

Final Report  
NASA

***PROTEIN CRYSTALLIZATION FOR DRUG DEVELOPMENT:  
A Prospective Empirical Appraisal of Economic Effects of  
ISS Microgravity***

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## Executive Summary

One of the basic missions of NASA is to use the International Space Station (ISS) to facilitate the growth of a commercial marketplace in low Earth orbit for scientific research, technology development, observation and communications, and human and cargo transportation. While the private sector has shown some interest, and while there exist significant potential commercial applications, the ISS currently lacks the ability to exist independently as a commercial entity due to significant technical, financial and policy barriers, as well as the lack of information among prospective users. Oft cited barriers include (i) transportation costs, frequency, and risk for cargo and research crew, (ii) intellectual property rights, and (iii) appropriate investment and tax incentives to entice the private sector.

Bioscience has long been promoted as one of the more promising applications in the effort to commercialize LEO. A specific application – expanding research in protein crystallization on the ISS's microgravity environment could prove important in the development and design of drugs to treat diseases such as arthritis, cardiovascular disease, multiple sclerosis, osteoporosis, cystic fibrosis, and even cancer. This is the focus of the present paper.

The paper is part of a set of five contributions taking a fresh look at the subject. Two of these papers follow a more "macro" approach (Mazzucato-Robinson; Tassej) while the remaining three follow a more "micro" approach (Link-Maskin; Lerner-Leamon-Speen; Vonortas). Mazzucato and Robinson provide an overview of shifting policy priorities for NASA and LEO's rising importance ending with some big picture recommendations. Tassej places LEO in the context of the innovation system and suggests three alternative approaches for promoting technology commercialization. Link and Manskin drive home one important idea: that LEO commercialization has until now suffered from the lack of information. Lerner, Leamon and Speen follow up by detailing the currently weak points of LEO tech business in the eyes of the private sector and the types of information, regulation, and regular service provision that will make business calculations more favorable towards LEO. This, in turn, links well with the present paper regarding the uncertainties faced by prospective investors in the specific example of protein crystallization in microgravity and the types of information necessary for calculating a specific cost-benefit model to guide the pharmaceutical industry in investing on growing protein crystals on the ISS. Our discussion of a possibly different approach to more generic and more applied protein research closes the loop by reminding Tassej's preferred third alternative approach for promoting technology commercialization through "holistic technology development infrastructure that allows joint management with industry partners of R&D project portfolios".

Humans contain over 100,000 proteins that are vital in their everyday functions. Full understanding of protein function requires information on the three dimensional structure of these proteins and leads to the development of better drugs that target these proteins more effectively. To obtain this information

scientists model proteins with a process called x-ray crystallography whose effectiveness, in turn, depends on the use of good quality protein crystals.

The ISS has for long been argued as the ideal place for protein crystallization. Crystals grown in microgravity do not face the same convection forces seen on Earth – such as wind and gravity – which adversely affect the orientation and size of crystals. While crystals grow much slower in microgravity, they provide massively more data points as crystals grown on Earth. Because of this, it is argued that the ISS has the potential of becoming the new frontier of pharmaceutical research, assisting in the discovery of new uses of proteins never before thought possible when tested on Earth.

The promise of opportunity notwithstanding, several constraints remain for the establishment of high-budget (i.e., viable) protein crystallization research on the ISS: proof of concept, experiment duration, size restraints, and transportation. At present, it is questioned whether there is strong enough evidence that crystal quality improvement is high enough to justify the effort of sending proteins to space. To answer this, Dr. Lawrence DeLucas from the University of Alabama is currently leading a study of 2000 membrane protein crystals grown in space versus Earth, which will likely be completed in the summer of 2015. DeLucas' April 2014 expedition purported to accomplish two goals: a) inform scientists on the structures of membrane proteins and b) conclusively measure the overall impact of microgravity on protein crystallization. The entire analysis is being performed as a "double blind" experiment. DeLucas' project becomes of critical importance in determining the additionality of the ISS in protein crystallization and thus enabling cost-benefit analysis of this line of activity on the ISS. At the time of this writing, there are only preliminary, yet very encouraging, results of the DeLucas study.

There are four stages of research with heavy contribution by protein crystallization to drug development:

1. Production of high quality crystals
2. Collection of generic information to identify and validate possible drugs
3. Modeling of a drug to a specific target during the preclinical stage
4. Fine tuning of the drug during the clinical stage

The first two stages can be described as generic research, with the results being of interest across the pharmaceutical industry (also including bio). The last two stages are appropriately described as private research of interest to individual companies. The ISS's contribution as currently envisioned falls squarely in the very first stage but its effects are very much felt all the way across. Assuming the distinction between more generic and more applied research stages holds, the policy approaches to address them are different.

On the one hand, *the more generic research stages may be addressed through a collaborative agreement between the main stakeholders on the supply side.* This is a tool well-tried out in the previous 2-3 decades in various sectors to alleviate the

conditions for suboptimal investment in generic (or precompetitive) research by the private sector (i) due to the presence of uncertainty regarding research paths and the prospective applicability of the results within the confines of individual companies and (ii) due to expectations of imperfect appropriability of the results. Compounded with the four barriers listed earlier in relation to the ISS, this creates a straightforward need for government intervention through the sanctioning of collaborative research as well as its subsidization.

On the other hand, *the more applied research stages may be addressed with better information about the expected benefits and costs and risks involved in order to facilitate private sector investment.* It is these stages of research that are the major focus of the latter part of the paper. The purpose here is to expose a specific model that can be utilized to empirically analyze the effect of protein crystallization in space to the pharmaceutical sector. To achieve this goal one needs to take two steps. First, one must evaluate the effect of improved (larger, clearer) protein crystals on drug development. Second, one must evaluate the additionality of ISS in developing such improved crystals in microgravity as compared to other channels of doing so.

It is shown that a detailed model recently developed by RTI researchers sponsored by the New York Academy of Sciences can indeed be used in carrying out the first step, i.e., evaluating the effect of improved (larger, clearer) protein crystals on drug development. The attraction of this model is that it estimates the effect of better infrastructure for research on the productivity of R&D for a specific disease. *The availability of better quality protein crystals can be considered in economic terms as better infrastructure leading to increased productivity of pharmaceutical R&D.* A model like the one showcased here can help assess the benefits of improved protein crystals on drug development much more precisely than has been the case until now.

