
2013 Immune Risk Standing Review Panel

Research Plan Review for: *The Risk of Crew Adverse Health Event Due to Altered Immune Response* Final Report

I. Executive Summary and Overall Evaluation

The 2013 Immune Risk Standing Review Panel (from here on referred to as the SRP) participated in a meeting with representatives from the Human Research Program (HRP) Human Health Countermeasures (HHC) Element and HRP management on February 3-4, 2014 in Houston, TX to review the updated Research Plan for the Risk of Crew Adverse Health Event Due to Altered Immune Response in the HRP Integrated Research Plan.

The SRP is impressed with the work the immune discipline has done since the 2012 SRP review and agrees with the new wording of the Gaps, no longer questions, now statements. The SRP also likes the addition of adding targets for closing the Gaps, but it is not clear how they got to some of the interim stages (interval percentages).

A major concern that the SRP has mentioned since the initial 2009 SRP meeting is that there is still not enough emphasis on the interdisciplinary aspect of the immune risk associated with other risks (i.e., nutrition, radiation, etc.). The SRP recommends that a “translational SRP” or advisory group be developed that is composed of members from all of the HRP SRPs. The SRP also thinks that the immune discipline should consider a more systems biology approach.

Lastly, the SRP is concerned that the risks observed in research from low Earth orbit (LEO) missions may not accurately reflect all the risks of longer duration flight beyond LEO. Also, there does not seem to be a concern for immune responses that may occur when someone is in space longer than six months, for example, a Mars mission would take three years. The absence of disease in past and current flight scenarios does not mean the risk may not be there in future flight settings.

II. Critique of Gaps and Tasks for the Risk of Crew Adverse Health Event Due to Altered Immune Response

1. *Have the proper Gaps been identified to address the Risk?*
 - a. *Are all the Gaps relevant?*
 - b. *Are any Gaps missing?*
2. *Have the appropriate targets for closure for the Gaps been identified?*
 - a. *Are the interim stages appropriate to close the Gaps?*
3. *Have the proper Tasks been identified to fill the Gaps?*
 - a. *Are the Tasks relevant?*
 - b. *Are any Tasks missing?*
4. *If a Gap has been closed, does the Rationale for Gap Closure provide the appropriate evidence to support the closure?*

Gaps and Tasks:

IM1: We do not know to what extent spaceflight alters various aspects of human immunity during spaceflight missions up to 6 months.

- The SRP thinks this Gap is relevant and appropriate.
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- The SRP thinks the Gap should be rewritten to read: *We do not know to what extent **orbital** spaceflight alters various aspects of human immunity during **orbital** spaceflight missions up to six months **and after return from flight**.*
 - The SRP thinks the targets for closure and interim stages seem appropriate for this Gap.
 - Missing Gap is effects of spaceflight on Type 1 interferons, toll-like receptor signaling, antigen processing cell function (e.g., dendritic cells) and B cell function.

Tasks:

- Flight-Induced Changes in Immune Defenses-DSO 498 – Task Completed
- Immune Countermeasures Development – Planned Task
- Immune Countermeasures Development – In-flight Validation – Planned Task
- Immune dysregulation and clinical risk: >6 month mission duration – Planned Task
- Incidence of Latent Virus Shedding During Space Flight-DSO 493 – Task Completed
- Nutritional Status Assessment: SMO-016E – PI: Scott Smith, Ph.D. – NASA Johnson Space Center
- Space Flight-Induced Reactivation of Latent Epstein-Barr Virus – Task Completed
- The Effects of Long-Term Exposure to Microgravity on Salivary Markers of Innate Immunity – PI: Richard Simpson, Ph.D. – University of Houston
- Validation of Procedures for Monitoring Crewmember Immune Function (Integrated Immune - SMO 015/SDBI 1900) – PI: Clarence Sams, Ph.D. – NASA Johnson Space Center
- Examination of Splenic and Thymic Immune Function in Mice (STS-135 Mouse Tissue Sharing Pilot Study) – Task Completed
- Microbial Risk Assessment and Integration – PI: Mark Ott, Ph.D. – NASA Johnson Space Center
- Space Biochemistry Profile – Planned Task
- Data Sharing Activity to Gather Evidence for Impaired Healing Risk – Planned Task
- Innate and Adaptive Immunity – Planned Task
- Assessing Telomere Lengths and Telomerase Activity in Astronauts – PI: Susan Bailey, Ph.D. – Colorado State University

IM2: It is necessary to define a flight standard related to spaceflight-associated immune system dysregulation.

