Photodynamic Therapy
Low Level Laser Therapy
Photodynamic Therapy (PDT)

Photosensitiser (retained in tumour) + Visible light - wavelength to activate phosensitiser ↓ Singlet oxygen ↓ Tumour cell death (necrosis+apoptosis)
The History of Photodynamic Therapy

• Sunlight used as therapeutic agent for 3000+ years
  • Egyptian, Indian, and Chinese civilizations
  • Psoriasis, rickets, vitiligo, skin cancer, psychosis
  • Greeks (Heliotherapy) – Herodotus

• 1903 - Jesionek/Tappeiner – the first administration of photosensitizer (eosin) in humans
  • eosin dye + light in skin cancer

• 1942 - Auler/Banzer - tumour-localizing properties of porphyrins

• 1960 - Lipson - localisation of haematoporphyrin derivative (HpD) in neoplastic tissue

• 1978 - Dougherty - HpD-PDT in cutaneous tumours

• 1990 - Kennedy - Topical ALA-PDT in skin tumours
What is Photodynamic Therapy?

- Dual selectivity of treatment (sometimes)
  - The PDT drug may accumulate at higher concentrations in malignant tissue, or the specific tissue to be treated. This is especially important for treating a specific layer in layered tissues.

- Primary selectivity can be achieved by limiting the region where the tissue is illuminated.
  - After injection, the drug goes everywhere in the body
  - There is only a biological effect where the drug is activated by light
What is Photodynamic Therapy?

This sucks!

Patient must avoid sunlight!

National Cancer Institute website, cis.nci.nih.gov/fact/7_7.htm accessed 1/17/02
What is Photodynamic Therapy?

- PDT is a method of light-activated chemotherapy
  - A photon is absorbed by a photosensitive drug, which leaves the compound in an excited state.
  - The excited drug can then pass its energy to oxygen to create singlet oxygen, a chemical radical.
  - Singlet oxygen attacks cellular structures by oxidation. Such oxidative damage might be oxidation of cell membranes or proteins.
  - When the accumulation of oxidative damage exceeds a threshold level, the cell begins to die.

![Diagram of Photodynamic Therapy (PDT)](image)
What is Photodynamic Therapy?

• Properties of singlet oxygen
  • Highly polarized zwitterion
  • Extremely reactive
  • Life time: 10-100 ms in organic solvents
  • Activity restricts to spherical volume of φ 10nm
  • In aqueous media lifetime: 2 ms, in cells less than 1 ms
  • Rate of singlet oxygen production is a function of light fluence rate, concentration and PS dose

• Properties of Photosensitizers
  • Chromophore absorption between 600nm and 800nm
  • Non toxic
  • Selective accumulation in tumors in high concentrations
  • Water soluble
  • Cleared in reasonable time from the body
  • Cleared rapidly from the skin
Topical PDT - Photosensitisers

1. 5-ALA
   - only one formulation, Levulan (DUSA, USA) is approved - for non-hyperkeratotic actinic keratoses on the face/scalp by the FDA. Several other formulations are available for off-label use (e.g. Porphin, Crawfords, UK).

2. Methyl aminolevulinate (MAL) Metvix (Galderma, Paris)
   - Esterified derivative, increased lipophilicity - 3hr application, improved selectivity described.
   - Approved for: Thin/non-hyperkeratotic and non-pigmented AK face/scalp where other therapies are considered less appropriate and for superficial and nodular BCC unsuitable for other therapies.
Topical PDT - Photosensitisers

- Epidermis
- Papillary dermis
- Reticular dermis
- Subcutaneous fatty tissue
  - 400 nm
  - 500-550 nm
  - 630-650 nm

Porphyric activation to 1-2 cm

Percentage of light penetration (width of arrow)

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Absorption at 630 nm, $e = 3000 \text{ M}^{-1}\text{cm}^{-1}$

Injections, 2-5mg/kg

Accumulation in skin for few weeks

Lung, skin, bladder, breast, gastric cancers
After treatment:
Common side effects:
Your skin and eyes will be very sensitive to bright light for about 30 days after the injection:
- Avoid direct sunlight or bright lights. You can watch TV or go to the movies.
- Stay away from undraped windows or skylights. Normal indoor light is okay.
- Avoid “helmet” type hairdryers (like those found in beauty salons). Hand held hair dryers on low settings are safer to use.
Other possible side effects:
- You may experience severe bladder irritation within a few days after PDT. This may include painful urination, blood in the urine, pain in the lower abdomen, rectal pain, and increased urinary frequency.
- Talk with your doctor about what to expect.

