# A New Non-coherent Light Source for Photodynamic Treatment of Cancer

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Since the coherence of laser light is not necessary for photodynamic treatment of superficial tumors, attempts have been made to construct a non-coherent light source able to deliver radiation of five different wavelengths for different photosensitisers: 522 nm, 630 nm, 650 nm, 670 nm, 690 nm, with power around 130 mW.
The biological effectiveness was proved by comparison with the radiation of a first-generation light source and its effect on tumor growth. Mice tumor (A22 hepatoma) was used as an experimental model. The results clearly showed that tumor growth inhibition under the same experimental conditions could be enhanced about 4 times, in comparison with a first-generation non-coherent light source.

**Key words:** photodynamic therapy (PDT), photosensitizer, $TPPS_4$, A22 hepatoma

## INTRODUCTION

Photodynamic therapy (PDT) has been designated as a promising new modality in the treatment of cancer since the early 1980s. This can be partly attributed to the very attractive basic concept of PDT – a combination of two therapeutic agents – a photosensitizing drug and light, which are both absolutely not toxic, but combined in the presence of oxygen ultimately cause more or less selective tumor destruction.

The clinical areas for which PDT has been predominantly used are superficial bladder cancer, lung cancer and cancer of skin and upper aerodigestive tract. To date, this therapy has been approved in Canada for prevention of recurrence of papillary bladder cancer and for reduction of obstruction and palliation of dysphagia in patients with completely or partially obstructing oesophageal cancer. In the Netherlands it has been approved for the treatment of early lung and oesophageal cancer as well for palliation in obstructive lung cancer and in Japan for early stage lung, gastric and cervical cancer (also in cervical dysplasia) and superficial oesophageal and gastric cancer (1).

Nevertheless, PDT has not yet been widely accepted by practicing oncologists because of certain problems. Photofrin – the mostly common first generation photosensitizer induces prolonged skin photosensitivity, and its absorption in red region of visible light (630 nm) where the tissue penetration of light is better is rather low. This induced the development of second generation sensitizers (more than 20), which absorbed light at far red much better, accumulated in tumor tissue more selectively and established a significantly less skin photosensitivity.

The other problem in PDT is light sources, mostly lasers, which are very expensive, large, and their use and maintenance necessitate the presence of a skilled technician. Thus, alternative non-coherent light sources have been developed. Moreover, in the treatment of superficial rather large skin lesions, non-coherent light devices are superior to laser systems (2). Especially in early clinical studies, incandescent lamp or slide projections were used. Recently, professional non-coherent light devices have been developed (3). The point is that new photosensitizers requiring light of different wavelength for excitation keep appearing in the world. Moreover, a new understanding of the use of different photosensitizers for different purposes is coming. It means that one light source with one fixed wavelength in laboratory for PDT treatment soon will not satisfy the clinicians.

To solve this problem in an optimal way (low price, multifunctionality), a second generation non-coherent light source suitable for treating cutaneous and subcutaneous tumors by different photosensitizers was constructed. Due to development of new technologies it can deliver radiation of 5 different wavelengths for different photosensitizers: 522 nm, 630 nm, 650 nm, 670 nm, 690 nm. As is mentioned above, incoherent light sources constructed before in different laboratories due to a broad spectral width of produced radiation were inefficient. A progress in the technology of optical filter coatings allowed to design and construct table-top incoherent light sources producing collimated narrow band light beams. For evaluation of the efficiency of new technique. A-22 hepatoma growth inhibition was measured, using one of the accepted photosensitizers – mesotetra(para-sulfo phenyl) porphyrin ($TPPS_4$).

## MATERIALS AND METHODS

**Light source.** As a primary light source a 400 W power incandescent lamp was used. The emitted light was collimated with the help of short focal length lens and subsequently twice reflected from dielectric narrow band optical mirrors having the bandwidth of about 50 nm. The central wavelength of the reflected light could be chosen by simply rotating the handle and therefore inserting proper optical elements into the optical path. The additional lens was used for focusing the beam into the spot of a desirable diameter (5–20 mm). Additional colour glass filters were used to cut out the radiation with the wavelengths far from the selected wavelength region, as dielectric filters have additional reflection peaks in other spectral regions.

