MIDWEST FREE-ELECTRON LASER PROGRAM

FINAL TECHNICAL REPORT

March 1, 1988 - October 31, 1991

Contract N00014-90-C-0028

I. Introduction

The Midwest Free-Electron Laser Program was managed by the Midwest Bio-Laser Institute, which is located at the Ravenswood Hospital Medical Center, 4550 N. Winchester Avenue, Suite 5507, Chicago, Illinois 60640-5205, Tel. (312) 728-3828. The various research projects were conducted at the Technological Institute and the Dept. of Chemistry at Northwestern University (NU) in Evanston, Illinois; the Dept. of Physiology at NU's Medical School; Department of Physics at the Illinois Institute of Technology (IIT); Wenske Laser Center (WLC) of Ravenswood Hospital Medical Center; and the Chicago Institute of NeuroSurgery and NeuroResearch (CINN) of Columbus Hospital, all in Chicago, Illinois. The management team consisted of L.J. Cerullo, M.D., Program Director; M. Epstein, Ph.D., Program Administrator; L.I. Grossweiner, Ph.D., P.I. at IIT and WLC; M.E. Marhic, Ph.D., P.I. at NU's Technological Insitute; W.Z. Rymer, M.D., Ph.D., P.I. at NU's Medical School and CINN; and K.G. Spears, Ph.D., P.I. at NU's Dept. of Chemistry. A one-year project (June 1, 1988-May 31,1989) was conducted at the Northwest Institute for Medical Research with L.L. Gershbein, Ph.D., as P.I.

The following are the progress reports of the individual research projects.

II. Laser Effects on Neural Tissue

P.I.: W. Zev Rymer, M.D., Ph.D., Dept. of Physiology, Northwestern University Medical School and Chicago Institute of NeuroSurgery and NeuroResearch, Chicago, Illinois.

Staff:

Project Director: W.Z. Rymer M.D., Ph.D.

Research Associate: Ursula Wesselman M.D., Ph.D

Research Technician: Mary Lynn Munson

Research Assistant: S. F. Lin Ph.D.

We have made significant progress in four areas.

1. <u>Peripheral Nerve Physiology</u>

Irradiation of the sciatic nerve of a rat with Q switched Neodymium Yag Laser at 1.06 microns wave length, for 7 seconds or more produces preferential impairment of action potential conduction in small caliber myelinated afferents. This reduction is not necessarily confined to, but certainly includes fibers responsible for pain transmission from the periphery to the spinal cord (Ad fibers). These conduction changes are not necessarily permanent although repeated laser applications produces preferential small fiber damage, with incomplete recovery, and there will often be some associated damage to large myelinated fibers as well.

Dr. S.F Lin developed a computer simulation in which he estimated the relative reduction in small fibers induced by IR laser irradiation, based upon changes in shape and size of the compound action potential elicited in the dorsal root by simulation of the sciatic nerve. These simulations supported the view that there was preferential damage in small fibers induced by the laser irradiation. This irradiation technique may ultimately prove to be useful as a means of producing selective mid or long term anesthesia for intractable pain or other sensory disfunctional states.

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Laser effects on neural tissue; infrared picosecond laser development and applications; infrared waveguide for laser-beam delivery; interaction of laser radiation with tissue.

19. ABSTRACT *(Continue on reverse if necessary and identify by block number)*

It has been shown that pulsed Nd:YAG irradiation of nervous tissue in both mammalian and frog preparations produces selective damage to conduction and axoplasmic transport in small caliber sensory afferent fibers, which may be those responsible for pain sensation. In addition, the thermal affects on peripheral nerve appear to be primarily on sodium channels. This preferential sodium effect can be enhanced or developed further for clinical use to provide novel interventions in anesthesia and surgical treatment of painful conditions.

A laser system was built to simulate the high energy pulses of a low repetition rate FEL in the infrared and was used to develop the necessary techniques for the study of transient pump-probe experiments with infrared probe wavelengths. It was employed as a transient IR probe of UV laser effects in the study of metal-ligand dissociation.

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19. ABSTRACT (continued)

A novel chrono-coherent imaging technique has been developed which uses time gating with coherent holographic recording. Utilizing short pulses, such as those from the FEL, this technique should provide a means of imaging inside the skin using optical wavelengths.

A unique method of short-range electron transfer across a single bond to form a dissociated ion pair has been studied as a function of solvent. Also, the laser mediated release of dye from liposomes has been investigated.

