RDT&E BUDGET ITEM JUSTIFICATION SHEET (R-2 Exhibit)									DATE February 2002	
APPROPRIATION/BUDGET ACTIVITY RDT&E, Defense Wide/BA 1							R-1 ITEM NOMENCLATURE In-House Laboratory Independent Research (ILIR) **PE 0601101D8Z**			
COST *(In Millions)*		FY2001	FY2002	FY2003	FY2004	FY2005	FY2006	FY2007	Cost to Complete	Total Cost
Total Program Element (PE) Cost		1.989	2.081	2.126	2.187	2.387	2.430	2.477	Continuing	Continuing
ILIR/P503		1.989	2.081	2.126	2.187	2.387	2.430	2.477	Continuing	Continuing

(U) A. Mission Description and Budget Item Justification

(U) BRIEF DESCRIPTION OF ELEMENT

(U) This program element supports basic medical research at the Uniformed Services University of the Health Sciences (USUHS) and provides the only programmed research funds received by the University. In addition, it facilitates the recruitment and retention of faculty; supports unique research training for military medical students and resident fellows; and allows the University`s faculty researchers to collect pilot data in order to secure research funds from extramural sources (estimated $25-$30 million annually). Eighty to 100 intramural research projects are active each year, including 20-25 new starts. Projects are funded on a peer-reviewed, competitive basis. Results from these studies contribute to the fund of knowledge intended to enable technical approaches and investment strategies within Defense Science and Technology (S&T) programs.

(U) The ILIR program at USUHS is designed to answer fundamental questions of importance to the military medical mission of the Department of Defense in the areas of Combat Casualty Care (CCC), Infectious Diseases (ID), and Military Operational Medicine (MOM). The portfolio of research projects will vary annually because this research is investigator-initiated. Examples of typical research efforts are:

(U) Combat Casualty Care: Ischemia and reperfusion injury, traumatic brain and peripheral nerve injury, neural control of pain, endotoxic shock, cryotherapy, malignant hyperthermia, inflammation, and wound healing.

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(U) Infectious Diseases: Immunology and molecular biology of bacterial, viral and parasitic disease threats to military operations. These threats include E. coli and their shiga toxins, HIV, HTLV-1, strongyloides, gonorrhea, streptococcus, staphylococcus, hepatitis A, helicobacter pylori, typhoid, influenza A, Venezuelan equine encephalitis (VEE), malaria, and bartonellosis.

Military Operational Medicine: Sustainment of individual performance; mapping and managing deployment and operational stressors; cognitive enhancement; and military & medical training readiness.

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(U) Project Number and Title: P503 ILIR

(U) PROGRAM ACCOMPLISHMENTS AND PLANS

(U) FY 2001 Accomplishments:

(U) Infectious Diseases: Representative projects included a family of epidemiological studies of both endemic and epidemic Bartonellosis in Peru that have recently combined information systems and molecular diagnostic technology to isolate a specific constellation of environmental factors associated with spread of the disease. Investigators attempting to develop new antibodies to E. coli and its Shiga toxins have completed their work; the project will now move into Phase I safety studies under the aegis of NIH. An ongoing investigation of the lifecycle and metabolism of *cryptosporidium parvum* (Cp) identified possible pathways for effective new drug treatments based on the location of 4 enzymes unique to Cp, which causes diarrheal illness. These projects supported essential military missions by advancing our understanding of the transmission and internal mechanisms of a spectrum of pernicious and/or common diseases that may be faced by military personnel at home or abroad. In turn, that understanding opens avenues to better control, diagnosis, and treatment of natural and man-made biological threats. ($ 0.639 million)

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(U) Military Operational Medicine: Studies of the protein melanopsin have shown a homology between the protein found in the skin of African frogs and that in the eyes of insects and mammals. A project investigating the circadian photoentrainment pathway in a murine model has developed the reagents needed to determine the chemical content of ganglion cells involved in the central circadian oscillator; the investigators have also completed two promising histochemical pilot studies. An exploration of electrochemical processes in the amygdala has partially characterized a mechanism that appears important in the formation and consolidation of emotional memory, and thence in the development of neuropsychological disorders resulting from battle experiences, such as depression and PTSD. A study of the effects of stress on suppression of the immune system identified a specific group of proteins that are both elevated during stress and critical to protecting lymph cells. Two epidemiological investigations, one of Gulf-War databases and one of direct responses from active-duty submarine personnel, have begun to identify life stressors commonly reported by deployed warfighters. These studies supported essential military missions by increasing our understanding of and ability to manipulate the physiological mechanisms of stress and immunity, human sleep and seasonal cycles, and neurological changes necessary to short- and long-term memory. In turn, their discoveries should enable warfighters to stay awake longer with fewer detriments to performance; lead to better strategies for enhancing and preserving memory and reasoning capabilities under battle conditions; help understand and ultimately prevent and treat neurospsychiatric illnesses such as depression and PTSD; and assist deployed troops and their families to better prepare for and contend with common, significant stressors. ($ 0.997 million)