The source had two outputs: one delivering the radiation with a fixed central wavelength of 630 nm, and the second one delivering radiation with 5 changeable central wavelengths: 522, 630, 650, 670, and 690 nm. The radiation in each spectral region had the bandwidth of about 45 nm (for the examples, see Fig. 1).

The power of the produced radiation in each case exceeded 120 mW (see Table 1), and the intensity of light in the focus (assuming the diameter of the spot as 10 mm) always exceeded 90 mW/cm$^2$.

This light source is also capable of delivering light via flexible lightguides or fiber bundles, although in this case the power of delivered light is lower.

Flatness of the irradiation field is very important for PDT. Therefore we performed an irradiance measurement as a function of the position in the focused beam for all spectral regions used. Typical spatial intensity distribution in the focal plane of the focusing lens is presented in Fig. 2. The system utilized ambient air for cooling and in such a way overcame many of the problems associated with the laser systems requiring dedicated rooms for use.

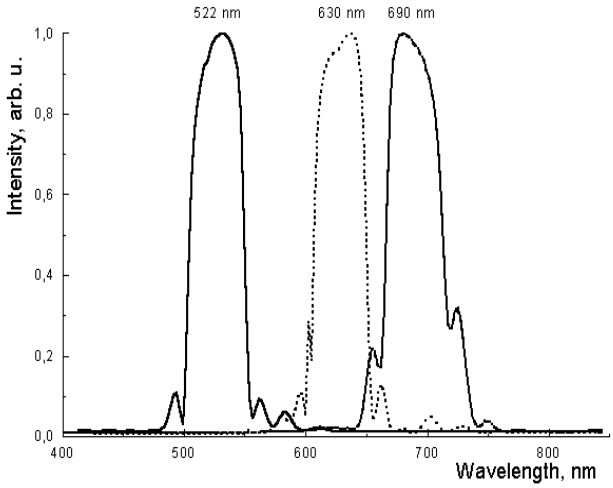


Fig. 1. Spectra of produced light with the central wavelength of 520, 630 and 690 mm

Table 1. **Paramerers of produced radiation**

| Central wavelength, nm | Bandwidth, nm | Power, mW | Suitable photo-sensitizers |
|---|---|---|---|
| 520 | 45 | 122 | |
| 630 | 45 | 128 | ALA, HPD |
| 650 | 45 | 135 | m-THPC |
| 670 | 45 | 135 | chlorins |
| 690 | 45 | 138 | BPD |

**Chemicals and photosensitizers.** Meso-tetra (para-sulfo phenyl) porphyrin ($TPPS_4$) was used as a photosensitizer and was prepared in sterile physiological saline (0.9% NaCl) (2.5 x $10^{-3}$ M). The solution was sterilized and stored below 10 °C in the dark.

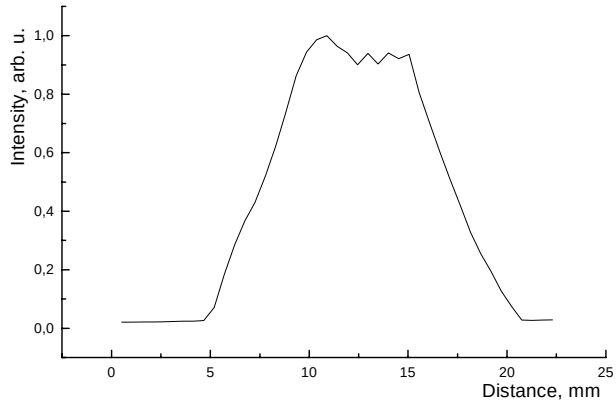


Fig. 2. Intensity distribution in the focal plane of focusing lens

**Tumors and animals.** A22 hepatoma transplanted into CBAxC$_{57}$ black mice was used as a tumor model in all experiments.

