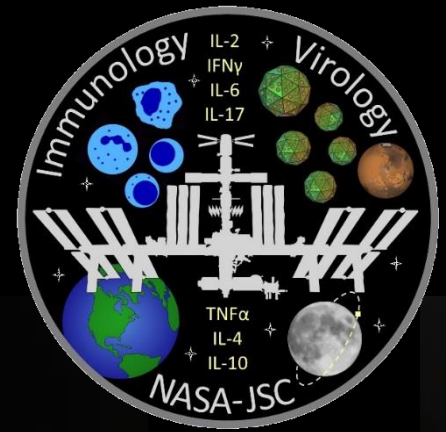
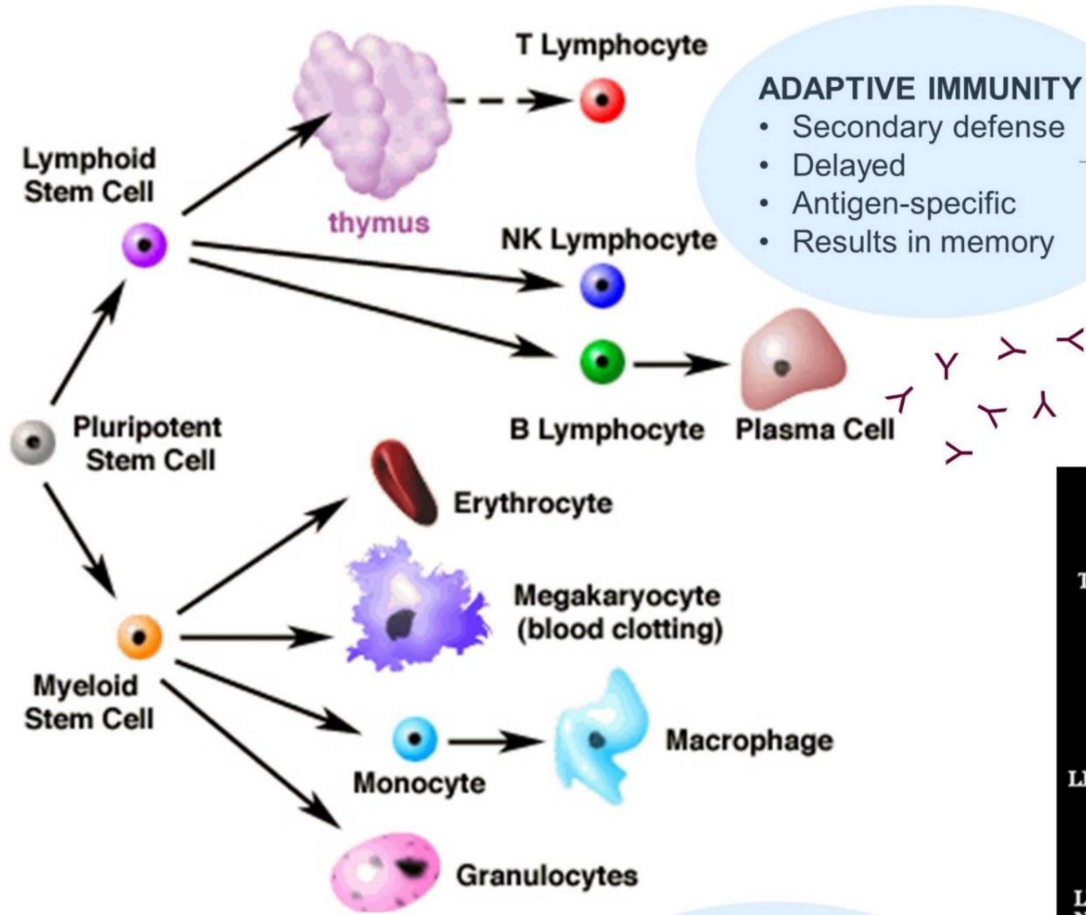


UPDATE ON SPACEFLIGHT IMMUNE SYSTEM DYSREGULATION, CLINICAL RISKS FOR DEEP SPACE MISSIONS, POTENTIAL COUNTERMEASURES



The Immune System



ADAPTIVE IMMUNITY

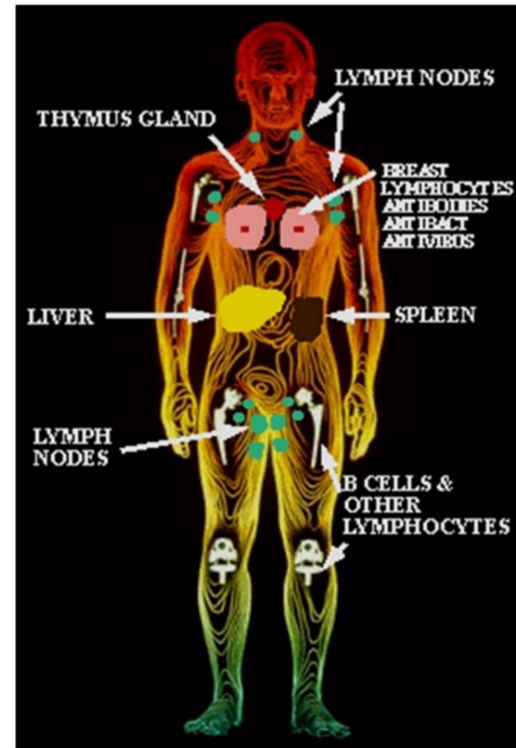
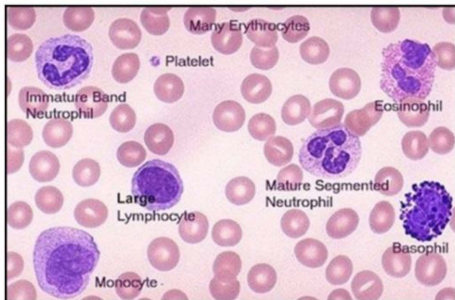
- Secondary defense
- Delayed
- Antigen-specific
- Results in memory

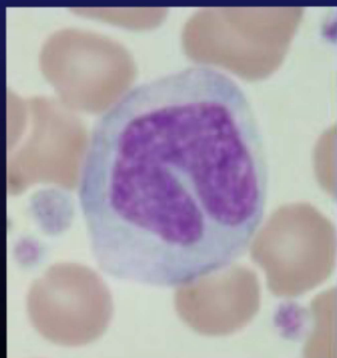
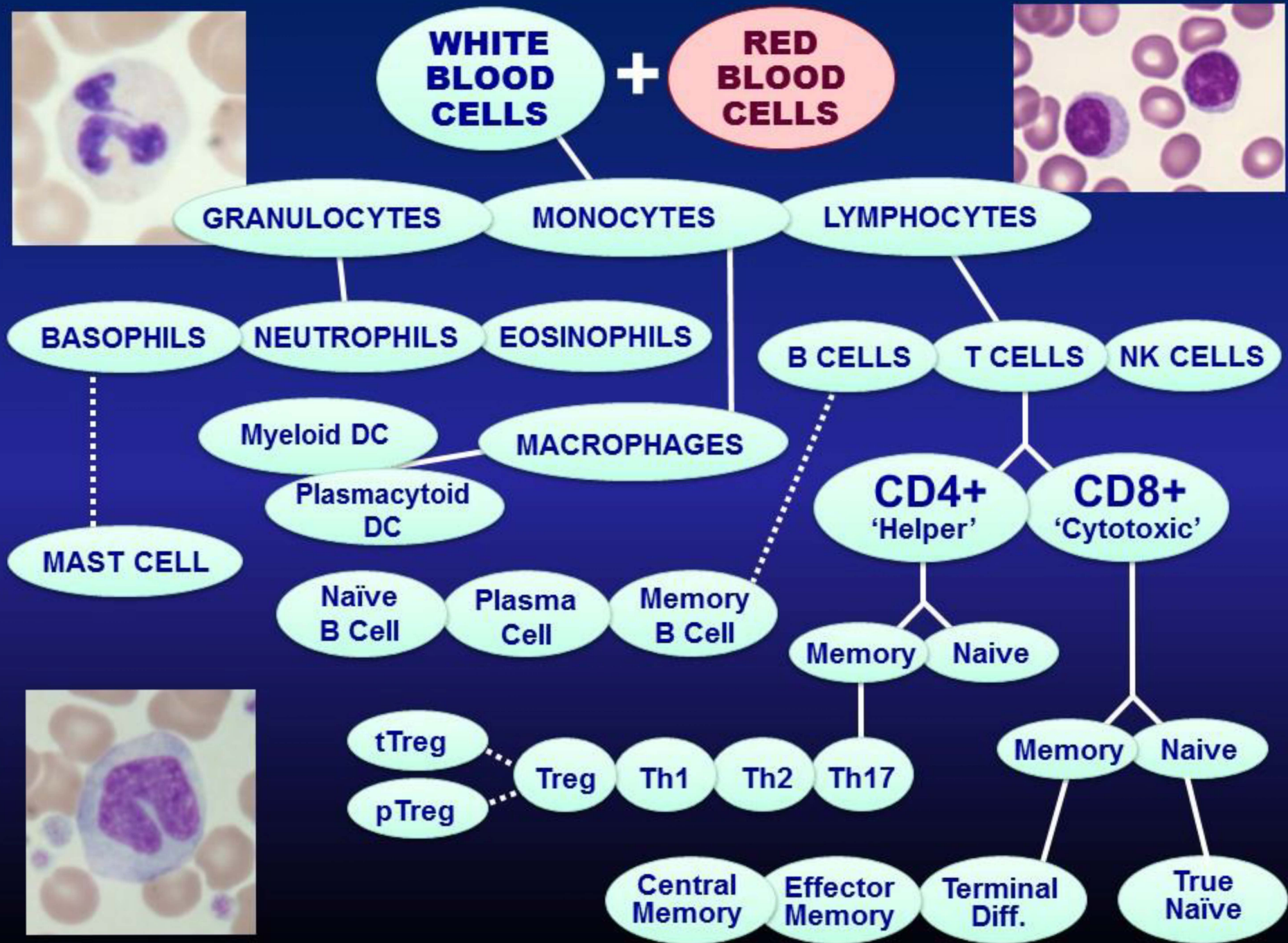
Cell mediated immunity:
Mediated by cytotoxic T lymphocytes which destroy viral infected cells, transplant cells, some tumor cells

Humoral immunity:
Mediated by B cells/Plasmacytes. Antibodies bind specific antigens, signals other cells to engulf and remove that target from the body.

