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NASA's International Space Station Program – Status and Issues

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Mr. Chairman, members of the Committee, thank you for inviting me to appear before you today to testify. My name is Cheryl Nickerson, and I am an Associate Professor in the Center for Infectious Diseases and Vaccinology at the Biodesign Institute at Arizona State University. My research focuses on understanding the molecular mechanisms and processes of infectious disease, with an important emphasis on investigating the unique effect of spaceflight on microbial pathogen responses. NASA's support of my research has resulted in multiple spaceflight experiments, which have provided novel insight into how microbial pathogens cause infection both during flight and on Earth, and hold promise for new drug and vaccine development to combat infectious disease.

Through awards such as the Presidential Early Career Award for Scientists and Engineers, and independent research funding from grants totaling over three million dollars, NASA has consistently recognized my laboratory's contributions to the United States Space Program into infectious disease risks for the crew during spaceflight and the general public here on Earth. I also serve as a scientific consultant for NASA at the Johnson Space Center in support of their efforts to determine and mitigate microbial risks to the crew during flight, and was honored to be selected as a NASA Astronaut candidate finalist for the Astronaut class of 2004. That being said, the views expressed in today's testimony are my own, but I believe they reflect community concerns.

In your invitation letter asking me to testify before you today you asked a series of questions regarding the utilization prospects of ISS research that I would like to address now in sequence.

1. What has been the nature of your space-based research, and what have been your findings to date?

I would like to begin by applauding NASA's foresight in funding our spaceflight research in the field of infectious disease. We were initially funded by NASA's Office of Biological and Physical Research and are currently funded by both the Advanced Capabilities Division and the Human Research Program in the Explorations Systems Mission Directorate. The connection between spaceflight and its influence on infectious disease was not immediately clear 10 years ago when NASA initially funded our research. As a result, NASA's support of my research through multiple spaceflight experiments has allowed us to provide novel insight into the molecular mechanisms that microbial pathogens use to cause infectious disease both during flight and on Earth, and has exciting implications for translation into human health benefits, including the development of new drugs and vaccines for treatment and prevention.

While the eradication or control of many microbial diseases has dramatically improved the health outlook of our society, infectious diseases are still a leading cause of human death and illness worldwide. Infectious disease causes 35 percent of deaths worldwide, and is the world's biggest killer of children and young adults. Within the United States, infectious disease has a tremendous social, economic, and security impact. Total cost for infectious disease in the U.S. exceeds $120 billion annually due to direct medical and lost productivity costs. Moreover, the future is threatened by new and re-emerging infectious diseases, an alarming increase in antibiotic resistance, and the use of microbial agents as a bioterrorist threat. Thus, research platforms that offer new insight into how pathogens cause infection and disease are desperately needed and will lead to novel strategies for treatment and prevention.

To enhance our understanding of how pathogens cause disease in the infected host, my laboratory uses innovative approaches to investigate the molecular mechanisms of infectious disease. It was this search for novel approaches that drove our initial investigations with NASA technology. As flight experiments are a rare opportunity, our early experimental efforts concentrated on the use of a unique bioreactor, called the Rotating Wall Vessel (RWV), designed at the NASA Johnson Space Center in Houston as a ground-based spaceflight analogue. The RWV bioreactor allows scientists to culture cells (microbial or mammalian) in the laboratory under conditions that mimic several aspects of spaceflight and can be used to induce many of the biological changes that occur during spaceflight. In addition, by using mathematical modeling, we found that this analogue, and true spaceflight, produce an environment that is relevant to conditions encountered by the pathogen during infection in the human host – thus enhancing the relevance of our findings for the development of new strategies to combat infectious disease on Earth.

We chose the model bacterial pathogen *Salmonella typhimurium* for both our spaceflight analogue and spaceflight studies, as it is the best characterized pathogen and poses a risk to both the crew during flight and the general public on Earth. *Salmonella* is the most readily and fully understood pathogen and belongs to a large group of bacteria whose natural habitat is the intestinal tract of humans and animals. This group includes most of the bacteria that cause intestinal and diarrheal disease, considered to be one of the greatest health problems globally. Indeed, *Salmonella* infection is one of the most common food-borne infections worldwide. In the United States an estimated 1.41 million

cases occur, resulting in 168,000 visits to physicians, 15,000 hospitalizations and 580 deaths annually. *Salmonella* accounts for approximately 30% of deaths caused by food-borne infections in the United States, and is even more detrimental in the developing world. The total cost associated with *Salmonella* infections in the US is estimated at three billion dollars annually. Moreover, in 1984, *Salmonella* was used in a bioterrorism attack by a religious cult in Oregon to cause a community-wide outbreak of foodborne illness in an attempt to influence the outcome of a local election. The organism is also an excellent choice for NASA as it is considered a potential threat to crew health as a food contaminant. There are currently no human vaccines to prevent *Salmonella* food borne illness.

Using the RWV ground-based technology, we conducted preliminary studies showing that *Salmonella* responded to this environment by globally altering its gene expression, stress resistance, and disease causing (virulence) profiles, thereby improving our chance of success and need for a spaceflight experiment. Subsequent analysis of the genes that were expressed after growth in this analogue suggested that the environment induced unique molecular mechanisms in the microbe to cause disease. Our information from these early experiments provided NASA with new insight toward understanding the risk of infection during flight. In addition, the unique molecular mechanisms that were identified held the potential to be used to develop new therapeutics and vaccines for the general public on Earth.

NASA and the scientific community continued their support of our ground-based findings by awarding us a grant to investigate the effect of true spaceflight on *Salmonella* virulence and gene expression responses. This was an exciting opportunity for us, as while the RWV bioreactor can simulate some aspects of the spaceflight environment, it cannot duplicate all of the physical parameters that organisms encounter during spaceflight or their biological responses. In September 2006, our first spaceflight experiment flew aboard STS-115, and we investigated the comprehensive changes in *Salmonella* when exposed to the truly unique environment of microgravity. The results from this experiment were remarkable and showed that during spaceflight, *Salmonella* altered its virulence and gene expression responses in unique ways that are not observed using traditional experimental approaches. These findings immediately advanced our knowledge of microbial responses to spaceflight and disease causing mechanisms used by this important human pathogen. Our first technical report from this spaceflight experiment was recently published in the *Proceedings of the National Academy of Sciences*, and our results demonstrated changes in *Salmonella* disease causing potential (virulence) during flight as compared to identical samples that were grown on the ground. Specifically, our findings demonstrated that spaceflight increased the virulence of *Salmonella*, and the pathogen was able to cause disease at lower doses. In addition, we identified 167 genes in *Salmonella* that changed expression in response to spaceflight. The identity of these genes allowed us to discover a key ”master switch” regulatory mechanism that controls *Salmonella* responses to spaceflight environments. This molecular target, and others that we identified, hold potential to be translated into new therapeutic and vaccine approaches to treat and prevent human enteric salmonellosis.

This experiment was a "first of its kind" in spaceflight biological study. It was the first study ever to investigate the effect of spaceflight on the disease-causing potential (virulence) of a pathogen, and the first ever to obtain the entire gene expression response profiles of a bacterium to spaceflight. In fact, very few studies contain data that document gene expression changes during spaceflight. It is also critical to mention that an important part of our spaceflight work is directly related to helping us understand how microbial pathogens cause infectious disease here on Earth. This is possible because the the unique environment of spaceflight encountered by microorganisms (including pathogens) are also relevant to conditions that these cells encounter here on Earth during the normal course of their lifecycles, including certain niches within the infected host, such as parts of the human intestine. Thus, an exciting part of this work is the opportunity to use spaceflight and the ISS as a novel enabling research platform for innovations in infectious disease control here on Earth - including novel insight into how pathogens cause disease and for the development of new therapeutics and vaccines for treatment and prevention.

The success of our flight experiment aboard STS-115 inspired a follow-up experiment aboard STS-123, which just flew in March 2008. While the data is still being analyzed, our preliminary findings are leading toward translational applications of our original data for the development of novel strategies to treat and prevent infection and disease during flight and here on Earth. Shortly, we expect NASA and the public to receive a direct benefit from their investment.

The ISS holds tremendous potential to provide novel insight into human health and disease mechanisms that can lead to groundbreaking new treatments to combat infectious disease and improve the quality of life.

2. What is your perspective on the future potential for use of the microgravity environment as a research tool?

The microgravity of spaceflight offers a unique environment for ground-breaking biotechnology and biomedical innovations and discoveries to globally advance human health in the following areas:

- Infectious disease
- Immunology
- Cancer
- Aging
- Bone and muscle wasting diseases
- Development of biopharmaceuticals
- Tissue engineering

It is not surprising that biological systems respond in novel ways to the spaceflight environment. Many breakthroughs in life sciences research have come from studying living systems in unique and extreme environments. It is from studying the response of biological systems under these environments that we have not only gained new fundamental insight into how they function and adapt to extreme conditions, but have also translated these findings into beneficial biotechnology and biomedical advances to improve our quality of life. Spaceflight is simply the next logical progression and extreme environment to study that holds tremendous potential to provide the next ground-breaking advances in public health.

