MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

- LEGISLATIVE HISTORY
  - Originated in HASC Amendment - May 1984
  - FY 1985 Appropriations Continuing Resolution - $10.0M
  - SAC for FY 1986 Appropriations - $12.5M
  - Conference Report FY 1987 Continuing Resolution - $15.0M
- CONGRESSIONAL DIRECTION
  - "Develop Five University - Based Multi-Disciplinary Regional Centers to Explore use of MFEL in Medical and Materials Sciences."

MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

- **SDIO REACTION TO CONGRESSIONAL DIRECTION:**

"MR. BATTISTA, FRANKLY WE ARE DELIGHTED TO LEND OUR MANAGEMENT EXPERTISE AND THE CAPABILITY THAT ALL OF OUR RESEARCH TOOLS AND OUR CONTRACT TEAMS OFFER TO THAT KIND OF APPROACH."

LIEUTENANT GENERAL ABRAHAMSON'S REMARKS TO THE SUBCOMMITTEE ON RESEARCH AND DEVELOPMENT OF THE HASC ON 19 MARCH 1985.

MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

SITE CHARACTERISTICS

SITE	ACCELERATOR TYPE	NOMINAL WAVELENGTHS	PULSE PARAMETERS	COMMENTS
STANFORD 1 CA	RF LINAC 43 MEV	2-10 MICRONS HARMONICS	~10 MICROSEC 60 ps	OPERATIONAL
	STORAGE RING 1 GeV	200 ANGSTROM UP	CW	COMPLETION SCHEDULED IN 1989
STANFORD 2 CA	SUPERCONDUCTING RF LINAC	1.6-4 MICRONS HARMONICS	10-100 MILLISEC	HELIUM REFRIGERATION BEING INSTALLED
U.C. SANTA BARBARA	VAN DeGRAFF 6 MEV	100-1000 MICRONS	CW, NO MICRO	OPERATIONAL
NATIONAL BUREAU OF STANDARDS, MD	RACETRACK MICROTRON	0.3-4 MICRONS	CW	UNDULATOR ADDITION
VANDERBILT UNIVERSITY, TN	RF LINAC 43 MEV	2-10 MICRONS HARMONICS	10 MICROSEC	COMMERCIAL
NATIONAL SYNCHROTRON LIGHT SOURCE AT BROOKHAVEN NATIONAL LABORATORY, NY	STORAGE RING 0.75 GEV	~60 ANGSTR UP	CW	UNDULATOR ADDITION

MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

CONTRACTS WITH

- 14 UNIVERSITIES
- 1 HOSPITAL
- 2 NATIONAL LABORATORIES
- 2 COMMERCIAL LABORATORIES
- NATIONAL BUREAU OF STANDARDS

REGIONAL CENTERS

- STANFORD UNIVERSITY, STANFORD, CALIFORNIA*
- VANDERBILT UNIVERSITY, NASHVILLE, TENNESSEE
- UNIVERSITY OF CALIFORNIA AT SANTA BARBARA*
- BROOKHAVEN NATIONAL LABORATORY — LONG ISLAND, N.Y.
- NATIONAL BUREAU OF STANDARDS, GAITHERSBURG, MARYLAND

*EXISTING FEL FACILITIES

7-2636

MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

CONTRACTS

UNIVERSITIES
- STANFORD UNIVERISTY*
- UNIVERSITY OF CALIFORNIA — SANTA BARBARA*
- UNIVERSITY OF UTAH
- NORTHWESTERN UNIVERSITY
- BAYLOR RESEARCH FOUNDATION
- UNIVERSITY OF CALIFORNIA — IRVINE
- UNIVERSITY OF MICHIGAN
- PURDUE UNIVERSITY
- PRINCETON UNIVERSITY
- BROWN UNIVERSITY
- VANDERBILT UNIVERSITY*
- SOUTHERN METHODIST UNIVERSITY
- UNIVERSITY OF TEXAS
- STATE UNIVERSITY OF NEW YORK AT BUFFALO

