Countermeasure Options for Immune System Dysregulation

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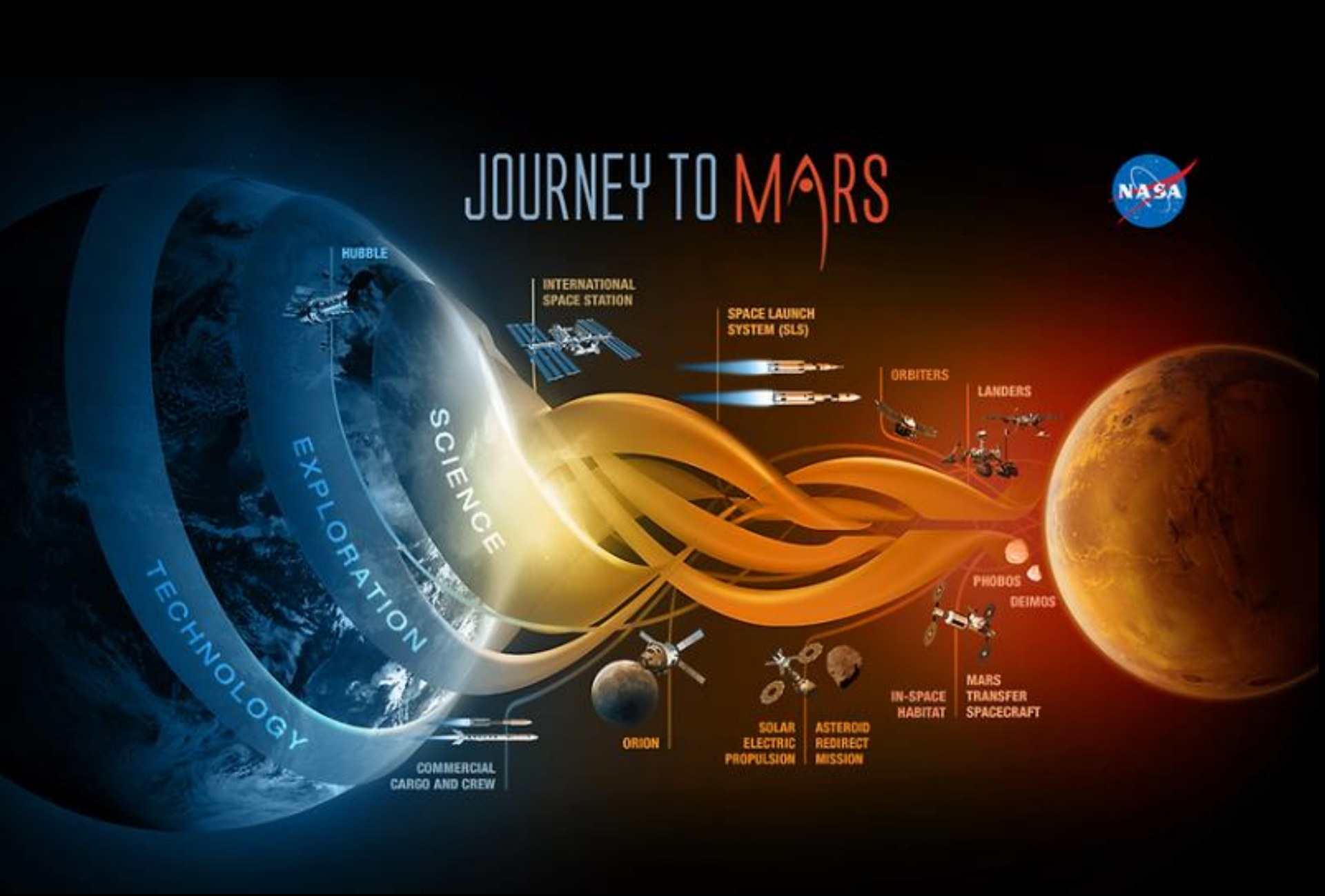
ISGP June 9, 2015


JOURNEY TO MARS
NASA
HUBBLE
INTERNATIONAL SPACE STATION
SPACE LAUNCH SYSTEM (SLS)
ORBITERS
LANDERS
SCIENCE
EXPLORATION
TECHNOLOGY
PHOBOS
DEIMOS
IN-SPACE HABITAT
MARS TRANSFER SPACECRAFT
ORION
SOLAR ELECTRIC PROPULSION
ASTEROID REDIRECT MISSION
COMMERCIAL CARGO AND CREW

Spaceflight Effects on Human Physiology

Muscle and bone weakening

Elevated kidney stone risk

Fluid Redistribution to upper body

Vision Issues

Plasma volume decreases, anemia

Otoliths in inner ear respond differently, eyes become main way to sense motion

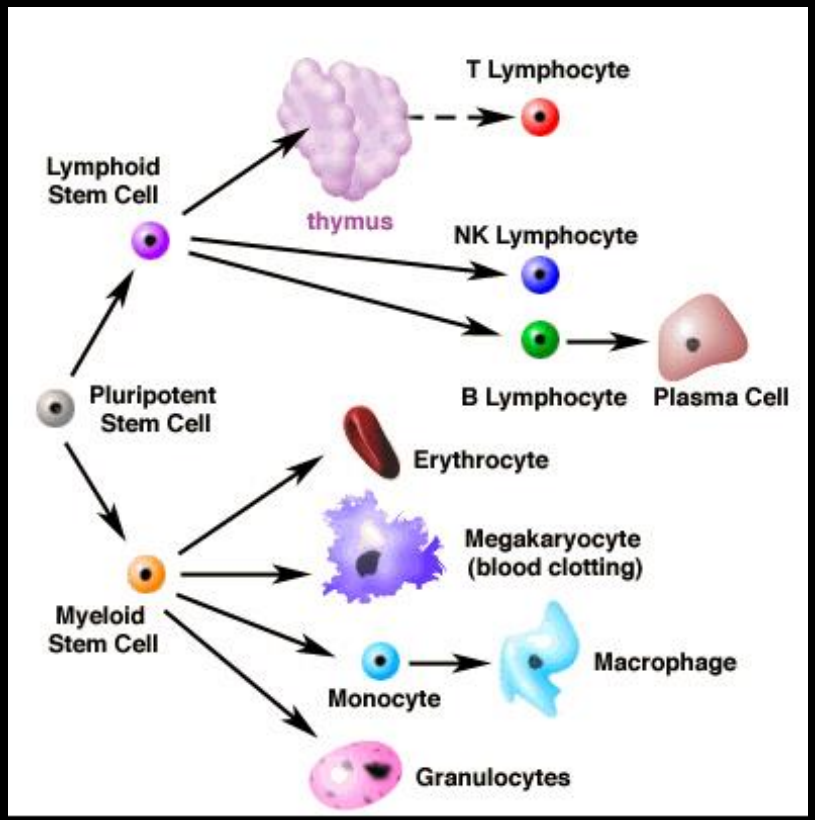
Elevated radiation may increase cancer risk

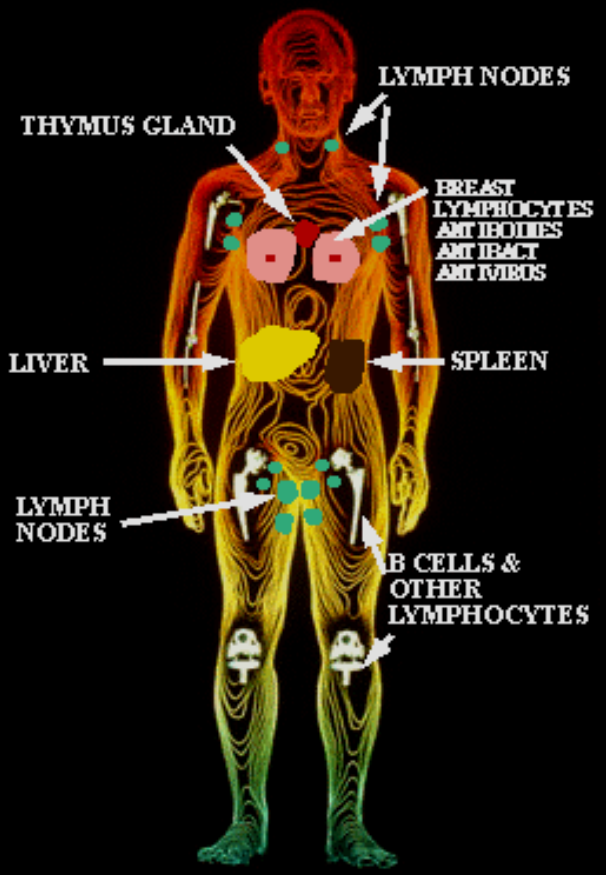
Dysregulation of the immune system

The Immune System

•One of largest tissues in the human body, although largely in fluid state.

•Consists primarily of white blood cells (WBCs) located in lymph nodes and the peripheral blood.





•Responsible for protection against viral and bacterial infection, latent viral reactivation, tumor surveillance, wound healing, etc.

•Dysregulation can result in increased infection rate, malignancy, autoimmunity, allergy, etc.

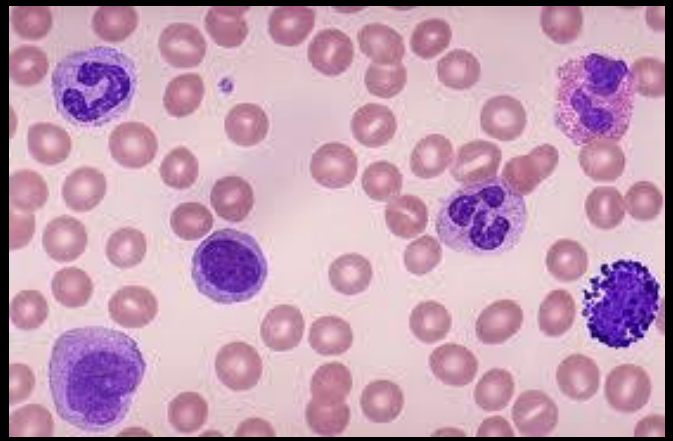
The Immune System

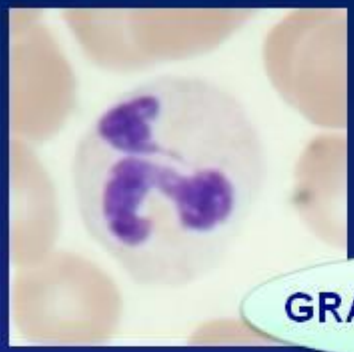
Innate Immunity - primary defense, immediate (constitutively present), non-specific, does not result in memory

Adaptive Immunity - Acquired; secondary defense, delayed (components not constitutively present), antigen-specific, results in memory

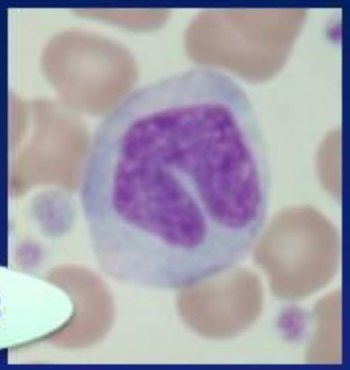
Humoral immunity - Antibody mediated, effector cell B cells/plasmacytes. Antibodies bind specific antigens, signals other cells to engulf, kill and remove that substance from the body

Cell mediated immunity - Cell mediated. Effector cell cytotoxic T lymphocytes which destroy viral infected cells, transplant cells, some tumor cells





WHITE BLOOD CELLS + RED BLOOD CELLS



GRANULOCYTES
MONOCYTES
LYMPHOCYTES

BASOPHILS
NEUTROPHILS
EOSINOPHILS

B CELLS
T CELLS
NK CELLS

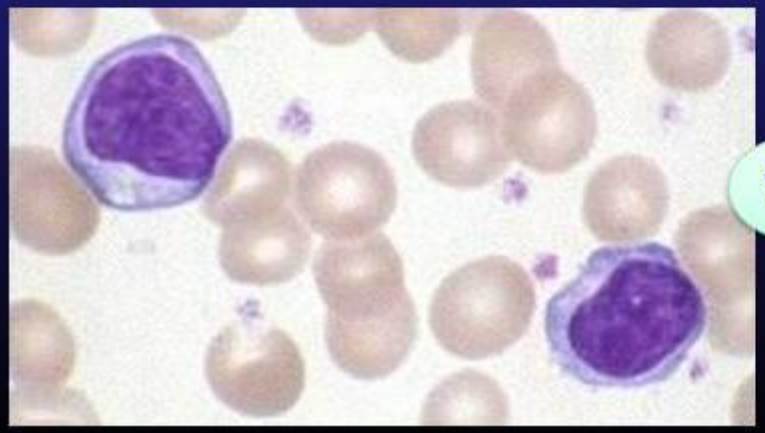
DENDRITIC CELL
MACROPHAGES

CD4+ 'Helper'
CD8+ 'Cytotoxic'

MAST CELL

PLASMA CELLS

Memory
Naive

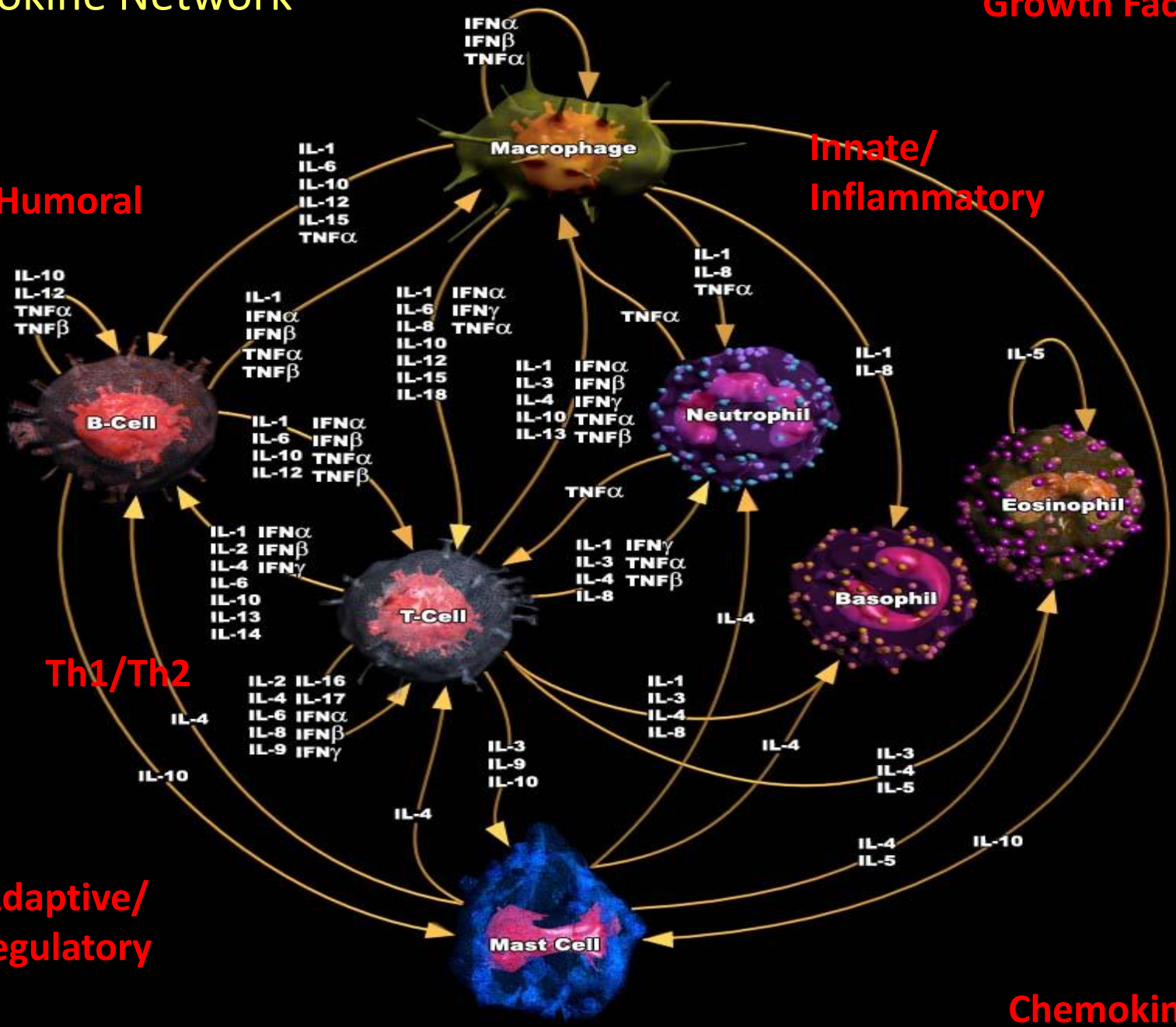


Th1
Th2
Th17
Treg

Memory
Naive

True Naive
Central Memory
Effector Memory
Termial Diff.

