Protein Crystal Growth and Structure Based Drug Discovery

Status, Plans, Connections to NASA's Mission and Vision and to the Space Architect's Capability Requirements

Organizing principles

NASA 2003 Strategic Plan

Goal 3
Create a more secure world and improve the quality of life by investing in technologies and collaborating with other agencies, industry, and academia. — **3.4***

Goal 7
Engage the public in shaping and sharing the experience of exploration and discovery. — **7.3***

Goal 10
Enable revolutionary capabilities through new technology. — **10.6***

* These objectives are reflected in the overall Research Partnership Program and thus not connected to specific requirements of any single research program.

Space Architect Perspective
Capability Requirements

2.0 Enabling Advanced Research and Technology

2.3 Habitation and Bio-astronautics
- Adaptation and Countermeasures 2.3.6
- Biological Systems 2.3.9

OBPR Organizing Questions

1. "How can we assure survival of humans traveling far from earth?"
   - 1a) What knowledge and tools are needed to enable the practice of medicine in space?
   - 1b) How does the human body and its physiology adapt to space flight, when is it appropriate to counteract those adaptive effects, and by what means can we do so?
2. "What must we know about how space changes life forms, so that humankind will flourish?"
   - 2a) Does space affect life at its most fundamental levels, from the gene to the cell?
   - 2b) How does long-term exposure to space affect organisms?
   - 2c) How does space affect the development and life cycles of organisms?
   - 2d) How do systems of organisms and their interactions change in space?
3. "What new opportunities can our research bring to enrich lives on earth and expand understanding of the laws of nature?"
   - 3a . How does the space environment change the behavior of physical and chemical processes and the technologies that rely on them?
   - 3b) What can we learn about the organizing principles from which structure and complexity arise in nature?
   - 3d. What are the fundamental physical, chemical, and biophysical mechanisms that drive the cellular and physiological behavior observed in the space environment?
4. "What technology must we create to enable the next explorers to go beyond where we have been?"
   - 4b) How can technology help human productivity and well being during extended isolation from Earth?
   - 4d) What is the optimal way to support environmental health for crewmembers of space flights?

Requirements

Requirement. Supporting the discovery of novel therapeutics and or vaccine experiments with protein crystal growth in microgravity is a necessary requirement to advance the discovery of certain drugs. Microgravity provides conditions for crystal growth that are unattainable here on Earth and have proven successful with repetitious experiments.

Requirement. Improved understanding of the human immune system, bone remodeling, chronic and infectious diseases, etc. will yield obvious improvements that can improve the quality of life on Earth as well as those traveling in space.

Requirement. Knowledge gained from studying the processes during protein crystal growth in microgravity conditions has implications for protein crystal growth experiments on Earth.

Plans

Plans. The next set of CBSE experimentation on the ISS will use a high density vapor diffusion apparatus with down linked video monitoring. While we have made much progress in this program in terms of understanding protein crystal growth in microgravity and microgravity hardware development, consistent and frequent access to space for these experiments is crucial. In the long term, a complete laboratory in space should be developed such that crystal can be grown and analyzed in space without subjecting them to the rigors of returning them to earth for analysis.

Capability: The CBSE is dedicated to understanding the structure and function of macromolecules as applied to new drug discovery via intelligent or structure-based, combinatorial design. Our multidisciplinary program includes:

Macromolecular Crystal Growth (ground-based and microgravity)
X-ray Crystallography
Biochemistry and Molecular Biology
Molecular Modeling and Graphics
Structural Thermodynamics
Lead Compound Design and Drug Development (medicinal and structure-guided combinatorial chemistry)

The Center's Engineering Division provides specialty laboratory instrumentation and software development services for the CBSE and research with capabilities that include:

Design and Analysis
-Mechanical
-Electrical and Electronic
-Software
Fabrication and Assembly
Test and Checkout
Complete Documentation
Use Best Commercial & Aerospace Practices

All of our capabilities could be used by NASA to cost effectively develop, research instruments, space based biosensors, and therapeutics targeted to astronaut health.

