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Cell Science and Protein Crystal Growth Research for the International Space Station

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Abstract The recent National Research Council report, *Future Biotechnology Research on the International Space Station,* evaluates NASA's plans for research in cell science and protein crystal growth to be conducted on the International Space Station. This report concludes that the NASA biotechnology programs have the potential to significantly impact relevant scientific fields and to increase understanding and insight into fundamental biological issues. In order to realize the potential impacts, NASA must focus its research programs by selecting specific questions related to gravitational forces' role in cell behavior and by using the microgravity environment as a tool to determine the structure of macromolecules with important biological implications. Given the time and volume constraints associated with space-based experiments, instrumentation to be used on the space station must be designed to maximize the productivity of researchers, and NASA's recruitment of investigators and support for space station experiments should aim to encourage and facilitate cutting-edge research. J. Cell. Biochem. 79:662–671, 2000.†

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The National Aeronautics and Space Administration (NASA) manages research programs in two areas of the rapidly expanding field of biotechnology: protein crystal growth and cell science. The protein crystal growth work focuses on using microgravity to produce higher quality macromolecular crystals for structure determination and on improving understanding of the crystal growth process. The cell science work focuses on basic research that contributes to understanding how the microgravity environment affects the fundamental behavior of cells, particularly in relation to tissue formation and the effects of space exploration on living organisms.

The National Research Council's Task Group for the Evaluation of NASA's Biotechnology Facility for the International Space Station was formed to examine and evaluate the use of the International Space Station (ISS) as a platform for research in these two areas. In this report, the task group offers a variety of recommendations and suggestions for improving the NASA biotechnology research program. It believes these changes are necessary if the NASA program is to fulfill the potential for scientific discovery and impact that is also outlined in this report.

The task group's observations are divided into three sections: scientific scope, instrumentation, and selection and outreach. Recommendations are made in technical areas, such as the kinds of instruments to be used on the space station, and the report also discusses changes that should be made in NASA's culture to improve its interaction with the scientific community. The overall goal of the report

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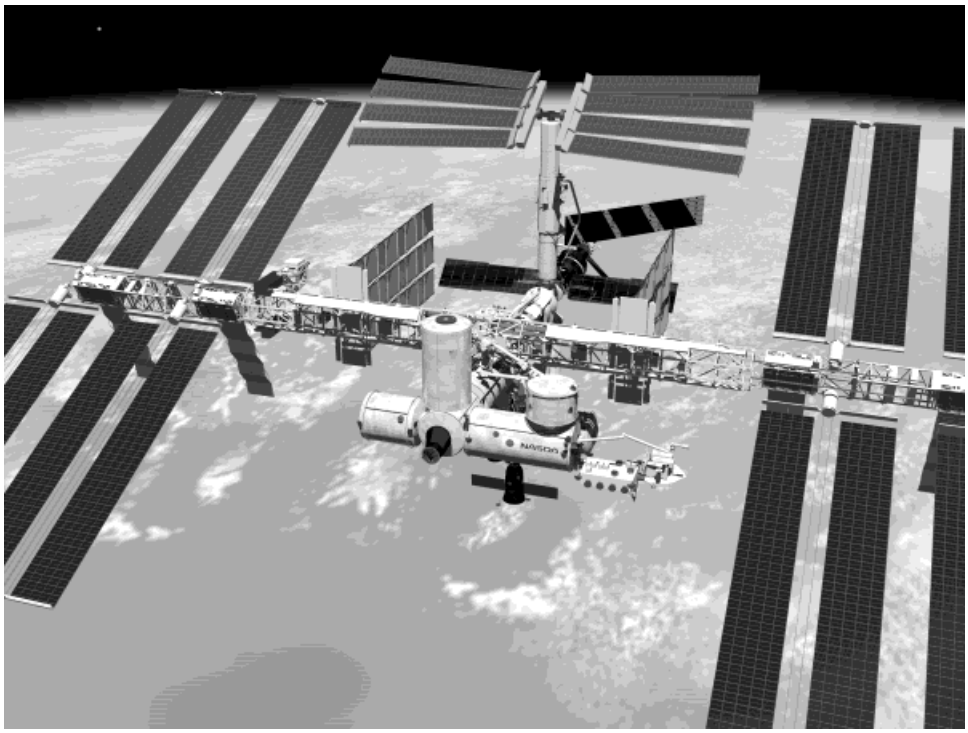

Fig. 1. This artist's concept shows how the International Space Station is expected to look when its assembly sequence has been completed. The illustration is from the NASA web site, http://spaceflight.nasa.gov/gallery/images/station/artistconcept/html/s98_11010.html.

is to help NASA perform biotechnology research effectively on the International Space Station. Several of the important findings and recommendations described in this article and in the report are outlined briefly below.