The Cytokine Network



NUTRITION

Proper nutrition is a requirement for a normal immune response. Deficiencies in any of several dietary requirements have been linked to diminished immune function and/or clinical illness

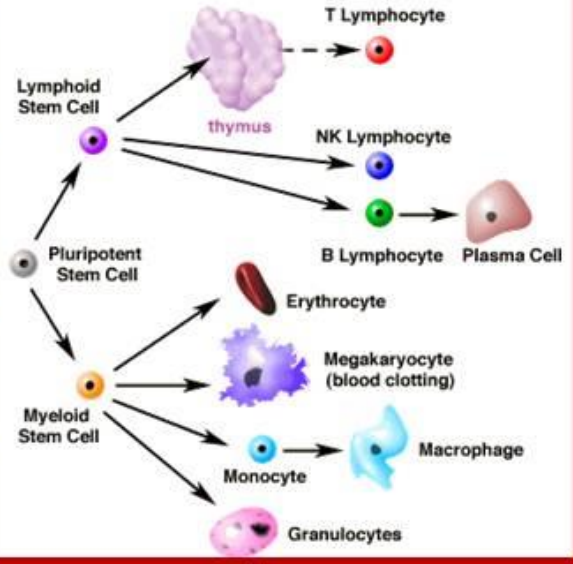
RADIATION

Immune cells generally susceptible to radiation damage. Peripheral T and B cells via apoptosis induction; and via lethal damage to marrow stem cells

BONE

Within the bone marrow cavity, cytokines produced by immune cells also have important effects on regulating bone homeostasis. RANKL, M-CSF, TNF, ILs, and IFNs, affect the differentiation and activity of osteoclasts and bone resorption. During chronic inflammation, the balance of bone modeling and remodeling can be greatly affected.

IMMUNE SYSTEM



NEUROLOGY

A reciprocal flow of information and functional connection exists between the nervous and immune systems. Communication occurs via soluble mediators and cell-cell contacts.

MICROBIOLOGY

Host-pathogen interactions determine susceptibility to disease. Microbial virulence in conjunction with immune status determines the magnitude and outcome of infection

EXERCISE

Research is uncovering a link between moderate, regular exercise and a strong immune system. However, there is also evidence that too much intense exercise can reduce immunity and may even make you sick

STRESS

MICROGRAVITY

RADIATION

ALTERED MICROBIAL VIRULENCE

ALTERED NUTRITION

ALTERED MICROBIOME

ISOLATION, PSYCHOLOGICAL STRESS

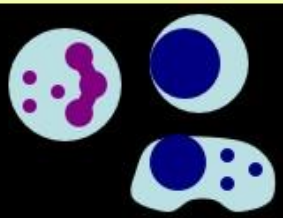
CIRCADIAN MISALIGNMENT

ALTERED IMMUNOCYTE DISTRIBUTION & FUNCTION

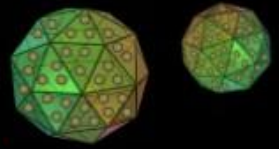
ALTERED CYTOKINE, REDOX, INFLAMMATORY BALANCE

LATENT VIRUS REACTIVATION

CLINICAL INCIDENCE



Th1/
Th2



CANCER

AUTOIMMUNITY

CONSEQUENCES OF PERSISTENT VIRAL REACTIVATION

CHRONIC ALLERGY/ HYPERSENSITIVITY

INFECTIOUS DISEASE

Skylab Data - 1973

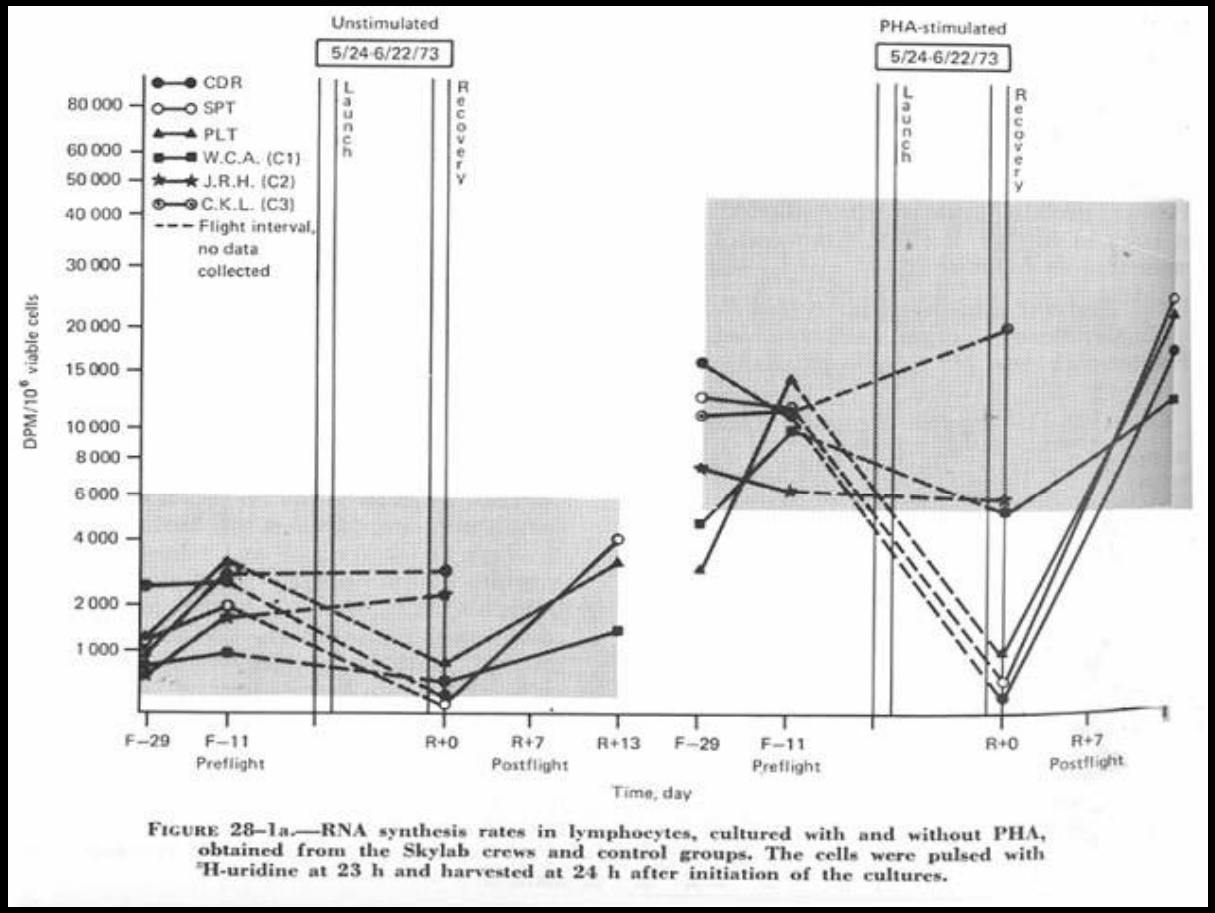
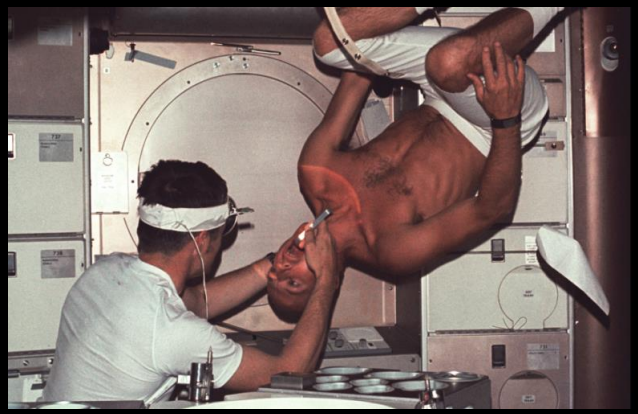


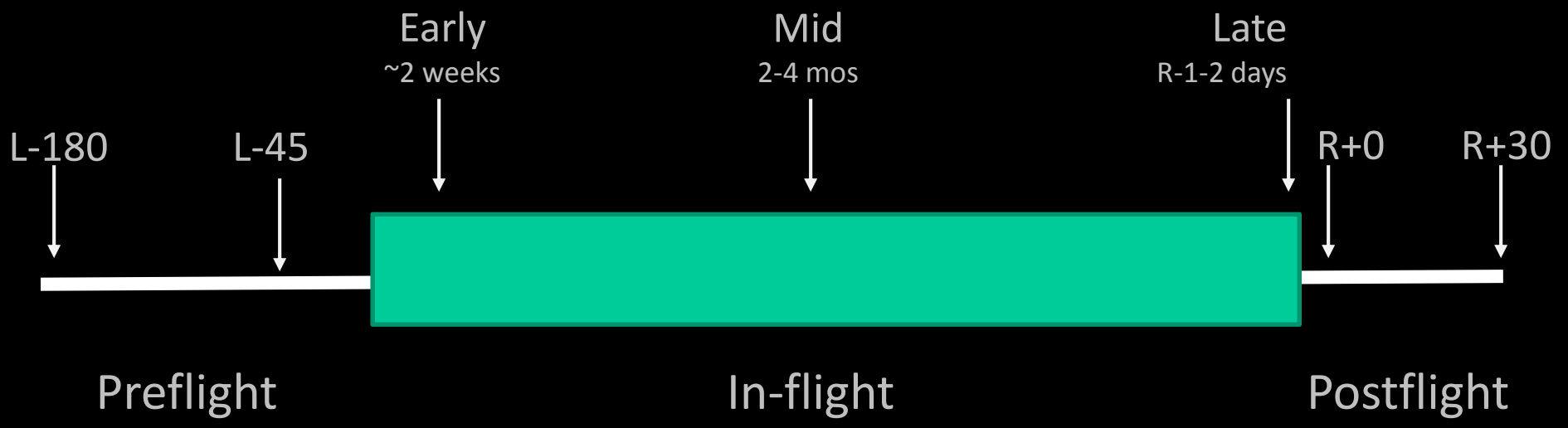
FIGURE 28–1a.—RNA synthesis rates in lymphocytes, cultured with and without PHA, obtained from the Skylab crews and control groups. The cells were pulsed with ^{3}H-uridine at 23 h and harvested at 24 h after initiation of the cultures.

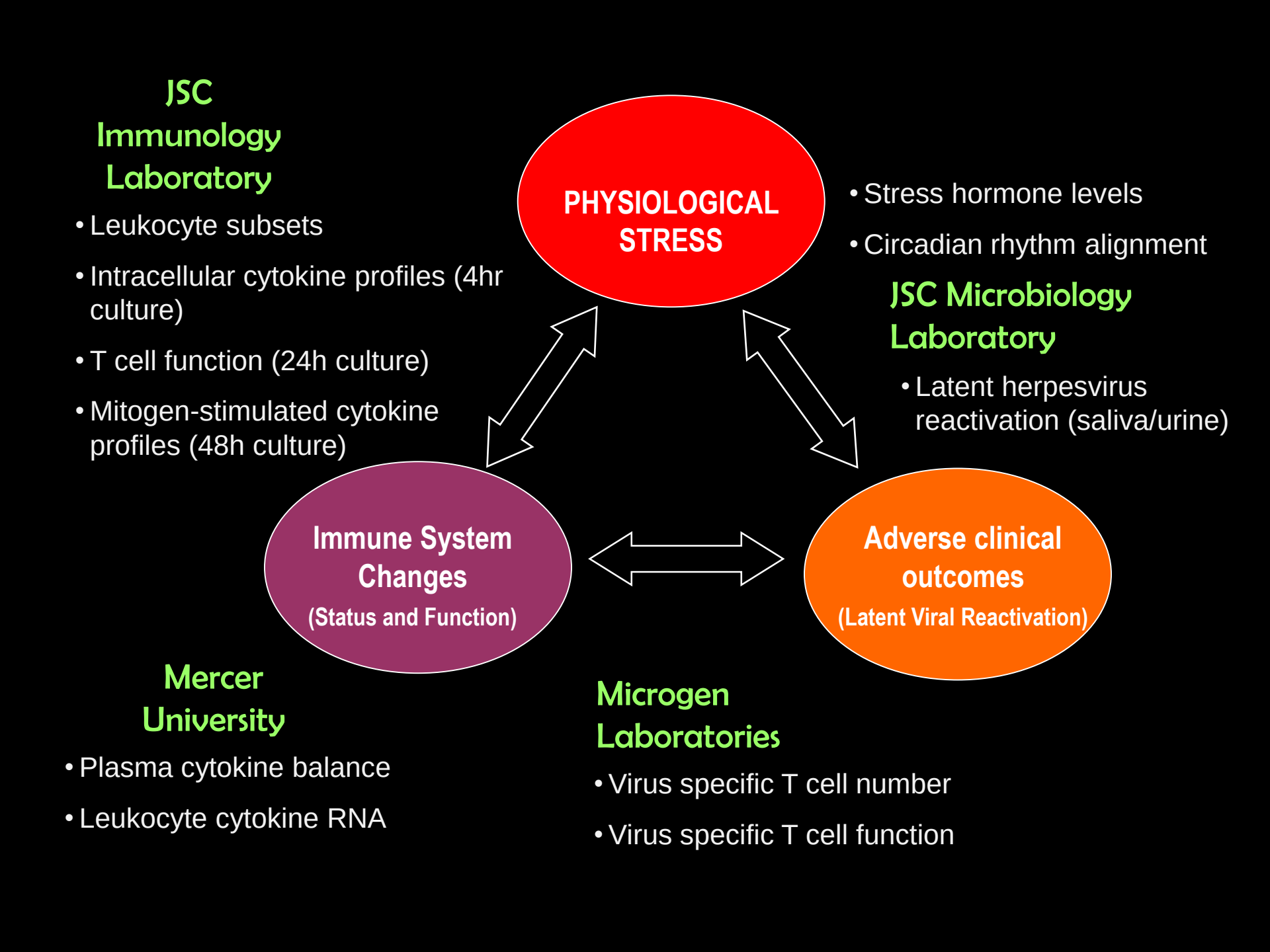


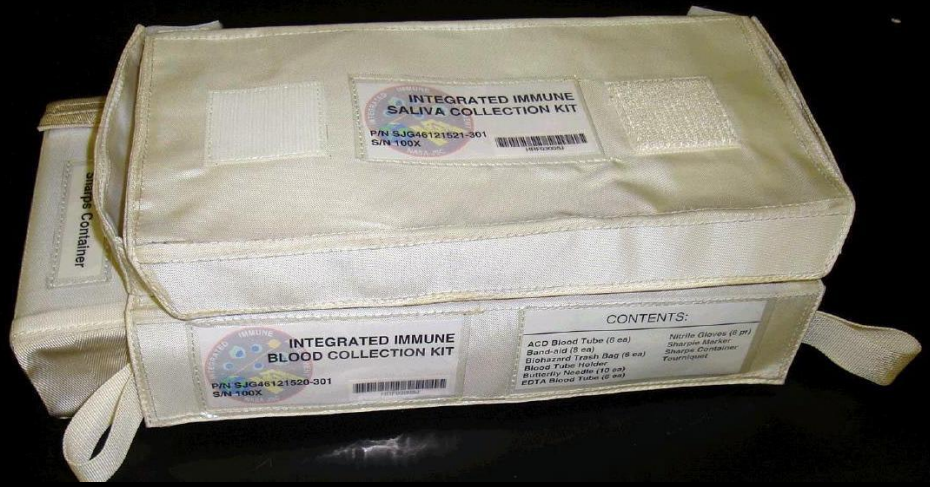
ISS Sample Types:

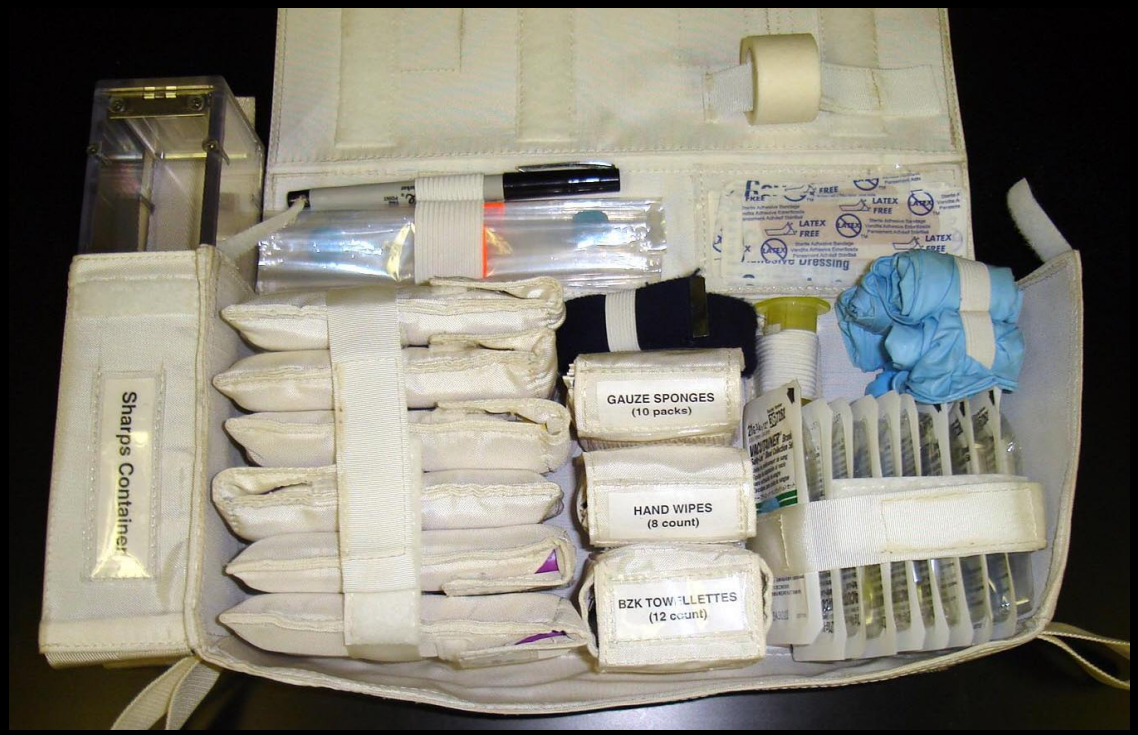
- Blood
- Saliva (Liquid)
- Saliva (Dry)
- Urine
- Health Survey

