

A photograph of the International Space Station (ISS) in orbit above Earth. The station's complex structure, including large solar panel arrays, is visible against the blackness of space. The Earth's blue and white surface is seen below, curving away into the distance.

The Human in Space: Lessons from ISS

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Content

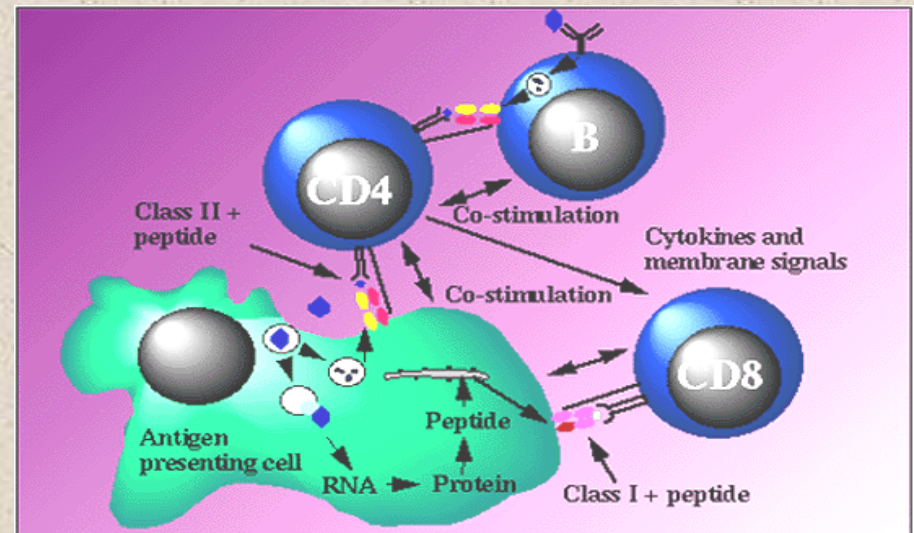
- Overview of space flight effects on crewmembers
- General overview of immune system
- How does space flight alter immune system?
- What factors associated with space flight interact with crewmember immune function and impact health risks?
- What is the current understanding of space flight effects on the immune system?
- Why should NASA be interested in immunology?
Why is it significant?

THE IMMUNE SYSTEM

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

Responsible for protection against viruses and bacteria, tumor surveillance, wound healing, etc.

Dysfunction results in increased infection rate, malignancy, autoimmunity, allergy, etc.



IMMUNE SYSTEM

Innate Immunity

- First line defense acting within mins-hrs
- Is a primitive response, largely conserved throughout evolution
- Non-specifically defends the body against infection

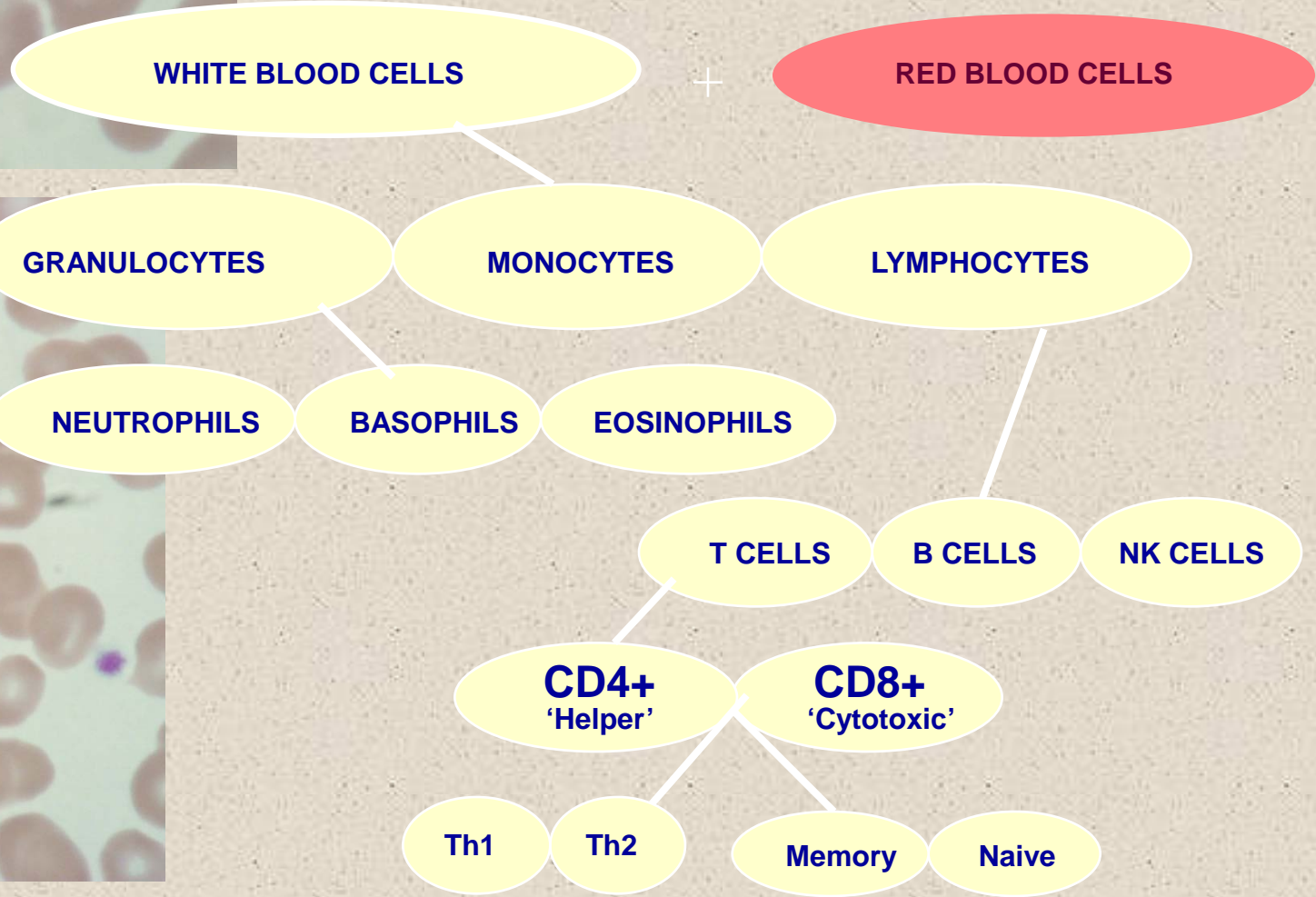
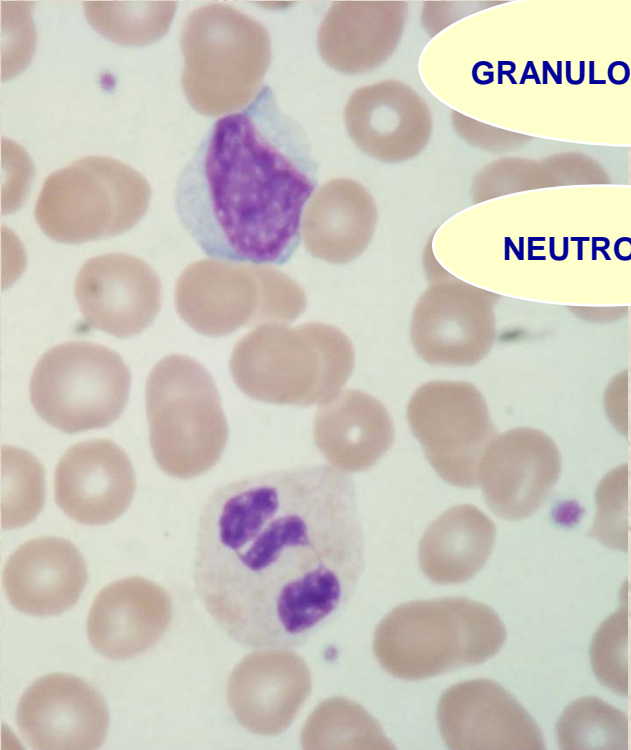
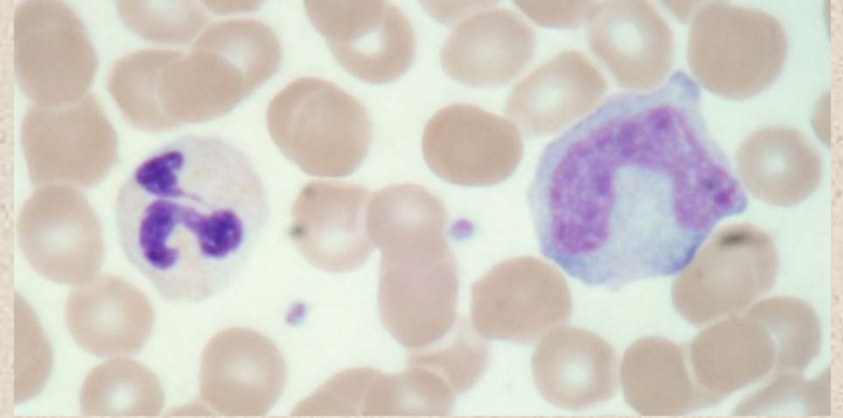
Acquired Immunity

