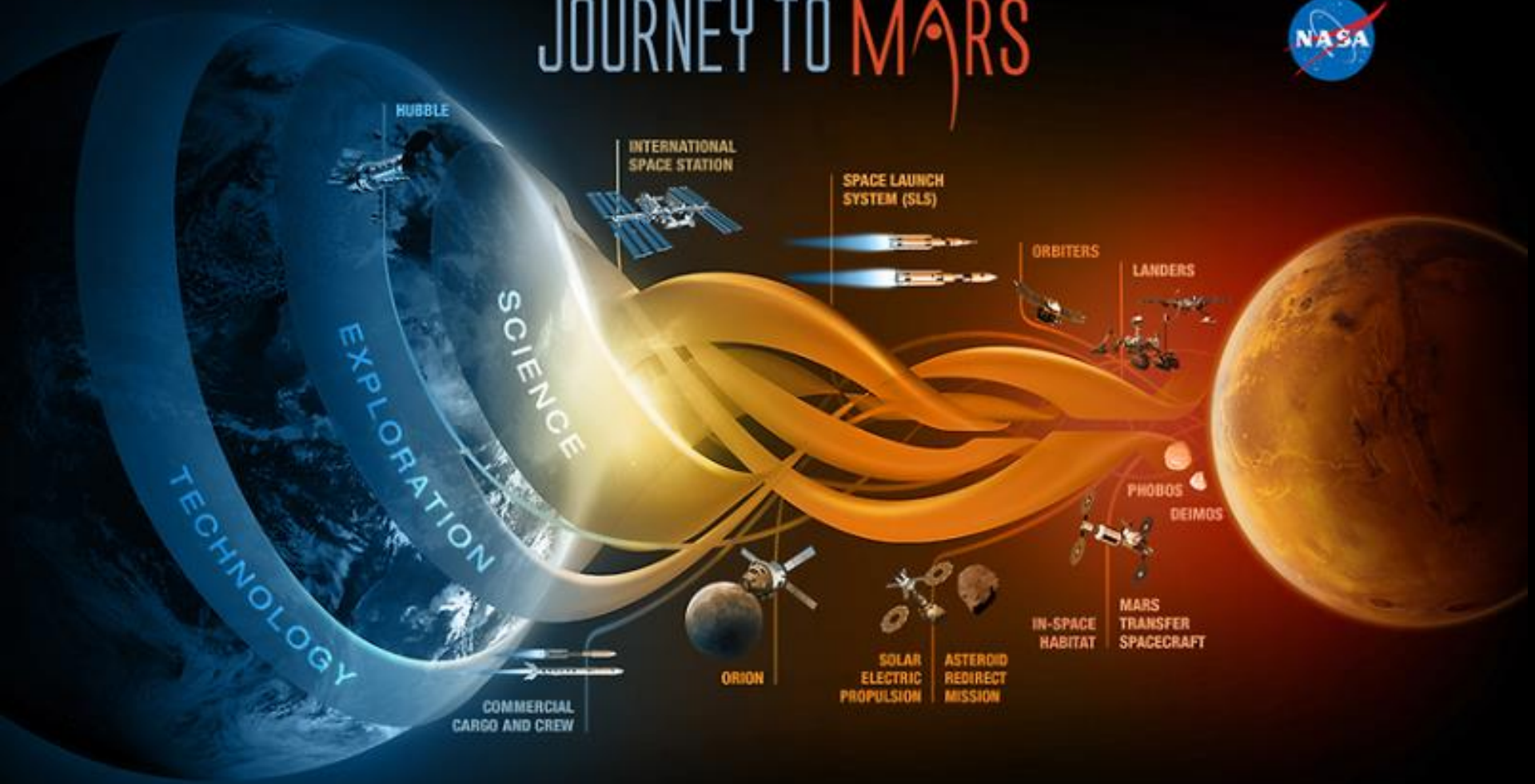




Countermeasure Options for Immune System Dysregulation



JOURNEY TO MARS



Spaceflight Effects on Human Physiology

Muscle and bone
weakening

Elevated kidney stone
risk

Fluid
Redistribution to
upper body

Plasma volume
decreases, anemia

Elevated radiation
may increase
cancer risk



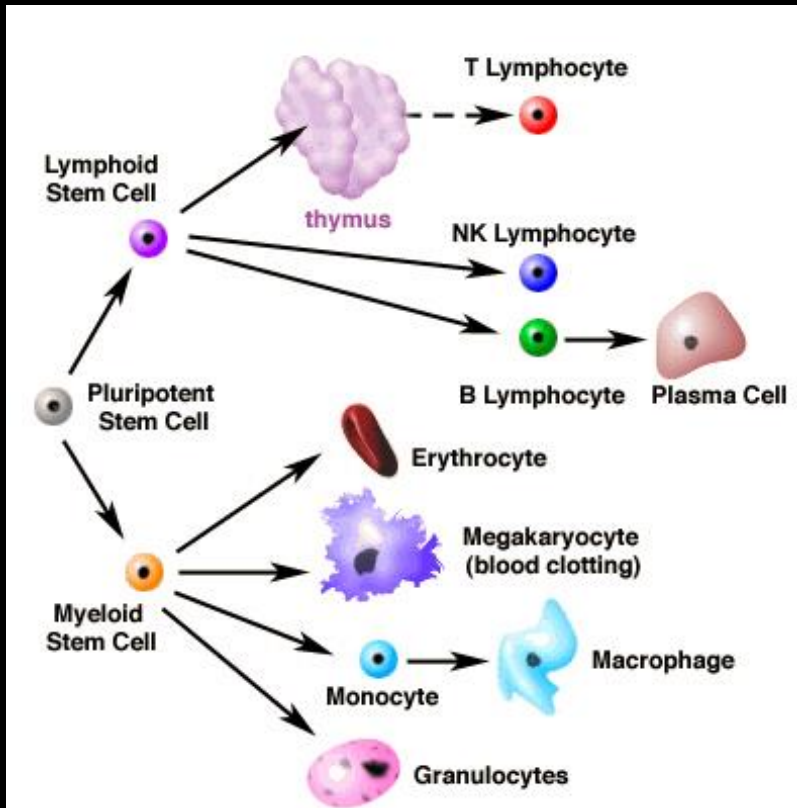
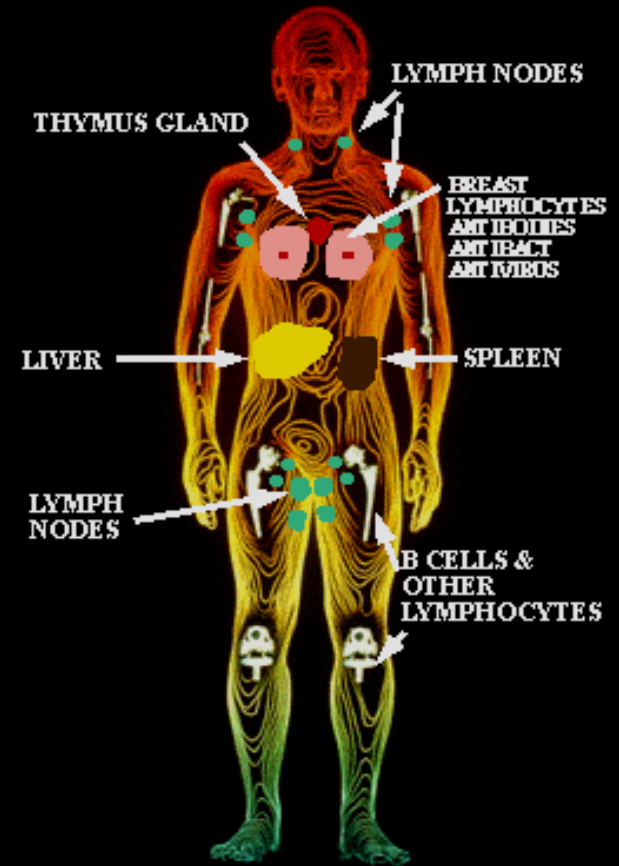
Vision Issues

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

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

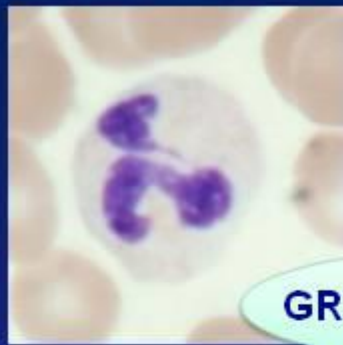
Innate Immunity - primary defense, immediate (constitutively present), non-specific, does not result in memory

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

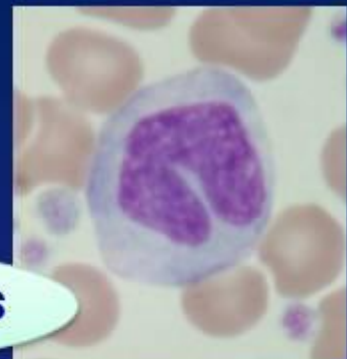




WHITE BLOOD CELLS

+

RED BLOOD CELLS



GRANULOCYTES

MONOCYTES

LYMPHOCYTES

BASOPHILS

NEUTROPHILS

EOSINOPHILS

B CELLS

T CELLS

NK CELLS

DENDRITIC CELL

MACROPHAGES

CD4+ 'Helper'

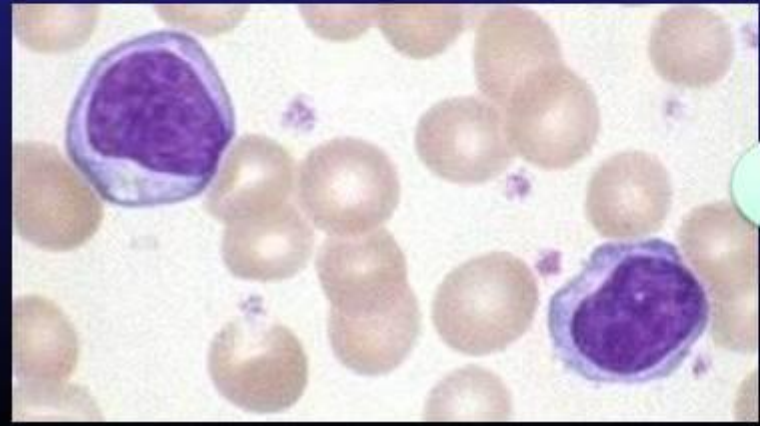
CD8+ 'Cytotoxic'