For the second step we must wait for the full results of DeLucas' study. Preliminary reported results of the study find considerable additionality. Assuming this holds, the improvement in commercial drug costs would be quite significant.

## 1. Introduction

One of the basic missions of NASA is to use the International Space Station (ISS) to facilitate the growth of a commercial marketplace in low Earth orbit for scientific research, technology development, observation and communications, and human and cargo transportation. While the private sector has shown some interest, the ISS currently lacks the ability to exist independently as a commercial entity due to significant technical, financial and policy barriers, as well as lack of information among prospective users. Oft cited barriers in this respect include (i) transportation costs, frequency, and risk for cargo and research crew, (ii) intellectual property rights, and (iii) appropriate investment and tax incentives to entice the private sector. An additional barrier that has transpired during the meetings with experts in the context of this panel is the apparent newness of the operation and, consequently, lack of awareness of the possibilities across industry until recently.<sup>1</sup> CASIS is one organization most closely involved with alleviating several of these barriers, increasing awareness, and facilitating access.

There are several potential commercial applications for the ISS. As has been argued throughout the years by a long list of experts and NASA itself, one of the more promising applications in the effort to commercialize LEO is bioscience. In particular, it is argued that expanding research in protein crystallization on the ISS is a low hanging fruit in terms of allowing CASIS – the manager of the federal laboratory - to develop a sustainable activity by leveraging an extant bioscience sector. There are strong expectations that the space station’s microgravity environment will prove

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<sup>1</sup> Link and Manskin's paper in this collection drives home the idea that the lack of information about previous projects has hindered the willingness of additional users to engage in R&D on the ISS. This message is picked up by the Lerner, Leamon and Speen's paper in this collection who provide a lot of detail through their VC interviews and literature review about what are the weak points of LEO tech business in the eyes of the private sector, what information is missing, and what types of information, regulation, and regular service provision will make business calculations more favorable towards LEO.

important in the development and design of drugs to treat diseases such as arthritis, cardiovascular disease, multiple sclerosis, osteoporosis, cystic fibrosis, and even cancer.

This paper explicitly addresses this issue. In a short time period we have tried to understand the added value of the ISS microgravity environment for building better quality protein crystals than is possible on the ground. The scientific implications of our study are quite broad as it involves a huge potential area of biomedical research spanning across diseases and NIH centers. In this case study, we are more interested in the economic aspects of protein crystallization on the ISS. Within a time span of 3-4 months we have tried to understand both what scientists say about it and how economists would approach the cost-benefit analysis of this activity. At this point, we think we understand to some extent the basic scientific idea and can propose a model that can guide a collection of appropriate data from industry experts in order to quantify microgravity's "value added", while taking into account the expected benefits, expected costs, and risks involved. Obviously, as any analysis of its kind, what is proposed here is based on certain assumptions and the required data for estimation will depend on past experience in pharmaceuticals (e.g., Tufts database) as well as on certain opinions from industry experts. In other words, there is some margin for error.

The paper proceeds as follows. Section two below discusses the topic of protein crystallization in biomedical research as well as our current understanding regarding the contribution of microgravity in developing better quality crystals. Section three addresses possible policy intervention, also including the introduction of a government funded consortium to diffuse risk. Section four outlines a specific model that has recently been developed by RTI International, which provides an interesting quantitative framework for measuring private sector costs.<sup>2</sup> The

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<sup>2</sup> We are indebted here to our co-panelist, Professor Al Link, who had participated in the specific RTI project and pointed out to us two critical outputs of it.

outcome of this section is essentially a list of needed data and data sources. Finally, Section five concludes.

## **2. Protein Crystallization and Biopharmaceutical Research**

### **2.1. Declining Research Productivity in New Drug Development**

The white paper published by the Federal Drug Administration more than ten years ago (FDA, 2004)<sup>3</sup> openly identified a critical challenge in biomedical research: an ever faster pace of basic science discoveries are not being translated quickly into more effective, affordable, and safe medical products for patients. In economic parlance, one would describe the problem as a decrease in biomedical research productivity. The problem was identified as concentrating on an outmoded medical product development path that has become increasingly complex, inefficient and, thus, very costly resulting in decreased numbers of both new drug and biologic applications submitted to FDA and medical device applications. In contrast, the costs of product development reportedly had soared over the previous decade. If the calculation of the cost of successful drug development reported in the academic literature is anything to go by, the situation has not improved since then. On the contrary, it is getting worse (DiMasi et al, 2003, 2007, 2014).

In FDA's view, the problem was said to be that applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The discovery process had accelerated much more rapidly than the technology development process. "[N]ot enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs."(FDA, 2014, p.ii). Developers were said to often use antiquated tools and concepts resulting in high product failure during clinical trials and significant loss of time and resources. Obviously, as in any industry,

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<sup>3</sup> And revisited more recently (FDA, 2014).

producers cross-subsidize failures from successes. In an industry where the costs of drug development are already high due to extensive regulation and complicated science, antiquated drug development structure further amplifies costs. It consequently also leads to greater attention towards a few potential mega-products.

The FDA white paper called for a new product development toolkit containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques (p.ii). Such a toolkit would improve predictability and efficiency along the path from laboratory concept to commercial product.

While there is no silver bullet to achieve this objective, this opens up a window of opportunity for improvements in the process of protein crystallization. *Better crystals can be considered as part of better research infrastructure* – exactly like better biomarkers, for instance – that would contribute to decreasing risk in the pre-clinical Phase of new drug development and allow better compounds to be differentiated from the chuff much earlier in the follow-up clinical research Phases.

## 2.2. Use of Protein Crystals in Biomedical Research

Humans contain over 100,000 proteins that are vital in their everyday functions. Without them, our bodies could not “repair, regulate, or protect themselves” (NASA, 2015). Full understanding of protein function requires information on the three dimensional structure of these proteins and leads to the development of better drugs that target these proteins more effectively. To obtain this information scientists model proteins with a process called x-ray crystallography whose effectiveness depends on the use of good quality protein crystals.

### 2.2.1. Protein Crystallization History and Process

Protein crystallization is the process by which protein molecules are formed into 3D crystals so that they can be studied much more effectively under a process called X-

ray crystallography. Using X-ray crystallography, scientists study the way proteins interact with other molecules, how they undergo conformational changes, and how they perform catalysis in the case of enzymes.

