TECHNICAL CORRESPONDENCE FROM THE INTERNATIONAL SPACE STATION U.S. NATIONAL LABORATORY

Microgravity Molecular Crystal Growth Onboard the ISS National Lab: **A Program Overview**

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EXECUTIVE SUMMARY

The International Space Station (ISS) U.S. National Laboratory provides a valuable platform for improved molecular crystal growth, and the many successful crystallization experiments conducted in space over the past three decades have demonstrated this value. Crystals grown in microgravity are often larger and more well-ordered than Earth-grown crystals.

In the analysis of organic molecules, high-quality crystals can lead to improved datasets for structure resolution, mosaicity (misalignment within the crystal lattice), and electron density. Larger crystals can also enable analysis by neutron diffraction (instead of more traditional diffraction analyses, which use X-rays), which provides greater structural detail by allowing for the determination of hydrogen positions within protein structures. For inorganic molecules, high-quality crystals can lead to advances in metal manufacturing, electronics, and radiation detection.

Several commercial entities, including pharmaceutical companies Merck & Co. and Eli Lilly and Company, are currently using the unique crystallization environment onboard the ISS National Lab to advance their research and development (R&D). The Center for the Advancement of Science in Space (CASIS) is committed to establishing an ISS National Lab Microgravity Molecular Crystal Growth (MMCG) Program to enable continued use of the ISS for crystallization studies and to enhance the commercialization potential of low Earth orbit (LEO) platforms for both organic and inorganic molecular crystallization.

To begin to outline the requirements and lay the foundation for a sustainable MMCG Program, CASIS held a technical interchange meeting in 2015 to gather input from experts in the field of protein crystallography. Combining lessons learned from past spaceflight crystallization R&D with expert recommendations from the interchange meeting, CASIS established criteria for informed molecule selection to aid in the identification of optimal organic molecules to study in microgravity (see the section titled "Expert Input and Informed Molecule Selection" for additional information). While these initial criteria apply only to organic molecule crystallization, CASIS also intends to gather expert input from the inorganic crystallization community to optimize the success of space-based inorganic crystal growth research that may benefit life on Earth.

The ISS National Lab MMCG Program specifically aims to provide the following:

- Opportunities for molecular crystal growth investigations on every cargo resupply (CRS) launch to the ISS.
- Rapid turnaround of samples—a 90-day cycle time from molecule identification to crystal return from the ISS.
- Hardware options that minimize preflight optimization steps through use of standard laboratory crystallization procedures to enhance readiness for analyses.
- Processes to support multi-year customer programs for crystallization.

The sections that follow provide a brief history of crystallization in microgravity, an overview of crystal growth investigations conducted onboard the ISS National Lab, and additional information on the CASIS technical interchange meeting and resulting expert recommendations. Also provided is a summary of applications for molecular crystal growth in microgravity, additional information on the MMCG Program and its goals and implementation, an overview of continued interest in microgravity molecular crystal growth research, and a discussion of future directions.

BACKGROUND

Microgravity has been used for more than 30 years to improve outcomes of molecular crystal growth—on U.S. space shuttle missions, onboard the Russian space station Mir, on free-flying spacecraft, and onboard the ISS.

Organic Macromolecular Crystal Growth in Microgravity

Observed benefits of organic crystallization in microgravity include larger, more well-ordered crystals with a higher diffraction resolution and lower mosaicity. The electron density maps from microgravity-grown crystals are often more detailed than those from Earth-grown crystals, improving the accuracy of protein structure determination. Researchers hypothesize that these improvements are due to the slower, more ordered diffusion-driven movement of molecules during crystallization in microgravity resulting in a more uniform incorporation of molecules into the crystalline lattice.

The first organic crystallization experiments in microgravity were conducted on U.S. space shuttle missions in the mid-1980s. In these early experiments, results were not definitive, and some crystals benefitted from growth in microgravity while others did not. However, these experiments demonstrated the central role that gravity plays in crystal growth and spurred interest within the crystallography community in the potential for microgravity to improve macromolecular crystal growth. Several factors limited these crystallization experiments, including the short duration and infrequency of the shuttle missions, uncertainty in the launch schedule, limited sample capacity and experiment volume, and instability in temperature. Conducting crystallization experiments onboard the ISS held promise to address several of these issues.