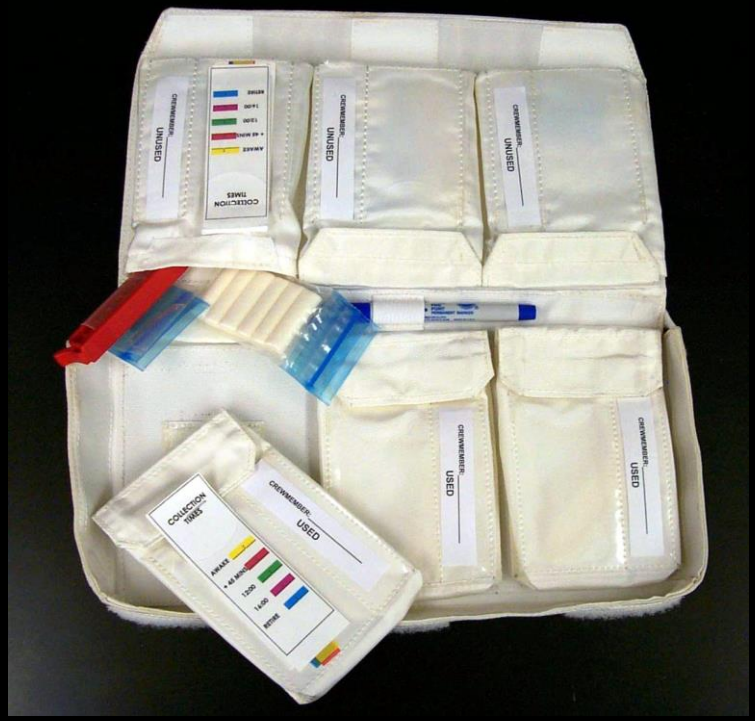
ISS Sample Schedule:




JSC Immunology Laboratory
• Leukocyte subsets
• Intracellular cytokine profiles (4hr culture)
• T cell function (24h culture)
• Mitogen-stimulated cytokine profiles (48h culture)
PHYSIOLOGICAL STRESS
• Stress hormone levels
• Circadian rhythm alignment
JSC Microbiology Laboratory
• Latent herpesvirus reactivation (saliva/urine)
Immune System Changes
(Status and Function)
Adverse clinical outcomes
(Latent Viral Reactivation)
Mercer University
• Plasma cytokine balance
• Leukocyte cytokine RNA
Microgen Laboratories
• Virus specific T cell number
• Virus specific T cell function

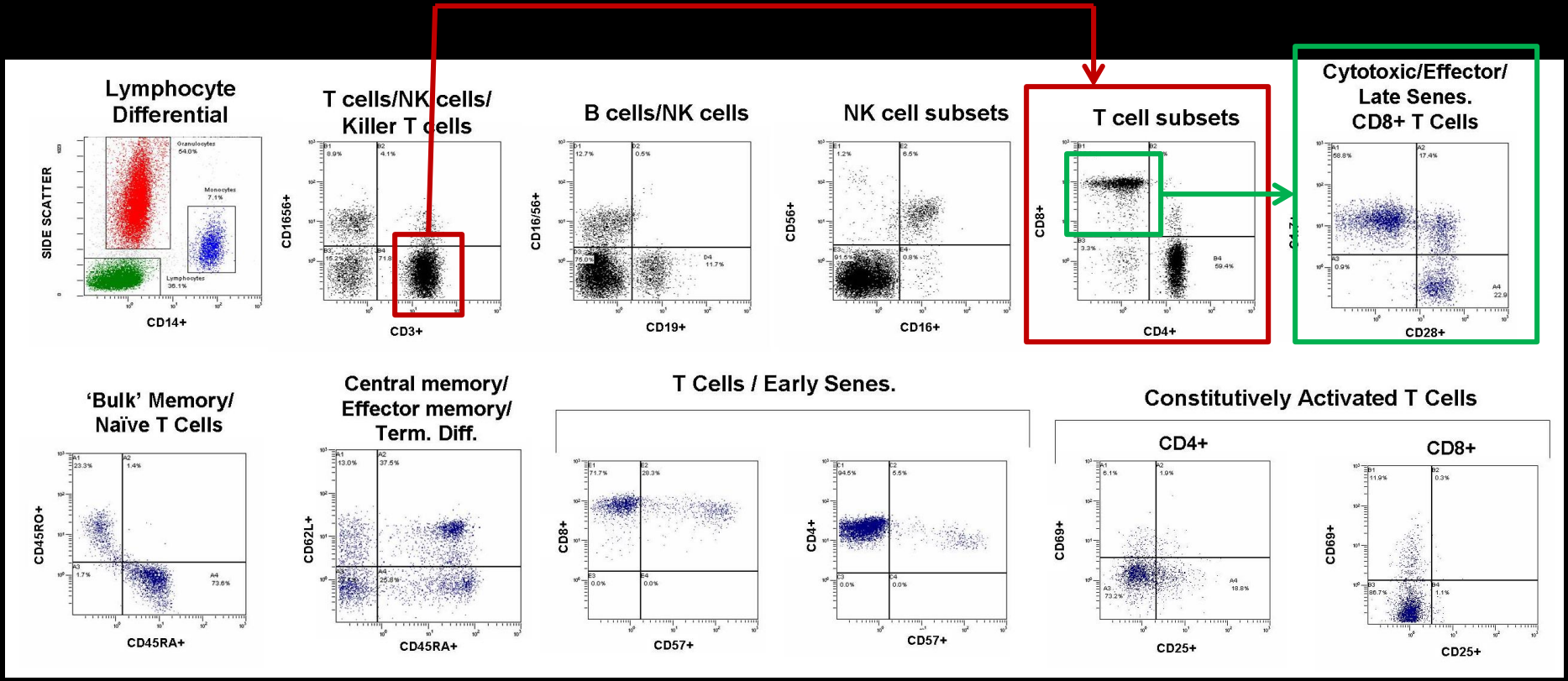

INTEGRATED IMMUNE
SALIVA COLLECTION KIT
P/N SJG46121521-301
S/N 100X
Sharps Container
INTEGRATED IMMUNE
BLOOD COLLECTION KIT
P/N SJG46121520-301
S/N 100X
CONTENTS:
ACD Blood Tube (6 ea)
Band-aid (8 ea)
Biohazard Trash Bag (8 ea)
Blood Tube Holder
Butterfly Needle (10 ea)
EDTA Blood Tube (6 ea)
Nitrile Gloves (6 pr)
Sharpie Marker
Sharps Container
Tourniquet


Sharps Container
GAUZE SPONGES
(10 packs)
HAND WIPES
(8 count)
BZK TOWELETTES
(12 count)
LATEX FREE


CREWMEMBER
UNUSED
CREWMEMBER
USED
COLLECTION TIMES
RETRO
1 HOUR
+ 48 HOURS
ANNEX


esa

Comprehensive Peripheral Phenotype



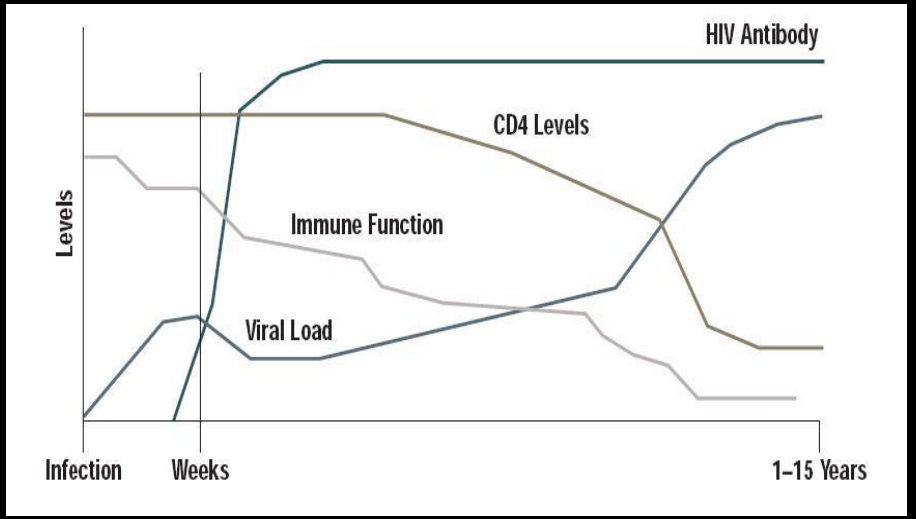
"Diseases are often accompanied by changes in the numbers or function of 'fine' lymphocyte subsets, even if changes in the bulk lymphocyte populations are not evident"

-De Rosa, Roederer, et. al. Nature Medicine 7(2), 245-255, 2001.

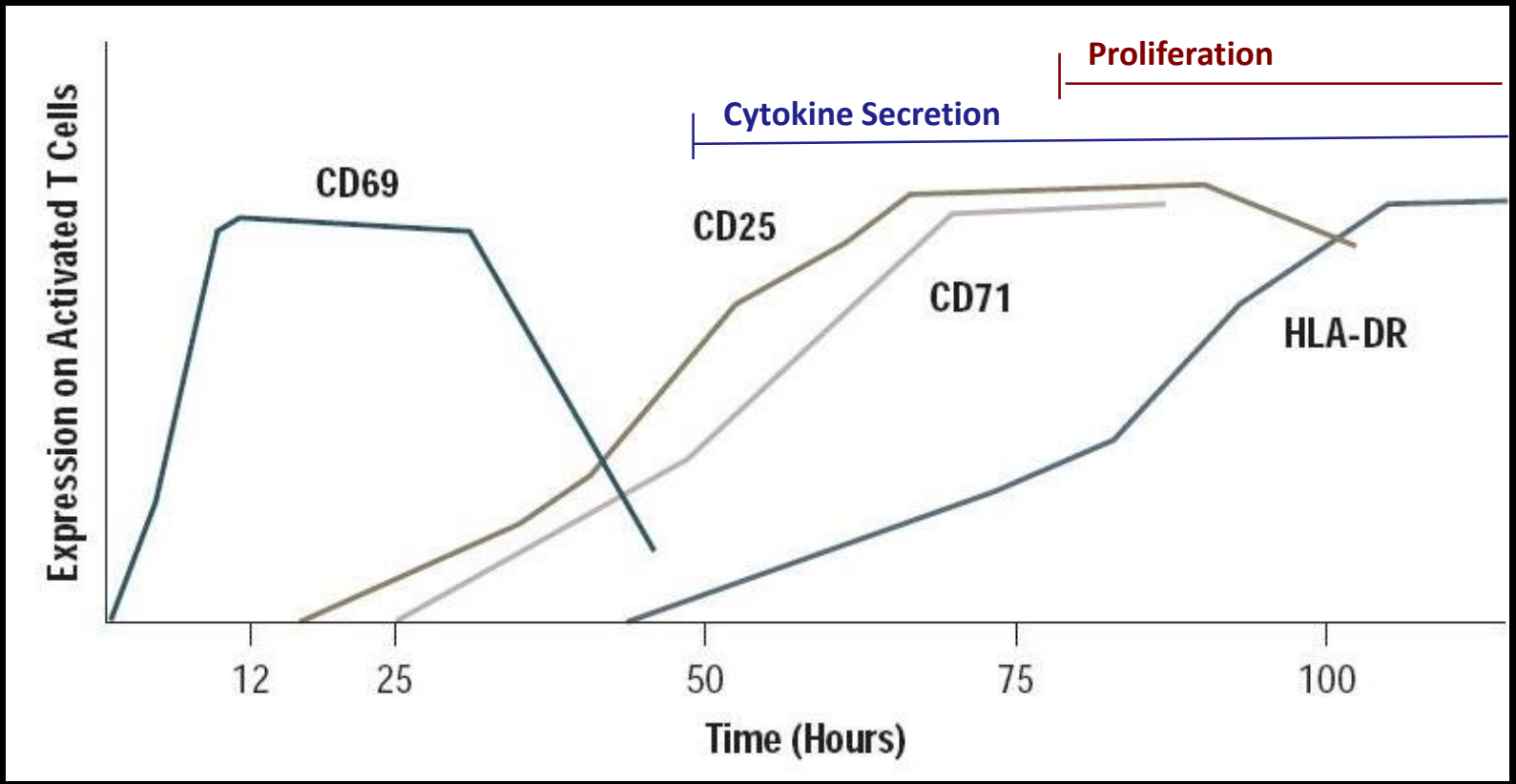
T cell function

- Remove cells from body
- Stimulate cells with mitogens during culture, mimics an in-vivo immune response

T Cell Function vs. Disease

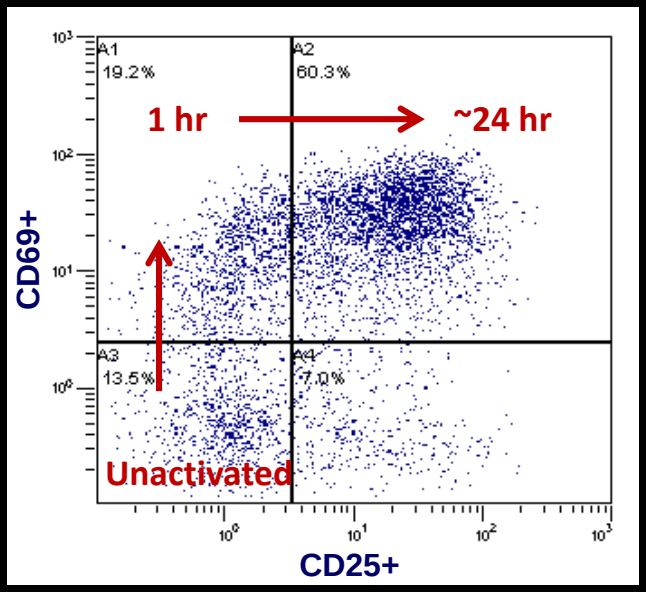


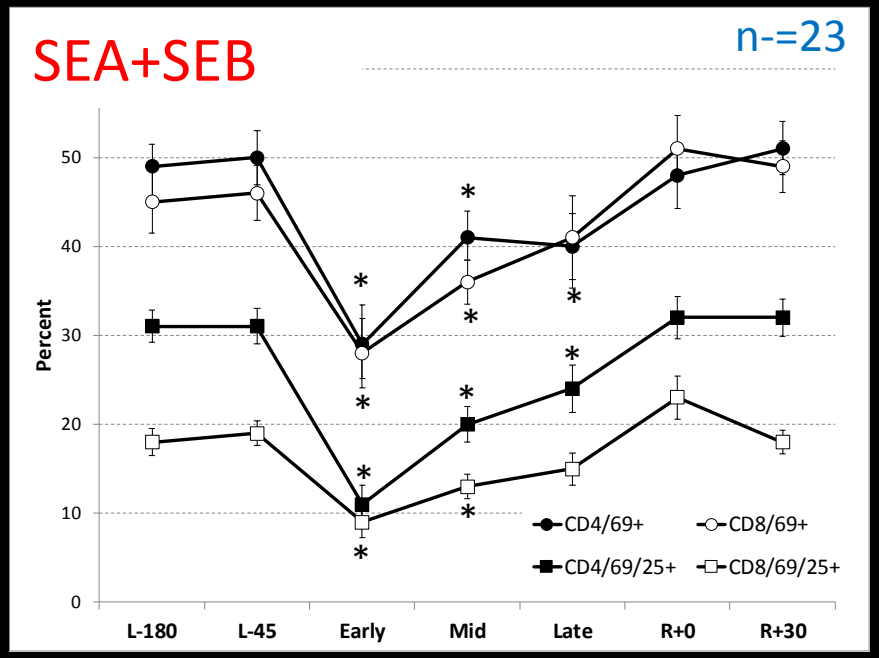
Kinetics of T Cell Activation

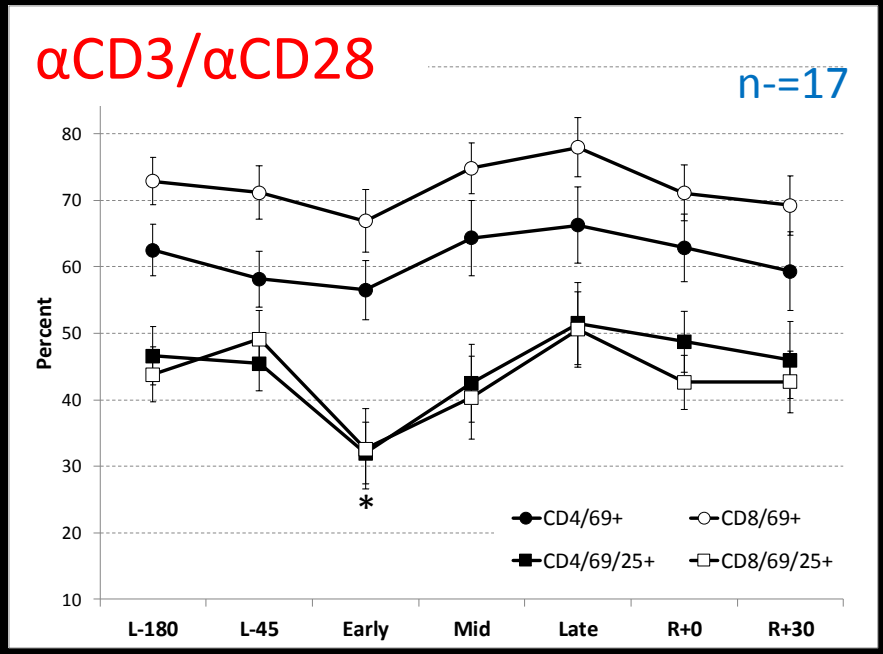


T Cell Function: Early Blastogenesis

(24hr Culture)

