
Human Research Program
Human Health Countermeasures Element
Immune Risk
Standing Review Panel
Final Report

November 2009

I. Executive Summary & Overall Evaluation

After thorough review of available data and in response to our charge, we provide the following document. Contained within our comments are those that provide both comfort to and challenges for the NASA Immune Risk Research Program. This report is a summary of opinions of our Standing Review Panel (SRP) members Sandeep K. Agarwal, M.D., Ph.D., Nancy Klimas, M.D., Janet Richardson, Ph.D., Pablo C. Okhuysen, M.D. and Gailen D. Marshall, M.D., Ph.D..

First, the somewhat comforting news involves the lack of clinical data that support significant immune dysfunction occurring in astronauts either in flight or post flight (short or long term) after almost 50 years of human spaceflight varying in duration from a few hours to a few months. Although our clinical database is incomplete (which is, itself, a concern - see below), there are no reports of significant intra – or post flight opportunistic infections, persistent infections or new appearance of hypersensitivity states such as allergy or autoimmunity. This suggests that spaceflight in the microgravity state (at least that experienced in LEO) does not, of itself, cause significant harm to the astronaut immune system. There are anecdotal clinical reports of increased nasal symptoms, “fungal” infections (anatomical site, duration and need for/response to intervention not disclosed) rashes and somewhat prolonged wound healing. According to incomplete clinical data reviewed by this panel, these clinical events appear to have been self limited with no major post flight sequelae reported and no long term immune/inflammatory risks seen in former astronauts out of proportion to the population at large.

However, there is also news that causes significant concern about the immune risks that need to be addressed. First, risks known to affect human immune function in ground based populations should reasonably be expected to have at least similar if not heightened effects on astronauts during space travel. Thus, issues related to immune effects of psychological stress, physical deconditioning, nutritional changes, and radiation exposure could be expected (either alone or in combination) to have adverse effect on crew health in terms of performance and disease risk, either immediately or longer term post flight. These concerns take into account that, while some risks may be unlikely, the consequence of such risk, if ultimately realized without appropriate countermeasures being in place, could be potentially devastating to both crew health and mission success. Second, the incomplete clinical database regarding infections, rashes, wound healing or other symptoms of immune dysfunction is concerning. It is our understanding that the correlation and cataloguing of these clinical data on astronauts either has not been completed or is considered protected medical information and thus not to be disclosed. We certainly have no need or desire to see individual medical records but summarized data regarding, for example, the

nature (i.e. organism, anatomic location, physical symptoms), duration and response to intervention of fungal infections is potentially important. While many ground based individuals with intact cellular immune responses can have chronic cutaneous fungal infections without clinical consequence, astronauts in a closed environment with prolonged exposure may be more of a cause for concern. Further, if there were other infectious episodes that occurred with regularity of which we are not aware, we as a panel cannot determine clinical significance with the information we have and thus cannot say with certainty that there is no risk based upon absence of data.

The Immune SRP acknowledges the high quality clinically based research on normal human immune function that we reviewed. Three major concerns need to be addressed:

1. Need for technology in studies that will identify individual subject risk for altered immune response.
2. Longer duration studies that allow the assessment of cumulative effects of various stressors on host immune response.
3. Interdisciplinary studies that examine the cumulative effects of the four most significant influences on astronaut immune status during and after spaceflight –these factors are chronic psychological stress (including anxiety and depression), physical deconditioning, nutritional deficiencies and intense and/or prolonged radiation exposure.

II. Review of Gaps and Tasks

RISK OF CREW ADVERSE HEALTH EVENT DUE TO ALTERED IMMUNE RESPONSE

A. Existing Gaps

The SRP believes that the existing gaps and tasks addressing the immune risk are relevant (listed below). We recommend that these gaps and tasks remain as written. We do suggest exploration of additional tasks for currently identified gaps. These tasks are recommended with equal priority as the existing tasks.

IM1: Does spaceflight alter immune function?

- This is a high priority for HHC. This data is currently unknown.

Suggested New Tasks for Gap IM1

1. Examine innate immune parameters that occur during spaceflight by using molecular technologies such as gene microarrays to provide rapid information into immune gene activation in various “real world” situations such as spaceflight itself, EVAs, exercise programs, etc.. The portfolio lacks the use of currently available and in development microtechnologies (i.e. micro PCR) that can be used to identify infectious agents in-flight and potentially useful to diagnose acute infections during flight.

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2. Examine the immune risk in longer duration flights with higher radiation exposures. This should be conducted in situations that take into account cofactors such as nutritional state, physical conditioning and chronic psychological stress levels.
 3. Obtain normative immune data to establish a normal clinical range for measures of immunity that could potentially exclude an astronaut from a given mission (or raise risk for adverse clinical events). This approach may well involve identification of stable markers that predict altered immune responses. Such factors will likely be genetic based. Additionally, it will be difficult to define “space normal” for the various immune measures with such a small n for study. Rather, the “normal” values should be established using closely matched ground based normal individuals that represent the diversity of the astronaut corps.

