ΥΠΟΣΧΟΜΕΝΕΣ ΕΦΑΡΜΟΓΕΣ ΤΩΝ LASER ΣΤΗ ΘΕΡΑΠΕΙΑ ΤΟΥ ΚΑΡΚΙΝΟΥ

Καρελιώτης Γ., Φυσικός Ιατρικής – Ακτινοφυσικός, Υ.Δ.

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24/11/2018

ΔΙΕΘΝΗΣ ΗΜΕΡΑ ΙΑΤΡΙΚΗΣ ΦΥΣΙΚΗΣ 2018

ΕΚΠΑΙΔΕΥΤΙΚΗ ΗΜΕΡΙΔΑ

Η ΧΡΗΣΗ ΤΩΝ LASERS ΣΤΗΝ ΙΑΤΡΙΚΗ. ΚΛΙΝΙΚΕΣ ΕΦΑΡΜΟΓΕΣ ΚΑΙ ΑΣΦΑΛΗΣ ΛΕΙΤΟΥΡΓΙΑ

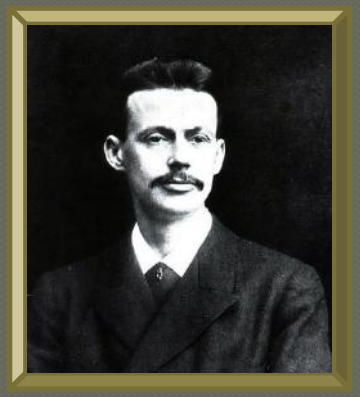
Ιατρική Φυσική και Καρκίνος

Φως και επιστήμες υγείας

Arthur Ashkin, Gérard Mourou and Donna Strickland

Βραβείο Νόμπελ
Φυσικής
2018

For the optical tweezers and their application to biological systems and for their method of generating high-intensity, ultra-short optical pulses".



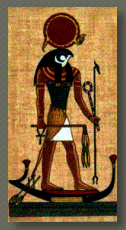
Niels Ryberg Finsen

Βραβείο Νόμπελ
Φυσιολογίας & Ιατρικής
1903

In recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science

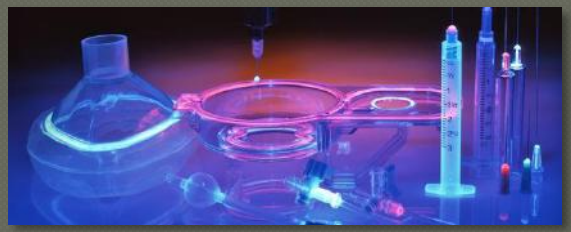
Φως και κλινική πράξη

Το φως χρησιμοποιείται στην ιατρική πράξη από την αρχαιότητα έως και σήμερα



1930. London's Institute of Ray Therapy. (FOX PHOTOS/GETTY IMAGES)

Στο μέλλον όμως;;



1 στους 4 θανάτους στον δυτικό κόσμο οφείλεται στον καρκίνο

Τα 4.500 ετών οστά άνδρα από τη Σιβηρία που πέθανε από καρκίνο [1]

Μούμια άνδρα 2.250 ετών που πέθανε από καρκίνο του προστάτη [2]

Φωτοθερμική Θεραπεία (PTT)

Laser-induced interstitial thermotherapy (LIIT)
Αξιοποιεί μη – ιοντίζουσα ακτινοβολία

$T \geq 43^{o}C$
$\Delta t \geq 60$ min

Θάνατος εντός 48 h [3]

$P \approx 12$ W
$\Delta t \approx 2 – 8$ min [3]

Ενέργεια φωτονίων

↓

Θερμότητα

↓

Θερμική καταστροφή του όγκου – στόχου

Συνδυασμός με MRI
(MR Thermometry)

↓

3D real – time χωρική κατανομή της θερμότητας [4]

Φωτοθερμική Θεραπεία (LIIT)

1971
Προτείνεται για 1η φορά η χρήση υπερθερμίας σε ενδοκρανιακούς όγκους [5]