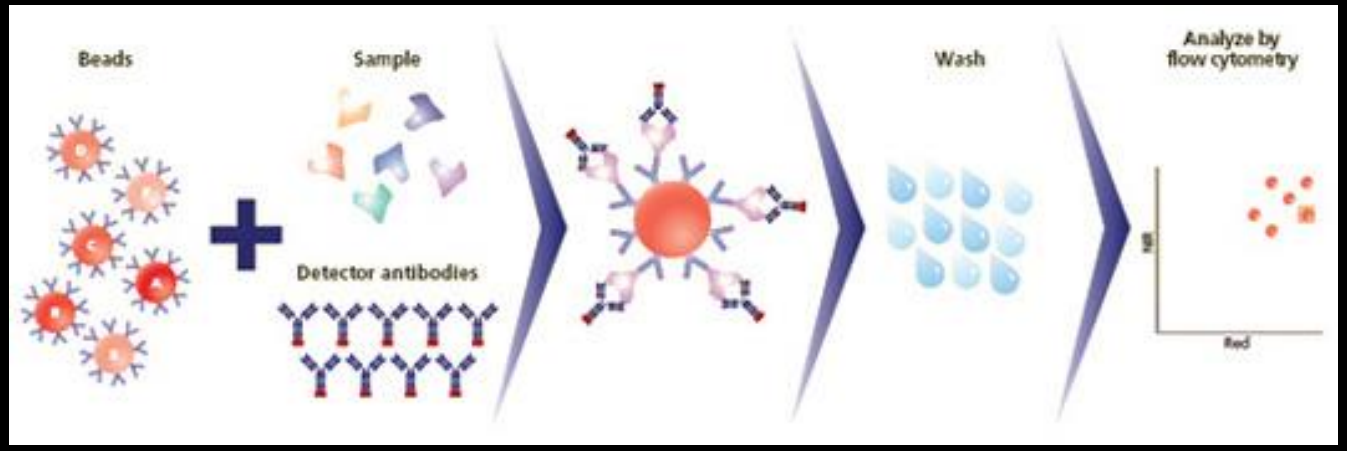




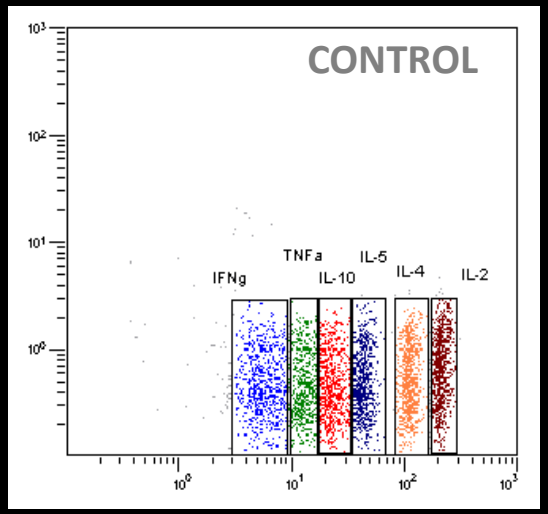


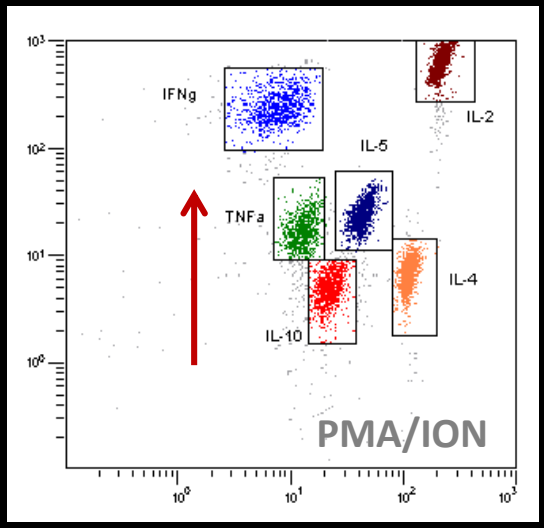
T cell function (early blastogenesis) data, expression of either CD69, or CD69/CD25 dual following 24hr culture in the presence of (A) staphylococcal enterotoxin A and B; or (B) antibodies to CD3 and CD28. Data are presented as mean ± standard error. Significance was evaluated by comparing all other data points to L-180 baseline data. Significant differences ($p \leq 0.05$) are indicated (*). Sample size for all data is 19 ISS astronaut subjects

Secreted Cytokine Profiles: Detection by Cytometric Bead Array



- Stimulate cells in the presence of any mitogen (anti-3/28, PMA-I, LPS)
- Incubate for 48 hours
- Isolate and purify supernatants
- Freeze for batch analysis
- Analyze for cytokine concentrations by CBA





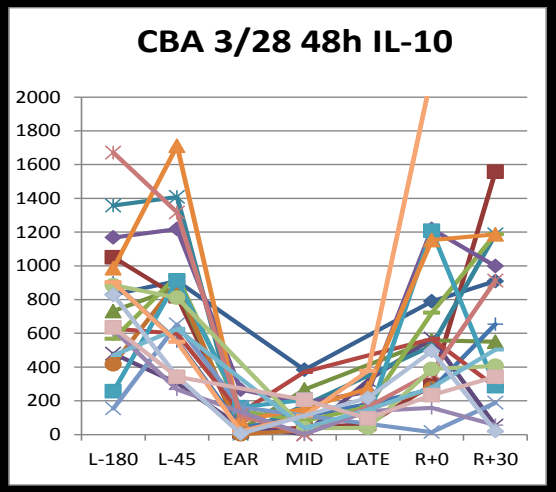
Cytokine concentration

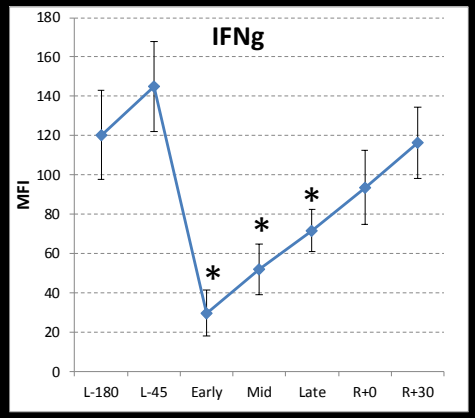
Bead populations

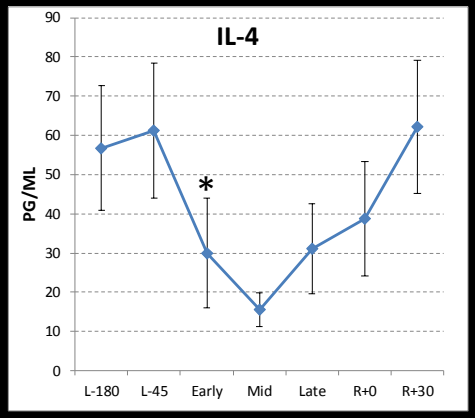
Secreted Cytokine Profiles: Mean ISS Data (n=17)

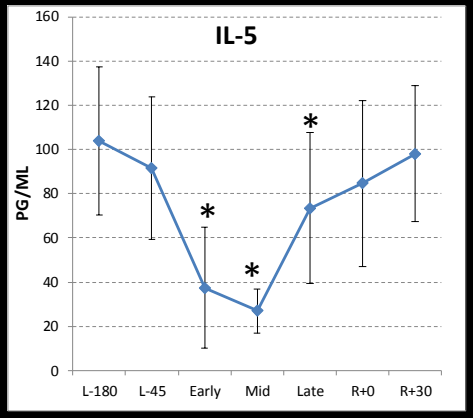
48hr Culture – anti CD3/CD28 Stimulation

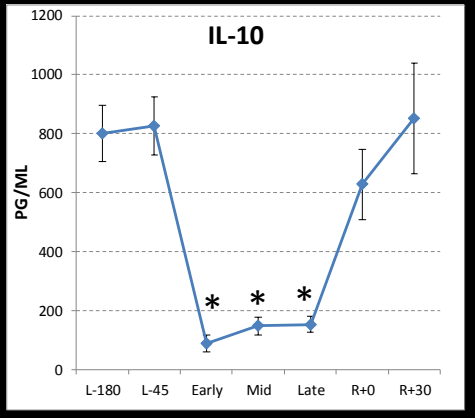
Mean secreted cytokine levels following mitogenic stimulation. Data are expressed mean concentration in pg/ml ± SEM. * indicates statistically significant difference p≤0.05. Significance was evaluated by comparing all other data points to L-180 baseline data. Significant differences (p≤ 0.05) are indicated (*). Sample size for all data is 19 ISS astronaut subjects

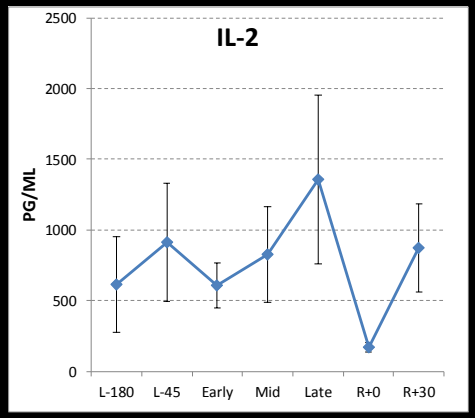


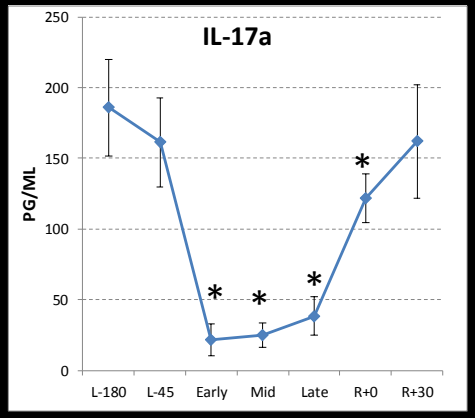


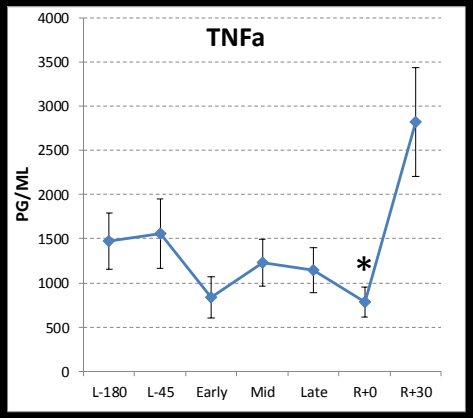


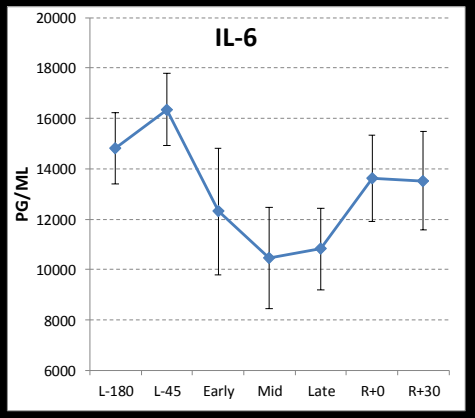






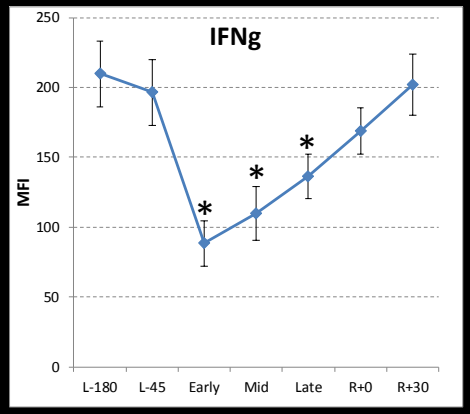


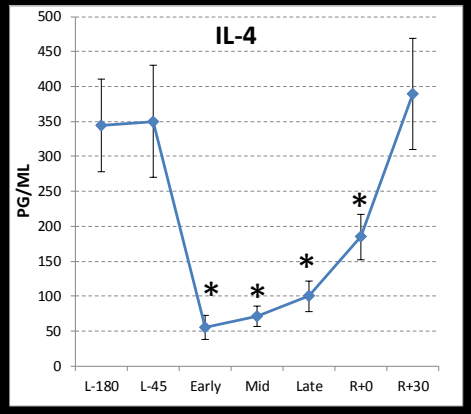


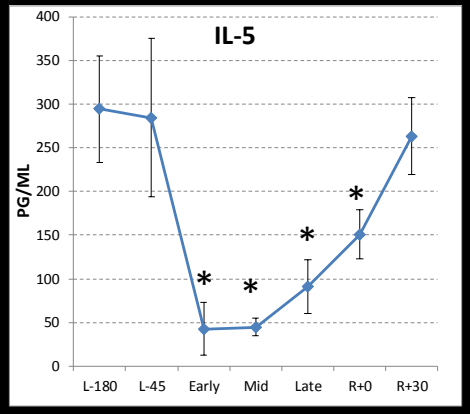


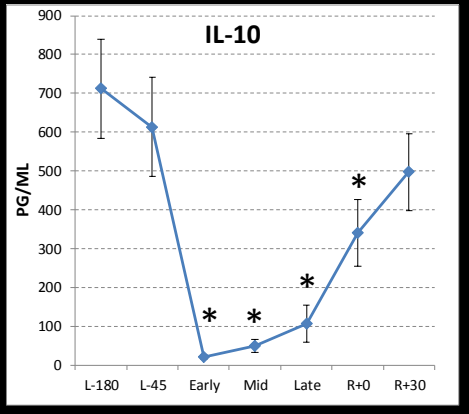
Secreted Cytokine Profiles: Mean ISS Data (n=23)

