Photodynamic Therapy
Low Level Laser Therapy

Photodynamic Therapy (PDT)

Photosensitiser (retained in tumour)

+

Visible light - wavelength to activate phosensitiser

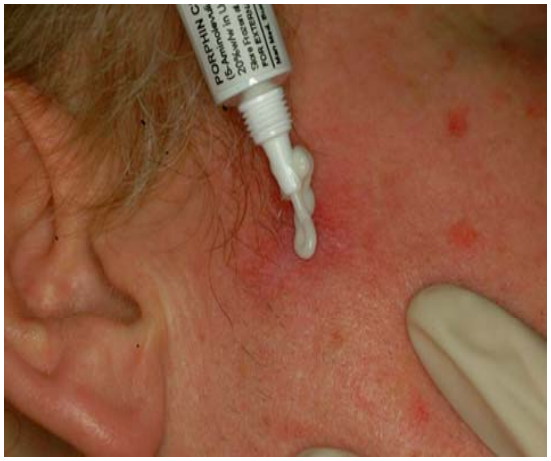
↓

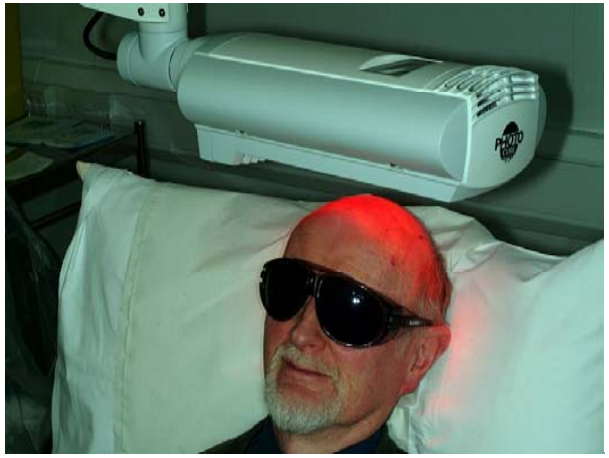
Singlet oxygen

↓

Tumour cell death

(necrosis+apoptosis)