The ISS provides a unique environment where researchers can explore fundamental questions about human health - like how the body heals itself and develops disease. Specifically, the ISS offers an orbiting laboratory to use microgravity as a tool to bring a new technological approach to understanding living systems and discover basic mechanisms we haven't seen before. That is because organisms and cells respond in unique ways to spaceflight and exhibit characteristics relevant to human health and disease that they do not when cultured using traditional conditions on Earth. Accordingly, cellular and molecular mechanisms that underlie disease can be studied, offering new opportunities to see how cells operate in these conditions, and giving new fundamental insight into the disease process. Many of these findings may translate directly to the clinical setting for novel ways to diagnose, treat and prevent disease here on Earth. This type of research creates exciting new opportunities for the utilization of ISS to advance the frontiers of knowledge and act as a commercial platform for breakthrough biomedical and biotechnological discoveries. I believe it is important to take advantage of this unique research facility to develop new advances in biotech and biomedicine that will globally advance human health and benefit the United States in the international economy.

Thus, it is anticipated that ISS life sciences research will lead to ground-breaking discoveries and innovations in human health, biotech and biomedical innovations, and will have a lasting impact on our nation's scientific capability, economy, and quality of our lives.

3. What are any potential applications of the basic research you have conducted to date or intend to pursue?

The investment that NASA has made in our research for innovations in infectious disease treatment and control will provide long lasting return in the protection of humans as they explore space and for the general public here on Earth. Regarding protection of the crew, the negative impacts of infectious disease range from impeded crew performance to potentially life threatening scenarios. As humans travel further away from our home planet, the risk to crew health and mission success becomes even greater. As we gain greater knowledge of the risks of microbial infection, prudent preventative operational activities, therapeutics, and other countermeasures can be implemented to mitigate the risk to the crew and mission success.

Perhaps the greatest application from this research will not apply directly to spaceflight, but rather to improving the quality of life on Earth through the development of novel strategies to combat infection and disease. Internationally, we face many challenges to our health by microbial threats. Antibiotic resistant strains are on the rise, regional diseases are expanding to new locations, the threat of bioterrorism looms, and a multitude of diseases have insufficient treatments. New treatment paradigms and testing methods are desperately needed. The knowledge from spaceflight experiments is providing novel insight into how microbes cause disease in the human body and is providing new targets for therapeutic and vaccine development. The goal is to identify target mechanisms in space and then investigate these mechanisms on Earth. By understanding more fully how these organisms function and react to novel stimuli, we can develop new methods to treat and prevent the spread of infectious agents.

In addition, the knowledge gained from spaceflight research can advance and accelerate therapeutic development and implementation of new strategies for translation of this research into health benefits for the developing world. The costs of therapeutics and vaccine development can be prohibitively high. Bringing a new drug to market can cost in excess of one billion dollars over a decade before it reaches the patient. If the knowledge gained from spaceflight studies provides even an incremental decrease in these costs and timelines (which studies strongly suggest is the case), then this research is of tremendous importance.

An example of a potential boon from spaceflight experiments is our laboratory's discovery that gene regulatory proteins participate in the spaceflight mechanistic response of microbial pathogens. Gene regulatory proteins affect every property of a cell including its ability to cause disease. Our laboratory is currently focusing on how this regulatory pathway works in *Salmonella* and how it can be manipulated to control that organism's virulence in flight and here on Earth. Once understood, we will use that knowledge to see which other microorganisms can be controlled in a similar fashion. A detailed understanding of how these gene regulatory proteins are controlled may offer new opportunities to design efficacious drugs and vaccines that would target this class of protein.

It is also relevant to note that there are exciting efforts underway to develop a nationwide Biotechnology Space Research Alliance (BSRA) Consortium that partners a world-class team of industry, university, and economic development organizations across the country to partner with NASA to utilize the ISS for breakthrough biomedical and biotechnology discoveries. It is anticipated that the discoveries made on ISS will engender scientific knowledge, technological capability, and commerce on Earth as a gateway to 21st Century exploration and development of space.

One key to our nation's economic success has been its ability to provide unique answers to the world's problems. We have the opportunity to advance in a field where the United States is a world leader. I believe space exploration and development will be one of the defining activities for our nation that will lead the world in this new millennium.