- The SRP thinks the definition of “flight standard” needs to be clarified.
- The SRP thinks that target for closure and interim stages are not appropriate for this Gap.
 - Even if IM1 is completed with crew on the International Space Station (ISS), that will not help close interim step 2 because there is no clinical relevance yet available for ground-based health assessment using these research tools. Interim steps 2 and 3 cannot be done until step 1 is developed; a standard correlated clinically.
 - The SRP recommends removing all of the percent closures from the metrics described as these are viewed as arbitrary and arguable.

Tasks:

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 - Examination of Splenic and Thymic Immune Function in Mice (STS-135 Mouse Tissue Sharing Pilot Study) – Task Completed
 - Space Biochemistry Profile – Planned Task
 - Innate and Adaptive Immunity – Planned Task

IM3: We have not defined and validated a terrestrial human analog for spaceflight-associated immune system dysregulation.

- The SRP thinks this Gap is relevant and appropriate.
- The SRP thinks that target for closure is excellent for this Gap.
- The SRP thinks that the variables in interim step 1 should be prioritized (quality, quantity, priority).
 - The proposed duration of an analog needs to be added to this step
 - Integration issues, like diet are also missing from the list of variables
- Interim Step 2 states the “analog is validated when publishable data is achieved...” The SRP thinks the word “peer reviewed” should be added.
 - There needs to be sufficient quantity and quality of results to gain consensus among various stakeholders
- Analogs:
 - What specific advantages do the analogs described in the interim steps have to offer?
 - Need functional immune data (i.e., responses to antigens) from analog study
 - Prioritize each analog

Tasks:

- 3D Tissue Analogs for the Study of Varicella-Zoster Virulence and Infectivity – Task Completed
- Antarctic Winterover Studies – Planned Task
- Apoptosis and Immune Homeostasis During Hindlimb Unloading – Task Completed
- Consequences of Long-term Confinement and Hypobaric Hypoxia on Immunity in the Antarctic Concordia Environment (CHOICE) – Task Completed
- Immune Analog Validation Studies – Planned Task
- Immune Function Changes During a Spaceflight-analog 12-day Undersea Mission (NEEMO IIIH ROI) – Task Completed
- Bed Rest and Immunity – Task Completed
- Flow Cytometer – Planned Task
- Identification of Cardiometabolic Vulnerabilities Caused by Effects of Synergistic Stressors that are Commonly Encountered during Space Missions – PI: Steven Shea, Ph.D. – Brigham and Women’s Hospital

IM6: We do not know the cumulative effects of chronic immune dysfunction on missions greater than six months.

- The SRP thinks this Gap should replicate IM1.
- More frequent assessments should be done on astronauts between L+1-30 (at least L+15).
- The SRP thinks the targets for closure and interim stages seem appropriate for this Gap.

Tasks:

- Immune dysregulation and clinical risk: >6 month mission duration – Planned Task

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- Consequences of Long-term Confinement and Hypobaric Hypoxia on Immunity in the Antarctic Concordia Environment (CHOICE) – Task Completed
 - Immune Countermeasures Development – In-flight Validation – Planned Task
 - Antarctic Winterover Studies – TBD – Planned Tasks

IM7: It is necessary to correlate the observed effects of spaceflight-associated immune system dysregulation with known terrestrial clinical conditions.

- The SRP thinks this Gap is relevant and appropriate.
- Before this Gap can be closed, a review of the literature on untreated populations is needed.
- The SRP suggests exploring accessible biorepositories at various locations that may have relevant clinical samples.
- The SRP suggests a proof of concept study and suggest starting with one disease most relevant to anticipated crew risks (not a list).
- Possible task: Reactivation of latent viral assays. What viruses are likely to reactivate? Is there a predictor (biomarker) of the viral reactivation?
- The SRP thinks the targets for closure and interim stages seem appropriate for this Gap.

Tasks:

- Immune/Viral/Nutritional Interrelationship Studies – Planned Task
- Clinical Immunology Study - European Collaboration – PI: Brian Crucian, Ph.D. – NASA Johnson Space Center
- JSC Clinical Studies – Planned Task

IM8: We do not know the influence, direct, or synergistic, on the immune system of other physiological changes associated with spaceflight.

- The SRP strongly supports the integrative nature of this Gap.
- Systems biology approach would likely be most optimal.
- The SRP thinks this Gap is relevant and appropriate.
- The SRP thinks the targets for closure and interim stages seem appropriate for this Gap.