Several types of flexible waveguides, suitable for the delivery of output beams of infrared FELs tunable within the 1 to 10 μm range and average power of up to 100 Watts, have been developed. It included both theoretical and experimental studies of hollow metallic waveguides, particularly of two types: whispering-gallery and hollow circular waveguides.

Extensive studies of tissue optics and the interaction of laser radiation with tissue included: a computerized, two-channel integrating sphere spectrophotometer for high-resolution measurement of diffuse reflection and transmission spectra ; an exact solution to the photon diffusion equation and of the laser-bioheat transfer equation with a convection boundary for incident gaussian beams; photosensitization tissue phantoms and analytical light dosimetry modeling for photodynamic tumor therapy; a Monte Carlo program for light distribution in tissues for incident uniform, finite radius, and gaussian beams.

A one-year study was conducted on the biological changes in the regenerating and intact rodent liver following exposure of the organ to lasers.

2. Changes in Peripheral Nerve Transport

Axoplasmic transport of horse-radish peroxidase was used to evaluate the potential changes in physiological behavior of small nerve fibers after IR laser irradiation. We applied HRP to the stump of laser radiated nerve, sectioned proximal to the site of the radiation, one week after laser irradiation. The objective here was to see if there had been selective structural or functional impairment of small fiber axoplasmic transport.

Evaluation of the relevant dorsal root ganglia showed that there was selective reduction in the number of small cells, supporting the view that small caliber afferents were permanently and preferentially damaged by the laser radiation. We further demonstrated that the laser effects were confined to sensory fibers, and did not appear to impact motor axons to a comparable degree. This comes from a study which compared the horse-radish transport to large vs. small motoneurons. (presumably alpha vs. gamma neurons). Since there was no loss of a small motoneurons it appears that sensory fibers are more severely impaired by the laser irradiation.

3. Thermal Sensitivity of Ion Channels in Frog Node of Ranvier.

Dr. Lin utilized a very sensitive voltage clamp approach towards quantifying the current flow through the various channels present in the frog node. He has been examining the relative sensitivity of sodium and potassium ion channels to abrupt steps in temperature injected by regulating radiation from a Nd:Yag laser with 1.32 micron wave length. Our findings were that for temperatures above 45 degrees there was severe impairment of the conductance for sodium as distinct from potassium and that these effects were usually not reversible once the temperature reached 50 degrees or higher. This work was also noteworthy because of the development of a shuttered controller which allowed abrupt changes in temperature to be developed in tissues.

4. Synaptic Transmission

We completed a study in which effects of 1.06 micron radiation on rat synaptic transmission in dorsal horn gray matter was evaluated. Our findings were that for temperatures of 45 degrees or more there was a selective loss of synaptic transmission, manifested by changes in the size of the longer latency waves of the potential evoked by an afferent volley, but that the afferent volley itself was much less sensitive to the infrared radiation.

Summary and Overview

Our studies have shown that pulsed Nd:YAG irradiation of nervous tissue in both mammalian and frog preparations produces selective damage to conduction and axoplasmic transport in small caliber sensory afferent fibers, which may be those responsible for pain sensation. In addition, the thermal affects on peripheral nerve appear to be primarily on sodium channels. It may be that this preferential sodium effect can be enhanced or developed further for clinical use. These approaches hold promise for providing novel interventions in anesthesia and surgical treatment of painful conditions.

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2. Lin S., Wesselman, U., Rymer, W. Z. Pulsed Laser Irradiation Effects on the Distribution of Conduction Velocities in the Sciatic Nerve of the Rat. *Progress in Biomedical Optics*, SPIE, Volume 1200: 334-342, 1990.

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4. Wesselmann, U., Rymer, W. Z., Lin, S-F.: Effects of Pulsed Infrared Lasers on Neural Conduction and Axoplasmic Transport in Sensory Nerves. *Progress In Biomedical Optics* SPIE, Volume 1200: 319-333, 1990.

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9. Lin, S-F., Wu, C. H., Rymer, W. Z.: Effects of Laser-Induced Hyperthermia on Ionic Permeability in Myelinated Nerve. *Journal of Membrane Biology*, 1991 (in preparation).

10. Wesselmann, U., Pymer, W. Z.: Retrograde Horseradish Peroxidase Transport in Motor Neurons After Nd:YAG Laser Irradiation of the Tibial Nerve in Rats. Submitted for Publication, 1991.