Crystallization experiments on the shuttle and Mir in the 1990s and onboard the ISS in the early 2000s further validated microgravity as a key factor in improved crystal growth in space. These experiments yielded numerous large-volume crystals with higher diffraction resolution and vast improvement in mosaicity. However, results continue to be mixed, with only some proteins exhibiting improved growth in microgravity.

Inorganic Crystallization in Microgravity

The elimination of gravity-driven forces (e.g., convection, sedimentation, and buoyancy) in microgravity also results in the synthesis of inorganic crystals that are larger and more well-ordered than crystals synthesized on the ground. Experiments conducted on sounding rockets and the shuttle in the 1990s, and later on the ISS, highlighted gravity as a key source of disturbing effects that occur during ground-based alloy solidification. These studies provided valuable benchmark data for validating solidification models. Experiments performed on the shuttle in the 1990s also sought to elucidate the effects of gravity on colloidal crystallization. These studies confirmed that gravity alters inherent aspects of colloidal crystallization, and investigators were able to crystallize samples that had not yet been crystallized on the ground in a matter of days in microgravity. Additionally, as with organic molecules, crystallization in microgravity yielded larger, higher-quality crystals, some exhibiting dendritic arms previously undetected in crystallization on the ground.

Additional solidification experiments conducted on the ISS in the 2000s found that adding magnetic fields to solidification in microgravity results in high-performance magnetostrictive materials. Other experiments used the Solidification Using a Baffle in Sealed Ampoules (SUBSA) furnace on the ISS to synthesize semiconductor crystals, facilitating the observation of melting and directional solidification in microgravity—toward ultimate application in electronic devices such as computers, medical imagers, and radiation detectors.

Crystallization Investigations on the ISS National Lab

The ISS National Lab has continued to provide a valuable platform for both organic and inorganic crystal growth research in microgravity and has enabled many crystallization successes to date.

Initial CASIS-sponsored organic crystal growth investigations conducted on the ISS National Lab stemmed from a 2012 CASIS solicitation for next-generation space-based protein crystallization research, and the resulting investigations were launched to the ISS National Lab on SpaceX CRS-3 and CRS-4 in 2014. Two of these investigations produced protein crystals of sufficient size for neutron diffraction, and many produced high-quality crystals for analysis. Since those initial flights, many additional commercial and academic crystal growth investigations have flown to the ISS National Lab (see Table 1). The majority of these investigations were focused on structural determination for functional studies and structure-based drug design, but others, including multiple investigations from the pharmaceutical company Merck, are using the improved crystal growth onboard the ISS National Lab for studies aimed at improving drug formulation, manufacturing, and storage. In the case of pharmaceutical researchers, multiple flight opportunities to the ISS National Lab in rapid succession provides an opportunity for investigators to adjust experimental design and maximize success of their R&D objectives by iteration. Moreover, a decrease in the time from proposal submission to flight allows companies with fast-paced R&D goals to obtain relevant results in a timely manner. For example, a recent project from the Michael J. Fox Foundation flew to the ISS National Lab less than one year after initial proposal submission—in fact, from specific molecule identification to flight, the process took less than three months.

Additionally, in 2016 a significant milestone in the effort to validate organic crystallization systems for microgravity that use common laboratory hardware was achieved as part of a CASIS-sponsored investigation by the pharmaceutical company Eli Lilly and Company. This investigation, which launched to the ISS National Lab on SpaceX CRS-8 in 2016, marked the first flight of a commercial-off-the-shelf (COTS) protein crystallization plate, developed by the biotechnology company MiTeGen. Expanding the use of COTS hardware is an important step toward streamlining preflight optimization work—lowering costs and shortening the time to crystal retrieval.

With respect to inorganic crystallization experiments launched to the ISS National Lab, two notable investigations utilizing the recently refurbished SUBSA furnace launched on Orbital ATK-7 in 2016. One of these investigations, led by Dr. Aleksandar Ostrogorsky of the Illinois Institute of Technology (who conducted some of the original ISS SUBSA experiments in 2002), sought to produce new types of semiconductor crystals, and the other, led by Dr. Alexei Churilov of Radiation Monitoring Devices, Inc., aimed to synthesize high-quality scintillation crystals—both seeking to improve materials for use in advanced radiation detection devices for homeland security applications.

