UPDATE ON SPACEFLIGHT IMMUNE SYSTEM DYSREGULATION, CLINICAL RISKS FOR DEEP SPACE MISSIONS, POTENTIAL COUNTERMEASURES
The Immune System

**Pluripotent Stem Cell**

**Myeloid Stem Cell**

**Lymphoid Stem Cell**

- **T Lymphocyte**
- **NK Lymphocyte**
- **B Lymphocyte**
- **Plasma Cell**

**ADAPTIVE IMMUNITY**
- Secondary defense
- Delayed
- Antigen-specific
- Results in memory

**Cell mediated immunity:**
Mediated by cytotoxic T lymphocytes which destroy viral infected cells, transplant cells, some tumor cells

**Humoral immunity:**
Mediated by B cells/Plasmacytes. Antibodies bind specific antigens, signals other cells to engulf and remove that target from the body.

**INNATE IMMUNITY**
- Primary defense
- Immediate
- Non-specific
- Does not result in memory

**INNATE IMMUNITY**
- Primary defense
- Immediate
- Non-specific
- Does not result in memory

**CELLS**
- **Erythrocyte**
- **Megakaryocyte**
- **Monocyte**
- **Macrophage**
- **Granulocytes**

**Thymus**

**LYMPH NODES**
- **Thymus Gland**
- **Liver**
- **Spleen**
- **Lymph Nodes**
- **B Cells & Other Lymphocytes**

**CELLS**
- **Platelet**
- **Immature Band Neutrophil**
- **Mature Segmented Neutrophil**
- **Lymphocyte**
- **Mast Cell**
- **Eosinophil**
- **Basophil**

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- **Erythrocyte**
- **Monocyte**
- **Macrophage**
- **Granulocytes**

**CELLS**
- **Erythrocyte**
- **Monocyte**
- **Macrophage**
- **Granulocytes**
MAST CELL

WHITE BLOOD CELLS  +  RED BLOOD CELLS

GRANULOCYTES  MONOCYTES  LYMPHOCYTES

BASOPHILS  NEUTROPHILS  EOSINOPHILS

Myeloid DC  Plasmacytoid DC

MAST CELL

MACROPHAGES

B CELLS  T CELLS  NK CELLS

CD4+  ‘Helper’  CD8+  ‘Cytotoxic’

Naïve B Cell  Plasma Cell  Memory B Cell

tTreg  pTreg

Treg  Th1  Th2  Th17

Central Memory  Effector Memory  Terminal Diff.

Memory  Naive

Memory  Naive

True Naïve
Eat microbes

Cause Allergy

Kill Infected Cells

Direct ‘Right’ Kind of Response

Fight Parasites

Fight Cancer

Make Antibodies

Keep ‘Control’

Protect you for life!

Inflammation

Pathogen-specific Response
CYTOKINE NETWORK

Humoral
- IL-10
- IL-12
- TNFα
- TNFβ

Innate/Inflammatory
- IL-1
- IL-6
- IL-10
- IL-12
- IL-15
- TNFα

Th1/Th2
- IL-1
- IL-2
- IFNα
- IFNβ
- TNFα
- TNFβ

Adaptive/regulatory
- IL-4
- IL-8
- IFNγ

Chemokines
- IL-1
- IL-8
- TNFα

Growth Factors
- IFNα
- IFNβ
- TNFα

Macrophage
- B-Cell
- T-Cell
- Neutrophil
- Eosinophil
- Basophil
- Mast Cell
ALTERED MICROBIAL VIRULENCE
HYPOXIA/CO2
RADIATION
PHYSIOLOGICAL STRESS
PSYCHOLOGICAL STRESS
ALTERED IMMUNOCYTE DISTRIBUTION & FUNCTION
ALTERED CYTOKINE, REDOX, INFLAMMATORY BALANCE
LATENT VIRUS REACTIVATION
CLINICAL INCIDENCE
AUTOIMMUNITY
CONSEQUENCES OF PERSISTENT VIRAL REACTIVATION
CHRONIC ALLERGY/HYPERSENSITIVITY
INFECTION DISEASE
CANCER
ALTERED NUTRITION
MICROGRAVITY
ALTERED MICROBIOME
CIRCADIAN MISALIGNMENT
TH1/TH2
Blood and Saliva Collection - ISS
Plasma Collection - ISS