In the cell science area, NASA's broad-based goal of exploring the fundamental effects of the microgravity environment on biological systems at the cellular level is appropriate, and the work in this area has the potential to have significant impact on the fields of cell science and tissue engineering. However, NASA needs to choose among the many possible areas of basic research in order to focus its grants programs and the instrumentation development activities.

NASA needs to fund a series of "proof-of-concept" grants to determine definitively the effects of microgravity on protein crystal growth. The success or failure of these research efforts will resolve the issue of whether the microgravity environment can be a valuable tool for researchers and the results should determine the future of the NASA protein crystal growth program. Currently, some biologically important macromolecules are still very hard to crystallize, and NASA could have significant impact by focusing on these types of proteins.

Some of the hardware currently in advanced stages of development greatly impressed the task group; examples include the X-ray crystallography facility for observing and analyzing protein crystals and the miniaturized and automated systems for growing cell and tissue cultures. The technological innovations reflected in these systems could have significant impact in ground-based laboratories as well as in space. However, the recent instabilities in the ISS budget are compromising equipment development. If money is repeatedly siphoned off from hardware development work, the quality of the equipment on the ISS will be significantly below that of the cutting-edge hardware available on the ground, and researchers will not be interested in using outdated equipment or willing to entrust precious samples to it.

Access to samples and equipment via shuttle flights will be infrequent, and the time astronauts will have for performing experiments on the ISS will be limited. Therefore, NASA should place a high priority on the automation

of routine tasks, development of systems and hardware for ground-based control of experiments (tele-operation), provision of on-orbit analytical capabilities for monitoring and real-time feedback, and transmission of digital data and real-time communications between astronauts and scientists on the ground.

NASA should improve its outreach activities in order to broaden the scientific community involved in its biotechnology research program and increase the number of cutting-edge projects submitted for funding. At the same time NASA must be careful to present a balanced picture of the program's successes and limitations. By allowing the widespread dissemination of vague or even inaccurate descriptions of the program, NASA is seriously diminishing the credibility of its work within the scientific community.

BACKGROUND AND SCIENTIFIC SCOPE OF NASA PROGRAMS

Protein Crystal Growth

The task group heard a great deal about experiments to date in NASA's macromolecular crystallography program. The results so far are inconclusive, and the impact of microgravity crystallization on structural biology as a whole has been extremely limited. At this time, one cannot point to a single case where a space-based crystallization effort was the crucial step in achieving a landmark scientific result. In many of the cases that have so far been listed as successful, the improvements obtained have been incremental rather than fundamental. In addition, the difficulty of mounting simultaneous efforts to produce the best possible crystals both on the ground and in space has limited the ability of researchers to make the comparisons between microgravity and Earth crystals that would be necessary to demonstrate that the microgravity environment can produce superior crystals.

Finding. The results from the collection of experiments performed on microgravity's effect on protein crystal growth are inconclusive. The improvements in crystal quality that have been observed are often only incremental, and the difficulty of producing the appropriate controls limit investigators' ability to definitively assess if improvements can be reliably credited to the microgravity environment. To date, the impact of microgravity crystallization on structural biology as a whole has been extremely limited.

Despite the lack of impact of microgravity research on structural biology up to now, there is reason to believe that the potential exists for crystallization in the microgravity environment to contribute to future advances in structure determination. Today's ground-based protein crystallization projects are increasingly sophisticated, and yet the diffraction characteristics of crystals of many important targets are still suboptimal. Improvements in diffraction that move a system from the margins of structure determination to well beyond that boundary will have a significant impact on the ability of the resulting structure to provide important insights into biological mechanisms. All research on protein crystallization in space has, up to now, been done under suboptimal conditions (short-duration experiments, insufficient vibration control, etc.), so the improved conditions for research provided by the ISS have the potential to produce much better results.

Finding. While enormous strides have been made in protein crystallization in the last decade, it is still the case that there are very important classes of compelling biological problems where the difficulty of obtaining crystals that diffract to high resolution remains the chief barrier to structural analysis of the crystals. It is here that the NASA program must look to maximize its impact.