TABLE 1: ISS NATIONAL LAB CRYSTALLIZATION INVESTIGATIONS

Investigation*	Launch Vehicle/Date	Aim
TITLE: Protein Crystals for Neutron Crystallography: Large Volume Crystal Growth for Inorganic Pyrophosphatase Complexes by Counter-Diffusion in Microgravity for Neutron Diffraction Studies (PC4NC) **PRINCIPAL INVESTIGATOR:** Joseph Ng; iXpressGenes, Inc.	SpX-3, 4/18/2014	Produce crystals of inorganic pyrophosphate phosphatase (IPPase) of sufficient size for neutron diffraction, toward structural determination of this medically important protein
TITLE: Microgravity Growth of Single Crystals for Structure Determination (Merck PCG) **PRINCIPAL INVESTIGATOR:** Paul Reichert; Merck Research Laboratories	SpX-3, 4/18/2014	Produce crystals of a human monoclonal antibody undergoing clinical trials for treatment of immunological disease, toward improved structural determination
TITLE: Crystallization of Human Membrane ABC Proteins in Microgravity (CASIS PCG HDPCG-2) **PRINCIPAL INVESTIGATOR:** Stephen Aller; University of Alabama at Birmingham	SpX-3, 4/18/2014	Produce crystals of medically important membrane proteins, including cystic fibrosis protein, toward structural determination
TITLE: Crystallization of Huntingtin Exon-1 Using Microgravity (CASIS PCG HDPCG-1) **PRINCIPAL INVESTIGATOR:** Pamela Bjorkman; University of Alabama at Birmingham	SpX-3, 4/18/2014	Produce crystals of huntingtin, a protein associated with Huntington's Disease, toward structural determination of regions that are difficult to crystallize on the ground
TITLE: Crystallization of Medically Relevant Proteins Using Microgravity (CASIS PCG GCF-2a) **PRINCIPAL INVESTIGATOR:** Sergey Korolev; St. Louis University	SpX-3, 4/18/2014	Produce improved crystals of two medically important proteins, toward structural determination
TITLE: Exploiting on-orbit crystal properties for structural studies of medically and economically important targets (CASIS PCG GCF-2b) **PRINCIPAL INVESTIGATOR:** Edward Snell; Hauptman Woodward Medical Research Institute, Inc.	SpX-3, 4/18/2014	Produce crystals of four medically important proteins, toward structural determination
TITLE: Optimization of Protein Crystal Growth for Determination of Enzyme Mechanisms through Advanced Diffraction Techniques (CASIS PCG 2-1) **PRINCIPAL INVESTIGATOR:** Constance Schall; University of Toledo	SpX-4, 9/21/2014	Produce crystals of three medically important proteins of sufficient size for neutron diffraction, toward structural determination
TITLE: A collaborative proposal for protein crystal growth in space to enable therapeutic discovery (Module-19 S/N 1002) **PRINCIPAL INVESTIGATORS:** Cory Gerdts; Protein BioSolutions and Matt Clifton; Beryllium Discovery Corp.	SpX-4, 9/21/2014	Produce crystals of two challenging therapeutic targets implicated in cardiovascular disease and cancer, toward structural determination