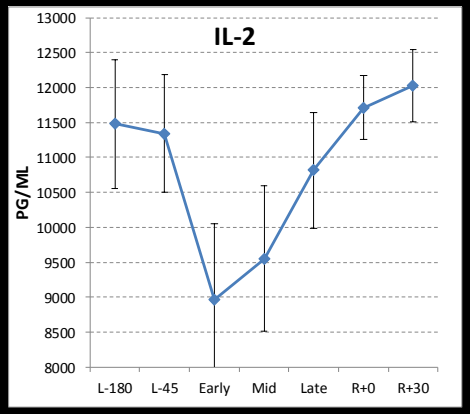
48hr Culture – PMA/I Stimulation

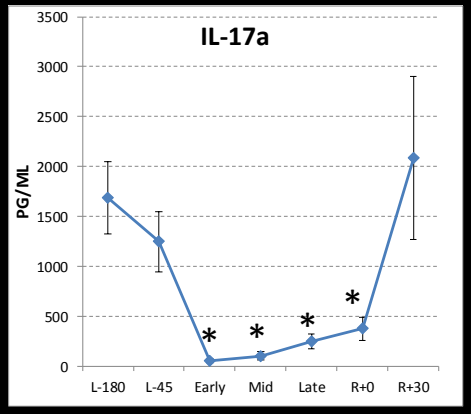


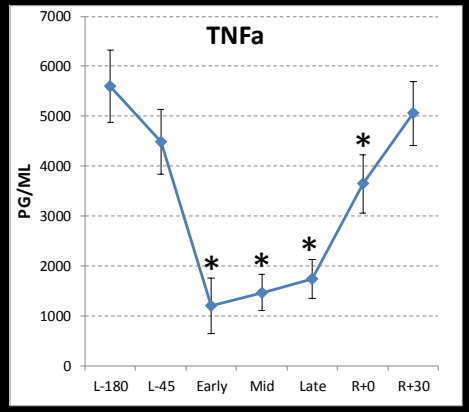


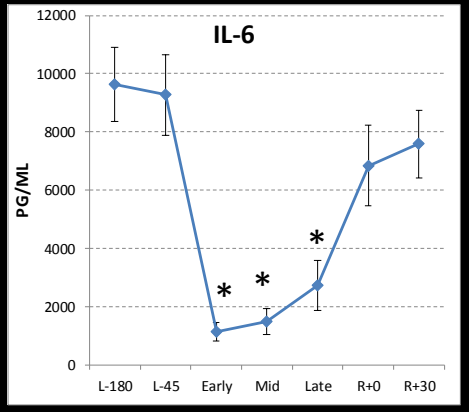


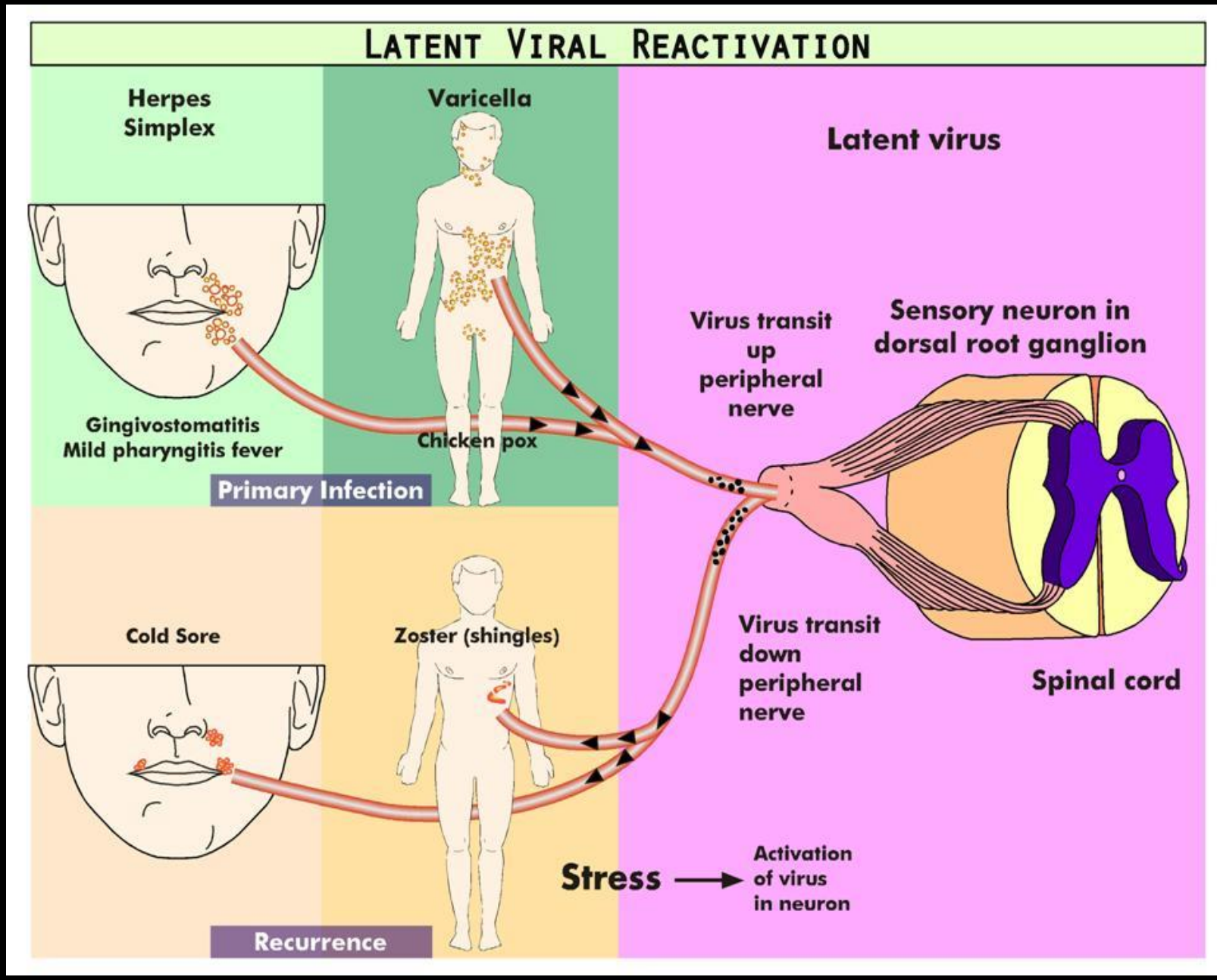




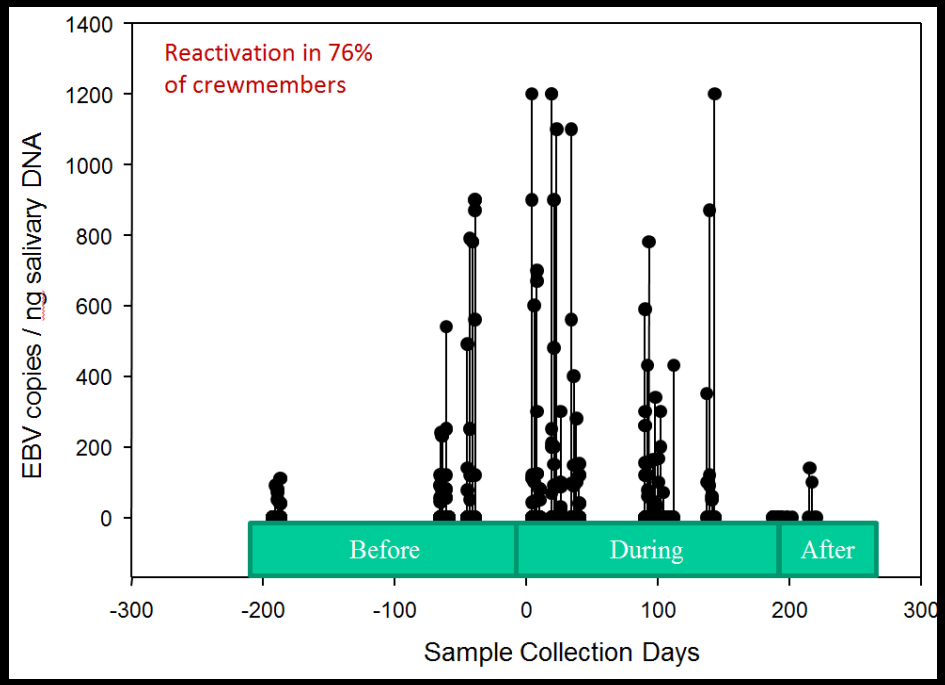


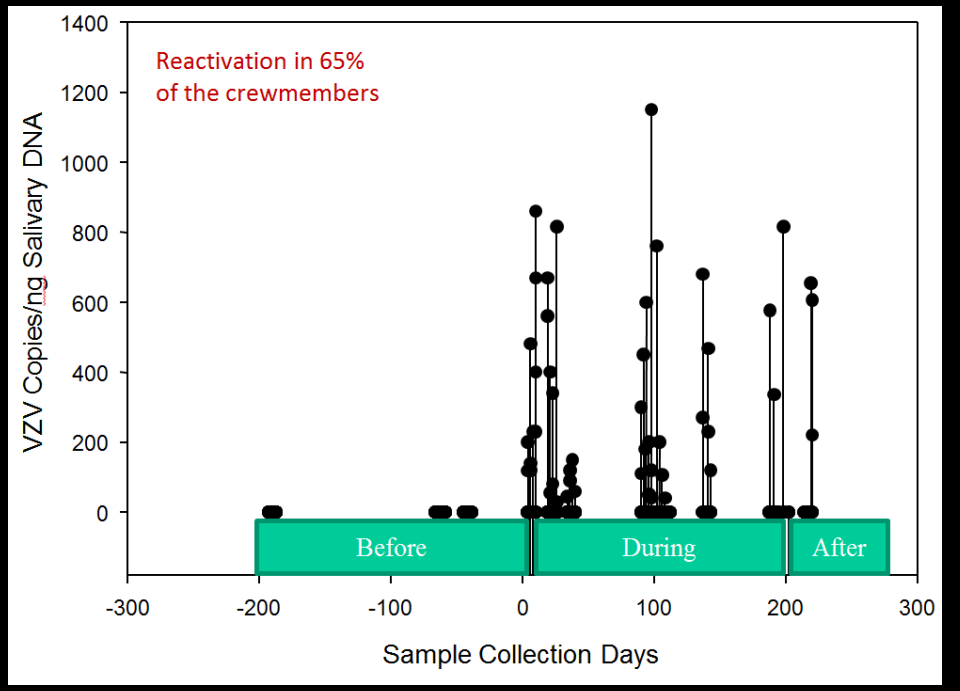




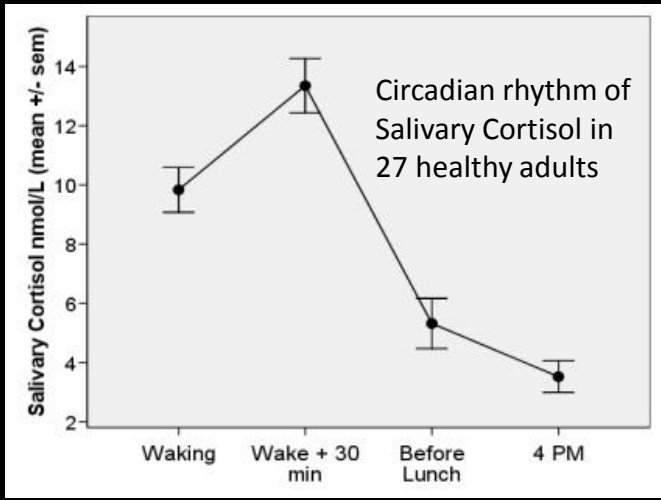

LATENT VIRAL REACTIVATION
Herpes Simplex
Varicella
Latent virus
Virus transit up peripheral nerve
Sensory neuron in dorsal root ganglion
Gingivostomatitis
Mild pharyngitis fever
Chicken pox
Primary Infection
Cold Sore
Zoster (shingles)
Virus transit down peripheral nerve
Spinal cord
Stress
Activation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

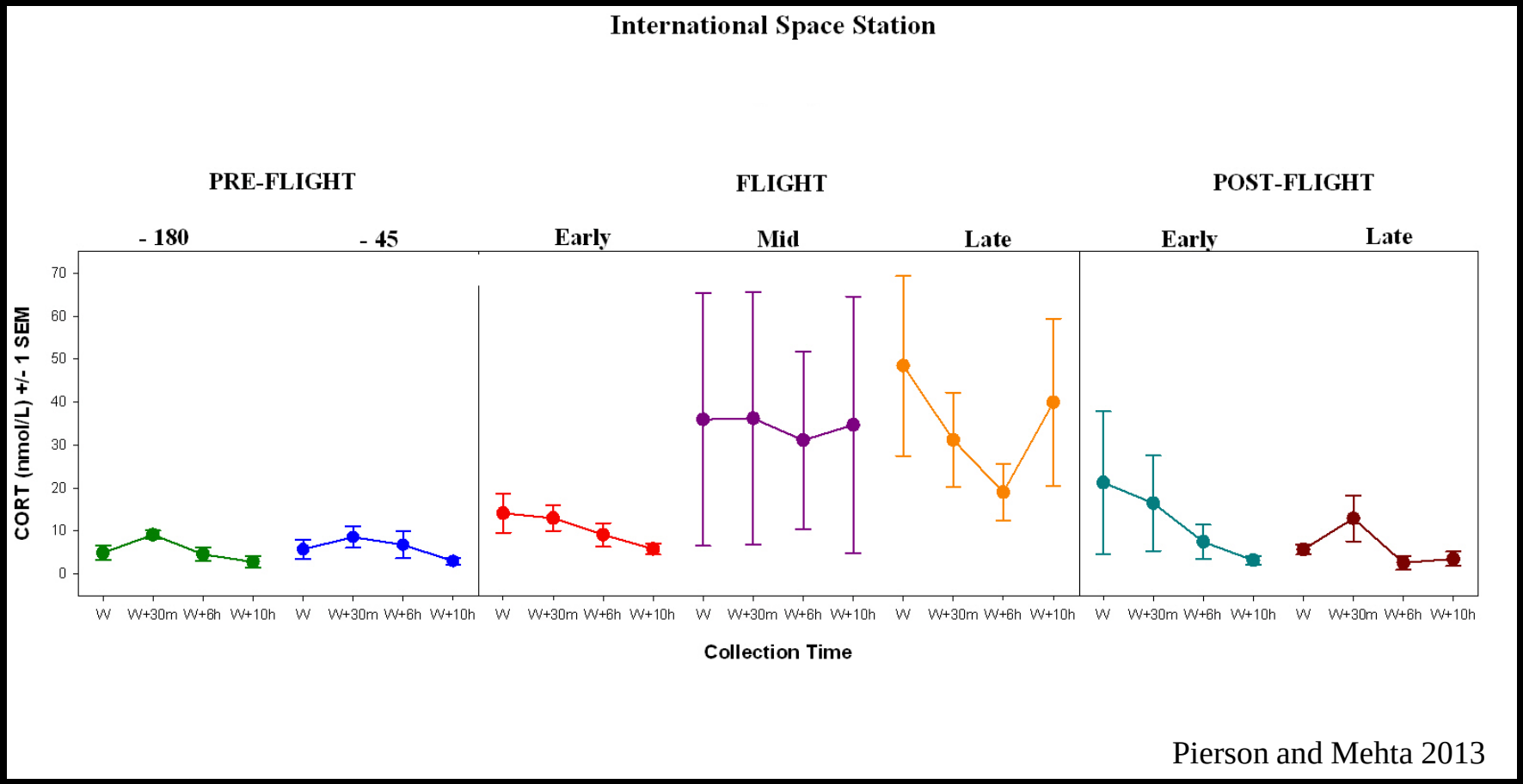
Latent Herpesvirus Reactivation in ISS Crewmembers





Circadian Misalignment in ISS Crewmembers





Pierson and Mehta 2013

Plasma Cytokine Analysis

SMO-018

Early
~2 weeks

FD15

FD30

FD60

Mid
2-4 mos

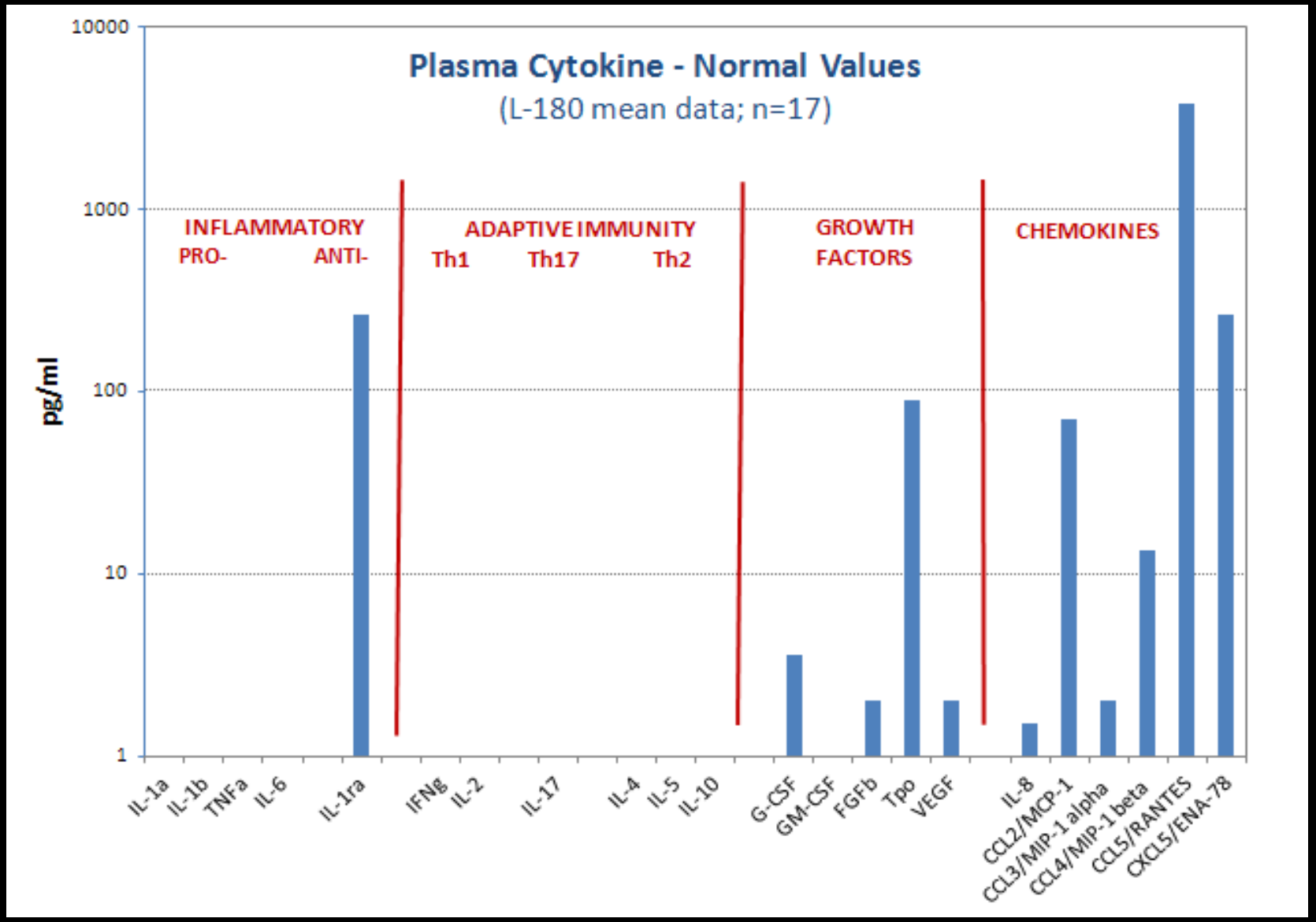
FD120

FD180

Late
R-1-2 days

SMO-016

Mean Baseline Cytokine Concentrations



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.