INNATE IMMUNITY

- Primary defense
- Immediate
- Non-specific
- Does not result in memory





Eat microbes

Fight Parasites

Direct
'Right'
Kind of
Response

Fight
Cancer

Inflammation

Cause
Allergy

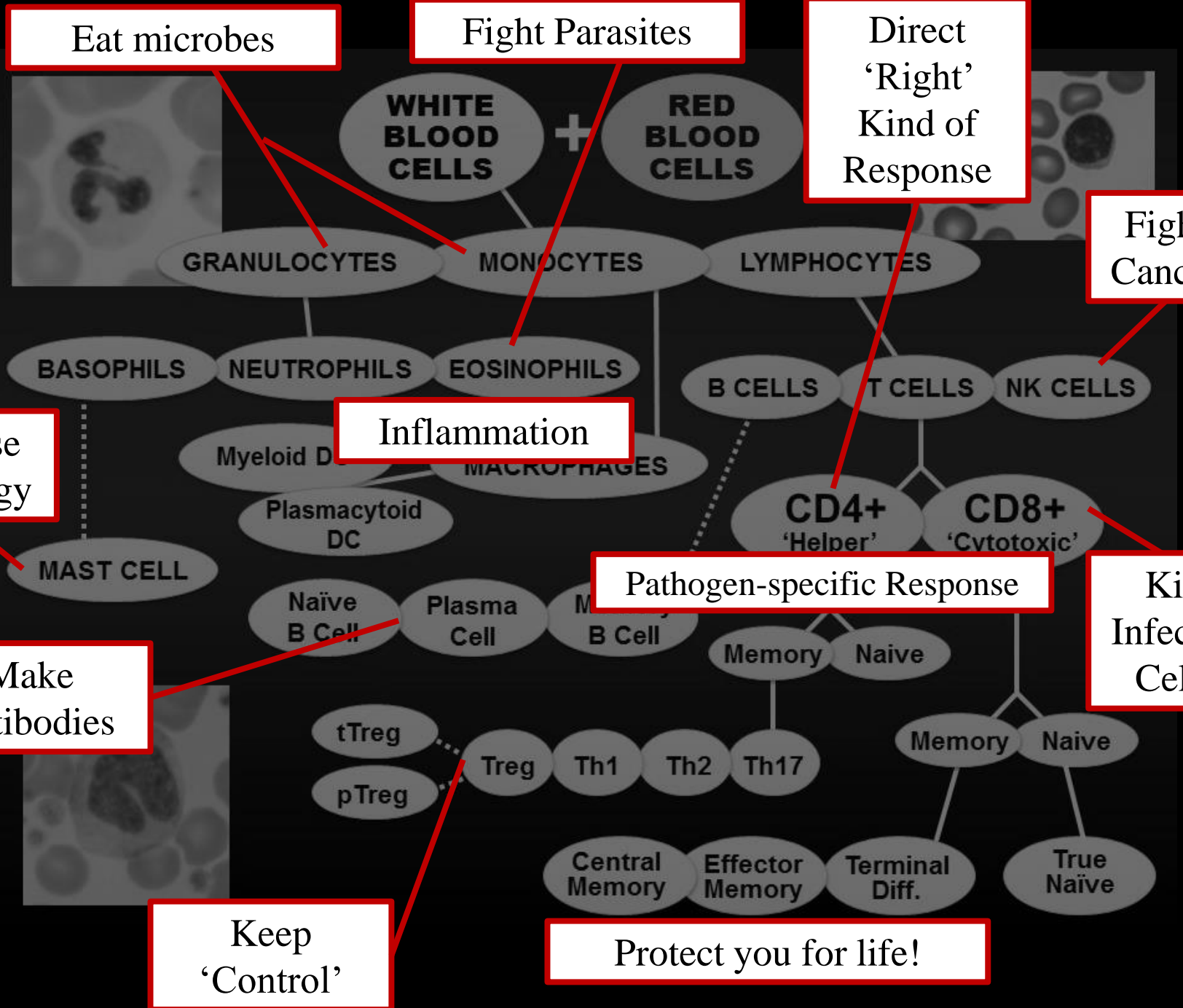
Pathogen-specific Response

Kill
Infected
Cells

Make
Antibodies

Keep
'Control'

Protect you for life!