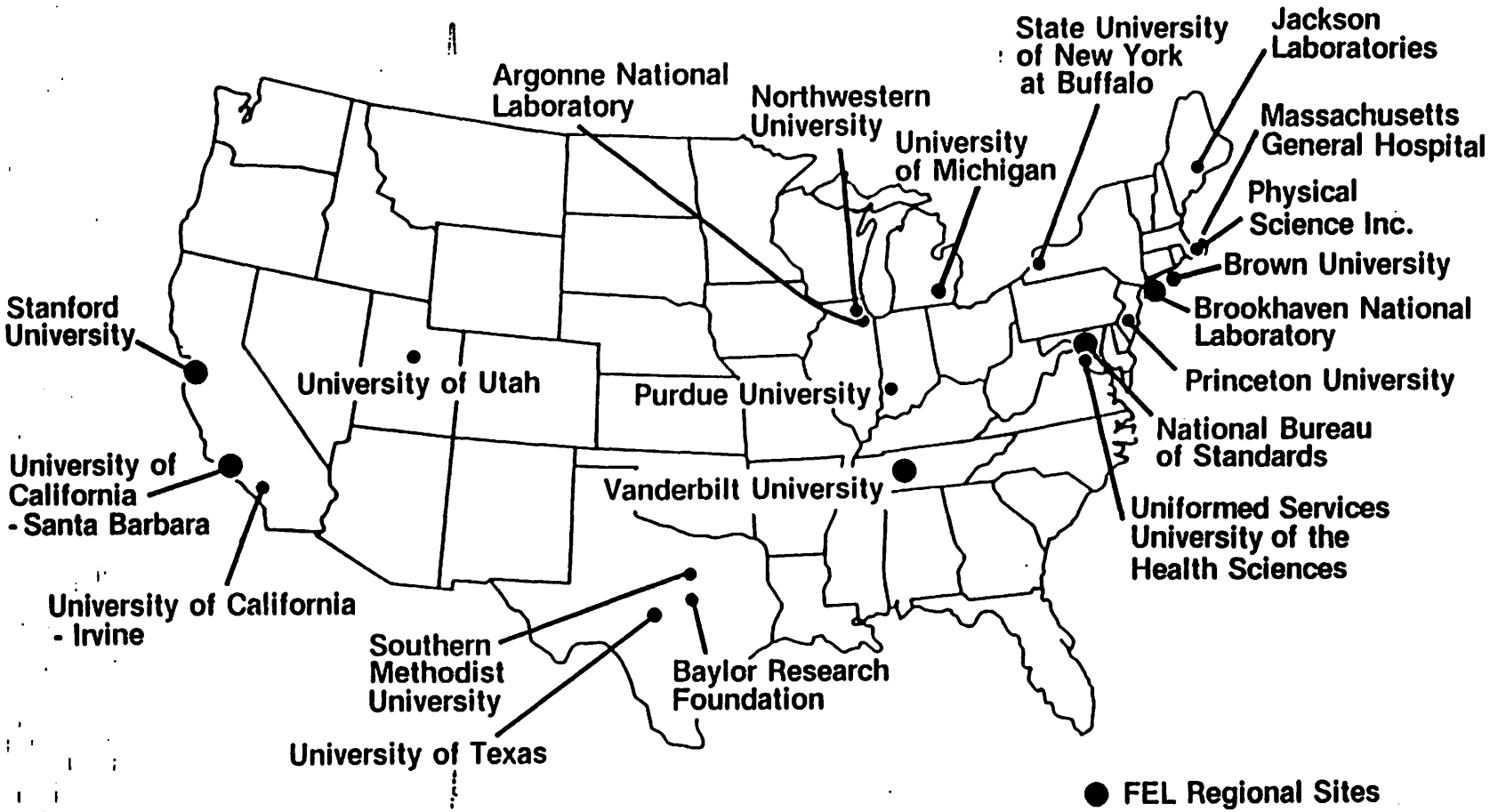
*FEL SITES

NATIONAL LABORATORIES
- ARGONNE NATIONAL LABORATORY
- BROOKHAVEN NATIONAL LABORATORY*

COMMERCIAL LABORATORIES
- JACKSON LABORATORIES
- PHYSICAL SCIENCE INC.