**Operational Nomenclature in parentheses.*

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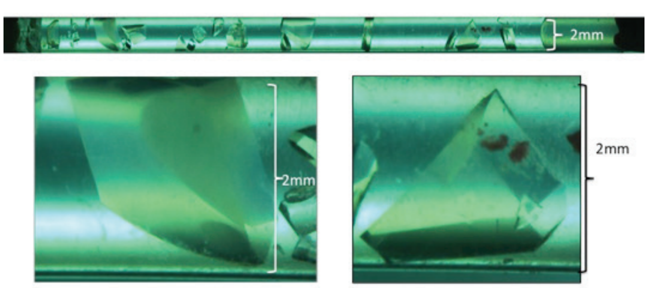
Investigation*	Launch Vehicle/Date	Aim
TITLE: Microgravity Growth of Crystalline Monoclonal Antibodies for Pharmaceutical Applications (CASIS PCG 3) **PRINCIPAL INVESTIGATOR:** Paul Reichert; Merck Research Laboratories	SpX-6, 6/28/2015	Produce crystals of medically important human monoclonal antibodies, toward improved drug formulation, manufacturing, and storage
TITLE: A Co-Crystallization in Microgravity Approach to Structure-Based Drug Design (CASIS PCG 4-1) **PRINCIPAL INVESTIGATOR:** Kristopher Gonzalez-DeWhitt; Eli Lilly and Company	SpX-8, 4/8/2016	Produce high-quality crystals of a medically important protein in complex with a small molecule ligand (potential therapeutic), toward improved structure-based drug design
TITLE: The Effect of Microgravity on the Co-Crystallization of a Membrane Protein with a Medically Relevant Compound (CASIS PCG 4-2) **PRINCIPAL INVESTIGATOR:** Michael Hickey; Eli Lilly and Company	SpX-8, 4/8/2016	Crystallize protein complexes consisting of a medically important membrane protein bound to a potential therapeutic compound, toward improved structure-based drug design
TITLE: The Effect of Microgravity on the Electrolysis of Silver Nitrate (NR Module-69) **PRINCIPAL INVESTIGATOR:** David Schlichting; Eaglecrest High School	SpX-9, 7/18/2016	Analyze the three-dimensional structure of silver crystals in microgravity to determine whether elimination of gravity produces higher-quality crystals (student investigation)
TITLE: Detached Melt and Vapor Growth of InI in SUBSA Hardware (IIT – SUBSA) **PRINCIPAL INVESTIGATOR:** Aleksandar Ostrogorsky; Illinois Institute of Technology	Orbital ATK-7, 9/15/2016	Synthesize new types of semiconductor crystals, toward advanced radiation detection capabilities
TITLE: Crystal Growth of Cs2LiYCl6:Ce in Microgravity (RMD – SUBSA) **PRINCIPAL INVESTIGATOR:** Alexei Churilov; Radiation Monitoring Devices, Inc.	Orbital ATK-7, 9/15/2016	Produce high-quality scintillation crystals, toward advanced radiation detection capabilities
TITLE: Microgravity Growth of Crystalline Monoclonal Antibodies for Pharmaceutical Applications (CASIS PCG 5) **PRINCIPAL INVESTIGATOR:** Paul Reichert; Merck Research Laboratories	SpX-10, 2/19/2017	Produce high-quality, uniform crystalline suspensions of a monoclonal antibody PD-1 drug, Keytruda, toward improved drug formulation, manufacturing, and storage
TITLE: The Effect of Macromolecular Transport on Microgravity Protein Crystallization (LMM Biophysics 1) **PRINCIPAL INVESTIGATOR:** Lawrence DeLucas; University of Alabama at Birmingham	SpX-10, 2/19/2017	Validate the hypothesis that the improved quality of microgravity-grown biological crystals is the result of two macromolecular characteristics that exist in a buoyancy-free, diffusion-dominated solution
TITLE: Growth Rate Dispersion as a Predictive Indicator for Biological Crystal Samples Where Quality can be Improved with Microgravity Growth (LMM Biophysics 3) **PRINCIPAL INVESTIGATOR:** Edward Snell; Hauptman Woodward Medical Research Institute, Inc.	SpX-10, 2/19/2017	Validate the hypothesis that growth rate dispersion could be an indicator of crystals whose quality may be improved in microgravity
TITLE: Neutron Crystallographic Studies of Human Acetylcholinesterase for the Design of Accelerated Reactivators (CASIS PCG 6) **PRINCIPAL INVESTIGATOR:** Andrey Kovalevsky; Oak Ridge National Laboratory	SpX-11, 6/3/2017	Produce crystals of a medically important protein of sufficient quality for neutron diffraction, toward structural determination
TITLE: Crystallization of LRRK2 under Microgravity Conditions (CASIS PCG 7) **PRINCIPAL INVESTIGATOR:** Marco Baptista; Michael J. Fox Foundation	SpX-12, 8/14/2017	Crystallize LRRK2, a protein associated with Parkinson's disease, toward structural determination of this difficult-to-crystallize protein

**Operational Nomenclature in parentheses.*



Joseph Ng of iXpressGenes, Inc. flew crystals of IPPase on SpaceX CRS-3, obtaining large crystals suitable for neutron diffraction.

Expert Input and Informed Molecule Selection

To continue to support the growing demand for crystallization onboard the ISS National Lab and begin to outline the basic requirements for a long-term crystallization program in space, CASIS held a technical interchange meeting in 2015 to gather in-depth feedback from experts across the field of protein crystallography. The technical interchange meeting focused on accessibility and timing, flight and ground resources, parallel education initiatives, and funding. Attendees discussed past and current crystallization research efforts, current technologies and capabilities in the field, and the needs of the protein crystallography community on the ISS National Lab. Information gained from the technical interchange initiated the path forward to implementation of an ISS National Lab MMCG Program to enable sustainable, repetitive, low-cost crystallization in microgravity. Details from this event can be found online (http://www.spacestationresearch.com/research-library/reports/2015pcg/).