- Late response
- Recognizes and attacks specific protein sequences of the foreign “intruder,” it also remembers them

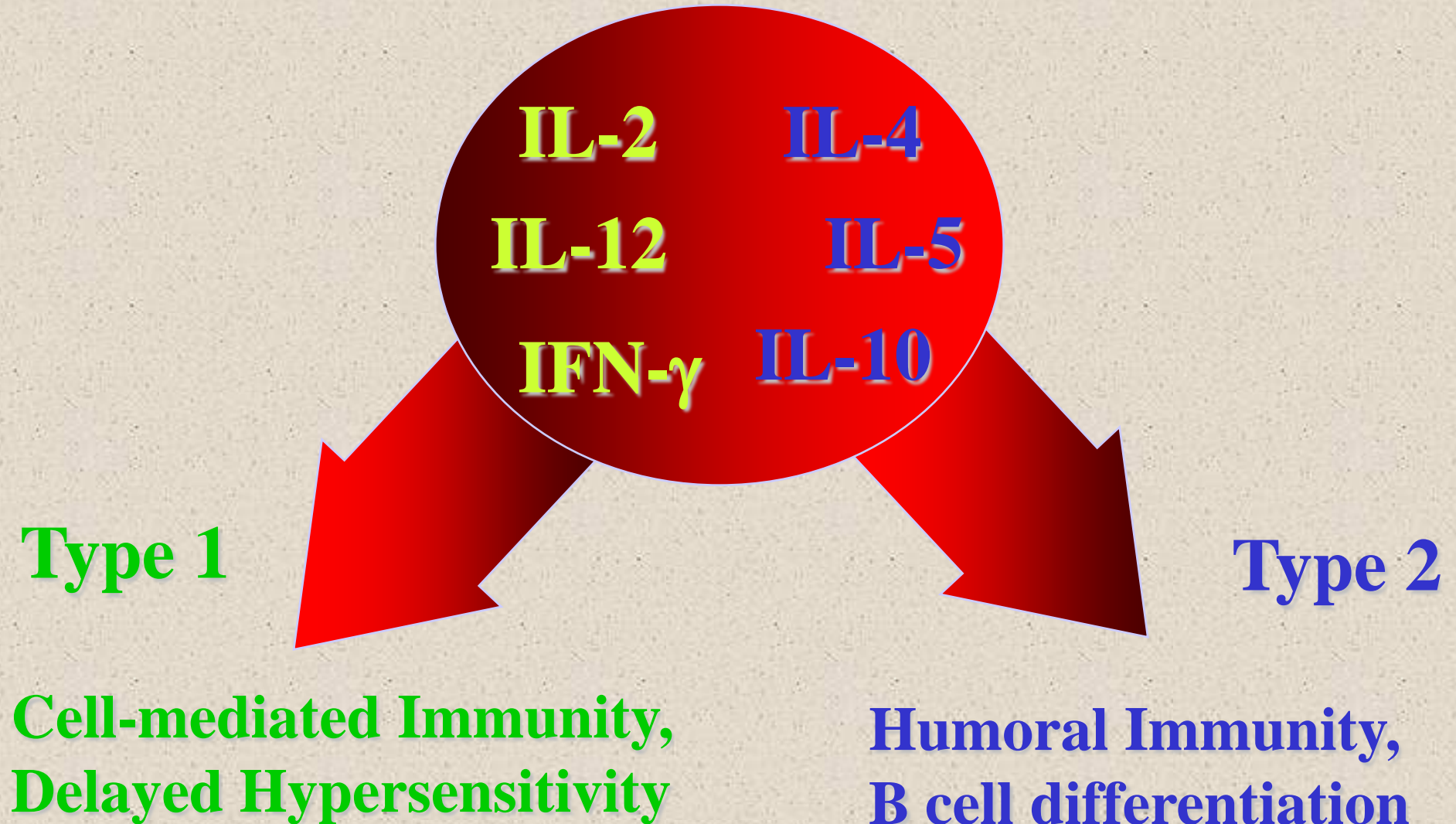
- Barriers to Infection
 1. Non-Specific Chemicals
 2. Non-Specific Cells
 3. Microbial Flora

- Lymphocytes
 1. B-cells
 - Plasma cells
 - Memory cells
 2. T-Cells

HUMAN BLOOD CELLS



Type 1 & Type 2 cytokine Response



Content

- General overview of immune system
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Adaptations to Long-Duration Space Flight

Ocular

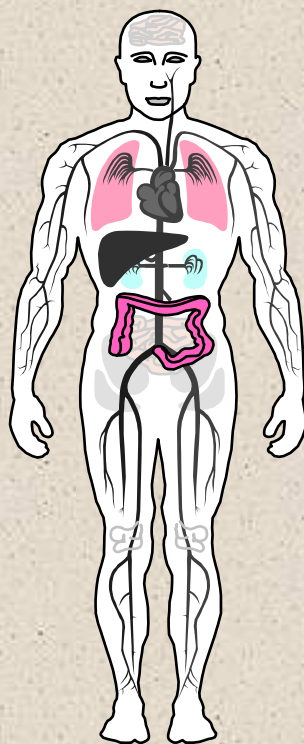
- ↑ intraocular pressure in flight
- ↑ retinal blood vessel constriction postflight
- ↓ visual motor task performance
- ↓ contrast discrimination
- ↓ visual field postflight
- ↓ intraocular pressure postflight

Cardiovascular

- ↑ resting heart rate
- ↑ stroke volume early in flight
- ↑ PACs & PVCs
- ↓ fluid volume
- ↓ orthostatic tolerance
- ↓ aerobic & anaerobic capacity
- ↓ resting blood pressure postflight
- ↓ central venous pressure (indirect)
- ↓ cardio/thoracic (CK) ratio postflight

Musculoskeletal/Bone

- ↓ muscle mass
- ↓ muscle endurance & strength
- ↓ bone mineral content
- ↓ bone integrity



Neurosensory

- ↑ vestibular disturbances
- ↑ space motion sickness early in flight
- ↓ postural stability
- ↓ sensorimotor function

Body Fluids

- ↑ hemoglobin & hematocrit postflight
- ↓ total body water
- ↓ plasma & urine volumes postflight

Electrolytes

- ↑ urinary Ca, PO₄ postflight
- ↓ plasma K & Mg postflight
- ↓ urinary Na, K, Cl, Mg

Hormones

- ↑ plasma ADH, ANF
- ↑ urinary aldosterone
- ↑ urinary ADH, cortisol postflight
- ↓ urinary epinephrine, androsterone postflight
- ↓ plasma ACTH, aldosterone, cortisol

Metabolites

- ↑ plasma glucose, creatinine, BUN postflight
- ↓ albumin, cholesterol, triglycerides, uric acid

Integrating Hypothesis: Stress-induced Dysregulation

Characteristics of the mission and the spacecraft environment represent a physiological and psychological stress to the crewmember.

Regulation of the immune system is altered during the period of stress and such alterations may induce specific medical risks to the crews.

