Modeling of Laser Activated Light Emitting Silica Nanorods for the Photodynamic Therapy of Cancer

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Photodynamic therapy (PDT) through Light Emitting Silica Nanorods (LESN) is a new approach of killing cancer cells. The photodynamic therapy (PDT) uses a drug that makes cancer cells sensitive to light (a photosensitizing drug), combined with a laser light. Photosensitizing drugs are injected into the bloodstream and absorbed by the cells throughout the body. And the photosensitizing drug is absorbed by both healthy and cancer cells whereas the healthy cells are more efficient at eliminating the drug. Light emitting Silica Nanorods (LESN) serve to absorb light from a light source and re-emit light at different wavelengths activating nearby photodynamic drug, thus treating the cancer cells in any site where the photodynamic drug and silicon nanorods are located and where light from a light source can activate the light emitting silicon nanorods. Targeting of silicon nanorods was enhanced through the attachment of an antibody that was bonded to specific blood vessels within a cancer cells. Photodynamic and light emitting silicon nanorods were covalently linked and attached to a polymeric backbone. Optical fiber composed of a biocompatible matrix with incorporated nanorods accompanied with an external laser source providing light to the fiber was utilized. The total internal reflection (TIR) lens was incorporated into the sheath. The total internal reflection (TIR) lens served to capture light emitted by silicon nanorods that would otherwise illuminate healthy tissues and to direct it to cancer cells. In this paper, optical fibers study is proposed by using COMSOL Multiphysics 4.2a.

Keywords
Therapy; Silica Nanorods; LESN

Introduction
The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person’s life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells.
Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues are what makes a cell a cancer cell. Cells become cancer cells because of damage to DNA. DNA is in every cell and directs all its actions. In a normal cell, when DNA gets damaged the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, but the cell doesn't die like it should. Instead, this cell goes on making new cells that the body does not need. These new cells will all have the same damaged DNA as the first cell does. Sometimes the cause of the DNA damage is something obvious, like cigarette smoking. But often no clear cause is found. In most cases the cancer cells form a tumor. Some cancers, like leukemia, rarely form tumors. Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular kind of cancer. Not all tumors are cancerous [1]. Tumors that aren't cancer are called benign. Benign tumors can cause problems – they can grow very large and press on healthy organs and tissues. But they cannot grow into (invade) other tissues. Because they can't invade, they also can't spread to other parts of the body (metastasize). These tumors are almost never life threatening.

Cell Cycle

Normal cells grow and divide in an orderly fashion, in accordance with the cell cycle. (Mutations in proto-ontogenesis or in tumor suppressor genes allow a cancerous cell to grow and divide without the normal controls imposed by the cell cycle.) The major events in the cell cycle are described in below Figure 1.

Profile of a Cancer Cell

Even though every cancer is different, there’s a shared set of behaviors that characterizes all cancer cells by the possibilities of uncontrolled growth, Lack of response to stop signals, Immortality, Ability to divide infinitely, Recruiting a food supply and Random migration.

Radiation Therapy for Cancer

Radiation therapy uses high-energy x-rays to kill cancer cells or shrink tumors. For cancer that has not spread too far, radiation therapy can sometimes cure the cancer, either by itself or along with other treatments. In advanced cancer, radiation therapy is often used to shrink tumors to reduce pain or other symptoms. This is called palliative radiation. There are different types of radiation therapies like External beam radiation therapy, internal radiation therapy (brachytherapy) and Radiopharmaceuticals.
Radiation Therapy Side Effects

Radiation treatments are much like x-rays and are not painful. The most common side effects are skin irritation and severe tiredness (fatigue). Fatigue is especially common when treatments go on for several weeks. It’s a feeling of extreme tiredness and low energy, which often does not get better with rest. People also report fatigue caused by the daily trips to the hospital to get their radiation treatments. Many people work throughout the course of their radiation treatments, though it’s common for them to adjust their schedules or work fewer hours until they feel better [3]. Sometimes people are not able to keep working during treatment because of the extreme fatigue or other side effects.