**Experimental design.** Homogenized A22 hepatoma cells were inoculated subcutaneously to healthy mice. Tumors were used for the experiments on the 7th day when they grew to a volume of about 200 mm$^3$. Tumor-bearing mice were injected i.p. with 20 mg/kg body weight TPPS$_4$. The tumor was irradiated with light source (photodynamic treatment) 24 h after TPPS$_4$ i. p. injection. To determine tumor responces, tumor volumes were measured 10 days after each treatment. The animals were under general anesthesia (ketamine hydrochloride, i.p.) during all experiments.

**A22 hepatoma tumor growth determination.** Relative tumor growth was measured every day by compasses up to the 10th day of its growth according to the equation:

$V = 1/2 / 4\pi/3 \times l/2 \times w/2 \times h$, where V is the volume of tumor, l is the length, w is the width, and h is the height of tumor.

**Pathohistological examination.** The tumor tissue was fixed in 10% formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin.

**Statistical evaluations.** In every experimental group at least 8 mice were used. Every experimental point is an average of 3 experiments. Standard errors were calculated for significance of data using the Excel programme.

## RESULTS

Figure 3 shows comparative mice A22 hepatoma tumor growth inhibition when first generation (■) (500 W lamp, 30 mW/cm$^2$ outcome) and second generation non-coherent light sources (▲) (400 W lamp, 90 mW/cm$^2$ outcome) were used for TPPS$_4$-based PDT treatment. Due to advanced technology, a second generation non-coherent light source (irradiation time 75 min in both cases) is able to increase tumor growth inhibition by up to 86%, whereas first generation non-coherent light source only by 40%.

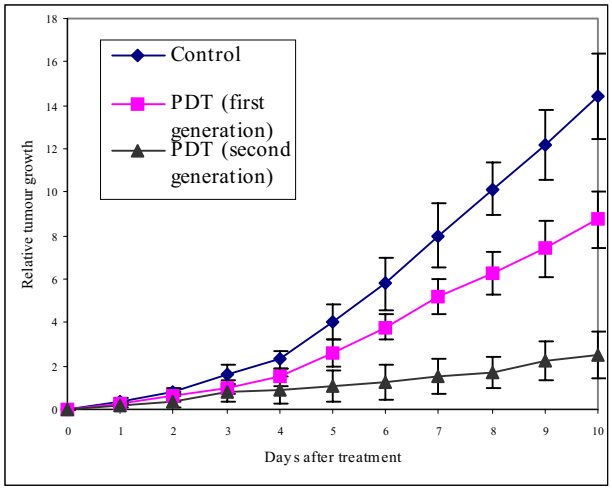


Fig. 3. A22 hepatoma tumor growth inhibition as a function of time after treatment with different light sources

Figures 4 and 5 show a histological picture of A22 hepatoma treated with TPPS$_4$ – PDT using new light source. It is possible that TPPS$_4$-based PDT is damaging first of all (as a hydrophilic photosensitizer) the vasculature of a tumor. Presumably, secondary tumor necrosis was observed 24 h after treatment. No significant tumor growth was detected 10 days after irradiation.

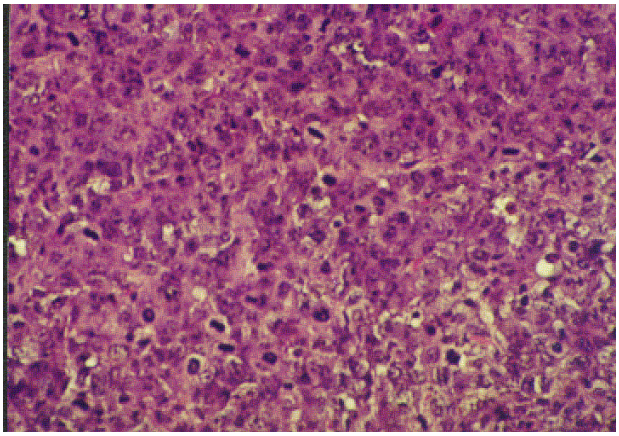

Fig. 4. Normal growing transplantable hepatoma without any changes in blood vessels, hematoxylin–eosin, 10 × 20