MAST CELL

PLASMA CELLS

Memory

Naive



Th1

Th2

Th17

Treg

Memory

Naive

True Naive

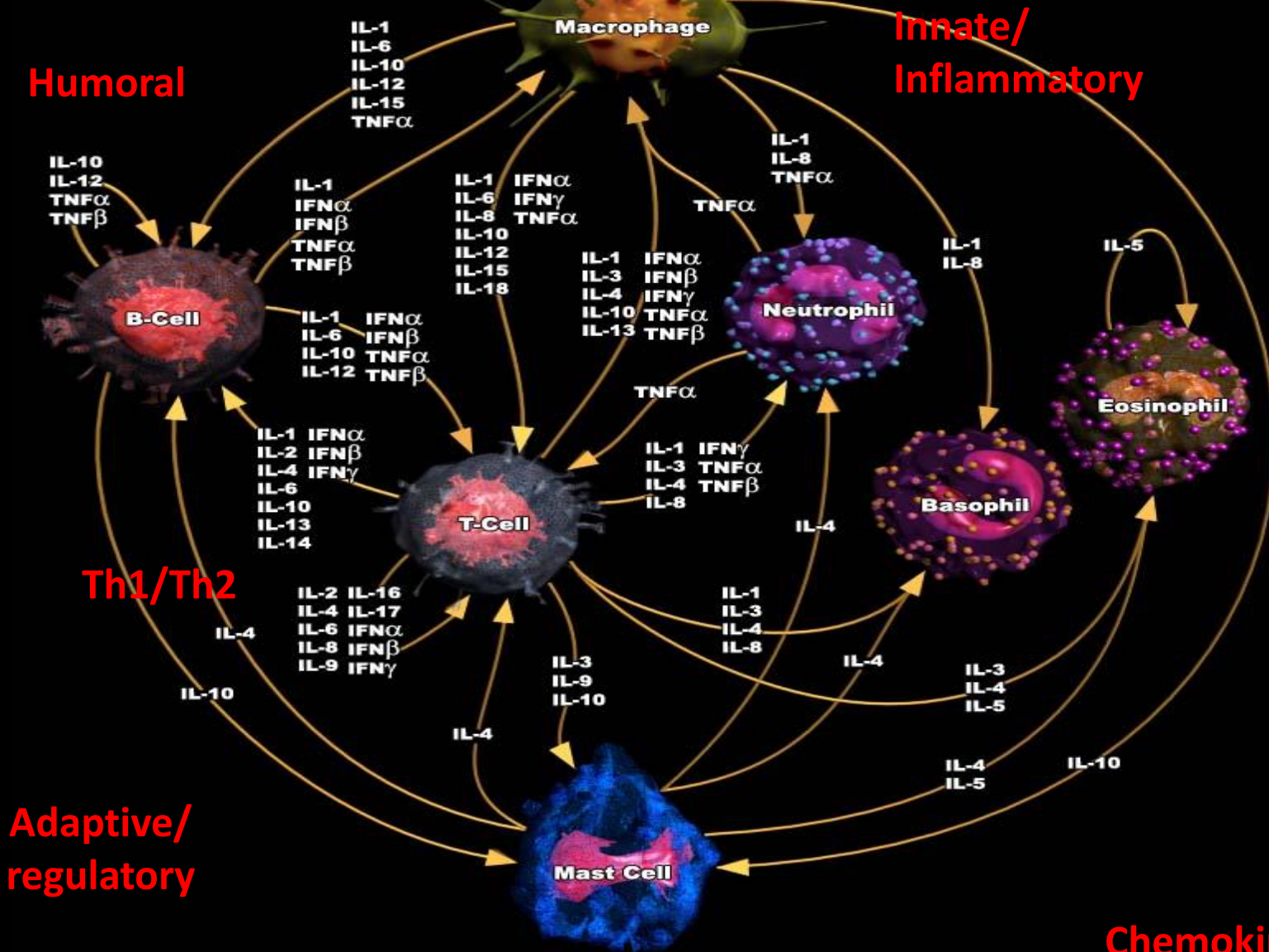
Central Memory

Effector Memory

Terminal Diff.

The Cytokine Network

Growth Factors



Humoral

Innate/
Inflammatory

Th1/Th2

Adaptive/
regulatory

Chemokines

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.

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.

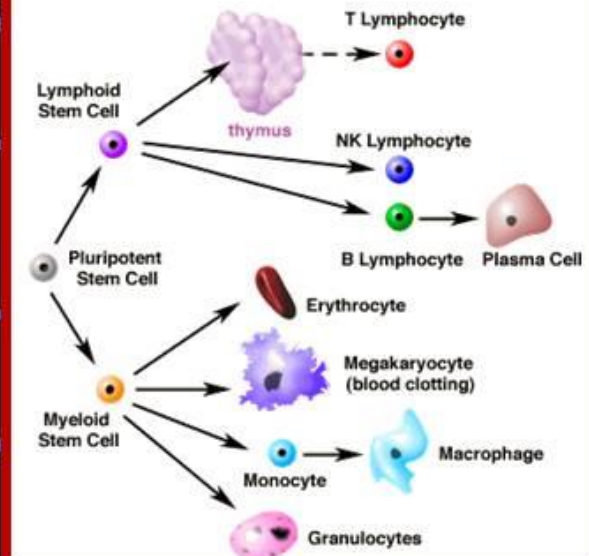
MICROBIOLOGY

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

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

IMMUNE SYSTEM



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**

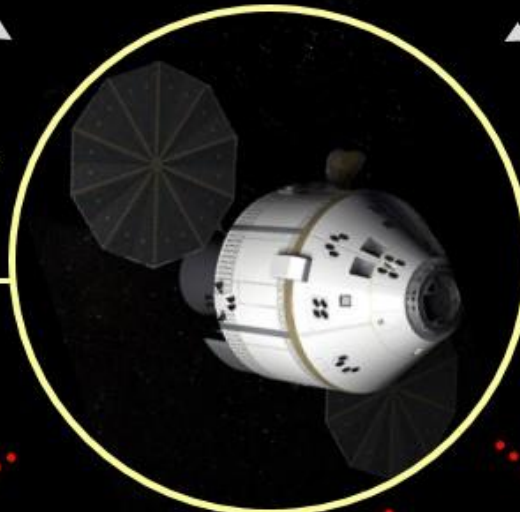
**CIRCADIAN
MISALIGNMENT**

**ALTERED
IMMUNOCYTE
DISTRIBUTION
& FUNCTION**

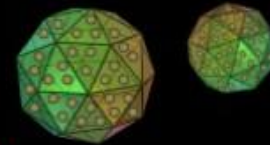
**ALTERED
CYTOKINE, REDOX,
INFLAMMATORY
BALANCE**

**LATENT VIRUS
REACTIVATION**

**CLINICAL
INCIDENCE**



**Th1/
Th2**



CANCER

AUTOIMMUNITY

**CONSEQUENCES OF
PERSISTENT VIRAL
REACTIVATION**

**CHRONIC ALLERGY/
HYPERSENSITIVITY**

**INFECTIOUS
DISEASE**



Skylab Data - 1973

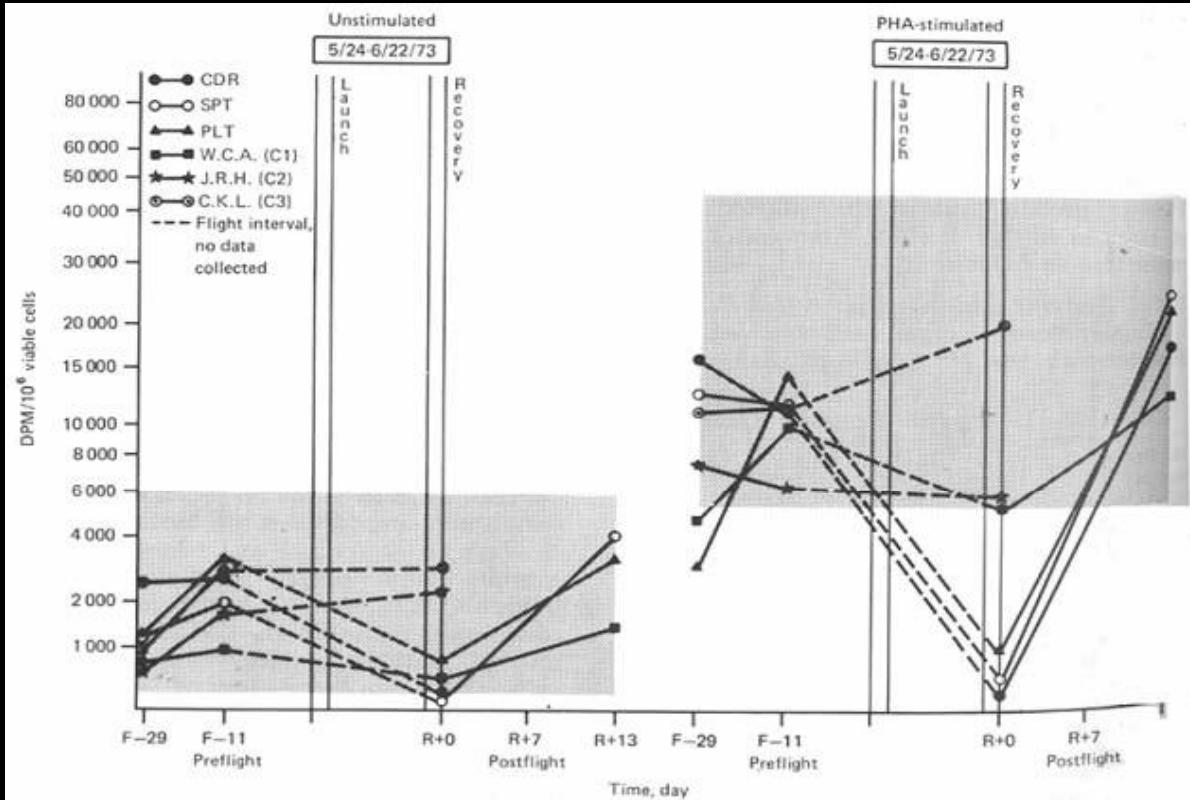
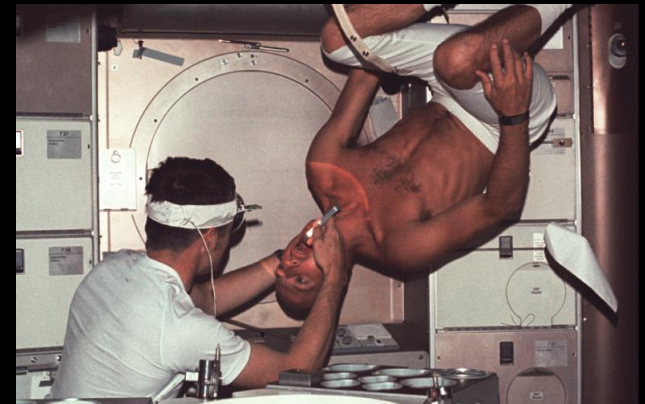
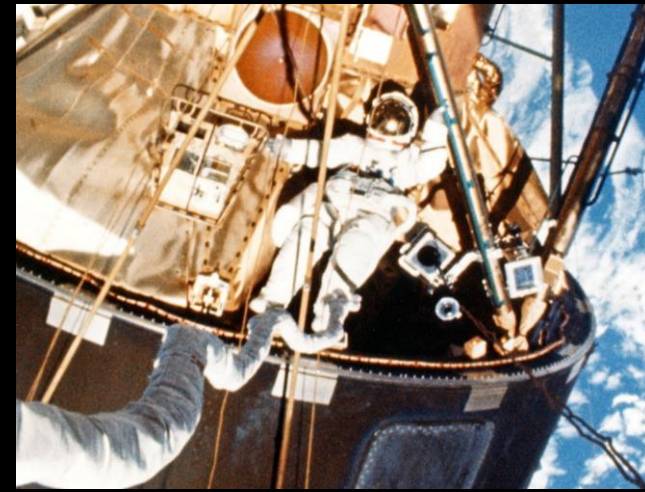


FIGURE 28-1a.—RNA synthesis rates in lymphocytes, cultured with and without PHA, obtained from the Skylab crews and control groups. The cells were pulsed with ³H-uridine at 23 h and harvested at 24 h after initiation of the cultures.