Μελέτες για εφαρμογή σε:

Θυρεοειδή [8]
Μαστό [9]
Ήπαρ [10]

Γλοιώματα ακτίνας > 1,4 cm [6]

Κίνδυνος οιδήματος

Για T > 50° C έχουμε αλλαγές των οπτικών ιδιοτήτων [7]

Υπολογισμός χρόνου ακτινοβόλησης:

$$\Delta t = A \cdot \exp\left[\frac{E}{R}(T + 273)\right]^4$$

Φωτοδυναμική Θεραπεία (PDT)

Μέθοδος αντιμετώπισης περιπτώσεων κακοήθειας (κυρίως)

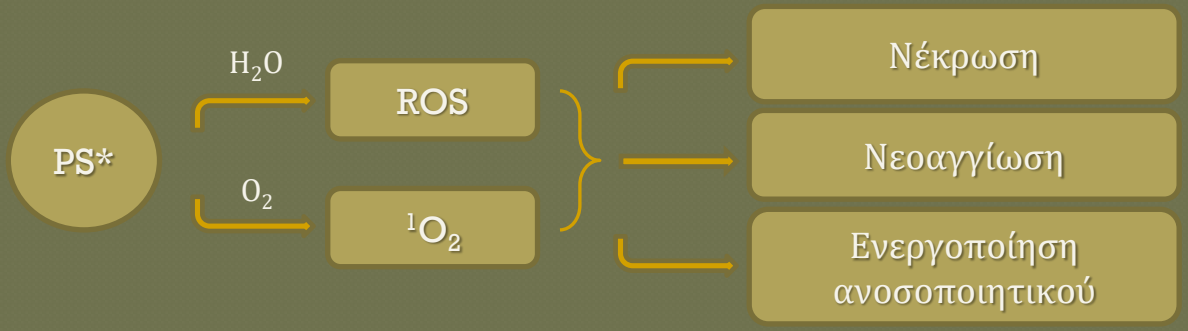
Αξιοποιεί μη – ιοντίζουσα ακτινοβολία

3 βασικά στοιχεία

Φωτοευαισθητοποιός ουσία

Οξυγόνο

Φως (laser)



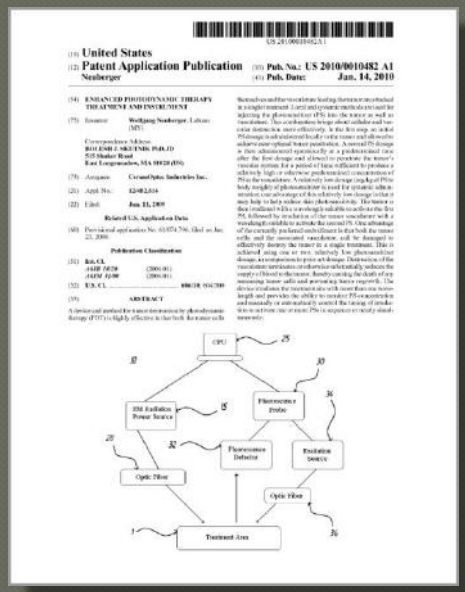
Φωτοδυναμική Θεραπεία (PDT)

1907

- Hermann von Tappeiner εισάγει τον όρο «Φωτοδυναμική θεραπεία» [11]

Ήδη από το 1978 η PDT χρησιμοποιείται πειραματικώς για δερματικούς καρκίνους με laser χρωστικών [12]

Μόλις το 1996 δίνεται έγκριση της FDA για χρήση της PDT στις Η.Π.Α.