Managing exposure to direct sunlight:
For 30 days:
- If possible, wait until sundown to do outside chores (such as shopping).

If you do go out during daylight hours, W-F-A-R:
- Long-sleeved shirt and slacks
- Tightly woven and light-colored fabrics
- Gloves
- Socks and shoes
- Wide-brimmed hat
- Dark sunglasses

On day 31:
- Test for photosensitivity by putting your hand in a paper bag with a 2-inch hole in it and expose it to direct sunlight for 10 minutes.
  If a reaction occurs (swelling, redness, or blistering) within 24 hours, continue to take precautions for another 2 weeks before retesting.
  If no reaction occurs within 24 hours, you may gradually increase your exposure to sunlight. Continue to watch for skin reactions.
  Call your doctor if your skin becomes red or blistered at any point following treatment.
PDT - Photosensitisers

- Foscan®

Absorption at 690 nm, $e = 3500 \text{ M}^{-1}\text{cm}^{-1}$

Injecions, 0.1 mg/kg

Accumulation in skin for up to 20 days

Lung, skin, throat, head, neck, prostate cancers
PDT - Photosensititisers

- **Levulan®**

Absorption at 635nm, $e = 5000 \ M^{-1} cm^{-1}$

Oral, **topical**

Accumulation in skin for up to 2 days

Actinic ceratosis, skin and gastric cancers, psoriasis,
PDT - Photosensitisers

• **Visudyne®**

Absorption at 690nm, $e = 3500 \text{ M}^{-1}\text{cm}^{-1}$

Injections, 0.1-2 mg/kg

Accumulation in skin for up to 5 days

Macular degradation, psoriasis, bone cancers
Advantages of PDT
Advantages of PDT

• **Advantage 1: PDT avoids systemic treatment.**
  - The treatment occurs only where the correct wavelength of light is delivered. The patient does not undergo needless systemic treatment when treating localized disease. Side-effects are avoided, from losing hair or suffering nausea to more serious complications. Without light the agent is harmless.

• **Advantage 2: PDT is selective.**
  - Some photosensitizing agents will selectively accumulate in cancer cells and not in surrounding normal tissues. Hence, there can be selective targeting of the cancer and sparing of surrounding tissues. Also, PDT treatment affects cellular tissues more than structural tissues.

• **Advantage 3: PDT when surgery is not possible.**
  - PDT kills cancer cells but does not damage collagenous tissue structures, and normal cells will often repopulate these structures. Hence, if a patient has cancer in a structure that cannot be removed surgically (e.g., the upper bronchi of the lung), PDT can still treat the site.

• **Advantage 4: PDT is low cost.**
  - PDT is a low-cost minimally invasive localized treatment.

• **Advantage 5: PDT is repeatable.**
  - Unlike radiation therapy, PDT can be used again and again. Hence, it offers a means of long-term management of cancer even if complete cure is not attainable.
Photodynamic therapy in action
85 year old man presenting with hemotemesis

Photodynamic therapy to tumor
PDT - Early Gastric Cancer

3 days after treatment
the tumour is undergoing necrosis

2 months after treatment
the tumour is healed
PDT - Lung Cancer

Cancer cells before PDT

Bronchus during PDT

Bronchus 24 months after

http://www.timtec.net/photogem/pdt07.htm
PDT for Recurrent Prostate Cancer after Radiotherapy