IMMUNE DYSREGULATION

Space Flight



**CRF, ACTH, Cortisol &
Other Pituitary - Adrenal Hormones**



Modulate Immune Function

Delayed healing

**Hypersensitivity
& allergies**

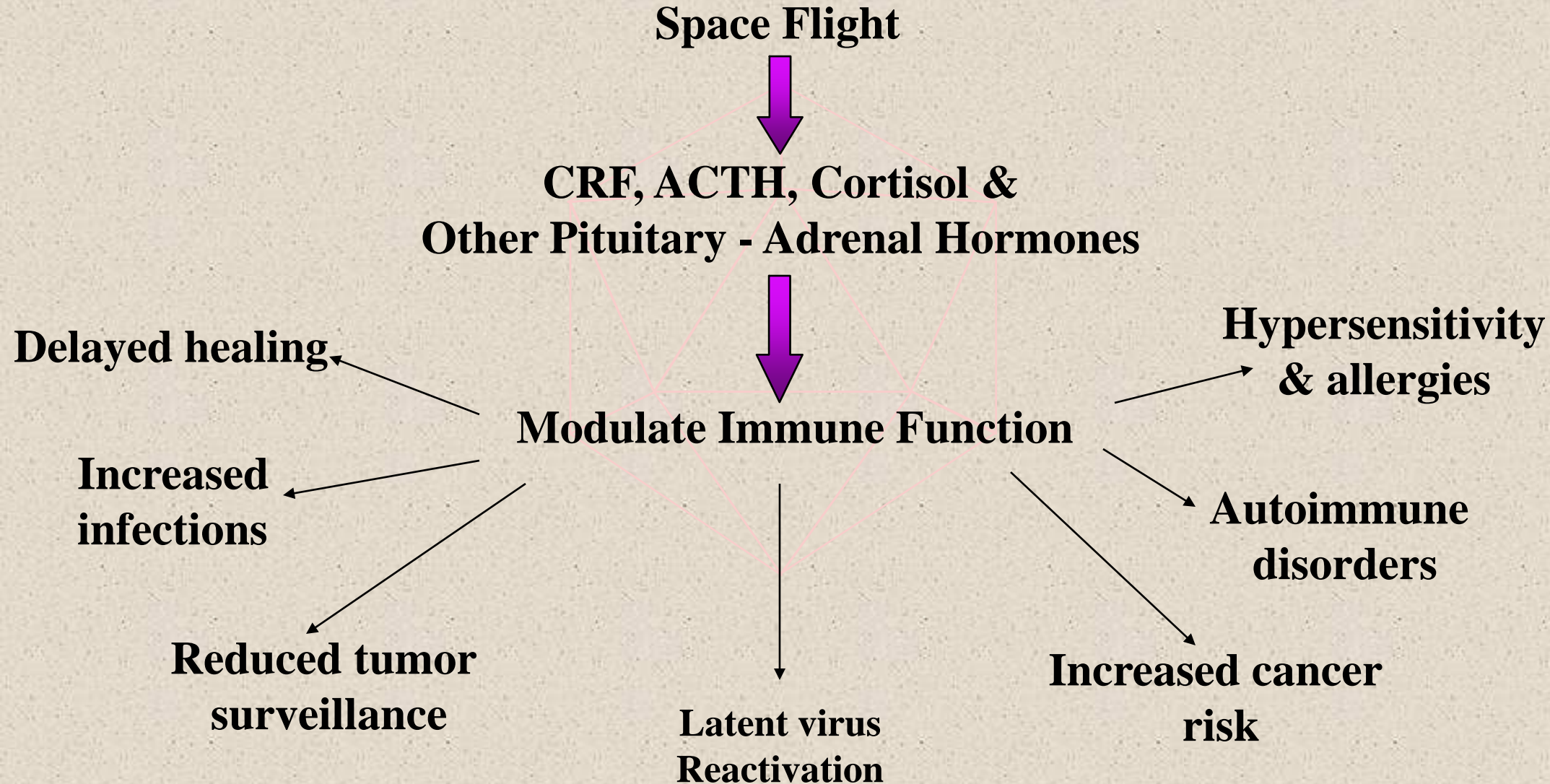
**Increased
infections**

**Autoimmune
disorders**

**Reduced tumor
surveillance**

**Increased cancer
risk**

**Latent virus
Reactivation**



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Crewmember Health: a balancing act



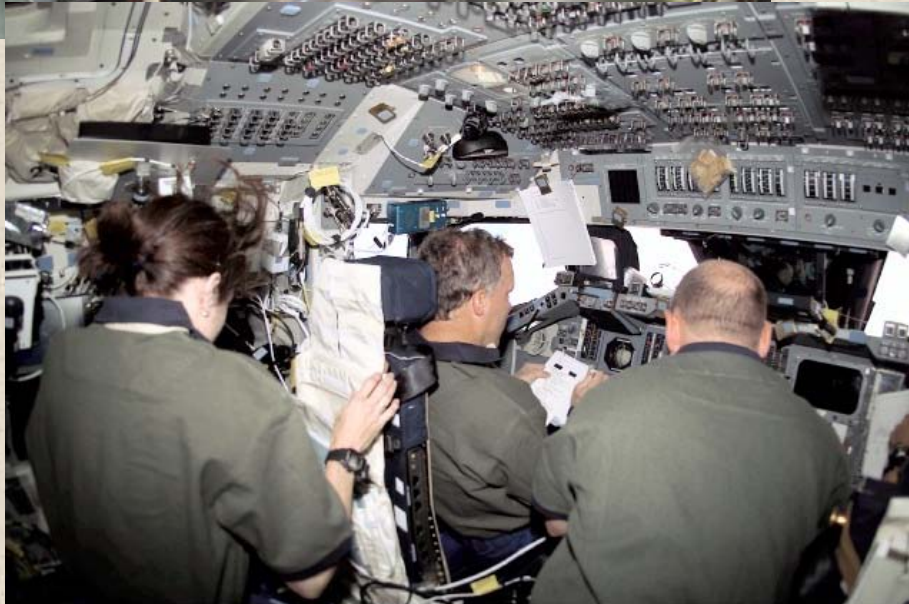
**Environmental
risk factors**

- microgravity
- radiation
- others

**Immune system
function**

Interplay of factors determines health outcome

Spacecraft Environmental Factors



- crowded, closed environment
- recycled air & water
- potential toxic exposures
- microgravity
- particulate exposures
- limited personal hygiene
- skin abrasion/injury
- continuous radiation exposure
- altered growth/virulence
- unique microbial ecosystem
- unique challenge scenarios
- psychological, physical stress

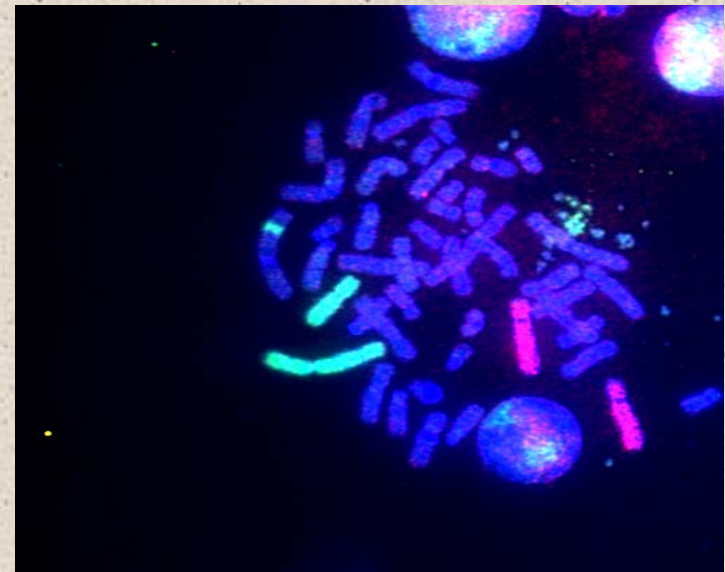
Unique challenge scenarios

- Due to microgravity there is increased potential for mucosal ocular exposure
- Systems failures may aggravate problem
- Some opportunistic pathogens may infect unique locations due to microgravity supported transmission routes



Continuous radiation exposure

- Radiation exposure can be significant for LD flight and exploration sorties
- Radiation directly reduces immune function
- Immune system restricts tumor development
- Interplay between these factors potentially increases crew risks



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Immune Responses to Space Flight (Pre- vs. Postflight)

- Reduced blastogenic response
- Altered cytokine production
- Decreased NK cell function
- Altered phagocytosis and oxidative burst
- Changes in circulating leukocyte populations
 - Increased granulocytes
 - Decreased lymphocytes and NK cells
 - Variable monocyte changes