			Spaceflight						
Cytokine	**L-180**	**L-45**	**FD15**	**FD30**	**FD60**	**FD120**	**FD180**	**R+0**	**R+30**
IL-1a	0.3 ± 0.1	0.4 ± 0.3	0.9 ± 0.5	0.3 ± 0.1	2.4 ± 1.9	0.6 ± 0.2	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
IL-1b	0.4 ± 0.1	0.7 ± 0.3	1.5 ± 1.0	0.8 ± 0.3	0.9 ± 0.5	1.3 ± 0.9	1.1 ± 0.8	0.5 ± 0.2	0.8 ± 0.3
TNFa	1.4 ± 0.1	1.4 ± 0.1	3.2 ± 1.0	**2.0*** ± 0.3	**2.1** ± 0.4	2.2 ± 0.5	2.0 ± 0.4	1.3 ± 0.1	1.7 ± 0.2
IL-6	0.3 ± 0.1	0.3 ± 0.1	0.5 ± 0.2	0.3 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	**1.1*** ± 0.2	0.3 ± 0.1
IL-8	2.0 ± 0.3	2.1 ± 0.3	**8.1*** ± 2.1	**7.9*** ± 2.3	**7.7*** ± 1.7	**7.3*** ± 2.1	**6.9*** ± 2.3	2.1 ± 0.3	2.3 ± 0.4
IL-1ra	383 ± 40	370 ± 35	**567*** ± 65	**563*** ± 80	**638*** ± 101	**728*** ± 129	**661*** ± 85	**682*** ± 118	568 ± 146
IFNg	0.8 ± 0.2	0.8 ± 0.2	0.6 ± 0.1	0.7 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.7 ± 0.3	**0.5*** ± 0.1	0.7 ± 0.2
IL-2	2.2 ± 0.6	**1.8*** ± 0.5	**1.7*** ± 0.5	2.6 ± 0.8	2.4 ± 0.7	2.5 ± 0.7	2.4 ± 0.8	2.4 ± 0.7	2.7 ± 0.9
IL-17	1.3 ± 0.3	1.1 ± 0.3	0.9 ± 0.2	1.0 ± 0.2	1.1 ± 0.3	1.1 ± 0.2	0.9 ± 0.3	**0.9*** ± 0.2	0.9 ± 0.2
IL-4	0.3 ± 0.1	0.5 ± 0.3	3.2 ± 1.7	0.3 ± 0.2	1.4 ± 0.7	2.1 ± 1.5	1.6 ± 1.2	0.4 ± 0.2	0.2 ± 0.1
IL-5	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
IL-10	0.2 ± 0.0	0.2 ± 0.1	0.4 ± 0.2	0.2 ± 0.0	0.2 ± 0.0	0.4 ± 0.2	0.2 ± 0.0	0.3 ± 0.1	0.4 ± 0.1
G-CSF	7.2 ± 1.9	7.0 ± 1.7	7.0 ± 1.8	4.5 ± 0.8	7.6 ± 2.0	14.7 ± 7.8	9.8 ± 3.2	**10.3*** ± 2.8	5.9 ± 1.4
GM-CSF	0.6 ± 0.3	0.3 ± 0.1	3.4 ± 1.9	**1.9*** ± 0.8	2.7 ± 1.3	2.8 ± 1.9	2.7 ± 1.9	0.7 ± 0.4	0.7 ± 0.4
FGFb	13.7 ± 5.4	15.4 ± 5.7	11.8 ± 3.3	21.9 ± 5.7	18.5 ± 4.9	12.1 ± 3.7	10.8 ± 2.7	11.7 ± 3.8	12.3 ± 4.3
Tpo	140 ± 16	146 ± 18	**184*** ± 18	**189*** ± 30	**191*** ± 22	**196*** ± 28	**221*** ± 24	141 ± 17	133 ± 16
VEGF	5.8 ± 0.9	6.2 ± 1.3	**10.9*** ± 1.9	**15.8*** ± 4.9	**11.3*** ± 1.7	**12.5*** ± 3.5	**11.7*** ± 1.9	5.1 ± 1.0	5.5 ± 0.9
CCL2/MCP-1	72.4 ± 6.8	78.5 ± 7.7	71.7 ± 5.4	66.0 ± 5.8	77.0 ± 7.0	84.0 ± 7.0	87.0 ± 7.7	**124*** ± 18.1	**90*** ± 7.5
CCL3/MIP-1a	20.3 ± 5.0	16.6 ± 5.0	25.9 ± 8.1	15.0 ± 4.4	19.1 ± 6.6	22.7 ± 7.4	21.7 ± 8.6	19.4 ± 6.3	18.1 ± 5.5
CCL4/MIP-1b	16.2 ± 2.2	16.7 ± 2.7	**22.3*** ± 2.9	**20.2*** ± 2.5	**22.2*** ± 2.8	24.3 ± 5.1	**21.6*** ± 3.3	17.3 ± 2.3	19.3 ± 4.0
CCL5/RANTES	3613 ± 263	3292 ± 246	3618 ± 202	3746 ± 195	3575 ± 185	3818 ± 217	4030 ± 202	3410 ± 266	3623 ± 219
CXCL5/ENA-78	231 ± 58	367 ± 219	**2065*** ± 371	**1858*** ± 310	**2015*** ± 360	**1749*** ± 309	**1860*** ± 388	190 ± 48	202 ± 55

Clinical Incidence onboard ISS?

- A definitive tabulation in the literature is lacking, although various NASA activities have created incidence numbers (Clinical Finding Forms, etc.)
- Inability to confirm diagnoses
- Restricted to electronic/remote examination
- Treatment options limited
- Data privacy restricted
- Missions vary in workload, stress
- Surgeons may record data differently
- Crew may be reluctant to report medical events

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ASTRONAUTS

Don't Sneeze in Space: When Astronauts Get Sick

A small problem on Earth can be a very big one in space. How science is trying to cut the risk

By Jeffrey Kluger | Oct. 22, 2012 | 14 Comments

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Few people had a worse time in space than the crew of Apollo VII. It wasn't just the 11 days they spent in orbit in 1968 test-driving the new — and decidedly cramped — Apollo command module. That's what they'd trained for, after all. What they hadn't banked on was that they'd all contract serious head colds — first Wally Schirra, the veteran commander, then his rookie crewmates Walt Cunningham and Donn Eisele. All three men grew cranky, snappish and downright mutinous, even breaking mission rules by refusing to wear their helmets during re-entry, lest their already clogged ears pop painfully. Schirra, who had announced in advance that Apollo VII would be his last mission, retired and went on to become a pitchman for, yes, the cold medicine Actifed. Cunningham and Eisele, who had been in line for

Time & Life Pictures/Getty Images

- Spacecraft a perfect 'petri dish' for germs (confined space, recycled air, touching common surfaces with less opportunity to wash)
- Aerosolized germs (microdroplets) do not settle out due to gravity
- Immune system inhibited, microbes more virulent

ISS Incidence Tabulation

Data tabulated from 37 long-duration ISS crewmembers
(Exp. 1-28/29; totals 16.63 person flight years)

Medical Conditions	Total events	Events/ person year
Allergic Reaction	1	0.06
Anaphylaxis	0	---
Upper Respiratory Infection (combination of rhinitis, nasal stuffiness and sneezing)	5	0.301
Eye Infection	0	---
Herpes Zoster	5	0.301
Otitis Media/Externa (ear pain, or ear stuffiness+congestion)	17	1.022
Pharyngitis (sore throat)	1	0.06
Sepsis	0	---
Sinus Infection	0	---
Skin Infection (including scalp pruritis, pus forming wounds on wrist, finger)	5	0.301
Skin Rash/Hypersensitivity (including skin conditions such as tinea versicolor, dermatitis, rosacea)	23	1.383
Urinary Tract Infection	1	0.06
Malignancies*	0	---
Autoimmunity*	0	---
Infections, Other*#	11	0.666
Total:	**69**	**4.18**

Case Study ISS Astronaut

- Unusually proficient medical record
- Typical busy pre-mission training schedule
- Launch on Soyuz; docking to ISS + 2 days
- 191 day mission onboard ISS
- 3 Shuttle dockings, 2 Progress dockings, 1 ATV docking
- 5 EVA activities (12 Shuttle EVA)
- Typically busy mission schedule
- Landing on Soyuz, GCTC 1 week

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

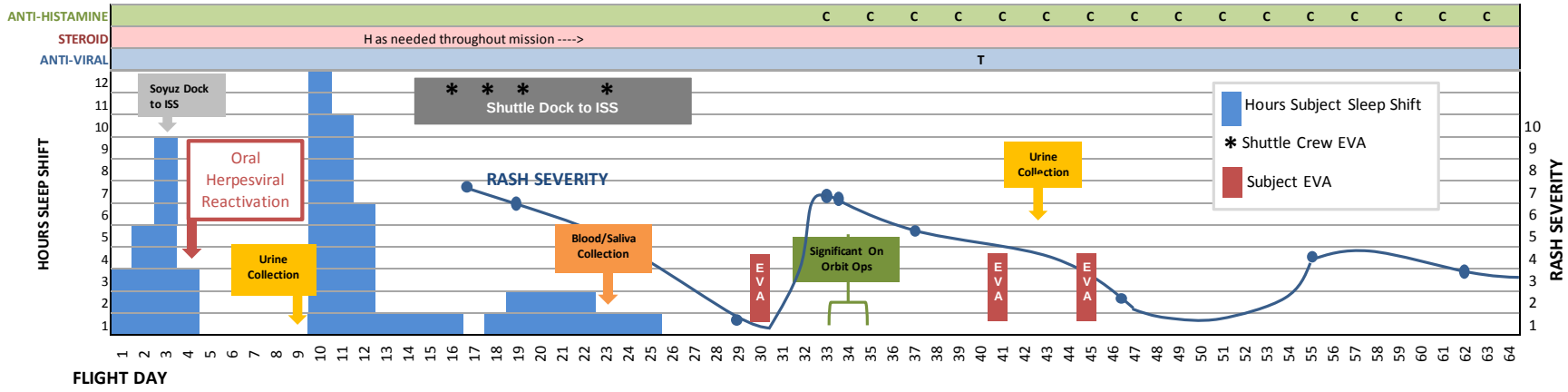
-A variety of treatments employed

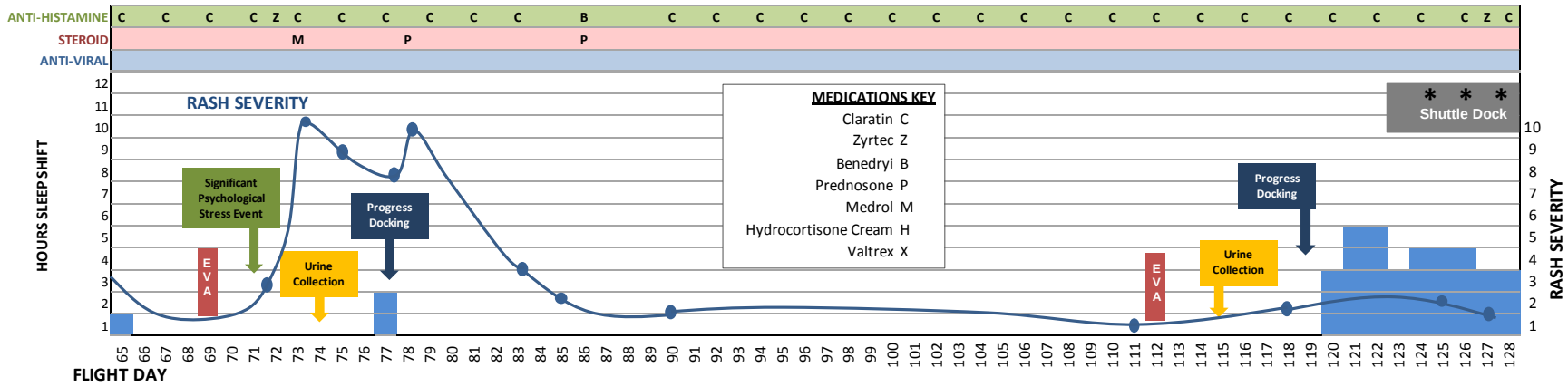
-At times the medications of choice were exhausted

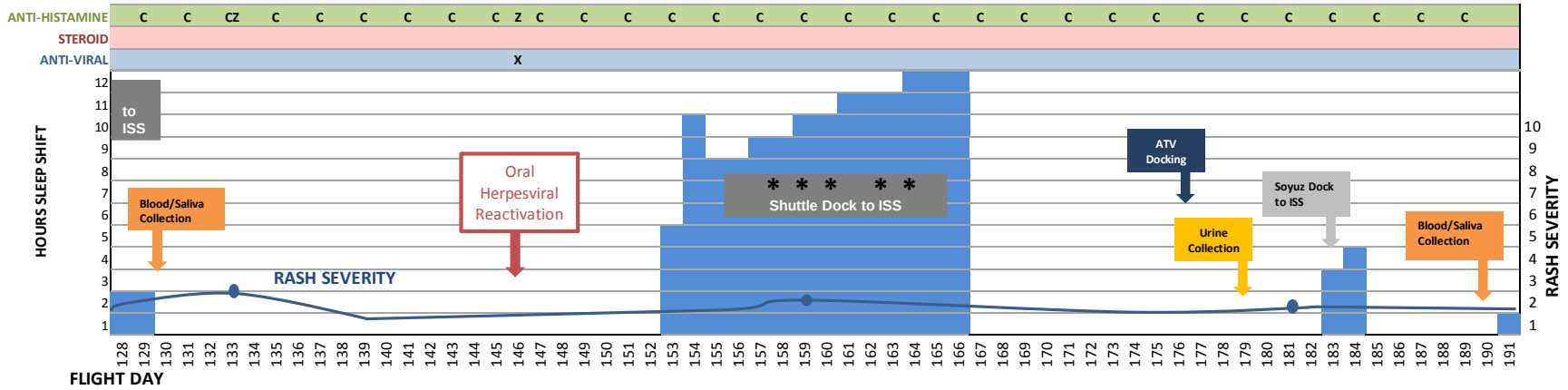
-Rash never resolved for the duration of the mission, although it was successfully managed to a tolerable level

-Rash spikes generally correlated well with operational stressors

-Research findings confirm immune dysregulation persisted for the duration of the mission


ANTI-HISTAMINE
STEROID
ANTI-VIRAL
H as needed throughout mission ---->
Soyuz Dock to ISS
Shuttle Dock to ISS
Oral Herpesviral Reactivation
RASH SEVERITY
Urine Collection
Blood/Saliva Collection
Significant On Orbit Ops
EVA
Hours Subject Sleep Shift
Shuttle Crew EVA
Subject EVA
HOURS SLEEP SHIFT
RASH SEVERITY
FLIGHT DAY