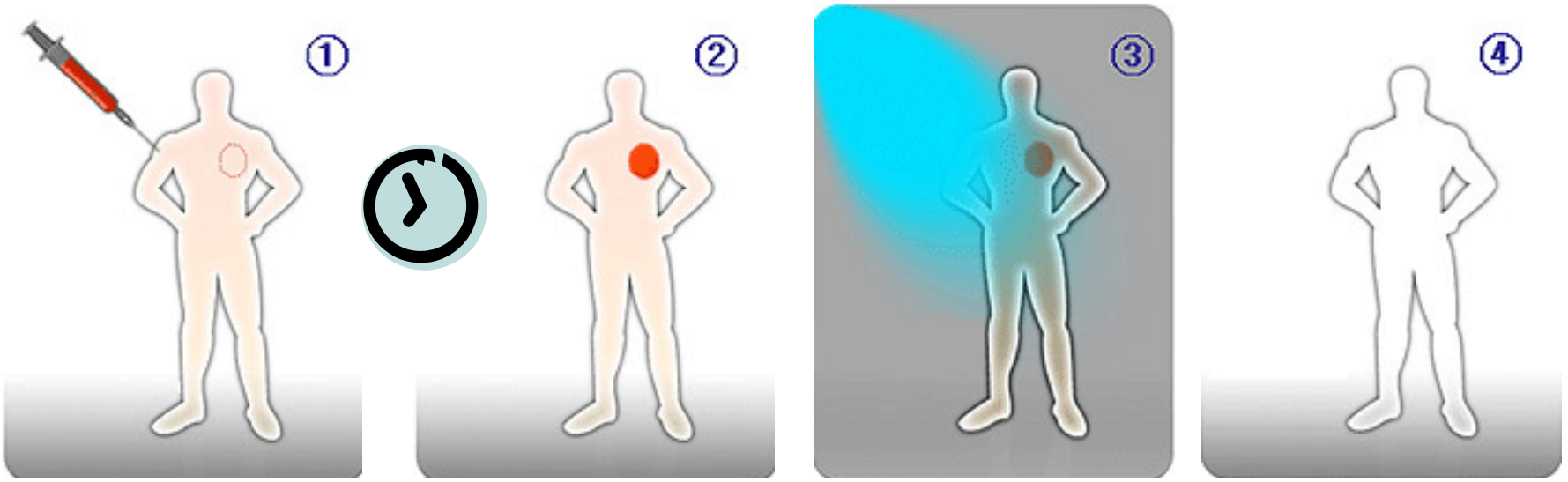


The History of Photodynamic Therapy

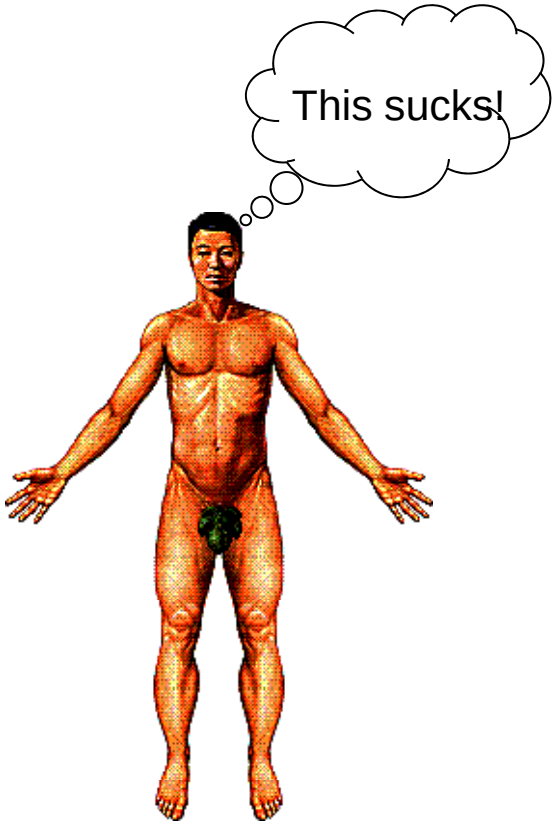
- **Sunlight used as therapeutic agent for 3000+ years**
  - Egyptian, Indian, and Chinese civilizations
  - Psoriasis, rickets, vitiligo, skin cancer, psychosis
  - Greeks (Heliotherapy) – Herodotus
- **1903 - Jesionek/Tappeiner – the first admnistration of photosensitizer (eosin) in humans**