Photodynamic Therapy

Photodynamic therapy (PDT) is a modality that may be used for local treatment of precancerous and cancerous tumors. PDT relies on the coexistence of a photosensitive compound (a photosensitizer), oxygen, and light. The photosensitizer is administered to the patient, where it accumulates selectively in the cancerous tissue [4]. Subsequent irradiation with non-ionizing radiation, such as laser light, causes a photochemical reaction to occur, which destructs the cancerous cells. The first clinical studies of PDT using hematoporphyrin derivative (HpD) took place during the 1960’s and the field has been expanding ever since. Today, PDT is approved for various clinical applications and commercial drugs and light sources are available. Some of the most important features of PDT are high selectivity, fast healing rates, and the ability to treat the same tissue several times, if necessary [5]. An important drawback is limited penetration of the therapeutic light. This disadvantage may be partly overcome by the development of photosensitizers, which are sensitive in the near-infrared wavelength range or by the use of interstitial PDT, where the therapeutic light is guided into the tumor using optical fibers. In this chapter, the basic mechanisms of PDT, and the parameters important for PDT are briefly discussed.

Mechanisms of Action

The therapeutic light, which must match an absorption band of the photosensitizer, excites the photosensitizer molecule from its singlet ground state to its first excited singlet state. From here the molecule may transfer to its first excited triplet state. Though this transition is spin forbidden, it has a relatively high probability of occurring due the small energy separation between the states. The final relaxation to the ground state is again spin forbidden, leading to a long life time (and 100 μs) and thus a high probability for interaction with the surrounding molecules. The excess energy of the photosensitizer may be transferred to oxygen molecules, which thereby are excited from their triplet ground state to one of the first excited singlet states, which are biologically active. Singlet oxygen is highly cytotoxic and its formation leads to degradation of the cancerous cells by various mechanisms. One of the advantages of PDT over other existing tumor treatment modalities, such as radiation therapy or cryo-therapy is that the photosensitizer accumulates selectively in the diseased tissue [6]. This means that irradiation of the healthy tissue occurs at low damage risk and that full treatment of precancerous or cancerous cells outside the visible tumor border can also be achieved. Other advantages count fast healing rates, modest scar formation, and the possibility for re-treatment several times if necessary. Finally, PDT is fairly uncomplicated to perform with few potential hazards involved. Pain is experienced in variable degree, but in general anaesthesia is not required. The generation of molecular oxygen in its excited single state is believed to be the primary cause of cell-damage in connection with PDT. This highly reactive oxygen species is generated by transfer of energy from the photosensitizer in its excited triplet state to molecular oxygen. In the transfer, the photosensitizer relaxes to its ground state from where it again is prone to excitation under the influence of the therapeutic light. In this way the cycle can be repeated. Singlet molecular oxygen reacts rapidly with various cellular components, such as unsaturated lipids, proteins, nucleic acids etc. The diffusion length of singlet oxygen in biological tissue is around 0.01-0.04 μm which is less than one percent of the diameter of a red blood cell (~ 7 μm). This indicates that it is the localization of the photosensitizer that determines the type of damage induced in the tissue during treatment [7]. If the photosensitizer is lipophilic, it will accumulate in the plasma and organellar membranes of cells and the photo-oxidation may result in a direct rupture of the membranes and inactivation of the enzymes and receptors affiliated with that membrane.

Hydrophilic photosensitizers, on the other hand, may accumulate in lysosomes and Endosomes, such that photo-oxidation results in the release of lysosomal enzymes in the cytoplasm. In this case another mechanism of tissue damage is induced. Studies show that the probability of cell damage per quantum of absorbed energy is higher for
lipophilic than for hydrophilic photosensitizers, indicating that the membranes are more vulnerable to treatment [8]. As for the case of ionizing radiation therapy, well oxygenated tissue is more vulnerable to cell destruction and thus to treatment than tissue with low oxygen content. Limitations in oxygen can occur during treatment either due to vascular damage, or to the fact that oxygen is consumed during treatment. When using oral or intravenous administration of the photosensitizer, a large amount will accumulate in the endothelial cells of the blood vessels, which may suffer permanent damage. Vascular damage results in a restricted blood perfusion in the tumor, and measurements of blood perfusion during treatment indeed indicate these vascular effects. Studies have been performed in which the treatment has been fractionated in various ways in order for the oxygen content to increase. In some cases fractionation leads to an improvement in treatment efficiency, but in others it does not imply a significant difference from continuous treatment.