<u>Abstracts</u>

1. Wesselmann, U., Lin, S-F., Rymer, W. Z.: Nd:YAG Laser Effects on Nervous Tissue in the Rat. *Society for Neuroscience, 18th Annual Meeting*, #279.32, p. 698, 1988.

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3. Wesselmann, U., Rymer, W. Z.: The Number of Substance P Containing Dorsal Root Ganglion Cells is Reduced After Laser Irradiation of the Rat Tibial Nerve. *Society for Neuroscience, 20th Annual Meeting*, #440.14, p. 1074, 1990.

<u>Theses</u>

Lin, S-F.: Electrophysiological Study of Pulsed ND:YAG Laser Effects on Neural Function of Rats. Northwestern University. Master Thesis. June, 1988.

Lin, S-F.: Effects of Laser-Induced Hyperthermia on Membrane Currents in Myelinated Nerve. Doctoral Thesis. December, 1991.

III. Infrared Picosecond Laser Development and Applications

P.I.: Kenneth G. Spears, Ph.D., Depts. of Chemistry and Biomedical Engineering, Northwestern University, Evanston, Illinois.

1. Simulation of Picosecond Infrared Pulses

A laser system was built to simulate the high energy pulses of a low repetition rate FEL laser in the infrared. The system was equipped with associated electronics and optics to do pump-probe experiments with probe wavelengths from 1-11 micrometers in the infrared and pump wavelengths in the visible and ultraviolet. The method used a picosecond pulsed Nd:YAG laser as the starting laser and then used a dye laser and various crystals to generate infrared wavelengths by pumped parametric generation methods (difference frequencies between two lasers). The method could generate as much as 40-150 microJoules in a 15 ps pulse,depending on the wavelength region. The basic method was innovative and was published [1]; it has proven to be very reliable in practical application.

2. Transient IR Probes of UV Laser Effects: Metal-Ligand Dissociation

The laser system for simulating FEL laser effects was setup to develop the necessary techniques for studying transient pump-probe experiments with infrared probe wavelengths. The equipment could create a time spectrum at one IR wavelength by stepwise scanning successive time delays of the probe beam relative to the pump beam. A series of such scans with 3 wave number (cm-1) changes in the infrared wavelength were used to provide a three-dimensional map of IR absorbance or concentration (z), wave number(x) and time (y). Such an experiment can reveal the spectroscopic signatures of intermediate species and new molecules created by the absorption of laser energy. This type of experiment is of general significance to FEL laser technique and applications. We selected an interesting molecular photo-dissociation problem to show the full potential of the method, and to also provide new information of wide importance to understanding photo- dissociation in liquids.

The problem was to understand how the energy of an ultraviolet absorption event at 300 nm or 266 nm is deposited in a molecule such as $Cr(CO)_6$ to dissociate a CO ligand and also control subsequent reactions of the reactive fragment. The reactions with the solvent create new products with unique IR absorptions and the transients, including vibrational excitation in products as well as the reactive fragment were all studied to understand this system. Ultimately, unique energy transfer processes internal to a molecule and to the solvent environment were found to control much of the observed effects, and these may be generalizable to other systems. A unique 4 beam experiment was required to fully understand and prove the existence of an active fragment and this is described in the most recent of the publications associated with this problem [2-5].

3. Chrono-Coherent Imaging (CCI)

The problem of using optical wavelengths to image inside the skin was addressed to identify new applications of short pulses such as those from the FEL. Time gating has been historically used to reduce the contribution of scattered paths to image formation, where the direct unscattered or minimally scattered light would provide image information without contributions of scatter. Our research efforts combined this old idea with the idea of coherent recording on holographic film (or CCD in the future). The method has been developed and a number of experiments have been done to identify its fundamental limitations, at least in the simplest formats. Currently, we believe that the fundamental limit may be defined by coherence loss effects so that only unscattered photons can give high resolution images over some tissue depth of 3-10 mm. Some extension of depth, with reduced resolution, can be obtained since we have shown that 2-3 scatter events still retains some coherence. Recent work on extensions to electronic detection have used optical mixing on photodetectors to extend the sensitivity, but at the sacrifice of two dimensional images. A number of papers have been presented on these subjects [6-11].

