in Dermatology

Used to treat nonmalignant skin disorders

Kulka et al., J. Am. Acad. Dermatol, 42(3), 389, 2000.
Fritsch et al., Arch. Dermatol., 134, 207, 1998.

- Psoriasis
- Viral diseases
- Vascular malformations
- Acne vulgaris
- Disorders of cutaneous adnexa (treatment of hirsutism)
- ...

PDT with second generation PS

5 - ALA / PpIX

- **Aerodigestive:-** **SCC in oral cavity** (Few CR excepting for dysplasia + healing without scarring).
  Fan et al., Cancer, 78, 1374, 1996.
  - **Dysplasia+early cancer in Barrett's esophagus**
    (CR: 10/10 for HGD; 17/22 for Cancer; FU 1-30 mths)
    Gossner et al., Gastroenterol., 114, 448, 1998.
  - **Colorectal, duodenal, esophageal tumors**
    Regula et al., Gut, 36, 67, 1995.
- **Urology:** - **Superficial bladder cancer:** (40% CR, 20% PR, 40% NR). Kriegmair et al., Br. J. Urol., 77, 667, 1996.
- **Gynecology:** - **Endometrial ablation**
  Wyss et al., Int. J. Gyn.&Obst., 60, 287, 1998.

Future Directions of PDT

- NON-CANCER PDT
  - Age-related macular degeneration (BPD-MA, Lutex, etc.)
  - Rheumatoid arthritis (BPD-MA)
  - Benign prostate hyperplasia (SnET2, mTHPC)
  - Dermatologic superficial lesions (ALA±esters-PPIX)
  - Artery diseases (Lutex, SnET2, BPD-MA)
  - Bacteria (Helicobacter Pylori) (ALA)
  - Immune modulation (BPD-MA)
  - Viral PDT (blood banking, etc.) (BPD-MA)
  - Decontamination of wounds
  - etc.

Photosensitization kinetics in Type I and Type II mechanisms

Photosensitizer excitation and desexcitation

EXCITATION

1) Absorption

$$^{1}S + h\nu \longrightarrow {}^{1}S^{*}$$

DECAY

2) Radiative decay (fluorescence)

$$^{1}S^{*} \longrightarrow {}^{1}S + h\nu'$$

3) Non-radiative singlet decay

$$^{1}S^{*} \longrightarrow {}^{1}S$$

4) Intersystem crossing

$$^{1}S^{*} \longrightarrow {}^{3}S^{*}$$

Photosensitization kinetics in Type I and Type II mechanisms

Type I mechanisms

FREE RADICAL DERIVATIONS

7) Hydrogen transfer

8) Electron transfer

REACTANT FORMATIONS

9) Hydrogen dioxide

10) Superoxide anion

Photosensitization kinetics in Type I and Type II mechanisms

Type II mechanisms

REACTANT FORMATION

7) Intermolecular exchange $^{3}S^{*} + {}^{3}O_2 \longrightarrow {}^{1}S + {}^{1}O_2^{*}$

OXIDATION

8) Cellular oxidation $^{1}O_2^{*} + X \longrightarrow X(O)$

CONCLUSION

- PDT is still going through a dynamic process of development, improvement, and standardization.

- The most important factors obstructing the widespread clinical application of PDT are close to be lifted:

  - Until 1999, legal approval has been granted for use of PDT with significant restrictions (small numbers of patients).

    But: Approvals of PDT have recently been, and will be obtained in the near future for important medical applications.

CONCLUSION Cont.

- The most important factors obstructing the widespread clinical application of PDT are close to be lifted (Cont.):

  - So far, the side effects induced by first and several second generation photosensitizers were too important.

    But: Numerous photosensitizers presenting minor side effects and optimized for specific therapies are close to be approved.

CONCLUSION Cont.

- PDT is effective in treating lesions which can not be treated with other well established methods.

- Among a large number of currently available minimally invasive therapies, PDT seems to be the most suited to take the lead.

Photodynamic Therapy

Light parameters

- Wavelength
- Drug - light interval
- Irradiance
- Duration of irradiation
- Total light dose

New Photosensitizers for PDT

What is required ?

- Efficacy $\geq$ 1st generation PS
- Rapid clearance → short skin phototoxicity
- Improved "tumor - to - normal tissue" selectivity
- High phototoxicity
- Activation at longer wavelengths than 630 nm
- Homogenous photosensitizer distribution within the tumor

Mechanisms of Selective Uptake and Localization of Photosensitizers in the Lesions

- NOT FULLY UNDERSTOOD !

- A ROLE IS PLAYED BY:
  - The Properties of the Lesion
  - The Molecular Nature of the Compound

Mechanisms of Selective Tumor Uptake and Localization of Exogenous Photosensitizers

- **The Properties of the Tumor**
  - Leaky Vasculature
  - Compromised Lymphatic drainage
  - Large interstitial space
  - Decreased pH value

    (reduces solubility of porphyrins

    aggregation + protein association)

Mechanisms of Selective Tumor Uptake and Localization of Exogenous Photosensitizers

- **The Properties of the Tumor (Cont.)**
  - Elevated numbers of low-density protein receptors
  - Presence of macrophages
    (take up large amounts of HPD)
  - High amount of newly synthesized collagen
    (that binds porphyrins)
  - High amount of Lipid
    (that has a high affinity for lipophilic dyes)
  - Membrane potentials of malignant cells

Mechanisms of Selective Uptake and Localization of Photosensitizers in the Lesions

- **The Molecular Nature of the Compound**

! Different localisation mechanisms for different groups of compounds !