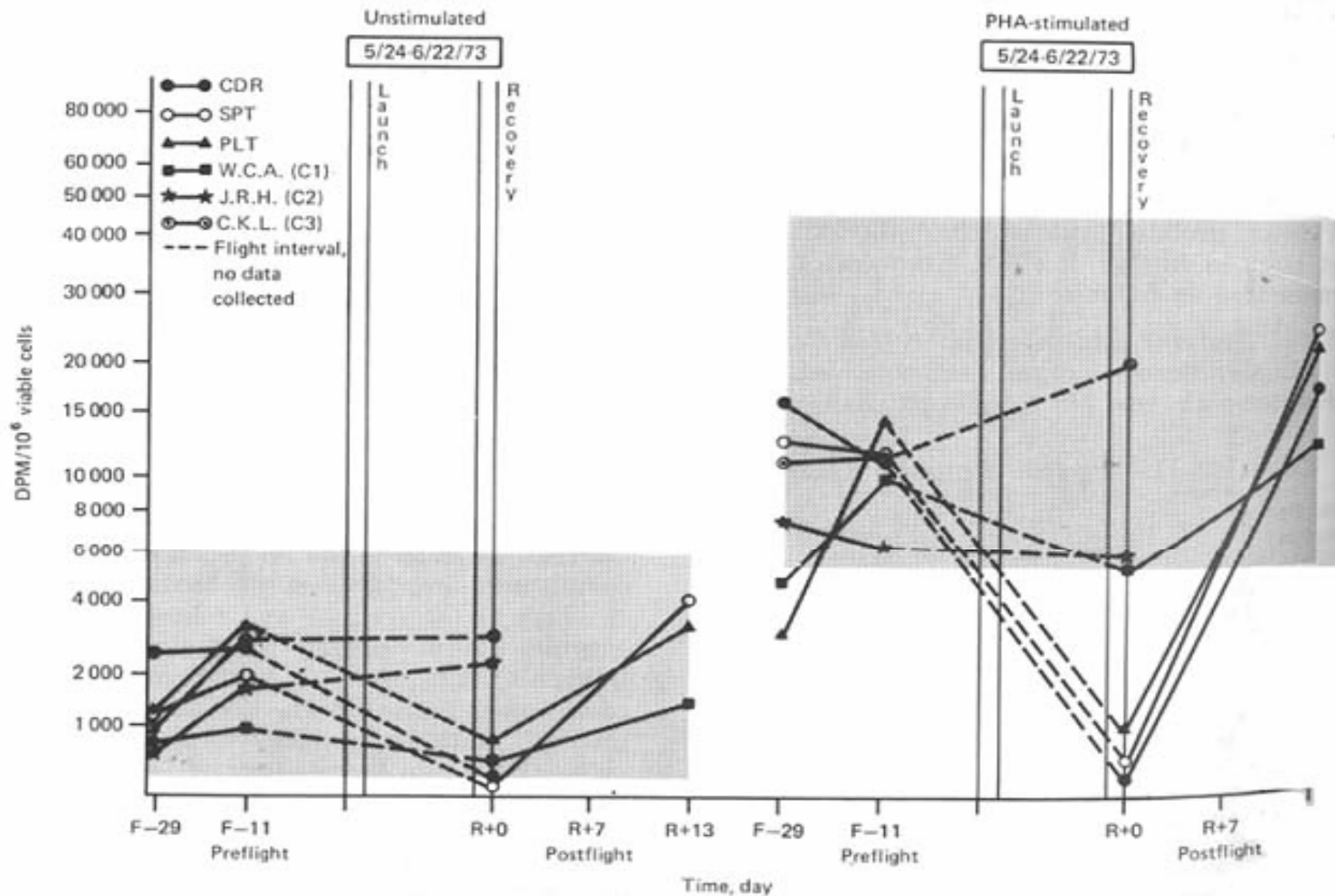


FIGURE 28-1a.—RNA synthesis rates in lymphocytes, cultured with and without PHA, obtained from the Skylab crews and control groups. The cells were pulsed with ³H-uridine at 23 h and harvested at 24 h after initiation of the cultures.

Innate Immunity Responses to flight

Neutrophils: Decreased Function

Phagocytosis ↓

Oxidative Burst ↓

Degranulation: No Change

Kaur et al. Brain, Behavior, & Immunity, 2004

Monocytes: Decreased Function

Phagocytosis ↓

Oxidative Burst ↓

Degranulation ↓

Kaur et al. Brain, Behavior, & Immunity, 2005

NK-Cells: Decreased Function

Cytotoxicity ↓

Mehta et al., J. Applied Physiology 2001

Immune Responses to Space Flight (during flight)

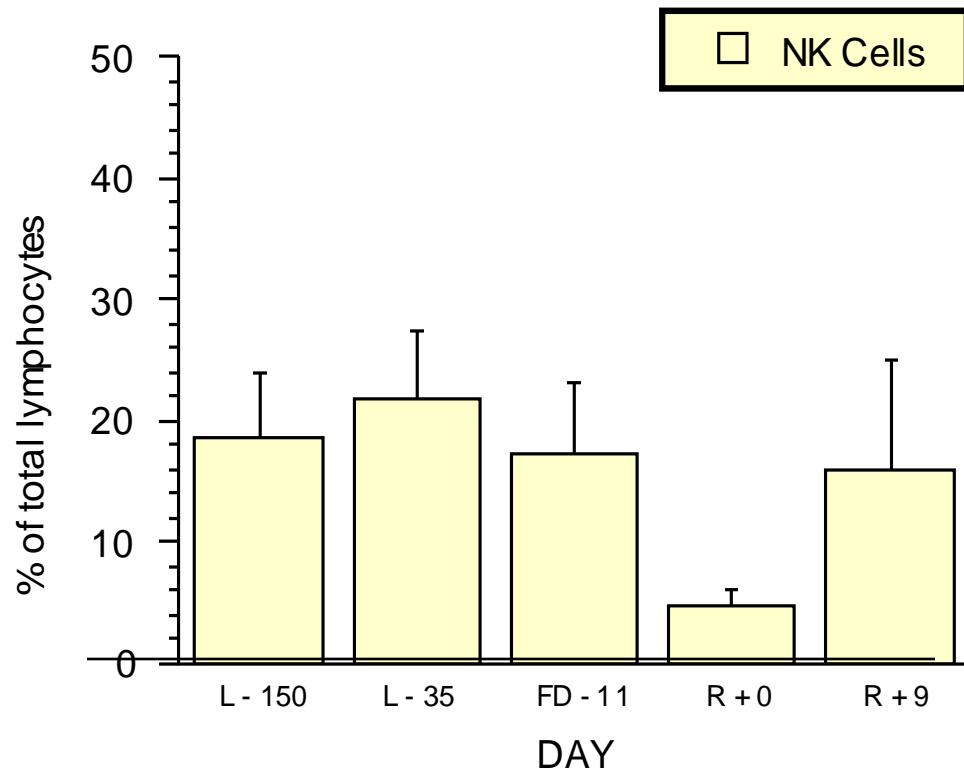


- Decreased cell-mediated immune function
- Distinct inflight and postflight circulating WBC phenotype
- Potentially altered NK cell function
- Normal antibody response to vaccination
- Altered in vitro lymphocyte activation & migration

in vivo Cell-Mediated Immunity reduced during flight

- Cell- mediated immunity tested during short and long duration flight
- Used commercial CMI multi-test assay
 - 7 antigen test panel and control
 - Configured into applicator device
- Reduced response observed in both short and long-duration crewmembers
- Similar observations from analogue studies