4. Electron Transfer: Biological Systems and Model Molecules for Dissociation of Bonds

A limited set of experiments have been done with electron transfer, where the main probe method was molecular fluorescence. A unique study of short range electron transfer across a single bond to form a dissociated ion pair has been studied as a function of solvent. The unique aspect of this system is that it is an excellent probe of how elecuron transfer processes are very dependent on the local environment around the photoactivated molecule, which in our case was a UV excitation of malachite green leucocyanide. Such optical control of ion pair formation may have applications to opto-electonic devices, although we have only emphasized the very unique fundamental aspects of the phenomena. This work is in the final draft [12] before submission in January, 1992. Another project involving electron transfer was a collaboration with Professor B.H. Hoffman of our department where we measured fluorescence lifetime quenching rates by electron transfer in a cytochrome c complex. This work is about to be submitted for publication [13].

5. Laser Mediated Release of Dye From Liposomes

The question of how short pulse durations can impact a biological system was studied in the specific context of liposome models for intracellular organelles and vesicles. A general issue was proving that a single pulse of laser energy can be used to activate a local site of absorption rather than the whole environment of the absorbers. These effects may be useful for laser induced delivery of therapeutic agents or other applications of lasers in cell modification.

Liposomes made from phospholipids and containing sulforhodamine dye (1-50 mM) have been irradiated with nanosecond and picosecond laser pulses. Individual liposomes were locally heated by laser absorption of dye dimers during a single laser pulse, and heating was sufficient to release the liposome contents. The extent of dye release produced by a single laser pulse was shown to be quantitatively dependent on several interdependent variables, including dye concentration, liposome size, laser excitation parameters and initial temperature of the dye-liposome system. Fluorescence lifetime data with three components have been obtained and analyzed in terms of three dye environments. Quantitative estimates support a photo-induced thermal mechanism for liposome lysis and release of its contents. This work has been recently submitted for publication [14-16] and has been published in conference proceedings.

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3. L. Wang, X. Zhu and K. G. Spears. Reactions of Naked Cr(CO)5 in Tetrahydrofuran Solution Observed By Picosecond IR Transient Absorption. *J. Phys.Chem.*, 93, 2-4 (1989).

4. K. G. Spears, L. Wang, X. Zhu and S. M. Arrivo. Picosecond Transient IR Absorption of Unsaturated Transition Metal Complexes. Picosecond and Femtosecond Spectroscopy from Laboratory to Real World, *Proc. SPIE* V1209, 32-42(1990).

5. J.R. Sprague, S.M. Arrivo and K.G. Spears.Identification of Uncoordinated Cr(CO)5 Intermediate in Cyclohexane with Picosecond Time Resolved IR Spectroscopy. in press, *J. Physical Chemistry*, Dec 1991.

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10. K. G. Spears, J. Serafin, H. Bjelkhagen.Chrono-Coherent Imaging for Medicine. *IEEE Engineering in Medicine and Biology Magazine*, December, 21-23 (1989).

11. K. G. Spears and J. Serafin.Chrono-Coherent Imaging: A Method For Viewing Inside Tissue. *Bio-Laser News.*, July, p. 1-4 (1989).

12. R. M. Miller, K. G. Spears, J. Gong and M. Wach.Short Range Non-Adiabatic Electron Transfer. To be submitted to *J. Physical Chemistry*.

13. Q. P. Zhang, S. Wallin, R. M. Miller, K. G. Spears, G.McLendon and B. M. Hoffman.Static and Time Resolved Energy Transfer Measurements: The Cytochrome c: Cytochrome c Peroxidase Complex. To be submitted to *J. Am. Chem. Soc.*

14. D. VanderMeulen, P. Misra, J. Michael, K. G. Spears and M.Khoka.Laser Mediated Release of Dye From Liposomes. Submitted to *Photochem. and Photobiol.* 11/91.

15. D.L. VanderMeulen, P. Misra, Jason Michael, K.G. Spears and M. Khoka.Quantitative Analysis at the Molecular Level of Laser-Neural Tissue Interactions Using a Liposome Model System. *Proceeding of SPIE, Intern. Symp. on Laser Spectroscopy* v1428, p91-98 (1991).

16. D.L. VanderMeulen, M. Khoka and K.G. Spears.Laser Neural Tissue Interactions Using Bilayer Membrane Models. *Proceedings of SPIE, Intern. Symp. on Laser Spectroscopy*, v1428, p84-90 (1991).

IV. Infrared Waveguide for Laser-Beam Delivery

P.I.: Michel E. Marhic, Ph.D., Dept. of Electrical Engineering and Computer Science, Technological Institute, Northwestern University, Evanston, Illinois.

