GROW IOWA VALUES FUND PROPOSAL – IOWA ASSOCATION OF INDEPENDENT COLLEGES AND UNIVERSITIES

Action Requested: Consider the proposal.

Executive Summary: The Iowa Association of Independent Colleges and Universities (IAICU) has submitted a proposal for a $200,000 Grow Iowa Values Fund (GIVF) award to support a project at the University of Dubuque, in Dubuque, Iowa. Appropriations require a one-to-one match of institutional dollars. If approved, funding for the proposal will be contingent on auditable and contracted procedures to be developed consistent with state code.

Brief Description of Project Proposal
The IAICU's proposal is summarized here. The complete proposal is attached.

The University of Dubuque requests $200,000 from the GIVF to provide equipment and support for research. Equipment to be purchased includes a fermentor, specimen freezer, stereo microscope, and a user-license for molecular-modeling software.

The proposal describes the proposed research as a commercialization opportunity. The funded research would be undertaken to establish whether or not a particular enzyme is involved in the uptake of iron by certain organisms. If such a relationship exists, still further research would be conducted to determine whether the enzyme can be used as a vaccine. The proposal does not identify the medical or commercial applications for such a vaccine. The proposal does not indicate whether the idea has been systematically evaluated for its commercial value.

According to the proposal, the project would create a job for a post-doctoral researcher and provide a summer stipend for a student research technician. The complete proposal includes information on matching funds sources and an outline of metrics to evaluate results.

Background:
The 2005 Iowa General Assembly's House File 809 appropriated $5 million annually through FY 2015 to the Board of Regents through a reconstituted Grow Iowa Values Fund. The funds are for capacity-building infrastructure in areas related to technology commercialization, entrepreneurship, and business development for the purposes of state economic development. HF 809 permits the Board of Regents to award funds to independent institutions of higher education for these purposes.

In September, 2005, the Board approved the Regent universities' plans for investing $4.8 million of the FY 2005-2006 budget award. The Board Office solicited a proposal from the Iowa Association of Independent Colleges and Universities to award the remaining $200,000. The Board Office provided the following guidelines to the Regent universities and the IAICU for the preparation of proposals:

Guidelines for GIVF Proposals

1. Proposals must include a description of the program and its projected duration. This description should include how the proposed activities relate to the objectives outlined in HF 809. HF 809 states that funding is intended for capacity building infrastructure in areas related to technology commercialization, marketing and business development efforts in areas related to technology commercialization, entrepreneurship, and business growth, and infrastructure projects and programs needed to assist in the implementation of activities to maximize and promote the economic benefit from research at Regents institutions.
2. Proposals must include recommended funding allocation from the GIVF.
3. Proposals must identify matching funds sources.
4. Proposals must identify the metrics to be used to demonstrate progress and outcomes.

Iowa Association of Independent Colleges and Universities

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John V. Hartung, President

November 18, 2005

Mr. Gary Steinke
Acting Executive Director
Chief Public Affairs Officer
Board of Regents,
State of Iowa
11260 Aurora Avenue
Urbandale, IA 50322

Dear Gary:

Attached to this short note is the IAICU proposal suggested for funding under the auspices of the Grow Iowa Values Fund (GIVF) in support of a project that has significant commercialization potential in the biosciences. Although the window of opportunity for submission of potential projects was not wide, fortunately this project fits the parameters as discussed in the bill and as evidenced by those funded under the 'Iowa Startup and Entrepreneurship Fund' at the University of Iowa and the 'Commercialization Program' at Iowa State University. While we realize these are all new ventures in a relatively undefined environment, the potential of finalizing a vaccine product that would inhibit the productivity of pathogenic bacteria that have become or are evolving towards resistance to current anti-biotics is not only exciting for the potential benefit to mankind, but, if perfected, promises the opportunity for considerable economic benefit to the community and the state.

Although future legislative actions and experience may create a different process for project approval, this project is submitted as the recommendation of IAICU for the current year. The project proposal has been examined by the IAICU presidential representative on the Biosciences of Iowa Board and by me. After consideration and clarification of the project's end-product potential, collaborative efforts, significant learning and growth opportunities with the very real chance to substantially contribute toward the growth and development of Iowa, we are pleased to recommend the project.

Please let me know if you need further information with regards to the completion of this process. Thank you very much.