Protein crystallization is a 100-year-old process that has gained notoriety as a drug discovery tool over history. Max von Laue has been credited for the discovery of the diffraction of X-rays by crystals in 1914. Using the process of X-ray diffraction, William Henry Bragg and William Lawrence Bragg won the Nobel Prize in 1915 for analyzing crystal structures at the atomic level. It was John Bernal and his student Dorothy Hodgkin in 1934 who produced the first X-ray diffraction photograph of a digestive enzyme, Pepsin, marking what many scientists consider the beginning of protein crystallography. Hodgkin went on to discover the structure of penicillin through protein crystallography, which allowed pharmaceutical companies to mass-produce the antibiotic. Herb Hauptman and Jerome Karle, who won the Nobel Prize in 1985, found a more efficient method for determining crystal structures that improved the accuracy and time of experiments.

Hauptman and Karle's improvement of protein crystallography has become an essential tool in today's drug discovery industry. More than 85 percent of known protein structures have been discovered through the process of protein-crystallography (NIH, 2007, 14). In this process, a pure, highly concentrated sample of a protein is combined with a variety of liquids that will eventually evaporate, resulting in the formation of a crystallized protein. The best crystals are long, three dimensional, and tightly packed with organized molecules. Since diffraction-quality crystals can be hard to produce, thousands of samples are often created for just one protein.

After creating a successful protein crystal, X-ray diffraction is preformed. Using a large machine called a synchrotron, X-rays are blasted through the crystals, which are being automatically rotated, to capture the full scope of diffraction data. Given data on diffraction patterns, proteins can be accurately modeled in three dimensions.

With the resulting three-dimensional protein model, pharmaceutical companies can design novel drugs that target a particular protein or engineer an enzyme for a specific industrial process. This development process is known as *structure-based drug design*. There are several empirical examples of protein crystallography's contribution to medicine throughout history. Notably in the 1980s, protein crystallography was vital in producing treatments for HIV. Scientists were able to model the structure of HIV protease, a protein that causes HIV to spread throughout the body. Using the three-dimensional structure, scientists engineered protein inhibitors – such as the drug Viracept – to slow down the progress of the disease. Because of the billions of molecules that can be studied under one protein crystal, the possibilities of using protein crystallization are said to be virtually endless.

Pharmaceutical companies often utilize protein crystallization during the early phases of the drug discovery process, even prior to the preclinical phase. When scientists want more information about the receptor site of the target drug, protein crystallization is used to identify and validate the target. Once there is a general idea of a leading target, protein crystallization can be used further during the drug design phase to model a drug specific to the target. Specifically, scientists use software to test fit a drug candidate to the molecule's receptor site. Protein crystallization is more commonly used in the drug discovery process due to the time it takes to effectively analyze crystals for new targets.

While the key to accurate 3D protein modeling is high quality protein crystals, protein crystallization has historically been the most difficult part of the crystallography process. Protein crystals are very fragile, and can be affected by small changes in heat or pressure. With a very low margin of error, scientists must increase the sample sizes of possible crystals, this way increasing both the cost and time of experiment. Another issue is that protein structure in a crystal is not always the same as in an actual cell. Biological structures are difficult to measure solely through a representative crystal. To address this, scientists complement their

analysis of the crystal structure with a protein's activity, which provides more accurate data but increases the time of experiment further. In the past 15 years, technology and automation of the process has significantly lowered costs and increased the purity of tested proteins (Netterwald, 2007).<sup>4</sup>

In 1992, Dr. Lawrence J. DeLucas strongly argued that the microgravity environment on the ISS would be ideal for growing better quality protein crystals. The question of the benefit from space crystallization still remains today. Why are crystals grown on the ISS better than the alternatives obtained on the ground? How much better are they and at what additional cost?

#### 2.2.2. ISS Additionality for Protein Crystallization

The ISS is argued as the ideal place for protein crystallization due to the Space Station's microgravity environment and the existing MERLIN hardware. Crystals grown in microgravity do not face the same convection forces seen on Earth – such as wind and gravity – which adversely affect the orientation and size of crystals. While crystals grow much slower in microgravity, they provide approximately twice as many data points as crystals grown on earth (Pool, 1989). Because of this, it is argued that the ISS has the potential of becoming the new frontier of pharmaceutical research, assisting in the discovery of new uses of proteins never before thought possible when tested on Earth.

The promise of opportunity notwithstanding, several constraints remain for the establishment of high-budget (i.e., viable) protein crystallization research on the ISS: proof of concept, experiment duration, size restraints, and transportation.

- Proof of concept: While it is generally understood that proteins crystallize better in microgravity than earth, it is still unknown to what extent exactly this is true and which proteins may be exceptions. According to CASIS,

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<sup>4</sup> See Appendix II for more detailed Protein Crystallization costs on earth.

protein resolution in low-earth orbit improves about 20-30% over crystals grown on earth (CASIS Opportunity Map, 2012, 27).

- Experiment duration: Length of experiment may be a most important issue. What might take 1-2 weeks on earth could take 6 months on the ISS. CASIS interviews indicate that the biotech industry would ideally like their results in 4-8 weeks.
- Lab size: The small size of the ISS could hinder pharmaceutical companies from testing large samples and executing a scalable model.
- Transportation to and from the ISS: The absence of a reliable workhorse transporting vehicle that will undertake the journey at regular, frequent, pre-announced dates places a lid on what can be done and at what cost (including operational and insurance).

At present, some within the community of possible business investors argue that there isn't yet strong enough evidence that crystal quality improvement is high enough to justify the effort of sending proteins to space (CASIS Opportunity Map, 2012, 27). Still, CASIS finds that protein crystallization has the potential to become one of the strongest commercial applications to the ISS.

Dr. Lawrence DeLucas from the University of Alabama is currently leading a blind study of 2000 membrane protein crystals grown in space versus Earth, which will likely be completed in the summer of 2015.<sup>5</sup> DeLucas' April 2014 expedition<sup>6</sup> purported to accomplish two goals: a) inform scientists on the structures of membrane proteins and b) conclusively measure the overall impact of microgravity on protein crystallization. The entire analysis is being performed as a "double blind"

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<sup>5</sup> Membrane proteins make up a 67% of commercial drugs, yet information about the structure of these proteins is lacking due to inability to grow proper crystals on earth. For this reason, Dr. DeLucas believes that membrane protein crystallization has the potential to be a strong piece of a commercial space industry. Other useful proteins with potential commercial application are "high-value aqueous proteins and protein complexes" (NASA, 2015).