Technical interchange invitees included former and current microgravity crystallographers, ground-based crystallographers, crystallography analytics experts, and crystallography hardware vendors. Key discussion points and recommendations from the technical interchange that helped to lay the foundation for the development of the MMCG Program and drive the program's goals are listed in Box 1, and a process for informed molecule selection for organic crystallization in microgravity was formulated based on input from the technical interchange.

Informed molecule selection criteria for the ISS National Lab MMCG Program:

1. *The protein should be able to achieve nucleation on the ground, preferably in the flight hardware.*
2. *The protein should be able to be produced in enough quantity and with enough uniformity to support experiment/operational design and improve the chances for successful crystallization. Material for at least three scrub refurbishments should be planned, and contingency plans should be in place in the event of additional delays.*
3. *If the user has a crystal of the protein, there should be a demonstrated need for improvement (e.g., larger or more uniformly produced crystals and improved diffraction resolution or electron density map). Examples include crystals that have a current resolution less than 4.0 angstroms or current crystals that diffract at 2.5 angstroms but higher quality is needed to provide additional data.*
4. *The user should know some characteristics of the protein's stability, such as temperature range and time-dependent deterioration.*

BOX 1: RECOMMENDATIONS FROM THE TECHNICAL INTERCHANGE MEETING

- The comparative advantage of crystal growth in microgravity should be documented, and outreach to the crystallography community stating these advantages (backed up by literature) is critical.
- Molecules of interest include any protein of high biological significance with an indication of scientific, medical, or commercial interest with a need for improved diffraction and/or electron density map. Molecules of interest include both organic molecules (e.g., membrane proteins, protein-protein and multi-protein complexes, protein-ligand interactions, enzymes, ion channel proteins, side chain configuration of proteins, and small molecules) and inorganic molecules (e.g., semiconductor/liquid crystals and zeolites).
- There is a need to grow both large crystals and small uniform crystals to meet a variety of research and manufacturing objectives, thus hardware and processes must be available to support both.
- It is crucial to provide reliable in-orbit access and secure return of samples to the user's lab or analyses location. It is also important to provide repetitive access for each user; typically, multiple flights are required to achieve crystals resulting in increased resolution of structure.
- There should be a focus on down-selecting to a small number of hardware pieces that work best and ensuring they are fully enabled to fly experiments rapidly.
- Although imaging is not required, it would be useful for both the science (e.g., knowing when nucleation took place or when the crystal started to degrade after growth) as well as educational outreach.
- A related science, technology, engineering, and mathematics (STEM) education program should expand reach and engage new funding opportunities.
- Support is needed for several crystallization techniques, including vapor diffusion, liquid-liquid diffusion, and batch crystallization for X-ray diffraction and neutron diffraction (the key analytic tools used by crystallographers).
- It is essential to reduce the "learning curve" for new users to translate laboratory-based crystallization successes to flight configurations. Efforts should be made to make crystallization compatible with the industry standard Society for Laboratory Automation and Screening (SLAS), formerly the Society for Biomolecular Screening (SBS), plates and automation.

THE ISS NATIONAL LAB MICROGRAVITY MOLECULAR CRYSTAL GROWTH PROGRAM

Progress has been made in the development and implementation of the ISS National Lab MMCG Program, which will provide a platform for discovery to users across many communities—commercial, government, academia, and private research—while also supporting future efforts toward the commercialization of LEO.

Applications for Molecular Crystal Growth in Microgravity

The MMCG Program encompasses both organic and inorganic crystallization, each with numerous applications (see Table 2). Organic microgravity crystallization has applications in the pharmaceutical and agricultural industries. The majority of pharmaceutical applications are aimed at protein structure determination for improved drug development. Many crystals grown in microgravity are larger and more detailed than those grown on Earth, providing protein structures that are more accurate, thus enabling better structure-based drug designs. Other pharmaceutical applications seek to produce high-quality uniform crystalline suspensions for improved drug formulation, manufacturing, and storage. Agricultural applications are aimed at developing improved agriculture formulations for pest control and growth enhancement.