DEPARTMENT OF COMMERCE
- NATIONAL BUREAU OF STANDARDS*

MEDICAL FREE ELECTRON LASER



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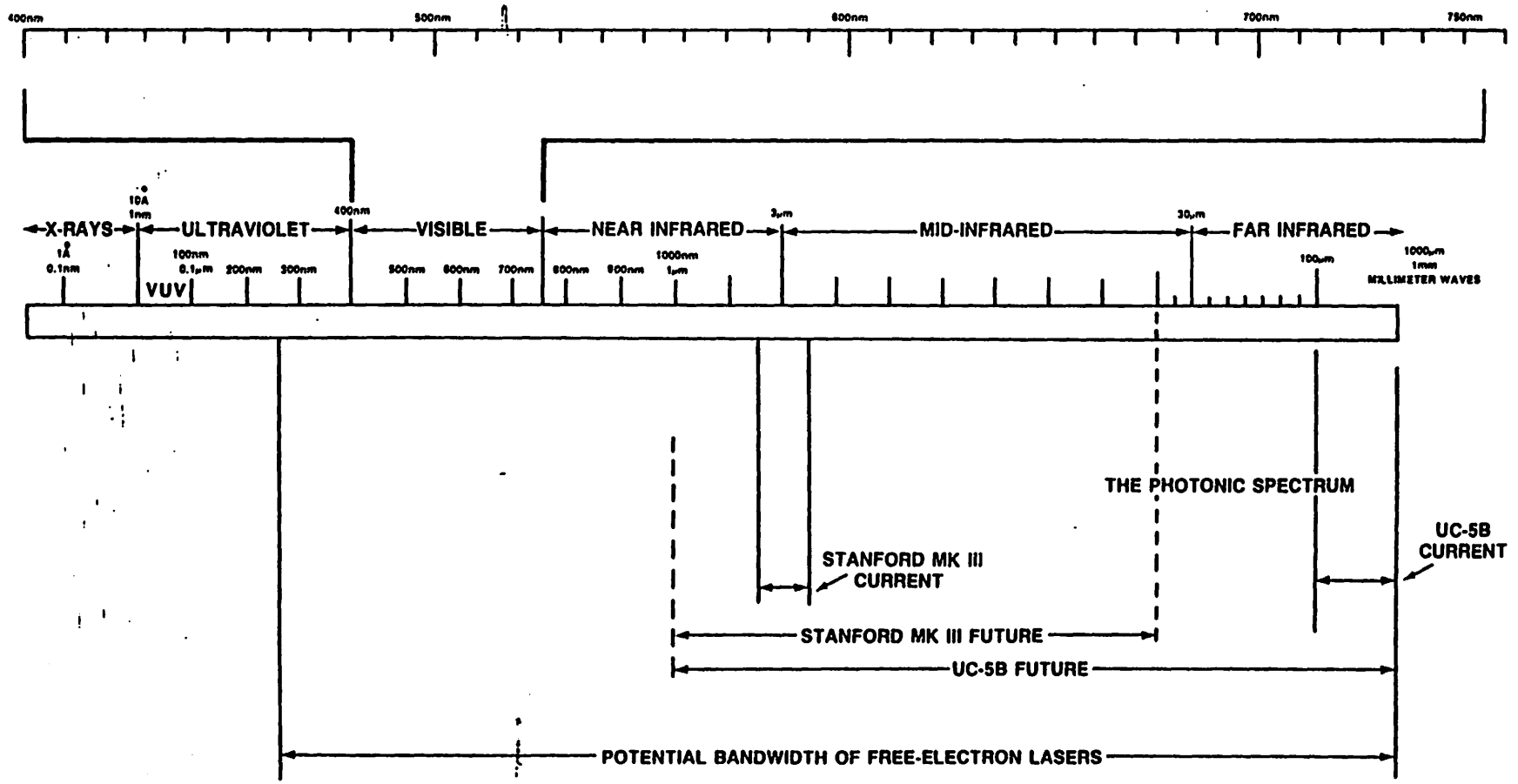
MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM



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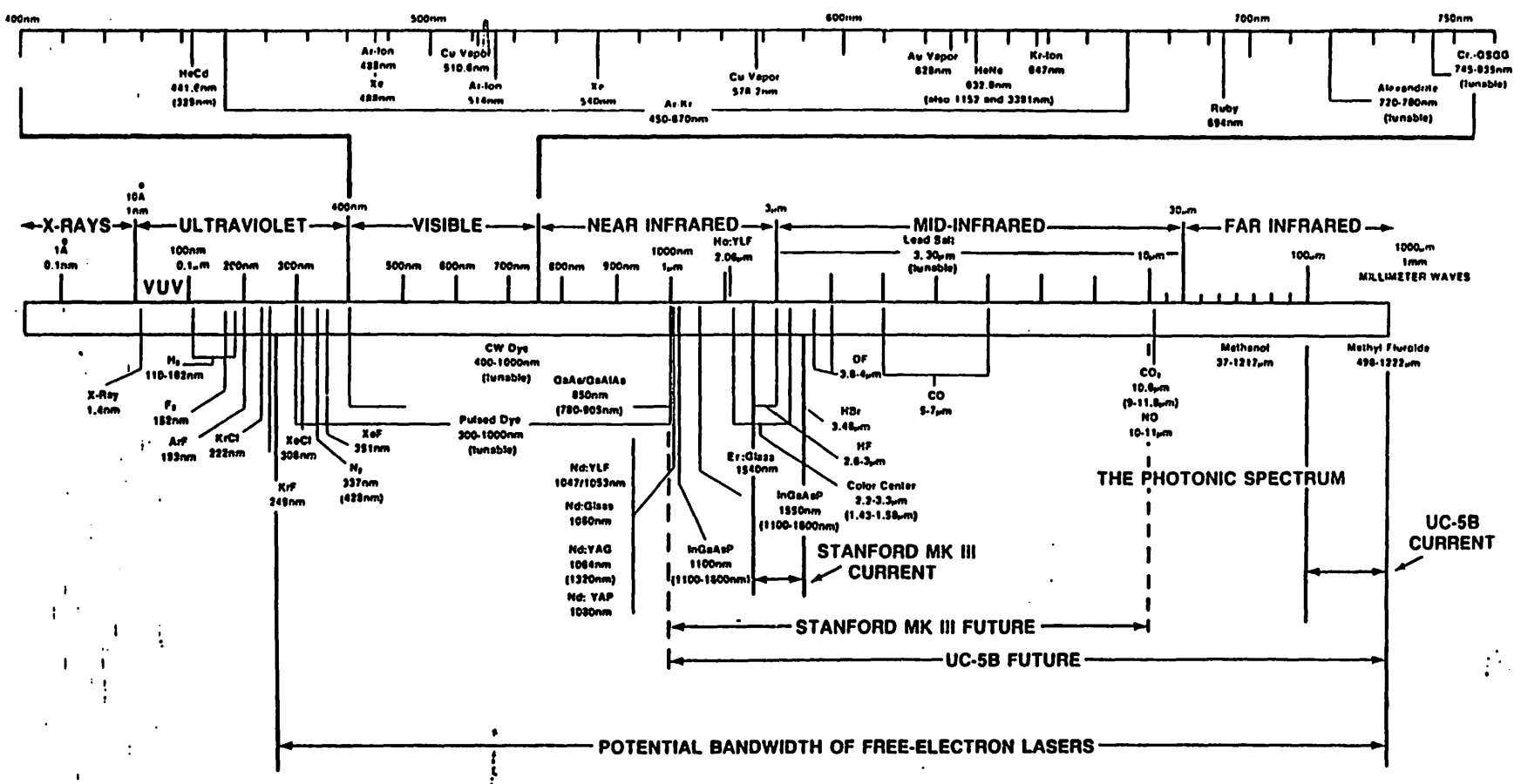
MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM



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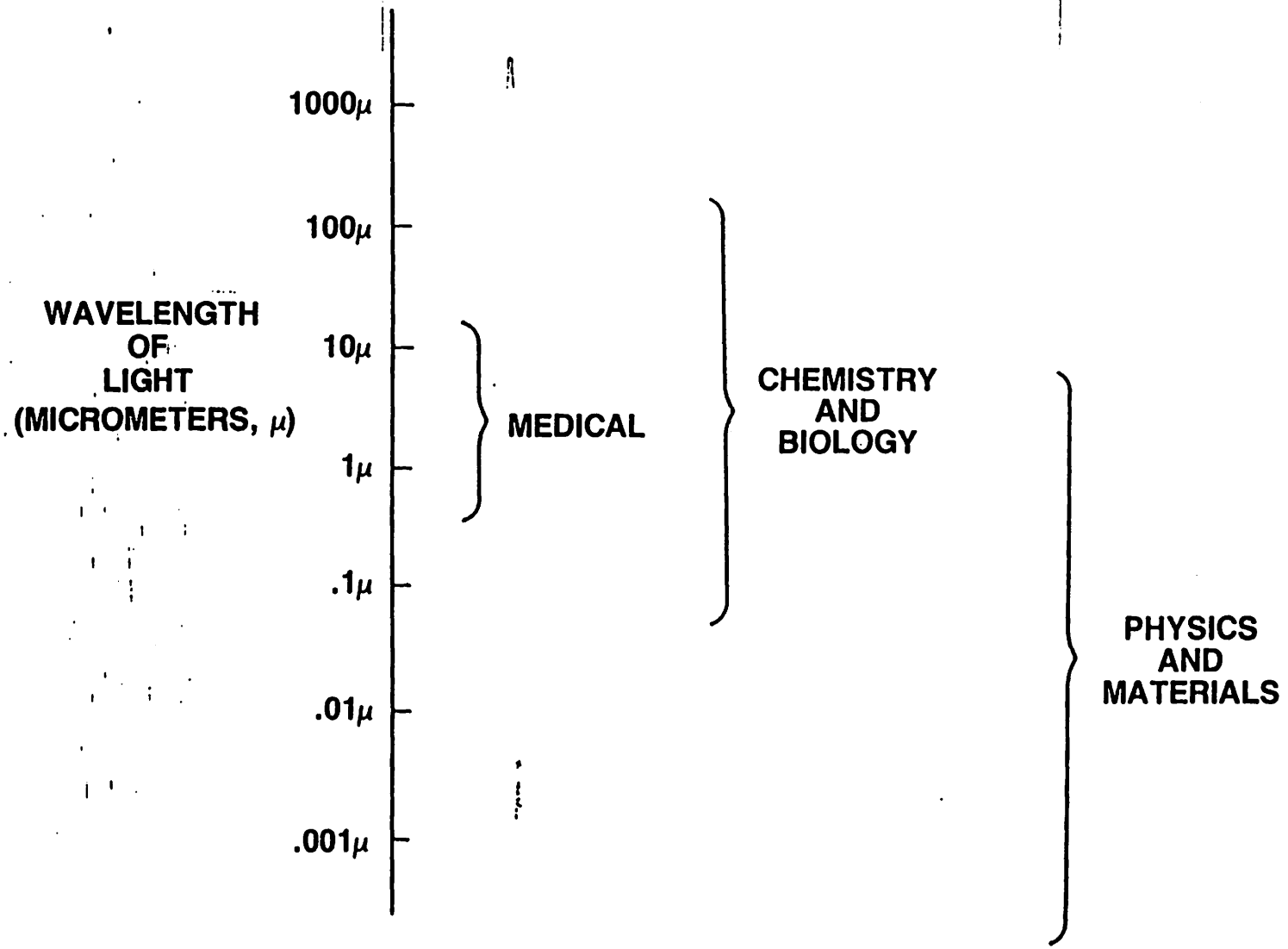
MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