  - eosin 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 ?

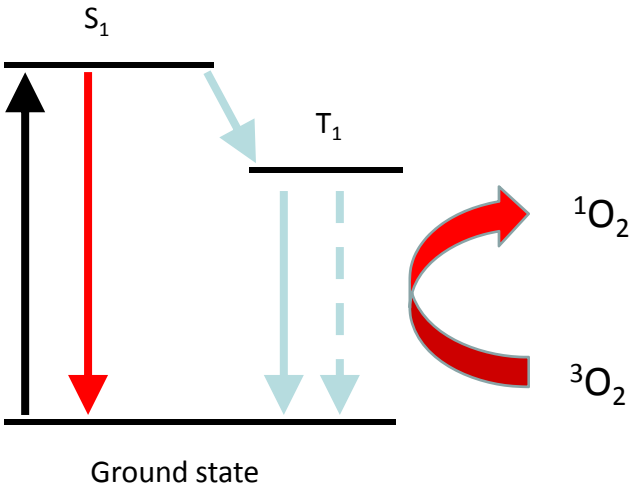


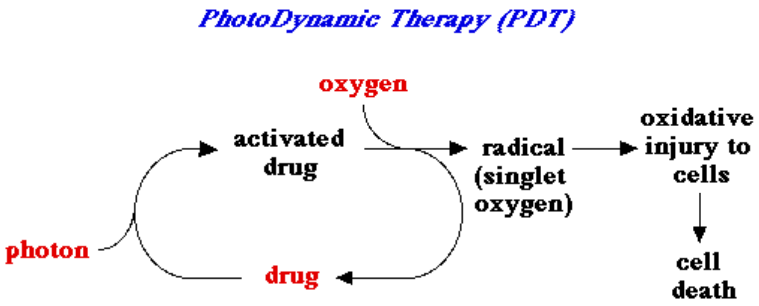
Patient must avoid sunlight!

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 photosenstive 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.





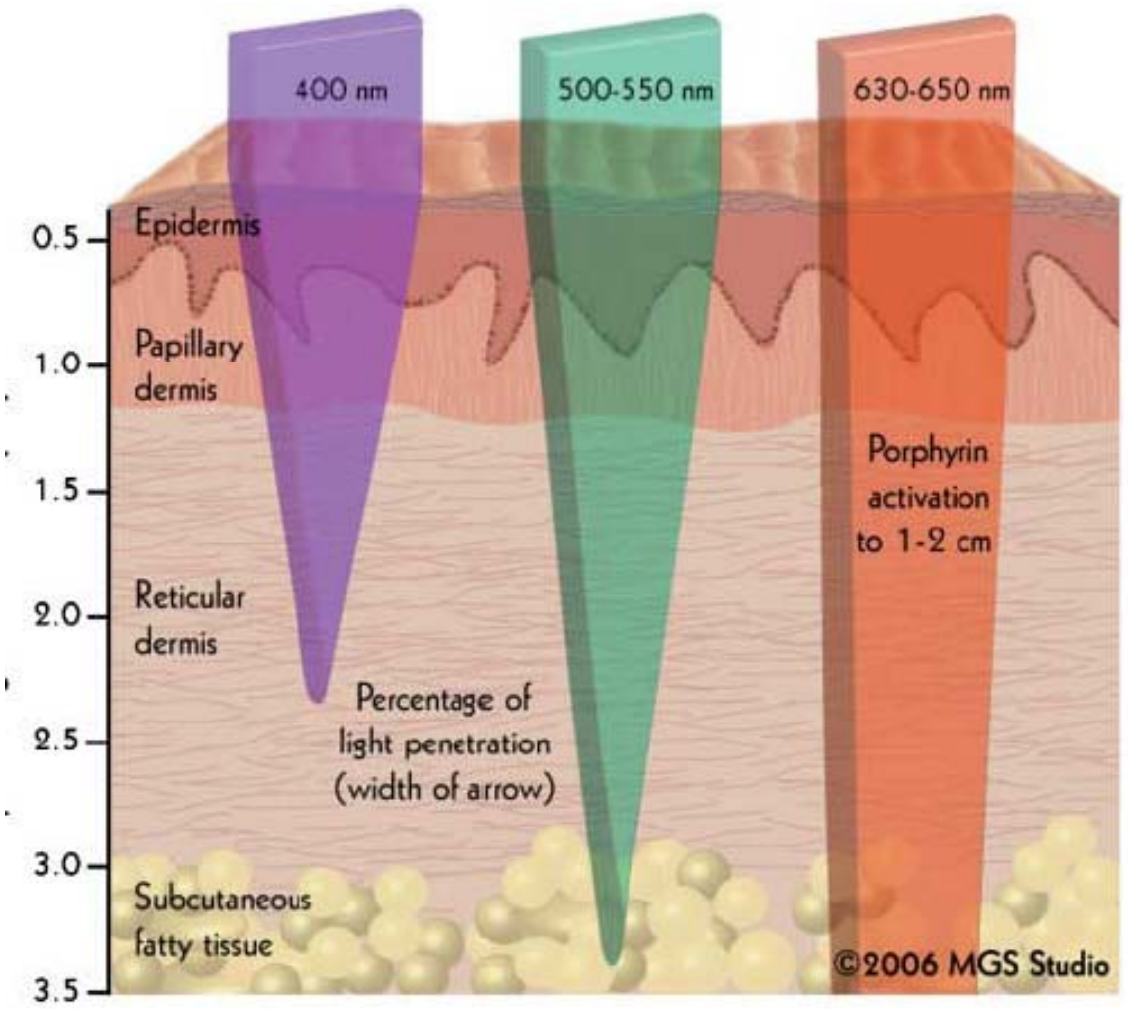
What is Photodynamic Therapy ?