Sincerely,

John V. Hartung
President

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• University of Dubuque

Proposal to the Grow Iowa Values Fund

November 2005

"Biotechnology Research for Vaccine Production and the Control of Bacterial Infections"

Summary:

It has long been known that iron acquisition is an absolute requirement for the growth of all pathogenic microorganisms. Many laboratories have made numerous unsuccessful attempts to block the iron acquisition process in order to control microbial growth; however, the known microbial uptake pathways have proven difficult to obstruct. The Principal Investigator (PI) has discovered a class of extracellular enzymes that chemically reduces iron at extremely rapid rates, and very likely represents a step in the iron acquisition process that has not previously been recognized. The proposed project seeks to block microbial iron acquisition by 1) developing a vaccine using purified extracellular microbial enzymes, and 2) identifying a small molecule inhibitor that would inhibit the enzyme's activity, thus blocking iron uptake. The enzymes will be crystallized and the enzyme surfaces will be mapped using molecular modeling software, and drug candidates that would bind to and inhibit enzyme activity will be identified. Such a drug would block the iron uptake process in a person with an antibiotic-resistant infection, with the practical result of eliminating these antibiotic-resistant microorganisms from a patient's tissues.

Organizational Background:

The University of Dubuque (UD) is a small, private university, located in Iowa's oldest city—Dubuque—on the Mississippi River where the borders of Wisconsin, Illinois, and Iowa meet. In the fall of 2005, UD opened its 154th year with the largest undergraduate enrollment in its history. UD has had record enrollments since the fall of 1998—an 87% increase in full-time undergraduates.

UD's Biology Program is within the Department of Natural and Applied Sciences (DNAS), which includes several scientific disciplines such as chemistry and biochemistry, geology, mathematics, physics, environmental science, and environmental toxicology. This spring the University began an addition to and remodeling of the Goldthorp Science Center, with a completion date set for December 2006. The current construction on the Science Center will not negatively impact this proposed project, and will ultimately enhance working conditions. The science center will house modern teaching and research laboratories, a modern media preparation room, a state-of-the-art tissue culture facility, and an animal suite. The planned improvements have been designed to create an environment conducive to inspiring learning and discovery.

Project Background:

Dr. Richard Cowart, PI, has been a prior recipient of a National Institutes of Health grant award (AI-22619) to study iron uptake by microorganisms. His prior work has led to his discovery of a new class of extracellular enzymes—produced by all bacteria thus far tested—that rapidly and efficiently mobilize iron, which is then available for microbial uptake. With one exception, all microorganisms have an absolute requirement of iron for growth, including all disease-causing bacteria. Thus, microorganisms must efficiently mobilize iron from their environment, including host tissues during infections. The current theory explaining iron uptake by microorganisms is inadequate, as the rates of the reactions for iron mobilization are too slow to be physiologically relevant.

Dr. Cowart has published numerous articles in peer-reviewed journals presenting evidence that there is a missing step in the uptake of iron by microorganisms, and that the enzyme he has discovered is feasibly involved in this process. He believes that once these enzymes from a variety of microbes are isolated and characterized, they can be utilized as a vaccine and as a target for drugs to abolish iron uptake activity. Thus, this research offers realistic hope that an efficient vaccine can be developed and that the treatment of antibiotic-resistant infections is possible.

Project Description:

Currently, the PI is working to completely purify the iron reductase from *Salmonella typhimurium* LT2. Once this is done he will send the purified protein to Iowa State University where they will determine the sequence of the first 15-20 amino acids of the enzyme, known as N-terminal sequencing. Since the whole genome of *S. typhimurium* LT2 has been sequenced, identification of the gene that is responsible for producing this enzyme should be simple. That gene will then be cloned into another microorganism, and large amounts of enzyme will be produced. Experimental animals will be injected with the purified enzyme and later challenged with a lethal dose of *S. typhimurium*. These experiments will determine if the enzyme can serve as an efficient vaccine.

The enzyme purified from *S. typhimurium* LT2 will also be crystallized and the 3-D structure will be determined at the Department of Biochemistry at the University of Iowa. Using molecular modeling, the surface of the enzyme will be mapped and an inhibitor identified that will bind to a targeted site with the goal of inactivating the enzyme. Potential drug candidates will be tested *in vitro* to access their efficacy in abolishing iron reducing activity. The identification of an appropriate inhibitor should prevent the uptake of iron by microbial pathogens, which will stop the growth of the microorganisms. This provides a theoretical basis for the successful treatment of patients suffering with antibiotic-resistant bacterial infections.

Should it be determined that the enzyme can serve as an efficient vaccine and that inhibitors can block activity, these experiments will be repeated using different microbial pathogens. Some of the organisms chosen for additional study include *Listeria monocytogenes*, *Escherichia coli*, and *Pseudomonas aeruginosa*. These studies will be essentially the same as described above. It will also be determined if cross-reactivity occurs (i.e., will the reductase from one microorganism protect an experimental animal from infection by one of the other pathogens?).

Timeline for Completion:

The PI has already conducted a significant amount of preliminary work. Two additional years of research should bring the project to completion, based on the following project timeline:

Timeframe	Tasks
Months 1-6	• Complete the isolation of the enzyme from *Salmonella typhimurium* and identify the gene responsible for its production. • Begin work in isolating these enzymes from other microorganisms. • Develop optimization and scale-up processes.
Months 7-12	• Begin animal studies to determine if the enzymes can serve as efficient vaccines. • Begin cloning work. • See if there is cross-reactivity (i.e., determine if an enzyme from one organism can protect against infection by an unrelated organism).
Months 13-18	• Crystallize the enzyme and determine the 3-D structure. • Map the protein surface and identify possible target sites for inhibitors. • Assess the feasibility of the commercialization of these enzymes.
Months 19-24	• Identify enzyme inhibitors as candidates for drugs. • Identify the best strategy for commercialization.