CYTOKINE NETWORK

Growth Factors

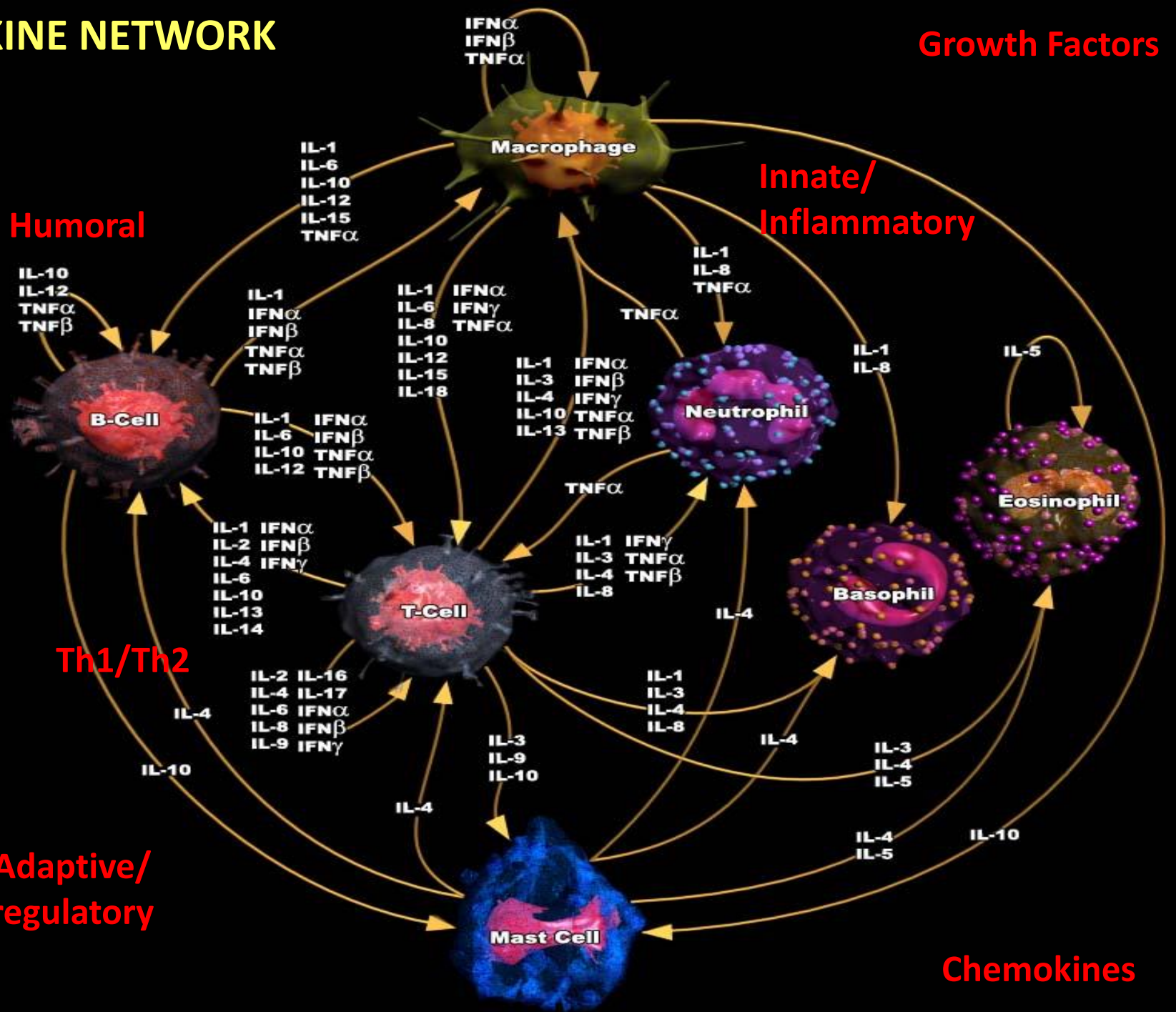
Humoral

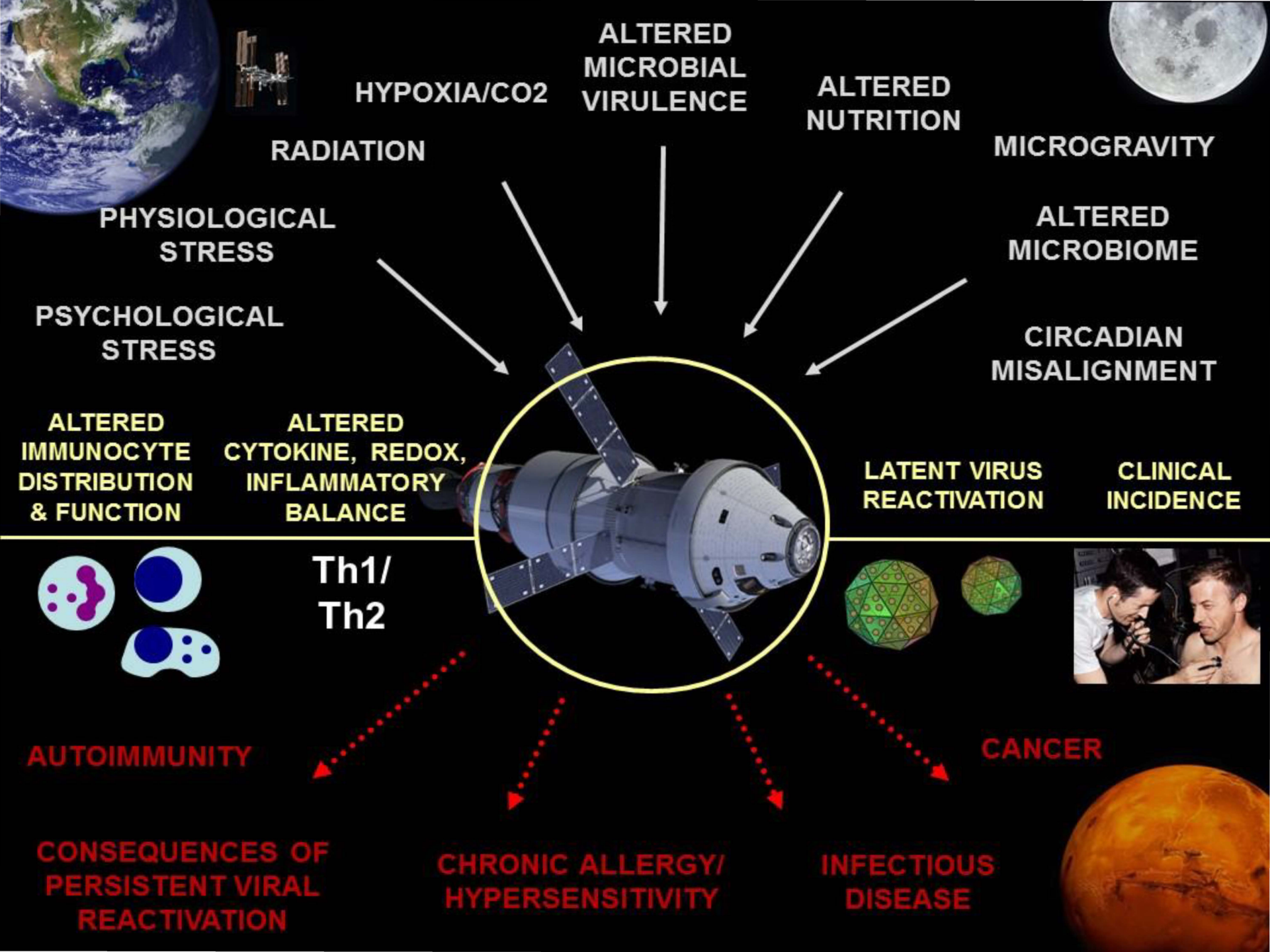
Innate/
Inflammatory

Th1/Th2

Adaptive/
regulatory

Chemokines





Immunity and Disease

VIRAL INFECTION

meningitis

- JC virus
- Measles
- LCM virus
- Arbovirus
- Rabies

Common cold

- Rhinoviruses
- Parainfluenza virus
- Respiratory syncytial virus

Eye infections

- Herpes simplex virus
- Adenovirus
- Cytomegalovirus

Parotitis

- Mumps virus

Pneumonia

- Influenza virus, Types A and B
- Parainfluenza virus
- Respiratory syncytial virus
- Adenovirus
- SARS coronavirus

Gingivostomatitis

- Herpes simplex type 1

Pharyngitis

- Adenovirus
- Epstein-Barr virus
- Cytomegalovirus

Cardiovascular

- Coxsackie B virus

Hepatitis

- Hepatitis virus types A, B, C, D, E

Skin infections

- Varicella zoster virus
- Human herpesvirus 6
- Smallpox
- Molluscum contagiosum
- Human papillomavirus
- Parvovirus B19
- Rubella
- Measles
- Coxsackie A virus

Sexually transmitted diseases

- Herpes simplex type 2
- Human papillomavirus
- HIV

Myelitis

- Poliovirus
- HTLV-I

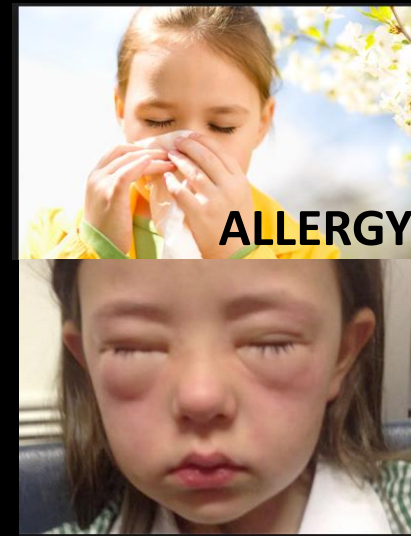
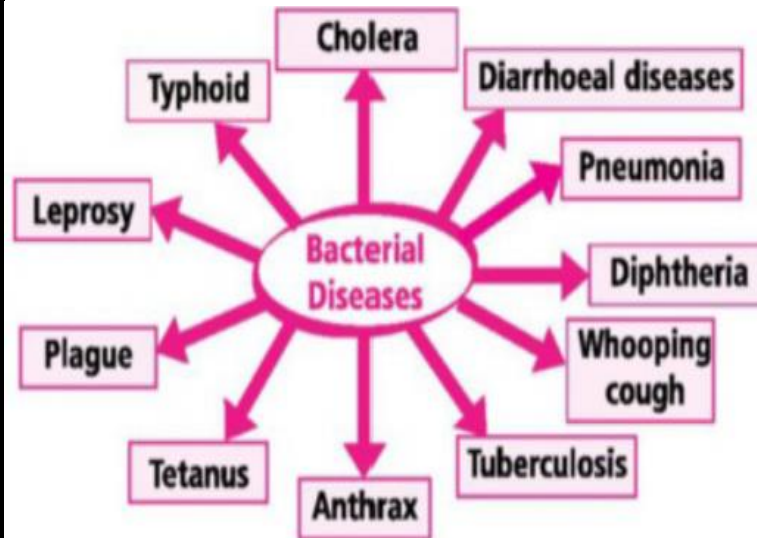
Gastroenteritis

- Adenovirus
- Rotavirus
- Norovirus
- Astrovirus
- Coronavirus

Pancreatitis

- Coxsackie B virus

BACTERIAL INFECTION



SHINGLES

SHINGLES

Hair shaft

Skin surface

Initial stage consists of burning pain and sensitive skin

Weakend immune system reawakens virus

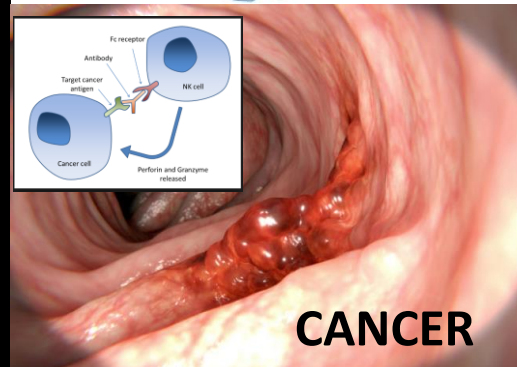
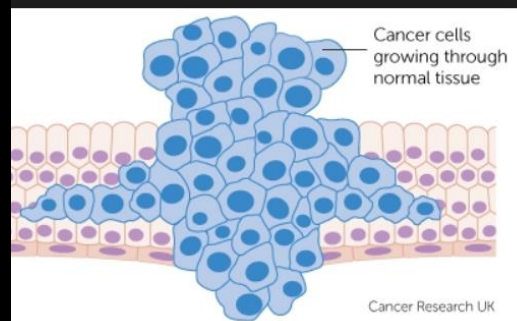
Dormant Varicella virus

Nerve fiber

Blisters develop resembling chicken pox and fill with pus

Blisters eventually burst, crust over and heal

Nerve damage can cause postherpetic neuralgia



AUTOIMMUNE DISEASE

Over 100 Different Types of Autoimmune Disorders

Brain

- Multiple Sclerosis
- Guilain-Barre Syndrome
- Autism

Thyroid

- Thyroiditis
- Hashimoto's Disease
- Graves' Disease

Bones

- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Polymyalgia Rheumatica

Muscles

- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Polymyalgia Rheumatica

Skin

- Psoriasis
- Vitiligo
- Eczema
- Scleroderma

Blood

- Leukemia
- Lupus Erythematosus
- Hemolytic Dysglycemia

GI Tract

- Celiac's Disease
- Crohn's Disease
- Ulcerative Colitis
- Diabetes Type I

Nerves

- Peripheral Neuropathy
- Diabetic Neuropathy

Lung

- Fibromyalgia
- Wegener's Granulomatosis

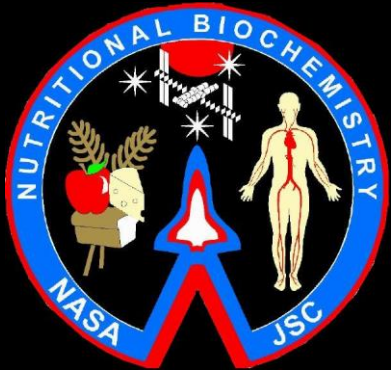
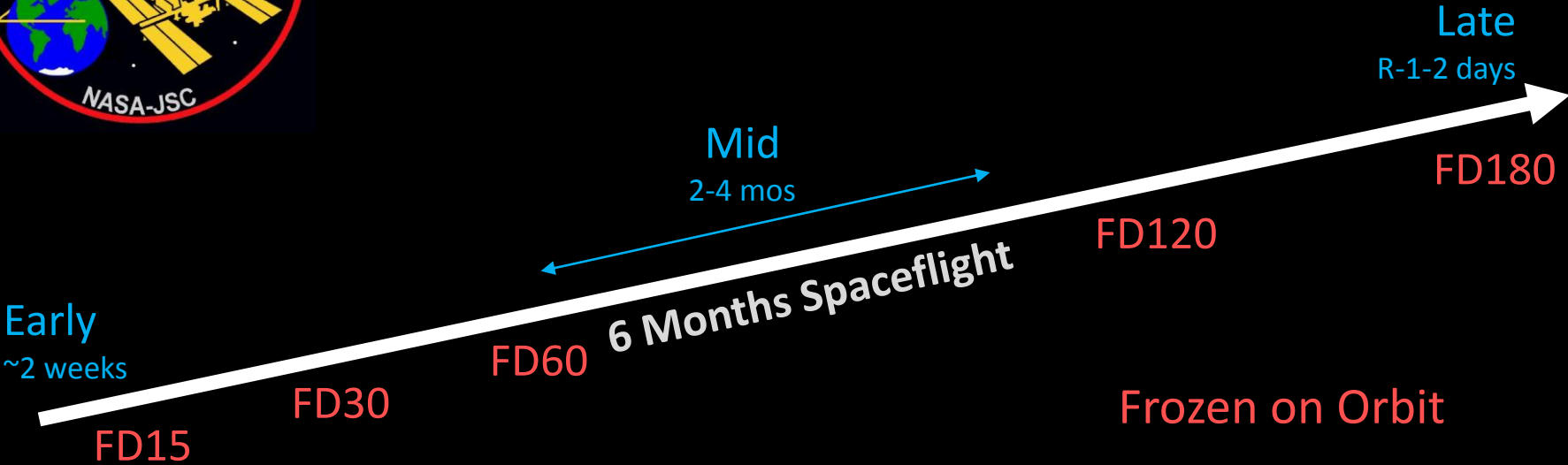
Blood and Saliva Collection- ISS