- **Properties of singlet oxygene**
  - Higly polarized zwitterion
  - Extremely reactive
  - Life time : 10-100 ms in organic solvents
  - Activity restricts to spherical volume of ϕ 10nm
  - In aqueus media lifetime: 2 ms, in cell less than 1 ms
  - Rate of singlet oxygene production is a function of light fluence rate, concentration and PS dose
- **Properties of Photosensitizers**
  - Chromophore absoprbtion between 600nm and 800nm
  - Non toxic
  - Selective cumulation in tumors in high concentrations
  - Water soluable
  - Cleared in reasonable time from the body
  - Cleared rapidly from the skin

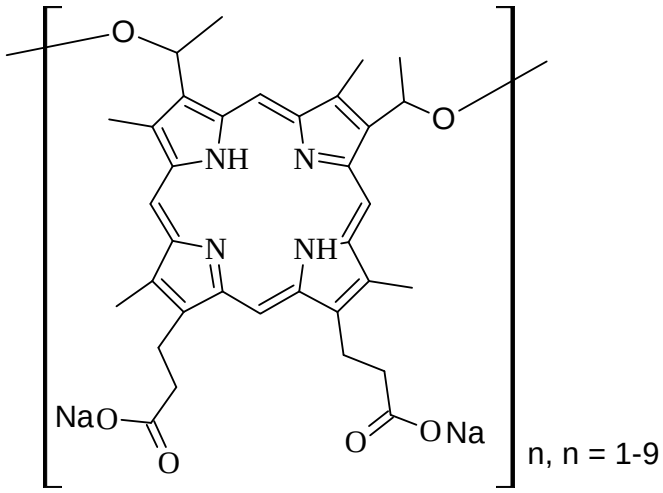
Topical PDT - Photosensitisers

- **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



PDT - Photosensitisers



Absorbtion at 630 nm, e = 3000 $M^{-1}cm^{-1}$

Injecions, 2-5mg/kg

Accumulation in skin for few weeks

Lung, skin, bladder, breast, gastral cancers

PDT - Photosensitisers

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, WEAR:
  - 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.

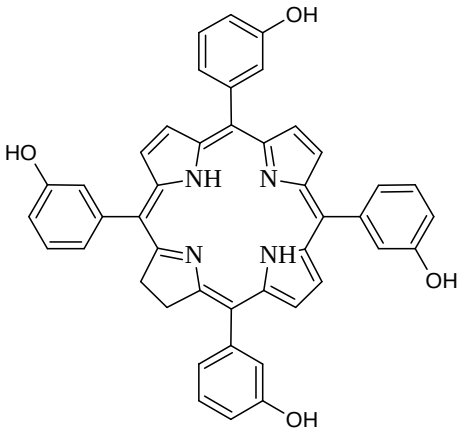
  If a reaction occurs (swelling, redness, or blistering) within 24 hours, continue to take precautions for another 2 weeks before retesting.

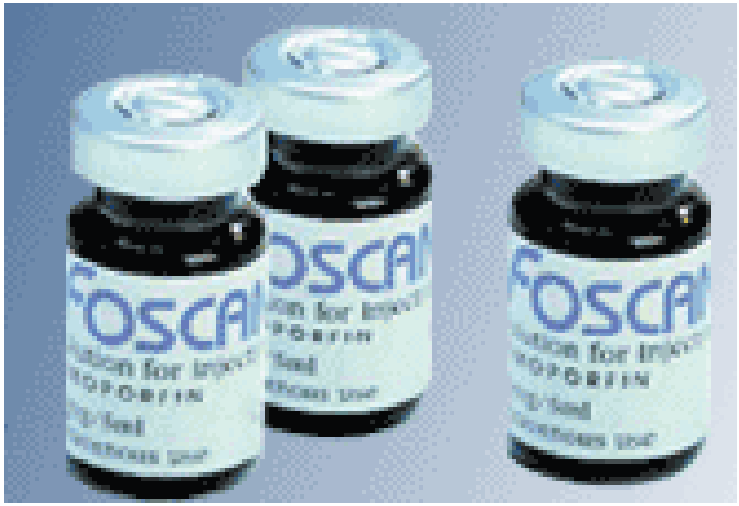
  If no reaction occurs within 24 hours, you may gradually increase your exposure to sunlight. Continue to watch for skin reactions.

Call your doctor if your skin becomes red or blistered at any point following treatment.