Hypotheses & Projects

Hypothesis: The microgravity environment will allows for a more uniform and regulated growth crystals thus improving the order and size of the crystals. This environment affords the opportunity to achieve higher resolution of structures determined from these crystals by x-ray crystallography.

Importance. Continual access to the microgravity environment will advance medical research to assure the safety of an astronaut's health and promote discoveries on Earth for improved therapeutics and or vaccines.

Project: PROTEIN CRYSTAL GROWTH AND STRUCTURE BASED DRUG DISCOVERY

Project description. The primary objective of this program is to take advantage of the microgravity environment of the Space Shuttle and International Space Station to produce high quality crystals of selected proteins therapeutic targets and to better understand the dynamics of growing crystals from proteins. The human body contains over 100,000 proteins that play important roles in the everyday function of the body such as the formation of major components of muscle and skin, and how the body fights diseases. In order to understand their function, three dimensional structural information becomes necessary. The structure of individual proteins can be studied with the growth of their high quality crystals in which the molecules of the protein are arranged in a regular, repeating pattern. Microgravity can provide an ideal environment for the growth of crystals. These space-grown crystals are returned to Earth and analyzed by a process called X-ray diffraction to construct computer models of the three dimensional structures of the protein molecules. The study of the protein molecule architecture plays a key role in establishing the structural foundations of molecular biology and biochemistry with important applications in medicine for structure based drug design. Understanding the structure enables researchers to design drugs that can prevent bone loss, immunosuppression, treat and or prevent chronic and infectious diseases, etc.

Status: Microgravity protein crystal growth experiments have 18 years of history on board the Shuttle and the International Space Station. Microgravity protein crystal growth experiments will continue using the vapor diffusion dialysis temperature induced and liguid-liguid diffusion techniques.
Project site(s): Center for Biophysical Sciences and Engineering/ University of Alabama at Birmingham

Research Partnership Centers Multiple Benefits

Immediate applications on Earth. The more we understand the effects of microgravity in our experiments the better we can adapt experimental situations that benefit the health and safety of humans, animals and plants. Two of the many medical conditions that would benefit from this type of microgravity research are bone loss and the compromised immune system. Anything that we could possibly develop would have a major impact on osteoporosis, post transplant immunosuppression, auto immune diseases and AIDS research.

Leverage NASA research funds. CBSE Partnerships in partnership with NASA enables NASA to stretch its research dollars.
Industrial:
3-D Pharmaceuticals, ArQule, Inc., BioCryst Pharmaceuticals, Inc., BrazSat, Bristol Myers Squibb, Eli Lilly and Co., GlaxoSmithKline, Ibbex, Johnson & Johnson, Pfizer, Schering-Plough Research Institute, SpaceHab, Inc., The Upjohn Company, Vertex Pharmaceuticals, Virtual Drug Discovery, Inc.

Government:
Argonne National Laboratory, Brookhaven National Laboratory, Marshall Space Flight Center, U.S. Naval Research Laboratory, John Glenn Research Center

Importance. Protein crystal growth will lead to an improved understanding of the human biological system. This information has the potential to generate new therapeutics and or vaccines for use in space and on Earth. Advances in the development of drug discoveries will aid in the medical compensation offered against the affects of microgravity on an astronaut's health thus ensuring safer and prolonged travel in space.

Knowns and unknowns

Known. On Earth, gravity driven convection and sedimentation may inhibit highly ordered crystal growth. In microgravity, convection flows are reduced and the absence of sedimentation allows for the growth of better and larger crystals that enable the definition of highly refined 3-D pictures of the protein.

Known. It is known that determining protein structures is the key to the design and development of effective drugs.

Known. Over a period of more than 18 years, NASA investigators have demonstrated by conducting crystallization in space, that the microgravity environment has significant impact on the quality of the growth of protein crystals thus enabling the high resolution of pictures of proteins important for structure based drug discovery.

Unknown. Optimal conditions, chemical and physical, that enhances the growth of highly refined macromolecular crystals in space.

Status: Prototype V.3
MacroVU® Analytics

Horn, R. E. Preliminary Thoughts on NASA Strategic Research

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