

Exhibit R-2a, RDT&E Project Justification							Date: February 2003	
Appropriation/Budget Activity RDT&E, D BA1				Project Name and Number <b>*In-house Laboratory Independent Research, Project P503, PE-0601101D8Z</b>				
Cost (\$ in millions)	FY 2002	FY 2003	FY 2004	FY2005	FY 2006	FY 2007	FY 2008	FY 2009
ILIR/P503	2.081	2.047	0	0	0	0	0	0
<p><b>* Beginning in FY2004, In-house Laboratory Independent Research will transfer to the Navy under PE-0601152N. The transfer will enable closer coordination with Service independent research efforts and will result in a more appropriate policy-level role by OSD.</b></p> <p><b>A. Mission Description and Budget Item Justification:</b></p> <p>(U) This project supports basic medical research at Uniformed Services University of the Health Sciences (USUHS); aids recruitment and retention of faculty; supports unique research training for military medical students and resident fellows; and allows faculty researchers to collect pilot data leading to extramural research funds. Eighty to 100 intramural projects are active each year, including 20-25 new starts. Projects are funded on a peer-reviewed, competitive basis. Results contribute to knowledge that enables technical approaches and investment strategies within Defense Science and Technology programs.</p> <p>(U) The ILIR program is designed to answer fundamental questions of importance to the military medical mission in areas aligned with major thrusts of the DoD Biomedical Science and Technology Program. The portfolio of research projects will vary annually because this research is investigator-initiated. Examples of typical research efforts are:</p> <p>(U) <i>Combat Casualty Care:</i> Ischemia and reperfusion injury, traumatic brain and peripheral nerve injury, neural control of pain, endotoxic shock, inflammation, and wound healing.</p> <p>(U) <i>Infectious Diseases:</i> 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.</p> <p>(U) <i>Military Operational Medicine:</i> Sustainment of individual performance; mapping and managing deployment and operational stressors; cognitive enhancement; and military &amp; medical training readiness.</p>								

<b>B. Accomplishments/Planned Program:</b>				
	FY 2002	FY 2003	FY 2004	FY 2005
<b>Combat Casualty Care</b>	0.386	0.276	0	0
<p><i>Representative studies in FY 2002</i> include investigation of possible new treatments for hemorrhagic shock and oxidative stress; a family of protocols exploring possible triggers, diagnostic methods and treatment options for malignant hyperthermia; a study of angiogenesis at high altitudes; development of new methods for slowing cell death after trauma; and identification of neural networks behavior after nerve injury.</p> <p>These studies support the essential military mission by (1) providing the basic science for development of methods to limit damage to essential biological systems and/or encourage regrowth of damaged tissue, particularly under environmental conditions made more likely by current US war efforts; (2) increasing our understanding of the mechanism of pain control for established treatments; and (3) identifying a possible cause, simple and portable diagnostic test, and viable treatment options for life-threatening complications of the exertion and injury common under battle conditions.</p> <p><i>Selected accomplishments in FY 2002:</i> A study of picroliv (a natural product derived from the roots of <i>picrorhiza kurrooa</i>) enhanced sprouting and migration of endothelial cells in a rat model, which may yield a method of restoring blood supply in limb ischemia and wound healing. A new project attempting to develop a method of inducing hypothermia in a pig model identified the optimal drainage points from the sternum into the circulatory system. Those drainage points will be used to pursue a feasibility study of injecting cold saline solutions for rapid induction of hypothermia and consequent suspended animation in the field environment.</p> <p><i>Plans for FY 2003:</i> Program composition will vary each year, to include both project continuations and new starts. Ongoing studies to be pursued in FY 2003 include a cellular-level investigation of methods to modulate apoptosis, development of a treatment strategy for hemorrhagic shock and oxidative stress, and two studies that aim to develop a genetic test for malignant hyperthermia. USUHS expects to add 3-5 new projects after the peer review meeting in late August and as new faculty join the University.</p>				

