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

Brian Crucian, PhD, MT(ASCP)
The Immune System

I Pluripotent Stem Cell

Myeloid Stem Cell

T Lymphocyte

NK Lymphocyte

B Lymphocyte

Plasma Cell

Pluripotent Stem Cell

Lymphoid Stem Cell

B Lymphocyte Plasma Cell

T Lymphocyte

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

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INNER IMMUNITY
• Primary defense
• Immediate
• Non-specific
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Eat microbes

Cause Allergy

Fight Parasites

Direct ‘Right’ Kind of Response

Kill Infected Cells

Fight Cancer

Inflammation

Pathogen-specific Response

Make Antibodies

Keep ‘Control’

Protect you for life!
Immunity and Disease

VIRAL INFECTION
- Meningitis - JC virus - Measles - LCM virus - Adenovirus - Rabies
- Pharyngitis - Adenovirus - Epstein-Barr virus - Cytomegalovirus
- Cardiovascular - Coxsackie B virus
- Hepatitis - Hepatitis virus types A, B, C, D, E
- Skin infections - Varicella zoster virus - Measles
- Sexually transmitted diseases - Herpes simplex type 2 - Human papillomavirus

Eye infections - Herpes simplex virus
- Parainfluenza virus
- Respiratory syncytial virus
- Parrotitis - Mumps virus
- Gingivostomatitis - Herpes simplex type 1
- Pneumonia - Influenza virus, Types A and B
- Parainfluenza virus
- Respiratory syncytial virus
- Adenovirus
- SARS coronavirus

BACTERIAL INFECTION
- Eye infections
- Adenovirus
- Cytomegalovirus
- Typhoid
- Cholera
- Diarrhoeal diseases
- Pneumonia
- Diphtheria
- Whooping cough
- Leprosy
- Plague
- Tuberculosis
- Anthrax

Cardiovascular - Adenovirus - Coxsackie B virus
- Hepatitis - Hepatitis virus types A, B, C, D, E
- Skin infections - Varicella zoster virus - Measles - Rabies
- Sexually transmitted diseases - Herpes simplex type 2 - Human papillomavirus

ALLERGY

SHINGLES
- Blister development
- Initial stage consists of burning pain and sensitized skin
- Blister development resembling chicken pox and fill with pus
- Blister eventually burst, crust over, and heal
- Nerve damage can cause postherpetic neuralgia

CANCER

AUTOIMMUNE DISEASE

Over 100 Different Types of Autoimmune Disorders

Blood
- SLE
- Lupus
- Systemic Lupus Erythematosus
- Hemolytic Anemia

Brain
- Multiple Sclerosis
- Guillain-Barré Syndrome
- Guillain-Barré Disease
- Multiple Sclerosis

Thyroid
- Hashimoto's Disease
- Grave's Disease

GI Tract
- Crohn's Disease
- Ulcerative Colitis
- Diabetes Type I

Nerves
- Peripheral Neuropathy
- Diabetic Neuropathy

Muscles
- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Polymyalgia Rheumatica

Skin
- Psoriasis
- Vitiligo
- Eczema
- Scleroderma

Lung
- Acromegaly
- Wegener's Granulomatosis

Different Types of Autoimmune Disorders
Blood and Saliva Collection - ISS
Plasma Collection - ISS

Return Ambient – 45h Delay

Early ~2 weeks

Mid 2-4 mos

Late R-1-2 days

FD15
FD30
FD60 6 Months Spaceflight
FD120
FD180

Frozen on Orbit

Nutritional Biochemistry - NASA JSC
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

• Peripheral leukocyte distribution in astronauts is relatively normal

- T cell, NK cell function is inhibited by microgravity
- T cell function is reduced in astronauts; appears to be a shift in the activation threshold
- NK cells are disarmed, reduction in lytic molecule content
- B cell function in astronauts appears unaltered (limited data)

• Innate immunocyte function dysregulated during spaceflight

- Plasma cytokine concentrations are altered in astronauts
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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. ("signal two" comes in two forms: B7-1 (CD80) and B7-2 (CD86).)

Graphs showing T cell function under different conditions:

- SEA+SEB
  - n=23
  - Four subpopulations of T cells over time:
    - CD4/69+
    - CD8/69+
    - CD4/69/25+
    - CD8/69/25+

- αCD3/αCD28
  - n=17
  - Four subpopulations of T cells over time:
    - CD4/69+
    - CD8/69+
    - CD4/69/25+
    - CD8/69/25+
NK Cell Function

TARGET CELLS ONLY
1X PBMC (NK:target = 1:6)
10X PBMC (NK:target = 1:1)
20X PBMC (NK:target = 3:1)

CD66 (NK Cells)
CD71 (Target Cells)
P.I. (Viability)
Spaceflight Reduces NK Cell Function

Data expressed as % change from baseline (L-180). NK-cell function did not differ between astronauts and controls at baseline.