**Therapeutic Light**

Coherent light sources, such as lasers, as well as incoherent light sources, such as filtered lamps or LEDs, are used for PDT. Due to their narrow bandwidth, lasers are able to minimize hyper thermal effects during PDT since they can be confined to the absorption band of the photosensitizer. Heating of the tissue due to absorption can thus be minimized by decreasing the light dose absorbed by non-PDT-active chromospheres. Furthermore, the spatial properties of lasers make them suitable for fiber coupling. Fiber guidance of the light facilitates the treatment of body-cavities using endoscopes or interstitial PDT, where fibers are inserted into the tumor using needles. LEDs and filtered lamps, such as Xenon lamps, may be used for superficial PDT, especially of larger lesions, where fiber guidance of the therapeutic light is unnecessary. Here we will focus on laser sources, which may be used for superficial and interstitial PDT in addition to PDT of body-cavities. In the beginning of the nineties, the typical lasers for PDT were Argon-ion or Copper-vapor laser pumped dye lasers in addition to frequency doubled Nd:YAG laser pumped dye lasers. These lasers are large, expensive, and complicated systems which require frequent service. Furthermore, they have high electrical energy consumption, and need extensive water cooling. An advantage is that, by using appropriate dyes, these lasers can be used for PDT with several different photosensitizers [9]. However, the dye introduces yet another disadvantage, since it has to be exchanged regularly in order to maintain high output power. Diode lasers are compact, easy to operate, require no water cooling, and are available at a reasonable cost. They are thus attractive in a clinical environment. Diode lasers are available at very high powers in the near-infrared. However, at these wavelengths no photosensitizers are available. In the late nineties, diode laser systems emitting at 635nm for ALA-PDT became commercially available. These laser systems deliver approximately 2W through a fiber with core diameter of 400 μm or more. Today, diode lasers are the most important laser light sources for PDT. They are available at several wavelengths matching various photosensitizers. Some of the important photosensitizers, which have commercial diode laser sources available at their absorption wavelengths for PDT. Common for all the diode laser sources for PDT, is that the therapeutic light is delivered through relatively thick optical fibers with core diameters of 400 μm or more. This is due to the poor spatial coherence of diode lasers and it sets a limitation for the procedure of interstitial treatments, where a thinner treatment fiber may be the optimal choice. By using a thinner treatment fiber with the commercial systems, a considerable amount of output power is lost. One of the aims of this work was to realize diode laser systems for ALA-PDT delivering the therapeutic light through thin optical fibers without discarding a large fraction of optical power from the diode laser.

**Nanoparticles in PDT**

In a comprehensive review on delivery of PS for PDT, published in 2001, Konan et al divided the processes into passive and active based on presence or absence of a targeting molecule on the surface. By this definition, the strategies used to deliver the PS specifically to diseased tissues using the target tissue receptors or antigens were termed ‘active’ while other formulations that enable parenteral administration and passive targeting namely, liposomes, oil-dispersions, polymeric particles and hydrophilic polymer–PS conjugates, were termed ‘passive’. This definition does not bring into consideration the role played by the nanoparticle carrier in the process of photocytotoxicity. This is understandable, as at that period, the only reported uses of nanoparticles were as controlled release vehicles for the PS. Subsequently, however, several formulations have been described whereby the carrier nanoparticles have an additional active intermediary role in the process of photodynamic activation [10]. Therefore, for nanoparticulate carriers only, we have replaced the former structural classification with a functional one. Functionally, use of nanoparticles used in PDT can be
broadly divided into two classes: as passive carriers and as active participants in PS excitation. Passive carriers can be sub-classified by material composition into

(a) Biodegradable polymer-based nanoparticles and

(b) Non polymer based nanoparticles,

e.g. ceramic and metallic nanoparticles. The major nanoparticles used in cancer treatment like Passive nanoparticles, Biodegradable nanoparticle carriers, Self-lighting nanoparticles, and up conversion nanoparticles.

Material and Methods
The concept of the new approach for the laser induced photodynamic treatment of cancerous tissue is based on the use of SNRs, located close to the external membrane or eventually inside a tumor cell. The laser light emitted by a NIR diode laser (@810 nm) is delivered through an optical fiber to the tumor site where the SNRs are located. The laser light is selectively absorbed by the SNR and then converted into thermal energy. If the SNRs are properly attached to the tumor tissue, a correct balance of the concentration of SNRs in the tumor volume and of the laser parameters can induce hyperthermia and so destruction of the cancer [11]. Aim of the modeling study is to evaluate the photodynamic conversion efficiency, independence of the settings parameters, in order to find reasonable parameter values prior than any experimental investigation (ex vivo or in vivo)[12].

Results and Discussions
Laser induced photodynamic therapy effects are at the basis of new minimally invasive therapeutic and diagnostic approaches in different medical fields (from Ophthalmology to Dermatology, Neurosurgery, Oncology, etc.). Nowadays new concepts are emerging, based on the activation of photodynamic effects through nanoparticles, in particular in the diagnosis and therapy of cancer [13]. The diagnosis of cancer may be pursued by the intravenous injection and selective accumulation of silica nanoparticles (SNPs) inside the malignant cells [14]. Then the SNPs may be used as highly effective contrast agents in a photo-detection arrangement. Interestingly the same SNP may be used to induce the apoptosis of the malignant cells by a photodynamic or photothermal microsurgery, as well as by the association of cytotoxic drugs [15]. In this work we designed a new approach based on the use of silica nanorods that selectively absorb near diode laser light. The intended photodynamic effect is hyperthermia of cancerous tissue. COMSOL Multiphysics 4.2a software was used to design the correct settings of the laser in order to induce effective temperature values in the biological tissue, avoiding inducing thermal damage at the nanoscale level to the SNR.

The Laser Source
Near infrared laser are usually selected for biological application because of their low absorption in a biotissue. In particular the absorption around 800 nm due to natural endogenous chromophores is quite low and the laser light can penetrate in the deep tissue. The light source used in the design of this new concept is a diode laser emitting at 810 nm. The light is delivered through an optical fiber with 600 μm inner core diameter [16]. The emission mode was a continuous wave. Optimal power density delivered to the GNR and duration time of the treatment was found by analyzing the post processing results of the FEM model.

The Comsol Model
Aim of the study was the analysis of the temperature range induced by the diode laser in the SNR and the environment close to it and in the biological tumor tissue. In order to do this, we developed two different models, the first one describing the designing of optical fiber and next one is cancer cell with silica nanorods. In both the models, the problem has a spherical symmetry, so we decided to study a bi-dimensional geometry. We studied a time dependent problem. The COMSOL modules were in both cases the same, the electromagnetic model.

Figure 2: Bidimensional Model of a GNR (the Rectangular Shape in the Center of the Draw) Inside a Biocompatible Biopolymer Circular Shell. Dimensions are in Micrometers

Fibers in Therapy: Optical Fiber
The optical fiber consists on core and cladding.
Core part is the center part of the optical fiber and the light is confined in to this core. And the cladding is the outer most layer of the optical fiber and this optical fiber is made up of silica glass material, it helps to prevent attenuation when the light is passing into the optical fiber core part.

**Figure 3:** Model of Optical Fiber with the Light Confinement in Comsol 4.2a (Electromagnetic Model)

**Treatment by Lasers**

The designing part of the cancer cell with absorbed light emitting nano rods is shown in the figure 4. The silica nanoparticles are absorbed by the cancer cells is shown in the middle part of the cancer cells in Figure 4. By this we can identify which one is the cancer cells and which one are the normal cells. Now we can easily target to kill the cancer cells over normal cells.

**Figure 4:** Model of Cancer Cells with the Silica Nanorods

The simple 2D-model of a cancerous, internal body tumor shows that it is possible to transfer laser light enough heat to the tumor to kill the cancerous cells. But for this to be realized it is necessary to increase the absorption of heat in the tumor, when fibers are used. Another possible solution to this is to incorporate more fibers [17]. This is not presenting new medical or technical problems, since the fibers are very thin. This project is still in the experimental and developing phase and the target is to make a 3D model. A 3D-model will give insight into how the fibers are to be placed to get the optimal heat generation and treatment time. Furthermore a 3D-model gives the opportunity to implement arbitrary forms of the tumor. In the 3D-model we may also experiment with laser signals corresponding to a pulsating function.

**Conclusion**

For a simple 2D-model with four thin optical fibers it is shown that it is possible to transfer enough heat to a body tumor to kill the cancerous cells in the whole tumor using external laser diodes. To use this method successfully a photosensitizer must be injected into the body. The optimal photosensitizer is pending. While such a product is being developed elsewhere, we will extend the model to 3D. For a 3D-model we can then begin developing optimization algorithms for the number of laser beams and the location of the end-points of the optical fibers for an arbitrary 3D form of a tumor.

**References**


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