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	FY 2002	FY 2003	FY 2004	FY 2005
<b>Infectious Diseases</b>	0.635	0.650	0	0
<p><i>Representative studies for FY 2002</i> include investigations of the pathogenesis of HIV-related infections, influenza, and <i>Salmonella</i> infection; work toward development of vaccines for HIV, gonorrhea, and other STDs; mapping of disease progression of <i>H. pylori</i> infection and investigation of two simple dietary treatments; and a family of projects regarding effective management of bartonellosis. These projects support the essential military mission by extending scientific understanding, control, and treatment of eminently possible biological threats, both natural and man-made, faced by Americans at home and abroad.</p> <p><i>Selected accomplishments in FY 2002:</i> An investigation of anaerobic bacterial infections mapped the metabolic pathways of two representative bacteria, demonstrating the essential roles of MT2 isozymes in the metabolism of <i>E. coli</i> as well as anaerobic bacteria. That knowledge should lay the basic-science groundwork for developing of methods of controlling growth and proliferation in a range of bacteria. Work toward a vaccine for HIV, conducted under a family of protocols in this category, was leveraged into a \$1.5M program (PO1) grant funded by the National Institutes of Health.</p> <p><i>Plans for FY 2003:</i> Program composition will vary each year, to include both project continuations and new starts. For FY 2003, continuing projects include investigations of the pathogenesis of <i>H. pylori</i>, HTLV-1, strongyloides, and <i>Salmonella</i>; analysis of toxin production of <i>Shigella</i>, <i>Salmonella</i>, and <i>E. coli</i>; a family of studies of transmission and disease vectors of bartonellosis; and a study of cytokine regulation of humoral immunity to a range of bacterial infections. Six to 8 new projects will be added after the August peer-review meeting and as new faculty members join USUHS. 8</p>				
	FY 2002	FY 2003	FY 2004	FY 2005
<b>Military Operational Medicine</b>	1.060	1.121	0	0
<p><i>Representative studies for FY 2002</i> include two studies of the protein melanopsin, now established as central to regulation of circadian rhythm; an electrochemical investigation of the amygdala, essential in formation of long-term memory; an array of studies aimed at correlating the effects of exercise and stress with neuroendocrine function, immune response, and environmental conditions; and an investigation of the body's natural protective measures for neuron survival.</p> <p>These projects support the essential military mission by increasing our ability to predict and manipulate the physiological mechanisms of stress, sleep, attention, and immunity, and to target those stressors most detrimental to deployed warfighters of both genders; by identifying the natural mechanisms by which the brain processes information and protects its neural pathways, so that those mechanisms may be safely and effectively enhanced; and the interaction of crucial biological systems, particularly under the types of stress common during military operations.</p> <p><i>Selected accomplishments in FY 2002:</i> A study of melanopsin, a light-sensitive ocular substance identified in the team's laboratory, established it as the prime candidate for the photoreceptor underlying the neural control of the mammalian circadian (day-night) rhythm. An investigation of the physiological regulation of peptide amidation, as catalyzed by the enzyme PAM, shed light on the mechanism of an important rate-limiting step in the generation of intercellular messengers involved in tissue growth. The neuroprotective action of N-methyl-D-aspartate (NMDA) receptors was shown to require cooperation between neurotrophin signaling and</p>				

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ionotropic glutamate receptor activity, thus establishing a possible explanation for the neuronal survival endowed by subtoxic concentrations of NMDA in neural cells. Using a patch clamp technique and calcium imaging fluorescence, a study of the electrophysiology of the amygdala determined that the alpha-1 adrenergic receptors may play an important role in the mechanisms involved in the establishment of stress-related disorders such as post-traumatic stress syndrome.

*Plans for FY 2003:* Program composition will vary each year, to include both project continuations and new starts. For FY 2003, continuing studies include investigation of the protective mechanisms of the brain, this year focusing on NMDA and calcium mediation; three studies of the neural mechanisms of long-term potentiation essential to learning and retention of information; a family of studies on the effects of heavy exercise and stress on neuroendocrine and immune function; and a separate family pursuing the mechanism behind regulation of circadian rhythm. The family of epidemiological studies of life stressors commonly reported by deployed warfighters has been supplemented by an analysis of the experiences reported by deployed women with children. Other new projects will be added after peer review in August, and as new faculty join USUHS.

**C. Other Program Funding Summary:** N/A

**D. Acquisition Strategy:** N/A

**E. Major Performers:** N/A