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

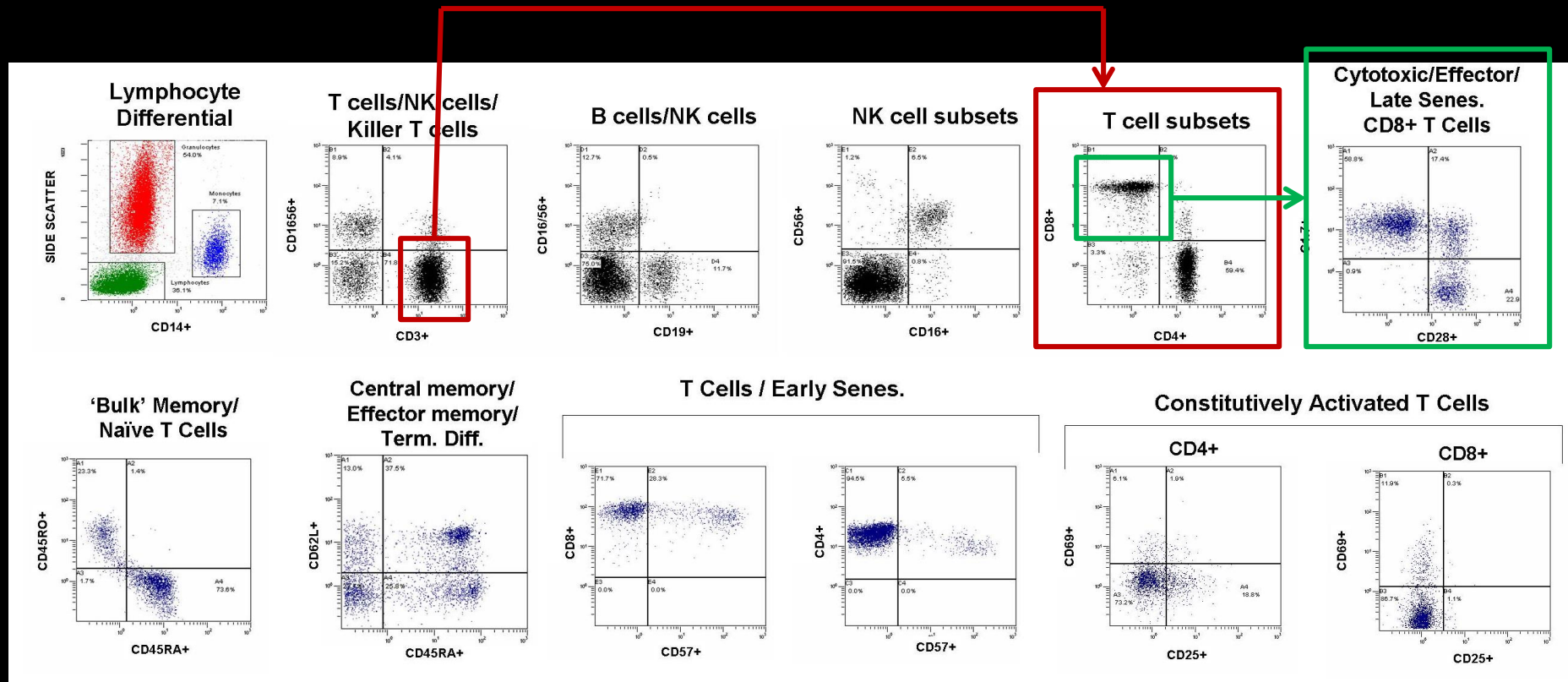
Microgen Laboratories

- Virus specific T cell number
- Virus specific T cell function





Comprehensive Peripheral Phenotype

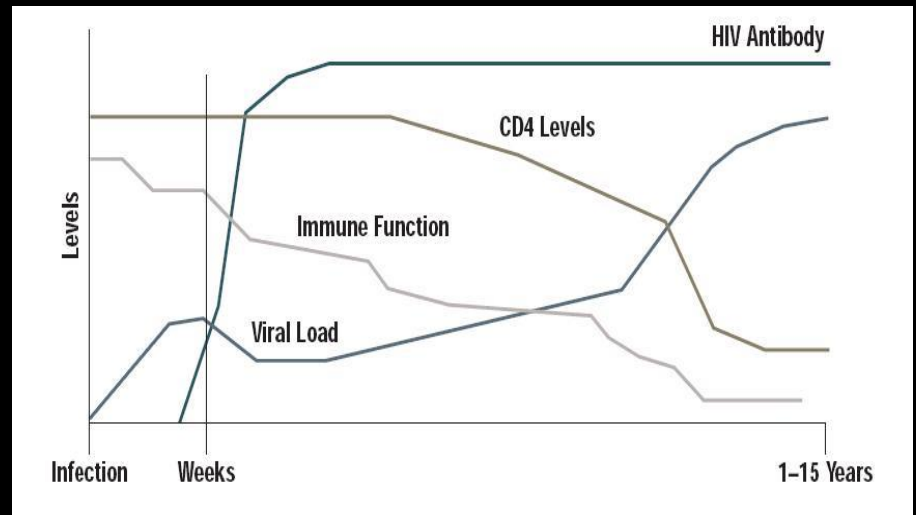


"Diseases are often accompanied by changes in the numbers or function of 'fine' lymphocyte subsets, even if changes in the bulk lymphocyte populations are not evident"