Inorganic crystallization in microgravity also has a multitude of applications. Microgravity enables the synthesis of high-quality semiconductor and scintillator crystals, which can be used for improved radiation detection, with applications in homeland security and medical imaging devices. Synthesis of higher-quality semiconductor crystals also leads to advances in electronics such as computers and smart phones. Alloy solidification research in microgravity is aimed at understanding how defects form during the solidification process and can lead to advances in metal manufacturing. Microgravity studies of electrochemical deposition (the process by which an electric current is used to form thin metal features on conductive surfaces such as electrodes) can help to elucidate the role gravity plays in the formation of imperfections on conductive surfaces, toward production of high-aspect-ratio structures with fewer imperfections.

Goals of the ISS National Lab MMCG Program

The overarching goal of the ISS National Lab MMCG Program is to implement processes to increase commercial utilization of LEO in the area of molecular crystal growth. The program seeks to make it easier and more economical for commercial users to take advantage of microgravity to advance their R&D objectives.

TABLE 2: APPLICATIONS FOR MICROGRAVITY CRYSTALLIZATION

ORGANIC	Pharmaceutical	Structural determination for drug development
		Uniform crystalline suspensions for drug formulation and delivery, manufacturing, and storage
	Agricultural	Agriculture formulation development
INORGANIC	Radiation detection	Semiconductor crystal growth
		Scintillator crystal growth
	Metal manufacturing	Alloy solidification with fewer structural defects
	Conductive surface (i.e., electrode) production	Improved formation of structures during electrochemical deposition process

For organic molecular crystallization, the MMCG Program was established with the following goals:

- **To provide repeat flight opportunities to investigators who fit a predefined set of criteria indicating that microgravity may help.** This criteria for “informed molecule selection” was set forth by experts in the field of crystallography who attended the CASIS protein crystal growth technical interchange meeting. The goal of the MMCG Program is not to replace crystallization techniques currently used on the ground, but rather to inform crystallographers of the ideal conditions in which microgravity could be a valuable tool to improve crystallization.
- **To streamline access to the ISS National Lab through dedicated launch opportunities, rapid turnaround of samples, and cost-effective set pricing.** The MMCG Program aims to fly and return samples within a three-month timeframe from the time of molecule construct determination, enabling a rapid return of samples to the research pathway.
- **To minimize risk and increase the probability of success through expanded use and validation of COTS hardware and through access to vetted service providers with expertise in microgravity investigation design.** The use of COTS hardware reduces both the cost of flight hardware as well as time and money spent on optimizing conditions.
- **To work toward multi-flight, multi-protein collaborations with other government organizations, research foundations, and commercial companies.** The MMCG Program has been specifically designed to meet the needs of commercial upstream R&D, and as a result, CASIS is already beginning to negotiate several multi-year, multi-flight programs.

A first step in developing the MMCG Program was to engage existing and potential new partners intent on providing relevant hardware and services. Toward this end, CASIS issued a solicitation in 2016 for proposals to provide support services—including laboratory services, integration, and hardware support—for investigators interested in conducting organic crystallization experiments onboard the ISS National Lab. The goals of the solicitation were to (1) standardize hardware for vapor diffusion, liquid-liquid diffusion, and batch crystallization; (2) identify service providers for specialized services such as protein expansion and crystal analyses; and (3) establish consistent fee-for-service with providers to streamline the customer experience.

As a result of the solicitation, the following preferred partners were chosen, and costs for hardware and implementation services were defined, locking prices for standard services for five years.

- The University of Alabama at Birmingham
- Teledyne Brown Engineering
- The Bionetics Corporation
- Techshot, Inc.

Likewise, CASIS intends to bring together the inorganic molecular crystallization research community to identify goals and needs to enhance the use of microgravity for inorganic crystal growth.

CUSTOMER ENGAGEMENT AND FUTURE DIRECTIONS

Increased outreach to the crystallography community will expand understanding of microgravity as a tool to improve molecular crystallization. To connect with the crystallography community, communicate the advantages of crystallization in microgravity, and provide information on the ISS National Lab MMCG Program, CASIS presented and exhibited at the 2016 American Crystallographic Association annual meeting—one of the largest gatherings of crystallographers—and exhibited at the 2017 annual meeting. CASIS also presented at the 2016 Frontiers in Structural Biology of Membrane Protein & Pittsburgh Diffraction Conference. Continued participation in key crystallography events is planned to further enable customer engagement and spur new interest in microgravity molecular crystal growth research (see Table 3). In addition, traditional targeted outreach to key thought leaders and commercial sectors is ongoing.