Plasma Collection - ISS

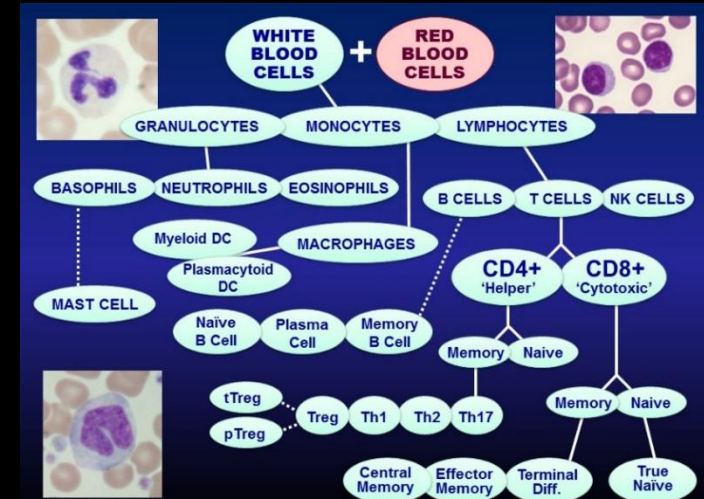


Return Ambient – 45h Delay

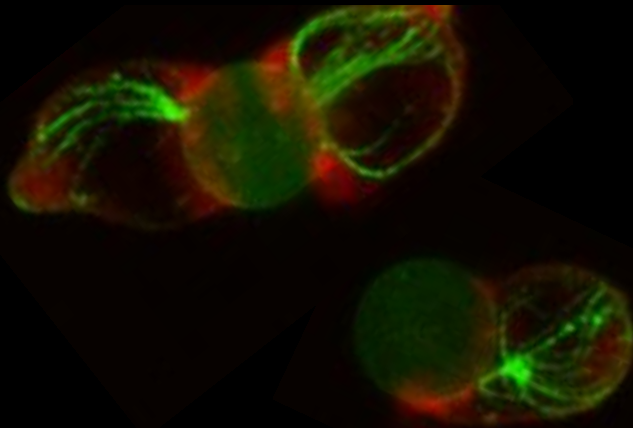
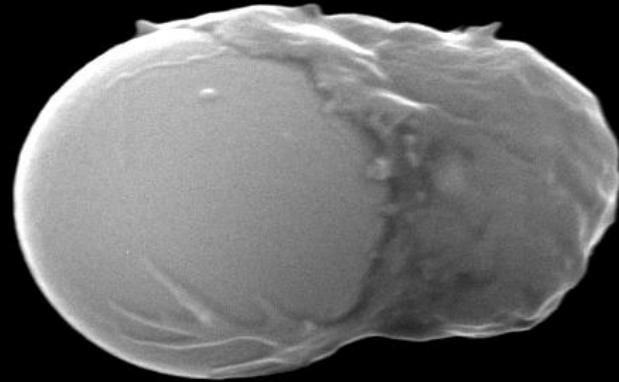
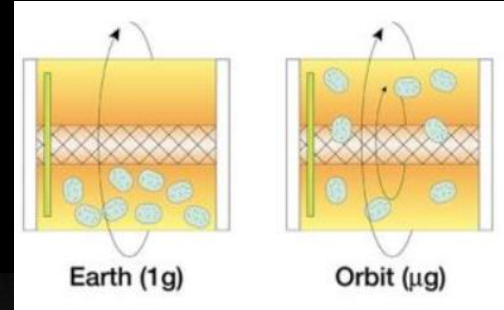
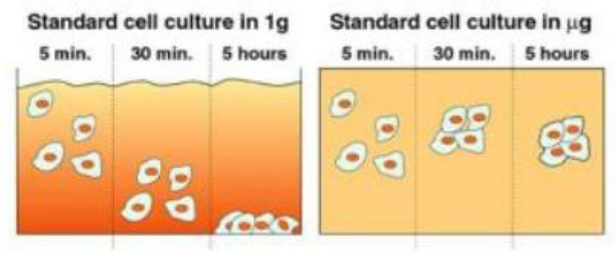


SPACEFLIGHT IMMUNE DYSREGULATION

- Peripheral leukocyte distribution in astronauts is relatively normal
- T cell, NK cell function is inhibited by microgravity
- T cell function is reduced in astronauts; appears to be a shift in the activation threshold
- NK cells are disarmed, reduction in lytic molecule content
- B cell function in astronauts appears unaltered (limited data)
- Innate immunocyte function dysregulated during spaceflight
- Plasma cytokine concentrations are altered in astronauts
- Astronauts experience persistent reactivation of latent herpesviruses, biomarker of reduced immunity
- Astronauts demonstrate elevated stress hormones and dysregulated circadian rhythms during spaceflight
- Astronauts have some degree of clinical incidence, primarily dermatitis, allergy and infections
- Dermatitis may be associated with viral etiology
- Some crew experience persistent symptoms requiring prolonged management



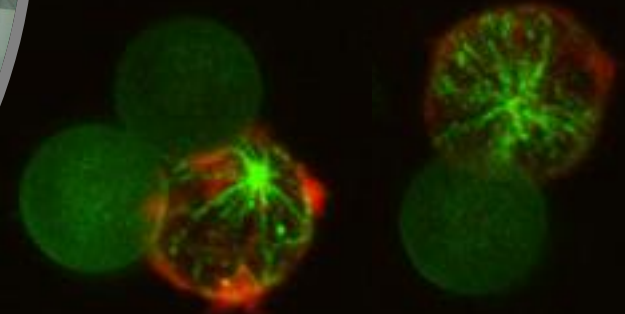
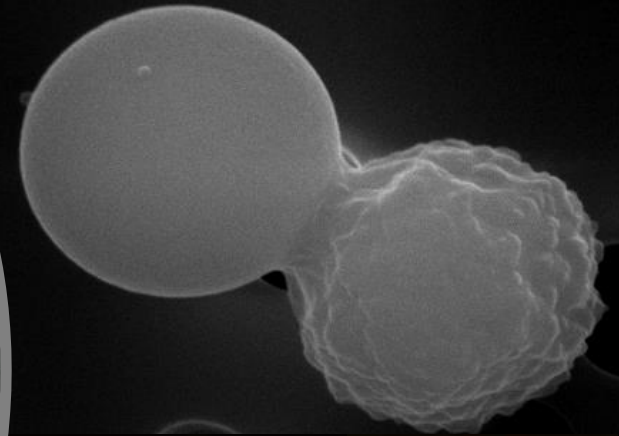
Microgravity Cell Culture



1xG CONTROL

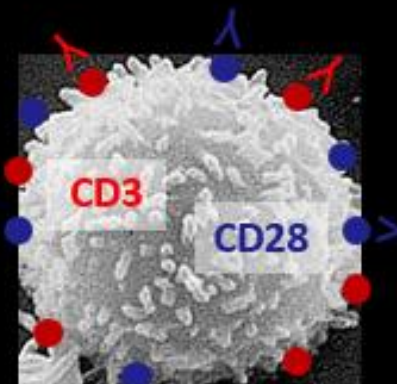
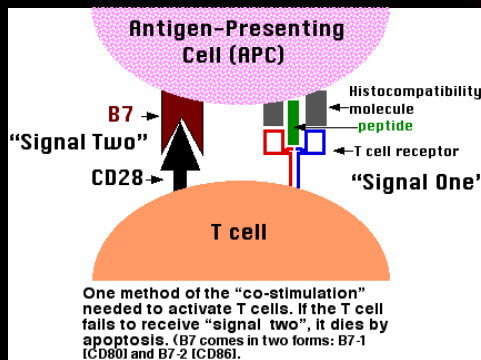
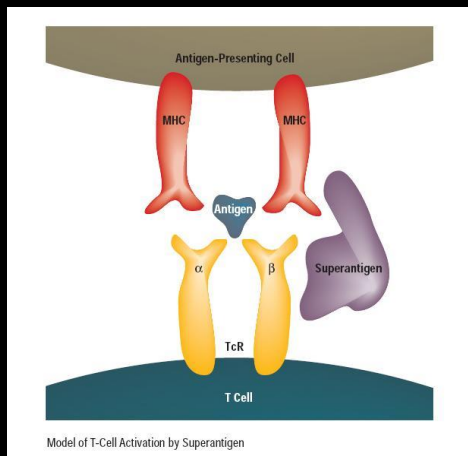
Red: Actin localization