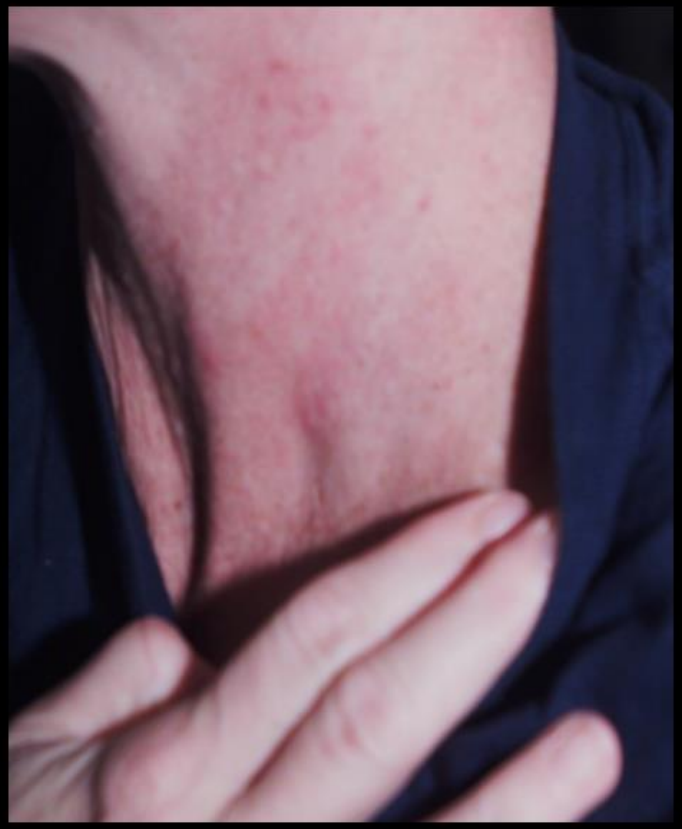

ANTI-HISTAMINE
STEROID
ANTI-VIRAL
RASH SEVERITY
MEDICATIONS KEY
Claratin C
Zyrtec Z
Benedryi B
Prednosone P
Medrol M
Hydrocortisone Cream H
Valtrex X
Shuttle Dock
Significant Psychological Stress Event
Progress Docking
Urine Collection
EVA
HOURS SLEEP SHIFT
RASH SEVERITY
FLIGHT DAY


ANTI-HISTAMINE
STEROID
ANTI-VIRAL
to ISS
Blood/Saliva Collection
Oral Herpesviral Reactivation
Shuttle Dock to ISS
ATV Docking
Soyuz Dock to ISS
Urine Collection
RASH SEVERITY
HOURS SLEEP SHIFT
RASH SEVERITY
FLIGHT DAY

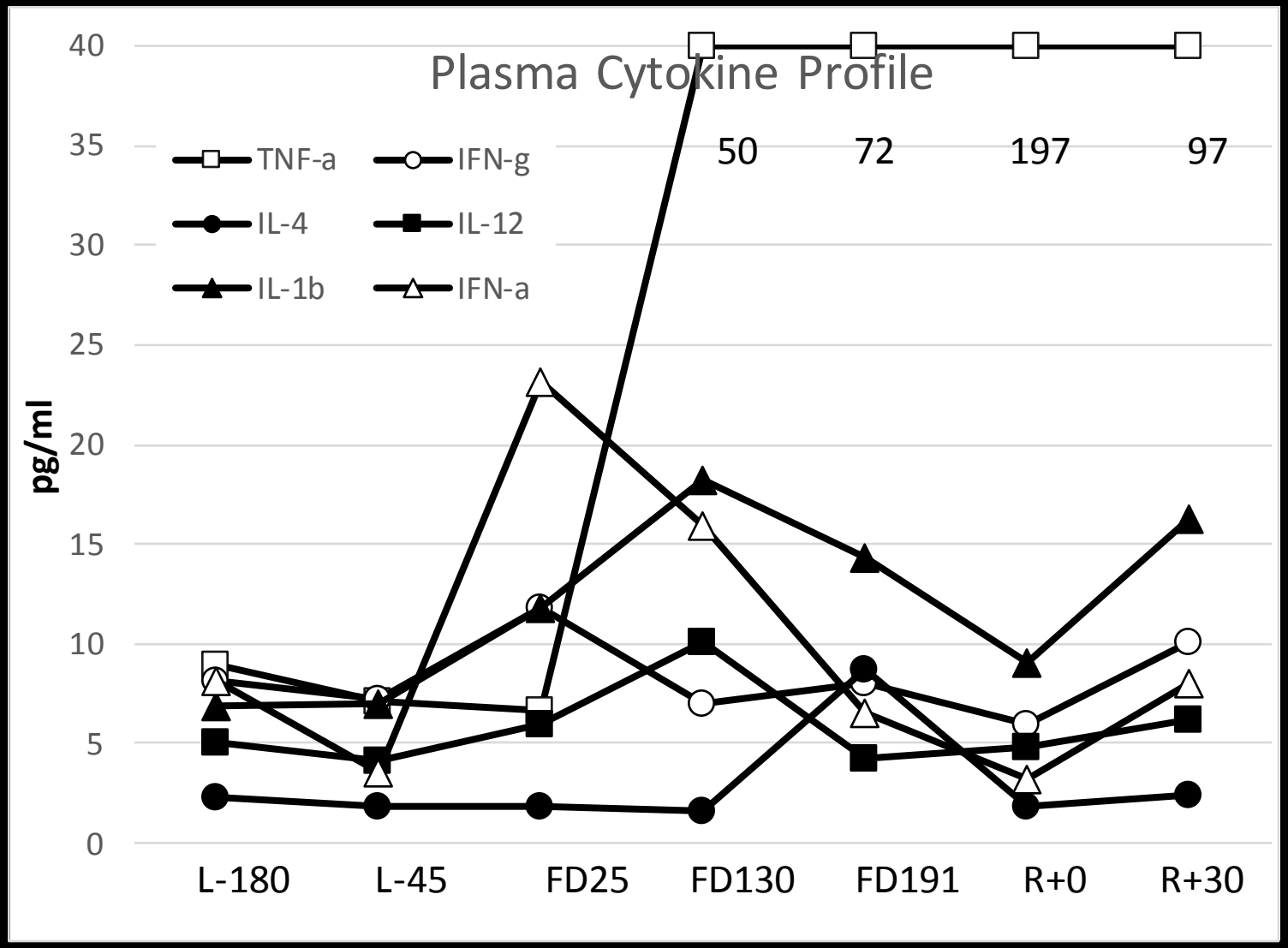
General Rash Characterization

- 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.

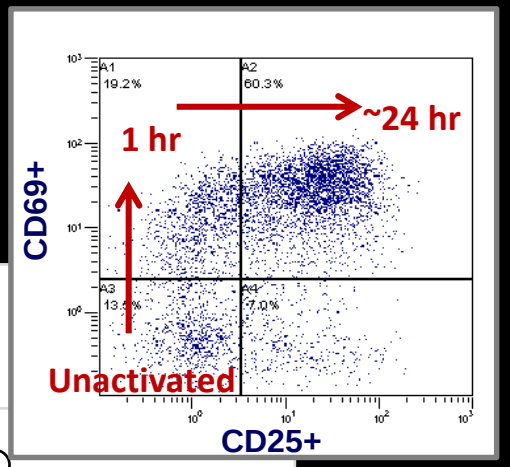


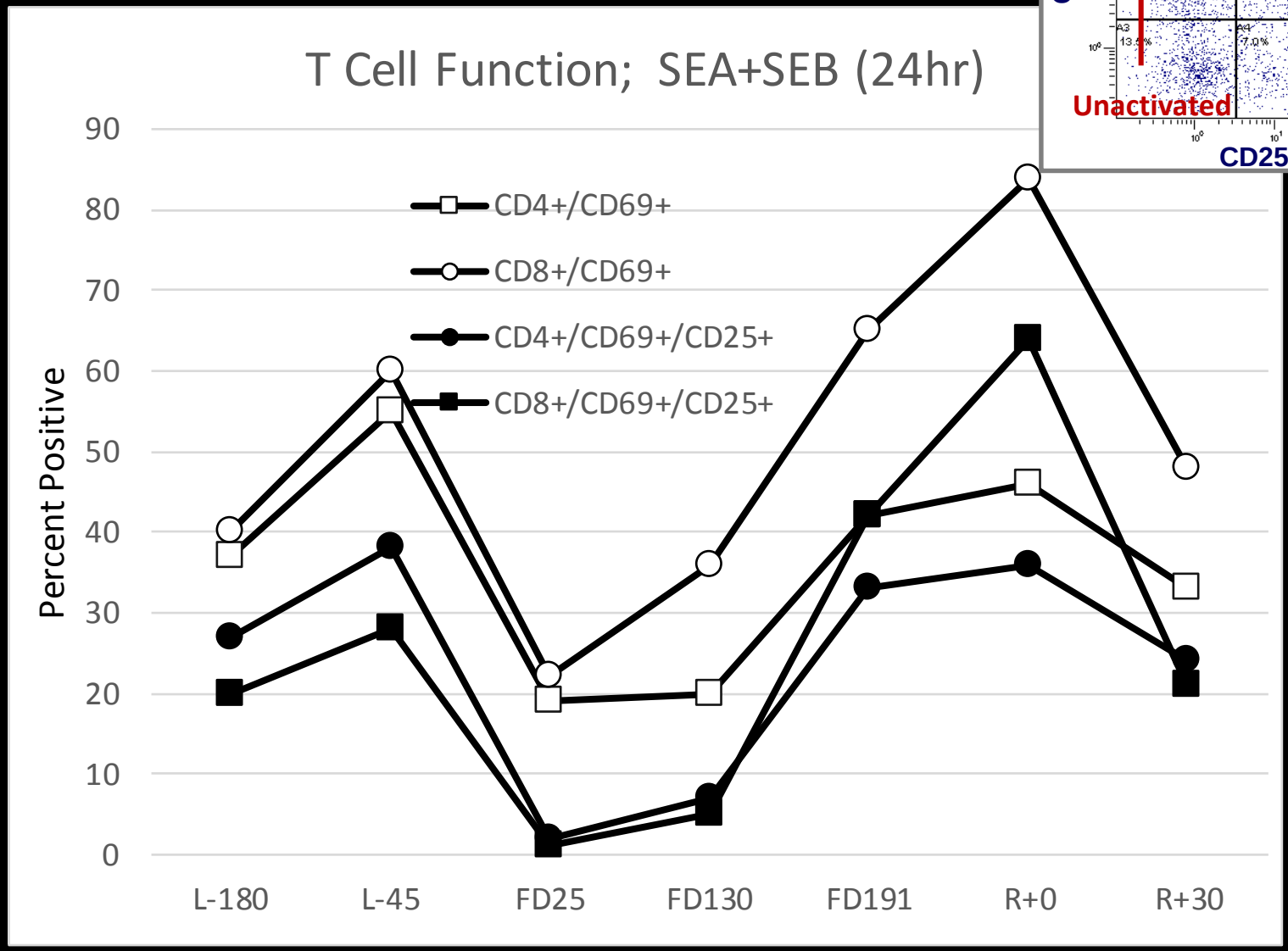
Plasma Cytokine Profile



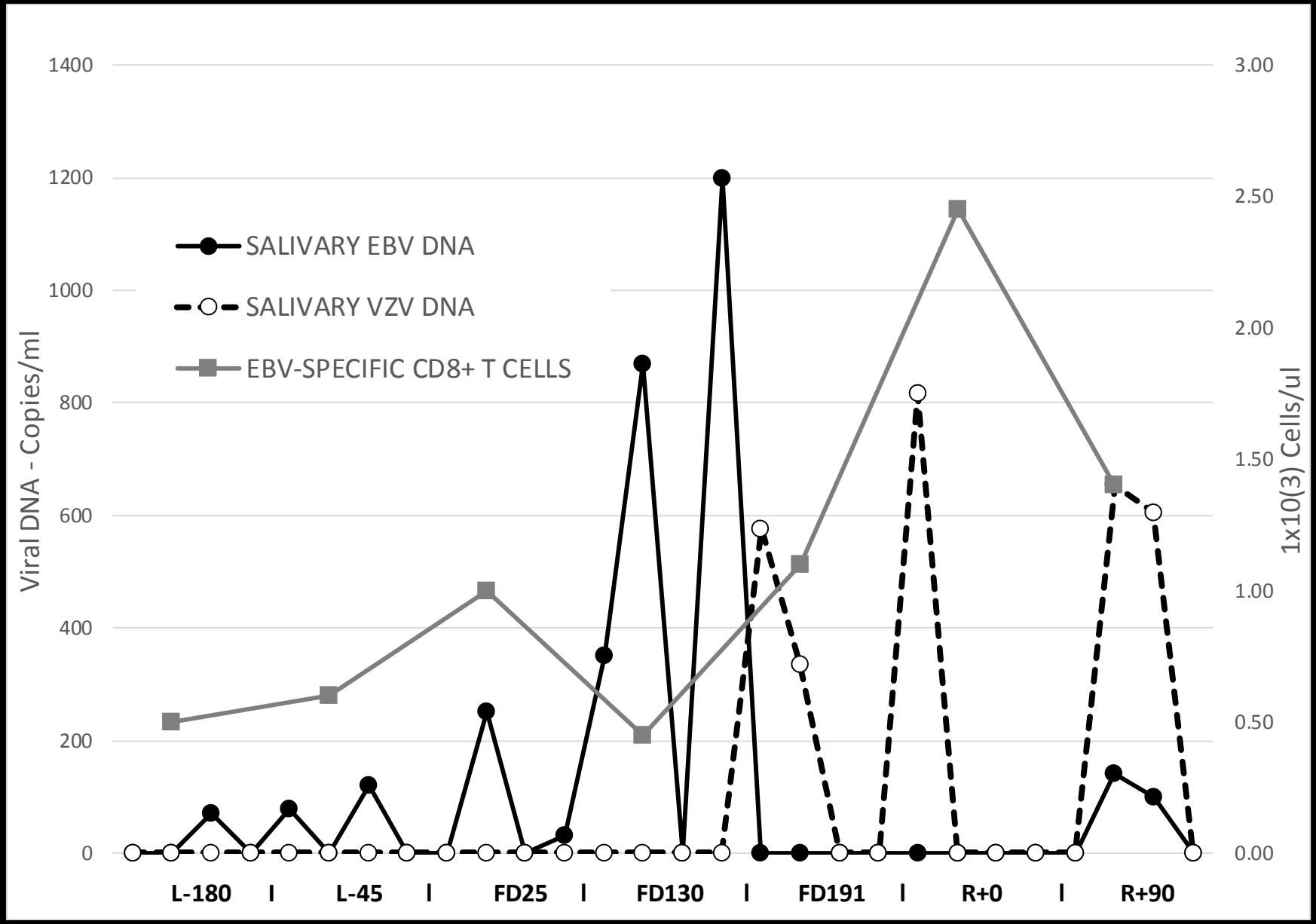
T Cell Function

SEA+SEB (24hr)

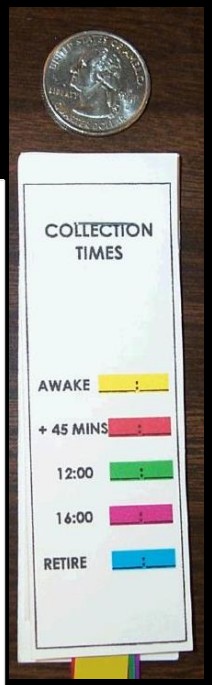


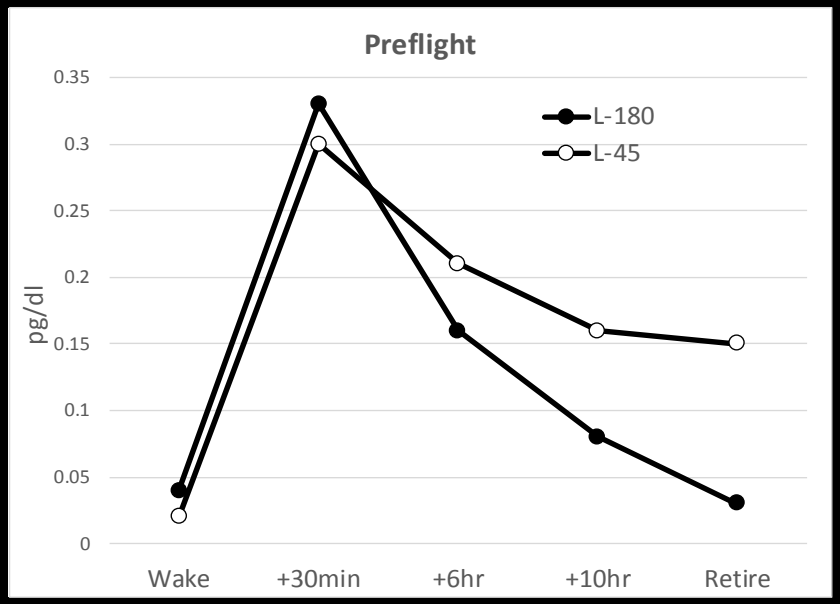


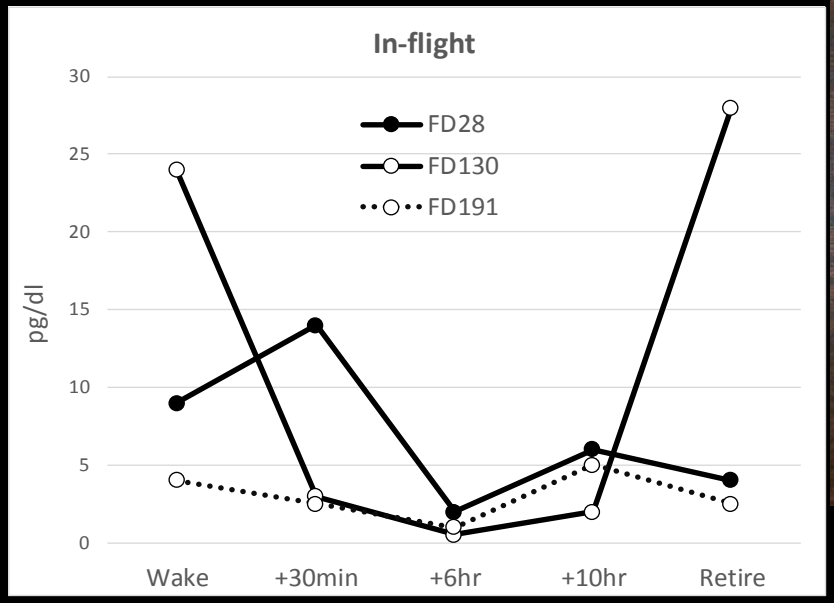
Latent Herpesvirus Reactivation; EBV Specific T Cells