In order to engage the research community, NASA must focus its support on programs that are developing technologically innovative equipment and engaging in the structure determination of crystals with important biological implications. While past NASA-supported research on the crystallization process has not been without value, NASA's priority should now be to resolve the community's questions about the usefulness of protein crystal growth in the microgravity environment for tackling important biological questions. Until the uncertainty about the value of space-based crystallization is resolved, a program of this fiscal magnitude is bound to engender resentment in the scientific community.

Although many pharmaceutical and biotechnology companies have participated in microgravity crystallization research, not one has yet committed substantial financial resources to the program. This is likely to remain the

case until the benefits of microgravity can be convincingly documented by basic researchers and until facilities in space can handle greatly increased numbers of samples in a much more user friendly manner.

Cell Science

NASA's cell science program focuses on studying the influence of low gravity on fundamental cell biology as it relates to tissue formation, and on providing insight into the effects of microgravity on cell, tissue, and organ system function, especially as it might affect participants in space exploration.

Finding. It is appropriate for NASA to support a cell science program aimed at exploring the fundamental effects of the microgravity environment on biological systems at the cellular level. Results from such basic research experiments could have a significant impact on the fields of cell science and tissue engineering. However, the specific important questions within cell biology that can best be tackled on the ISS do not seem to have been defined yet. Narrowing the broad sweep of the current program may focus instrument development efforts and accelerate progress toward complete understanding of the effects of microgravity on specific biological phenomena.

A key to determining the success of cell science experiments in space will be designing appropriate controls for experiments. In space, cell cultures experience a low gravitational environment that reduces convection, buoyancy-driven flows, and sedimentation, and it is difficult to separate the various factors causing differences between space- and Earth-grown samples [NRC, 1998]. In addition, the tremendous progress that has been made in three-dimensional tissue development on Earth, under unit gravity, provides a wide range of options for ground-based experiments that may produce results similar to those achieved in microgravity. To evaluate the relative merits of various experimental control groups, and also to enable the detailed evaluation of samples returned from space, it is important that quantitative measures of cell and tissue structure and function be developed and studied.

Finding. Appropriate experimental controls for space-based cell science experiments have not yet been determined. The best controls would be those that enable researchers to separate and investigate the multiple factors—including launch and reentry, effects of microgravity on the culture medium, and direct effects of microgravity on cellular behavior—that produce the changes observed in cells and tissues grown in space. Analytical techniques that measure the molecular mechanisms underlying cellular functions will be essential to provide data for comparing proposed experimental controls and quantifying the observed changes in cell and tissue samples.

At NASA, the work viewed by the task group was being carried out in the biotechnology section of the Microgravity Research Division. The themes of the cell science research under way in this program overlap with the scope of work ongoing in the NASA Life Sciences Division. The complementary nature of these two programs needs to be recognized so that NASA personnel and external researchers can take full advantage of the potential synergies. While there is already a sharing of flight hardware, a mechanism to establish projects that are jointly funded by the Life Sciences Division and the Microgravity Research Division should be considered.

Recommendation. The research strategies and projects of the cell science work in the biotechnology section of the Microgravity Research Division should be more closely coordinated with the work of NASA's Life Sciences Division to take advantage of overlapping work on bone and muscle constructs and of potential synergies between in vitro and in vivo research projects.

INSTRUMENTATION

The International Space Station (ISS) is currently under construction; assembly is scheduled to be complete in 2005. However, NASA plans to begin research on the facility as early as 2000, using equipment that has been flown on the shuttle and that can be temporarily installed in modules of the ISS as they are completed. As the ISS grows and more station-specific hardware is ready, the research program will expand and more permanent instrumentation will be fitted into the ISS.

Protein Crystal Growth

A variety of equipment has already been used to grow and observe crystals in space, and innovative hardware continues to be developed today. Having multiple laboratories involved in

this process encourages variety and creativity and also prevents NASA from getting locked in to a single hardware approach. However, the efforts of hardware developers need to be coordinated and communications between them must be improved to ensure that different programs are not producing instruments with duplicative capabilities and that technological advances are quickly shared and integrated into all equipment where appropriate.

Recommendation. The efforts of external hardware developers should be coordinated to ensure that instruments are compatible, to prevent duplication of efforts, to ensure that technical innovations are shared, and to facilitate input from the scientific community in defining the goals and capabilities of protein crystal growth equipment for the ISS. NASA must also be prepared to discontinue development projects that do not use cutting-edge technologies or that are out of tune with the most current scientific goals.