Green: Microtubules/MTOC



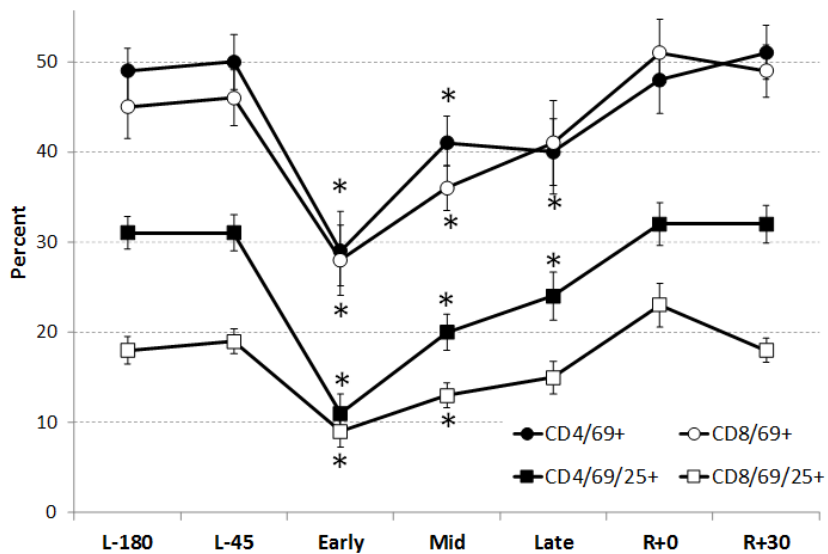
MODELED MICROGRAVITY

T Cell Function



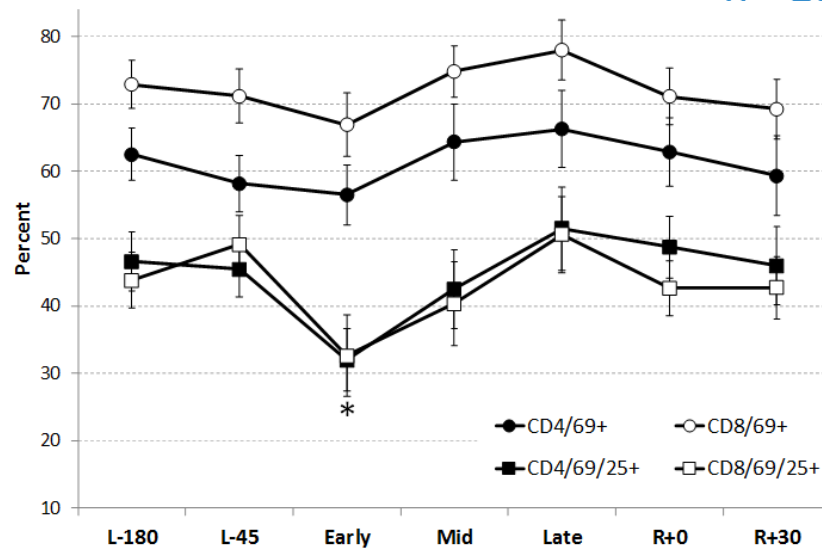
SEA+SEB

n=23

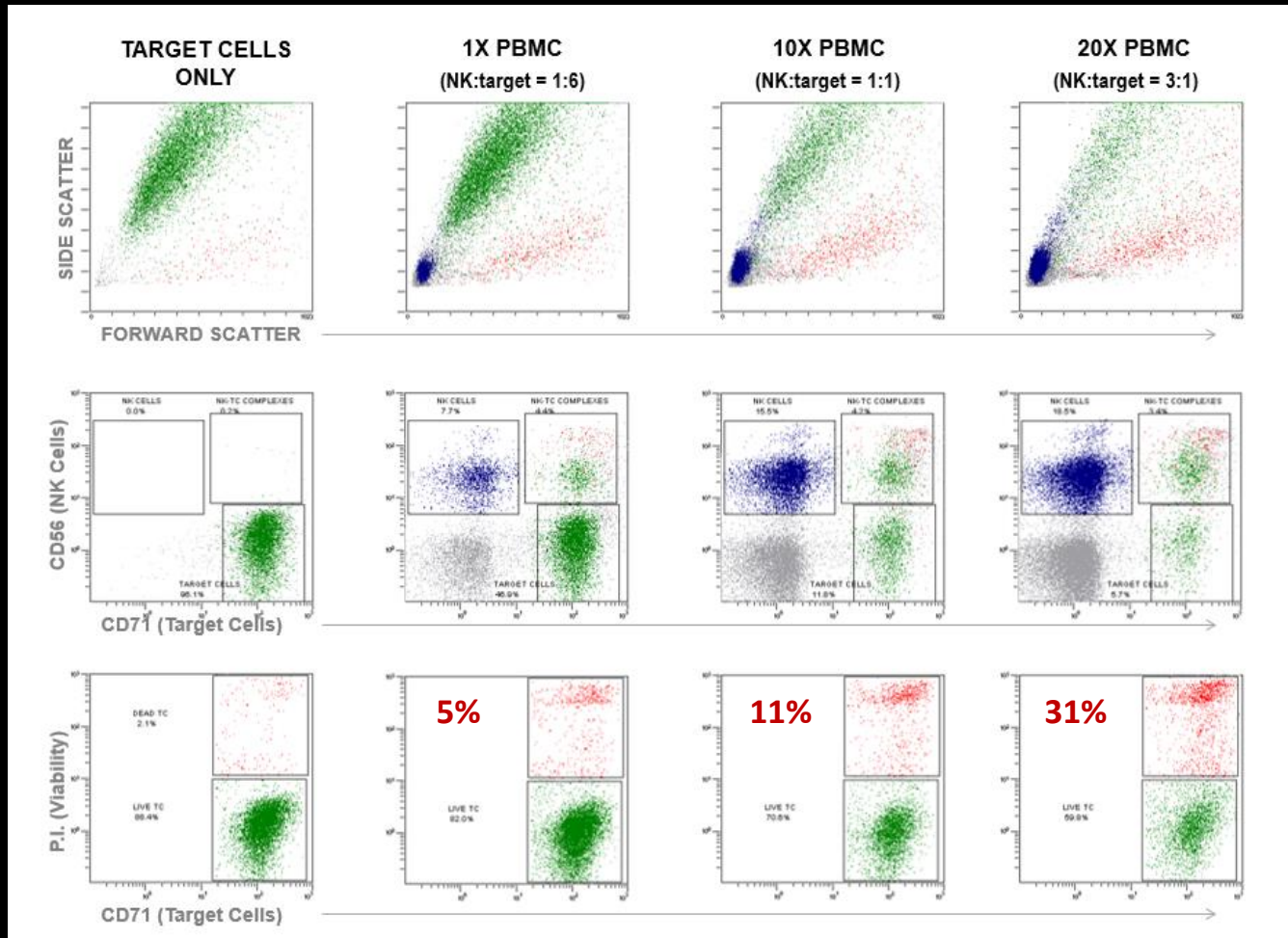
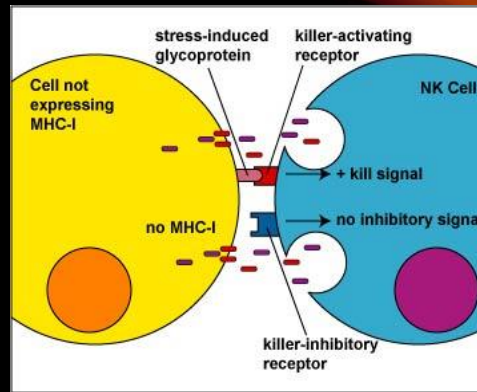


αCD3/αCD28

n=17



NK Cell Function

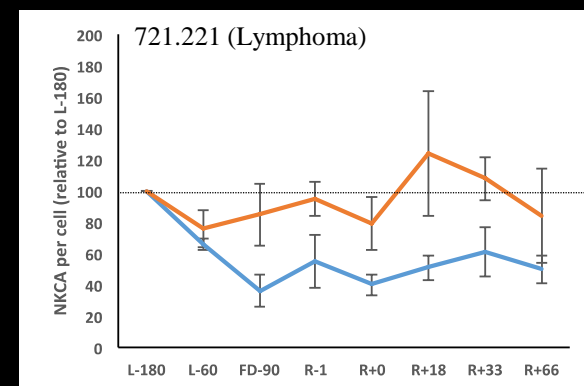
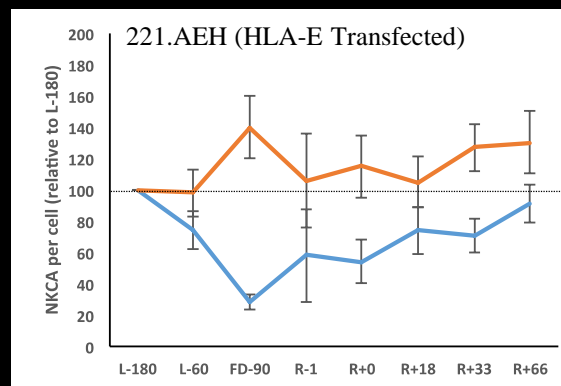
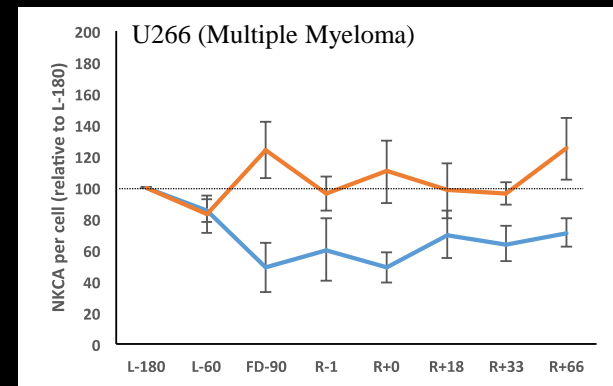
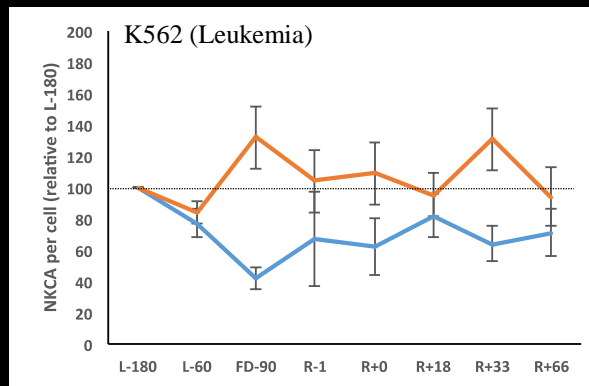