Σήμερα εφαρμόζεται **με έγκριση**[13] στον καρκίνο:

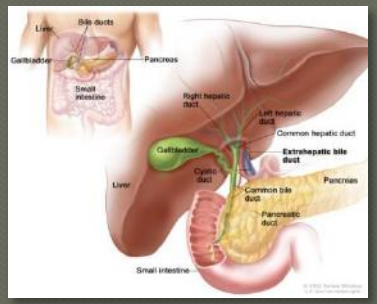
- του δέρματος *(παγκοσμίως)*
- της κεφαλής και του τραχήλου *(Ευρώπη)*
- του πνεύμονα *(Ιαπωνία)*
- του χοληφόρου πόρου *(**orphan status in EU/USA**)*

Φωτοδυναμική Θεραπεία
Καρκίνος του χοληφόρου πόρου

Συνήθως έχει ταχύ ρυθμό εξάπλωσης, επιβίωση 4 – 6 μήνες και επιλέγονται παρηγορητικές θεραπείες & τοποθέτηση stents

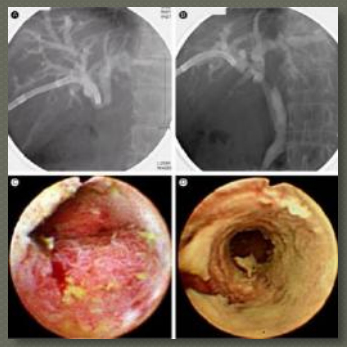
PDT

Επιβίωση 3 – 18,6 μήνες [14]

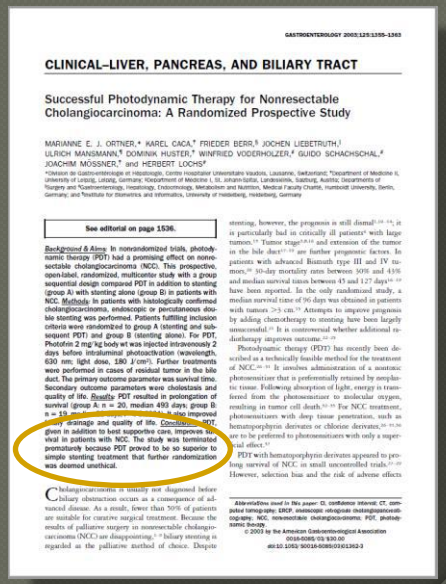


Ανατομία του εξωηπατικού χοληφόρου πόρου (**NCBI - NIH**)

Κλινική μελέτη που τερματίστηκε νωρίτερα λόγω πολύ μεγάλης αποτελεσματικότητας της PDT…



Καρκίνος χοληφόρου πόρου πριν (αριστερά) και 4 μήνες μετά την **PDT** (δεξιά) [14]



GASTROENTEROLOGY 2003;125:1355–1363

CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Successful Photodynamic Therapy for Nonresectable Cholangiocarcinoma: A Randomized Prospective Study

MARIANNE E. J. ORTNER,* KAREL CACA,‡ FRIEDER BERR,§ JOCHEN LIEBETRUTH,‖ ULRICH MANSMANN,¶ DOMINIK HUSTER,# WINFRIED VODERHOLZER,** GUIDO SCHACHSCHAL,** JOACHIM MÖSSNER,‡ and HERBERT LOCHS*

See editorial on page 1536.