A significant factor affecting equipment development is the instability in the budget for the ISS. If money is repeatedly siphoned off from the hardware development work, the equipment on the ISS will be of much lower quality than the cutting-edge hardware available on the ground, and researchers will not be interested in using the outdated equipment or willing to entrust precious samples to it.

The equipment developed by and for NASA should aim to provide a high level of control over samples, equipment, and procedures. On the ISS, crew time will be limited, and the human access to samples and the feedback to the investigators enabled by shuttle trips will be infrequent, so automation and ground-based control of experiments are essential. If principal investigators are able to make decisions about experimental parameters and to adjust experiments in real time, the research results produced in each experiment will be of higher quality, and involvement in the NASA program will be more attractive. Therefore, hardware development efforts should emphasize the importance of automation, monitoring, real-time feedback, telemanagement, and sample recovery (via mounting and freezing).

Effective analysis, preservation, and reentry of promising crystal samples is especially necessary given the key role synchrotrons are playing in protein structure determination. If the NASA program is to attract researchers interested in important and challenging biological problems, ISS hardware must be designed to produce and safely return to Earth crystals of the appropriate size and quality to be analyzed at a synchrotron. However, it is not NASA's responsibility to arrange or guarantee this next step. Building a synchrotron beam line is expensive and would not be the most efficient use of NASA's scarce resources. Assuming that NASA's peer review process is selecting the most scientifically rigorous and interesting projects, successful crystallization should enable researchers to compete effectively for the necessary beam time, and success in this extra layer of peer review should further validate the NASA program within the scientific community.

The X-ray Crystallography Facility (XCF) being designed for the ISS is a multipurpose facility designed to provide for and coordinate all elements of protein crystal growth experiments in space: sample growth, monitoring, mounting, freezing, and X-ray diffraction. The task group was impressed by the XCF, by the robotics, the remote control, and the range of experimental capabilities provided. The X-ray diffraction module provides valuable information about whether a given crystal will diffract—this real-time feedback is key to making decisions about the success or failure of a particular crystallization experiment and will help allocate scarce freezer resources by ensuring that the most promising crystals are preserved and returned to Earth.

Finding. Automation, monitoring, real-time feedback, telemanagement, and sample recovery (via mounting and freezing) will be vital for successful protein crystal growth experiments on the ISS. The XCF, through its use of robotics and a variety of experimental and observational capabilities, provides many of the tools researchers need to take full advantage of the microgravity environment.

The XCF is typical of several hardware development projects for NASA in that the technologies it employs can be applied to ground-based research capabilities as well as to those based in space. Currently, however, the scientific community is mostly unaware of the quality of the automation displayed in the prototype of the robotic crystal sample preparation system and of the combined capabilities of the X-ray optics and the low-power source that will be used in the XCF. While commercial entities

may need to protect their proprietary work, scientists must have access to full information about all relevant technologies and equipment for the ISS in order to effectively design and execute cutting-edge research in space.

Cell Science

A variety of instruments are being developed to support cell science research on the ISS, including a basic incubator, a perfused stationary culture system, and a rotating-wall perfused vessel (a bioreactor). Overall, the NASA-funded cell science work to date has emphasized the use of bioreactors to support three-dimensional tissue growth. While the development of rotating-wall vessels has had, and should continue to have, a significant impact on cell and tissue culturing methodology on the ground, the task group has a variety of concerns about the effectiveness and appropriateness of this approach for research in the microgravity environment. Issues include the relatively small amounts of data generated per unit volume and the difficulty of accessing the vessel on orbit.

Recommendation. Given the current status of equipment in development, finite fiscal resources at NASA, and the limited amount of volume on the ISS, the task group recommends that future research on the ISS should deemphasize the use of rotating-wall vessel bioreactors, which are already established, and continue to encourage the development of new technologies such as miniaturized culture systems and compact analytical devices.

The final determination on what sort of instrumentation will be most effective for cell and tissue growth in microgravity has yet to be made, and it is important that the relative merits of various pieces of instrumentation be carefully evaluated and that NASA maintain the necessary administrative and engineering flexibility to adopt the most effective systems employing the most advanced technologies and to discontinue hardware development projects that are not attuned to the most current scientific needs of the cell science communities. Close interaction is needed between scientists and the NASA operational personnel responsible for developing and constructing the hardware to ensure maximum flexibility and responsiveness to evolving research goals.