NK Cell Function

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)
----- Baseline NKCA



Plasma Cytokine Analysis

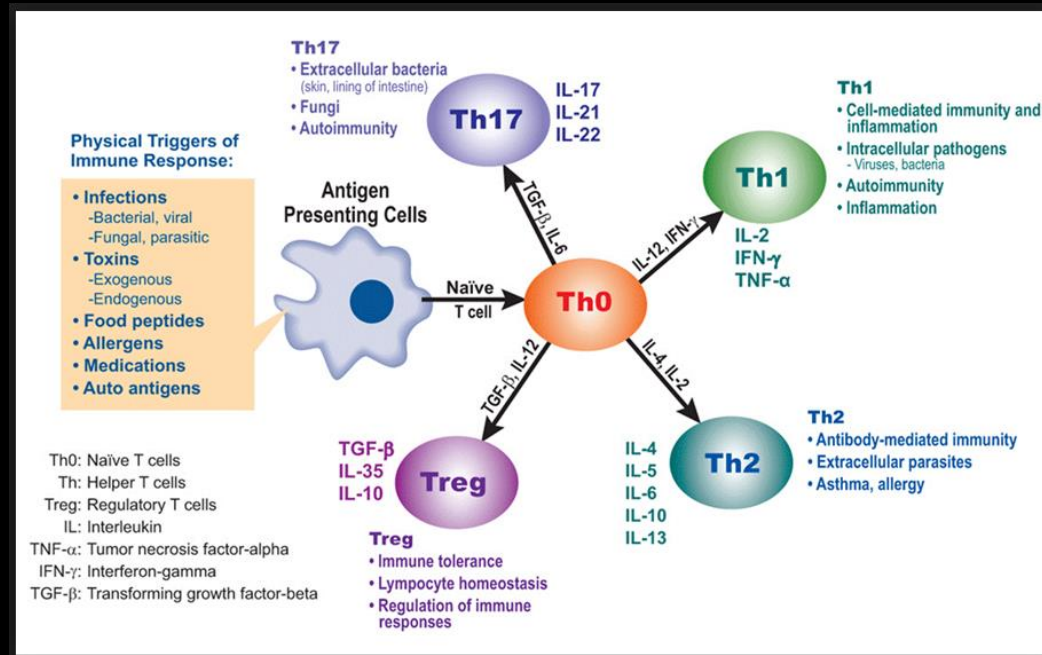


Table 1: Twenty two cytokines for analysis by category

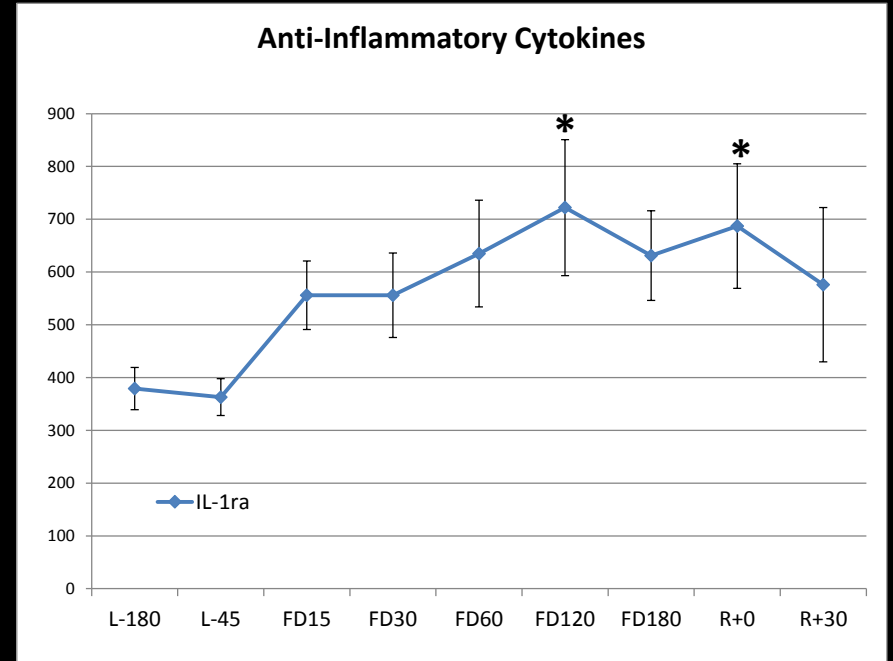
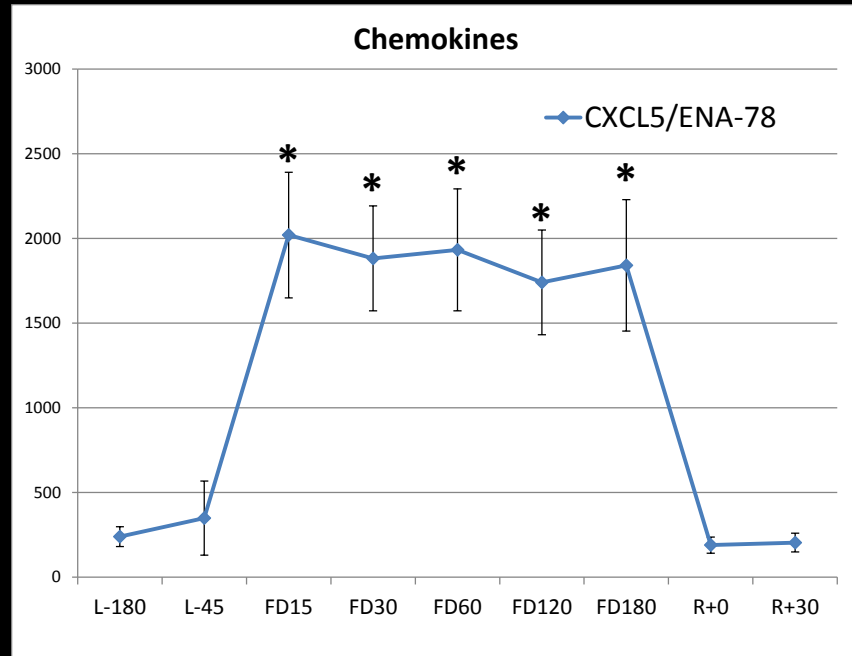
Inflammatory	Anti-Inflammatory	Adaptive/Regulatory	Growth Factors	Chemokines
IL-1 α	IL-1ra	IFN γ	G-CSF	CCL2/MCP-1
IL-1 β		IL-2	GM-CSF	CCL3/MIP-1 alpha
TNF α		IL-17	FGF basic	CCL4/MIP-1 beta
IL-6		IL-4	Tpo	CCL5/RANTES
IL-8		IL-5	VEGF	CXCL5/ENA-78
		IL-10		

Plasma Cytokine Analysis

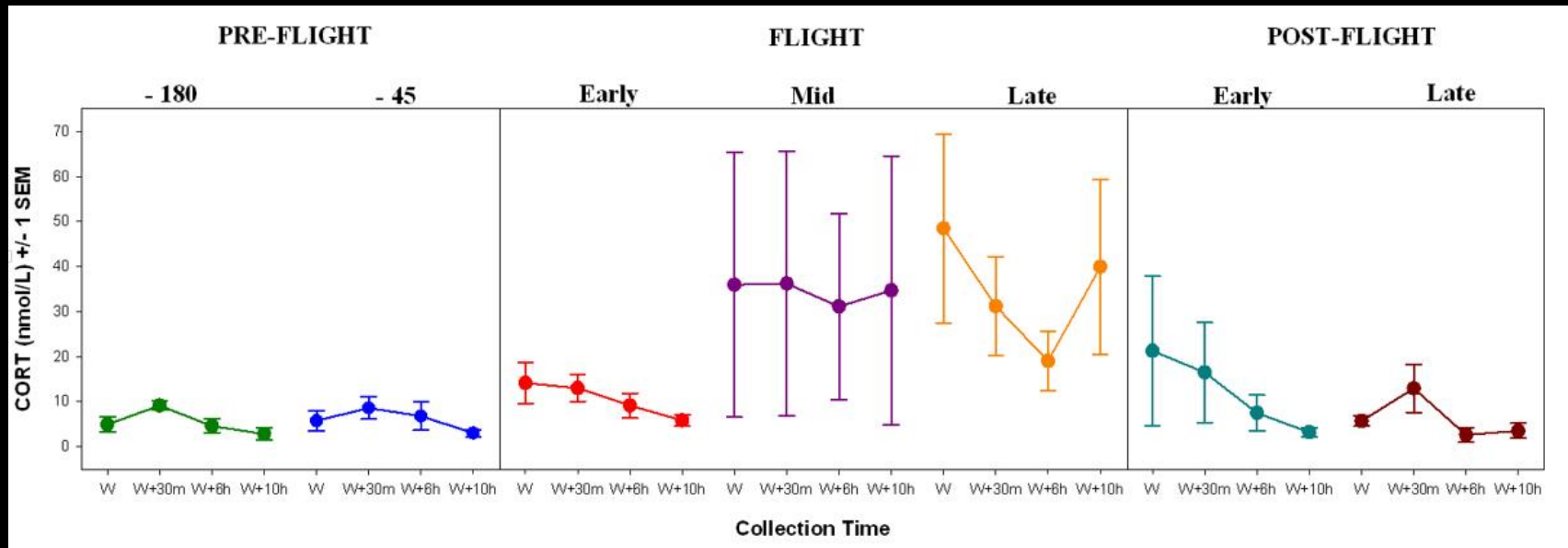
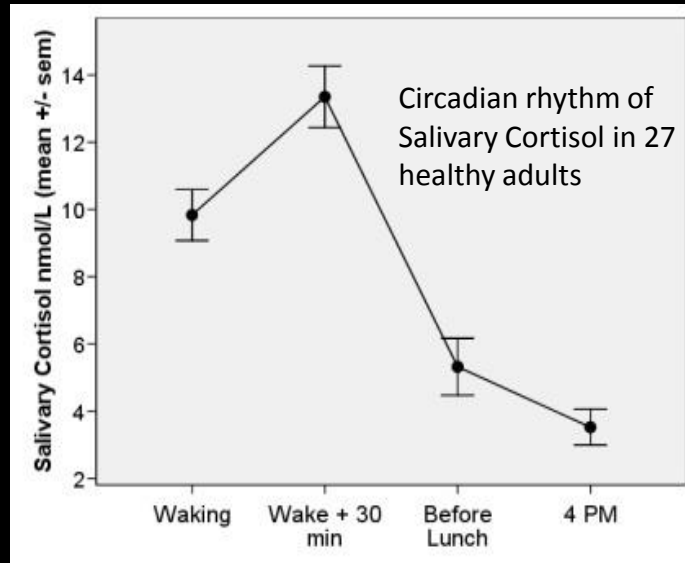
Table 2: Mean plasma cytokine levels for ISS astronauts before, during, and following spaceflight. Data are expressed as mean concentration pg/ml \pm SEM. Bold indicates statistically significant difference $p \leq 0.05$; $n=28$.