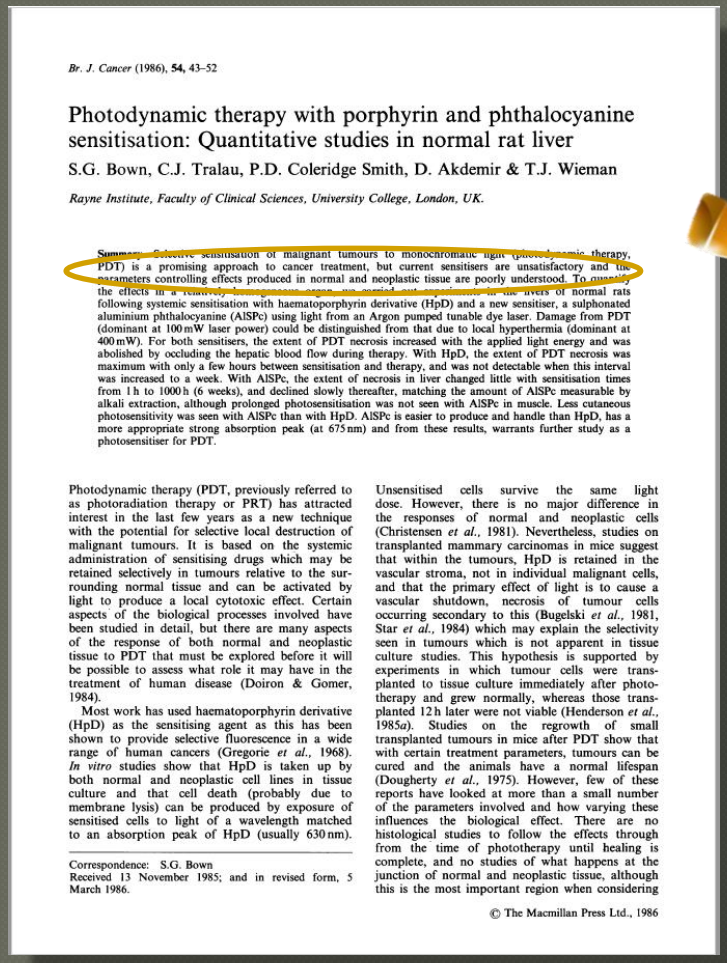
Background & Aims: In nonrandomized trials, photodynamic therapy (PDT) had a promising effect on nonresectable cholangiocarcinoma (NCC). This prospective, open-label, randomized, multicenter study with a group sequential design compared PDT in addition to stenting (group A) with stenting alone (group B) in patients with NCC. **Methods:** In patients with histologically confirmed cholangiocarcinoma, endoscopic or percutaneous double stenting was performed. Patients fulfilling inclusion criteria were randomized to group A (stenting and subsequent PDT) and group B (stenting alone). For PDT, Photofrin 2 mg/kg body wt was injected intravenously 2 days before intraluminal photoactivation (wavelength, 630 nm; light dose, 180 J/cm²). Further treatments were performed in cases of residual tumor in the bile duct. The primary outcome parameter was survival time. Secondary outcome parameters were cholestasis and quality of life. **Results:** PDT resulted in prolongation of survival (group A: n = 20, median 493 days; group B: n = 15, [illegible]) and also improved [illegible] drainage and quality of life. **Conclusions:** PDT, given in addition to best supportive care, improves survival in patients with NCC. The study was terminated prematurely because PDT proved to be so superior to simple stenting treatment that further randomization was deemed unethical.

Cholangiocarcinoma is usually not diagnosed before biliary obstruction occurs as a consequence of advanced disease. As a result, fewer than 50% of patients are suitable for curative surgical treatment. Because the results of palliative surgery in nonresectable cholangiocarcinoma (NCC) are disappointing,[1–3] biliary stenting is regarded as the palliative method of choice. Despite stenting, however, the prognosis is still dismal[1,10–14]; it is particularly bad in critically ill patients[4] with large tumors.[15] Tumor stage[5,6,16] and extension of the tumor in the bile duct[17–22] are further prognostic factors. In patients with advanced Bismuth type III and IV tumors,[20] 30-day mortality rates between 50% and 63% and median survival times between 45 and 127 days[10–12] have been reported. In the only randomized study, a median survival time of 96 days was obtained in patients with tumors >3 cm.[23] Attempts to improve prognosis by adding chemotherapy to stenting have been largely unsuccessful.[24] It is controversial whether additional radiotherapy improves outcome.[25–29]

Photodynamic therapy (PDT) has recently been described as a technically feasible method for the treatment of NCC.[30–33] It involves administration of a nontoxic photosensitizer that is preferentially retained by neoplastic tissue. Following absorption of light, energy is transferred from the photosensitizer to molecular oxygen, resulting in tumor cell death.[34–35] For NCC treatment, photosensitizers with deep tissue penetration, such as hematoporphyrin derivates or chlorine derivates,[36–37] are to be preferred to photosensitizers with only a superficial effect.[38]