PDT - Photosensitisers

- **Foscan®**





Absorbtion at 690 nm, e = 3500 $M^{-1}cm^{-1}$

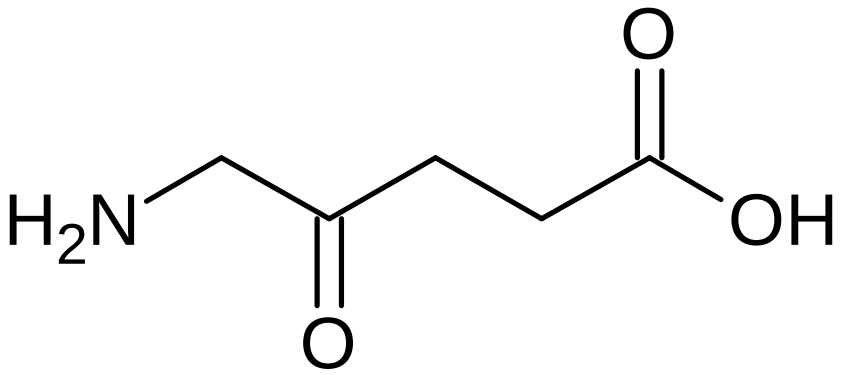
Injecions, 0.1 mg/kg

Accumulation in skin for up to 20 days

Lung, skin, throat, head, neck, prostate cancers

PDT - Photosensitisers

- **Levulan®**



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

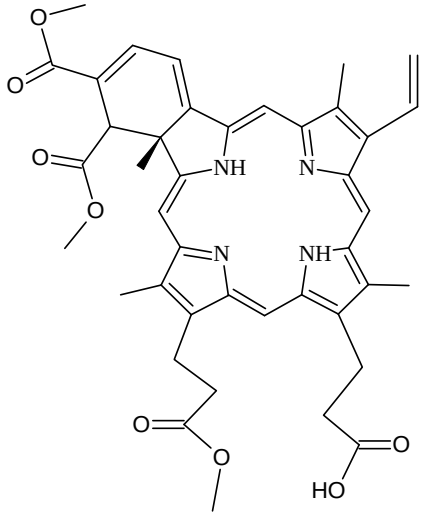
Oral, **topical**

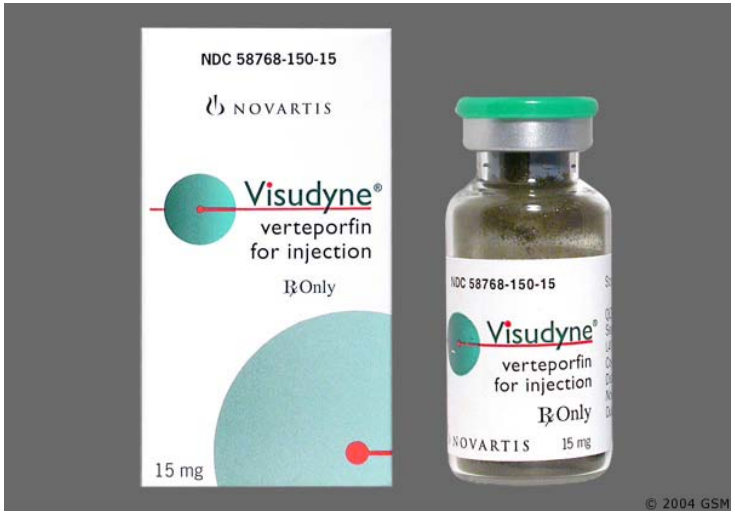
Accumulation in skin for up to 2days

Actinic ceratosis, skin and gastral cancers, psoriasis,

PDT - Photosensitisers

- **Visudyne®**





Absorbtion at 690nm, e = 3500 $M^{-1}cm^{-1}$

Injecions, 0.1-2 mg/kg

Accumulation in skin for up to 5 days

Macular degradation, psoriasis, bone cancers

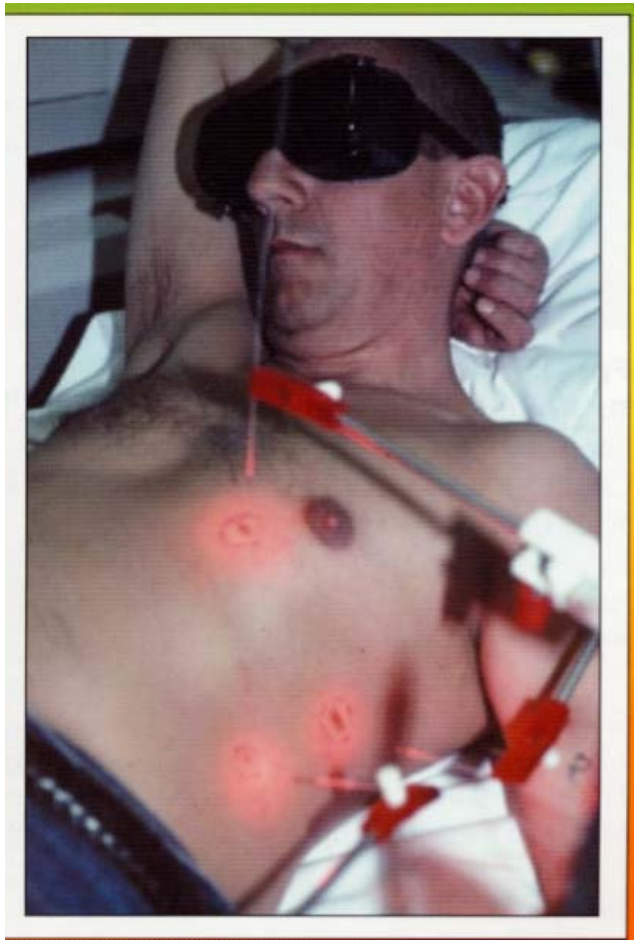
Advantages of PDT

Advantages of PDT

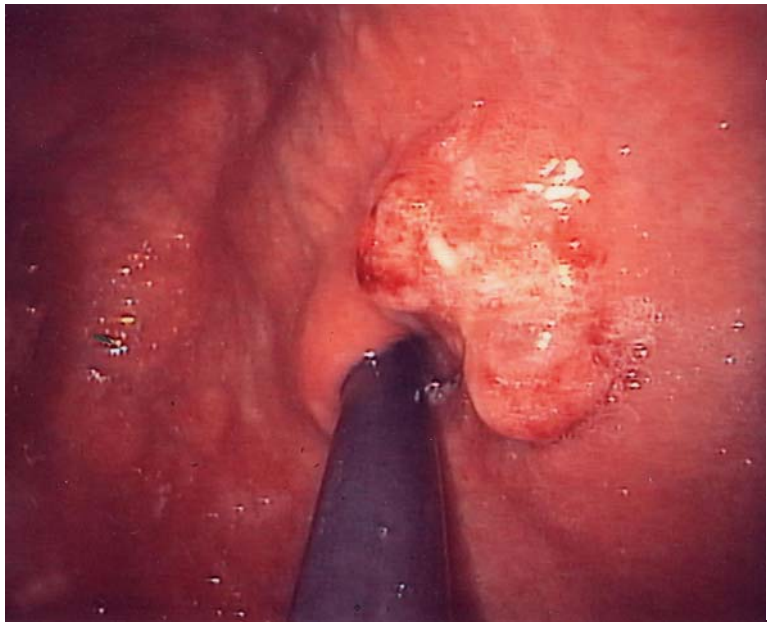
- **Advantage 1: PDT avoids systemic treatment.**
  - The treatment occurs only where the correct wavelength of light is delivered. The patient does not undergo needless systemic treatment when treating localized disease. Side-effects are avoided, from losing hair or suffering nausea to more serious 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.