Natural Killer Cells decrease postflight

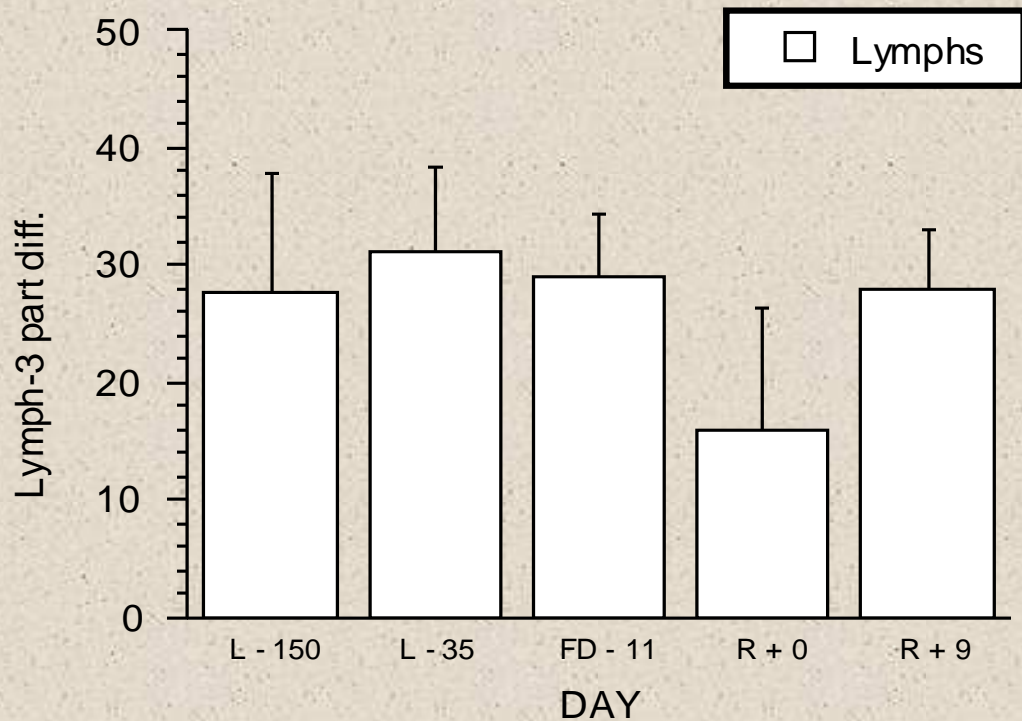


NK cells decreased after landing

NK cell cytotoxicity decreased at landing

Potentially decreased function during long duration flight

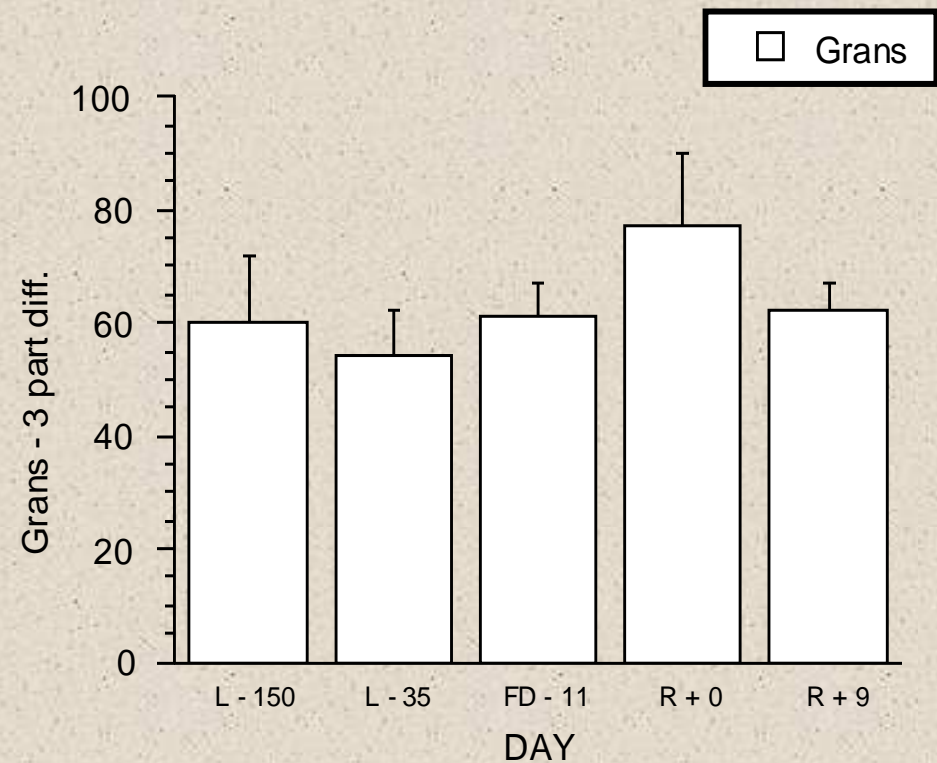
Lymphocytes decrease postflight



- Lymphocytes decrease on landing day
- Numbers return to baseline within 3 days
- Mitogen-induced proliferation is lower
- May reflect delayed S-phase entry

Granulocytes increase postflight

- Granulocytes increase at landing
- Demargination of grans into circulation
- Similar to changes induced with exercise
- Resolves quickly after landing (3 days)



Overview of in-flight phenotype

- Gross phenotype of circulating WBCs late in-flight similar to pre-flight values
- Landing day phenotype significantly altered
- Must be factored into assessments of pre- & post studies of immune system
- Post-flight analysis may not reflect in-flight functional status

Humoral Immunity

Experimental Objectives

Determine ability of crewmembers to respond to an immune challenge during flight

Method:

Assess antigen specific response to an immunization during space flight

- 1) vaccinate crewmember inflight**
- 2) measure antibody response**

First vaccination of a crewmember during flight



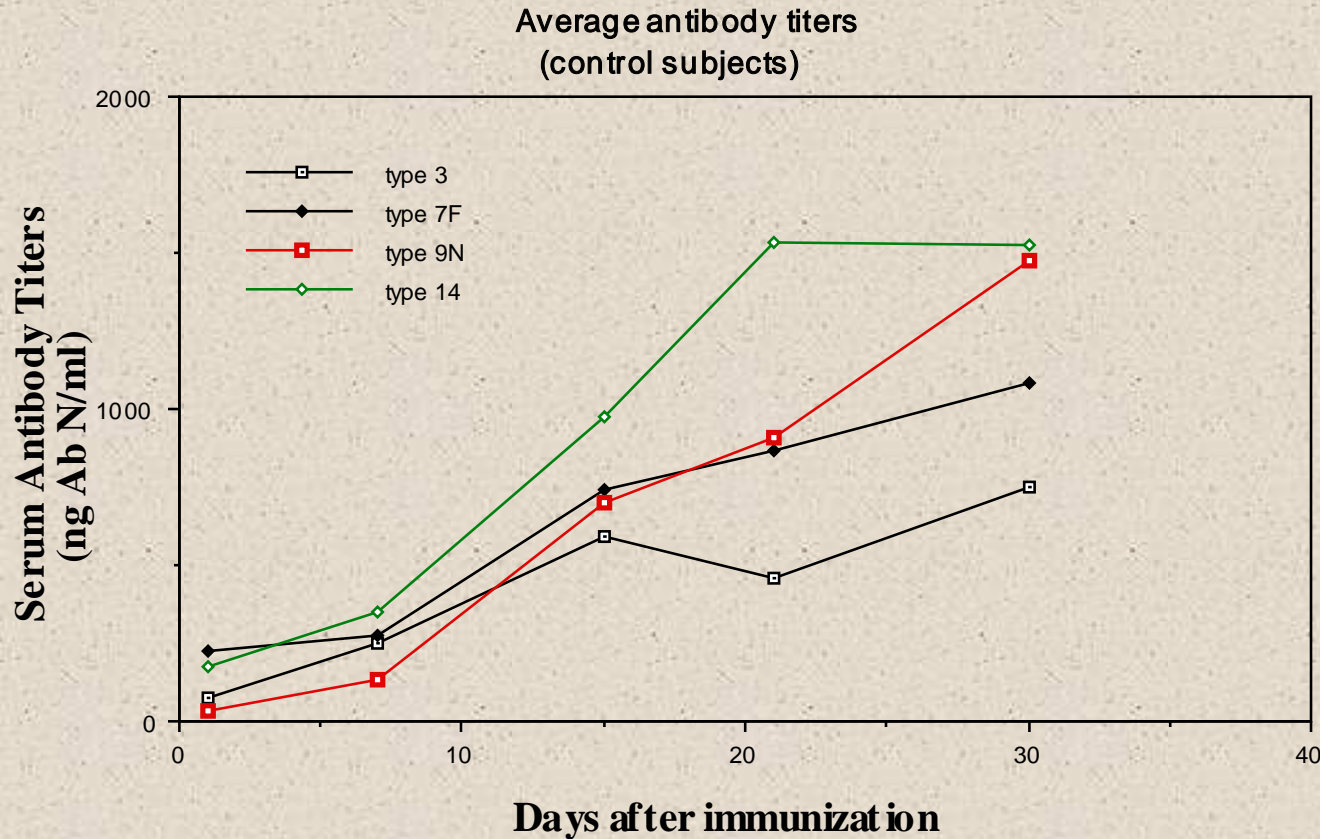
Vaccine

- **Pneumococcal vaccine selected for use**
- **Vaccine is used to prevent respiratory infections**
- **2 million doses/year US**
- **Low incidence of adverse events**

Target Population

- **elderly individuals with depressed immune systems**
- **AIDS patients**
- **patients on life support**
- **patients in confined environments (ICUs, rest homes, etc)**