CHARACTERISTICS OF FEL'S ATTRACTIVE FOR BIOMEDICAL AND MATERIALS RESEARCH

- BROAD WAVELENGTH SELECTION
- TUNABILITY
- HIGH PEAK POWER, SHORT DURATION PULSES
- HIGH AVERAGE POWER

MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM



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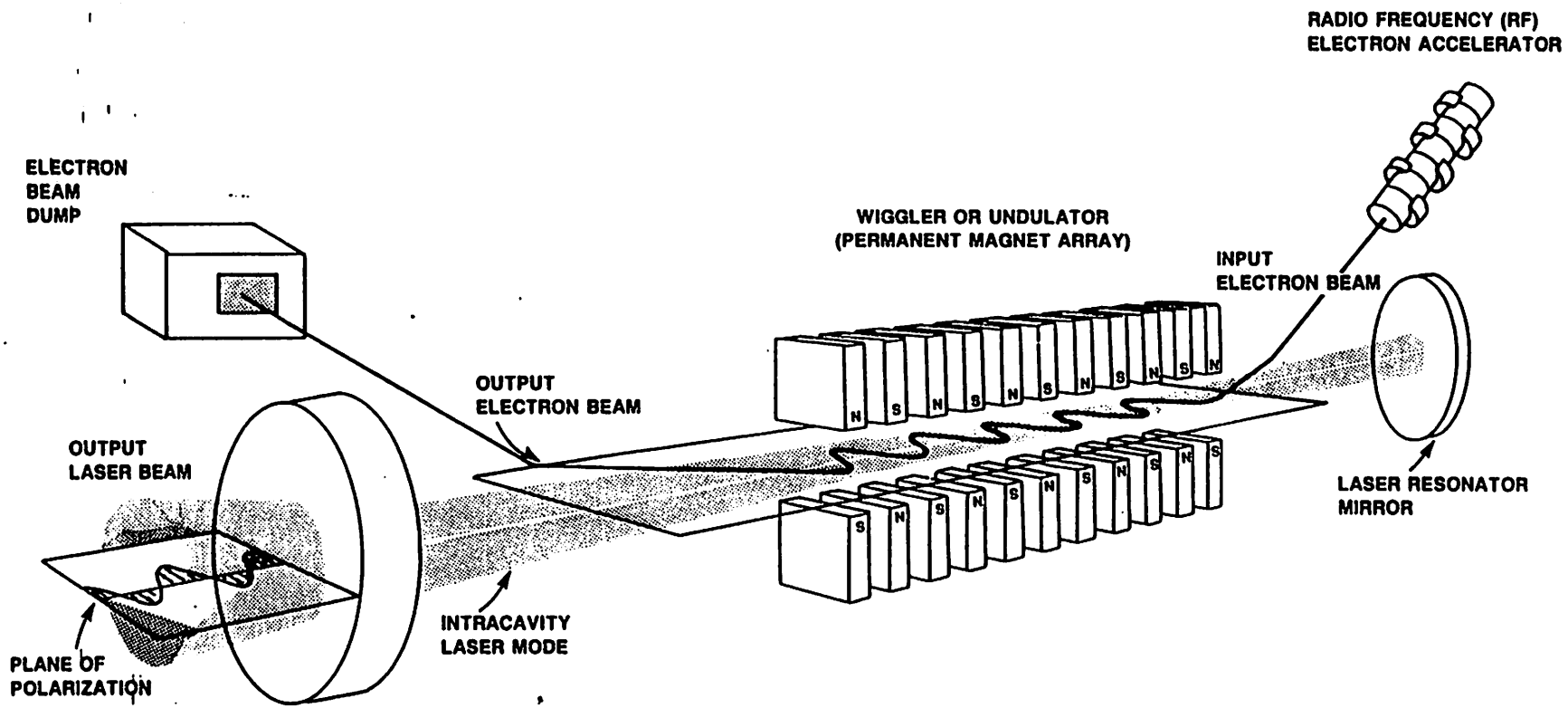
MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM



THE FREE-ELECTRON LASER

7-2638

MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

MASSACHUSETTS GENERAL HOSPITAL (MASSACHUSETTS EYE AND EAR INFIRMARY)

- FRAGMENTATION OF KIDNEY STONES AND GALLSTONES — PLASMA MECHANISMS
- FEMTOSECOND OPTICAL RANGING
- PHOTODYNAMIC THERAPY — TWO PHOTON PROCESSES
- TISSUE ABLATION MECHANISMS
  - PULSED UV/VIS — CORNEA & LENS
  - PULSED IR — SKIN GRAFTS/BURN THERAPY
- SPECTROSCOPIC DIAGNOSIS TECHNIQUES — PULSE/PROBE
- LASER ANGIOPLASTY — VARIABLE WAVELENGTH

MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

UC-IRVINE/BECKMAN LASER INSTITUTE

- CELLULAR EFFECTS OF NEAR AND FAR-IR
- ACTION SPECTRA ON SEVERAL CELL LINES
  - THERMAL CONTROLS
  - HISTOLOGY AND EM ANALYSIS
  - MUTAGENICITY
  - BIOCHEMISTRY (PROTEINS, RNA, ...)

MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

UNIVERSITY OF UTAH

1. LITHOTRIPSY
2. TISSUE INTERACTIONS — THERMAL MODELLING
3. SINGLE & MULTIPHOTON LUMINESCENCE
4. PHOTOTHERAPY — IN VIVO
5. SPECTROSCOPIC ANALYSIS OF TISSUE (IN VIVO)

NORTHWESTERN UNIVERSITY

1. LASER DELIVERY SYSTEMS
2. TISSUE HOLOGRAPHY
3. ENERGY ABSORPTION MODELS FOR TISSUE
4. OPTICAL DOSIMETRY
5. NEUROPHYSIOLOGY & NEUROSURGERY (IN VIVO)

MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

BAYLOR UNIVERSITY

CELLULAR LEVEL

1. UPTAKE AND COMPARTMENTALIZATION OF ORGANIC DYES
2. MODELS FOR MICROTHERMAL DAMAGE
3. DNA INTEGRITY

TISSUE LEVEL

1. THERMAL MODELLING, ESPECIALLY IN MID-IR
2. ABLATION MECHANISMS
3. DYE UPTAKE AND SPECIFICITY

MOLECULAR LEVEL

1. PROTEIN DYNAMICS VIA TIME-DEPENDENT FLUORESCENCE

MEDICAL FREE ELECTRON LASER (MFEL) PROGRAM

U. MICHIGAN/STEEL

1. NONLINEAR LASER SPECTROSCOPY OF PROTEIN-LIPID INTERACTIONS
2. OPTICAL PHASE — CONJUGATION TO ELIMINATE SCATTERING

PURDUE U./PROHOFSKY

THEORETICAL ANALYSIS OF DNA MELTING MODES

PRINCETON U./AUSTIN

SPIN TUNNELING IN HEME PROTEINS

U. TEXAS/WELCH

COMPUTER MODELS FOR TISSUE—LIGHT INTERACTIONS

JACKSON LABS/SAFFER

EFFECTS OF FAR—IR ON GENE EXPRESSION

PHYSICAL SCIENCES INC.

THEORETICAL MODELS FOR TISSUE/CALCULI ABLATION

PURDUE U./VAN ZANDT

INFORMATION STORAGE ON DNA PLYMER CHAINS

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
F. EDWARD HÉBERT SCHOOL OF MEDICINE
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799

SCHOOL OF MEDICINE

25 February 1987

TEACHING HOSPITALS
WALTER REED ARMY MEDICAL CENTER
NAVAL HOSPITAL BETHESDA
MALCOLM GROW AIR FORCE MEDICAL CENTER
MALFORD HALL AIR FORCE MEDICAL CENTER

Colonel James A. Ball, USAF
Director of Civil Applications Office
Strategic Defense Initiative Organization
Washington, D.C. 20301-7100

Dear Colonel Ball:

Enclosed are the summaries which you requested.

Kenneth E. Kinnamon, D.V.M., Ph.D.
Director, Medical Applications of
Advanced Laser Technology Project

cc:

Dr. Simmonds
Dr. Holmes
Dr. O'Brien
Dr. Van De Merwe

MEDICAL APPLICATIONS OF ADVANCED LASER TECHNOLOGY

CLINICALLY RELEVANT RESEARCH IN EXPERIMENTAL ANIMALS - I

PROGRAM DESCRIPTION:

Studies are being conducted in animal models to explore the applications of advanced laser technologies to problems of immediate human relevance. At present, nine research projects are active. These address a broad range of subjects such as the nonsurgical removal of atherosclerotic plaque, clearance of blocked liver bile ducts, kidney stone fragmentation, inner ear surgery, and cancer and peptic ulcer treatment.

"GAS EXCHANGE AND LUNG MECHANICS IN HIGH FREQUENCY OSCILLATION" (GM76AZ ABBRECHT)
Dr. Abbrecht is developing a laser technique to study lung function by measuring alveolar wall displacement with double-pulsed laser interferometry. He specifically is studying high frequency oscillations with the long-term goal of developing a simple, easy-to-use, respirator. This has direct application to mass casualty situations and field military medicine.

"LASER ANGIOPLASTY OF ATHEROSCLEROTIC VASCULAR OCCLUSIONS" (GM8394 GOLDSTEIN)
The ability of laser technology to provide a means of removing atherosclerotic blocked blood vessels is being investigated in a pig model. Laser energy will be delivered with a prototype catheter to the areas of vessel blockage. This procedure, if successful, will offer an alternative to heart surgery.

"ACUTE AND CHRONIC EFFECTS OF RADIATION ON GASTROINTESTINAL BLOOD FLOW" (GM8395 DUBOIS)
Laser flowmetry and velocitometry are being used in studies into the gastrointestinal effects of ionizing radiation. This approach offers the potential for developing non surgical methods for gastrointestinal studies.

"LASERS IN BILIARY OBSTRUCTION: RADIOLOGIC APPLICATION" (GM8916 DACHMAN)
Patients with obstruction of the liver bile duct must undergo great discomfort, and face a significant chance of complications including the possibility of surgery. This study is designed to develop a non surgical laser therapy by percutaneous catheter using a Nd:YAD laser to clear the ducts.