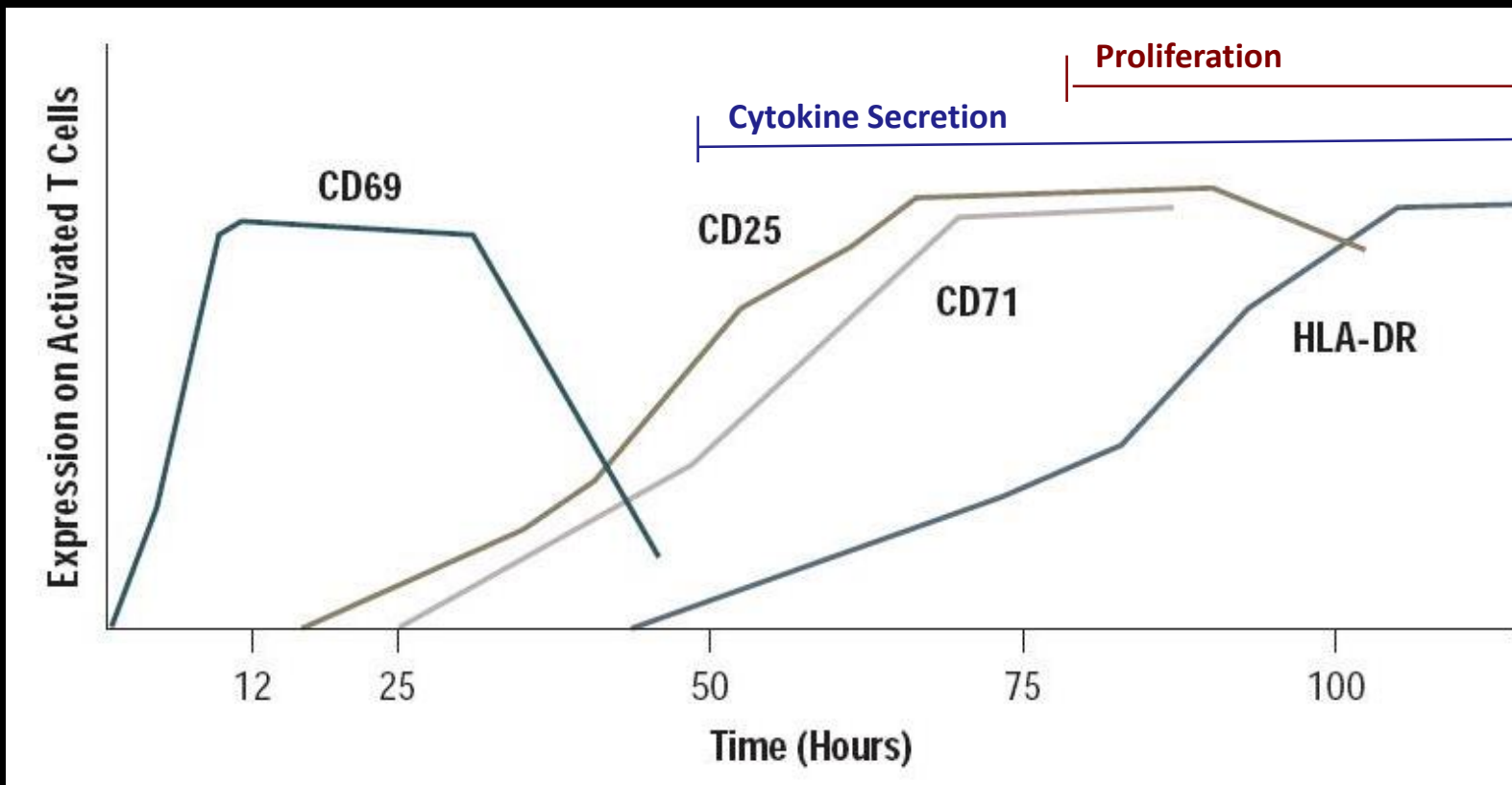
T cell function

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

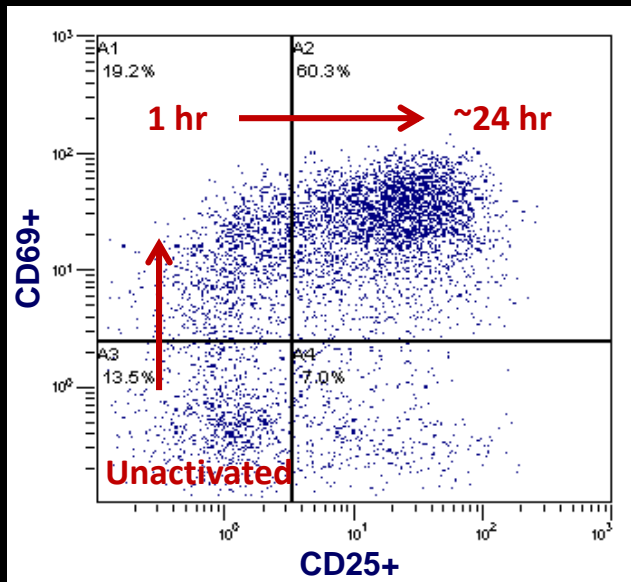
T Cell Function vs. Disease



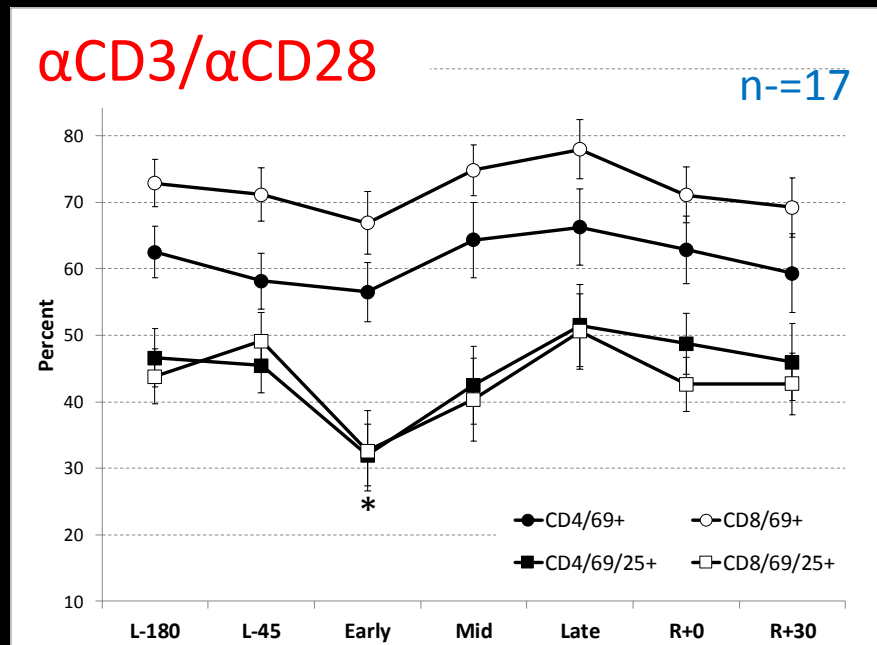
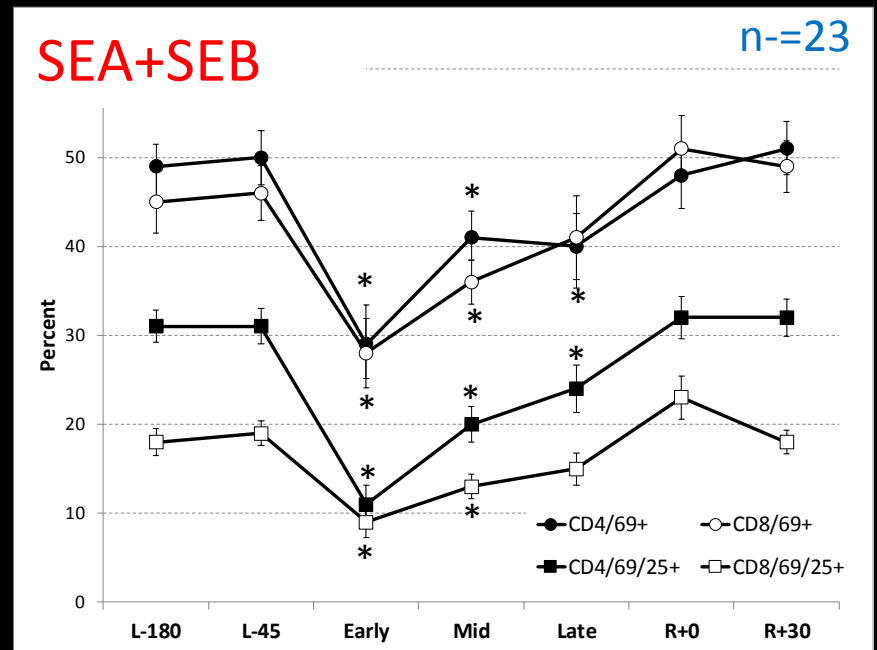
Kinetics of T Cell Activation



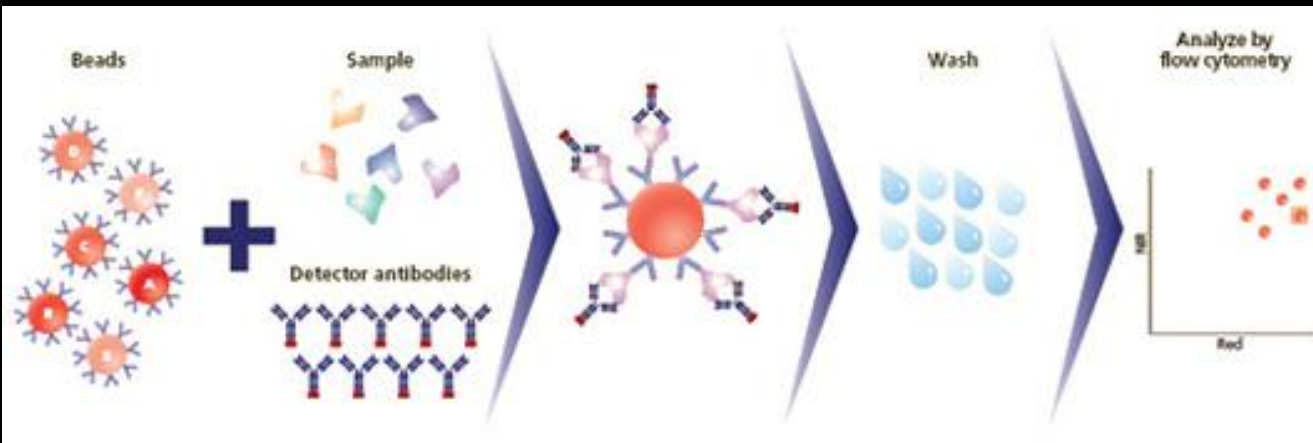
T Cell Function: Early Blastogenesis (24hr Culture)



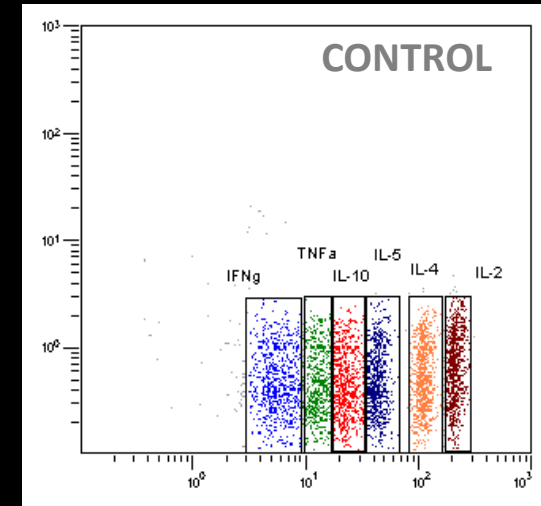
T cell function (early blastogenesis) data, expression of either CD69, or CD69/CD25 dual following 24hr culture in the presence of (A) staphylococcal enterotoxin A and B; or (B) antibodies to CD3 and CD28. Data are presented as mean \pm standard error. Significance was evaluated by comparing all other 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



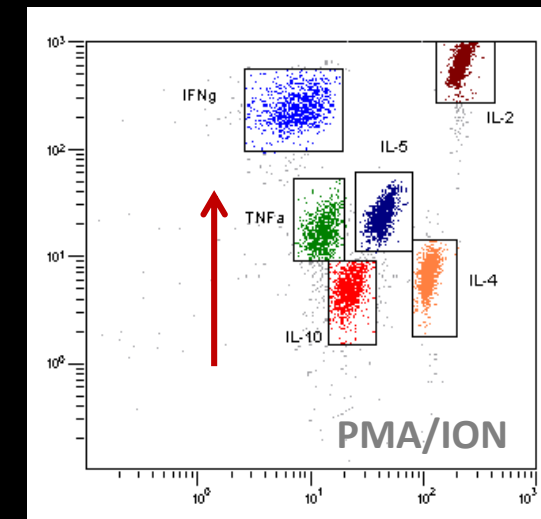
Secreted Cytokine Profiles: Detection by Cytometric Bead Array



- 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

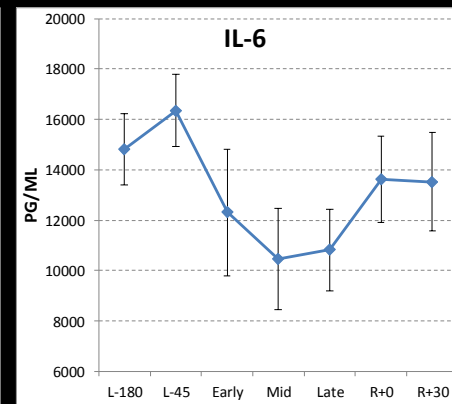
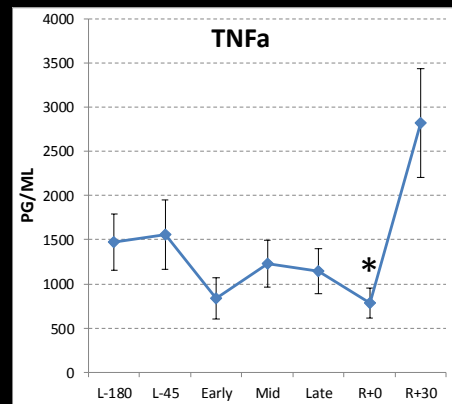
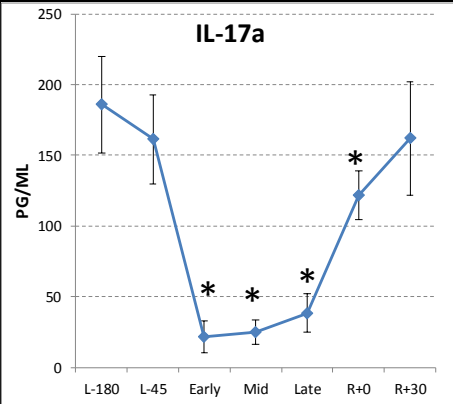
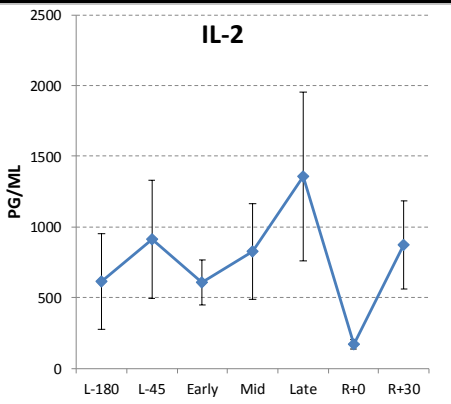
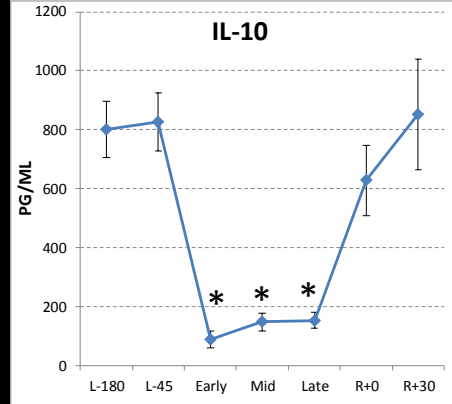
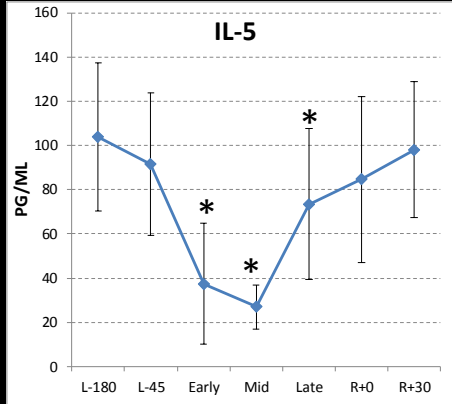
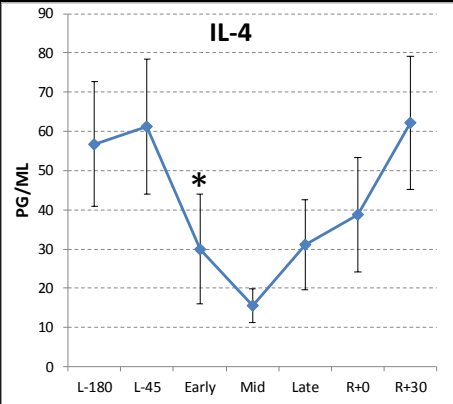
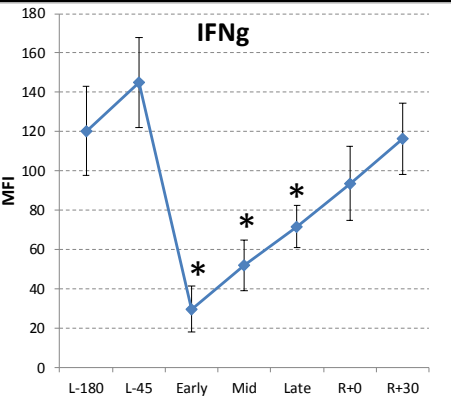
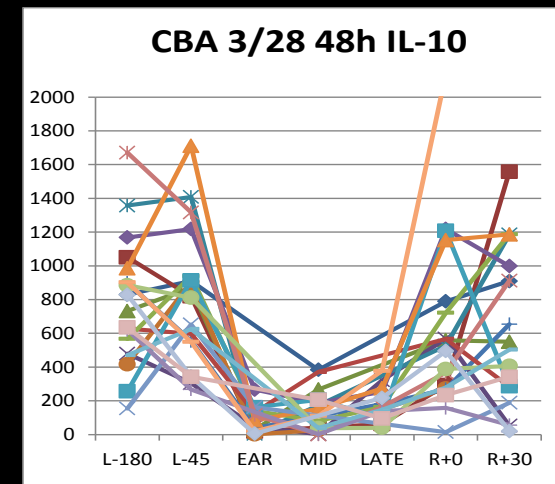


Bead populations

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

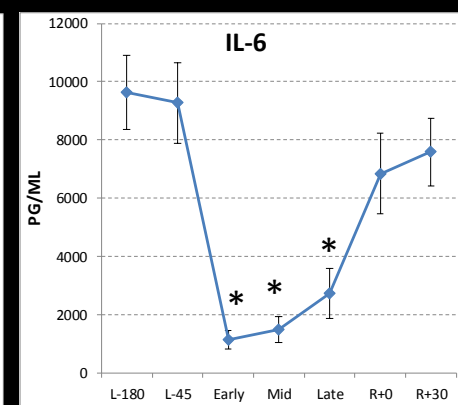
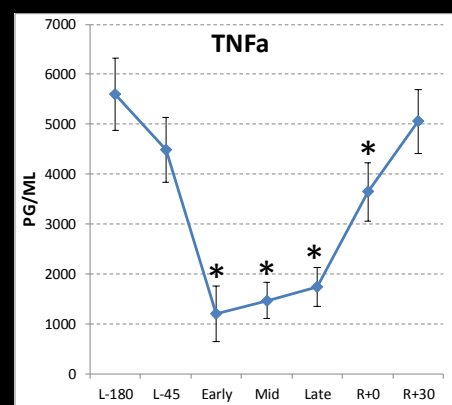
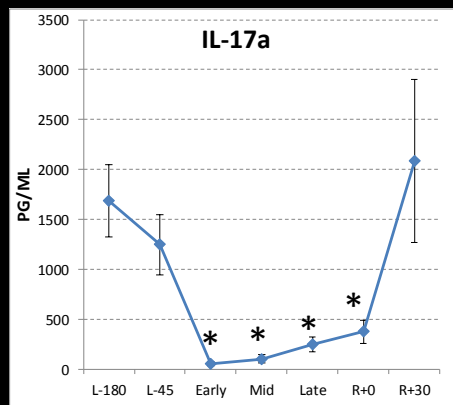
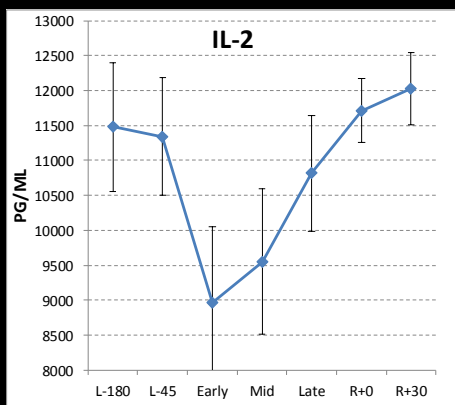
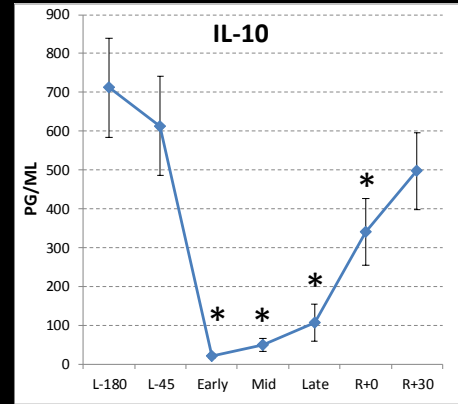
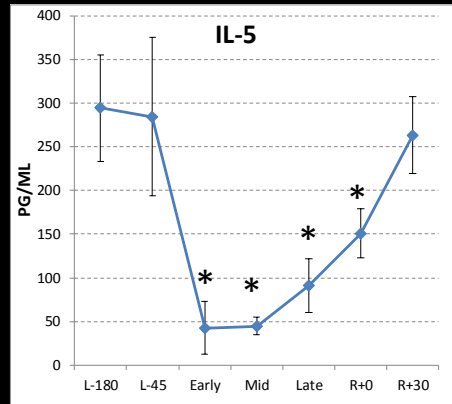
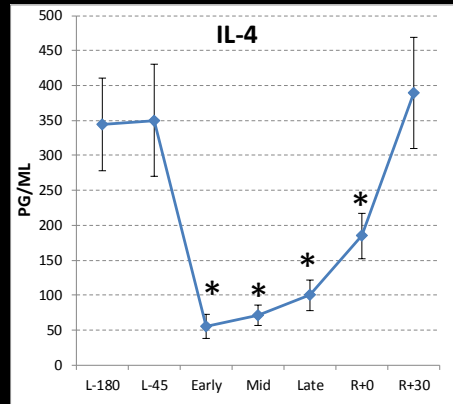
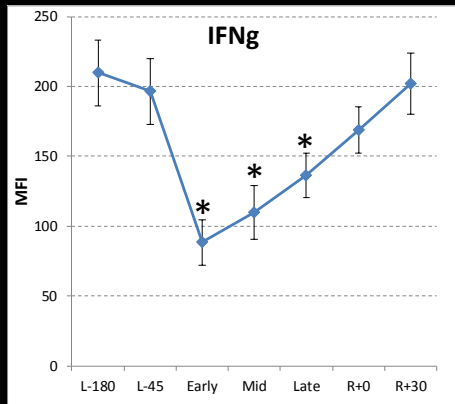
48hr Culture – anti CD3/CD28 Stimulation

Mean secreted cytokine levels following mitogenic stimulation. Data are expressed mean concentration in pg/ml \pm SEM. * indicates statistically significant difference $p \leq 0.05$. 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: Mean ISS Data (n=23)

48hr Culture – PMA/I Stimulation

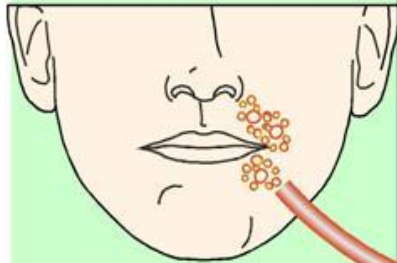


LATENT VIRAL REACTIVATION

Herpes Simplex

Varicella

Latent virus



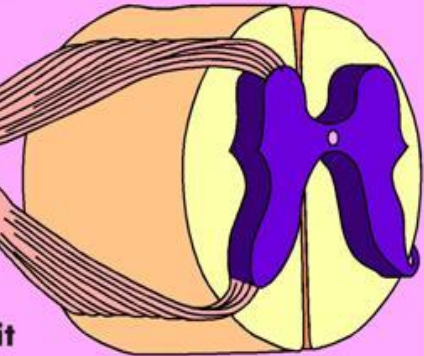
Gingivostomatitis
Mild pharyngitis fever

Chicken pox

Primary Infection

Virus transit
up
peripheral
nerve

**Sensory neuron in
dorsal root ganglion**



Spinal cord

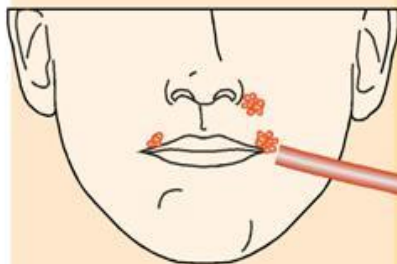
Virus transit
down
peripheral
nerve

Cold Sore

Zoster (shingles)

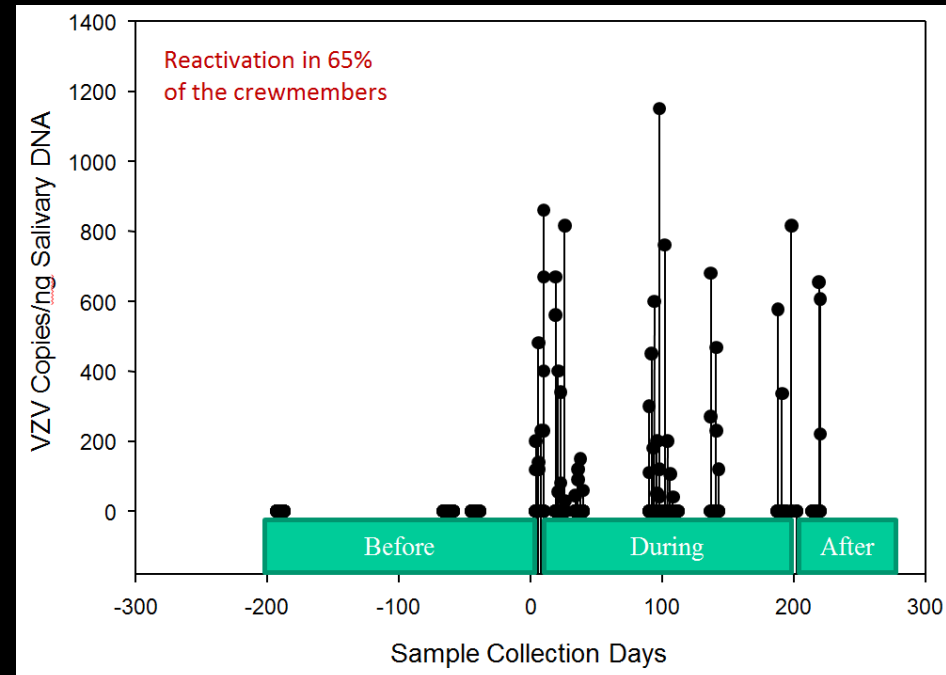
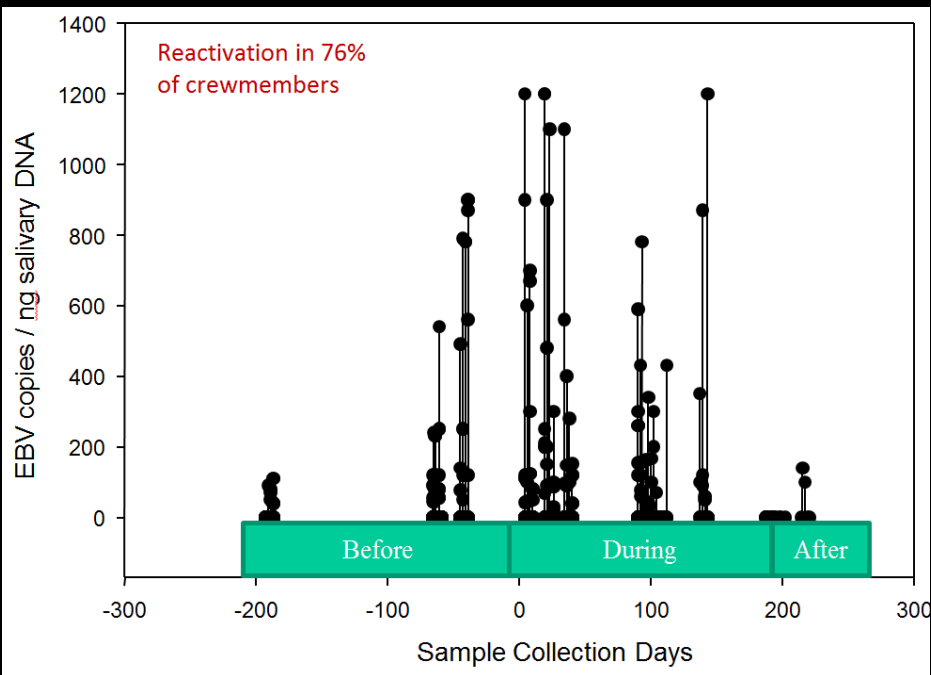
Stress

Activation
of virus
in neuron

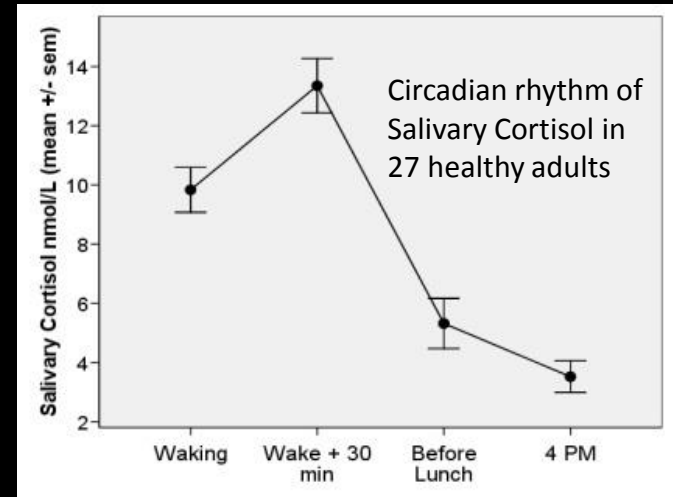


Recurrence

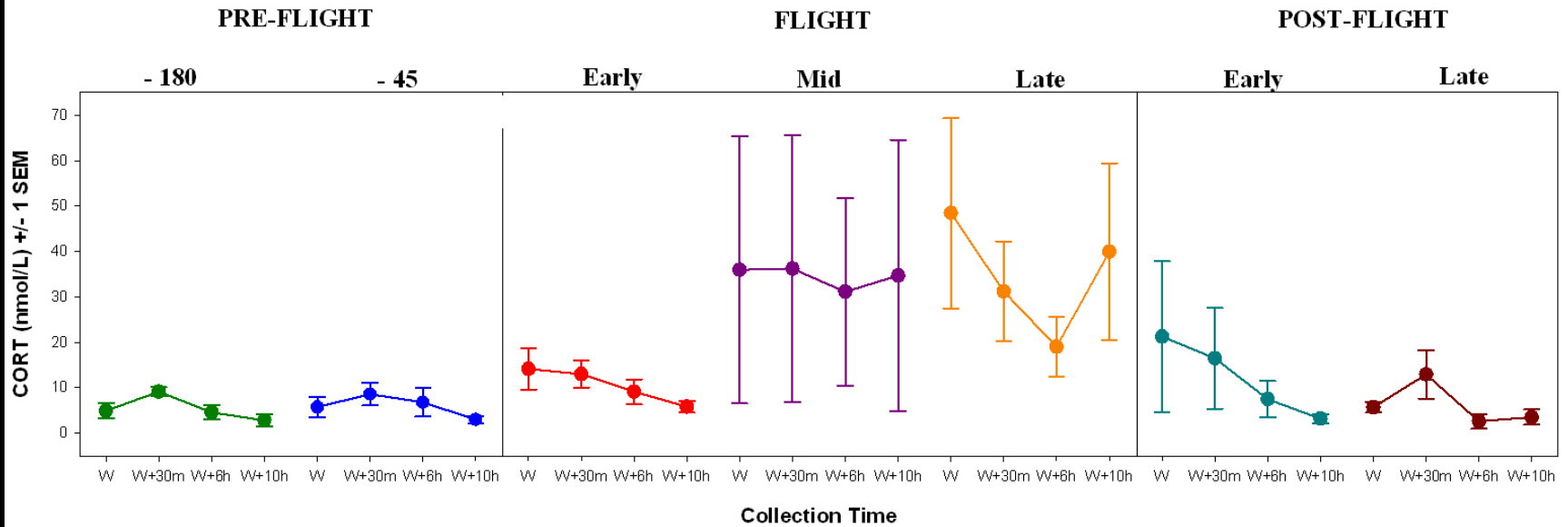
Latent Herpesvirus Reactivation in ISS Crewmembers



Circadian Misalignment in ISS Crewmembers



International Space Station



Plasma Cytokine Analysis



SMO-018

Early
~2 weeks

FD15

FD30

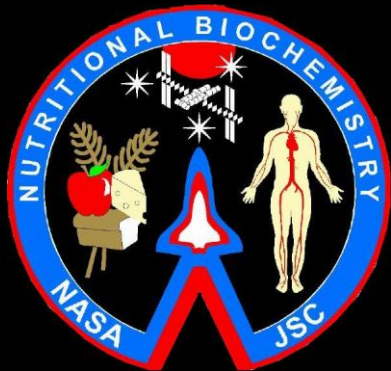
FD60

Mid
2-4 mos

FD120

Late
R-1-2 days

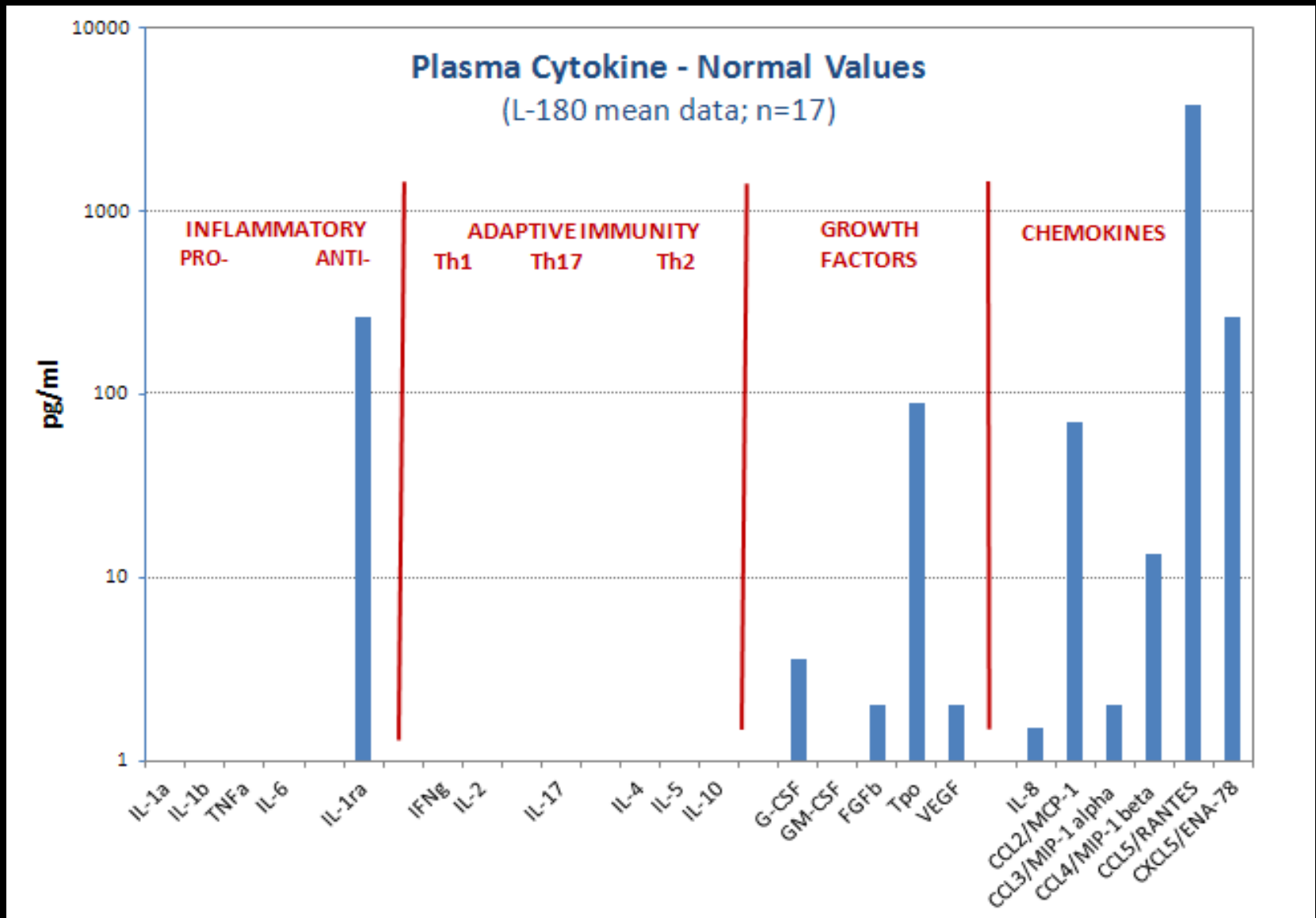
FD180



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 \pm SEM. Bold indicates statistically significant difference $p \leq 0.05$; $n=28$.

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

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



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

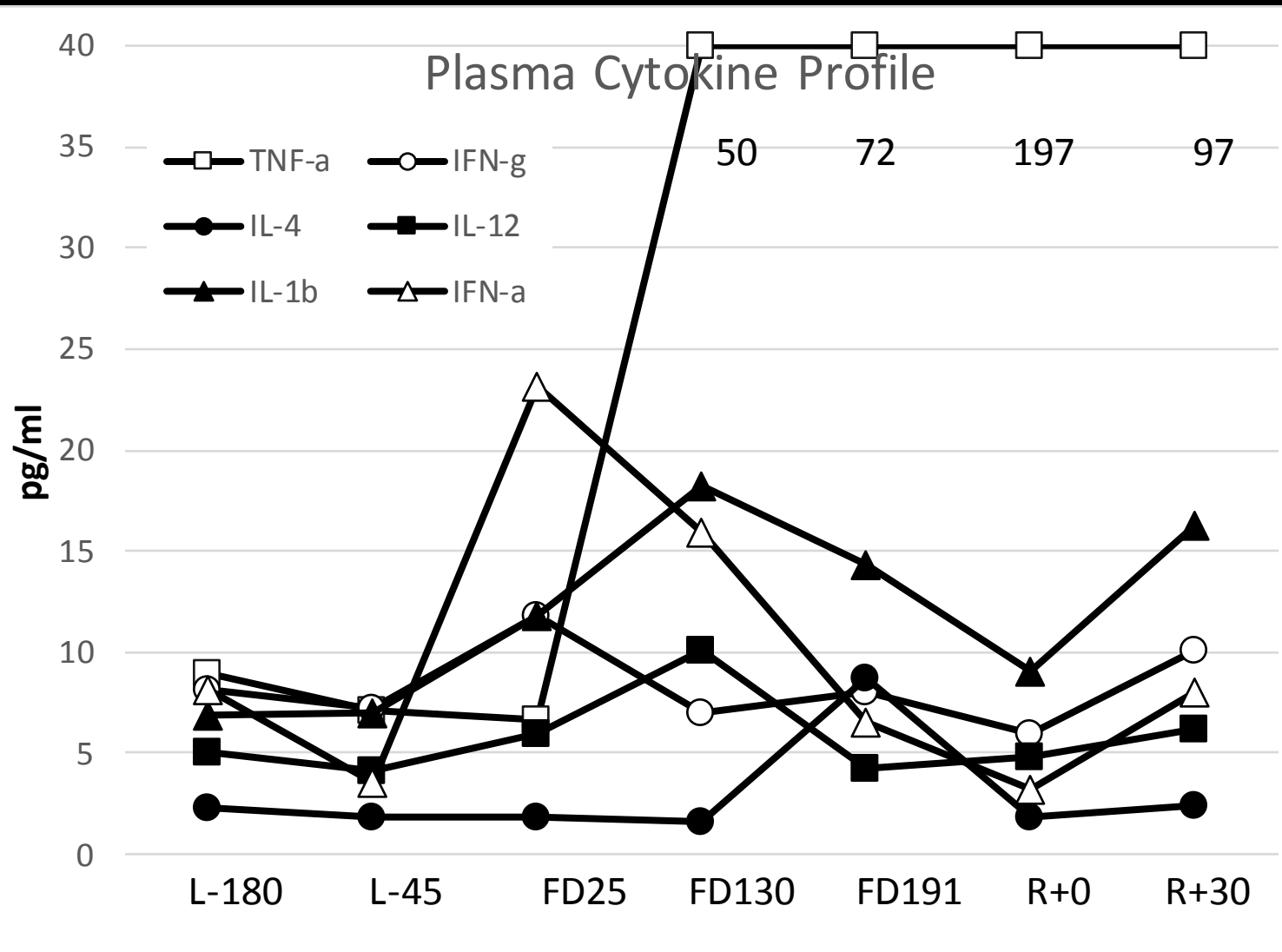


General Rash Characterization

- 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.

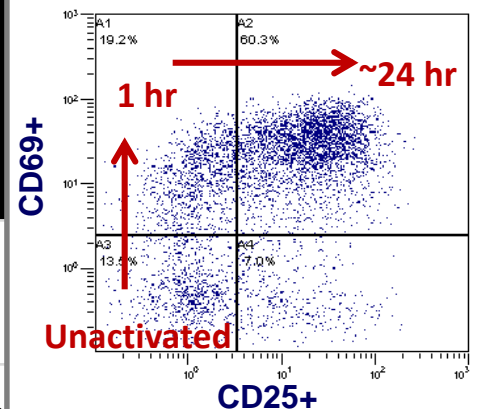


Plasma Cytokine Profile

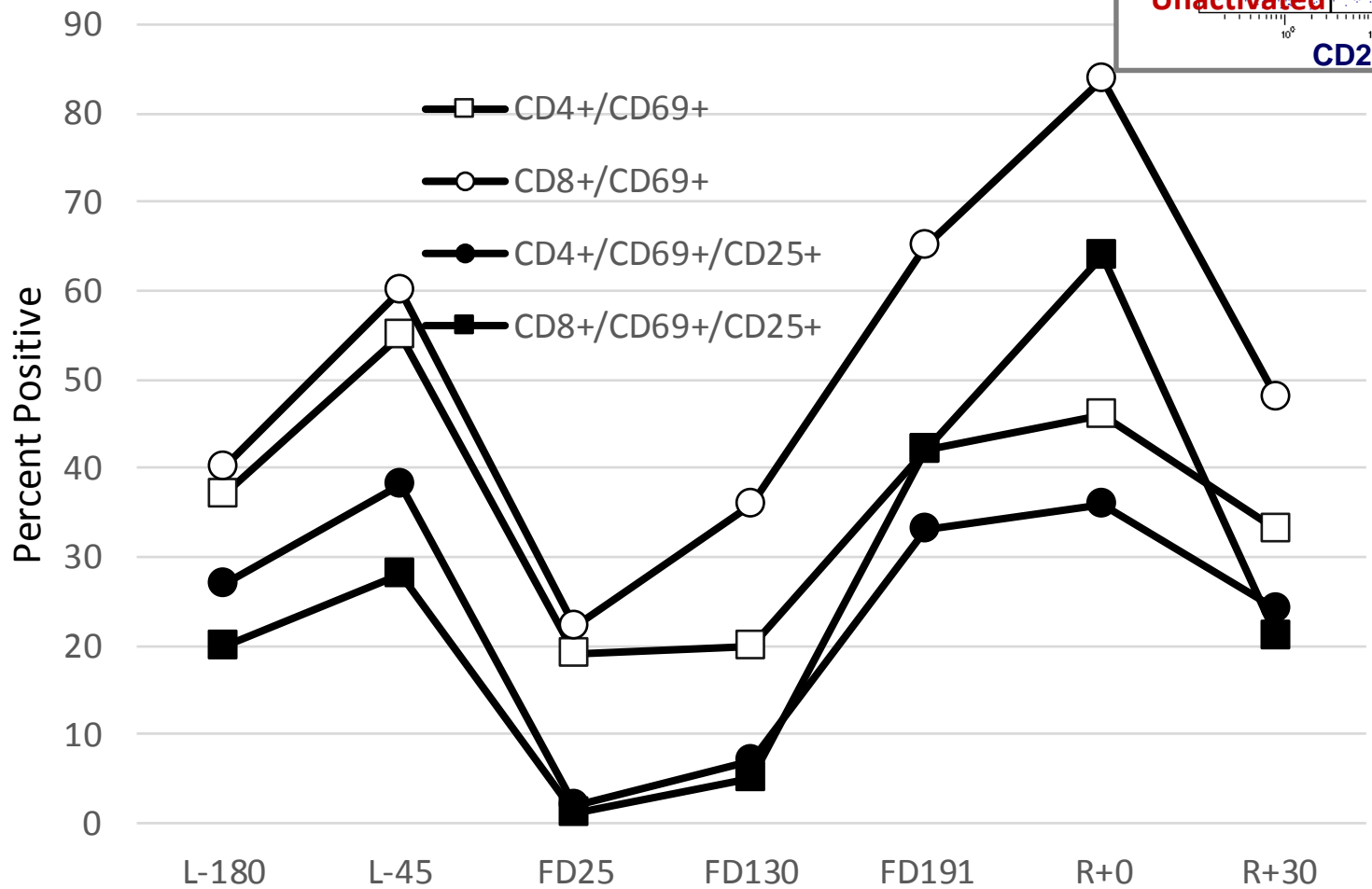


T Cell Function

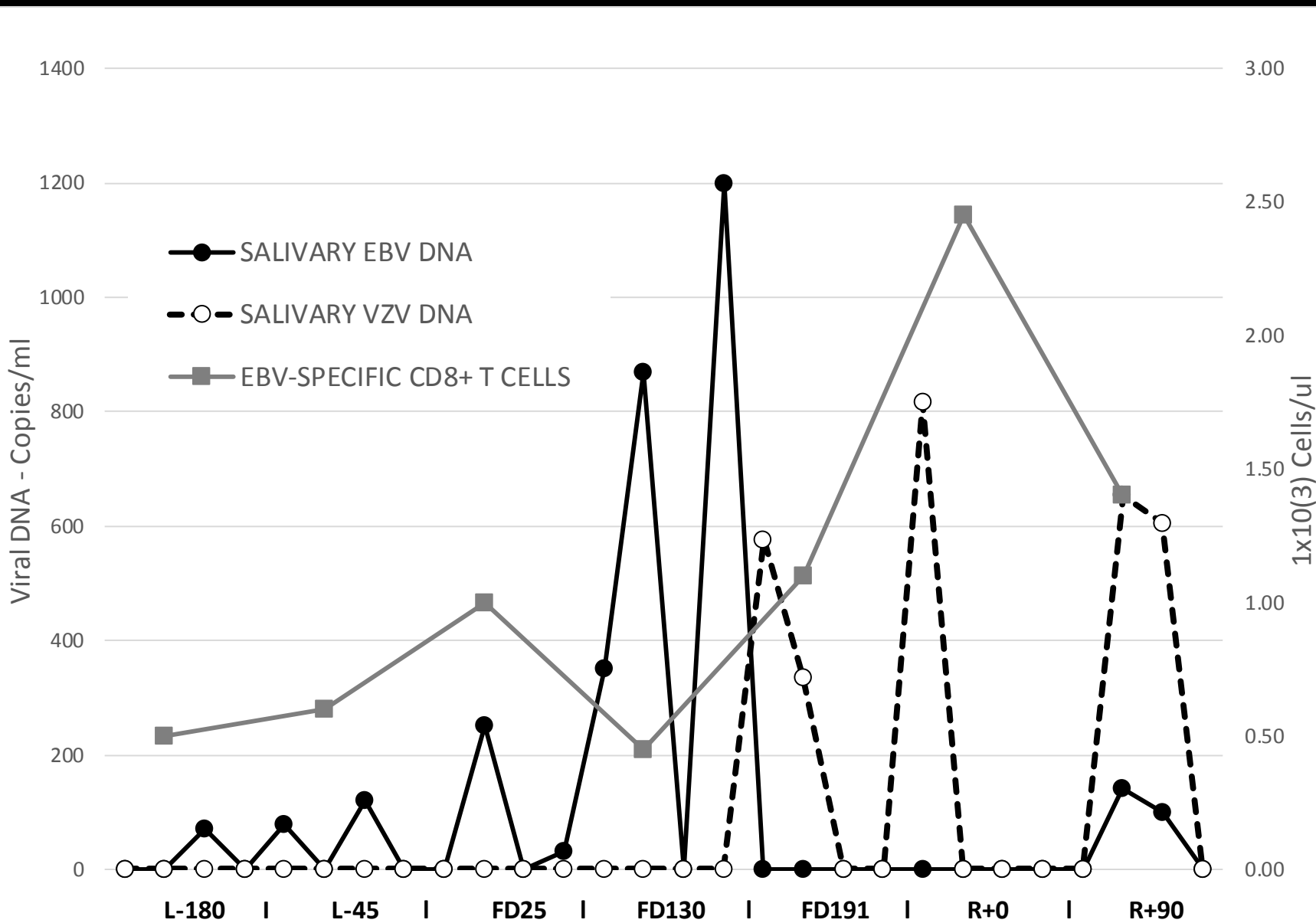
SEA+SEB (24hr)



T Cell Function; SEA+SEB (24hr)