The aim of this part of the program was to develop flexible waveguides suitable for the delivery of the output beams of infrared FELs, namely beams potentially tunable within the 1 to 10 micron range, and with average power of up to 100 Watts. The program had both a theoretical and an experimental component. Hollow metallic waveguides were the main waveguides studied, particularly the two classes of: whispering-gallery (WG) waveguides; hollow circular waveguides.

THEORY.

On the theoretical side, we refined earlier work to ascertain the limitations on the losses due the biconcave shape of the WG waveguide. We were able to derive analytic expressions for the results, in two distinct ways, which showed that guides with typical parameters should exhibit loss due primarily to the first curvature, and not affected by the second curvature.

We also studied in detail the possibility of coating WG guides with multiple dielectric layers in order to reduce the TE losses substantially below the value associated with a simple metallic coating. We showed that such reduction should in principle be achievable. For instance, two quarterwave layers, one of Germanium and the other of Barium Fluoride, would reduce the losses by a factor of 17. Increasing the number of layers would lead to further improvements.

We have also studied multiple-layer arrangements which could be suitable for broadband low-loss transmission over the entire 1 to 10 micron range. We have identified some suitable configurations, although their physical realization may be difficult due to the need to have nonuniform layers in order to average out isolated transmission peaks.

In the process of studying these multiple layers, we have come up with a novel theoretical formulation for the reflectivity of such layers, which may be important in the design of many other types of dielectric coatings.

In our study of hollow circular waveguides, we have also achieved some important theoretical results. By initially modeling such guides as slab waveguides, we have developed a novel algorithm to calculate the roots of the characteristic equation. This method presents substantial advantages over other existing methods, both in terms of speed and accuracy of convergence. Considering then an actual cylindrical model, we have for the first time obtained the inverse matrix of the characteristic equation in closed form, in terms of Bessel functions. This, plus novel algorithms to generate the Bessel functions, leads to considerable computational advantages in calculations of this type.

EXPERIMENTS.

On the experimental side, most progress was accomplished in developing the WG guides. A reproducible technique was developed to make these guides by a nickel electroforming and gold coating method. Using this approach, a technician can now reliably make such guides with low loss, in a routine manner. During the course of the program, the losses at 10 microns were reduced from about 6 percent per turn to about 4 percent, all figures corresponding to a final gold layer. The guides are suitable for delivery of medium average power: several hundred Watts can be delivered on a steady-state basis, with a tolerable rise in temperature, and no guide deterioration.

Much experimental work went into the deposition of such dielectric layers. Unfortunately, due to a number of reasons including the complex shape of the WG guides as well as purity and compatibility of materials, we have to date not been successful in achieving a marked improvement over the case of a bare metal. We are continuing work in this interesting area, currently studying the sputter deposition of Germanium and Zinc Selenide to alleviate some of the deposition problems. We are also considering the possibility of using MOCVD as an alternate deposition technique; suitable reactors are being installed here as part of the new Center for Quantum Devices.

Concerning hollow circular waveguides, we developed a novel fabrication technique, relying on a soluble glass mandrel, to make thin flexible guides of unprecedented smoothness of the inner surface. This was also extended by heat-deformation of the mandrel to the fabrication of waveguides with tapers and bends, difficult to make by any other means, and possibly applicable to a variety of medical applications (dental, brain surgery, etc.).

We also worked on a rather different type of hollow circular guides, namely a hollow plastic tube filled with bromine. While the results are of scientific interest, they are far from being practical in that it is difficult to keep the bromine pure (and thus lossless) during and even after filling the tube. Furthermore, the highly corrosive nature of bromine severely limits its areas of possible use.

PUBLICATIONS

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2. " Boundary Layer Analysis of Infrared Whispering-Gallery Waveguides," W. L. Kath, J. Jiao, and M. E. Marhic, *SIAM J. Applied Math.*, 50, pp. 537-546 (1990).

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4. " Numerical Study of Attenuation in Multilayer Infrared Waveguides by the Circle Chain Convergence Method," L. Sun and M. E. Marhic, *J. Opt. Soc. Amer.* B, 8, pp. 478-483 (1991).

5. " Electroformed Nickel Waveguide for Carbon Dioxide Laser Beam Delivery," M. E. Marhic, R. Haidle, and R. Altkorn, *Nickel*, p.4, December 1991.

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7. " Teflon-Clad Bromine Infrared Waveguides," R. Altkorn, M. E. Marhic, and F. Tang, *SPIE Conference O-E/Fibers '87*, San Diego, CA, August 16-21, 1987.