IM2: Is an improved immune standard needed?

- Data must be obtained to determine if the standard is accurate and adequate.

Suggested New Task for Gap IM2

1. Obtain normative immune data to establish a normal clinical range for measures of immunity that could potentially exclude an astronaut from a given mission (or raise risk for adverse clinical events). This approach may well involve identification of stable markers that predict altered immune responses. Such factors will likely be genetic based. Additionally, it will be difficult to define “space normal” for the various immune measures with such a small n for study. Rather, the “normal” values should be established using closely matched ground based normal individuals that represent the diversity of the astronaut corps.

IM3: Are there suitable analogs for immune dysregulation?

Current Tasks:

- Rapid Operational Investigation (ROI): Immune function changes during a spaceflight-analog 12-day undersea mission (NEEMO Immune ROI)
- 3D Tissue Analogs for the Study of Varicella-Zoster Virulence and Infectivity (VZV ROI)
- Apoptosis and Immune Homeostasis During Hind limb Unloading (Immune Homeostasis)
- Consequences of Long-term Confinement and Hypobaric Hypoxia on Immunity in the Antarctic Concordia Environment (CHOICE)

IM4: Can in-flight hardware to evaluate hematology/infection/immunity be developed?

Current Tasks:

- Flow Cytometer

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- Lunar Lab Analysis – Lander/Outpost In-flight Lab Analysis -ARC

IM5: What is the time course and etiology of immune changes?

Current Tasks:

- Flight-Induced Changes in Immune Defenses (Immune Function – DSO 498/SDBI 1498) (Immune Function)
- Incidence of Latent Virus Shedding During Space Flight: (Latent Virus – DSO 493/SDBI 1493)
- Space Flight-Induced Reactivation of Latent Epstein-Barr Virus (Epstein-Barr – DSO 500/E 129) (Epstein-Barr)

Suggested New Tasks for Gap IM5

1. Determine duration of latent herpesvirus reactivation after L+0. Assuming that latent herpesvirus may well be a marker for T cell dysfunction, knowing the duration of viral shedding post-flight may be a sensitive measure of immune dysfunction.
2. Determine whether other latent viral infections associated with various human diseases (i.e., coxsackievirus, JC virus, papillomavirus) are reactivated during or for a defined period post-flight.
3. Determine whether the immune dysfunction seen during space travel increases the risk for opportunistic infections due to the reactivation of latent infections (endemic fungi, dermatophytes, toxoplasma) or if they occur with increased frequency during or after flight.

B. Recommended Gaps for IRP Consideration

We include the following comments based upon additions to the existing five gaps (IM1-5). These gaps are recommended with equal priority as the existing gaps.

New Gap #1:

Increased risk of altered wound healing during spaceflight.

There is a lack of plan to determine if there is an increased risk of altered wound healing during spaceflight. There have been suggestions that certain astronauts have reported that small cuts and abrasions experienced during spaceflight took a prolonged time to heal. There has been no suggestion that this has caused any sort of compromised performance but rather has been more related to nuisance reports. However, if there is significant potential adverse wound healing issues for a more serious injury, concerns about secondary infection and/or strength of healed wound site should develop. With other identified risk factors known to affect wound healing in ground based populations (psychological stress, physical deconditioning, nutrition and radiation exposure).

New Gap #2:

Cumulative effects of chronic immune dysregulation.

There is a lack of longer duration studies (> 6 months) that address cumulative effects of chronic immune dysregulation that can have long term but not necessarily short term clinical effects (i.e., increased risk for coronary artery disease, chronic herpesvirus reactivation, osteoporosis, etc.). While these issues have not been known to be relevant to astronauts so far, the intensity and duration of the adverse influences mentioned above (especially physical deconditioning and radiation exposure) would likely be magnified in any prolonged space missions (such as lunar and/or Mars missions).

New Gap #3

Long term clinical consequences of altered immune responses including impact on hypersensitivity conditions and immune response.

There is a lack of knowledge on the long term clinical consequences of altered immune responses including impact on hypersensitivity conditions (i.e., allergic, autoimmune) and immune response. The immune alterations described in astronaut studies to date are similar to those hypothesized to precede the development of hypersensitivity states. Many historical clinical studies have focused on associations between altered immune parameters seen with greater prevalence in disease states than in comparable normal controls. There are very few longitudinal studies that have investigated the clinical course of abnormal immune values (particularly with today's technology) and subsequent development of inflammatory diseases. Most of the studies demonstrate that such abnormal immune changes are risk factors for allergy and asthma in children. There are no comparable longitudinal studies in adults.