Latent Herpesvirus Reactivation; EBV Specific T Cells



Circadian Rhythm of Salivary Cortisol



COLLECTION TIMES

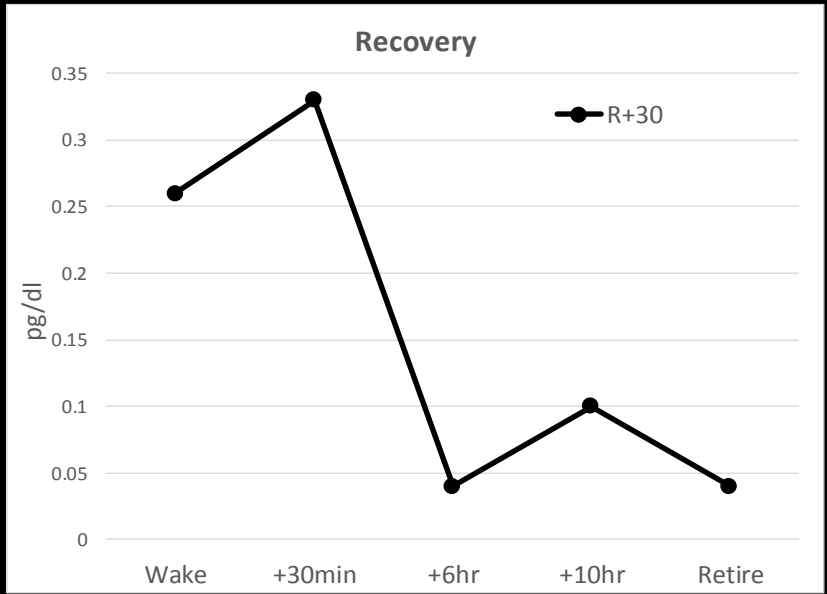
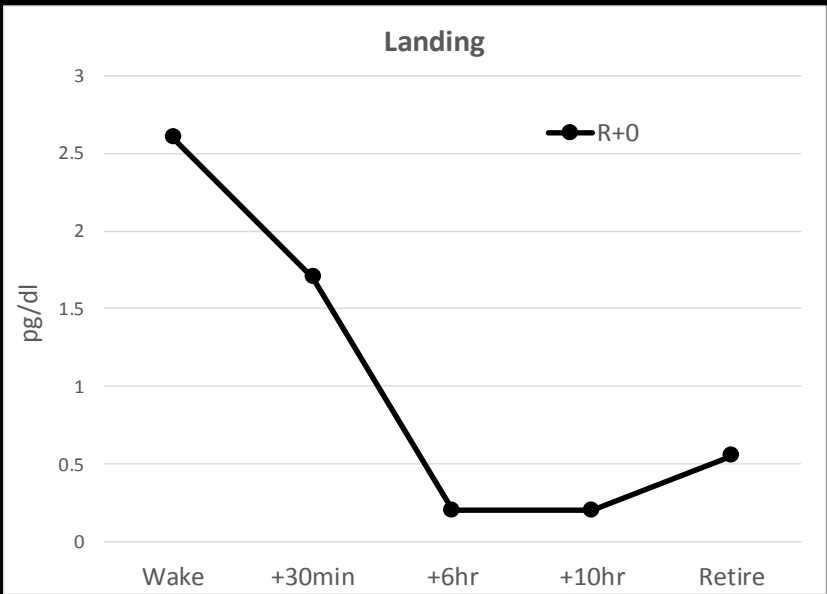
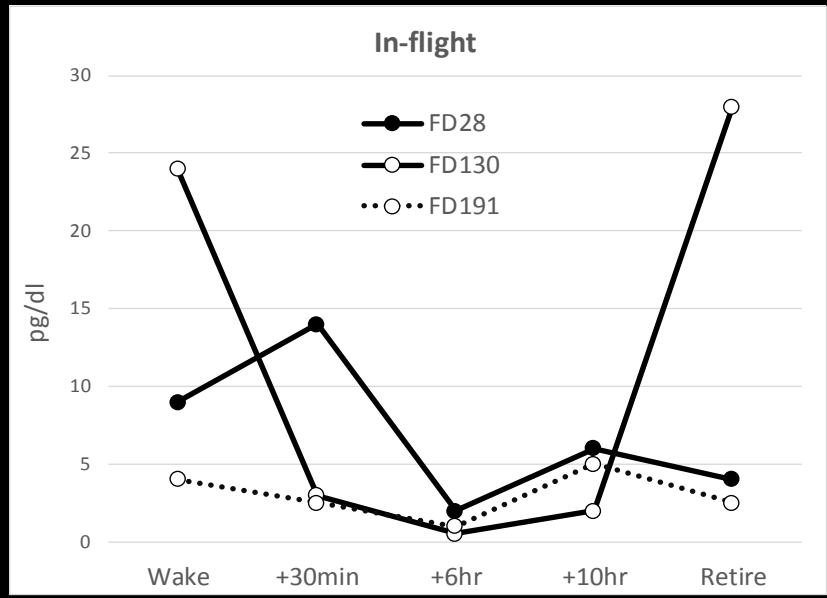
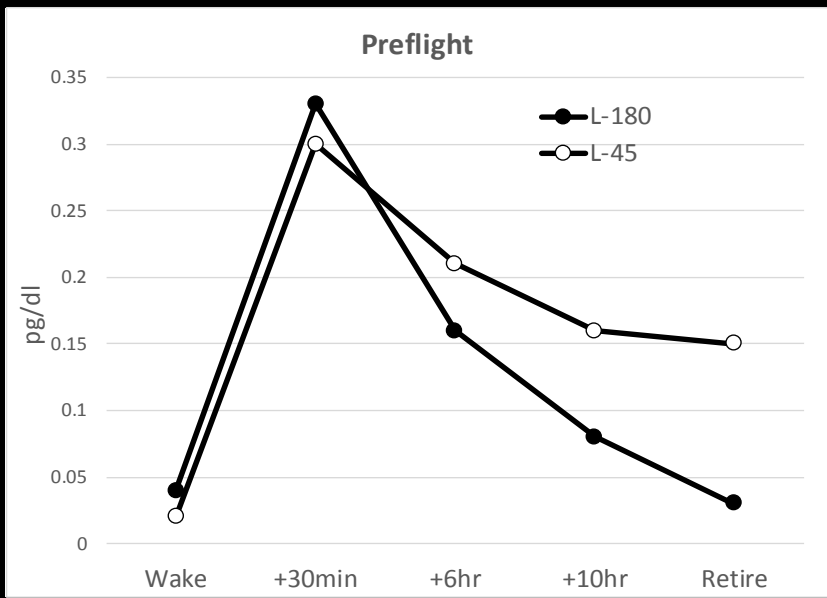
AWAKE

+ 45 MINS

12:00

16:00

RETIRE



Working Hypothesis: Spaceflight Summary Effects on Immunity

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

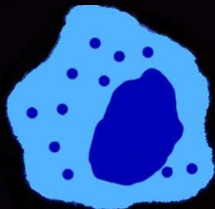
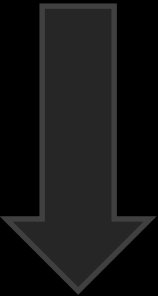
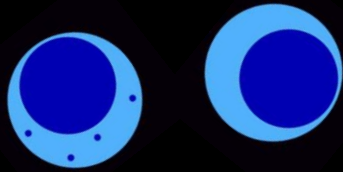
ADAPTIVE

- ↓ 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)

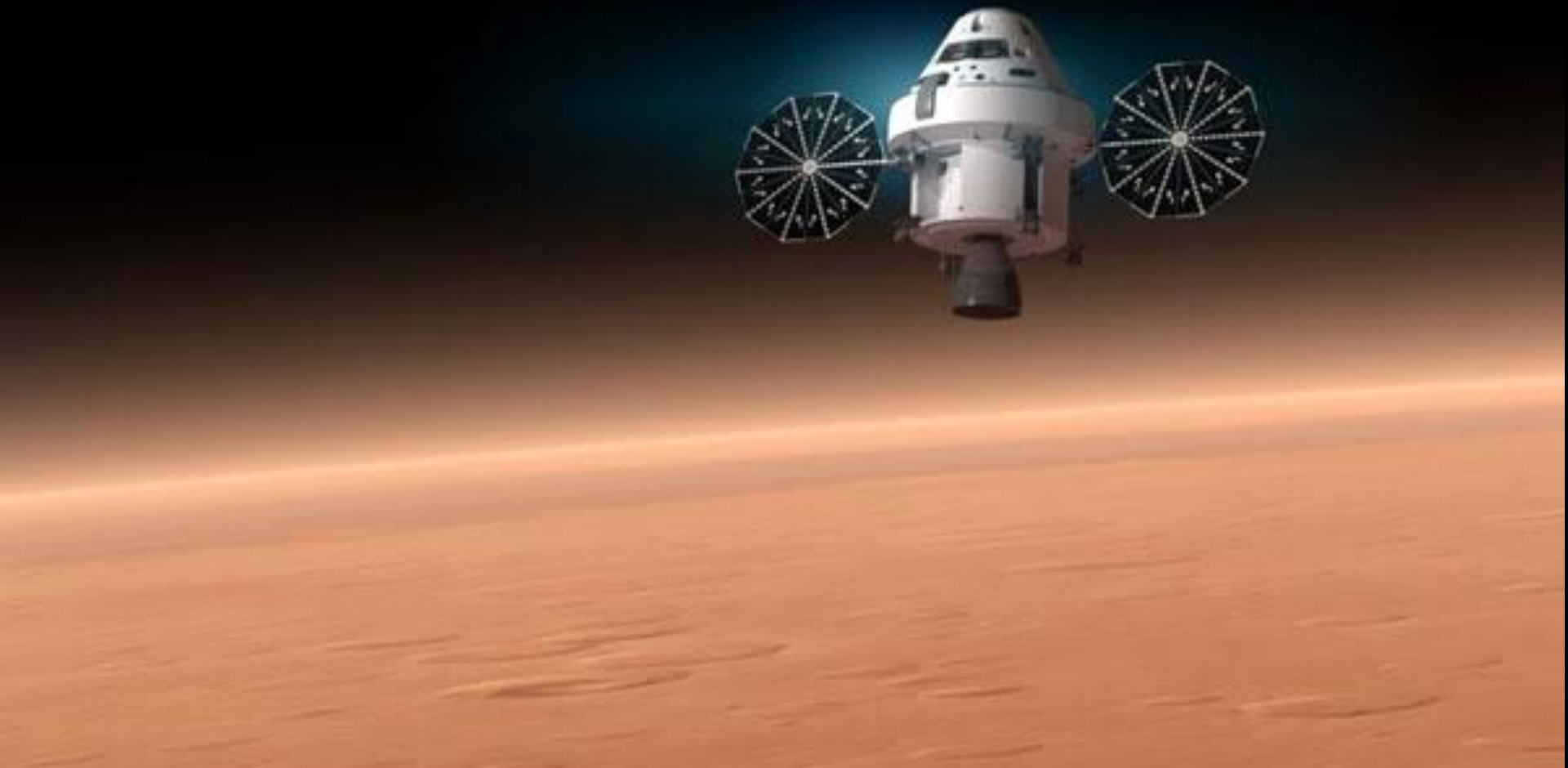


Conclusions

- 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”

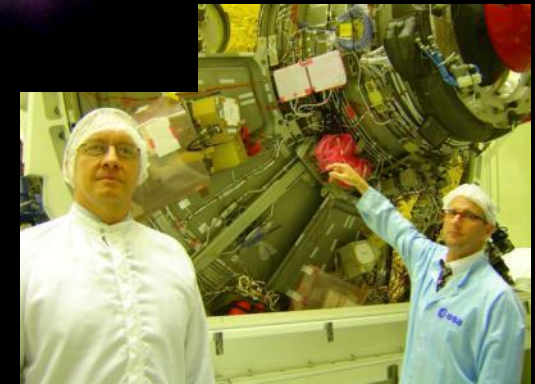
- Serological H. Pylori IgG and IgA antibody test results; Urea Breath Test results, if indicated

Tier 0

Already in place

Preflight Microbiological Monitoring

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



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

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

Immune Countermeasures

- 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
 - α -lipoic acid
 - L-selenomethionine
 - Coenzyme Q10
 - vitamin E succinate
 - D-selenomethionine

Tier 2

Nutritional supplementation

Immune Countermeasures

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

Tier 2

Nutritional supplementation

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 of dietary vitamins and minerals



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.



Tier 3

Pharmacological intervention

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

Immune Countermeasures?

Treatment of Medical Events

- Antibiotics
- Antiviral
- Corticosteroids

Tier 0 Summary Chart - Immunology Countermeasures Tier 1

Already in place

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

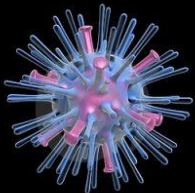
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N-acetyl cysteine, ascorbic acid
a-lipoic acid
L-selenomethionine
Coenzyme Q10
vitamin E succinate
D-selenomethionine

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



Other options

- Antiviral (VZV) vaccination

Tier 1

Multidiscipline, benign

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

Tier 3

Pharmacological intervention

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







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