<sup>6</sup> The protein samples were launched to the ISS on April 18, 2014, and returned to the investigator on October 27, 2014.

experiment to eliminate any perceived bias by colleagues. They use a statistically relevant number of different proteins and for each analyzed protein a statistically relevant number of crystals. Assuming results in well-defined statistical confidence intervals, DeLucas' project becomes of critical importance in determining the additionality of the ISS in protein crystallization and thus enabling cost-benefit analysis of this line of activity on the ISS.<sup>7</sup>

The most relevant results of DeLucas' project to the question under investigation in our study will be the measured differences of protein crystals in microgravity and earth. Evidence of significant additional value of microgravity will support NASA's goal to commercialize this capability of the ISS. Dr. DeLucas' earlier press release notes that even a small improvement in crystals would have "a significant impact on scientist's ability to use the resulting structures to provide insights into biological mechanisms" (NASA, 2015). This "significant impact" can be critical in reducing the cost of existing infrastructure and R&D.

At the very last moment of this writing, Larry DeLucas announced preliminary results of his study (DeLucas, 2015). The data were interesting and the pictures compelling in the sense of pointing out that in certain cases of those examined the obtained protein crystals were largely improved in microgravity as compared to those created on Earth. Yet, it is still difficult to determine why these proteins could be so important to medicine. Appendix I presents the layman's view of these proteins, communicated to us by Dr. Lynn Harper of NASA Ames Research Center.<sup>8</sup> It is important to underline that these are preliminary impressions of preliminary results. While strong caveats apply, there are indications here for very significant and widely applicable results.

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<sup>7</sup> Participants included government labs (Oak Ridge, Los Alamos, Scripps, NIH), industry (Emerald Biostructures, Astra-Zeneca, Ixpress Genes, St. Jude Research Hospital), and 24 universities (including the University of California, the California Institute of Technology, New York University, Columbia University, University of Leeds, and Martin Luther University).

<sup>8</sup> Email of April 28.

More information has just come to surface regarding the costs of and demand for protein crystallization in microgravity. This information can be seen in Appendix II.

### **3. Policy Considerations**

One can distinguish four stages of research with heavy contribution by protein crystallization to drug development that may be liable for possible policy intervention. The stages can be seen below:

5. Production of high quality crystals
6. Collection of generic information to identify and validate possible drugs
7. Modeling of a drug to a specific target during the preclinical stage
8. Fine tuning of the drug during the clinical stage

The first two stages can be described as generic research, with the results being of interest across the pharmaceutical industry (also including bio). The last two stages are appropriately described as private research of interest to individual companies. The ISS's contribution as envisioned comes squarely in the very first stage but its effects are very much felt all the way across. Assuming the distinction between more generic and more applied research stages holds, the policy approaches to address them are different. The more generic stages may be addressed through a collaborative agreement between the main stakeholders on the supply side. The more applied stages may be addressed with better information about the expected benefits and costs and risks involved in order to facilitate private sector investment.

#### **3.1 Collaborative Agreement**

There has been a long strand of research in the economics, business management, and policy literatures on collaborative research.<sup>9</sup> The reason for the development of this extensive literature in its earlier phases in the 1980s and 1990s sounds tantalizingly similar to the first two stages of protein crystallization contribution seen above. In a few words, generic (or precompetitive) research creates the conditions of suboptimal investment by the private sector (i) due to the presence of uncertainty regarding research paths and the prospective applicability of the results within the confines of individual companies and (ii) due to expectations of imperfect appropriability of the results (Arrow, 1962, Nelson, 1959). Compounded with the four barriers listed earlier in relation to the Space Station (Section 2.2.2), this creates a straightforward need for government intervention through the sanctioning of collaborative research as well as its subsidization.

### 3.2 Key Questions

As the manager of the national lab, CASIS already subsidizes research related to protein crystallization on the ISS. The question, of course, is if the subsidy is enough and if it is used to support generic research rather than just basic research.<sup>10</sup>

In order to understand whether the subsidy is at the appropriate level, one needs to consider several issues:

- 1) Is there additionality of the ISS microgravity environment in building better protein crystals?
- 2) Assuming significant additionality, should there be a collaborative undertaking involving protein crystallization using the ISS microgravity environment?

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<sup>9</sup> Starting in the early 1980s, the literature on collaborative R&D has grown really large. There are several surveys of this literature, some contributed by two members of this panel. See, for example, Vonortas (1997), Jankowski, Link and Vonortas (2001), Vonortas and Zirulia (2015), and Hagedoorn, Link and Vonortas (2000).

<sup>10</sup> Basic research produces, of course, a public good which is supported by the public purse.

- 3) What does it take to build such a collaborative agreement? Does it make sense to build it solely among American firms and research institutes or, given that ISS is a 15-nation endeavor, build it across all partners?
- 4) How should the latter two stages of protein crystallization's contribution to the private sector – specifically pharmaceutical research – be considered in these calculations?
- 5) What are the true private and social benefits to consider in a proper cost-benefit analysis?

We must await the full results of Robert DeLucas' ongoing study (Section 2.2.2) to answer the first question. Assuming significant additionality, the argument to answer the second question should be affirmative. A recent study of the National Research Council (2015) summarizes this argument for collaborative generic research in a different technology area (flexible electronics) in a form that can readily be applied here. But the argument has been settled long ago in detailed investigations of the theoretical and empirical aspects of the rationale of cooperative R&D needed to support legislation like the National Cooperative Research Act (NCRA) of 1984 and its sequel, the National Cooperative Research and Production Act (NCRPA) of 1993.<sup>11</sup>

Calculating the optimal level of support for this type of consortium (third question) could be the subject of an entirely separate analysis. The government could take several approaches in determining the size of public expenditure. One approach is to match private investment, as seen in other consortiums. Alternatively, the government could fund all costs associated with obtaining better protein crystals from space (e.g. space travel and samples). Generic protein crystals could then be distributed (or sold) to pharmaceutical companies for further collaboration and

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<sup>11</sup> Vonortas (1997) provides an almost exhaustive review of the theoretical and empirical arguments utilizing mainstream economic concepts from transaction cost economics, public goods and externalities, and investment behavior under conditions of uncertainty, impactedness and opportunism. Hemphill and Vonortas (2003) expand to arguments from the management literature such as real options and competitive advantage.

examination. No matter what method, the government must contribute enough to ease the uncertainty and risk involved from obtaining space crystals.

