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## 2013 Immune Risk Standing Review Panel

### Evidence Review for:

### *The Risk of Crew Adverse Health Event Due to Altered Immune Response*

## Final Report

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### I. Executive Summary and Overall Evaluation

The 2013 Immune Risk Standing Review Panel (from here on referred to as the SRP) met for a site visit in Houston, TX on February 3-4, 2014. The SRP reviewed the new Evidence Report for the Risk of Crew Adverse Health Event Due to Altered Immune Response (from here on referred to as the 2013 Immune Evidence Report), as well as the Research Plan for this Risk that is in the current version of the Human Research Program's (HRP) Integrated Research Plan (IRP).

Overall, the SRP thinks the well-qualified research team has compiled an excellent summary of background information in the 2013 Immune Evidence Report.

### II. Review of the Evidence for the Risk of Crew Adverse Health Event Due to Altered Immune Response

#### 1. Evaluate the 2013 Immune Evidence Report using the following criteria:

- A. *Does the 2013 Evidence Report provide sufficient evidence that the Risk is relevant to long-term space missions?*

The SRP thinks that the 2013 Immune Evidence Report provides sufficient evidence that the Immune Risk is relevant to long-term space missions.

- B. *Are the Risk Title and Statement properly stated in the current version of the HRP Integrated Research Plan (IRP)?*

The SRP thinks the Risk Title is properly stated in the current version of the HRP IRP.

The HRP IRP currently reads: "Given that the spaceflight environment results in an alteration of the immune system and reactivation of latent herpes viruses, there is a possibility that the crew will experience certain disease states, including persistent latent viral reactivation, during exploration class missions." The SRP suggests rewording the Risk Statement to: "Given that the spaceflight environment results in an alteration of the immune system and reactivation of latent herpes viruses, there is a possibility that the crew will *potentially experience certain immune dysfunction*, including persistent latent viral reactivation that may affect disease susceptibility during exploration class missions."

- C. *Is the text of the Risk Context provided in the HRP IRP clear?*

The 2013 Immune Evidence Report references a cytokine and viral reactivation paper that has been submitted for publication. Therefore, the Risk Context should not state that the: "Human immune function has been documented to be altered in- and post-flight, but it is unclear if these changes lead to any increased susceptibility to disease. Reactivation of latent viruses has been documented in crewmembers, though this reactivation **has not been** directly correlated with the immune changes and is clinically asymptomatic." The SRP suggests rewording the second

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sentence to read: “Reactivation of latent viruses has been documented in crewmembers, though *it is still unknown if* this reactivation *is* directly correlated with the immune changes and is asymptomatic.”

*D. Does the evidence base make the case for the knowledge-type gaps presented?*

The SRP does think that the evidence base makes the case for the knowledge-type gaps presented.

*E. Are there any additional knowledge-type gaps that should be considered for this specific Risk?*

The SRP thinks that the 2013 Immune Evidence Report is lacking in information about other areas of the innate and adaptive immune system that have not been studied (e.g., T cells, B cells, Type 1 interferon dendritic cells, and toll-like receptor cells). These are knowledge-type gaps and part of the immune system that should be addressed and discussed in the 2013 Immune Evidence Report.

*F. Does the Evidence Report address relevant interactions between this Risk and others in the HRP IRP?*

The SRP does not think the 2013 Immune Evidence Report adequately addresses relevant interactions with other HRP Elements. The immune discipline needs to more actively interact with other disciplines including behavioral, bone, exercise, and radiation.

*G. Are the qualifications of the author(s) appropriate for identifying the evidence base necessary to characterize the given Risk?*

Yes, the SRP thinks the authors of the 2013 Immune Evidence Report are very knowledgeable and have the appropriate expertise to make assessments. The SRP strongly recommends adding a clinician scientist to the current team. This would strengthen the team immensely by adding a translational component for correlating the vast amount of immune data being generated to human disease risk, provide guidance in developing/assessing new immune measures in future studies and practically contribute to develop countermeasures that medical officers would accept as reasonable for their patients (crewmembers) and could thus advocate for the implementation in future space missions.

*H. Is there information from other HRP disciplines that need to be included in the 2013 Evidence Report?*

The SRP suggests a more interdisciplinary mindset and encourages the immune discipline to examine other disciplines for information that may affect immune response and should be included in their Evidence Report such as: nutritional data that relate to clinical caloric intake, vitamin and/or other trace element metabolisms/wasting during flight, current and projected radiation exposures expected or possible after unforeseen crises during both short- and long-term spaceflight; impact of physical conditioning status over the duration of long term spaceflight and individual crewmember susceptibility to biobehavioral challenges associated with specific missions.

*I. Is the breadth of the cited literature sufficient?*

The SRP thinks the authors have cited a comprehensive literature in the 2013 Immune Evidence Report.