New Gap #4

Correlation of observed laboratory immune changes during spaceflight with known clinical conditions.

There is a lack of knowledge on the correlation of observed laboratory immune changes during spaceflight with known clinical conditions (i.e., infections, hypersensitivity). This gap is based upon the fact that most immune abnormalities reported in astronauts are from research technologies that can detect differences in populations but have limited value in individuals. As a result, population studies in both ground based clinical models and even more limited astronaut studies that show immune dysfunction, the above factors some statistically significant, some not. Since the numbers of astronauts that fly missions are highly limited, immune tests that will have both high positive and negative predictive values are lacking.

New Gap #5

Correlation of immune risks with other risks, particularly psychological stress, physical deconditioning, nutrition and/or radiation.

There is a lack of formal integrative relationships with other HHC groups in the joint design and data analysis of studies that correlate immune risks with other risks, particularly psychological stress, physical deconditioning, nutrition and/or radiation. This was perhaps the greatest concern of the Immune SRP since there have been very few studies that integrate psychological stress, physical deconditioning, nutritional differences and deep space levels of radiation on otherwise normal humans. The lack of interdisciplinary immune studies is a significant gap since the changes may be more than just additive but rather multiplicative as different in intensity and/or duration of varying combinations of the above noted factors.

III. Immune Risk SRP Charge

The SRP is chartered by the Human Research Program (HRP) Program Scientist at the NASA Johnson Space Center (JSC). The purpose of the SRP is to review and provide analysis on the status and progress of HRP Elements and Projects. Your report will be provided to the HRP Program Scientist and will also be given as a courtesy to the HHC Element and Projects at JSC.

The SRP should (to the fullest extent practicable):

1. Evaluate the ability of the Integrated Research Plan (IRP) to satisfactorily address the risks by answering the following questions:
 - A. Have the proper Gaps have been identified to address the Risks?
 - i) Are all the Gaps relevant?
 - ii) Are any Gaps missing?
 - B. Have the proper Tasks have been identified to fill the Gaps?
 - i) Are the Tasks relevant?
 - ii) Are any Tasks missing?
2. Identify the strengths and weaknesses of the IRP, *and* identify remedies for the weaknesses, including answering these questions:
 - A. Are the risks addressed in a comprehensive manner?
 - B. Are there obvious areas of potential integration across disciplines that are not addressed?
3. Address (as fully as possible) the questions provided in the charge addendum and to comment on any additional information provided to the Panel that is not addressed in #1 or #2 above.
4. Expect to receive review materials at least five weeks prior to the site visit.
5. Participate in a SRP teleconference to discuss any issues, concerns, and expectations of the review process approximately three weeks prior to the face-to-face meeting
 - A. Discuss the SRP charge and address questions about the SRP process
 - B. Identify any issues the SRP would like to have answered prior to the site visit
6. Attend the SRP meeting at NASA/JSC
 - A. Attend Element and risk panel presentations, question and answer session, and briefing
 - B. Prepare a draft report including recommendations from the SRP that will be briefed to the Program Scientist by the SRP chairperson or panel. The report should address #1 and #2 above, the questions in the charge addendum, and any other information considered relevant by the SRP.
7. Prepare a final report (within one month of the site visit) that contains a detailed evaluation of the risks and provides specific recommendations that will optimize the scientific return to the HRP. The final report should provide a comprehensive review of Item #1 and #2 above,

address the questions in the addendum to the charge, and any additional information the SRP would like to provide.

8. Consider the possibility of serving on a non-advocate review panel of a directed research proposal or on a solicited research peer review panel; or otherwise advise the Program Scientist.

Addendum to charge: (Element Specific Concerns):

1. Are there obvious, unrealistic aspects in the IRP schedule?
2. Is the portfolio of tasks sufficiently complete to acquire an adequate description of the risks? For example, will “space normal” be adequately defined?
3. Is the portfolio of tasks developing the appropriate technologies?
4. Does the portfolio contain a sufficient number of countermeasure development tasks?
5. Is the portfolio properly balanced among risk description, countermeasure development and technology development activities?
6. Are the appropriate analogs being used?
7. Is it reasonable to begin countermeasure work prior to complete description of risks?

IV. Immune Risk SRP Roster

Panel Chair:

Gailen Marshall, M.D., Ph.D.

University of Mississippi Medical Center

Panel Members:

Sandeep Agarwal, M.D., Ph.D.

The University of Texas Medical School at Houston

Nancy Klimas, M.D.

University of Miami School of Medicine

Janet Nicholson, Ph.D.

Centers for Disease Control

Pablo Okhuysen, M.D.

The University of Texas Medical School at Houston