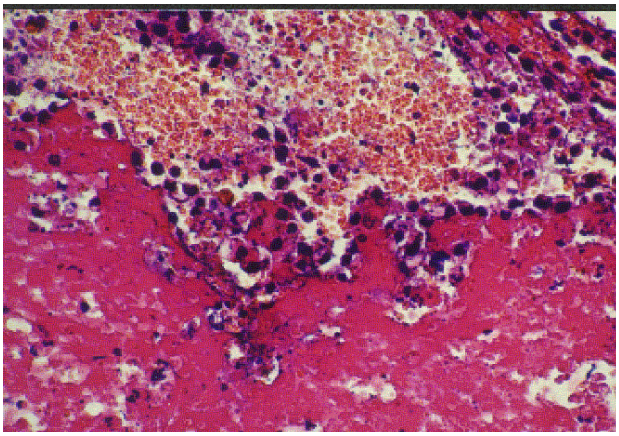

Fig. 5. A-22 hepatoma 24 h after treatment with new non-coherent light source. Almost total necrosis, wide hematomas, hematoxylin–eosin, 10 × 20

## DISCUSSION

Since coherence of laser light is not necessary for PDT in most cases, attempts have been made to

construct a non-coherent light source more reliable, simpler and cheaper than lasers. The only disadvantage of non-coherent light sources and the only problem that remains to be solved is the light intensity level which is lower than that of lasers. Current non-coherent lamps are able to deliver 50 mW/cm$^2$, whereas laser systems reach 150–200 mW/cm$^2$ (5). Our previous light source delivered 30 mW/cm$^2$ and was an excellent tool for irradiation of cell cultures, but not tumors. A recent development is a light source based on a 400 W power incandescent lamp. It is well known that increasing the light power decreases the irradiation time. But, on the other hand, the irradiation dose above 200 J/cm$^2$ initiates hyperthermia processes which significantly complicate the light dosimetry (6).

In conclusion, the modern non-coherent light sources (90 W/cm$^2$ power) for PDT are a viable and cost-effective alternative to laser systems or first generation lamp light sources. Such sources are about two times less expensive in comparison with laser light sources, stable and easy to operate, requiring very little maintenance. As long as they can easily produce radiation in the entire visible and near-infrared spectral regions, the user can select the wavelength and waveband optimally suited his purposes. So, it offers the user the benefits of wavelength and waveband selection, whereas most laser systems are wavelength/waveband specific.

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**NAUJAS NEKOHERENTINĖS ŠVIESOS ŠALTINIS FOTODINAMINIAM VĖŽIUI GYDYTI**

S a n t r a u k a

Sukurtas nekoherentinės šviesos šaltinis fotodinaminės navikų terapijos (FNT) pagalba gydyti paviršinius ir odos navikus. Šviesos šaltinis pritaikytas dirbti su įvairiais fotosensibilizatoriais, nes spinduliuoja 5 skirtingus bangos ilgius: 522 nm, 630 nm, 650 nm, 670 nm, 690 nm. Spindulio galia siekia 130 mW. Aparato efektyvumas buvo įvertintas lyginant jį su pirmos kartos nekoherentinės šviesos šaltiniu. Eksperimentai parodė, kad A22 hepatomos augimo inhibicija po FNT 4 kartus didesnė dirbant su antros kartos šviesos šaltiniu.

**Raktažodžiai**: fotodinaminė terapija, fotosensibilizatorius, FNT4, A22 hepatoma