- Hydrophobicity
- Molecular charge (positive and delocalized)
- pKa
- Aggregation
- Affinity to proteins (LDL, albumin, etc.)
- Incorporation into amphiphilic systems, e.g., phospholipid vesicles or oil emulsions (SnET2, BPD-MA, Zn-Phthalocyanine)

Mechanisms of Tissue Destruction

- **Tissue/cellular Targets of Photosensitizer:**
  - **Mitochondria** → **Apoptosis**
    (Photofrin®, ALA-PPIX)
  - **Plasma membrane** → **Necrosis**
    (damage to the plasma membrane observed within minutes after light exposure)
  - **Lysosomes**

Mechanisms of Tissue Destruction Cont.

- **Tissue/cellular Targets of Photosensitizer:**
  - **Vasculature** (The vascular effects differ greatly with different photosensitizers)
    - **Photofrin®**
      - Vessel constriction
      - Macromolecular vessel leakage
      - Leukocyte adhesion
      - Thrombus

→ **Platelet activation + Release of thromboxane**

Mechanisms of Tissue Destruction Cont.

- **Tissue/cellular Targets of Photosensitizer:**
  - **Vasculature**
    - **Phthalocyanine derivatives**
      - **Vascular leakage**
    - **mono-L-aspartyl chlorin e6**
      - **Blood flow stasis (Platelet aggregation)**

All these vascular effects may include damage of the endothelium !

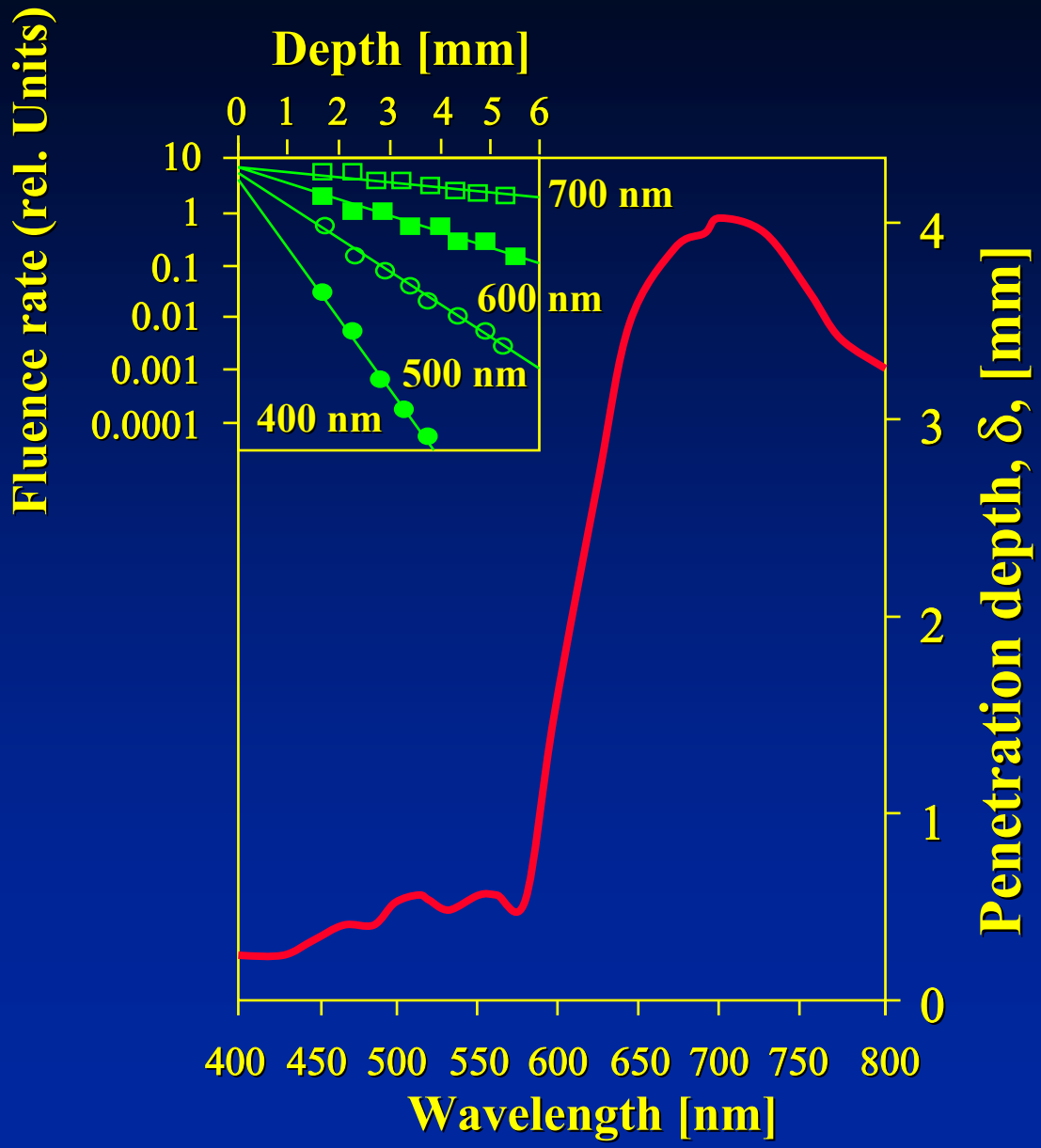
Mechanisms of Tissue Destruction Cont.

- **Tissue/cellular Targets of Photosensitizer:**
  - **Nuclear membrane of tumor cell**

    (since most photosensitizers do not accumulate in cell nuclei, PDT has a low potential of causing DNA damage)

  - **Inflammatory and immune host system**

Light penetration in the skin



Fluence rate and light penetration in a human ear tip *in vivo*.

Source: J. Moan et al., Action spectra of dyes relevant for photodynamic therapy; in: Photodynamic Tumor Therapy, 2nd and 3rd generation photosensitizers; J. Moser Ed., Harwood acad. Publish., 1998.