"LASER FRAGMENTATION OF URINARY CALCULI" (GM9064 SIHELNIK)
Kidney stones are a serious problem, in many cases requiring surgery. Dr. Sihelnik is working to develop a small, flexible, fiberoptic delivery system to fragment urinary calculi, and thus eliminate the need for surgery. In vivo and in vitro studies will be initiated to determine the requirements for stone fracture and tissue damage.

"CO2 AND ARGON LASERS AS ADJUNCTS TO PERILYMPHATIC FISTULA REPAIR" (GM9065 GONZALEZ)
Hearing deficiencies resulting from abnormal communication between the middle ear space and inner ear fluids currently require grafting with adipose tissue. The anatomy of the middle ear cleft makes this a very difficult procedure, with failure rates as high as 47%. This study proposes to use Argon and CO2 lasers to repair these ear defects employing a chinchilla animal model.

"APPLICATION OF LASER DOPPLER VELOCIMETRY FOR CNS BLOOD FLOW MEASUREMENT"
(GM9229 FEUERSTEIN)
The ultimate goal of this project is to develop a noninvasive method for continuous measurement of blood flow in the brain and spinal cord. The study will use a Laser Doppler Velocimeter to study microcirculation in the central nervous system, and assess the accuracy of the technique under pathological states.

"LASER-ENHANCED TRANSDERMAL DOSIMETRY" (GM7593 PECK)
The use of therapeutic drugs via absorption across the skin is best exemplified by the use of nitroglycerin patches for angina patients. The study proposed here is to reverse that application, and use skin patches to collect and measure body exposure to compounds such as cancer chemotherapy agent and hazardous industrial compounds. The ability of an excimer laser to enhance passive outward migration of chemicals into skin patches will be studied.

"CARDIOVASCULAR EFFECTS OF PHOTODYNAMIC THERAPY" (GM8027 FREAS)
A new approach to the treatment of several forms of cancer is photodynamic therapy. A photosensitive compound, generally hematoporphyrin, is infused. The compound does not stay in normal tissue, but it does collect in malignant cells. This method offers a way to detect and kill malignant tissue via exposure to laser light. A problem has been cardiovascular toxicity. Dr. Freas is studying the toxic side effects, with the goal of enhancing the effectiveness of therapy.

"USE OF LASERS TO RESTRICT GASTRIC ACIDITY" (GM9074 RICH)
The primary method for treating peptic ulcers which do not respond to medication is surgery to reduce gastric acidity. This is accomplished by either cutting various nerves to the stomach or removing the acid secreting cells. The study being conducted here will attempt to use laser light to kill selected stomach cells as an alternative to surgery.

BASIC MEDICAL RESEARCH AT THE CELLULAR LEVEL - II

PROGRAM DESCRIPTION:

The applications of various advanced laser technologies to understanding the basic mechanisms of the cell offer significant opportunities for major contributions to biomedical research. Studies are being conducted into the assembly and replication of nerve cells, the potential biohazard of sublethal irradiation, induction of latent virus expression, and interferon action.

"EFFECT OF LASER ENERGY ON CORNEAL ENDOTHELIUM" (GM9061 BAHN)
The ability of the corneal endothelium of the eye to repair and maintain its cellular integrity is crucial to vision. A badly compromised endothelium often results in blindness, requiring a corneal transplant to restore sight. Cellular repair of the corneal endothelium is the basic mechanism by which the eye repairs itself. In these studies, the response to damage will be studied. The normally transparent cornea will be deliberately compromised by direct laser light with a neodymium doped yttrium-aluminum-garnet laser. Pigmented cells will be damaged with a tuneable dye laser and the cellular process of repair studied.

"LASER INACTIVATION OF CELL DIVISION IN THE EYE" (GM7071 BEEBE)
This project proposes to utilize state-of-the-art laser technologies to prevent growth of certain cells associated with vascular diseases of the eye. Photoreactive inhibitors of specific cellular enzymes will be developed that will be uniquely sensitive to laser light. Biologic response can be predicted only at wave lengths that interact with cellular components. It is possible then to develop unique "photosensitive" chemicals that can be activated with a single wavelength of laser light, causing little or no damage to normal cellular components.

"ASTROCYTIC RESPONSE TO SELECTIVE NEURAL OR GLIAL TRAUMA BY LASER" (GM7072 ANDERS)
Laser microbeam technology is being utilized to study how the central nervous system repairs itself. Scar-forming cells called astrocytes cause a significant amount of the damage to the nervous system following insult. The laser will be used to create precise, nonlethal lesions. Scar formation following injury to the central nervous system and the underlying cellular mechanisms will be studied.

"LASER MICROSURGERY OF SINGLE AXONS IN VIVO" (GM7073 FORMAN)
Laser technology has provided micro precision never before available to study the dynamic event in neural tissue. Dr. Forman will be using video-enhanced light microscopy to study the regeneration of neurons following laser-induced lesions.

"APPLICATIONS OF LASER TECHNOLOGY TO STUDIES ON THE COMPLEMENT LESION" (GM7161 HU)
Use of laser to crosslink proteins and lipid probes will be utilized to study the insertion of complement into membranes in an effort to obtain a better understanding of the body's immune system.