Cellular systems are very sensitive to environmental perturbations. A continuous power supply to maintain appropriate and stable environments during experiments and for sample storage and transport is essential to ensure valid results. A variety of systems are under development to manage power distribution, and care must be taken, particularly during ISS construction, to ensure that cell science experiments are not compromised by power fluctuations. Another issue that will be problematic, particularly during ISS construction but also after the station is complete, is the limited amount of crew time available for research. The automation of routine tasks and ground-based control of experiments will be essential if investigators are to make efficient use of the ISS platform.

Two key supports for automation and ground-based control are 1) sensors to enable physiological control of the cell/tissue culture media environment and 2) analytical equipment to provide feedback about the status of cell and tissue samples. The data from the sensors and the on-orbit analyses should be transmitted electronically in real time to investigators to enable ground-based control of experiments. Scientists on the ground then could select the most important samples for the scarce storage space and could study the changes wrought in samples by freezing and reentry.

Finding. The limited amount of crew time available for research-related work and the infrequency with which investigators will have access to their samples via shuttle trips mean that automation of routine tasks, ground-based control of experiments, on-orbit analytical capabilities, and real-time transmission of digital data are vital for conducting effective cell science research on the ISS.

Refrigeration and freezer capability and transport space are not the only factors limiting the throughput of cell science research on the ISS. Other factors that will affect the size of the program and the number of primary publications include crew time required for the experiments, the amount and reliability of the power supply, adequate storage space and appropriate environments for samples and supplies, shuttle flight schedules to and from the ISS, the volume of materials to be transported, and, of course, the size of the budget provided for cell science hardware development and research support. A window of opportunity has been created by the advances in molecular, cel-

lular, and biochemical approaches (e.g., functional genomics and proteomics) that are occurring as the ISS research platform becomes available. The task group recommends that to most efficiently exploit this opportunity, emphasis should be placed on integration of the different approaches and on collaboration between principal investigators and other researchers inside and outside NASA.

Recommendation. Mechanisms should be developed to enable collaborative research projects that maximize the amount of data obtained from each cell or tissue sample by executing multiple analyses on each sample.

Overall Volume Allotment for Biotechnology Research on the ISS

Currently, NASA plans call for peer-reviewed biotechnology research to occur within one rack on the ISS. This rack would be shared by protein crystal growth and cell science work. In addition, two racks are reserved for the hardware associated with the X-ray Crystallography Facility (XCF) being developed for the NASA Space Product Development Division. The task group considered this arrangement and the needs of the various research communities and recommends a shift in the allotments. Namely, the XCF rack devoted to crystal growth and monitoring should be transferred from Space Product Development to the Microgravity Research Division's protein crystal growth program, where experiments are selected by a centralized peer-review process and a full complement of hardware is available. The rack currently scheduled to be shared by cell science and protein crystal growth can then be dedicated entirely to cell science research.

The task group makes this recommendation based on several considerations. A primary issue is the basic incompatibility between the technical needs of cell science and protein crystal growth equipment on the ISS. The flow of gases and fluids required to maintain rigorous environmental control for cell and tissue culture will produce vibrations that cannot be tolerated by a crystal growth facility. If cell science and protein crystal growth equipment are housed in one rack, one or both of the disciplines will be forced to operate under suboptimal conditions.

The task group also carefully considered the needs of the various research communities expected to use the biotechnology facilities on the ISS. For cell science, there was concern that the amount of data and results generated by half a rack of equipment would not be substantial enough to maintain interest within the scientific community, whereas a full rack's worth of instrumentation could raise the program to a critical threshold. For protein crystal growth, the research community is still uncertain about the benefits of growing crystals in a microgravity environment, so protein sample flight programs are undersubscribed and commercial interest is low. By focusing the protein crystal growth research efforts on biologically challenging problems and by emphasizing hardware capable of monitoring and preserving samples, NASA could direct its resources to validating the program. The current volume commitment of half a rack of general macromolecular research is insufficient to establish the value of the crystal growth program, but a full rack, filled with peer-reviewed experiments that employ all types of available hardware and have access to the capabilities of the XCF, should be adequate to give the program a fair chance of success. If, after several years, the results from the protein crystal growth work have provided sufficient proof of microgravity's benefits and the academic and commercial demand for facilities on the ISS increases, then high-throughput hardware should be developed and the allotment of space on the ISS reconsidered based not only on the demand for macromolecular crystallography research volume but also on the results to that point from the cell science program. Alternatively, if the work done through the augmented commitment recommended here fails to clearly demonstrate the value of microgravity for work on structural biology, then the protein crystal growth program can justifiably be terminated.

