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

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.
Eat microbes

Cause Allergy

Make Antibodies

Direct ‘Right’ Kind of Response

Kill Infected Cells

Fight Parasites

Fight Cancer

Inflammation

Pathogen-specific Response

Keep ‘Control’

Protect you for life!
CYTOKINE NETWORK

Innate/Inflammatory

Humoral

Th1/Th2

Adaptive/regulatory

Chemokines

Growth Factors

Humoral

Th1/Th2

Adaptive/regulatory

Chemokines
ALTERED MICROBIAL VIRULENCE
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
**VIRAL INFECTION**

- Meningitis: JC virus, Measles, LCM virus, Arbovirus, 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, herpesvirus 6, Smallpox, Molluscum contagiosum, Human papillomavirus, Parvovirus B19, Rubella, Measles, Coxsackie A virus
- Sexually transmitted diseases: Herpes simplex type 2, Human papillomavirus, HIV

**Bacterial Infections**

- Eye Infections: Herpes simplex virus, Adenovirus, Cytomegalovirus
- Parotitis: Mumps, virus

**Cancer**

- Hair shaft: Hair loss
- Skin surface: Initial stage consists of burning pain and sensations
- Widespread immune system: Systemic rash/patches
- Diarrhea: Diarrhea
- Viruses: Varicella zoster virus, Human herpesvirus 6

**Autoimmune Disease**

- Over 100 Different Types of Autoimmune Disorders
  - Blood: SLE, Lupus, Systemic Lupus Erythematosus, Hemolytic Anemia
  - GI Tract: CD, Crohn's Disease, Celiac Disease, Ulcerative Colitis, Diabetic Type 1
  - Nerves: Peripheral Neuropathy, Diabetic Neuropathy
  - Bones: Rheumatoid Arthritis, Ankylosing Spondylitis, Polymyalgia Rheumatica
  - Muscles: Rheumatoid Arthritis, Ankylosing Spondylitis, Polymyalgia Rheumatica

**Autoimmune Infections**

- Allergy:
  - Sensitization:
    - Blister: Allergy
    - Blister: With pus
    - Blister: Eventually burst, crust over
    - Hair shaft: Hair loss
    - Skin surface: Initial stage consists of burning pain and sensations
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**Cancer**

- Cancer cells growing through normal tissue

**SHINGLES**

- Blisters develop resembling chicken pox and fill with clear fluid
- Blisters eventually burst, crust over and heal
- Nerve damage can cause postherpetic neuralgia

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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

INTEGRATED IMMUNE ASSESSMENT
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

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)).

- SEA+SEB, n=23
- αCD3/αCD28, 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)

CD66 (NK Cells)

CD71 (Target Cells)

P.I. (Viability)
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**

**Controls (n=6)**
**Astronauts (n=6)**

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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>VEGF</td>
<td></td>
<td>CXCL5/ENA-78</td>
</tr>
<tr>
<td></td>
<td>IL-10</td>
<td></td>
<td></td>
<td></td>
</tr>
</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>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* ± 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>
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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>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>
</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>IL-13</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>
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<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>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>
<td>0.5 ± 0.3</td>
<td>3.2 ± 1.7</td>
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<td>0.2 ± 0.1</td>
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<tr>
<td>IL-5</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</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>
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<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>
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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>
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<td>VEGF</td>
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<td>CCL2/MCP-1</td>
<td>224 ± 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>
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<td>CCL3/MIP-1a</td>
<td>20.3 ± 5.0</td>
<td>16.6 ± 5.0</td>
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<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>
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**Plasma Cytokine Analysis**

**Chemokines**

![Chemokine Graph](image)

**Anti-Inflammatory Cytokines**

![Anti-Inflammatory Cytokine Graph](image)
Stress Hormones/Circadian Rhythm

Circadian rhythm of Salivary Cortisol in 27 healthy adults

PRE-FLIGHT

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<th>CORT (nmol/L) ± 1 SEM</th>
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<tbody>
<tr>
<td>W</td>
<td></td>
</tr>
<tr>
<td>W+30m</td>
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</tr>
<tr>
<td>W+6h</td>
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<th>CORT (nmol/L) ± 1 SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>W</td>
<td></td>
</tr>
<tr>
<td>W+30m</td>
<td></td>
</tr>
<tr>
<td>W+6h</td>
<td></td>
</tr>
<tr>
<td>W+10h</td>
<td></td>
</tr>
</tbody>
</table>

POST-FLIGHT

<table>
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<th>Collection Time</th>
<th>CORT (nmol/L) ± 1 SEM</th>
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</table>
Latent Herpesvirus

Latent Viral Reactivation

Herpes Simplex
- Gingivostomatitis
- Mild pharyngitis
- Fever

Varicella
- Chicken pox

Latent virus

Virus transit up peripheral nerve

Sensory neuron in dorsal root ganglion

Spinal cord

Cold Sore

Zoster (shingles)

Stress → Activation of virus in neuron

Recurrence
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

4.18
- 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

**Steroid**
- Prednosone P
- Medrol M
- Hydrocortisone Cream H

**Anti-Viral**
- Valtrex X

**Significant On-Orbit Ops**
- Shuttle Dock to ISS

**Urine Collection**
- Shuttle Dock to ISS
- Soyuz Dock to ISS

**Blood/Saliva Collection**
- Soyuz Dock to ISS
- ATV Docking

**Rash Severity**
- Shuttle Crew EVA
- Subject EVA

**HOURS SLEEP SHIFT**
- 1 to 12

**FLIGHT DAY**
- 0 to 30
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></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 <em>(CT-22; 5.4x10^6 copies per ng total DNA)</em></td>
<td>Positive <em>(CT-15; 1.4x10^9 copies per ng total DNA)</em></td>
<td>Negative</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 <em>(CT-29; 2.4x10^4 copies per ng total DNA)</em></td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
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.
Immune System Dysregulation During Spaceflight: Potential Countermeasures for Deep Space Exploration Missions


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

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

Personalized/Precision Medicine

Frontiers in Immunology; June 2018; doi: 10.3389/fimmu.2018.01437
**Immune Countermeasures**

**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?**

<table>
<thead>
<tr>
<th>Pre-flight Launch Transit Phase</th>
<th>Cis-Lunar Station/Lunar Surface Ops</th>
<th>Mars Flyby or Orbit/Mars Surface Ops</th>
</tr>
</thead>
</table>
Spaceflight Immunologists