from Oregon Medical Laser Center

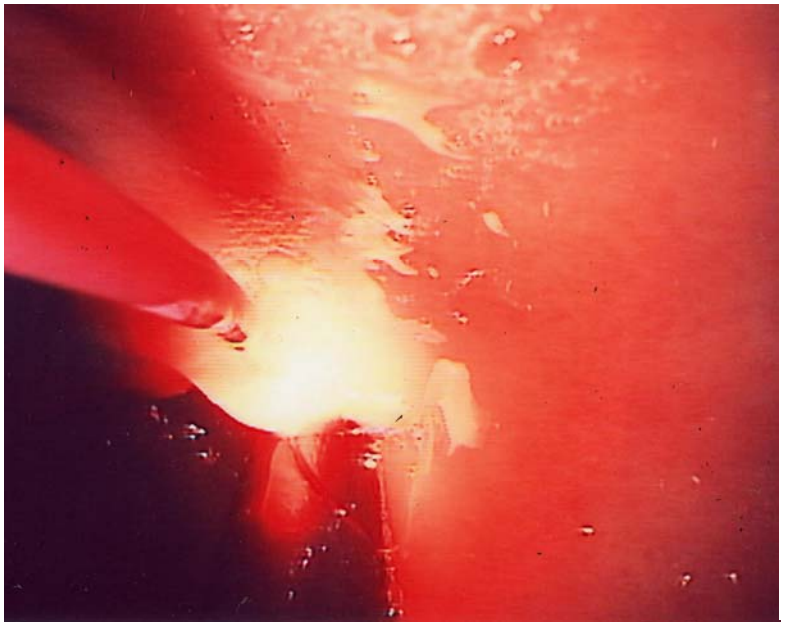
Photodynamic therapy in action



PDT - Early Gastric Cancer

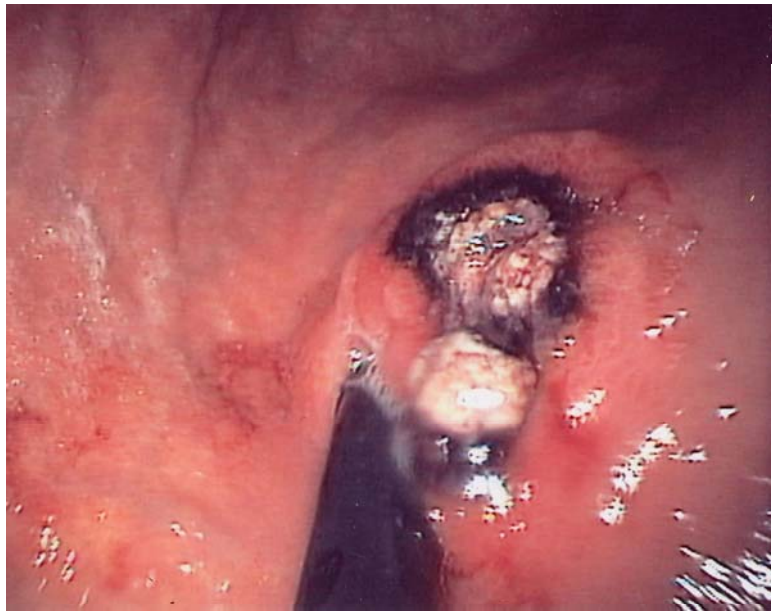


85 year old man presenting with hemotemesis

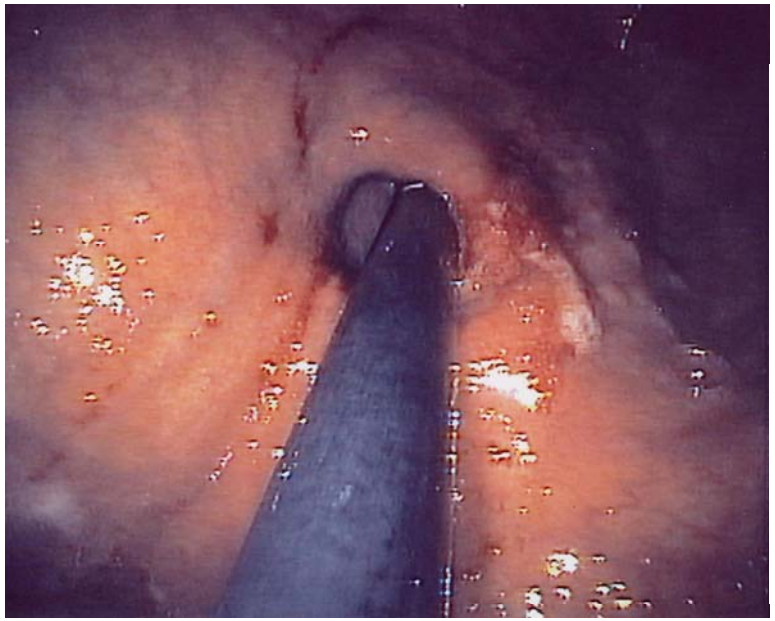


Photodynamic therapy to tumor

PDT - Early Gastric Cancer

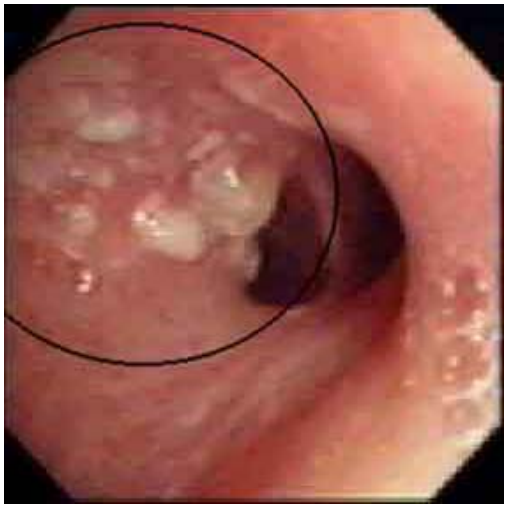


3 days after treatment
the tumour is undergoing necrosis

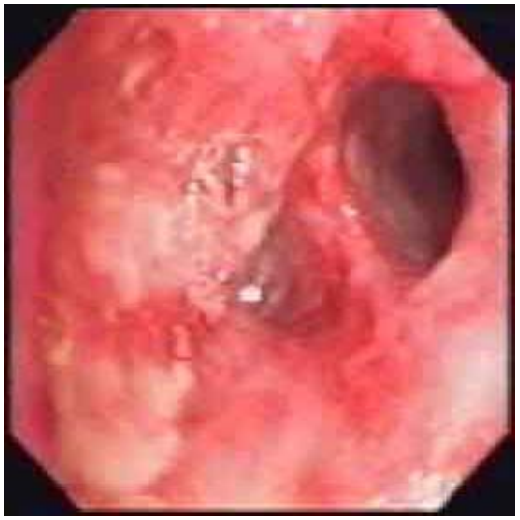


2 months after treatment