Recommendation. The volume allotment for biotechnology work on the ISS should be redistributed as follows: The mounting, freezing, and diffracting equipment of the X-ray Crystallography Facility (XCF) should occupy one rack (as currently planned); the cell science work should occupy the entirety of what is currently designated the Biotechnology Facility; and the rack presently assigned to the XCF growth equipment and managed by NASA Space Product Development should be officially

dedicated to the peer-reviewed macromolecular research run out of the Microgravity Research Division.

SELECTION AND OUTREACH

NASA research in cell science and protein crystal growth is funded through a collection of approximately 90 active 4-year grants; the total size of the program is roughly $19 million per year [NASA, 2000]. Both ground-based and flight projects are selected through a peer-review process that occurs every other year. While the current grant solicitation mechanism (NASA Research Announcements, or NRAs) is appropriate, it is inadequate to attract the involvement of the best scientists or bioengineers. The task group believes that as the program goes forward, it would benefit from a strengthening of the outreach, selection, and support offered by NASA to ensure that the proposals submitted for consideration are of the highest quality and that everything possible is done to give flight experiments the best chance of success.

Both protein crystal growth scientists and cell science researchers identify themselves with a variety of professional organizations, publications, and conferences, so NRAs should be disseminated to a wider variety of newsletters and announcements in order to reach the multiple communities that might be interested in using NASA biotechnology facilities on the ISS. Another approach to expanding the pool of potential researchers would be to issue NRAs in collaboration with other federal agencies, such as the National Institutes of Health (NIH), the Biotechnology Program in the Engineering Directorate of the National Science Foundation (NSF), the NSF Biological Sciences and Regulatory Biology Divisions, and the Department of Energy. More could also be done to provide sufficient background information for potential investigators who are not familiar with NASA programs. More detail about the special opportunities and constraints of space-based research as well as about the hardware available for the ISS would make it easier for NASA to recruit new applicants for its grants and for those researchers unfamiliar with the NASA program to put together appropriate proposals. Access to information about failed projects would also improve the quality of experiments designed with NRAs in mind and would increase the likelihood of success. In general, results of projects already under way could be more broadly disseminated; however, the task group cautions that presentations should give a balanced portrayal of successes and limitations so as not to raise unrealistic expectations. Misperceptions about the accomplishments of NASA programs can also be gained from press releases that target the general public and portray potential future applications of NASA-funded research as completed or current work. This dissemination of vague or even inaccurate descriptions of its programs, seriously diminishes NASA's credibility within the scientific communities.

Recommendation. NASA should improve its outreach activities in order to involve a broader segment of the scientific community in its biotechnology research program and to increase the number of cutting-edge projects submitted for funding. It needs to disseminate NRAs and program results more widely and to provide more complete background information on failed projects and how to design flight experiments.

As the pool of applicants expands, the process of evaluating proposals may also need to be adjusted. NASA's program suffers from longer time scales than are compatible with the current pace of biotechnology research. For example, the 2-year gap between NRA grant submission opportunities is likely to inhibit applications directed at the most cutting-edge research issues. Also, the delay between project selection and flight manifesting of an experiment means that NASA does not always have the hardware flexibility to respond to changes in the field based on new developments in ground-based research (for example, the increased reliance on cryoprotection and freezing of crystals or the use of scaffolding for three-dimensional tissue constructs). Finally, the uncertainties surrounding the NASA budget and the continual schedule changes make people cautious about getting involved in a program that is unable to reliably predict how much money will be available or the schedule for access to the ISS.

One critical step toward raising the profile of the NASA program and the quality of the grant application pool would be to counter the current perception of recipients of NASA funds as a closed community with a fixed membership. On the whole, external input into NASA's priorities for the biotechnology program seems to

be relatively limited. Advisory groups are composed of many of the same people that make up the pool of grantees and contribute to the perception that NASA is not really interested in outside input. By reaching out to a broader slice of the protein crystal growth and cell science communities, NASA would not only increase the quality of the advice it receives but would also be able to educate a new group of people about its programs.