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

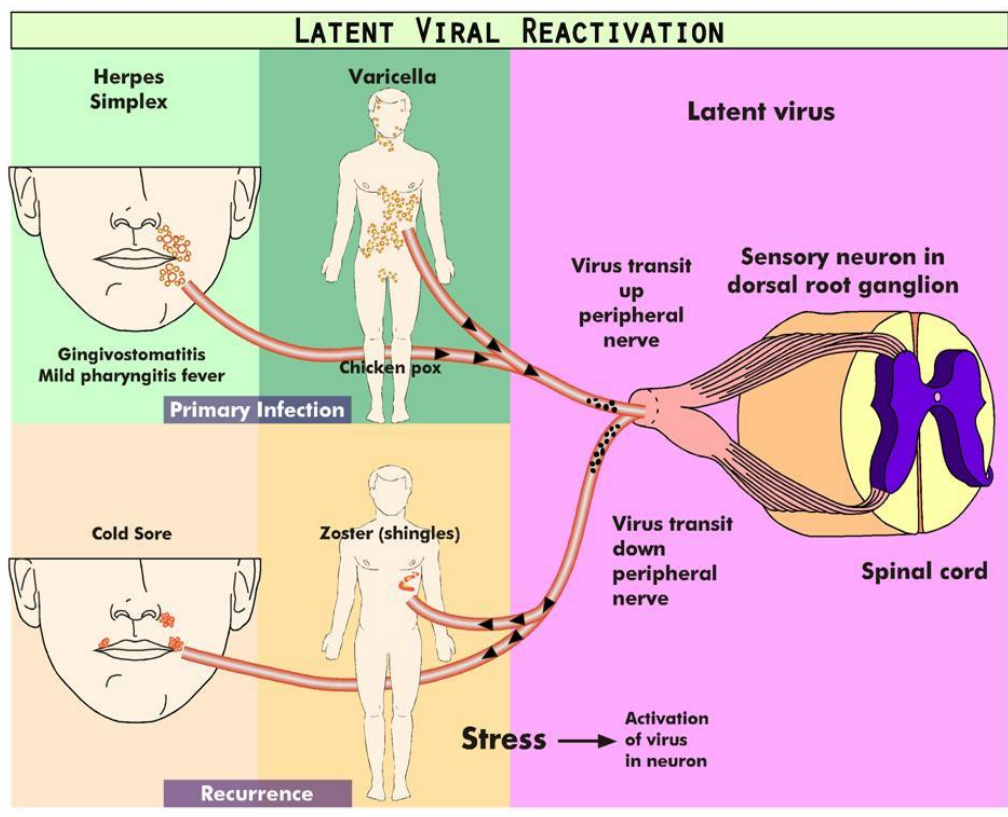
Plasma Cytokine Analysis



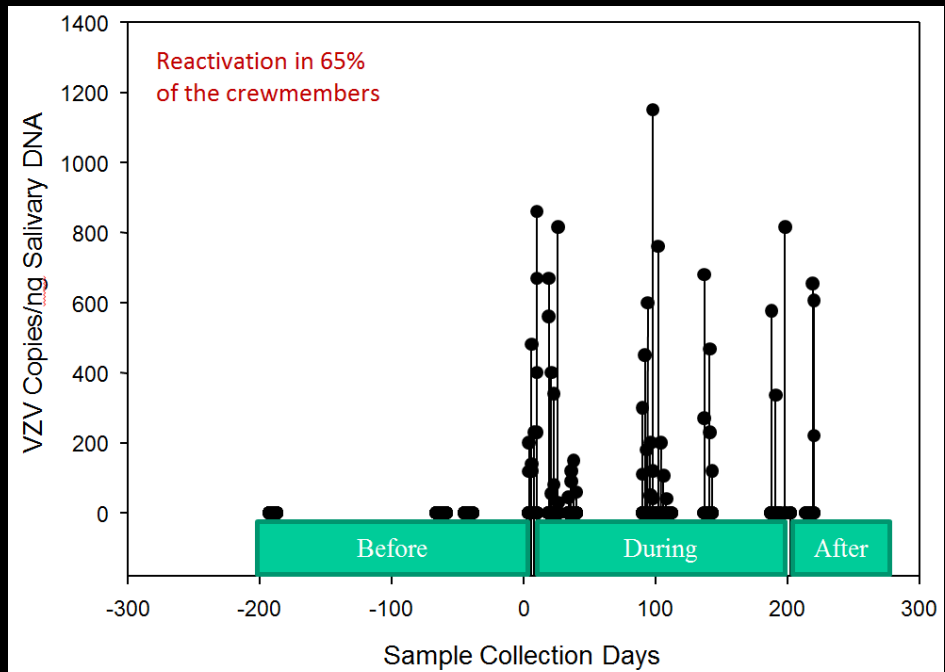
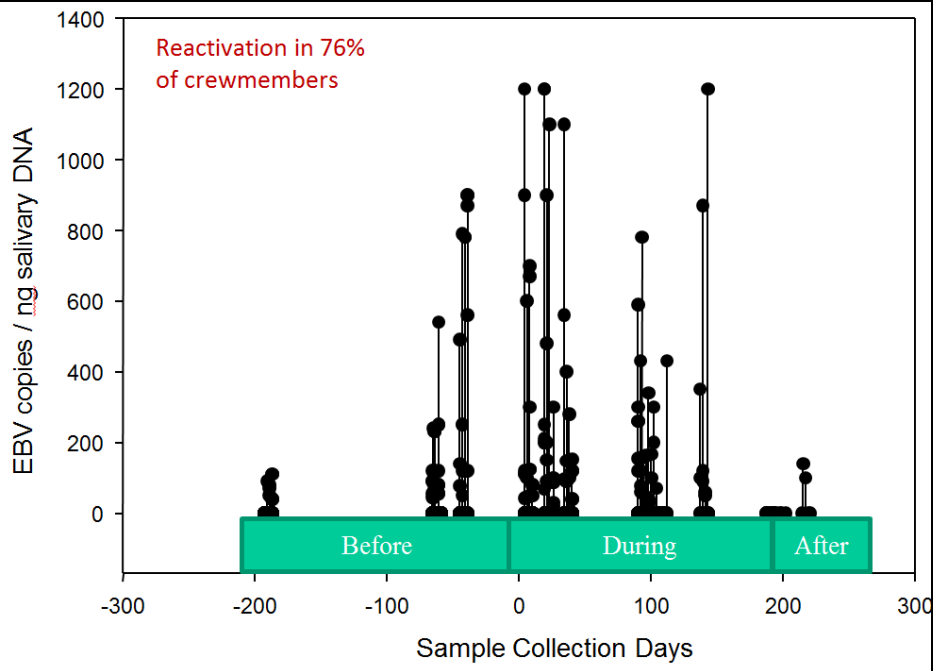
Stress Hormones/ Circadian Rhythm



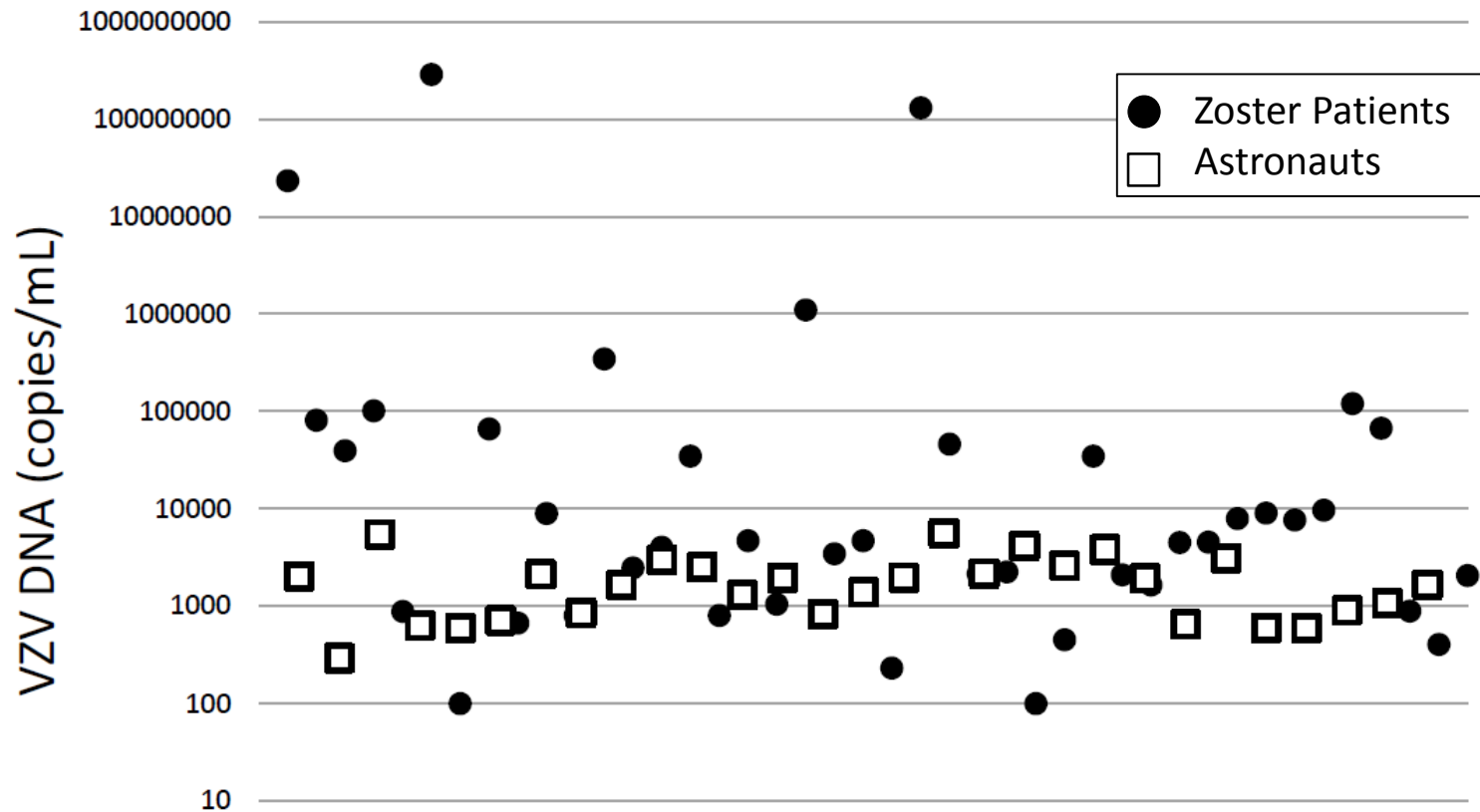
Latent Herpesvirus



Latent Herpesvirus



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

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

Clinical Incidence

Case Study ISS Astronaut

-Allergic symptoms in a non-allergic subject

-Subject developed an Atopic Dermatitis on mission day 17

-Rash was bothersome, at times severe

-A variety of treatments employed

-At times the medications of choice were exhausted

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

-Rash spikes generally correlated well with operational stressors

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

Clinical Communications

A case of persistent skin rash and rhinitis with immune system dysregulation onboard the International Space Station



Brian Crucian, PhD^a, Smith Johnston, MD^b,
Satish Mehta, PhD^c, Raymond Stowe, PhD^d,
Peter Uchakin, PhD^a, Heather Quiariarte, BA^c,
Duane Pierson, PhD^a, Mark L. Laudenslager, PhD^f, and
Clarence Sams, PhD^b