Return Ambient – 45h Delay

Early
~2 weeks

FD15
FD30
FD60  6 Months Spaceflight
FD120
FD180

Mid
2-4 mos

Late
R-1-2 days

Frozen on Orbit
Innate immunocyte function dysregulated during spaceflight

- Plasma cytokine concentrations are altered in astronauts
- Astronauts experience persistent reactivation of latent herpesviruses, biomarker of reduced immunity
- Astronauts demonstrate elevated stress hormones and dysregulated circadian rhythms during spaceflight
- Astronauts have some degree of clinical incidence, primarily dermatitis, allergy and infections
- Dermatitis may be associated with viral etiology
- Some crew experience persistent symptoms requiring prolonged management
Microgravity Cell Culture

1xG CONTROL

Red: Actin localization
Green: Microtubules/MTOC

MODELED MICROGRAVITY

Mayra Nelman-Gonzalez
T Cell Function

One method of the "co-stimulation" needed to activate T cells. If the T cell fails to receive "signal two", it dies by apoptosis. B7 comes in two forms: B7-1 (CD80) and B7-2 (CD86).

**Graphs:**

- **SEA+SEB**
  - n=23
  - Graph shows percent changes over time (L-180, L-45, Early, Mid, Late, R+0, R+30) for CD4/69+ and CD8/69+.

- **αCD3/αCD28**
  - n=17
  - Graph shows percent changes over time (L-180, L-45, Early, Mid, Late, R+0, R+30) for CD4/69+ and CD8/69+.
Data expressed as % change from baseline (L-180). NK-cell function did not differ between astronauts and controls at baseline.

Spaceflight Reduces NK Cell Function

- **K562 (Leukemia)**
  - Controls (n=6)
  - Astronauts (n=6)
  - Baseline NKCA

- **U266 (Multiple Myeloma)**

- **221.AEH (HLA-E Transfected)**

- **721.221 (Lymphoma)**

Dr. Richard Simpson
### Table 1: Twenty two cytokines for analysis by category

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Anti-Inflammatory</th>
<th>Adaptive/Regulatory</th>
<th>Growth Factors</th>
<th>Chemokines</th>
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</thead>
<tbody>
<tr>
<td>IL-1α</td>
<td>IL-1ra</td>
<td>IFNγ</td>
<td>G-CSF</td>
<td>CCL2/MCP-1</td>
</tr>
<tr>
<td>IL-1β</td>
<td>IL-2</td>
<td>IL-17</td>
<td>GM-CSF</td>
<td>CCL3/MIP-1</td>
</tr>
<tr>
<td>TNFα</td>
<td>IL-17</td>
<td>IL-2</td>
<td>FGF basic</td>
<td>CCL4/MIP-1</td>
</tr>
<tr>
<td>IL-6</td>
<td>IL-4</td>
<td>IL-5</td>
<td>Tpo</td>
<td>CCL5/RANTES</td>
</tr>
<tr>
<td>IL-8</td>
<td>IL-5</td>
<td>IL-10</td>
<td>VEGF</td>
<td>CXCL5/ENA-78</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>
### Plasma Cytokine Analysis

Table 2: Mean plasma cytokine levels for ISS astronauts before, during, and following spaceflight. Data are expressed as mean concentration pg/ml ± SEM. Bold indicates statistically significant difference p≤0.05; n=28.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>L-180</th>
<th>L-45</th>
<th>FD15</th>
<th>FD30</th>
<th>FD60</th>
<th>FD120</th>
<th>FD180</th>
<th>R+0</th>
<th>R+30</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1a</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.3</td>
<td>0.9 ± 0.5</td>
<td>0.3 ± 0.1</td>
<td>2.4 ± 1.9</td>
<td>0.6 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>IL-1b</td>
<td>0.4 ± 0.1</td>
<td>0.7 ± 0.3</td>
<td>1.5 ± 1.0</td>
<td>0.8 ± 0.3</td>
<td>0.9 ± 0.5</td>
<td>1.3 ± 0.9</td>
<td>1.1 ± 0.8</td>
<td>0.5 ± 0.2</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td>TNFa</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>3.2 ± 1.0</td>
<td>2.0* ± 0.3</td>
<td>2.1* ± 0.4</td>
<td>2.2 ± 0.5</td>
<td>2.0 ± 0.4</td>
<td>1.3 ± 0.1</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>IL-8</td>
<td>2.0 ± 0.3</td>
<td>2.1 ± 0.3</td>
<td>8.1* ± 2.1</td>
<td>7.9* ± 2.3</td>
<td>7.7* ± 1.7</td>
<td>7.3* ± 2.1</td>
<td>6.9* ± 2.3</td>
<td>2.1 ± 0.3</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>383 ± 40</td>
<td>370 ± 35</td>
<td>567* ± 65</td>
<td>563* ± 80</td>
<td>638* ± 101</td>
<td>728* ± 129</td>
<td>661* ± 85</td>
<td>682* ± 118</td>
<td>568 ± 146</td>
</tr>
<tr>
<td>IFNg</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>0.7 ± 0.3</td>
<td>0.5* ± 0.1</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>IL-2</td>
<td>2.2 ± 0.6</td>
<td>1.8* ± 0.5</td>
<td>1.7* ± 0.5</td>
<td>2.6 ± 0.8</td>
<td>2.4 ± 0.7</td>
<td>2.5 ± 0.7</td>
<td>2.4 ± 0.8</td>
<td>2.4 ± 0.7</td>
<td>2.7 ± 0.9</td>
</tr>
<tr>
<td>IL-17</td>
<td>1.3 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>0.9 ± 0.3</td>
<td>0.9* ± 0.2</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>IL-4</td>
<td>0.3 ± 0.1</td>
<td>0.5 ± 0.3</td>
<td>3.2 ± 1.7</td>
<td>0.3 ± 0.2</td>
<td>1.4 ± 0.7</td>
<td>2.1 ± 1.5</td>
<td>1.6 ± 1.2</td>
<td>0.4 ± 0.2</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>IL-5</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.2 ± 0.0</td>
<td>0.2 ± 0.1</td>
<td>0.4 ± 0.2</td>
<td>0.2 ± 0.0</td>
<td>0.2 ± 0.0</td>
<td>0.2 ± 0.0</td>
<td>0.2 ± 0.0</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>G-CSF</td>
<td>7.2 ± 1.9</td>
<td>7.0 ± 1.7</td>
<td>7.0 ± 1.8</td>
<td>4.5 ± 0.8</td>
<td>7.6 ± 2.0</td>
<td>14.7 ± 7.8</td>
<td>9.8 ± 3.2</td>
<td>10.3* ± 2.8</td>
<td>5.9 ± 1.4</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>0.6 ± 0.3</td>
<td>0.3 ± 0.1</td>
<td>3.4 ± 1.9</td>
<td>1.9* ± 0.8</td>
<td>2.7 ± 1.3</td>
<td>2.8 ± 1.9</td>
<td>2.7 ± 1.9</td>
<td>0.7 ± 0.4</td>
<td>0.7 ± 0.4</td>
</tr>
<tr>
<td>FGFb</td>
<td>13.7 ± 5.4</td>
<td>15.4 ± 5.7</td>
<td>11.8 ± 3.3</td>
<td>21.9 ± 5.7</td>
<td>18.5 ± 4.9</td>
<td>12.1 ± 3.7</td>
<td>10.8 ± 2.7</td>
<td>11.7 ± 3.8</td>
<td>12.3 ± 4.3</td>
</tr>
<tr>
<td>Tpo</td>
<td>140 ± 16</td>
<td>146 ± 18</td>
<td>184* ± 18</td>
<td>189* ± 30</td>
<td>191* ± 22</td>
<td>196* ± 28</td>
<td>221* ± 24</td>
<td>141 ± 17</td>
<td>133 ± 16</td>
</tr>
<tr>
<td>VEGF</td>
<td>5.8 ± 0.9</td>
<td>6.2 ± 1.3</td>
<td>10.9* ± 19</td>
<td>15.8* ± 4.9</td>
<td>11.3* ± 1.7</td>
<td>12.5* ± 3.5</td>
<td>11.7* ± 1.9</td>
<td>5.1 ± 1.0</td>
<td>5.5 ± 0.9</td>
</tr>
<tr>
<td>CCL2/MCP-1</td>
<td>72.4 ± 6.8</td>
<td>78.5 ± 7.7</td>
<td>71.7 ± 5.4</td>
<td>66.0 ± 5.8</td>
<td>77.0 ± 7.0</td>
<td>84.0 ± 7.0</td>
<td>87.0 ± 7.7</td>
<td>124* ± 18.1</td>
<td>90* ± 7.5</td>
</tr>
<tr>
<td>CCL3/MIP-1a</td>
<td>20.3 ± 5.0</td>
<td>16.6 ± 5.0</td>
<td>25.9 ± 8.1</td>
<td>15.0 ± 4.4</td>
<td>19.1 ± 6.6</td>
<td>22.7 ± 7.4</td>
<td>21.7 ± 8.6</td>
<td>19.4 ± 6.3</td>
<td>18.1 ± 5.5</td>
</tr>
<tr>
<td>CCL4/MIP-1b</td>
<td>16.2 ± 2.2</td>
<td>16.7 ± 2.7</td>
<td>22.3* ± 2.9</td>
<td>20.2* ± 2.5</td>
<td>22.2* ± 2.8</td>
<td>24.3 ± 5.1</td>
<td>21.6* ± 3.3</td>
<td>17.3 ± 2.3</td>
<td>19.3 ± 4.0</td>
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<tr>
<td>CCL5/RANTES</td>
<td>3613 ± 263</td>
<td>3292 ± 246</td>
<td>3618 ± 202</td>
<td>3746 ± 195</td>
<td>3575 ± 185</td>
<td>3818 ± 217</td>
<td>4030 ± 202</td>
<td>3410 ± 266</td>
<td>3623 ± 219</td>
</tr>
</tbody>
</table>
Plasma Cytokine Analysis

Chemokines

- CXCL5/ENA-78

Anti-Inflammatory Cytokines

- IL-1ra
Stress Hormones/Circadian Rhythm

Circadian rhythm of Salivary Cortisol in 27 healthy adults

- Waking
- Wake + 30 min
- Before Lunch
- 4 PM

**Pre-Flight**

**Flight**

**Post-Flight**

- 180
- 45
- Early
- Mid
- Late
- Early
- Late

**CORT (nmol/L) +/- 1 SEM**

**Collection Time**
Latent Herpesvirus

Latent Viral Reactivation

Herpes Simplex
- Gingivostomatitis
- Mild pharyngitis
- Fever

Varicella
- Chickenpox

Primary Infection

Cold Sore

Zoster (shingles)

Spinal cord

Latent virus

Virus transit up peripheral nerve

Sensory neuron in dorsal root ganglion

Virus transit down peripheral nerve

Stress

Activation of virus in neuron

Recurrence
Latent Herpesvirus

Reactivation in 76% of the crew members

EBV copies / ng salivary DNA

Sample Collection Days

Before | During | After

VZV Copies / ng salivary DNA

Sample Collection Days

Before | During | After

Reactivation in 65% of the crew members
Latent Herpesvirus

Zoster Patients (n=42) 100% positive
Astronauts (n=23) 2-3 samples per crew= 59 total samples – 29/59 positive (49%)
No VZV DNA was detected pre-flight for any crew (L-180 or L-45)
### Clinical Incidence

<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>Total events</th>
<th>Events/person year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Reaction</td>
<td>1</td>
<td>0.06</td>
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<tr>
<td>Anaphylaxis</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Upper Respiratory Infection (combination of rhinitis, nasal stuffiness and sneezing)</td>
<td>5</td>
<td>0.301</td>
</tr>
<tr>
<td>Eye Infection</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>5</td>
<td>0.301</td>
</tr>
<tr>
<td>Otitis Media/Externa (ear pain, or ear stuffiness+congestion)</td>
<td>17</td>
<td>1.022</td>
</tr>
<tr>
<td>Pharyngitis (sore throat)</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Sinus Infection</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Skin Infection (including scalp pruritis, pus forming wounds on wrist, finger)</td>
<td>5</td>
<td>0.301</td>
</tr>
<tr>
<td>Skin Rash/Hypersensitivity (including skin conditions such as tinea versicolor, dermatitis, rosacea)</td>
<td>23</td>
<td>1.383</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Malignancies*</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Autoimmunity*</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>Infections, Other*#</td>
<td>11</td>
<td>0.666</td>
</tr>
</tbody>
</table>

**Total:** 69  **4.18**

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*Indicates additional conditions or symptoms categorized, beyond the original 13 IMM conditions.

#Additional infectious processes not characterized within other categories such as lymphadenitis, lymphadenopathy, mild fever and intestinal problems with such symptoms as diarrhea, excessive intestinal gas and bloating.
Clinical Incidence

Case Study ISS Astronaut

- Allergic symptoms in a non-allergic subject
- Subject developed an Atopic Dermatitis on mission day 17
- Rash was bothersome, at times severe
- A variety of treatments employed
- At times the medications of choice were exhausted
- Rash never resolved for the duration of the mission, although it was successfully managed to a tolerable level
- Rash spikes generally correlated well with operational stressors
- Research findings confirm immune dysregulation persisted for the duration of the mission
Clinical Incidence

- Rashes were observed to occur in the following locations: scalp, face, neck, chest, back, trunk, abdomen, arms and hands.

- The appearance of the rashes generally consists of bumps/nodules and/or small brown scaly patches, with or without petechiae, redness/hyperemia and itching.
Clinical Incidence

Herpes Simplex Virus type-1 reactivation associated with a case of persistent dermatitis during Spaceflight
Clinical Incidence

<table>
<thead>
<tr>
<th></th>
<th>In-Flight</th>
<th>R+0</th>
<th>R+14</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saliva</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HSV1</td>
<td>Positive (CT-22; 5.4x10^6</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>copies per ng total DNA)</td>
<td>(CT-15; 1.4x10^9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>copies per ng total DNA)</td>
<td></td>
</tr>
<tr>
<td><strong>Skin Lesion</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>VZV</td>
<td>Negative</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>HSV1</td>
<td>Positive (CT-29; 2.4x10^4</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>copies per ng total DNA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Tertiary* infection using the cells and media from the secondary infection. Negative control (*left*), Serial dilution 10^{-1} (*center*), and serial dilution 10^{-6} (*right*).
Peripheral leukocyte distribution in astronauts is relatively normal.

T cell function is inhibited by microgravity.

T cell function is reduced in astronauts; appears to be a shift in the activation threshold.

NK cell function is reduced in astronauts.

NK cells are disarmed, reduction in lytic molecule content.

B cell function in astronauts appears unaltered (limited data).

Plasma cytokine concentrations are altered in astronauts.

Astronauts experience persistent reactivation of latent herpesviruses, biomarker of reduced immunity.

Astronauts demonstrate elevated stress hormones and dysregulated circadian rhythms during spaceflight.

Astronauts have some degree of clinical incidence, primarily dermatitis, allergy and infections.

Some crew experience persistent symptoms requiring prolonged management.
Recent studies have established that dysregulation of the human immune system and the reactivation of latent herpesviruses persists for the duration of a 6-month orbital spaceflight. It appears certain aspects of adaptive immunity are dysregulated during flight, yet some aspects of innate immunity are heightened. Interaction between adaptive and innate immunity also seems to be altered. Some crews experience persistent hypersensitivity reactions during flight. This phenomenon may, in synergy with extended...
Potential Immunologic Countermeasures for Deep Space Missions

**Precision Countermeasures**

**Pre-Mission Immunological Screen**
Pre-mission immunological screen may include:
- Personal history of allergy/hypersensitivity, etc.
- Medication history (antihistamines, etc.)
- Leukocyte distribution (NK cell subsets)
- Cytokine concentration: Th1/Th2, etc.
- Allergy screen, patch testing
- Latent herpesvirus sero-positivity

**Pathogen-Specific Mitigations**
Antiviral (VZV) vaccination

**General Countermeasures**

**Already in Place/Will be Optimized**
- Pre-flight medical operations screening of crewmembers
- Pre-flight quarantine
- Microbial screening of vehicle/payloads/foods
- Environmental control
- Optimized exercise equipment
- Radiation shielding

**Multisystem Countermeasures**
- Optimized exercise regimen
- Adequate sleep schedules
- Psychological support - family communication
- Stress relieving techniques

**Specific Countermeasures**

**Nutritional Countermeasures**
- Diet optimized to reduce nutrient deficiency
- Functional foods/bioactive compounds
- Nutritional supplements:
  - Antioxidants
  - Probiotics
  - Omega 3 fatty acids
  - Supplemental nucleotides
  - AHCC
  - Pegylated-IL-2

**Pharmacological Intervention**
- Beta blockers
- Anti-cortisol
- Antibiotics
- Antiviral
- Anti-inflammatory
- Cytokine therapy

**In-flight Monitoring of Immune Parameters?**

PRE-FLIGHT

LAUNCH

TRANSIT PHASE

CIS-LUNAR STATION/
LUNAR SURFACE OPS

MARS FLYBY or ORBIT/
MARS SURFACE OPS
Spaceflight
Immunologists
NASA JSC
Immunology/Virology Laboratory