According to NASA, the Biotechnology Discipline Working Group (DWG) is the main mechanism for receiving advice about the strategic direction of the Microgravity Research Division's biotechnology programs. The group is responsible for providing input to both the protein crystal growth and cell science sides of the program, but in view of the very different scientific objectives and instrumental requirements, having a single working group for these two disparate areas serves no real purpose. If the DWG is split into two groups, each would be able to focus on the issues most relevant to its own scientific area, and the increased number of slots available for each area would give greater breadth to the groups. Care must be taken in selecting new members to ensure that there is not a bias towards those already working with the NASA program. To attract prominent outside researchers to the DWG, the task group suggests that the name be changed to more accurately reflect the group's role as a high-level advisory panel with input on the scope of research announcements, peer review practices, and future programmatic directions.

Recommendation. The separate identities of the protein crystal growth and cell science sections of NASA's biotechnology research program should be emphasized. One key step should be splitting the Discipline Working Group into two strategic advisory committees to reflect the different issues facing each area of research. Prominent scientists not familiar with NASA's programs but aware of the broader issues facing the fields should be recruited to serve on these committees.

An important issue for execution of research in the unforgiving environment of space is the potential for conflict between the scientific goals of an experiment and the engineering limitations associated with a space-based platform like the ISS. Within the biotechnology scientific community, there is the perception that the NASA culture does not emphasize the importance of communication between scientists and operations personnel, nor does it provide tangible assurances to the research community that the execution of high-quality research in hardware designed to answer the most cutting-edge scientific questions is a NASA priority. The community would be reassured by seeing NASA place bioengineers and biological scientists with the appropriate appreciation of research goals and scientifically oriented reflex responses in high enough decision-making positions to ensure that research opportunities are optimally utilized.

Recommendation. The NASA culture tends to limit communication and coordination between operations personnel and researchers during hardware development; between astronauts and investigators before and during experiment execution; and between decision makers and scientists about the allotment of resources in times of crisis. To attract the best investigators to its biotechnology program, NASA must create an environment geared toward maximizing their ability to perform successful experiments.

Protein Crystal Growth

At present, the primary goal of NASA's protein crystal growth program should be to demonstrate microgravity's effect on protein crystal growth and to determine whether studies of macromolecular assemblies with important biological implications will be advanced by use of the microgravity environment. To this end, the task group proposes that NASA instigate a high-profile, nation-wide series of grants to support researchers engaging in simultaneous efforts to get both the best possible crystal on the ground and the best possible crystal in space of biologically important macromolecules. The projects funded by these grants should address the uncertainties that have plagued the NASA protein crystal growth program, by using the ISS for a reliable, long-term microgravity environment, by comparing space-grown crystals to the best ground crystals, and by focusing on challenging systems and hot scientific problems. Their results should definitively show whether the use of microgravity can produce crystals of a higher quality than those grown using the best technologies available on Earth. If none of the projects produces a space-grown crystal that enables a breakthrough for the structure deter-

mination of a biologically important macromolecular assembly, then NASA should be prepared to terminate its protein crystal growth program. However, if the projects supported by this high-profile, nationwide series of grants succeed in validating the use of crystallization in microgravity to tackle important and challenging problems in biology, demand for the facilities on the ISS can be expected to increase. At that time, NASA should develop an external user program (similar to synchrotron user programs) in which projects are selected by a peer-review committee that includes NASA staff representatives.

Recommendation. NASA should fund a series of high-profile grants to support research that uses microgravity to produce crystals of macromolecular assemblies with important implications for cutting-edge biology problems. The success or failure of these research efforts would definitively resolve the issue of whether the microgravity environment can be a valuable tool for researchers and would determine the future of the NASA protein crystal growth program.

Cell Science

NASA has built a very productive relationship with the NIH based on the development and use of rotating-wall vessels. The NASA/NIH Center for Three-Dimensional Tissue Culture was started in 1994 to expose a wider community to bioreactor technology by allowing researchers from government agencies (e.g., NIH, the Food and Drug Administration, and the Department of the Navy) to test new model systems for biomedical research and basic cell and molecular biology in the rotating-wall vessel hardware with technical assistance from experienced NASA personnel [NASA, 2000]. The task group believes that this outreach program is an excellent idea and recommends that a wider range of investigators be reached by opening this introductory phase of this program to extramural (nongovernment) researchers.

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