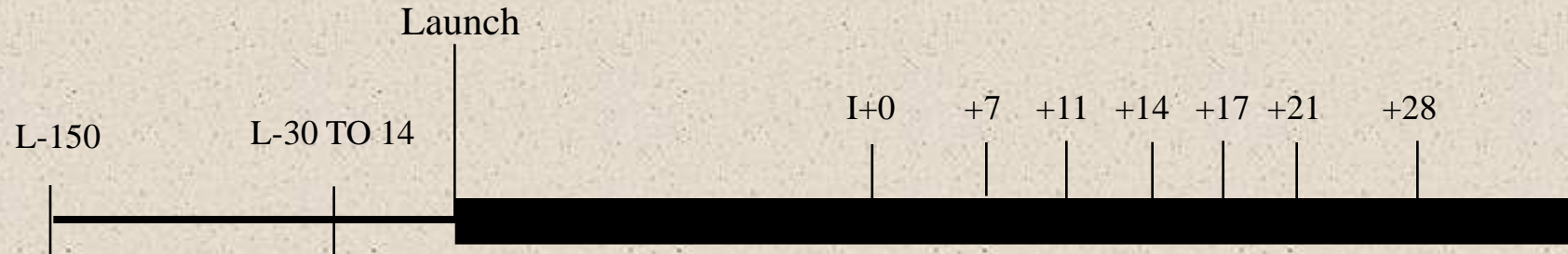
Response to immunization



Protective antibodies are produced within 2-4 weeks after the Immunization

Doubling of baseline antibody titer or levels exceeding 800 ng Ab N/ml are positive

Experiment timeline

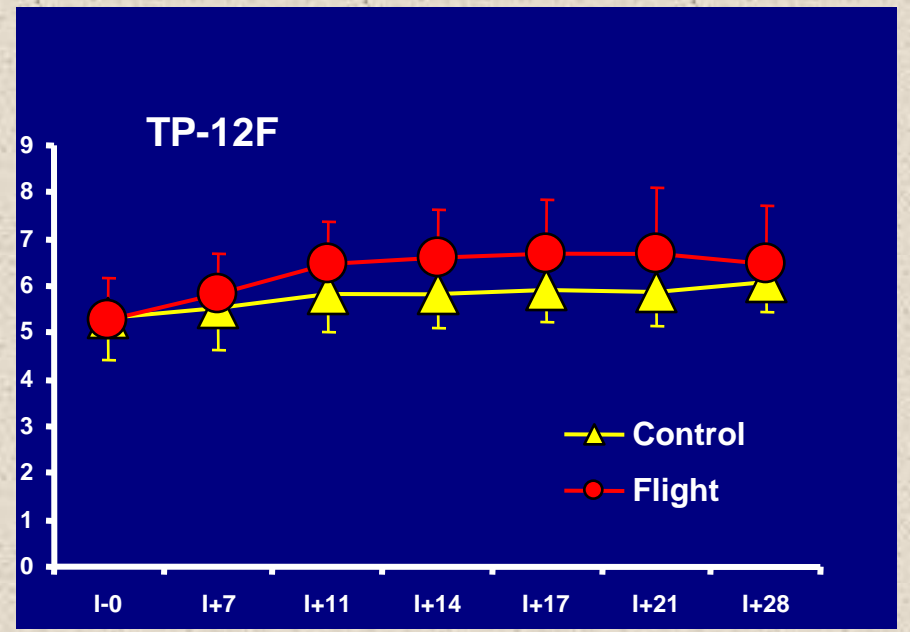
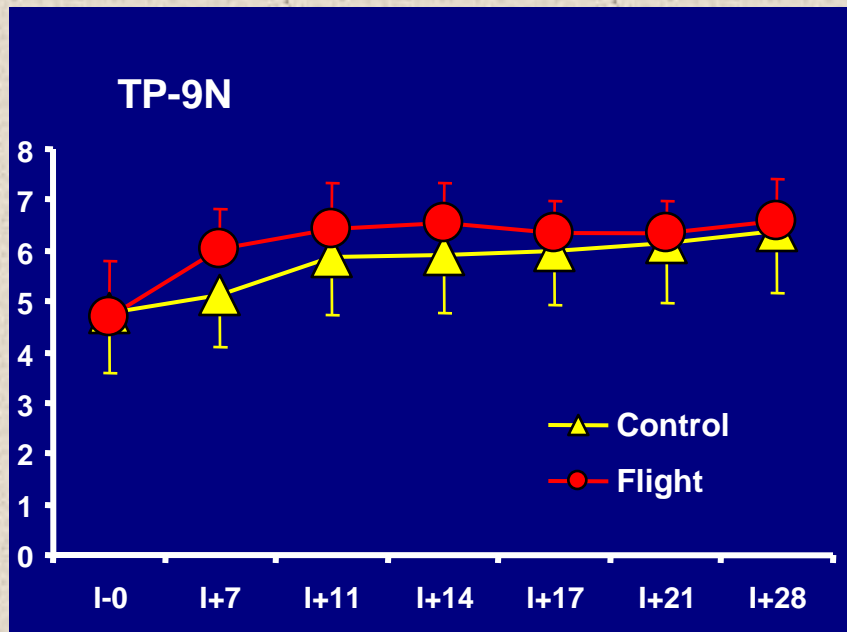
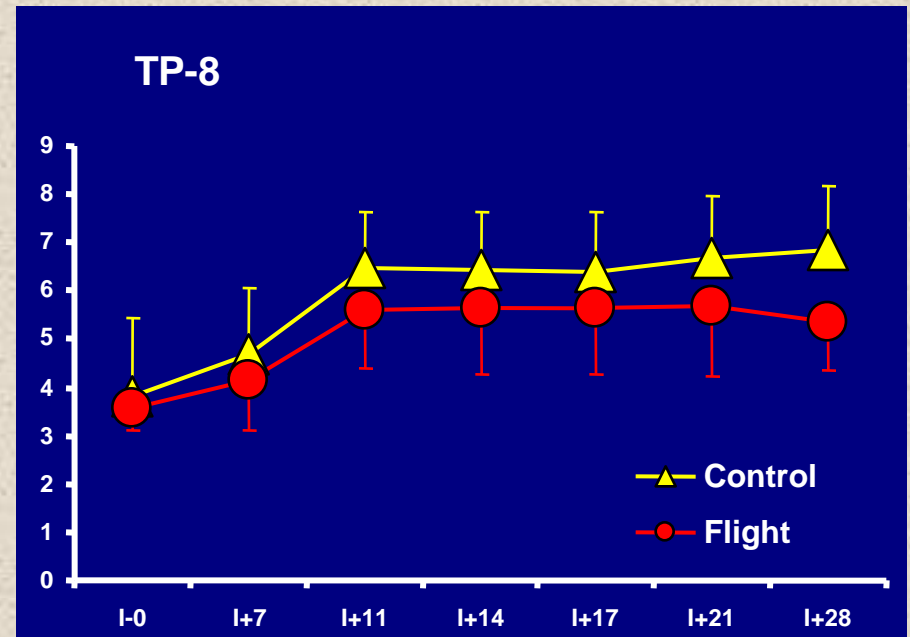
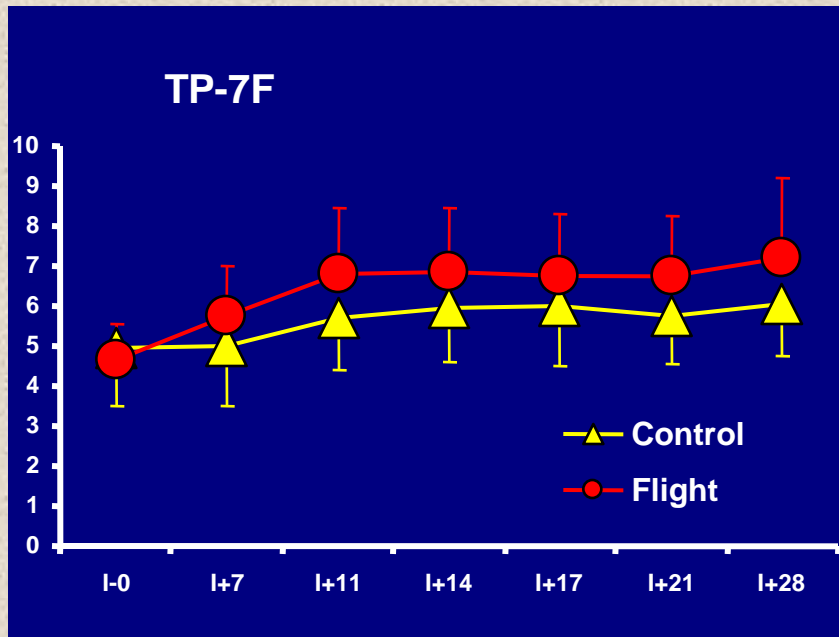