Proposed Budget:

The total amount requested from the Grow Iowa Values Fund is $200,000. A New Brunswick BioFlo 110 fermentor is needed to grow large quantities of culture in order to obtain the amounts of enzyme necessary for these studies. A non-frost free freezer is requested to store enzymes necessary for the molecular biology research, and an Olympus stereo microscope is requested to view crystals. This is an important aspect of crystallography, as protein crystals must be distinguished from ordinary salt crystals to be properly selected for transport to the Crystallization Facility at the University of Iowa. There is currently no charge for collaboration with the Protein Crystallography Center; however, upon receipt of grant funds, the Crystallography Center charges a fee of $5,000/year for determining 3-D structures.

The University of Dubuque's Department of Natural and Applied Sciences recently obtained two H-P Linux workstations that operate ICM Pro molecular modeling software. This software, used by pharmaceutical companies in drug discovery, bioinformatics research, and protein structural analysis, will be used for characterizing the enzymes once the 3-D structures are determined. The university is currently using ICM Pro under a teaching license; to use this software for research, a single academic research license will need to be purchased for $3,200 a year.

Funds are also requested for salaries, supplies, publication costs, and travel to scientific conferences. The PI requests one month's salary as he is on an 11-month contract but will be working full-time during the summer on this project.

University of Dubuque - Biotechnology Research Budget		
Description	**Year 1**	**Year 2**
Salaries:		
FT Post-doctoral researcher	40,000	40,500
PI - 1 mo summer salary	5,000	5,400
Fringe Benefits @28%	12,600	12,850
Student researchers – summer stipend	4,000	4,250
Supplies:		
Molecular Biology disposables – cloning vectors, media, pipets, chemicals, misc. disposables	4,500	4,600
Bacterial Strains from American Type Culture Collection	500	
Mice (Purchase breeding stock and mice bred for use in UD's animal facility)	400	
Chromatography resins, supplies, columns	1,000	1,000
Crystallization of enzyme supplies		3,000
Equipment:		
Non-frost free 16-18 cu. ft. upright freezer	900	
New Brunswick Fermentor	22,000	
Equipment repair/maintenance	1,500	1,500
Olympus SZ61 Stereomicroscope with camera for viewing and photographing protein crystals		4,800
Travel:		
Scientific conference, University of Iowa, and/or Molsoft, LLC in San Diego for discussion of modeling/crystallizing the enzymes	2,000	2,000
Dissemination:		
Publication		800
Other:		
N-terminal sequencing of reductases once isolated. Conducted at Iowa State University on enzymes from four bacterial strains.	2,400	
MolSoft ICM Pro license	3,200	3,300
University of Iowa Crystallography Center-user fee		5,000
Identification of candidate drugs to act as inhibitors of the enzymes		11,000
Total	**100,000**	**100,000**

University of Dubuque - Biotechnology Research Matching Funds	
Description	**Amount**
AMSCO autoclave	$37,000
LabConCo Clean Hood for media preparation room	6,500
LabConCo Scientific Glassware washer for media preparation room	6,500
Ice machine	3,500
Water purification system for laboratories	140,500
Animal cages/racks, and other equipment items for animal room	15,000
GE Healthcare 2-D electrophoresis unit	10,000
Total (In-kind) Matching Funds	**$ 219,000**

Impact:

This project will significantly contribute to the development of biotechnology in Iowa. It will provide jobs for post-doctoral or technician researchers, provide funds for student involvement in this research, and possibly lead to the development of an efficient vaccine and an effective means for treating antibiotic-resistant infections.

The University of Dubuque has entered into an agreement with Dr. Cowart after review by an internationally recognized scientific authority in the field and consultation with the university attorney, and supports the continuation of this work, which will include patent protection. At some point during the research it will become apparent if commercialization is feasible. If so, a business plan will be developed with the goal of keeping the commercial development in Iowa.

Principal Investigator:

Richard E. Cowart, Associate Professor of Biology and Chair of the Department of Natural and Applied Sciences at the University of Dubuque, has a Ph.D. in microbiology and postdoctoral training in biochemistry. His experiences include protein purification, molecular biology, enzymology, infectious disease microbiology, protein crystallization, and molecular modeling. He has held faculty positions at Oral Roberts University School of Medicine, the University of Maryland Center of Marine Biotechnology, and the University of Texas M.D. Anderson Cancer Center. Dr. Cowart is a member of the American Society for Microbiology and the American Society of Biochemistry and Molecular Biology.