8. " Hollow Metallic Waveguides for Free-Electron Lasers," M. E. Marhic, *Third Annual Contractors Meeting on Medical Free Electron Lasers*, Salt Lake City, UT, May 15-18, 1988.

9. " Losses of Infrared Biconcave Metallic Whispering-Gallery Guides," J. Jiao, W. L. Kath, X. Fang, and M. E. Marhic, *Fourth International Conference on Infrared Physics*, Zurich, Switzerland, August 22-26, 1988.

10. " Losses for Vector Solutions of Infrared Whispering-Gallery Waveguides," W. L. Kath, J. Jiao, X. Fang, and M. E. Marhic, *Annual Meeting of SIAM*, Minneapolis, Minnesota, July 11-18, 1988.

11. " Hollow Metallic Waveguides for Delivery of Free-Electron Laser Beams," M. E. Marhic, *Fourth Annual Contractors Meeting on Medical Free-Electron Lasers*, Dallas, TX, September 22-24, 1989.

12. " Curved CO2 Laser Waveguides for Neurosurgery," R. Altkorn, T. Helenowski, R. Haidle, and M. E. Marhic, *SPIE Conference: Laser Surgery: Advanced Characterization, Therapeutics, and Systems II*, Los Angeles, CA, January 17-19 1990.

V. Interaction of Laser Radiation with Tissue

P.I.: Leonard I. Grossweiner, Ph.D., Physics Department, Illinois Institute of Technology and Wenske Laser Center at the Ravenswood Hospital Medical Center, Chicago, Illinois.

The emphasis of this program component was on tissue optics and laser interactions with biological tissues. The research accomplishments include:

1. A computerized, two-channel integrating sphere spectrophotometer was fabricated that provides high-resolution diffuse reflection and transmission spectra of turbid layers from 350-1350 nm at 1 nm spectral resolution.

2. An exact solution to the photon diffusion equation was carried out for incident gaussian beams. The results were verified with measurements on large tissue sections illuminated with Nd:YAG and He-Ne laser through a multimode optical fiber. It was shown that the radial-averaged flux density distribution is exponentially attenuated in depth for any incident beam profile.

3. The laser-bioheat transfer equation was solved for incident gaussian laser beams with a convection boundary condition. The results were verified with measurements on large tissue sections illuminated with a pulsed Nd:YAG laser.

4. Photosensitization tissue phantoms were developed for photodynamic tumor therapy (PDT) consisting of light scattering particles, solubilized Photofrin II, and a soluble enzyme as the biological target. It was demonstrated experimentally and with diffusion approximation calculations that the rate of energy absorption is independent of the scatterer concentration.

5. Analytical light dosimetry modeling for PDT was employed for treatment planning in conjunction with clinical trials at Ravenswood Hospital Medical Center. Since 1986, 52 patients have been treated for malignancies of the skin, head and neck, and lower female genital tract. The average histological complete response rate at three months post-PDT is 80.1%.

6. A Monte Carlo program for light distributions in tissues was implemented for incident uniform, finite radius, and gaussian beams.

Publications Supported by this Project

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VI. Biological Changes in the Regenerating and Intact Rodent Liver Following Exposure of the Organ to Lasers (The period of this project was June 1, 1988 to May 31, 1989.)

P.I.: Leon L. Gershbein, Ph.D., Northwest Institute for Medical Research, Chicago, Illinois.

This study was undertaken with the view of deriving a sensitive criterion based on liver regeneration for the assessment of laser toxicity with emphasis on mammalian liver and for application to FEL, among others. A poignant query to be answered was to whether the administration of varying levels of radiation leads to differences in resistance according to surgical status by comparison of coagulation patterns and pathology as a result of blood vessel and bile duct damage. The results of this work were reported at the SDIO Fourth Annual Contractors' Meeting on Medical Free Electron Lasers, on September 22-24, 1989 in Dallas, Texas. A reprint of the abstract and two other publications are included with this report.

Publications.

1. Biological Changes in the Regenerating and Intact Rodent Liver Following Exposure of the Organ to Lasers : Gershbein LL, Denton RW, Schifano MJ, *Research Communications in Chemical Pathology and Pharmacology*, Vol. 74, pp. 327-347 (1991).

2. Biochemical and Anatomical Changes in Rat Liver Exposure of the Organ to Nd:YAG laser: Gershbein LL, *Transactions of the Illinois State Academy of Science*, Supplement to Volume 82, Abstract 48, (1989).