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*J. What is the overall quality and readability of the 2013 Evidence Report?*

The SRP thought the 2013 Immune Evidence Report was well written and organized.

*2. Provide comments on any important issues that are not covered by the criteria in #1 above.*

The SRP thinks the authors of the 2013 Immune Evidence Report should reevaluate the data in Appendix 1: Additional Representative Evidence by Category. Currently, the “Level of Evidence” for all the categories listed is “2”. The SRP thinks this is an error because it believes that the level of evidence for all the categories is not equivalent.

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### **III. 2013 Immune Risk SRP Evidence Review: Statement of Task for the Risk of Crew Adverse Health Event Due to Altered Immune Response**

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In 2008, the Institute of Medicine reviewed NASA's Human Research Program Evidence Books that described the Risks that were identified in NASA's Human Research Program Requirements Document (PRD). The 2013 Evidence Report for the Risk of Crew Adverse Health Event Due to Altered Immune Response has not been reviewed since the last IOM review and there have been significant changes to the evidence base for the Risk.

The 2013 Immune Risk Standing Review Panel (SRP) is chartered by the Human Research Program (HRP) Chief Scientist to review the Evidence Report for the Risk of Crew Adverse Health Event Due to Altered Immune Response. The 2013 Immune Risk SRP will generate a final report of their analyses of the evidence base, including any recommendations on how to improve the current Evidence Report, and submit it to the HRP Chief Scientist. Your report will also be made available on the Human Research Roadmap (HRR) website.

#### **The 2013 Immune Risk SRP is charged to:**

3. Evaluate the 2013 Immune Risk Evidence Report based on each of the following criteria:
  - A. Does the 2013 Evidence Report provide sufficient evidence that the Risk is relevant to long-term space missions?
  - B. Are the Risk Title and Statement properly stated in the current version of the HRP Integrated Research Plan (IRP)?
  - C. Is the text of the Risk Context provided in the HRP IRP clear?
  - D. Does the evidence base make the case for the knowledge-type gaps presented?
  - E. Are there any additional knowledge-type gaps that should be considered for this specific Risk?
  - F. Does the Evidence Report address relevant interactions between this Risk and others in the HRP IRP?
  - G. Are the qualifications of the author(s) appropriate for identifying the evidence base necessary to characterize the given Risk?
  - H. Is there information from other HRP disciplines that need to be included in the 2013 Evidence Report?
  - I. Is the breadth of the cited literature sufficient?
  - J. What is the overall quality and readability of the 2013 Evidence Report?
4. Provide comments on any important issues that are not covered by the criteria in #1 above.

#### **Additional information regarding this review:**

1. After the 2013 Immune Risk SRP members have received the review materials and had the opportunity to look over the documents, the panel members will participate in a conference call to discuss any issues, concerns, and expectations of the review process to start the review prior to the meeting.
  - A. Discuss the 2013 Immune Risk SRP Statement of Task and address questions about the SRP process.
  - B. Identify any issues the 2013 Immune Risk SRP would like to have answered prior to or during the meeting.
2. Attend a meeting at the NASA JSC on February 3 – 4, 2014 to discuss the Evidence Report with the Human Health Countermeasures (HHC) Element. At this meeting, prepare a draft report that addresses each of the evaluation criteria listed in the panel charge (A-J) including any

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recommendations on how to improve the Evidence Report. 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.

3. Prepare a draft final report (within one month of the site visit debrief) that contains a detailed evaluation of the Evidence Report specifically addressing items #1 and #2 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 two 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 Immune 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/>).

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**To clarify, the Risk Statement and Risk Context are defined as follows:**

**Risk Statement:**

“Given the CONDITION, there is a possibility that a CONSEQUENCE will occur”.

Condition: a single phrase briefly describing current key circumstances, situations, etc. that are causing concern, doubt, anxiety, or uncertainty – something that keeps you up at night.

Consequence: a single phrase or sentence that describes the key, negative outcome(s) of the current conditions.

**Notes:**

The condition-consequence format provides a more complete picture of the Risk, which is critical during mitigation planning. The condition component focuses on what is currently causing concern. This is something that is true or widely perceived to be true. This component provides information that is useful when determining how to mitigate a Risk.

The consequence component focuses on the intermediate and long-term impact of the risk.

Understanding the depth and breadth of the impact is useful in determining how much time, resources, and effort should be allocated to the mitigation effort.

A well-formed Risk Statement usually has only one condition, and has one or more consequences.

**Risk Context:**

Purpose: provide enough additional information about the Risk to ensure that the original intent of the Risk can be understood by other personnel, particularly after time has passed.

Description: capture additional information regarding the circumstances, events, and interrelationships not described in the Risk Statement.

An effective context captures the what, when, where, how, and why of the Risk by describing the circumstances, contributing factors, and related issues (background and additional information that are NOT in the Risk Statement).

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#### IV. 2013 Immune Risk Standing Review Panel Roster

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