As a result of increased customer engagement, the MMCG Program continues to attract preeminent industry and academic researchers, as can be seen in the upcoming crystallization investigations planned for launch to the ISS National Lab within the next few increments (see Table 4). The multitude of commercial and academic investigators currently utilizing the microgravity environment on the ISS National Lab to advance their crystallization research demonstrates the effectiveness of CASIS outreach and the growing interest within the crystallography community. CASIS is committed to establishing an MMCG Program to support these investigators and enhance the commercialization potential of a LEO platform for crystallization research.

TABLE 3: SELECT UPCOMING MMCG EVENTS

Event	Type of Engagement	Date	Location
American Society for Gravitational and Space Research (ASGSR) 2017 Annual Meeting	Symposium	10/28/17	Seattle, WA
American Crystallographic Association (ACA) 2018 Annual Meeting	Exhibit and panel session	7/22/18	Toronto, Canada
ISS Research and Development (R&D) 2018 Conference	Crystal growth technical sessions	7/23/18 – 7/26/18	San Francisco, CA

In summary, the MMCG Program aims to streamline access to the ISS National Lab by providing a reliable flight schedule, optimized hardware, rapid turnaround of samples, cost-effective set pricing, and repeat flight opportunities. CASIS is working with COTS hardware manufacturers and the user community to optimize current hardware designs to enable a smoother transition for users going from standard ground-based crystallization to spaceflight crystallization and to enhance readiness of samples for analyses. Moreover, to aid in the identification of optimal organic molecules for growth in microgravity, CASIS has developed criteria for informed molecule selection based on lessons learned from past spaceflight R&D and expert feedback—and additional investigations are underway to help further refine the process for informed molecule selection. Finally, CASIS is working toward establishing multi-flight collaborations with commercial entities, government agencies, and research foundations and has specifically designed the MMCG Program to meet the needs of commercial upstream R&D. As a result, CASIS is currently in the process of negotiating several multi-year, multi-flight programs.

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TABLE 4: SELECT UPCOMING ISS NATIONAL LAB CRYSTALLIZATION INVESTIGATIONS

Investigation	Aim
TITLE: Nemak Alloy Solidification Experiments **PRINCIPAL INVESTIGATOR:** Dr. Glenn Byczynski; Nemak	Elucidate critical parameters behind the formation of hot tearing, which causes defects in the solidification of metal alloys, toward improvements in metal manufacturing
TITLE: 2017 Wisconsin Crystal Growing Competition and Lecture tour **PRINCIPAL INVESTIGATOR:** Ilia Guzei; University of Wisconsin, Madison	Provide a flight opportunity for the middle and high school student winners of the 2017 Wisconsin Crystal Growing Competition, allowing the students to test their optimized conditions for Earth-based crystallization against microgravity-based crystallization
TITLE: Microgravity Crystallization of Glycogen Synthase-Glycogenin Protein Complex **PRINCIPAL INVESTIGATOR:** Dr. David Chung; Dover Lifesciences	Crystallize a medically important protein in complex with inhibitor molecules, toward structural determination
TITLE: An ISS Experiment on Electrodeposition **PRINCIPAL INVESTIGATOR:** Dr. Kirk Ziegler; University of Florida	Elucidate the role of gravity in the formation of interfacial instability patterns during electrochemical deposition, the process by which an electric current is used to form thin metal features on conductive surfaces such as electrodes, toward production of high-aspect-ratio structures with fewer imperfections
TITLE: Microgravity Crystal Growth for Improvement in Neutron Diffraction **PRINCIPAL INVESTIGATOR:** Dr. Timothy Mueser; University of Toledo	Crystalize three medically important proteins with sufficient quality for neutron diffraction, toward structural determination
TITLE: Microgravity Investigation of Cement Solidification **PRINCIPAL INVESTIGATOR:** Dr. Aleksandra Radlinska; Penn State University	Study the microstructural development of cement, which occurs in stages during the hydration reaction and hardening process and results in elaborate combinations of different crystals, toward better understanding of the complex process of cement solidification

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