Two preflight samples

Approximately mid-mission

- a) in-flight baseline
- b) immunization

Post immunization samples at
7, 11, 14, 17, 21 & 28 days

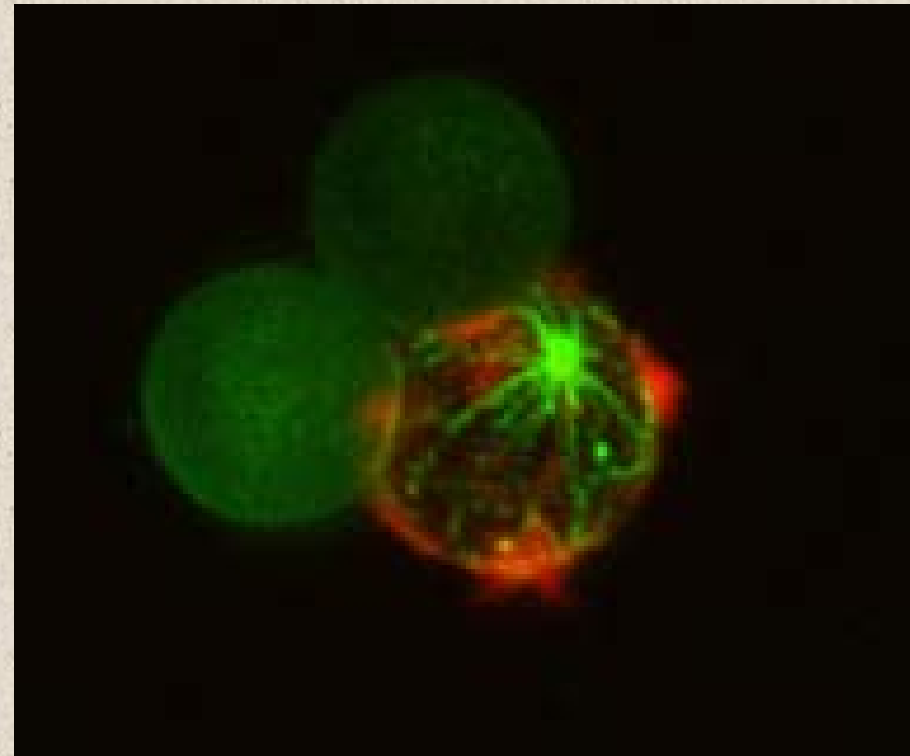


Overview of HI Results

- All crewmembers responded well to all measured antigens compared to control groups
- 2 of 7 crewmembers immunized during flight developed significant injection site reactions
- One of approx 24 control subjects had reportable adverse response to vaccination
- Possible increased hypersensitivity response during space flight
- Data from HI study suggests humoral immunity is not reduced by space flight

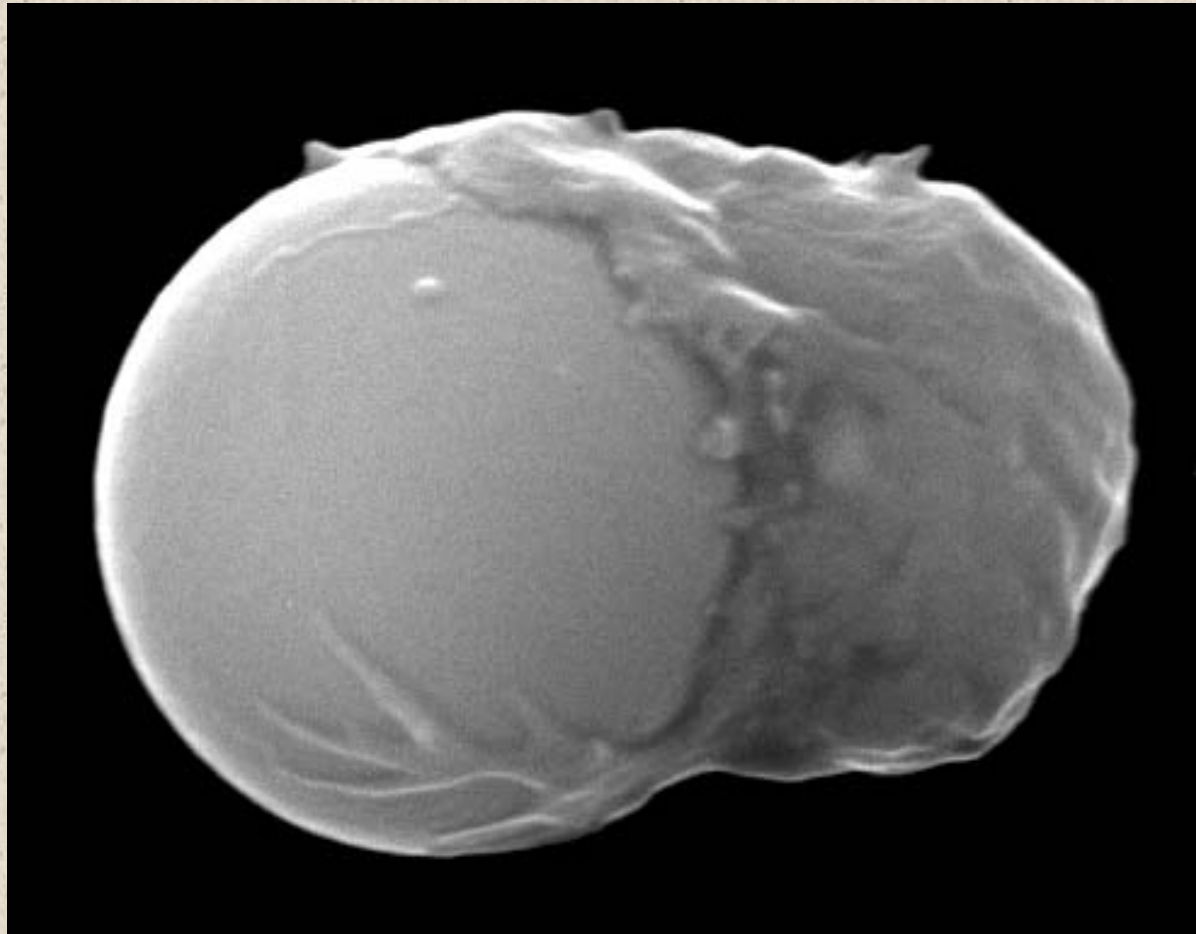
Cellular studies indicate reduced immune cell function in microgravity

- Reduced proliferation
- Reduced migration
- Altered signal transduction
- Altered cytoskeletal structure
- Indicates sensitivity of immune cell to mechanical forces
- Reflects a direct effect of microgravity on cells