• Background:
  • Recurs in up to 60% by 5 years after radiotherapy
  • Median survival after local recurrence: 33 months (5 year disease specific survival 30%)
  • Potentially, up to 1/2 of recurrences may be cured by local treatment, especially if identified early using PSA

• Treatment Protocol
  • Sensitization with 0.15mg/kg mTHPC, 3 days prior to PDT
  • Needles and fibres placed percutaneously with TRUS guidance
  • Delivery of red light at 652nm from laser
Photodynamic therapy in the canine prostate
Advantages of PDT

• Effect localised to area of light delivery
• Connective tissue largely unaffected (no heat involved), so mechanical integrity of hollow organs maintained
• No cumulative toxicity, so can be repeated
• Can be used after radiotherapy
• Gentle to tissue with good healing
Conclusions

• Modern and effective way of treating cancers
• Already in clinical phase, but quite expensive
• A lot of new drugs in Phase I, Phase II and preclinical phase of clinical status
• New photosensitizers still to be obtained (2PA mechanisms is explored, different mixtures to improve delivery and pharmacokinetics)
Dr. Z rechecks the laser dosimetry
PRETTY DAMNED TRENDY
P.D.T.
EST ARRIVÉ
DANS LA
BASEMENT.
LLLT - What’s in a Name?

• Therapeutic Laser
• Low Level Laser Therapy
• Low Power Laser Therapy
• Low Level Laser
• Low Power Laser
• Low-energy Laser
• Soft Laser
• Low-reactive-level Laser

• Low-intensity-level Laser
• Photobiostimulation Laser
• Photobiomodulation Laser
• Mid-Laser
• Medical Laser
• Biostimulating Laser
• Bioregulating Laser
What Does It Do?

• Laser light waves penetrate the skin with no heating effect, no damage to skin & no side effects.

• Laser light → biostimulative light energy to the body’s cells which convert into chemical energy to promote natural healing & pain relief.

• Optimizes the immune responses of blood & has anti-inflammatory & immunosuppressive effects.
Main areas of application of LLLT

hv, 600-950-nm,

Cellular photoreceptor

- Wound healing
- Tissue repair
- Prevention of tissue death
- Relief of inflammation
  - Pain, edema
  - Acute injuries
  - Chronic diseases
- Neurogenic pain
- Neurological problems
- Acupuncture
Physiological Effects

• Biostimulation – improved metabolism, increase of cell metabolism
  • Increases speed, quality & tensile strength of tissue repair

• Improved blood circulation & vasodilation
  • Increases blood supply

• Increases ATP production

• Analgesic effect
  • Relieves acute/chronic pain

• Anti-inflammatory & anti-edematous effects
  • Reduces inflammation
Physiological Effects

• Stimulation of wound healing
  • Promotes faster wound healing/clot formation
  • Helps generate new & healthy cells & tissue

• Increase collagen production
  • Develops collagen & muscle tissue

• Increase macrophage activity
  • Stimulates immune system

• Alter nerve conduction velocity
  • Stimulates nerve function
Tissue & Cellular Response

• Red light affects all cell types
  • Absorbed by the mitochondrial present in all cells
  • Cytochromes (respiratory chain enzymes) within the mitochondria have been identified as the primary biostimulation chromophores (primary light-absorbing molecules).
  • Since enzymes are catalysts with the capability of processing thousands of substrate molecules, they provide amplification of initiation of a biological response with light.

• Infrared light is more selective absorbed by specific proteins in the cell membrane & affects permeability directly
Tissue & Cellular Response

• Cytochromes function to couple the release of energy from cellular metabolites to the formation of high energy phosphate bonds in adenosine triphosphate (ATP)
  • ATP is used to drive cell metabolism (maintain membrane potentials, synthesize proteins & power cell motility & replication).