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>
</tr>
</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></td>
<td>IL-2</td>
<td>GM-CSF</td>
<td>CCL3/MIP-1 alpha</td>
</tr>
<tr>
<td>TNFα</td>
<td>IL-17</td>
<td></td>
<td>FGF basic</td>
<td>CCL4/MIP-1 beta</td>
</tr>
<tr>
<td>IL-6</td>
<td>IL-4</td>
<td></td>
<td>Tpo</td>
<td>CCL5/RANTES</td>
</tr>
<tr>
<td>IL-8</td>
<td>IL-5</td>
<td></td>
<td>VEGF</td>
<td>CXCL5/ENA-78</td>
</tr>
<tr>
<td></td>
<td>IL-10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Physical Triggers of Immune Response:

- Infectious - Bacterial, viral - Fungal, parasitic
- Toxins - Exogenous - Endogenous
- Food peptides
- Allergens
- Medications
- Auto antigens

Th0: Naive T cells
Th: Helper T cells
Treg: Regulatory T cells

IL: Interleukin

Th17: Extracellular bacteria (e.g., lung, intestine)
Th1: Cell-mediated immunity and inflammation
Th2: Antibody-mediated immunity

Th1: Inflammation
Th2: Anti-inflammatory

Antigen Presenting Cells

TNF-α: Tumor necrosis factor-alpha
IFN-γ: Interferon-gamma
TGF-β: Transforming growth factor-beta

Th1: Intraacellular pathogens - Viruses, bacteria
Th2: Asthma, allergy
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>
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<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>
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<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>
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<tr>
<td>TNFα</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</td>
<td>2.2 ± 0.4</td>
<td>2.0 ± 0.4</td>
<td>1.3 ± 0.1</td>
<td>1.7 ± 0.2</td>
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<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>1.1* ± 0.2</td>
<td>0.3 ± 0.1</td>
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<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>
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<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>
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<tr>
<td>IFNγ</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>
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<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>
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<tr>
<td>IL-17</td>
<td>1.3 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>0.9 ± 0.2</td>
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<td>1.1 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>0.9 ± 0.3</td>
<td>0.9* ± 0.2</td>
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<td>IL-4</td>
<td>0.3 ± 0.1</td>
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<td>3.2 ± 1.7</td>
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<td>IL-5</td>
<td>0.1 ± 0.0</td>
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<td>IL-10</td>
<td>0.2 ± 0.0</td>
<td>0.2 ± 0.1</td>
<td>0.4 ± 0.2</td>
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<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>
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<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>
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<td>FGFβ</td>
<td>13.7 ± 5.4</td>
<td>15.4 ± 5.7</td>
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<td>21.9 ± 5.7</td>
<td>18.5 ± 4.9</td>
<td>12.1 ± 3.7</td>
<td>10.8 ± 2.7</td>
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<td>12.3 ± 4.3</td>
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<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>
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<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>
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<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>
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<tr>
<td>CCL4/MIP-1b</td>
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<td>16.7 ± 2.7</td>
<td>22.3* ± 2.9</td>
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<td>22.2* ± 2.8</td>
<td>24.3 ± 5.1</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

PRE-FLIGHT
- 180
- 45

FLIGHT
Early
Mid
Late

POST-FLIGHT
Early
Late

Collection Time

CORT (nmol/L) +/- SEM
Latent Herpesvirus

**Latent Viral Reactivation**

- **Herpes Simplex**
  - Gingivostomatitis
  - Mild pharyngitis
  - Fever
  - Primary Infection
  - Cold Sore
  - Zoster (shingles)
- **Varicella**
  - Chicken pox
- **Latent virus**
  - Virus transit up peripheral nerve
  - Sensory neuron in dorsal root ganglion
  - Virus transit down peripheral nerve
  - Spinal cord
- **Stress**
  - Activation of virus in neuron
- **Recurrence**
Latent Herpesvirus

- Reactivation in 76% of the crewmembers

- Reactivation in 65% of the crewmembers
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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total events</strong></td>
</tr>
<tr>
<td><strong>Events/person year</strong></td>
</tr>
<tr>
<td>Allergic Reaction</td>
</tr>
<tr>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Upper Respiratory Infection (combination of rhinitis, nasal stuffiness and sneezing)</td>
</tr>
<tr>
<td>Eye Infection</td>
</tr>
<tr>
<td>Herpes Zoster</td>
</tr>
<tr>
<td>Otitis Media/Externa (ear pain, or ear stuffiness+congestion)</td>
</tr>
<tr>
<td>Pharyngitis (sore throat)</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Sinus Infection</td>
</tr>
<tr>
<td>Skin Infection (including scalp pruritis, pus forming wounds on wrist, finger)</td>
</tr>
<tr>
<td>Skin Rash/Hypersensitivity (including skin conditions such as tinea versicolor, dermatitis, rosacea)</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
</tr>
<tr>
<td>Malignancies*</td>
</tr>
<tr>
<td>Autoimmunity*</td>
</tr>
<tr>
<td>Infections, Other*#</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
</tr>
</tbody>
</table>
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

**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*).

<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><strong>VZV</strong></td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>
|          | **HSV1**                   | Positive  
(CT-22; 5.4x10^6 copies per ng total DNA) | Positive  
(CT-15; 1.4x10^9 copies per ng total DNA) | Negative |
| **Skin Lesion** | **VZV**       | Negative | N/A                         | N/A                         |
|          | **HSV1**                   | Positive  
(CT-29; 2.4x10^4 copies per ng total DNA) | N/A                         | N/A                         |
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.

Summary
Immune System Dysregulation During Spaceflight: Potential Countermeasures for Deep Space Exploration Missions


Operational Procedures
Functional Foods
Nutritional Supplements
Nutraceuticals
Probiotics
Pharmacological
Exercise
Vaccination
Behavioral Countermeasures
Bone Countermeasures

Personalized/Precision Medicine

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**
- 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