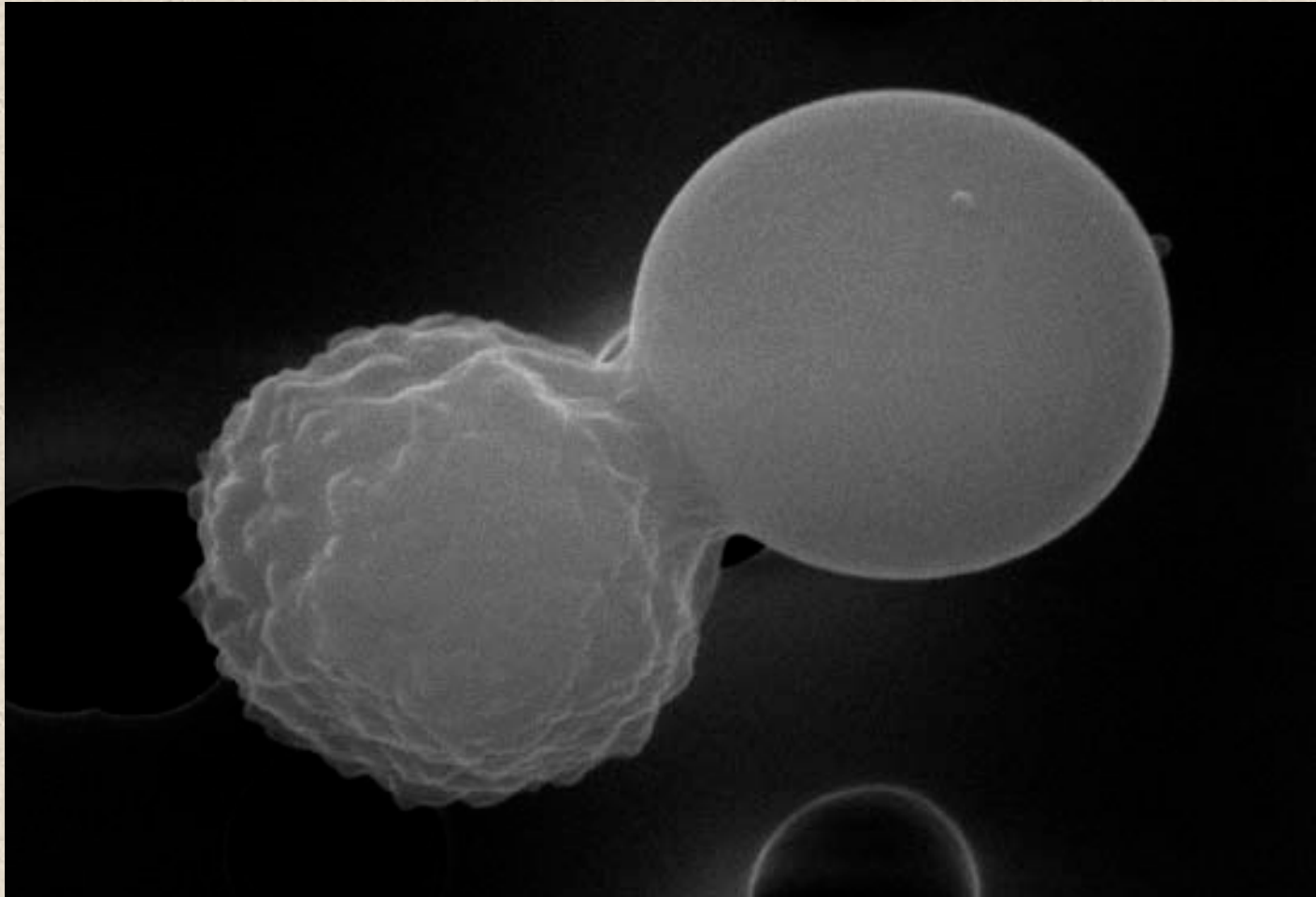
T CELL ACTIVATION

1xG



T CELL ACTIVATION

0xG (clinorotation)



Summary Immune Observations

- Reduced cell-mediated immunity
- Humoral function maintained
- Possible increased allergic hypersensitivity
- Altered cytokine patterns
- Data suggest a dysregulation of immune system
- Data are consistent with that observed in some model scenarios

Limitations of currently available data

Pre- and postflight data may not accurately reflect immune parameters existing during flight

- effects of reentry and re-ambulation
- time before assay (recovery effects)

Some systems have received little study

- Target specific cellular responses

Inflight studies are relatively simplistic due to operational constraints

Further assessment of immune status *during* flight is required for determining immune-related crew health risks

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 - Relationship to immune standards
 - Relationship to Immune SMO

Immune-Related Disorders With Potential Mission Impact

- respiratory congestion
- infections
- delayed healing of wounds
- hypersensitivity/allergic reactions
- rashes/skin disorders
- reactivation of latent viruses



INFECTIOUS DISEASES IN ASTRONAUTS

STS-1 Through STS-108

- Fungal infections
- Flu-like syndrome
- Urinary tract infections
- Aphthous stomatitis
- Viral gastrointestinal disease
- Subcutaneous skin infections
- Other viral diseases
- URI (common cold, sore throat)
- Sty

IMMUNE-RELATED SYMPTOMS

- Allergic rhinitis
- Hypersensitivity
- Coughing/Sneezing
- Rashes/Skin disorders
- Infections
- Delayed wound healing



Critical immune events

- Considered de-orbiting crewmember due to a sustained contact hypersensitivity (28 days)
- UTI that progressed to near sepsis
- Pronounced injection site reactions during vaccination (2 of 7 inflight, no equivalents in 24 ground)
- Significant hypersensitivity or infection can threaten crewmember within course of mission
- Will present as challenge/response problem

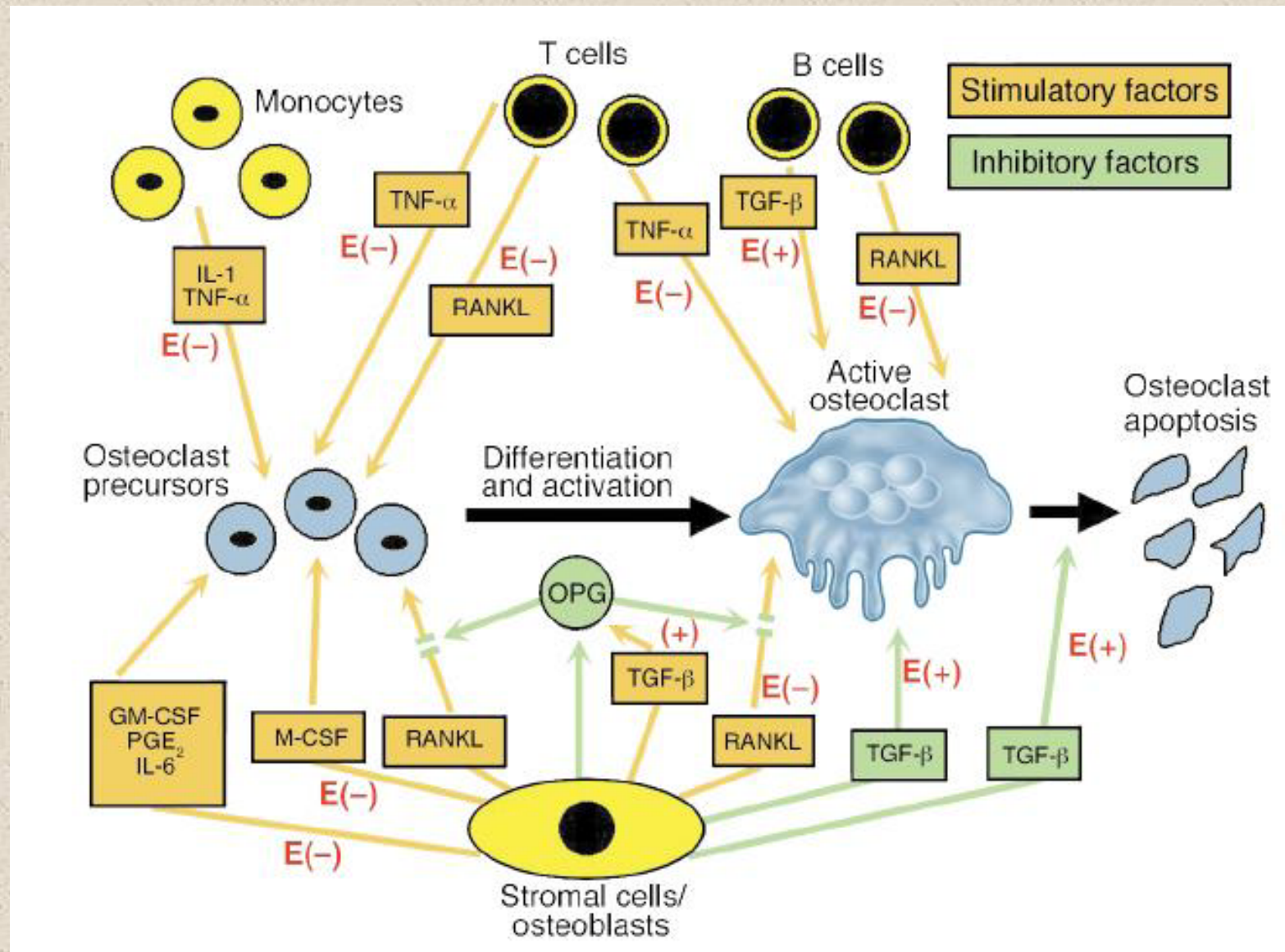
Exploration Concerns

- Infections or hypersensitivity can progress to critical within course of mission
 - Appear to have heightened hypersensitivity and reduced CMI
- CMI performs tumor surveillance and restricts latent virus expression.
 - appears to be down regulated during flight
 - may interact with radiation increasing risk of tumors
- Immune system has an integrating role in maintenance of some other systems (e.g., bone)
- Viral reactivation approaches clinical thresholds and has unique characteristics not common terrestrially
- Understanding this system is necessary to set requirements for vehicle and ops

Bone and Immune

- Cytokines directly modulate bone metabolism
- Immune cells produce bone regulatory factors
- Immune cells interact with bone cells at sites of remodeling
- Immune cells are involved in osteoclast differentiation and development
- Evidence for burst of osteoclast production early in flight

RANK picture



Immune standard

- Written to terrestrial clinical limit values
- Values chosen for lack of ambiguity in terrestrial clinical settings
- