PHOTODYNAMIC THERAPY FOR THE DESTRUCTION OF THE SYNOVIAL IN THE TREATMENT OF RHEUMATOID ARTHRITIS AND THE INFLAMMATORY ARTHRITIDES


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ABSTRACT
A method of treating proliferative diseases of the synovial joint using photodynamic therapy. In particular the method of the invention may be used to destroy synovial tissue in inflammatory joint conditions associated with diseases such as rheumatoid arthritis, lupus erythematosus and other rheumatoid variants. A number of methods of delivery are provided, some of which are non-invasive.

16 Claims, 5 Drawing Sheets
FIG. 2
PHOTODYNAMIC THERAPY FOR THE DESTRUCTION OF THE SYNOVIAL IN THE TREATMENT OF RHUMATOID ARTHRITIS AND THE INFLAMMATORY ARTHRITIDES

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

Funding for the work described herein was provided by the Federal Government Office of Naval Research Grant No. N0001491C0084. The federal government has certain rights to the invention.

BACKGROUND OF THE INVENTION

The invention relates to the use of photodynamic therapy for the destruction of diseased synovium.


The HPD semipurified mixture of porphyrins was later further purified to a combination of esters and ethers of dihematoporphyrin (DHE). The formulation predominantly in use is marketed as Photofrin® and HPD/Photofrin® was the first FDA approved photosensitizing agent available for PDT trials. Photofrin® has subsequently been tested extensively for the destruction of multiple tumors in numerous medical disciplines (Dougherty et al., In Photodynamic Therapy of Neoplastic Disease, Kessel ed., CRC Press, Boca Raton, Fla., 1989).

The mechanism of action for hematoporphyrin derivatives such as Photofrin® in the treatment of neoplastic disease is well delineated. For the porphyrins, large molecular aggregates accumulate around tumor neovascu- lature. Poor lymphatic drainage of neoplastic tissues may be the cause of retarded clearance times from these tissues. Once sequestered, the molecular aggregates dissociate, and the hydrophobic components partition Photofrin® into cell membranes. The primary cellular sites of photodynamic activity are thought to be cellular and mitochondrial membranes. Nucleic acids and proteins are also damaged by photooxidation (Henderson et al., Porphyrin Localization and Treatment of Tumors, Doiron and Gomer eds., Liss, New York, 1984, pp. 601–612).

Initiation of photodynamic activity is caused by excitation of the sensitizer by light that falls within its absorption band. The wavelength specificity is dependent on the molecular structure of the photosensitizer, where a greater degree of conjugation within a molecule leads to greater absorbance at longer wavelengths. Activation of photosensitizers occurs with sub-ablative light fluences. Toxicity is achieved by O2 radical toxicity. The singlet O2 reacts with double bonds, and or-ganoperoxides. These, in turn, initiate free radical chain reactions which degrade and disorganize membranes, uncouple oxidative phosphorylation and lead to cellular disruption (Jori et al., Photodynamic Therapy Of Neoplastic Disease, Kessel ed., CRC Press, Boca Raton, Fla., 1989; and Weishaupt et al., Cancer Res 36:2326–2329, 1976).


Photosensitizing agents are non-toxic until activated by specific frequencies and dosages of light energy. In addition, photosensitizers may be activated when transient differences in uptake occur between pathological and normal tissues. Differences in both temporal and geographic biodistribution in tissues may be taken advantage of for selective destruction of pathological tissue.

Carson, U.S. Pat. No. 5,028,594 describes a method for the selective elimination of hematopoietic cells involved in rheumatoid arthritis by use of photactivatable cytotoxic agents in combination with light. The photo-activated agents are tagged with ligands such as sugars, which target lymphocyte cells. In the example, monoethylenediamine monoxide was administered to rats in combination with light, bringing about a reduction in joint swelling and inflammation.

Kennedy, U.S. Pat. No. 5,079,262 describes a method of detecting and treating tissue abnormalities such as skin lesions and tumors by the administration of aminolevulinic acid in combination with photoactivating light. Kennedy suggests the use of ALA, a metabolic precursor of protoporphyrin IX in a variety of PDT applications.

Attempts at destroying diseased synovium with non-selective toxic compounds have been unsuccessful (Goldberg et al., Arthritis Rheum. 19:737, 1976; Mitchell et al., JBJS 55-B:814, 1973; and Oka et al., Acta Rheum Scan 15:35, 1969). Most recently, in an effort to develop minimally invasive techniques, synovecotomies have been performed with radioactive compounds (Zuckerman et al., J. Orthop Res. 7:50–60, 1989 and Sledge et al., Clin Orthop Rel Res 182:37–40, 1984). Although success has been achieved to a small degree, the use of radioactive precludes widespread use.

SUMMARY OF THE INVENTION

The invention features a method of treating a proliferative inflammatory joint disease in a patient. The joint
Other features and advantages of the invention will be apparent from the following description and from the claims.

**BRIEF DESCRIPTION OF THE DRAWING**

The drawings will first be briefly described.

**Drawings**

FIG. 1 is a photograph of the synovial tissue of the knee from a rabbit 11 weeks following initial skin sensitization according to the antigen induced arthritis protocol, 5 weeks after knee joint challenge with the antigen with no photodynamic therapy applied to the joint.

FIG. 2 is a photograph of the synovial tissue of the knee from a rabbit 11 weeks following initial skin sensitization according to the antigen induced arthritis protocol, 5 weeks after knee joint challenge with the antigen, and 4 weeks after photodynamic treatment with Photofrin® and light.

**FIG. 3** is a graph of the biodistribution of Photofrin® in the synovium, articular cartilage, skin, and muscle between 0–80 hours after administration.

**FIG. 4** is a graph of in vivo laser induced fluorescence of diseased synovial tissue following systemic administration of BPD.

**FIG. 5** is a graph of the localization of the precursor to protoporphyrin IX, ALA, to the synovium.

**DESCRIPTION OF THE PREFERRED EMBODIMENTS**

Rheumatoid arthritis is a disease characterized by proliferative erosive synovial tissue which destroys intra-articular and periarticular tissues. For patients failing medical management through pharmaceutical administration open surgical synovectomy or more aggressive procedures such as joint replacement have been the only treatment options. Photodynamic therapy synovectomy now offers an effective, less invasive new therapeutic alternative. Photoactive chemicals are injected into diseased joints either locally or systemically. The local joint region is then exposed to light via optical fibers threaded through small gauge hypodermic needles or, alternatively, the light source may also be provided extracorporeally by trans illumination. This treatment destroys the diseased synovium and potentially benefits the large population of patients for whom surgery is poorly indicated.

Examples A–D, below, demonstrate that photoactivatable chemicals localize selectively to the diseased synovium and are, therefore, promising for the treatment of the arthritic diseases. Photofrin® which is a mixture of hematoporphyrins and is the most widely used of the anti-neoplastic photosensitizing agents has been investigated most thoroughly for its therapeutic promise. In one example, Photofrin®, is demonstrated to be effective for the treatment of antigen induced arthritis. Biodistribution studies performed have documented that Photofrin® is selectively taken up in synovium at 24 and 48 hours post systemic injection. Results demonstrating destruction of synovium without significant side effects indicate that photochemical synovectomy is an effective new treatment for rheumatoid arthritis (FIGS. 1 and 2).

Photofrin® is but one example of a photoactivatable therapeutic which is an aspect of the invention. Its characteristics are illustrative of the localization and clearance characteristics of many other photodynamic compounds. Example A, below, illustrates that Photofrin®
localizes to the diseased proliferating synovial tissues. Example A below, indicates that Photofrin® kills cells in the diseased synovium. Examples C and D indicate that this is a general effect with photodynamic compounds and their precursors when they come into contact with diseased synovium. Numerous possibilities exist for delivery of both photosensitizing agents and light energy to the joints. Determining the most appropriate parameters for any photodynamic compound to be used for the treatment of arthritis may be done using the experimental techniques provide herein.

I. Delivery of Photoactivating Light

Newer photosensitizing compounds without systemic skin photosensitivity effects, activated in the near infrared and longer wavelength visible spectrum allow for light activation. This may be done via joint transillumination. Optical fibers may be passed via arthroscopes with direct visual targeting and activation of the compounds. Optical fibers may also be passed directly via small gauge hypodermic needles. Light may also be passed via percutaneous instrumentation using optical fibers or cannulated waveguides. Transillumination may be performed using a variety of devices involving laser or non-laser sources, i.e. lightboxes or convergent light beams. Activation may also be performed by open arthroscopy. Development of these parameters allows for minimally invasive, or non invasive means (via transillumination) for performing photodynamic synovectomies.

II. Delivery of Photodynamic Compounds

Local injection of the therapeutic chemical into joints may eliminate the need for systemic injection. The use of localized versus systemic injection is determined, in part, by the number of joints to be treated during a given therapeutic regime. The therapeutic compounds to be administered for use in photodynamic therapy can be formulated for pharmaceutical or veterinary use by combination with an acceptable diluent, carrier or excipient and/or in unit dosage form. In using the therapeutic compounds in the methods of the invention, conventional pharmaceutical or veterinary practice may be employed to provide suitable formulations or compositions. Thus, the formulations of this invention can be applied to parenteral administration, for example, intravenous, intraarticular, subcutaneous, intramuscular, intraventricular, intracapsular, intraspinal, intraperitoneal, topical, intranasal, aerosol, scarification, and also oral, buccal, rectal or vaginal administration.

Parenteral formulations may be in the form of liquid solutions or suspensions; for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

Methods well known in the art for making formulations are to be found in, for example, "Remington's Pharmaceutical Sciences." Formulations for parenteral administration may, for example, contain as excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes, biocompatible, biodegradable lactide polymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the present factors. Other potentially useful parenteral delivery systems for the factors include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, liposomes, and antibody conjugates. Formulations for inhalation may contain as excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for parenteral administration may also include glycocholate for buccal administration, methoxyxysalicylate for rectal administration, or citric acid for vaginal administration.

The present factors can be used as the sole active agents or can be used in combination with other active ingredients.

The concentration of the present factors in the formulations of the invention will vary depending upon a number of issues, including the dosage to be administered, and the route of administration.

In general terms, the factors of this invention may be provided in an aqueous physiological buffer solution containing about 0.1 to 10% w/v compound for parenteral administration. General dose ranges are from about 0.2 mg/kg to about 1 g/kg of body weight per day; a preferred dose range is from about 0.1 mg/kg to 2 mg/kg of body weight per day. The preferred dosage to be administered is likely to depend upon the type and extent of progression of the joint condition being addressed, the overall health of the patient, the make up of the formulation, and the route of administration.

III. Method of Screening Therapeutics for Use in PDT if Arthritis

A. Development Antigen Induced Arthritis Rabbit

The following is a protocol which may be used to generate antigen induced arthritis in rabbits. Rabbits prepared in the manner can then be used to screen various phototherapeutics for their application to the treatment of arthritic disorders.

Protocol: 200 mg ovalbumin is weighed and dissolved in 10 ml normal saline and filtered through a millipore filter into a sterile beaker. Ovalbumin solution is then drawn into a sterile 20-30 cc glass syringe. In addition, 10 ml of Freund's adjuvant is drawn into another sterile glass syringe. Using a sterile metal 3 way stopcock, the two solutions are mixed by transferring them back and forth between syringes until solution is thick and white. The suspension is then transferred to sterile vials or sterile 25 ml erlenmeyer flasks with rubber stoppers. 0.2 ml of this sensitization solution is then injected via a 23 or 25 gauge needle into 5 areas in the back of each rabbit. Sensitization is repeated 3 weeks after initial immunization.

Joint challenge: 10 mg/ml ovalbumin is added to normal saline followed by millipore filtration into a sterile vial. Rabbits are anesthetized and their knees shaved. 0.25 ml of challenge solution is injected directly into the knee joint.

Using this technique monoarticular synovitis is achieved within 4 days and continues over two weeks. Animals left up to six months will exhibit cartilage erosion, occasional osteophyte formation and synovial infiltration.
B. Animal Studies of Photodynamic Therapeutics Using Rabbits with Antigen Induced Arthritis

New Zealand white rabbits weighing 3–4 kg are divided into 3 groups as summarized in Table 3. All animals then undergo a six week sensitization period according to the Antigen Induced Arthritis Rabbit protocol. Bilateral knee joints of all animals are challenged at 60 days with intra-articular injections of 0.25% of ovalbumin solution with a concentration of 2.5 mg/ml. Injections require sedation with rompen and ketamine. Six days post challenge, 24 animals in group A will receive a systemic injection of 2 mg/kg of the therapeutic to be tested in compound solution via 25 gauge needle into an ear vein. 16 animals in group B will serve as controls and not receive injections of the therapeutic agent. Localized injection may also be used 48 hours post compound injection, or at any other time indicated by drug clearance studies. Animals in groups A and C will be again sedated with rompen and ketamine. Bilateral knees of all animals in group A and the right knee of animals in group C will receive light activation treatments. 400 nm–690 nm wavelength light energy, or any wave length which is activating for the chosen therapeutic, will be transmitted via 400 micron optical fiber through a 23 gauge needle into the knee joint cavities. Alternatively, light may be applied extracorporeally. A total light energy of 100J/cm2, or that energy range deemed appropriate for a given compound, will be applied to each joint over 20 minutes with an average laser power setting of 3–5 watts, or that wattage and time which is effective for a given compound. 6 animals from group A and 4 animals from both group B and group C are sacrificed at one week, two weeks, four weeks and 10 weeks post compound injection. Gross observations at time of harvest are then recorded. Samples of synovium, articular cartilage, meniscus and tendon are harvested and fixed in formalin. Specimens and then imbedded in paraffin, sectioned and stained with hematoxylin and eosin. Specimens are then examined microscopically for inflammation, scarring and necrosis. This general schedule is summarized below. It is understood that specific modifications in dosage, timing, light wavelength and duration are made for each therapeutic compound tested. These general parameters are known to those skilled in the art and are summarized, in part, in the following papers and references cited therein: Gomer, Photochemistry and Photobiology 54:1093–1107, 1991; Maziere et al., J. Photochem. Photobiol. B: Biol. 8:231–360, 1991; Allison et al., Photochemistry and Photobiology 54:709-715, 1991; Allison et al., SPIE Proc., In Press, 1991; Allison et al., Photochemistry and Photobiology 52:501–507, 1990; Poon et al., J. Neurosurg. 76:679–686, 1992; Reddi et al., Br. J. Cancer 61:407–411, 1990; Richter et al., Br. J. Cancer 63:87–93, 1990.

This protocol allows the practitioner to:
1) Document, with pathology, the ability of an activated photosensitizing agent to destroy synovium.

Samples of synovium from animals at all termination dates are fixed, imbedded in paraffin, stained and examined microscopically. Gross observations at time of harvest are to be noted. Knee inflammation at the time of light application will be examined clinically and recorded. Knee dissection observations will be recorded at time animals are sacrificed.

2) Document the non-deleterious effects of activated Photofrin® on articular cartilage, meniscus and other periarticular tissues.

Samples of articular cartilage, meniscus, tendon and muscle from animals as all termination dates are fixed, imbedded in paraffin, stained and examined microscopically. Gross observations at time of harvest are noted. Knee dissection observations are recorded at time of tissue harvest.

The following examples are meant to illustrate not limit the invention.

IV. EXAMPLES

Four examples relating to photochemical synovectomy are provided.

The first study, Example A, is a biodistribution study performed with 30 rabbits (60 knees) 1) to reestablish the animal model after making modifications suggested by the pilot study; 2) to establish selective uptake of hematoporphyrin derivative, Photofrin® (PF), in inflamed synovium; 3) to identify the temporal distribution of Photofrin® in synovium to optimize future delivery of light energy for photochemical activation; 4) to quantify Photofrin® uptake in synovium as a suggestion of feasibility in destruction of synovium; 5) to document biodistribution of Photofrin® in articular cartilage, muscle and skin.

Example B was a study conducted with 12 animals 1) to establish the feasibility of using photodynamic therapy for the treatment of an inflammatory condition; 2) to establish the antigen induced arthritis rabbit model; 3) to identify potential sources of difficulty prior to proceeding with a larger scale animal study and 4) to establish our surgical approach and route of administration of light energy. These experiments were done with Photofrin®.

Thirdly, Example C is a study presented which demonstrates that the phototherapeutic BPD is also localized effectively to the synovium allowing the generalization of results regarding issues of localization and clearance for other photodynamic compounds localized in neoplastic tissue but not yet demonstrated to specifically localize to synovial tissues.

The fourth study, Example D, demonstrates that aminovuclinic acid (ALA) may be administered as a precursor to yield the photosensitizer Protoporphyrin IX in situ in the synovium.

EXAMPLE A: BIODISTRIBUTION OF PHOTOFRIN®

Methods

Thirty New Zealand White rabbits weighing 2–4 kg were sensitized over a six week period with two cutaneous injections of ovalbumin suspended in Freund's adjuvant. At six weeks, the knee joints of all animals were challenged with an intra-articular injection of ovalbumin solution. Seven days following joint challenge, 25 animals received systemic intravenous injections with Photofrin® (2.0 mg/kg). Animals were killed at 6, 12, 24, 48 and 72 hours post Photofrin® injection and tissue samples were obtained of skin, quadriceps muscle, knee synovium, articular cartilage, meniscus, bone and tendon. Tissue weight was measured (Mettler AE 163 balance) and tissue samples were frozen at −90 degrees C. (Revco Ultra Low Freezer) until dye extraction.

For extraction, tissue samples were homogenized (Homogenizer, Model PT 10/35, Brinkman Instru-
light activation of the knee joints at 48 hours after systemic Photofrin® injection may be performed for the isolated destruction of inflamed synovium. Photofrin® uptake in articular cartilage, meniscus, muscle and tendon appears insignificant suggesting minimal risk to other intra-articular and peri-articular tissues.

Example B: PDT Using Photofrin® for the Treatment of Arthritis

Methods

Photochemotherapeutic synovectomy was performed on an antigen induced arthritis (AIA) model in 12 New Zealand white rabbits in a double control study. After a six week sensitization period, the joints of all animals were challenged bilaterally with an injection of albumin suspended in Freund’s adjuvant. After five days, eight animals received systemic injections of 2 mg/kg of Photofrin® II. At 24 hours, four animals underwent bilateral arthroectomy procedures. The right knee joint of each was exposed to 100J/cm2 of 630 nm laser light over a 20 minute period. The left knees, not receiving the laser light application, served as controls. At 48 hours post HPD injection, an additional 4 animals underwent the identical operative procedures. Post-operatively, all animals were returned to their cages and allowed free movement. Four animals, serving as a second set of controls, did not undergo surgery or receive laser light treatment. At one month post treatment, animals were sacrificed, knee joint synovium was then harvested, fixed, and stained with H and E for pathological evaluation.

Results: Three of four control animals displayed acute bilateral synovial inflammation. One of the four control animals did not react to the antigen challenge and showed no inflammation on pathology. Two of four animals treated at 24 hours post injection demonstrated a marked decrease in synovial inflammation in the right knee relative to the left control. Two knees showed a qualitative difference between right and left. Healing was comparable to the seen in previous experimentation with radiation synovectomy. Of the animals treated at 48 hours post injection, one died in anesthesia, and one showed a decrease in inflammation in treatment relative to controls. These results are shown in FIGS. 1 and 2.

Example C: Use of BPD for PDT

New Zealand white rabbits weighing 3-4 kg were sensitized to ovalbumin according to the aforementioned antigen induced arthritis model protocol. 5-7 days post joint challenge, knee joints were observed to be inflamed. Animals were sedated with Rompun and Ketamine and received a continuous infusion of intravenous saline. A 20 guage angiocath was inserted percutaneously into the right knee joint of the animal via an anteromedial portal. A 600 µm quartz optical fiber, attached to a laser induced fluorescence system, was passed via the angiocath into the knee joint. The distal tip of the cleaved fiber was placed in gentle contact with the synovium overlaying the fat pad in the anterior knee joint.

Laser induced fluorescence system. The output of a pulsed nitrogen laser (VSL-337ND Laser Science Inc., Cambridge, Mass.) was used to pump a dye laser (DLM 220, Laser Science, Inc., Cambridge, Mass.) containing rhodamine 610 dye (Exciton Chemical Co., Dayton, Ohio). The 610 nm excitation pulses were launched into
TABLE 1-continued

Diseases of the Joint Which May Be Treated with PDT

Störren's Syndrome
Mixed Connective Tissue Disease
Hemophilia
Sickle Cell Disease and Trait
Arthritis Associated with Metabolic or Endocrine Disease
Arthritis Associated with Hemochromatosis
Arthritis Associated with Wilson's Disease
Arthritis Associated with Gaucher's Disease
Arthritis Associated with Alcaptonuria-Ochronosis
Arthritis Associated with Hyperlipoproteinemia
(Type II and Type IV)
Arthritis Associated with Multicentric Reticulohistiocytosis
Arthritis Associated with Acronymegaly, Hyperparathyroidism, and Hypoparathyroidism
Arthritis Associated with Hematologic Disease
Crystal-induced Arthritis: Pseudogout and Hydroxyapatite

TABLE 2

Compounds for Photodynamic Therapy of Diseases of the Joint

1. Photofrin ®
2. Synthetic diporphyrins and dichlorins
3. Hydrophyrins such as chlorins and bacteriochlorins of the tetrapyrrrole series
4. Phthalocyanines
5. O-substituted tetraphenyl porphyrins (picket fence porphyrins)
6. 3,3'-meso tetraphenyl porphyrin (porphyrin)
7. Verdisin
8. Purpurins
9. Chlorins, chlorin e6, and meso-tetapyrrole derivatives of octaethylporphyrin (NT2)
10. Benzoporphyrin derivatives (BPD)
11. Benzoporphyrin monomeric derivatives
12. Tetracyanoethylene adducts of benzoporphyrin
dimethyl acetylenedicarboxylate adducts of benzoporphyrin
diels-adler adducts
13. Low density lipoprotein-mediated localization parameters
14. Similar to those observed with hematoporphyrin derivative (HBP)
15. Sulphonation of aluminium PC as sulphonated AIPc
diosulphonated (AIPcS)
tetrasulphonated derivative
sulphonated aluminium naphthalocyanines
16. Zinc naphthalocyanines
17. Anthracenediones
18. Anthrapyrazoles
19. Aminanthraquinones
20. Phenoxyxanines
21. Phenothiazine derivatives
22. Chloraquinopyrylum dyes
catonic sulfa and tellurapyrylum derivatives
23. Ring-substituted catonic PC
24. Porphorbid a
25. Hematoporphyrin (HP)
26. Porphorybin
27. 5-amino levulinic acid

TABLE 3

Schedule for Test Compounds

Group A: Experimental, 24 animals: + photosensitizer + light activation to right knee, no light activation of left knee.

Day 0 Sensitize animals, skin injection
Day 30 Sensitize animals, skin injection
Day 60 Challenge joints with ovalbumin solution, create synovitis reaction
Day 66 Systemic injection of the compound, treatment animals
Day 68 Light activation of the compound via optical fiber, transillumination or open delivery via arthroscopy incision to the right knee of all 24 animals
### TABLE 3-continued

<table>
<thead>
<tr>
<th>Schedule for Test Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 75 Kill 6 treatment rabbits, harvest both knees</td>
</tr>
<tr>
<td>Day 83 Kill 6 treatment rabbits, harvest both knees</td>
</tr>
<tr>
<td>Day 98 Kill 6 treatment rabbits, harvest both knees</td>
</tr>
<tr>
<td>Day 148 Kill 6 treatment animals, harvest both knees</td>
</tr>
</tbody>
</table>

Group B: Control animals; no photosensitizer, light activation R knee, no light activation L knee

| Day 0 | Sensitize animals, skin injection |
| Day 30 | Sensitize animals, skin injection |
| Day 60 | Challenge joints with ovalbumin solution, create synovitis reaction |
| Day 66 | Systemic injection of compound all animals |
| Day 68 | NO Light activation of compound |
| Day 75 | Kill 4 animals |
| Day 83 | Kill 4 animals |
| Day 98 | Kill 4 animals |
| Day 148 | Kill 4 animals |

### TABLE 4

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Dt (h)</th>
<th>Intracellular PPIX (4 h) (a moles/cell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBT-2 (rat bladder carcinoma)</td>
<td>13.5</td>
<td>160</td>
</tr>
<tr>
<td>5PAM (mouse squamous cell carcinoma)</td>
<td>14</td>
<td>160</td>
</tr>
<tr>
<td>EJ (human bladder carcinoma)</td>
<td>23</td>
<td>100</td>
</tr>
<tr>
<td>HSF (human skin fibroblast)</td>
<td>27</td>
<td>40</td>
</tr>
</tbody>
</table>

What is claimed is:

1. A method of treating a proliferative inflammatory joint disease in a patient, said method comprising:
   a) administering to said patient a photoactivatable cytotoxic compound or precursor thereof so that said compound or precursor accumulates in synovial tissue of said patient, and then

   b) administering light of a photoactivating wavelength to said synovial tissue to activate said compound or precursor to cause destruction of said tissue.

2. The method of claim 1 wherein said photoactivatable compound is a benzoporphyrin derivative.

3. The method of claim 1 wherein said photoactivatable compound is a product of aminolevulinic acid.

4. The method of claim 1 wherein said compound is delivered systemically.

5. The method of claim 1 wherein said compound is delivered locally to the area of the joint.

6. The method of claim 1 wherein said light is administered directly to the joint.

7. The method of claim 6 wherein said administration is by an arthroscopic instrument.

8. The method of claim 6 wherein said administration is by a fiber optic instrument.

9. The method of claim 1 wherein said light is provided by a laser light source.

10. The method of claim 1 wherein said light is provided by a non-laser light source.

11. The method of claim 1 wherein said light is derived from a broad band light.

12. The method of claim 1 wherein said disease is an inflammatory arthritis disease.

13. The method of claim 12 wherein said disease is rheumatoid arthritis.

14. The method of claim 1 wherein said disease is hemophilia.

15. The method of claim 1 wherein said compound has a therapeutic index of at least 50.

16. The method of claim 1 wherein said compound has a therapeutic ratio of at least 10.

* * * * *