"CARCINOGENESIS BY LASER-INDUCED MULTIPHOTON PROCESSES" (GM7498 SAMID)
Lasers are capable of generating intense bursts of monochromatic radiation in very short times, producing multiphoton excitation of various biomolecules that would normally not occur and certainly would not result from long-term exposures. Dr. Samid will be studying these effects at the cellular level, and determining the potential for hazardous effects resulting from exposure of cells to sublethal doses of high intensity vs low-intensity UV laser radiation.

"LASER MICROBEAM STUDY OF MOTILITY IN AMOEBOFLAGELLATES" (GM7070 ADELMAN)
The functioning of cellular cytoskeletal components will be studied using laser microsurgery and digital image processing. This study will provide insight into intracellular movement of structures critical to cell division.

"EFFECT OF CO2 LASER IRRADIATION ON THE INTERFERON SYSTEM" (GM7496 FRIEDMAN)
The cellular effects of irradiation by CO2 lasers on the production and action of interferon will be determined. Also to be determined will be the possibility that laser light could induce the expression of dormant viruses.

"BIOPHYSICAL ANALYSIS OF INTERFERON SIGNAL TRANSMISSION" (GM74AQ GRIMLEY)
Interferon is a biochemical produced by cells and has profound effects on cell growth, immune responses, and has major implications for leukemia therapy. Dr. Grimley has proposed to use microlaser methods to study the mechanism by which interferon acts on cell membrane, and how "chemical" messages are communicated across cell membranes.

BASIC MEDICAL RESEARCH AT THE MOLECULAR LEVEL - III

PROGRAM DESCRIPTION:

Recent developments in laser technologies are providing opportunities for new and innovative approaches to understand the basic chemical principles of biochemical processes. The ability to covalently crosslink transiently associated molecules in extremely short time periods is allowing for studies of cancer gene expression, viral replication, and hormone action. Other laser technologies are allowing structure determinations in rapidly changing dynamic biological events such as in enzymatic reactions.

"UV-LASER RAMAN SPECTROSCOPY OF NUCLEIC ACIDS" (GM7159 JOHNSTON)
Dr. Johnston is utilizing a tuneable UV-laser for the amplification of resonances to determine the macromolecular structure of a nucleic acid (2-5A) crucial to gene expression.

"PROTEIN STRUCTURE FROM LASER RAMAN SPECTROSCOPY" (GM7160 WILLIAMS)
Ultraviolet laser Raman spectroscopy is being developed to study protein structure. A long-term goal is to determine structure during folding and the kinetics of transient protein-substrate intermediates.

"PROBING THE MOLECULAR MECHANISMS OF CARCINOGENESIS" (GM7494 CHANG)
Certain types of cancer have been associated with a specific gene called a C-myc oncogene. Dr. Chang is utilizing the ability of lasers to crosslink transiently associated macromolecules to determine the protein product of the C-myc oncogene. This project is an effort to identify the sequence of events in the process of carcinogenesis

"RAPID KINETICS OF DNA-PROTEIN INTERACTIONS" (GM74AA MINTON)
Laser UV light is being used to study the kinetics of nucleic acid-protein interactions using an electrically interfaced excimer laser and a stop-flow reactor. This device wil allow precise millisecond interval measurements of important biologic reactions between DNA and proteins.

"ANALYSIS OF VIRUS ASSEMBLY USING LASER TECHNOLOGY" (GM74AB HOLMES)
The molecular biology of viral replication is being studied by covalently linking RNA virus-peptide aggregates during viral assembly. Attempts will also be initiated to develop a new technique for targeting laser damage to specific intracellular organelles.

"LASER-INDUCED PHOTOLYSIS FOR STUDY OF HORMONE RECEPTORS" (GM8522 FITZ)
The biochemistry of the reproductive process is being elucidated by studying cellular receptor-mediated mechanisms. The ability of laser light to covalently bind specially designed photoaffinity probes to their biologic targets will be utilized.

"PHOTOACTIVATION OF THE Ca-ACTIVATED CATION CHANNELS" (GM7176 BEELER)
The ability to control the movement of calcium into and out of cells is an important mechanism by which cells respond to their environment and control many intercellular processes. Dr. Beeler has proposed to take advantage of the ability of the Ng:YAG laser to measure extremely rapid reactions, and will be determining Ca release through Ca-activated channels. These channels will also be perturbed with high energy laser pulses interacting with laser-sensitive photochromophores to gain a better understanding of the channel's function.

"LASER PROBING OF VIRUS STRUCTURE AND FUNCTION" (GM7374 HAY)
The biochemical mechanisms in herpes virus infection are to be investigated using the unique features of laser technology to probe protein-nucleic acid complexes, and provide anchored cell analysis and sorting.

"MECHANISM OF ACTION OF 2-5A-DEPENDENT RNase" (GM74AP SILVERMAN)
Laser technologies will be used to probe the molecular mechanisms by which an enzyme (2-5A-dependent RNase) recognizes and cleaves biological compounds. The system being probed involves a critical step in the control of gene expression.