The remaining two questions pertain to the cost-benefit analysis of protein crystallization contribution to new drug development. It would be easier, but misguided, to build the argument on the basis of the first two stages of protein crystallization contribution only (first paragraph Section 3). All four stages should be considered instead. The estimation can follow the standard approach in health economics of calculating the costs and benefits of new drug development, then try to disentangle the purely private from the purely social benefits.

#### **4. Modeling Drug Development Costs**

The purpose of this section is to explore a specific model that can be utilized to empirically analyze the effect of protein crystallization in space (ISS) to the pharmaceutical sector. To achieve this goal one needs to take two steps. First, one must evaluate the effect of improved (larger, clearer) protein crystals on drug development. Second, one must evaluate the additionality of ISS in developing such improved crystals in microgravity as compared to other channels of doing so.

##### 4.1. Phases of Pharmaceutical Research

The literature has advanced an aggregate model paradigm that depicts the drug development process as pretty much linear with several Phases.

**Preclinical.** The preclinical Phase of the drug development process typically encompasses discovery and preclinical development testing. *Discovery programs* aim at synthesizing compounds that then undergo *preclinical testing* in assays and animal models.

**Clinical.** The clinical part of the drug development process refers to human testing.

Clinical testing typically proceeds through three successive phases:

- Phase I: a small number of usually healthy volunteers are tested to establish safe dosages and to gather information on the absorption, distribution, metabolic effects, excretion, and toxicity of the compound.
- Phase II: trials are conducted with human subjects who have the targeted disease or condition. These trials are conducted on larger numbers of subjects than in phase I (maybe hundreds) and are designed to obtain evidence on safety and preliminary data on efficacy.
- Phase III: testing typically consists of a number of large-scale trials designed to establish efficacy and to uncover side-effects that occur infrequently. The number of subjects is now the largest and can total in the thousands.

#### 4.2. Effect of Improved Protein Crystals: Model Development and an Example<sup>12</sup>

We use as a base the model by Scott et al (2014) [also in NY Academy of Sciences (2013)], which measures the cost of drug development as a function of cost, time, and risk. The expected cost of developing a new drug is given by the sum of the risk-adjusted, capitalized cost of each Phase of development:

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where  $t_{\text{start}}$  denotes time in months from start of Phase to date of new drug approval  
 $t_{\text{end}}$  denotes time in months from end of Phase to date of new drug approval  
 $c$  is cost per month per compound in Phase  
 $p$  is the probability that a compound undergoing this Phase of development is ultimately approved for marketing  
 $r$  is cost of capital as an annual interest rate.

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<sup>12</sup> This section borrows heavily from Scott et al (2014) and NY Academy of Sciences (2013). It also consults extensively DiMasi and Grabowski (2007) and DiMasi, Hansen and Grabowski (2003). A new study recently released by the Tufts Center for Drug Development (DiMasi, 2014) was not available to us at the time of this writing.

Drug development is a lengthy process, implying substantial time costs to investing in R&D long before any potential returns can be earned. The time costs of drug development can be captured by capitalizing costs forward to the point of marketing approval at an appropriate discount rate. Capitalization is achieved by continuous compounding at the annual interest rate  $r$ , which can be set at 10.5-11% through the CAPM model or otherwise for the biopharmaceutical industry (Harrington, 2012; DiMasi and Grabowski, 2007).

Capitalized costs are the sum of out-of-pocket (cash) costs and time costs. It should be noticed that in order to obtain time costs one needs, in addition to an appropriate discount rate, a timeline over which out-of-pocket costs are capitalized forward to marketing approval. Using data for several compounds, DiMasi and Grabowski (2007) and DiMasi et al. (2003) estimate average Phase and regulatory review lengths. On the other hand, in their case study on Alzheimer’s disease Scott et al (2014) obtain estimates of duration – as well as estimates of cost and probability (to progress to next Phase) – by experts in Alzheimer’s research and drug development. They used data provided by experts.

**Table 1.** Duration of Drug Development Phases (Months)

Phase	Typical New Biopharmaceutical (DiMasi & Grabowski, 2007)	Alzheimer’s Disease*	
		Existing (Scott et al., 2014)	Improved
Preclinical	52.0	50.1	49.9
Phase I	12.3	12.8	12.6
Phase II	26.0	27.7	25.2
Phase III	33.8	50.9	39.4
Regulatory Review	18.2	18.0	16.9

\* Durations are presented with 95% confidence

Source: Adapted from NY Academy of Sciences (2013), Table B-2.

**Table 2.** Transition Probabilities\* Between Phases

Phase	Typical New Biopharmaceutical (DiMasi & Grabowski, 2007)	Alzheimer's Disease*	
		Existing (Scott et al., 2014)	Improved
Phase I to II <sup>(1)</sup>	0.71	0.67	0.69
Phase II to III <sup>(2)</sup>	0.44	0.47	0.42
Phase III to Approval <sup>(3)</sup>	0.68	0.24	0.58
Phase II to Approval <sup>(2)x(3)</sup>	0.30	0.11	0.24
Phase I to Approval <sup>(1)x(2)x(3)</sup>	0.21	0.07	0.16
Ratio of Phase II failures to total failures in Phase II and III	0.80	0.60	0.77

\* Average reported

Source: Adapted from NY Academy of Sciences (2013), Table B-3.

**Table 3.** Average Costs (typical new biopharmaceutical - \$m)

Phase	Out-of-pocket (monthly) Typical New Biopharmaceutical (\$m./molecule in development) (DiMasi & Grabowski, 2007; DiMasi et al, 2003)	Capitalized at 11% Typical New Biopharmaceutical (\$m/new drug approved) (DiMasi & Grabowski, 2007; DiMasi et al, 2003)
	Preclinical	0.72
Phase I	2.73	338
Phase II	2.00	312
Phase III	5.64	385
Total		1,565

Source: Adapted from NY Academy of Sciences (2013), Table B-4.

The older estimates above have been calculated on the basis of data from the Tufts database on drugs developed by traditional pharmaceutical companies (DiMasi et al., 2003) and by biotechnology companies (DiMasi and Grabowski, 2007). The latter paper concentrated on the types of molecules on which biotech companies focus, specifically recombinant proteins and monoclonal antibodies (mAbs). Thirteen of a

total seventeen examined compounds<sup>13</sup> first entered clinical testing during 1990-2003; the remaining four compounds examined in this study were from the Tufts database. The newer estimates specific to Alzheimer's disease were developed on the basis of detailed expert interviews from the pharmaceutical industry and academia (Scott et al., 2014; NY Academy of Sciences, 2013).

Tables 4 and 5 below use steps mathematically identical to the formula presented earlier in this section to highlight (i) the expected cost of entering a drug candidate in Phase I trials and (ii) the total capitalized cost of a new drug approval. *The important take-away here is how even small (apparent) changes in the cost, likelihood of successful completion, and time length of a Phase lead to dramatic decreases in overall costs of successful drug development.*

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<sup>13</sup> The sample consisted of 9 recombinant proteins and 8 mAbs.

**Table 4.** Cost of Alzheimer’s Disease-Modifying Development with Existing Infrastructure

Eventual Outcome For a Compound Entering Phase I	Out-of-pocket Cost (\$m)	Cost Capitalized to Date Development Stops or Drug Approved (\$m.)	Cost at Phase I Start (Present Value) (\$m., 11% discount rate)	Probability
Development stops after Phase I	71	89	79	0.33
Development stops after Phase II	126	177	122	0.35
Development stops after Phase III	413	648	280	0.24
Drug is approved	413	765	280	0.07

Expected present-value cost =  $(79 \times 0.33) + (122 \times 0.35) + (280 \times 0.24) + (280 \times 0.07) = \$ 157 \text{ m}$

Cost per new drug approval =  $\$157\text{m} / 0.07 = \$ 2,087 \text{ m}$

Cost capitalized to date of drug approval =  $\$2,087\text{m} \times e^{(109.4)(0.11/12)} = \$5,693\text{m}$

(Phase I starts an average of 109.4 months prior to approval)

**Notes:** (1) Numbers have been rounded. For example, \$2,087m comes from dividing approximately \$156.5m by approximately 0.075.

(2) Out-of-pocket cost is the monthly cost for each Phase (Table XX) times the number of months spent in that Phase (Table 1):

$$71 = (0.72)(50.1) + (2.73)(12.8) \quad 126 = 71 + (2.00)(27.7) \quad 413 = 126 + (5.64)(50.9)$$

(3) Present-value cost is the value of costs incurred at the beginning of Phase I: XXXX

(4) Probabilities are derived from Table 2 (they may not sum to 1 because of rounding):  $0.33=1-0.67$ ,  $0.35=(0.67)(1-0.47)$ ,  $0.24=(0.67)(0.47)(1-0.24)$ .

**Source:** NY Academy of Sciences (2013), Table B-5.

**Table 5.** Cost of Alzheimer’s Disease-Modifying Development with Recommended Infrastructure

Eventual Outcome For a Compound Entering Phase I	Out-of-pocket Cost (\$m)	Cost Capitalized to Date Development Stops or Drug Approved (\$m.)	Cost at Phase I Start (Present Value) (\$m., 11% discount rate)	Probability
Development stops after Phase I	70	87	78	0.31
Development stops after Phase II	121	167	118	0.40
Development stops after Phase III	343	507	250	0.12
Drug is approved	343	592	250	0.17

Expected present-value cost =  $(78 \times 0.31) + (118 \times 0.40) + (250 \times 0.12) + (250 \times 0.17) = \$ 144 \text{ m}$

Cost per new drug approval =  $\$144\text{m} / 0.17 = \$ 855 \text{ m}$

Cost capitalized to date of drug approval =  $\$855\text{m} \times e^{(94.1)(0.11/12)} = \$2,027\text{m}$

(Phase I starts an average of 94.1 months prior to approval)

**Notes:** (1) Numbers have been rounded. For example, \$855m comes from dividing approximately \$143.5m by approximately 0.168.

(2) Out-of-pocket cost is the monthly cost for each Phase (Table XX) times the number of months spent in that Phase (Table 1):

$$70 = (0.72)(49.9) + (2.73)(12.6) \quad 121 = 70 + (2.00)(25.2) \quad 343 = 121 + (5.64)(39.4)$$

(3) Present-value cost is the value of costs incurred at the beginning of Phase I: XXXX

(4) Probabilities are derived from Table 2 (they may not sum to 1 because of rounding):  $0.31=1-0.69$ ,  $0.40=(0.69)(1-0.42)$ ,  $0.12=(0.69)(0.42)(1-0.58)$ .

**Source:** NY Academy of Sciences (2013), Table B-6.

Finally, Table 6 shows the estimated costs of developing a disease-modifying drug for Alzheimer’s across the industry (NY Academy of Science, 2013). This is the typical way the literature has reported estimates for drug development costs and include the cost of failures by multiple companies expected by the interviewed experts before one drug is approved by the FDA for marketing. Notice that totals of each column match the totals in Tables 4 and 5 respectively.

**Table 6.** Average Costs (Alzheimer’s disease - \$m)

Phase	Capitalized at 11% Existing Infrastructure (\$m./new drug approved)	Capitalized at 11% Recommended Infrastructure (\$m/new drug approved)
Preclinical	1,658	642
Phase I	1,193	458
Phase II	1,048	387
Phase III	1,794	539
Total	5,693	2,027

Source: Adapted from NY Academy of Sciences (2013), Table B-4.

#### 4.3. ISS Additionality in Developing Improved Protein Crystals

We are unable to provide much input here in terms of actual numbers before the conclusion of the ongoing study led by Larry DeLucas (Section 2.2.2).

#### 4.4 Summing Up

The same, or very similar, model to that outlined in Section 4.2 can be utilized to assess the effect of improved protein crystals on R&D targeting a specific disease. Assuming the use of average data regarding the effects across various types of diseases – e.g., across all types of cancer or all types of diabetes – one can estimate

average estimates for the industry. The important limitation currently is missing data on:

- a) the duration (number of months) of the various phases of drug development
- b) the cost per month, and
- c) the probabilities that the compounds under investigation will pass through each phase successfully.

Appendix 1 of the NY Academies of Science (2013) study provides the questionnaire utilized in that study<sup>14</sup> to elicit such data through interviews with a significant number experts including 27 industry representatives and 5 academics. The majority of the industry interviewees were reported to be at the level of vice president (or equivalent) and above in 11 companies pursuing Alzheimer's disease drug discovery and development and they themselves were responsible for research either on Alzheimer's disease directly or on diseases of the central nervous system more broadly. The 5 non-industry interviewees each had more than 20 years experience in Alzheimer's related research.

The interviewees were provided with estimates on cost, cycle times, and transition possibilities found for pharmaceuticals in general and were asked to customize them for Alzheimer's disease twice: with and without a new environment of better infrastructure which was clearly defined.

How does this translate to our research project on protein crystallization in microgravity? *The availability of better quality protein crystals can be considered in economic terms as better infrastructure leading to increased productivity of pharmaceutical R&D.*<sup>15</sup> A model like the one shown in this section should then help assess the benefits of improved protein crystals on drug development much more precisely than has been the case until now.

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<sup>14</sup> Troy Scott, Alan O'Connor, and Al Link for RTI and Diana L. van de Hoef for the NY Academy of Sciences.

<sup>15</sup> One could think of it as analogous to what economists argue about basic research and its impact on applied research and development.

If a questionnaire is to be utilized to collect data, a well-defined target must be selected in order for the interviewed experts to provide more accurate answers. A follow up final step would be to calculate the societal cost savings from reducing disease.

## 5. Concluding Remarks

Protein crystallization is an essential part of protein crystallography – the main process used in drug discovery today. Advancements in the technology of protein crystallization over the last hundred years have been remarkable. The prospect of improving protein crystals through the use of the International Space Station has the potential to be the next great chapter in drug discovery history.

We must wait for the full results of Lawrence DeLucas' study – which measures the true value-added of space on protein crystallization – before we make any firm conclusions. Preliminary reported results of the study find considerable additionality. Assuming this holds with the final results, the improvement in commercial drug costs would be significant. For the private sector, better protein crystals mean better 3D models of proteins in the preclinical stage. The improved modeling should carry over in clinical stages as well, advancing overall drug infrastructure. Recent relevant work supported by the New York Academy of Sciences for a specific disease strongly indicates that even marginal improvements in infrastructure can *significantly* reduce costs in overall drug development.

The leap from earth crystals to drastically pricier (yet better quality) space crystals may be too risky of an investment to expect from private pharmaceutical companies, even with significant projected cost reductions. A government-subsidized consortium may be the best plan to alleviate some of the early-stage, precompetitive financial risk. The government therefore may wish to fund space missions for

*protein crystals for generic use*, where improvements in these proteins' 3D models could lead to extensive efficiencies in drug discovery and development for a wide range of diseases. While pharmaceutical companies would still be in competition, improving their overall infrastructure of basic protein knowledge could provide an overwhelmingly public and private benefit.

While private cost reduction can be measured with the model seen in Section 4, public benefit from disease treatment and potential government revenue are difficult to measure. The potential costs to pharmaceutical companies – even with the easing of a consortium – must also be measured to gauge private interest. If public/private benefits outweigh public/private costs, then investment in protein crystallization on space is a fiscally viable use of ISS resources. Pending the final results of Lawrence DeLucas' study and other missing pieces of information, we will be able to more effectively weigh the costs and benefits of protein crystallization aboard the International Space Station.

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## Appendix I – Proteins that Showed Significant Difference in Space Versus Ground Crystallization in the DeLucas Study

The following proteins showed significantly better crystallization in space versus ground in the DeLucas ISS double blind protein crystallization study:

<p><b>3902c</b> (Slide 20)</p>	<p>An unknown missense variant of the pathogen responsible for Grönblad–Strandberg syndrome, a genetic disease that causes fragmentation and mineralization of elastic fibers in some tissues. The most common problems arise in the skin and eyes, and later in blood vessels in the form of premature atherosclerosis. The mechanism of action is similar to sickle cell disease.</p>
<p><b>Vibrio cholera</b> (Slide 20)</p>	<p>According to the World Health Organization, cholera causes the deaths of 120,000 children under the age of 5 each year.</p>
<p><b>Aspartate carbamoyltransferase</b> (Slide 21, 45)</p>	<p>This enzyme is an archetypal example of protein regulation important to a wide range of basic and applied research areas as it modulates some of the most important metabolic processes in all living organisms. Aspartate carbamoyltransferase catalyzes the first step in the pyrimidine biosynthetic pathway, which makes the building blocks of DNA.</p>

The following showed a significant difference between flight and ground, but the double blind study is still underway so we do not know which was better (ground or flight):

<p><b>PadA</b> (Slide 31)</p>	<p>A theory that is gaining increased support is that an infectious agent plays a role in cardiovascular disease. Among several pathogens identified, the oral bacterium <i>Streptococcus gordonii</i> has been implicated as a plausible agent. Removal of the protein PadA prevents the Strep from implementing a critical step in the infection process and is thus a therapeutic target for drug design.</p>
<p><b>SPMV</b> (Slide 32, 36)</p>	<p>SPMV is particularly relevant to increasing field yields of crops used in biofuels. Satellite panicum mosaic virus (SPMV) is a plant satellite virus. A satellite is a subviral</p>

	agent composed of nucleic acid that depends on the co-infection of a host cell with a helper or master virus for its replication. This provides understanding of the nature of such a satellite virus, which can then be used to develop agents that either block the infection of the master virus or use it as a vehicle to deliver antiviral agents.
<b>Bacterial Cellulose Synthetase</b> (Slide 34)	Bacterial Cellulose Synthetase plays a critical role in the production of bacterial cellulose. Bacterial cellulose can be tailored to have specific desirable properties, including unique mechanical properties and applications to biotechnology, microbiology, and materials science. With advances in the ability to synthesize and characterize bacterial cellulose, the material is being used for a wide variety of commercial applications including textiles, cosmetics, and food products, as well as medical applications. While cellulose is a basic structural material of most plant substances, it is also produced by bacteria. Bacterial cellulose has different properties from plant cellulose and is characterized by high purity, strength, moldability and increased water holding ability. While bacterial cellulose is produced in nature, many methods are currently being investigated to enhance cellulose growth from cultures in laboratories as a large-scale process. Many patents have been issued in microbial cellulose applications and several active areas of research are attempting to better characterize microbial cellulose and utilize it in new areas.
<b>Putative citrate synthase 2</b> (Slide 34, 46)	The enzyme citrate synthase exists in nearly all living cells and stands as a pace-making enzyme in the first step of the Citric Acid Cycle (or Krebs Cycle). The Krebs Cycle is one of the essential processes for most life on Earth. The Krebs Cycle is not only part of the pathway for the breakdown of glucose into energy, but also for the breakdown of all metabolites, including other sugars, amino acids and fatty acids. Each of these groups of molecules has a pathway that leads into the Krebs Cycle. Basically, this is how we get energy from food.
<b>FE++ Alcohol Dehydrogenase</b> (Slide 35, 40)	Iron based Alcohol Dehydrogenase occurs in bacteria and fungi. In fuel cells, alcohol dehydrogenases can be used to catalyze the breakdown of fuel for an ethanol fuel cell.
<b>Horse Hemoglobin</b>	It may help in the development of artificial hemoglobin. Hemoglobin is the protein that makes blood red because

