Basic principles of Photodynamic therapy

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9th Congress of the EADV
Principle of PDT

**PHOTOSENSITIZER ADMINISTRATION**
(systemic or topical)

**HEALTHY TISSUE**

**LESION**

**PS**

**LIGHT SOURCE**

"SELECTIVE" DESTRUCTION

"SELECTIVE" ILLUMINATION

\[ \Delta t \]
Photophysical Processes in:

Fluorescence detection

Photodynamic Therapy

\[ S_0 \rightarrow S_1 \rightarrow S_2 \]

\[ \text{Fluorescence} \quad \text{630 nm} \]

\[ \text{Absorption} \quad \text{400 nm} \]

\[ \text{400 nm} \quad \text{630 nm} \quad \text{700 nm} \]

\[ \tau = 1 \text{ns} \]

\[ \text{ISC} \]

\[ \text{collision energy transfer} \]

\[ \tau = 10 \mu\text{s} \]

\[ \Delta \quad d = 45 \text{ nm} \]

\[ 1 * \text{O}_2 \]

\[ \text{Singlet Oxygen production} \]

\[ 3 \text{O}_2 \]

Porphyrrins spectroscopy
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).


! LASERS + OPTICAL FIBERS !

1993  First approval (by the Canadian health agency) of PDT with Photofrin® for the prophylactic treatment of bladder cancer.
<table>
<thead>
<tr>
<th>Indication</th>
<th>States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal Cancer</td>
<td>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).</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>USA (E+A), Japan (E), France (A), The Netherlands (E+A), Germany (E+A), Finland (A), UK (A), Sweden (A), Italy (A), Ireland (A).</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>Canada (A)</td>
</tr>
<tr>
<td>Gastric Cancer</td>
<td>Japan (E)</td>
</tr>
<tr>
<td>Cervical Cancer / Dysplasia</td>
<td>Japan (E)</td>
</tr>
</tbody>
</table>

(A): Advanced Stage Tumors; (E): Early Stage Tumors. In July 2000
## Approved Indications for Visudyne™- PDT (BPD-MA; QLT / Ciba-vision)

<table>
<thead>
<tr>
<th>Indication</th>
<th>States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-related macular degeneration in patients with predominantly classic subfoveal choroidal Neovascularization</td>
<td>USA, Canada, Switzerland</td>
</tr>
<tr>
<td></td>
<td>Argentina, Australia, Brazil</td>
</tr>
<tr>
<td></td>
<td>Colombia, Malta, Korea</td>
</tr>
<tr>
<td></td>
<td>Norway and EU.</td>
</tr>
</tbody>
</table>

In October 2000
<table>
<thead>
<tr>
<th>Indication</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hyperkeratotic actinic keratoses of the face and scalp.</td>
<td>USA</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>PS</th>
<th>Dose (mg/kg)</th>
<th>D / L (hours)</th>
<th>WL (nm)</th>
<th>Light dose (J/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTHPC</td>
<td>0.075 - 0.15</td>
<td>96</td>
<td>652</td>
<td>5 - 20</td>
</tr>
<tr>
<td>ALA-PpIX</td>
<td>60</td>
<td>4 - 6</td>
<td>635</td>
<td>10 - 200</td>
</tr>
<tr>
<td></td>
<td>Topical 20%</td>
<td></td>
<td>BLUE</td>
<td></td>
</tr>
<tr>
<td>BPD-MA</td>
<td>0.3</td>
<td>1 - 2</td>
<td>690</td>
<td>50 - 150</td>
</tr>
<tr>
<td>NPe6</td>
<td>0.5 - 1</td>
<td>4 - 8</td>
<td>664</td>
<td>50 - 100</td>
</tr>
<tr>
<td>Lu-Tex</td>
<td>0.6 - 7</td>
<td>3</td>
<td>732</td>
<td>150</td>
</tr>
<tr>
<td>SnET2</td>
<td>1.2</td>
<td>24</td>
<td>660</td>
<td>200</td>
</tr>
</tbody>
</table>
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)
    - Actinic Keratoses (86% lesions cleared)
      Phase III trials reported by DUSA Inc.
    - SCC, Bowen’s disease, mycosis fungoides, psoriasis, etc.
PDT in Dermatology
Used to treat precanceroses and malignant tumors


- 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


- 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

• Urology: - Superficial bladder cancer: (40% CR, 20% PR, 40% NR).

• 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

\[ S + h\nu \rightarrow S^* \]

DECAY

2) Radiative decay (fluorescence)

\[ S^* \rightarrow S + h\nu' \]

3) Non-radiative singlet decay

\[ S^* \rightarrow S \]

4) Intersystem crossing

\[ S^* \rightarrow S \]
Photosensitization kinetics in Type I and Type II mechanisms

**Type I mechanisms**

**FREE RADICAL DERIVATIONS**

7) Hydrogen transfer

\[ S + RH \rightarrow SH + R \]

8) Electron transfer

\[ S + RH \rightarrow S + RH \]

**REACTANT FORMATIONS**

9) Hydrogen dioxide

\[ SH + O_2 \rightarrow S + HO_2 \]

10) Superoxide anion

\[ S + O_2 \rightarrow S + O_2 \]
Photosensitization kinetics in Type I and Type II mechanisms

Type II mechanisms

**REACTANT FORMATION**

7) Intermolecular exchange

\[
3^* + \text{O}_2 \rightarrow 1^* + \text{O}_2
\]

**OXIDATION**

8) Cellular oxidation

\[
\text{O}_2^* + X \rightarrow X(\text{O})
\]
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.**
- PDT is effective in treating lesions which cannot 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 ≥ 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)
  - $pK_a$
  - 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

<table>
<thead>
<tr>
<th>Wavelength [nm]</th>
<th>Penetration depth, δ, [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>0.0001</td>
</tr>
<tr>
<td>500</td>
<td>0.001</td>
</tr>
<tr>
<td>600</td>
<td>0.01</td>
</tr>
<tr>
<td>700</td>
<td>0.1</td>
</tr>
<tr>
<td>800</td>
<td>10</td>
</tr>
</tbody>
</table>

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