Tasks:

- Identification of Cardiometabolic Vulnerabilities Caused by Effects of Synergistic Stressors that are Commonly Encountered during Space Missions – PI: Steven Shea, Ph.D. – Brigham and Women’s Hospital
- Nutritional Status Assessment: SMO-016E – PI: Scott Smith, Ph.D. – NASA Johnson Space Center
- Microbial Risk Assessment and Integration – PI: Mark Ott, Ph.D. – NASA Johnson Space Center
- Evaluation of the combined effects of gamma radiation and high dietary iron on oxidative damage and antioxidant status in rats (Immune Assessment) – Task Completed
- Space Biochemistry Profile – Planned Task

III. Discussion on the strengths and weaknesses of the IRP and identify remedies for the weaknesses, including answering these questions:

Is the Risk addressed in a comprehensive manner?

- The SRP thinks the Risk is addressed in a comprehensive manner, but integration should be more evident in immune risk research plan.

Are there obvious areas of potential integration across disciplines that are not addressed?

- The SRP thinks the immune discipline should have more integration with all of the HRP Elements, but specifically with the nutrition, radiation health, bone, and behavioral health disciplines.

IV. Evaluation of the progress in the IRP since the 2012 SRP meeting

- The SRP likes the new wording of the Gaps.
- The SRP likes the addition of the targets for closure and interim steps.
- There is some emerging recognition of need for an integrated approach to the risk and countermeasures, but not enough.

V. 2013 Immune Risk SRP Research Plan Review: Statement of Task for the Risk of Crew Adverse Health Event Due to Altered Immune Response

The 2013 Immune Risk Standing Review Panel (SRP) is chartered by the Human Research Program (HRP) Chief Scientist. The purpose of the SRP is to review the Human Health Countermeasures (HHC) Element's section of the current version of the HRP's Integrated Research Plan which is located on the Human Research Roadmap (HRR) website (<http://humanresearchroadmap.nasa.gov/>). Your report will be provided to the HRP Chief Scientist and will also be made available on the HRR website.

The 2013 Immune Risk SRP is charged (to the fullest extent practicable) to:

1. Based on the information provided in the current version of the HRP's IRP, evaluate the ability of the IRP to satisfactorily address the Risk by answering the following questions:
 - A. Have the proper Gaps been identified to address the Risk?
 - i) Are all the Gaps relevant?
 - ii) Are any Gaps missing?
 - B. Have the appropriate targets for closure for the Gaps been identified?
 - i) Are the interim stages appropriate to close the Gaps?
 - C. Have the proper Tasks been identified to fill the Gaps?
 - i) Are the Tasks relevant?
 - ii) Are any Tasks missing?
 - D. If a Gap has been closed, does the Rationale for Gap Closure provide the appropriate evidence to support the closure?
2. Identify the strengths and weaknesses of the IRP, *and* identify remedies for the weaknesses, including answering these questions:
 - A. Is the Risk addressed in a comprehensive manner?
 - B. Are there obvious areas of potential integration across HRP disciplines that are not addressed?
3. Please evaluate the progress in the IRP since your 2012 SRP meeting.
4. Please comment on any important issues that are not covered in #1, #2, or #3 above. If addendum questions are provided below, please address each of the questions as fully as possible.

Additional Information Regarding This Review:

1. Expect to receive review materials at least four weeks prior to the meeting.
2. Participate in a 2013 Immune Risk SRP conference call to discuss any issues, concerns, and expectations of the review process approximately three weeks prior to the meeting.
 - A. Discuss the 2013 Immune Risk SRP Statement of Task and address questions about the SRP process.
3. Attend the 2013 Immune Risk SRP meeting at NASA JSC on February 3 - 4, 2014.
 - A. Attend Element or Project presentations, question and answer session, and briefings.
 - B. Prepare a draft report that addresses each of the evaluation criteria listed in the panel charge. Debrief the HRP Chief Scientist and a representative from the HHC Element on the salient points that will be included in the final report and specifically the items in the panel charge.
4. Prepare a draft final report (within one month of the site visit debrief) that contains a detailed evaluation of the current IRP specifically addressing items #1, #2, #3, and #4 of the SRP charge. The draft final report will be sent to the HRP Chief Scientist and he will forward it to the appropriate Element for their review. The HHC Element and the HRP Chief Scientist will have 2 business days to review the draft final report and identify any misunderstandings or errors of fact and then provide official feedback to the SRP. If any misunderstandings or errors of fact are identified, the SRP will have 10 business days to address them and finalize the 2013 SRP Final Report. The 2013 SRP Final Report will be submitted to the HRP Chief Scientist and copies will be provided to the HHC Element that sponsors the nutrition discipline and also made available to the other HRP Elements. The 2013 SRP Final Report will be made available on the HRR website (<http://humanresearchroadmap.nasa.gov/>).

VI. 2013 Immune Risk Standing Review Panel Roster

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