(U) Combat Casualty Care: Representative studies include an ongoing investigation of signal transduction that has now identified two antibodies pinpointing the mu opioid receptor in the brain, an essential step to understanding the mechanism of opiate effects on pain relief and neural functioning. A controlled study of individuals susceptible to malignant hyperthermia (MH) has demonstrated that MH-susceptible individuals exhibit slower rates of lactate removal with strenuous exercise, which may explain the sudden, severe symptoms, similar to heat stroke, that such individuals can experience under physical stress. A project that explores the response of Schwann cells in neuroregeneration after removal of an axon identified two optimal sites of regeneration. These studies supported essential military missions by further exploring the mechanism of pain control for an established treatment; providing the groundwork for effective treatments to limit nerve damage and encourage regeneration; and identifying a possible cause of life-threatening complications of the combination of exertion and injury common under heavy battle conditions. ($ 0.353 million)

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(U) FY 2002 Plans:

(U) Infectious Diseases: Work continues toward development of vaccines for HIV, gonorrhea, and other STDs; understanding of the pathogenesis of VEE, HTLV-1, and influenza A; effective management of infections by *H. pylori* and bartonellosis; and analysis of Hendra virus envelope glycoproteins. New projects include a study of initial host-parasite interactions in *Salmonella typhi* infections, the regulation of virulent products of infection (such as toxins), and investigation of a possible marker for typing staph infections. These studies continue to support essential military missions by extending scientific understanding, control, and treatment of eminently possible biological threats, both natural and man-made, faced by Americans at home and abroad. ($ 0.780 million)

(U) Military Operational Medicine: Representative new studies address the relationship between axonal growth and synaptic hyperconnectivity in the brain; the direct effects of exogenous neural growth factor on the cerebral cortex in limiting the effects of lesions and stroke; and the effects of lithium prophylaxis on neurochemical imbalances (e.g., in dopamine and acetylcholine). Continuing projects include analysis of the circadian photoentrainment pathway in a murine model; regulation of peptide amidation; cortical information processing; and immediate early gene requirements for long-term potentiation and learning. Studies of deployment risk factors and of stress in relation to eating disorders, nicotine use, physical exertion, and immunosuppression also continue, as do investigation of transcriptional control of neural cell differentiation, the role of AP-1 proteins in synergistic signaling, and the role of neuromodulators in neuroplasticity in the amygdala. These studies support essential military missions by increasing our understanding of effective mechanisms of pain control, leading to enhancement of their potencies and limitation of their side-effects; identifying the processes of learning and memory at the physiological level; sorting out factors and effects in the sleep-wake cycle; and maximizing the effectiveness of DoD measures to support warfighters and their families as they contend with common deployment stressors. ($ 0.942 million)

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(U) Combat Casualty Care: Ongoing projects include an investigation of signal transduction; analysis of cellular mechanisms of endotoxin sensitivity; exploration of the mechanism of liver failure in a disulfiram-based model; analysis the role of aurin tricarboxylic acid in apoptosis; and studies of malignant hyperthermia, aimed primarily at developing a reliable, noninvasive diagnostic test and genetic marker. New studies include an exploration of a possible protective mechanism against cell death based on the addition of phosphorus via aurin tricarboxylic acid, and an animal-model feasibility study of rapid induction of hypothermia via interosseus fluid infusion to produce suspended animation. Each of these studies supports essential military missions by protecting those injured in battle; by targeting and controlling likely sources of systemic toxicity due to serious trauma; by preserving essential organs (such as the liver and kidneys) and supporting crucial life functions (blood pressure, normal brain activity, anti-shock mechanisms) once a warfighter has sustained serious injury on the battlefield; and by developing a simple, portable test to identify those at particular risk of a specific, life-threatening complication to injury. ($ 0.359 million)

(U) FY 2003 Plans:

(U) Efforts will continue in all of USUHS's major research areas (CCC, ID, and MOM) in FY 2003. Since specific, investigator-initiated projects compete for funding each year, no detailed description of the research is possible at this time. ($2.126 million)

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(U) B. Program Change Summary	FY 2001	FY 2002	FY 2003	Total Cost
Previous President's Budget Submission	2.007	2.086	2.094	Continuing
Delta	-0.018	0.011	0.000	Continuing
FY 2002 Amended President's Budget Submission	1.989	2.097	2.094	Continuing
Appropriated Value	2.007	2.097		Continuing
Adjustments to Appropriated Value				
a. Congressionally Directed Undistributed Reduction	0.000	-0.016	0.000	Continuing
b. Rescission/Below-threshold Reprogramming, Inflation Adjustment	-0.018	0.000	0.000	Continuing
c. Other	0.000	0.000	0.032	Continuing
Current FY 2003 Budget Submission	1.989	2.081	2.126	Continuing

Change Summary Explanation:

(U) **Funding**: FY 2001 reductions reflect Section 8086 adjustments.

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(U) **Schedule**: N/A

(U) **Technical**:

(U) **C.** **OTHER PROGRAM FUNDING SUMMARY COST**: N/A

(U) **D.** **ACQUISITION STRATEGY**: N/A

(U) **E.** **SCHEDULE PROFILE**: N/A