(Slide 35)	<p>it carries oxygen throughout the body. Blood transfusions have saved countless lives. However, the need for matching blood type, the short life of stored blood, and the possibility of contamination are still major concerns. An understanding of how hemoglobin works, based on decades of biochemical study and many crystallographic structures, has prompted a search for blood substitutes and artificial blood. The most obvious approach is to use a solution of pure hemoglobin to replace lost blood. The main challenge is keeping the four protein chains of hemoglobin together. In the absence of the protective casing of the red blood cell, the four chains rapidly fall apart. To avoid this problem, novel hemoglobin molecules have been designed where two of the four chains are physically linked together and two additional glycine residues form a link between two of the chains, preventing their separation in solution. The blood of the newborn horse was found to have a higher affinity for oxygen than that of the mother. Unlike many other species, the hemoglobins of the newborn and adult horse have been shown to be structurally identical, which offers the possibility of using this factor to enhance artificial hemoglobin.</p>
<p><b>O-methyltransferase Family Protein 85</b> (Slide 39, 42, 45)</p>	<p>Methyltransferases are found in many metabolic pathways and are implicated in genetic diseases, cancer, and metabolic diseases. The O-methyltransferases have also been associated with brain disorders.</p>
<p><b>Acyl-CoA dehydrogenases</b> (Slides 39, 40)</p>	<p>This class of enzymes' function is to catalyze the initial step in each cycle of fatty acid <math>\beta</math>-oxidation in the mitochondria of cells. Deficiencies in these enzymes are linked to genetic disorders involving fatty acid oxidation (i.e. metabolic disorders), including sudden infant death syndrome.</p>
<p><b>Enoyl-CoA hydratase</b> (Slide 40):</p>	<p>This enzyme is essential to metabolizing fatty acids from foods to produce energy efficiently and quickly. At least 11 mutations have been found involving this enzyme that potentially cause neurological problems such as movement disorders and problems with thinking ability (cognition) by enabling acids to accumulate in the fluids that surround and protect the brain and spinal cord.</p>
<p><b>Short-chain dehydrogenase</b> (Slide</p>	<p>The short-chain dehydrogenases/reductases family is a very large family of enzymes that have a great diversity of</p>

40)	functions. The clinical findings in those with confirmed short-chain acyl-coA dehydrogenase (SCAD) deficiency in newborns, for example, range from severe (dysmorphic facial features, feeding difficulties/failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, seizures, hypotonia (weak muscles), dystonia (involuntary muscle contractions), and myopathy(muscles do not function) to normal.
<b>Flockhouse Virus (FHV) (Slide 41)</b>	FHV has been shown to overcome the kingdom barrier and to replicate in plants, insects, yeast and mammalian cells. When adult mosquitoes were orally fed or injected with the virus, FHV antigen was detected in various tissues and infectious virus was recovered. This can provide insight into the mechanisms of viral replication and potentially identify novel targets for broadly effective antiviral agents.
<b>Inorganic Pyrophosphatase (PP(i))</b>	This enzyme catalyzes the conversion of one molecule of pyrophosphate to two phosphate ions. Dysregulated cellular PP(i) production, degradation, and transport all have been associated with disease, and PP(i) appears to directly mediate specific disease manifestations. In addition, natural and synthetic analogs of PP(i) are in use or currently under evaluation as prophylactic agents or therapies for disease. The functionality of this enzyme plays a critical role in lipid metabolism (including lipid synthesis and degradation), calcium absorption and bone formation, and DNA synthesis, as well as other biochemical transformations.
<b>Novo Nordisk Lipase</b>	Unknown
<b>FadE1_3</b>	Unknown

## Appendix II – New Details Regarding Costs of and Demand for Protein Crystallization in Microgravity<sup>16</sup>

### Estimated Protein Crystallization Costs on Earth<sup>17</sup>

<b>Protein Type</b>	<b>Description</b>	<b>Cost</b>
Aqueous protein:	Most common	\$10K-\$30K
Large/complex proteins:	Make up a substantial percentage of proteins of interest to Pharma	\$100K
Membrane proteins, protein-protein complexes, protein-ligand complexes:	Wide range of applications	\$1M

### Added Protein Crystallizations Costs in Space (Estimations)<sup>18</sup>

<b>ISS Specification</b>	<b>Cost</b>
Price/lb in flight:	\$15K/lb
Flight cost for protein crystallization unit:	\$1.5M

### Market for Protein Crystallization<sup>19</sup>

There is large demand for high quality protein crystals. There are over 8,000 highly valued proteins that have not been crystallized with significant quality on Earth and over 100,000 of general interest to medicine, according to the NIH.<sup>20</sup> As a response, the NIH created the Protein Structure Initiative (PSI) to assemble a collection of three-dimensional protein structures for research and drug development:

<b>Project Period</b>	<b>Number of Centers</b>	<b>Total Costs</b>	<b>Number of PSI structures</b>	<b>Average value of protein structure</b>
July 2005 – June 2010	14	\$325M (funded mostly by National Institute of General Medical Sciences)	4,800	\$325M/4,800 = \$67K

<sup>16</sup> All information courtesy of Lynn Harper (June 8 email). It is preliminary; strong caveats apply.

<sup>17</sup> Cost includes isolation, crystallization, diffraction, and determination of protein structure.

<sup>18</sup> One ISS protein crystallization unit can hold about 1000 crystallization samples (25 lb) plus the incubator holding the proteins (80 lb).

<sup>19</sup> PSI data as of August 2010.

<sup>20</sup> See <http://www.nature.com/nrd/journal/v5/n10/full/nrd2132.html> for list generated in 2006

