Exhibit R-2, RDT&E Budget Item Justification						Date: February 2005		
Appropriation/Budget Activity RDT&E, DW/ BA2				R-1 Item Nomenclature Medical Free Electron Laser, PE 0602227D8Z				
Cost ($ in Millions)	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011
Total PE Cost	17.919	18.322	9.845	10.096	10.392	10.153	10.351	10.591
Medical Free Electron Laser/P483, Subtotal Cost	17.919	18.322	9.845	10.096	10.392	10.153	10.351	10.591

A. Mission Description and Budget Item Justification

(U) The Medical Free Electron Laser (MFEL) program seeks to develop advanced, laser-based applications for military medicine. Free electron lasers (FELs) provide unique pulse features and tunable wavelength characteristics that are unavailable in other laser devices. Thus, FELs broaden the experimental options for the development of new laser-based medical technologies.

(U) This program is focused on developing advanced procedures and equipment for rapid diagnosis and treatment of battlefield-related medical problems. Specific applications under investigation include soft tissue repair, hard tissue surgery, therapies for thermal and chemical burns, warfighter vision correction, photochemical treatment of difficult infectious agents, and new medical imaging modalities. Unique, innovative laser applications will be clinically tested in medical centers, leading to Food and Drug Administration (FDA) approval. There is a high potential for dual use in civilian medicine. Thus far, more than 30 clinical procedures have been developed in several medical specialties, including ophthalmology, orthopedics, thermal and chemical burn treatment, and neurosurgery. Work in these areas will continue in FY 2005 under the current three-year center grants, with the primary focus of the work remaining on the development of militarily relevant laser medicine applications.

(U) Plans include efforts to strengthen interactions of the grantee institutions with military medical research facilities in order to improve both the content of the grant programs and the implementation of new techniques in military medicine.

Exhibit R-2, RDT&E Budget Item Justification	Date: February 2005

B. Program Change Summary:

	FY 2004	FY 2005	FY 2006	FY2007
Previous President's Budget:	18.518	9.668	9.850	10.072
Current FY2006 President's Budget Submission:	17.919	18.322	9.845	10.096
Adjustments to Appropriated Value:	-0.599	+8.654	-0.005	+0.024
Congressional Program Reductions:	-0.139	-0.346		
Congressional Rescissions:				
Congressional Increases:		9.000		
Reprogrammings:				
SBIR/STTR Transfers:	-0.460			
Program Adjustment:			-0.005	+0.024

C. Other Program Funding Summary: Not Applicable

D. Acquisition Strategy: Not Applicable

E. Performance Metrics: Performance in this program is monitored using instances of successful commercialization of new instruments and techniques; the transfer of new clinical methods to regular clinical use; the number, quality and placement of publications in the open scientific literature; and the numbers and content of patent applications filed.

Exhibit R-2a, RDT&E Project Justification						Date: February 2005		
Appropriation/Budget Activity RDT&E, DW/BA 2				Project Name and Number Medical Free Electron Laser, PE 0602227D8Z				
Cost ($ in millions)	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011
Project/Thrust Cost	17.919	18.322	9.845	10.096	10.392	10.153	10.351	10.591

A. Mission Description and Budget Item Justification:

(U) The MFEL Program seeks to develop advanced, laser-based applications for military medicine.

(U) The majority of this program is focused on developing advanced procedures for rapid diagnosis and treatment of battlefield-related medical problems.

(U) A small part of this program is focused on related materials research.

(U) Overall management plans for FY 2005 include continued efforts to strengthen the interactions of the grantee institutions with military medical research facilities in order to improve both the content of the grant programs and the implementation of new techniques in military medicine. Increased emphasis will be placed on investigations of potential photochemical treatments of infectious diseases.

B. Accomplishments/Planned Program

(Cost in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Imaging Technology	4.474	3.951	2.480	2.542

Optical Coherence Tomography (OCT) applications have been developed to assess the clinical status of burns by combining polarization sensitivity for tissue structure and birefringence with Doppler detection to simultaneously measure blood flow in the tissue. Resolution of the extent of the burn can be made to between 2 and 10 um. OCT applications also have been developed for diagnosis and monitoring of surgical repair of orthopedic injuries and injuries to the trachea and respiratory tract using hand-held probes for imaging. Work on improving the resolution and speed of OCT imaging continues, with resolutions down to 1 um shown to be possible with short pulse lasers. Resolution to 3 um has been obtained and an ophthalmic imaging system using this capability has been made, and is in regular clinical use. A 72-fold increase in imaging speed also provides opportunity to detect subtle changes in tissue to improve the management of various injuries. A tunable, monochromatic x-ray system has been developed using the electron beam of a radio frequency accelerator to scatter beams from a terawatt laser, producing the x-rays through an inverse Compton effect. The monochromatic x-ray system provides significantly improved images when compared

with standard x-ray sources. Other potential technologies include a Pulsed Photothermal Radiometry technique that can be used to determine changes in the optical properties of the skin and provide diagnostic information on wound management and absorption on the skin of possible chemical agents, and Photon Migration techniques to non-invasively monitor hemodynamic parameters such as oxy/deoxy-hemoglobin ratios. Optical diagnostic methods based on Raman scattering and terahertz spectroscopy are being studied to detect and rapidly characterize important biomolecules of interest. Optical methods are also being used to investigate molecular processes in cells tagged with microparticles, and the specific capabilities of molecular biosensors. The potential use of near-field infrared microscopy in cellular imaging is also being examined. Plans for 2005 include work on improving the contrast and depth of OCT imaging with emphasis on its use in burn injury, development of new ultrasmall fiber optic endoscopy systems, continued development of monochromatic x-ray and Pulsed Photothermal Radiometry applications, new applications of Near Field Optical Microscopy, and other IR microscopy techniques.