• Assuming cytochromes also can absorb energy directly from illumination, it is possible that during LLLT light energy can be transferred to cell metabolism via the synthesis of ATP.
Tissue & Cellular Response

- Magnitude of tissue’s reaction are based on physical characteristics of:
  - Output wavelength/frequency
  - Density of power
  - Duration of treatment
  - Vascularity of target tissues

- Direct effect - occurs from absorption of photons
- Indirect effect – produced by chemical events caused by interaction of photons emitted from laser & the tissues
High vs. Low Level Lasers

• High
  • Surgical Lasers
  • Hard Lasers
  • Thermal
  • Energy – 3000-10000 mW

• Low
  • Medical Lasers
  • Soft Lasers
  • Subthermal
  • Energy – 1-500 mW
  • Therapeutic (Cold) lasers produce maximum output of 90 mW or less
  • 600-1000 nm light
Parameters

• Patient
  • Need medical history & proper diagnosis
    • Diabetes – may alter clinical efficacy
  • Medications
    • Photosensitivity (antibiotics)
  • Pigmentation
    • Dark skin absorbs light energy better

• Laser
  • Wavelength
  • Output power
  • Average power
  • Intensity
  • Dosage
Parameters – Energy Density

• Dosage (D)
• Amount of energy applied per unit area
• Measured in Joules/square cm (J/cm²)
  • Joule – unit of energy
  • 1 Joule = 1 W/sec

• Dosage is dependent on:
  • Output of laser in mW
  • Time of exposure in seconds
  • Beam surface area of laser in cm²

• Various dosage ranges per site (1-9 J/cm²)
Parameters – Energy Density

• **Recommended Dosage Range**
  - Therapeutic response = 0.001-10 J/cm\(_2\)
  - Minimal window threshold to elicit response
  - Too much – suppressive effect
  - Open wounds – 0.5-1.0 J/cm\(_2\)
  - Intact skin – 2.0-4.0 J/cm\(_2\)
  - Average treatment – 6 J/cm\(_2\)
**Indications**

- Soft tissue injuries
- Fractures
- Osteoarthritis, Rheumatoid Arthritis
- Pain
- Wounds & Ulcers
- Acupuncture
Contraindications

• Application over eyes
• Possibly can damage cellular structure or DNA
• Cancerous growths
• Pregnancy – over & around uterus
• Over cardiac region & Vagus nerve
• Growth plates in children
• Over & around thyroid gland & endocrine glands
• Patients who have been pre-treated with one or more photosensitizers
Treatment Precautions

• Better to underexpose than to overexpose

• Avoid direct exposure into eyes (If lasing for extended periods of time, safety glasses are recommended)

• May experience a syncope episode during treatment during chronic pain, but very rare

• If icing – use BEFORE phototherapy
  • Enhances light penetration

• If using heat therapy – use AFTER phototherapy
  • Decreases light penetration
Procedure

- The laser handset is held over the skin for a few minutes in each setting, although it can be used through clothes for intimate areas. Different programmes use a range of settings with various wavelengths and phasing to penetrate to the best level within the body and interact directly with the appropriate cells. Sessions last no more than an hour and most clients notice the benefits from the very first session.
Treatment Techniques

• Simple

• For general application, only treatment time & pulse rate vary

• Dosage
  • Most important variable in laser therapy & may be difficult to determine because of the above conditions

• Handheld applicator

• Tip should be in light contact with skin while laser is engaged for calculated time

• Maintain laser perpendicular to treatment surface

• Firm contact unless open wound

• Clean area prior to treatment

• Begin with minimal treatment and gradually increase

• Check for pre/post-treatment changes

• Ask the patient how they are doing prior to next treatment
  • May have to adjust dosage
Equipment

• Dynatron’s Solaris D880 Infrared Therapy
  • 880 nm wavelength – SLD (32) (deep)
  • 660 nm – LED (4) (superficial)
  • 10 minute max. treatment or 60 Joules
  • Place probe on treatment area. Maintain constant contact with the skin.
    • Do not bathe the area with the probe.
  • FDA cleared to “provide topical heating for temporary increase in blood circulation, temporary relief of minor muscle & joint aches, pain & stiffness & relaxation of muscles; for muscle spasms & minor pain & stiffness associated with arthritis.”
    • Dynatron Solaris 709
Equipment

- MedX Laser & Light Therapy
  - Laser probe
  - SLD (2)