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

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
Eat microbes
Cause Allergy
Make Antibodies
Direct ‘Right’ Kind of Response
Fight Cancer
Kill Infected Cells
Fight Parasites
Inflammation
Pathogen-specific Response
Keep ‘Control’
Protect you for life!
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
INFECTIOUS DISEASE
CANCER
**Immunity and Disease**

**Viral Infection**
- Meningitis
  - JC virus
  - Measles
  - LCM virus
  - Adenovirus
  - Rabies
- Parotitis
  - Mumps virus
- Gingivostomatitis
  - Herpes simplex type 1
- Pharyngitis
  - Adenovirus
  - Epstein-Barr virus
  - Cytomegalovirus
- Cardiovascular
  - Coxsackie B virus
- Hepatitis
  - Hepatitis virus type A, B, C, D, E
- Skin Infections
  - Varicella zoster virus
  - Herpes zoster virus
  - Smallpox
  - Molluscum contagiosum
  - Human papillomavirus
  - Parvovirus B19
- Nerve fiber
  - Varicella zoster virus
  - Human herpesvirus 6
  - Smallpox
  - Molluscum contagiosum
  - Human papillomavirus

**Shingles**
- Blister development
- Pustule formation
- Blisters eventually burst, crust over, and heal
- Postherpetic neuralgia

**Bacterial Infection**
- Typhoid
- Cholera
- Diarrhoeal diseases
- Pneumonia
- Diphtheria
- Whooping cough
- Plague
- Anthrax
- Tuberculosis

**Autoimmune Disease**
- Over 100 different types of autoimmune disorders
- Sketch of autoimmune disorders

**Allergy**
- Image of a person sneezing

**Cancer**
- Cancer cells growing through normal tissue
- Diagram of cancer cells

**Autoimmune Disorders**
- Multiple Sclerosis
  - Guillain-Barré Syndrome
  - Ankylosing Spondylitis
  - Polyarteritis Nodosa
  - Lupus Nephritis
  - Inflammatory Bowel Disease
  - Crohn's Disease
  - Ulcerative Colitis

**Blood**
- Autoimmune Hemolytic Anemia
- Systemic Lupus Erythematosus
- Rheumatoid Arthritis

**GI Tract**
- Crohn's Disease
- Ulcerative Colitis
- Irritable Bowel Syndrome
- Diabetic Autonomic Neuropathy

**Skin**
- Psoriasis
  - Vitiligo
  - Eczema
  - Scleroderma

**Lung**
- Rheumatoid Arthritis
- Wegener's Granulomatosis
Plasma Collection - ISS

Return Ambient – 45h Delay

Early
~2 weeks
FD15

Mid
2-4 mos
FD120
FD30
FD60
6 Months Spaceflight

Late
R-1-2 days
FD180

Frozen on Orbit

Nutritional Biochemistry
NASA-JSC
• 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

• 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
T Cell Function

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

### SEA+SEB

- CD4/69+
- CD8/69+
- CD4/69/25+
- CD8/69/25+

### αCD3/αCD28

- CD4/69+
- CD8/69+
- CD4/69/25+
- CD8/69/25+

* n = 23
* n = 17
NK Cell Function

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

- Forward Scatter
- Side Scatter
- CD56 (NK Cells)
- CD71 (Target Cells)
- PI (Viability)
Data expressed as % change from baseline (L-180). NK-cell function did not differ between astronauts and controls at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=6)</th>
<th>Astronauts (n=6)</th>
<th>Baseline NKCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pre-Flight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-Flight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Flight</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Spaceflight Reduces NK Cell Function**

**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>IL-4</td>
<td>FGF basic</td>
<td>CCL4/MIP-1 beta</td>
</tr>
<tr>
<td>IL-6</td>
<td>IL-5</td>
<td>Tpo</td>
<td>VEGF</td>
<td>CCL5/RANTES</td>
</tr>
<tr>
<td>IL-8</td>
<td>IL-10</td>
<td></td>
<td></td>
<td>CXCL5/ENA-78</td>
</tr>
</tbody>
</table>
### 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 \( p \leq 0.05 \); \( n=28 \).

<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>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 ± 0.5</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>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>
</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>0.4 ± 0.2</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>FGFβ</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>
</tr>
<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
Latent Herpesvirus

Latent Viral Reactivation

Herpes Simplex
Varicella

Latent virus

Virus transit up peripheral nerve
Sensory neuron in dorsal root ganglion
Virus transit down peripheral nerve

Spinal cord

Cold Sore
Zoster (shingles)

Primary Infection
Recurrence

Stress → Activation of virus in neuron

Gingivostomatitis
Mild pharyngitis fever
Chicken pox
Latent Herpesvirus

Reactivation in 76% of 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>
<th>Total events</th>
<th>Events/person year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Reaction</td>
<td>1</td>
<td>0.06</td>
</tr>
<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

**Total Events/person year:** 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**

**ANTI-HISTAMINE**
- Claratin C
- Zyrtec Z
- Benedryl B
- Prednosone P
- Medrol M
- Hydrocortisone Cream H
- Valtrex X

**STEROID**
- As needed throughout mission

**ANTI-VIRAL**
- HOURS SLEEP SHIFT
  - Flight Day
  - Shuttle Dock to ISS
  - Significant On-Orbit Ops
  - Shuttle Crew EVA
  - Subject EVA

**RASH SEVERITY**
- Oral Herpesviral Reactivation
- Significant Psychological Stress Event
- Progress Docking
- Shuttle Dock
- ATV Docking

**MEDICATIONS KEY**
- Shuttle Dock to ISS
- Blood/Saliva Collection
- Shuttle Dock to ISS
- ATV Docking
- Blood/Saliva Collection
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</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>(CT-22; 5.4x10⁶ copies per ng total DNA)</td>
<td>(CT-15; 1.4x10⁹ copies per ng total DNA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin Lesion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>Negative</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>HSV1</td>
<td>Positive</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>(CT-29; 2.4x10⁴ copies per ng total DNA)</td>
<td></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*
- 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