PDT with hematoporphyrin derivates appeared to prolong survival of NCC in small uncontrolled trials.[31–33] However, selection bias and the risk of adverse effects

Φωτοδυναμική Θεραπεία Καρκίνος του ήπατος



Br. J. Cancer (1986), **54**, 43–52

Photodynamic therapy with porphyrin and phthalocyanine sensitisation: Quantitative studies in normal rat liver

S.G. Bown, C.J. Tralau, P.D. Coleridge Smith, D. Akdemir & T.J. Wieman

Rayne Institute, Faculty of Clinical Sciences, University College, London, UK.

Summary Selective sensitisation of malignant tumours to monochromatic light (photodynamic therapy, PDT) is a promising approach to cancer treatment, but current sensitisers are unsatisfactory and the parameters controlling effects produced in normal and neoplastic tissue are poorly understood. To quantify the effects in a relatively homogeneous organ, we carried out experiments in the livers of normal rats following systemic sensitisation with haematoporphyrin derivative (HpD) and a new sensitiser, a sulphonated aluminium phthalocyanine (AlSPc) using light from an Argon pumped tunable dye laser. Damage from PDT (dominant at 100 mW laser power) could be distinguished from that due to local hyperthermia (dominant at 400 mW). For both sensitisers, the extent of PDT necrosis increased with the applied light energy and was abolished by occluding the hepatic blood flow during therapy. With HpD, the extent of PDT necrosis was maximum with only a few hours between sensitisation and therapy, and was not detectable when this interval was increased to a week. With AlSPc, the extent of necrosis in liver changed little with sensitisation times from 1 h to 1000 h (6 weeks), and declined slowly thereafter, matching the amount of AlSPc measurable by alkali extraction, although prolonged photosensitisation was not seen with AlSPc in muscle. Less cutaneous photosensitivity was seen with AlSPc than with HpD. AlSPc is easier to produce and handle than HpD, has a more appropriate strong absorption peak (at 675 nm) and from these results, warrants further study as a photosensitiser for PDT.

Photodynamic therapy (PDT, previously referred to as photoradiation therapy or PRT) has attracted interest in the last few years as a new technique with the potential for selective local destruction of malignant tumours. It is based on the systemic administration of sensitising drugs which may be retained selectively in tumours relative to the surrounding normal tissue and can be activated by light to produce a local cytotoxic effect. Certain aspects of the biological processes involved have been studied in detail, but there are many aspects of the response of both normal and neoplastic tissue to PDT that must be explored before it will be possible to assess what role it may have in the treatment of human disease (Doiron & Gomer, 1984).

Most work has used haematoporphyrin derivative (HpD) as the sensitising agent as this has been shown to provide selective fluorescence in a wide range of human cancers (Gregorie *et al.*, 1968). *In vitro* studies show that HpD is taken up by both normal and neoplastic cell lines in tissue culture and that cell death (probably due to membrane lysis) can be produced by exposure of sensitised cells to light of a wavelength matched to an absorption peak of HpD (usually 630 nm). Unsensitised cells survive the same light dose. However, there is no major difference in the responses of normal and neoplastic cells (Christensen *et al.*, 1981). Nevertheless, studies on transplanted mammary carcinomas in mice suggest that within the tumours, HpD is retained in the vascular stroma, not in individual malignant cells, and that the primary effect of light is to cause a vascular shutdown, necrosis of tumour cells occurring secondary to this (Bugelski *et al.*, 1981, Star *et al.*, 1984) which may explain the selectivity seen in tumours which is not apparent in tissue culture studies. This hypothesis is supported by experiments in which tumour cells were transplanted to tissue culture immediately after phototherapy and grew normally, whereas those transplanted 12 h later were not viable (Henderson *et al.*, 1985*a*). Studies on the regrowth of small transplanted tumours in mice after PDT show that with certain treatment parameters, tumours can be cured and the animals have a normal lifespan (Dougherty *et al.*, 1975). However, few of these reports have looked at more than a small number of the parameters involved and how varying these influences the biological effect. There are no histological studies to follow the effects through from the time of phototherapy until healing is complete, and no studies of what happens at the junction of normal and neoplastic tissue, although this is the most important region when considering

Correspondence: S.G. Bown
Received 13 November 1985; and in revised form, 5 March 1986.

Από το 1986 μελετάται η χρησιμότητα της PDT σε ηπατικούς όγκους αρουραίων [15]

Η αποτελεσματικότητα περιοριζόταν από τις φωτοευαίσθητες ουσίες και την έλλειψη γνώσης των παραμέτρων τους

Από το 1999 φαίνεται η αποτελεσματικότητα της PDT σε ηπατικούς όγκους [16]

Πλήρης ύφεση του όγκου στο 87% των πειραματόζωων

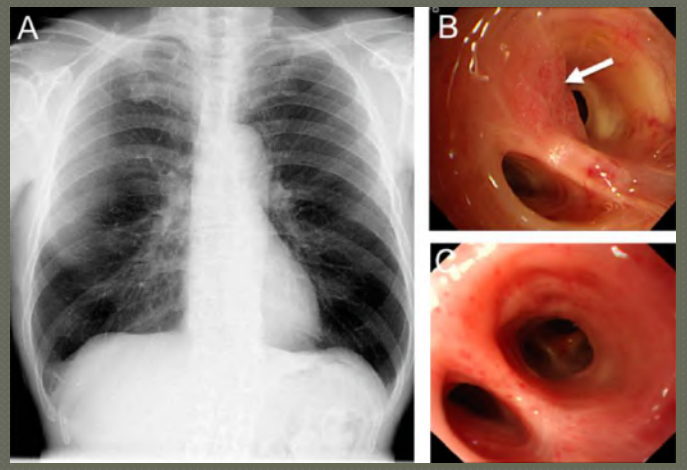
Φωτοδυναμική Θεραπεία
Καρκίνος του πνεύμονα

Μελετάται από το 1984 [17,18]

Συνήθως με χρήση Photofrin
(Φωτοευαισθητοποιητής 1ης γενιάς)

Talaporfin Sodium (TS)
(Φωτοευαισθητοποιητής 2ης γενιάς)

Διεγείρει την αντίδραση του ανοσοποιητικού συστήματος



PDT σε καρκίνο του πνεύμονα. 6 μήνες μετά πλήρης υποχώρηση του όγκου [19].

MV 6401
(Φωτοευαισθητοποιητής 2ης γενιάς)

Επιδρά στη νεοαγγείωση

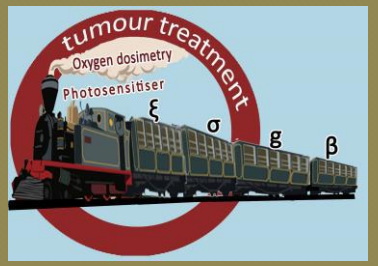
Πού έγκειται η δυσκολία;

Symbol	Definition
β (μM)	Oxygen quenching threshold concentration $\frac{k_4+k_8[A]}{k_2}$
δ (μM)	Low concentration correction
η (cm^2 mW^{-1} s^{-1} μM)	Hypoxic reaction consumption rate $\Phi_t\frac{\varepsilon}{h\nu}\frac{k_8[A]}{k_2}$
ξ (cm^2 mW^{-1} s^{-1})	Specific oxygen consumption rate $\xi = \xi_{II} + \xi_I = S_\Delta\Phi_t\frac{\varepsilon}{h\nu} + S_I\Phi_t\frac{\varepsilon}{h\nu}$
σ (μM^{-1})	Specific photobleaching ratio $\sigma = (\xi_{II}\sigma_{II} + \xi_I\sigma_I)/\xi$ where $\sigma_{II} = k_{12}\tau_\Delta$ and $\sigma_I = k_{11}\tau_s$
g (μM s^{-1})	Macroscopic maximum oxygen supply rate
ε (cm^{-1} μM^{-1})	Photosensitizer extinction coefficient
τ_f (s)	Fluorescence lifetime $\frac{1}{k_3+k_5}$
τ_Δ (s)	Singlet oxygen lifetime $\frac{1}{k_{12}([S_0]+\delta)+k_6+k_{72}[A]}$
τ_s (s)	Superoxide (ROS) lifetime $\frac{1}{k_{11}([S_0]+\delta)+k_{71}[A]}$
τ_t (s)	Triplet state lifetime $\frac{1}{k_4+k_2[^3O_2]+k_8[A]}$
$[A]$ (μM)	Singlet oxygen receptors, considered a constant during PDT because it is too large to be changed during PDT.
S_Δ	Fraction of triplet-state photosensitizer-$^3O_2$ reactions to produce $^1O_2$
S_I	Fraction of triplet-state photosensitizer reactions involved in Type I reactions
S_{NL}	Fraction of triplet state photosensitizer reactions that are non-luminescent $S_\Delta + S_I + S_{NL} = 1$
Φ_Δ	Singlet oxygen quantum yield $S_\Delta\frac{k_5}{k_3+k_5}$
Φ_{ROS}	Superoxide anion quantum yield $S_I\frac{k_5}{k_3+k_5}$
Φ_f	Fluorescence quantum yield $\frac{k_5}{k_3+k_5}\frac{k_{3R}}{k_3}$, where k_{3R} is fluorescence radiative decay rate between S_1 and S_0
Φ_t	Triplet quantum yield $\frac{k_5}{k_3+k_5}$

Κύριες παράμετροι στη PDT [20].

Μεγάλο πλήθος παραμέτρων που πρέπει να ληφθούν υπόψη

Ιδιαιτέρως πολύπλοκη η εξατομικευμένη δοσιμετρία [21]