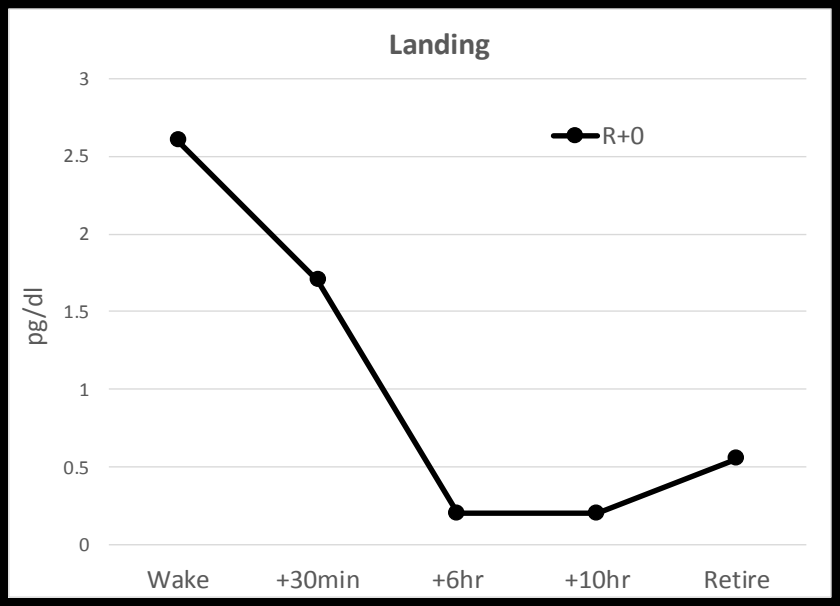


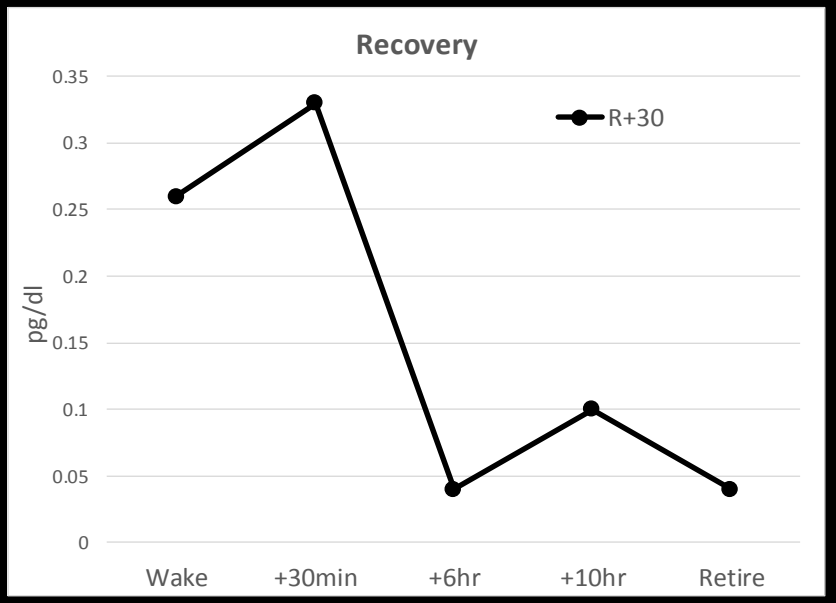
Circadian Rhythm of Salivary Cortisol



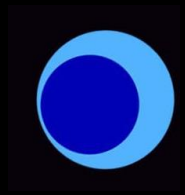




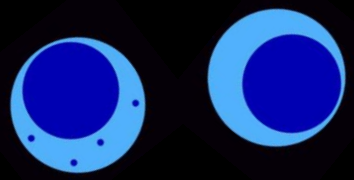




Working Hypothesis: Spaceflight Summary Effects on Immunity



No known effect on humoral immunity
(MIR-18 vaccination study)

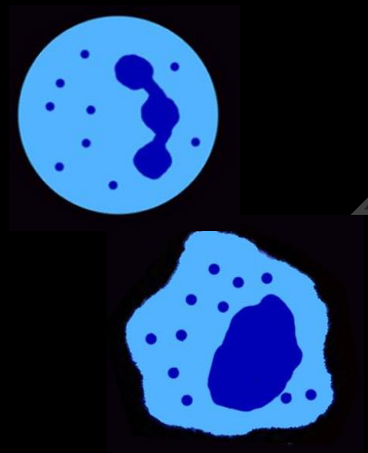


ADAPTIVE

↓ Skin DTH during flight
↓ T cell Function (general and virus specific)
↓ Adaptive immunity cytokine profile
↑Persistent herpesvirus reactivation

Th1→Th2 Cytokine Bias shift

INNATE



↓ NK cell function
↑Persistent hypersensitivity/pro-allergy
↑ Persistent systemic low-grade inflammation
(Possible localized inflammation)

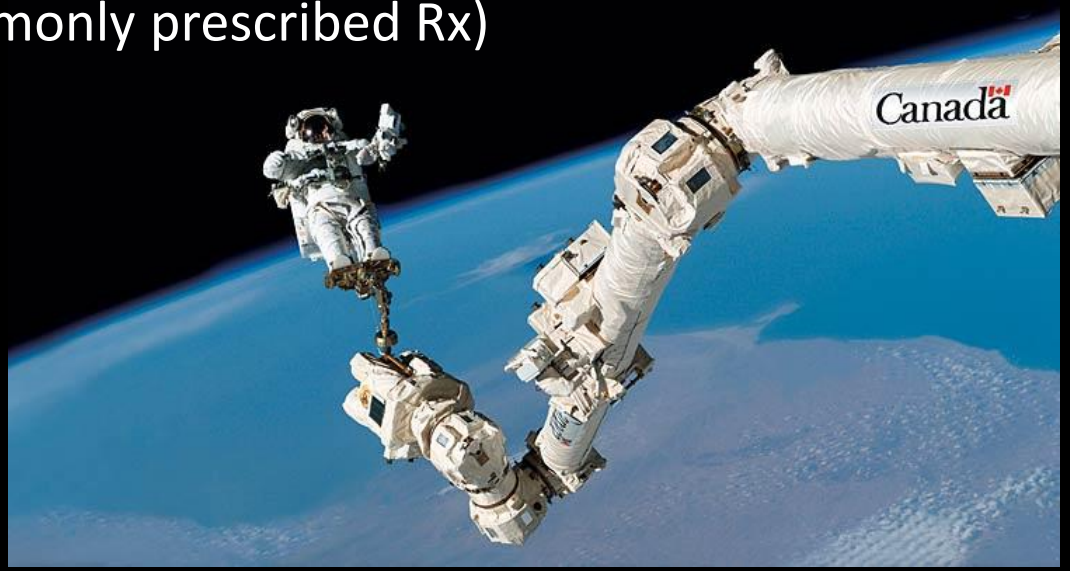
Conclusions

Immune System dysregulation persists during 6-month orbital spaceflight

Appears to be a pan-suppression of adaptive function, some sensitization of innate immunity

Latent herpesviruses, including VZV, persistently reactivate for the duration of a 6-month ISS mission.

Circadian misalignment occurs, difficult to regain a ‘normal’ circadian rhythm. (Sleep meds most commonly prescribed Rx)



Conclusions

- Case study: Mission events correlated well with observed symptomology
- Spaceflight is a granular experience consisting of chronic stress interspersed with periodic acute stressors
- Immune dysregulation during flight appears to be polar, with some adaptive processes depressed (T cell function, HV shedding); whereas some innate and other processes are elevated (inflammation, hypersensitivity reactions)
- Exploration immune countermeasures must be considered carefully

Immune Countermeasures for Exploration Missions?

Considerations

Have we completely characterized in-flight immune dysregulation?

Is there a clinical risk from the observed pattern of dysregulation?

Is the phenomenon likely to be exacerbated beyond Earth orbit?

What specific cellular dysregulation should be targeted for correction?

Countermeasures must be carefully targeted

Can immune countermeasures exacerbate elevated incidence hypersensitivity reactions?

What is the interdisciplinary/multi-system impact of an immune countermeasure?

Upcoming Immune Investigations onboard ISS

Functional Immune (NASA)

*Immuno-2/*Neyroimmunitet (ESA/RSA)

Moroze (RSA)

Exploration Atmosphere (NASA)

Categories Immunology Countermeasures

Tier 0

Already in place

Tier 1

Multidiscipline, benign

Tier 2

Nutritional supplementation

Tier 3

Pharmacological intervention

Tier 0

Already in place

Pre-flight quarantine/Health Stabilization Program

The primary purpose of the Flight Crew Health Stabilization Program (HSP) is to mitigate the risk of occurrence of infectious disease among astronaut flight crews in the immediate preflight period.

Infectious diseases are contracted through direct person-to-person contact, and through contact with infectious material in the environment.

The HSP establishes several controls to minimize crew exposure to infectious agents. The HSP provides a quarantine environment for the crew that minimizes contact with potentially infectious material.

The HSP also limits the number of individuals who come in close contact with the crew.

The infection-carrying potential of these primary contacts is minimized by educating them in ways to avoid infections and avoiding contact with the crew if they are or may be sick.

Primary contacts are also strongly encouraged to maintain updated vaccinations.

Tier 0

Already in place

Vehicle Design Controls

- HEPA air filters
- In-line water filters
- Contamination resistant surfaces
- Water biocides
- Water pasteurization systems
- Minimize condensation
- Contain trash and human waste

Tier 0

Already in place

Pre-Flight Screen of Crewmembers

MedB 2.1 (L-90; L-30) *"The examination will include collection of blood and urine from crewmembers for analyses to enhance the physician's medical evaluation of crew health prior to flight"*

- CBC/Differential
- CRP
- Mouse IgE Allergen Panel

MedB 2.4 (L-90, L-30) "…to determine transfer or acquisition of Methicillin-Resistant *Staphylococcus aureus* (MRSA)"

- Nasal Screen for Methicillin Resistant *Staphylococcus aureus* (MRSA)

MedB 2.2 (L-21/18 months) "To detect and eradicate H. Pylori from crewmembers preflight to mitigate risk"

- Serological H. Pylori IgG and IgA antibody test results; Urea Breath Test results, if indicated

Tier 0

Already in place

Preflight Microbiological Monitoring

- Crewmembers
- Food
- Potable water
- Vehicle surfaces
- Vehicle air
- Cargo
- Biosafety review of paylo

C. Mark Ott, Ph.D., NASA Microbiologist

Tier 0

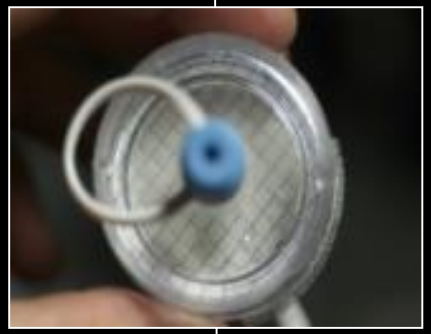
Already in place

Microbiological Monitoring Onboard ISS

Surfaces

Air

Water



Quantified in-flight and returned to JSC for identification

C. Mark Ott, Ph.D., NASA Microbiologist

Tier 1

Multidiscipline, benign

Immune Countermeasures

- Environmental control
- ISS ‘Seat Swapping’
- Stress relieving techniques
- Exercise
- Sleep schedules
- Family communication
- Radiation shielding
- Propulsion/faster transit
- Yoga

Tier 2

Nutritional supplementation

- Supplemental nucleotides: Uridine/uridine (immune function)
- AHCC: active hexose-correlated compound (Th2 shift; innate immunity)
- Pegylated-IL-2 (NK cell #/function)
- Antioxidants (radiation effects, oxidative stress)

  N-acetyl cysteine, ascorbic acid
  a-lipoic acid
  L-selenomethionine
  Coenzyme Q10
  vitamin E succinate
  D-selenomethionine

Tier 2

Nutritional supplementation

- Omega 3 fatty acids (anti-inflammatory properties)
- *Probiotics*
- Wellimmune™
- BAM-FX (Zero Grav Sol. Inc.)
- Plant Extracts

Tier 2

Nutritional supplementation

Langston Immune Countermeasures Study

Probiotics/Extracts of Probiotics

- Probiotics modulate innate and adaptive immunity (Aureli 2011)
- Mechanisms and actions of probiotics not fully understood (Oelschlaeger 2010)
- Supplementation with probiotics has positive benefits on the response to vaccination for influenza (Olivares 2007), polio (De Vrese 2005) and cholera (Paineau 2008)
- Positive effects may be via the release of cytokines after ingestion (Maassen 2008)

Plant Extracts

- 47% of pharmaceuticals trace to natural origins (Newman 2007)
- Plant derived medicines also modulate immune responses.
- Saikosaponin from Bupleurum falcatum – increased IL-2 production (Yamaguchi 1985)
- Silybum marianum (milk thistle) immunostimulatory (Wilasrusmee 2002)

Biochemistry

- Transcriptomic data from probiotics and plant compounds
- Combinations of lead compounds with and without addition o tary vitamins and minerals

LANGSTON UNIVERSITY

Tier 3

Pharmacological intervention

Medication Use onboard ISS

Sinus congestion and allergy symptom treatments included OTC antihistamines, decongestants, and adrenergics as well as prescription antihistamines and mast cell stabilizers.

Sleep medications among the most prescribed on-orbit

Medication efficacy may be altered during Spaceflight (no data).

Fluid shifts may effect absorption and distribution of medications.

There are some animal studies that indicate drug metabolism, ie liver enzymes, may be altered.

Wotring, V.E., Medication Use by U.S. Crewmembers on the International Space Station (Abstract #1023.1). *Experimental Biology 2015*, March 28-April 1, 2015, Boston, Mass.

Tier 3

Pharmacological intervention

Immune Countermeasures?

- Anti-Cortisol (Ketoconozole)
- Non-Steroidal anti-Inflammatory
- Beta blockers (Propranolol)
- Cytokine Antagonists/Blockers (IL-1, TNF, IL-4, IL-9, IL-13)
- Recombinant Cytokine Therapy

Treatment of Medical Events

- Antibiotics
- Antiviral
- Corticosteroids

Summary Chart - Immunology Countermeasures

Tier 0

Already in place

- Pre-flight quarantine
- Microbial screening of vehicle/payloads/foods
- Med ops screening

Tier 1

Multidiscipline, benign

- Environmental control
- Stress relieving techniques
- Exercise
- Sleep schedules
- Family communication
- Radiation shielding
- Propulsion/faster transit

Tier 2

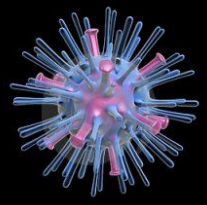
Nutritional supplementation

- Supplemental nucleotides: Uridine/uridine (immune function)
- AHCC: active hexose-correlated compound (Th2 shift; innate immunity)
- Pegylated-IL-2 (NK cell #/function)
- Antioxidants (radiation effects, oxidative stress)
  - *N*-acetyl cysteine, ascorbic acid
  - a-lipoic acid
  - L-selenomethionine
  - Coenzyme Q10
  - vitamin E succinate
  - D-selenomethionine
- Omega 3 fatty acids (anti-inflammatory properties)
- *Probiotics*
- Wellimmune™
- BAM-FX (Zero Grav Sol. Inc.)

Tier 3

Pharmacological intervention

- Ketoconozole
- Antibiotics
- Antiviral
- Anti-inflammatory
- Beta blockers
- Cytokine therapy



Other options

- Antiviral (VZV) vaccination

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