Clinical Implications

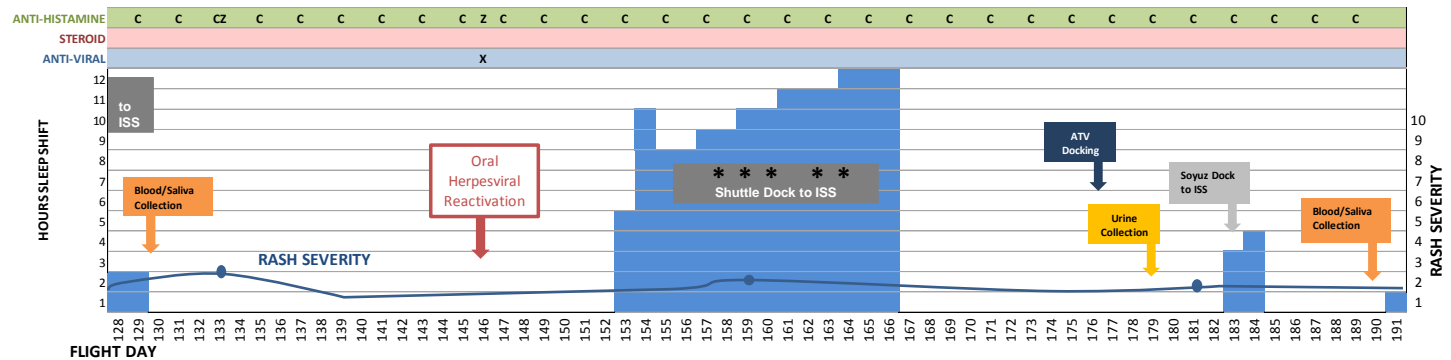
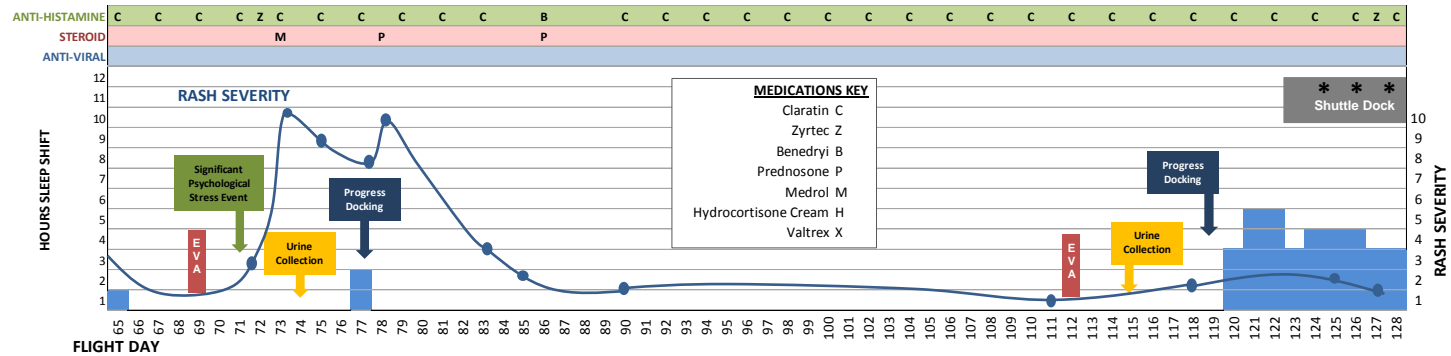
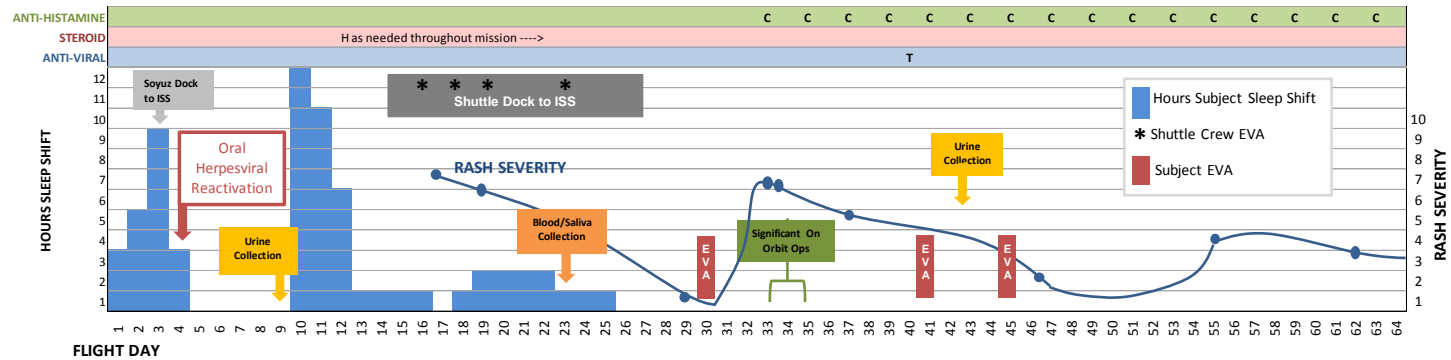
- Factors associated with spaceflight, including microgravity and stress, induce dysregulation of the human immune system. In some astronauts, this phenomenon may associate with adverse clinical outcomes observed during flight such as rashes or persistent rhinitis.

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



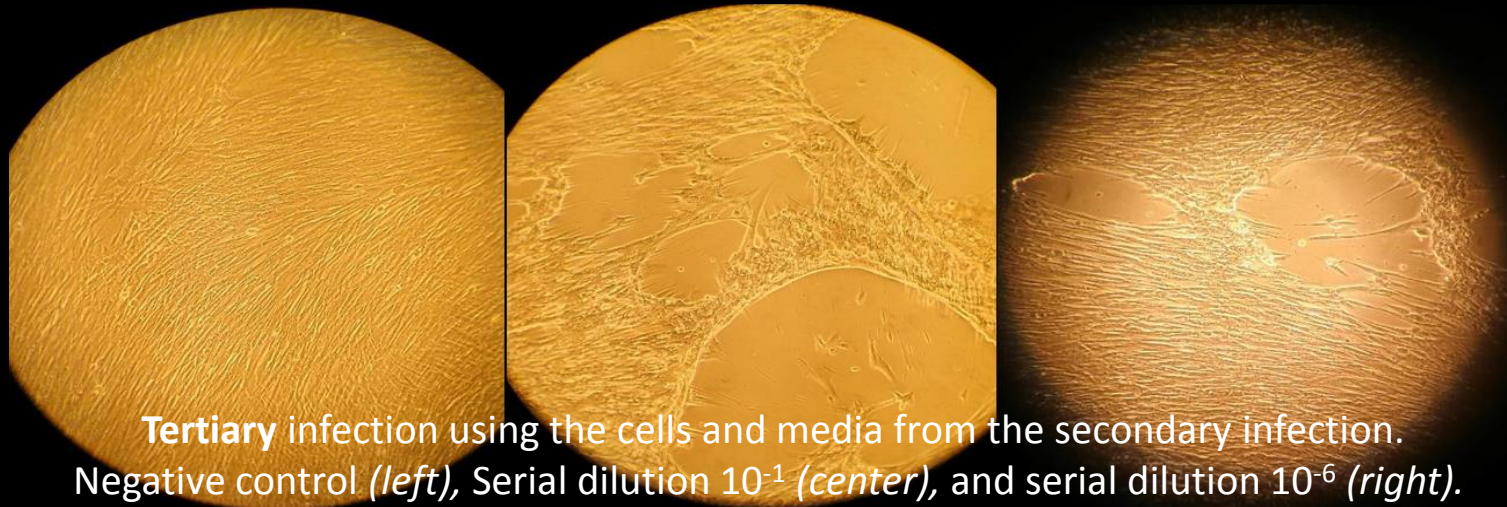
Clinical Incidence

Herpes Simplex Virus type-1 reactivation associated with a case of persistent dermatitis during Spaceflight



Clinical Incidence

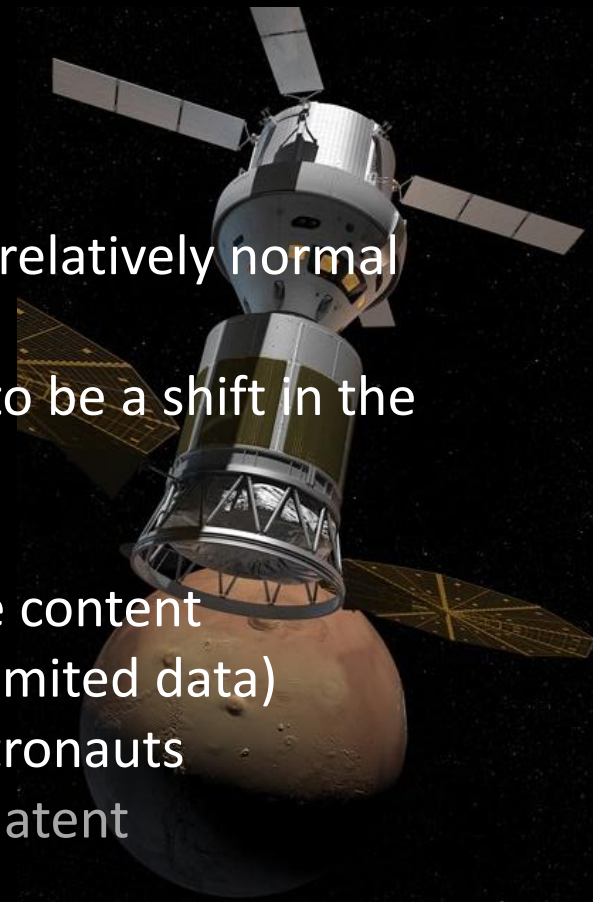
		In-Flight	R+0	R+14
Saliva	VZV		Negative	Negative
	HSV1	Positive (CT-22; 5.4x10(6) copies per ng total DNA)	Positive (CT-15; 1.4x10(9) copies per ng total DNA)	Negative
Skin Lesion	VZV	Negative	N/A	N/A
	HSV1	Positive (CT-29; 2.4x10(4) copies per ng total DNA)	N/A	N/A



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*).

Summary

- 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 Countermeasures



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

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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

Immune Countermeasures

Potential Immunologic Countermeasures for Deep Space Missions

Precision Countermeasures

Pre-Mission Immunological Screen

Pre-mission immunological screen may include:
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



PRE-FLIGHT

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



LAUNCH



TRANSIT PHASE

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

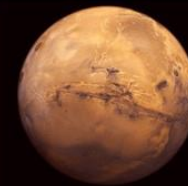
Pharmacological Intervention

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

In-flight Monitoring of Immune Parameters?



CIS-LUNAR STATION/
LUNAR SURFACE OPS



MARS FLYBY or ORBIT/
MARS SURFACE OPS

Spaceflight Immunologists



NASA JSC Immunology/Virology Laboratory