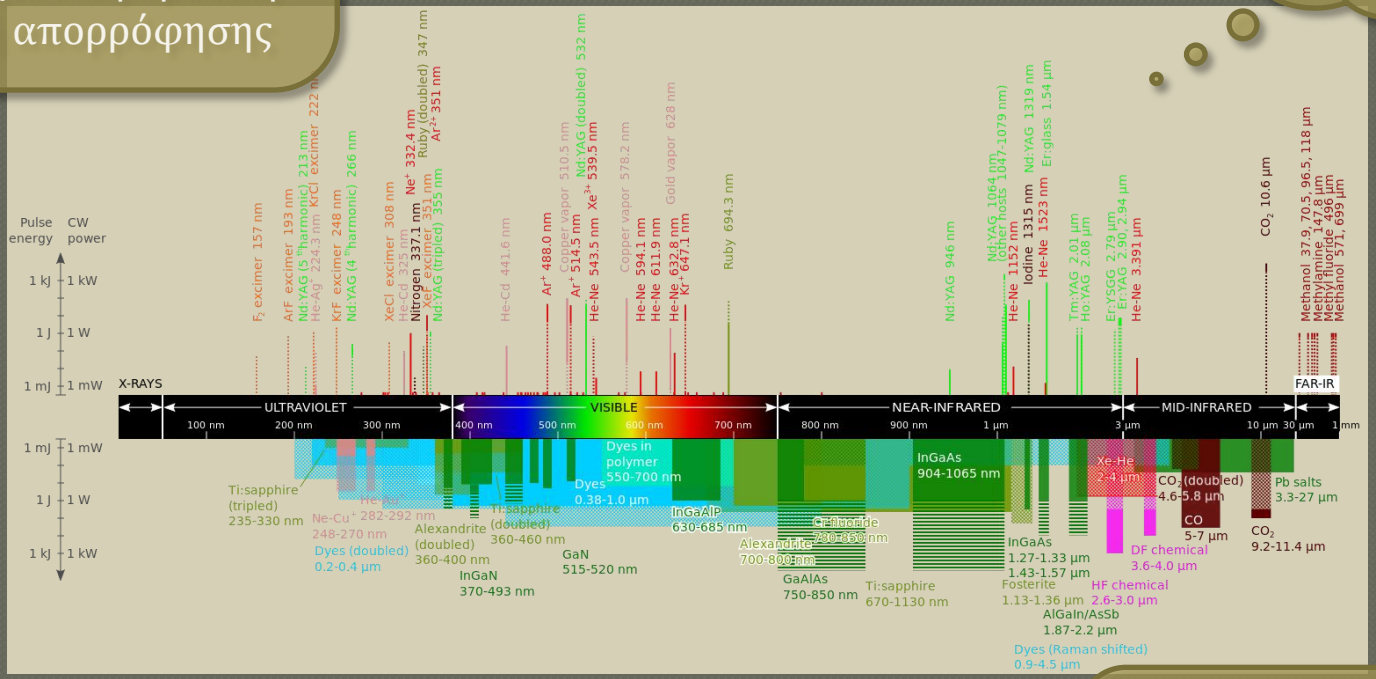


Μόνο 4 φωτοευαισθητοποιητές έχουν πάρει έγκριση και FDA και EMA [13]

Πού έγκειται η δυσκολία;

Κάθε φωτοευαίσθητη ουσία έχει διαφορετική κορυφή απορρόφησης

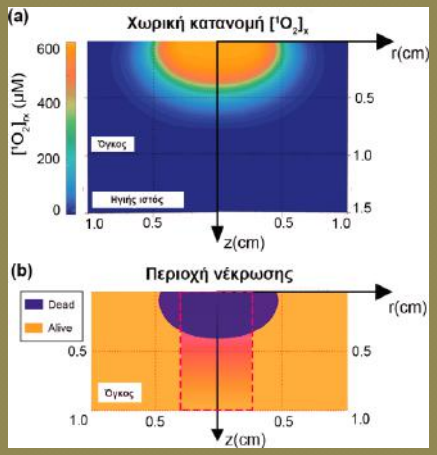
~ 70….



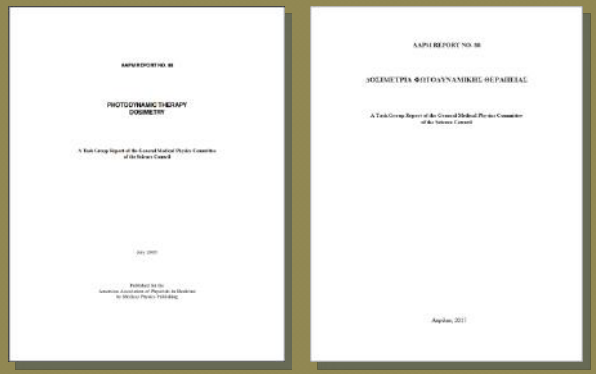
Μεγάλη ποικιλία laser (με βάση το λ τους)

Πού έγκειται η δυσκολία;

Επενεργούμε μόνο όπου ακτινοβολούμε;



Σε αντίθεση με τις θεραπείες με ιοντίζουσα ακτινοβολία δεν υπάρχουν ευρέως αποδεκτά και πλήρη πρωτόκολλα



Συνδυαστικές θεραπείες

Η χρήση νανοδομών ενισχύει σημαντικά το αποτέλεσμα της PTT και της PDT [22, 23,24]

Πρόσφατες μελέτες για τη συνεργατική δράση νανοδομών – PTT – PDT [23, 25]

Μελέτες

- PTT + ακτινοθεραπεία [26]
- PDT + ακτινοθεραπεία [27]
- PDT + πυρηνική ιατρική [28]
- ….

Νανοδομές με κορυφή απορρόφησης στο NIR → Αυξημένο βάθος διείσδυσης στους ιστούς

Remember

Logic will get you from A to B. Imagination will take you everywhere…

Albert Einstein

Αναφορές

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Ευχαριστώ για την προσοχή σας !

Ερωτήσεις