(Cost in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Laser Surgery Methods	2.125	2.576	1.561	1.624

FELs continue to be used in experimental surgery studies in animals and humans. An FEL has been used in the surgical removal of a human brain surface tumor, and in optical nerve sheath fenestration. Experimental surgery studies are developing laser beam delivery endoscopes for the precision surgical requirements of optic nerve repair and neurosurgical treatment of epileptic foci. Studies examining the most effective laser wave length and pulse duration variables for cutting hard tissue and optimizing post-ablation bone regeneration and healing are also in progress. Studies to determine optimal methods for using lasers for properly shaping collagen materials for use in reconstructive surgery are examining the molecular nature and behavior of the collagen during the reshaping process. Proper shape and shape memory of the material are of critical importance in success of reconstruction efforts. Work under this program has also led to the observation of laser effects on chondrocyte regeneration, critical for effective treatment of arthritic degeneration. An effective animal model for study of corneal healing after laser vision correction surgery has been developed, and subsequent work using this model has described important steps to minimize the scarring which can adversely affect vision correction efforts. Plans for 2005 include continuing studies in neurological and ophthalmic surgery applications of lasers, as well as continuing work on optimal laser parameters for dermal and hard tissue cutting and subsequent healing. New efforts will examine the application of laser-based imaging and laser effects on chondrocyte regeneration for orthopedic repair of cartilage.

(Cost in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
General Clinical Medicine Techniques	2.703	3.271	1.580	1.643

The use of photosensitive materials that can bind to cells, become activated on illumination, and cause a subsequent change in cell activity has been shown to have a number of clinical applications. Photosensitive compounds can be used to tag specific bacteria and lead to virtually complete elimination of the organisms. Antibiotic resistant strains remain vulnerable to such photodynamic

therapy. Wounds infected with ordinarily fatal strains of *Psuedomonas* and various *Staphylococcus* organisms were completely healed following treatment with photosensitive compounds. Studies on the effect of using this technique for the treatment of difficult infections such as Leishmaniasis have being initiated and appear promising. Other photosensitive compounds attached to cells have been shown to be able to modulate cellular activity. For example, chondrocytes, activated by light sensitive molecules, have been able to initiate complex processes that prevent inflammatory destruction of collagen explants. Similarly, light absorbing nanoparticles have been shown to affect various properties of cells, including their permiability, which may provide the possibility of controlling cell processes, as well as improving drug uptake and effectiveness. Photochemical controlled tissue bonding studies have led to the development of materials that provide wound closure that is superior to current mechanical or adhesive methods. The photochemical bonding material was first demonstrated in the closure of the flaps generated during laser vision correction surgery. The material, a sensitizing dye that photochemically crosslinks the tissue surfaces, has been used in repair of blood vessels, the cornea and skin. It is now being tested for effectiveness in nerve and tendon repair, and repair of damage to the trachea. In 2005, studies will continue on photochemical bonding of tissue, developing new photosensitizers and methods for their delivery, mechanisms for controlling various cellular activities, and the use of photodynamic therapy in treating infections of selected microorganisms.

(Cost in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Laser/Tissue Interactions and Wound Healing Studies	2.230	2.502	1.471	1.534

A wide range of studies has examined the interactions of laser energy with tissues, cells and biological macromolecules. Models for laser ablation have been developed and used to examine the course of the post-ablation healing process. Studies using the unique single micropulse capability of the Stanford FEL continue and will provide valuable information on the role of wavelength, pulse structure and pulse sequence in the ablation process on the molecular level. Confocal microscopy with subcellular resolution is being used to follow the processes of fibronectin growth and wound closure. Vasodialation, which is an important factor in wound healing, has also been shown to be sensitive to the application of UVA and blue light *in vivo*. Studies examining the effect on wound healing of this phenomenon and its enhancement by norepinephrin, a known vasoconstrictor, are also underway. Studies on laser ablation and the subsequent healing processes will continue in 2005, with a continuing focus on determining tissue viability at the wound site, as this is critical for effective wound management. Work on wound closure using photochemical tissue bonding will also be a significant focus. Vasodilation studies for treating ischemic wounds will also be continued.

(Cost in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Physical and Materials Science Research	0.947	0.908	0.335	0.335

Research on the improvement of the performance and reliability of the FELs is a continuing effort. Such work includes the development of new materials for waveguides through which the laser energy may be routed as well as refinements in the existing laser systems. In addition, basic efforts are carried out using laser-based spectroscopy methods, on the structure and nature of biologically important macromolecules, on the dynamics of various surface-based processes, and on the nature, formation and deposition processes of complex thin films. Continued work on spectroscopy methods, surface-based processes, and the nature and formation of thin films are planned for 2005.

(Cost in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Laser Operations Support	5.440	5.113	2.418	2.418

A major upgrade in the components of the Duke University FEL system has been completed, greatly improving the efficiency and overall capability of the system for research. Protocols for the use of the system are being developed. A total of more than 5,000 hours of beam time has been provided for the use of various scientists at the three FEL facilities combined. Plans for 2005 include continued efforts to improve FEL performance and reliability at each of the FEL sites, and to supply increased beam time for use by investigators in all of the disciplines noted above.

C. Other Program Funding Summary: Not Applicable

D. Acquisition Strategy: Not Applicable

E. Major Performers: Laboratories/Centers:

Beckman Laser Institute, University of California-Irvine, Irvine, CA
Duke University, Durham, NC
Stanford University Picosecond FEL Center, Stanford, CA
Vanderbilt University FEL Center for Research, Nashville, TN
Wellman Laboratories, Massachusetts General Hospital, Boston, MA