the tumour is healed

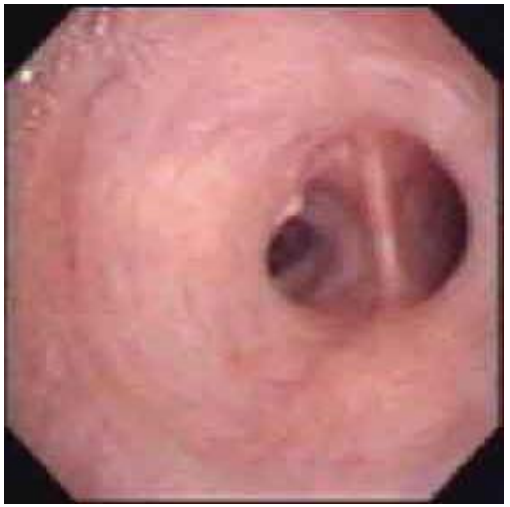
PDT - Lung Cancer



Cancer cells before PDT



Bronchus during PDT



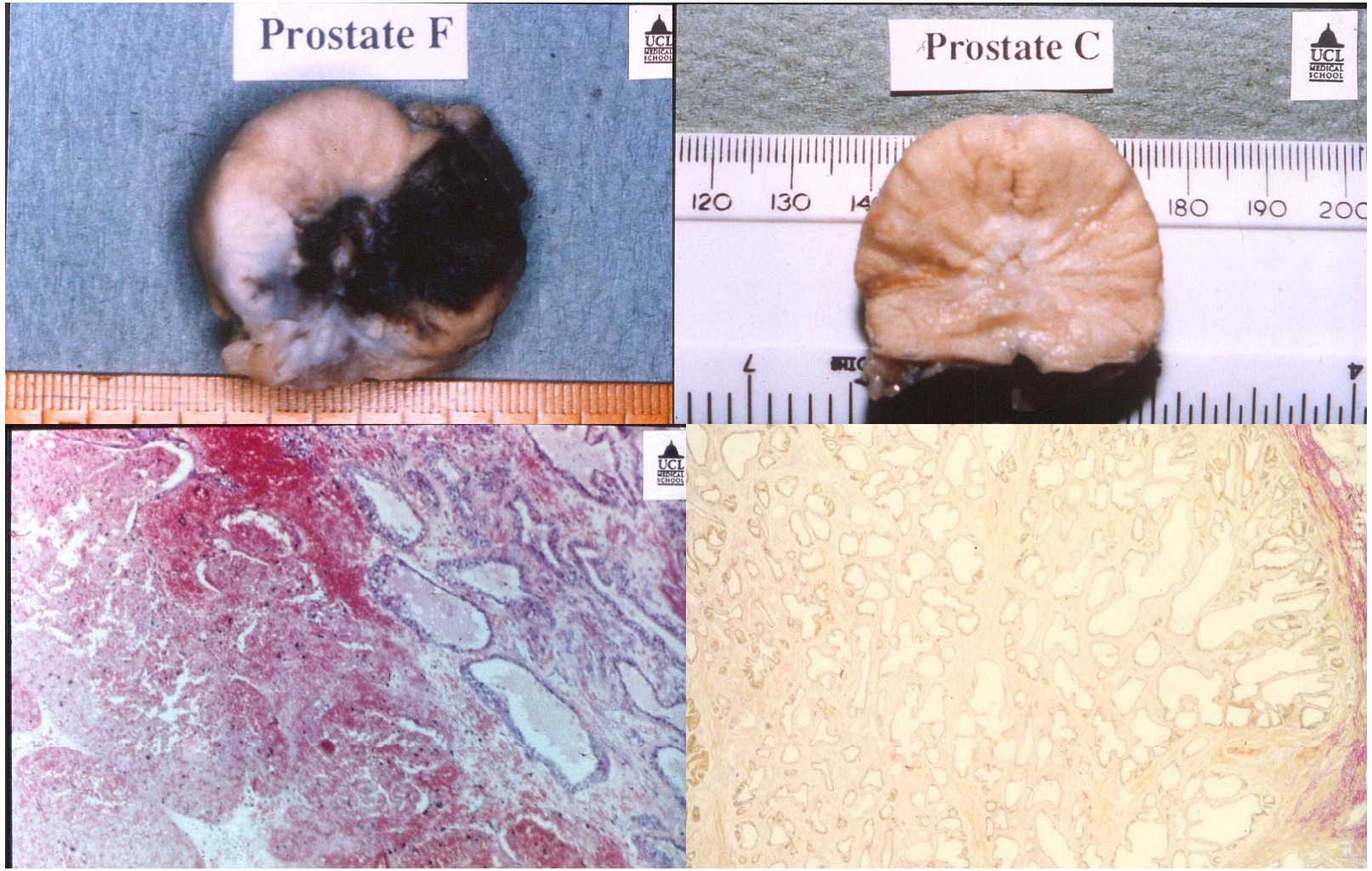
Bronchus 24 months after

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

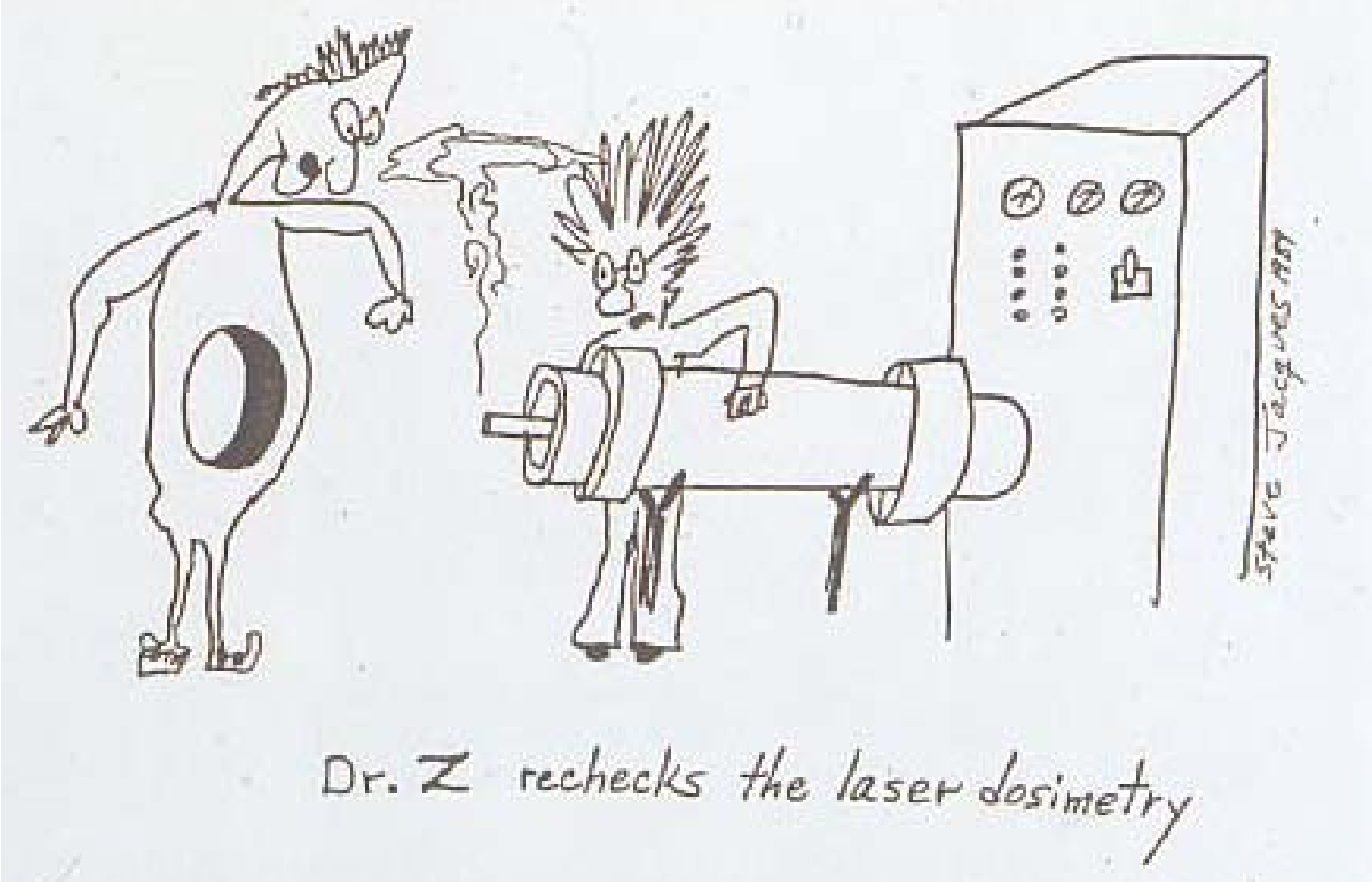


Advantages of PDT

- 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 expesive
- 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

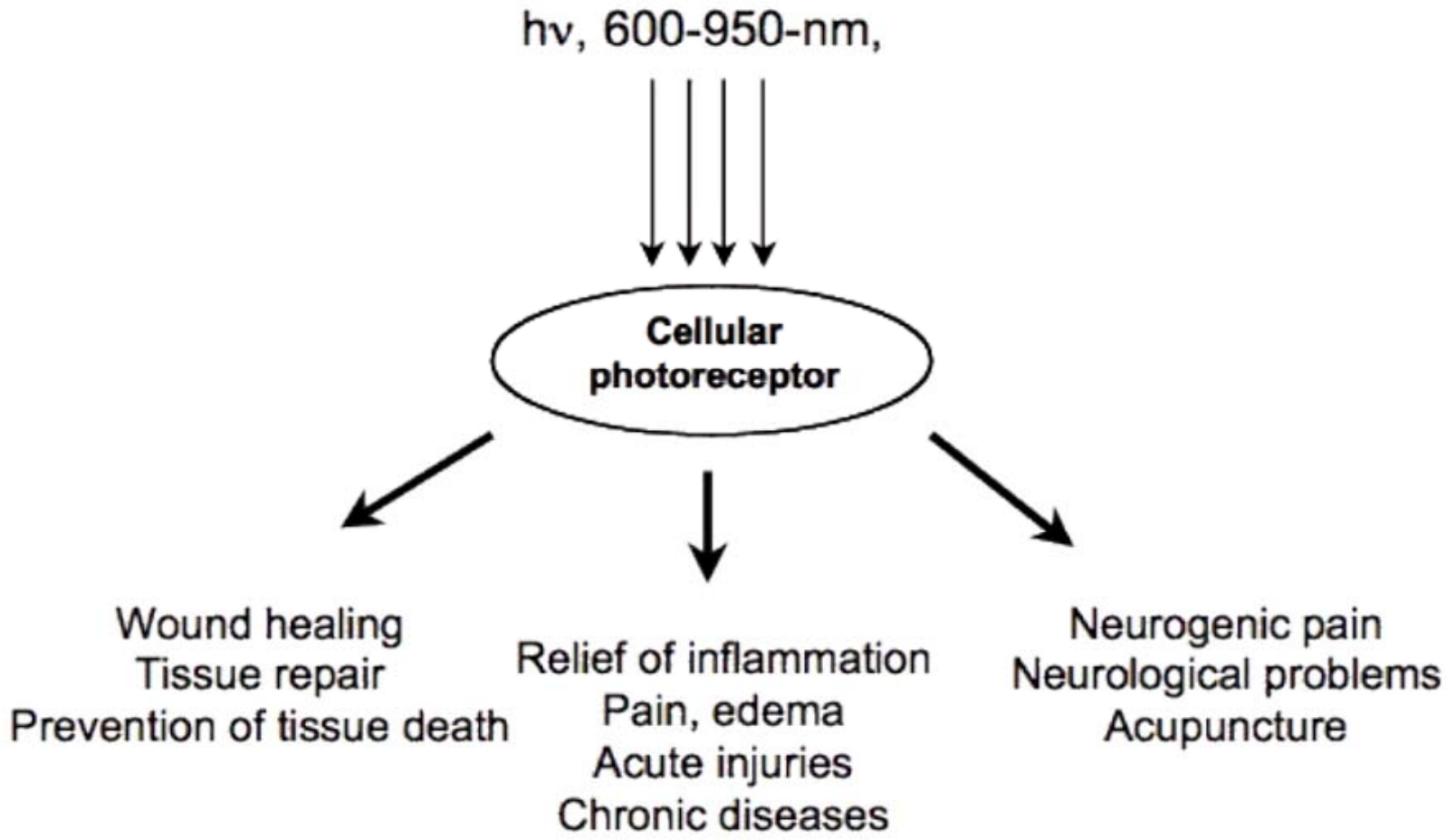
What Does It Do?

- **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



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/cm^2)**
  - 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 cm^2
- **Various dosage ranges per site (1-9 J/cm^2)**

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 /cm_2

Indications

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

Contraindications

- **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 wave-lengths 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)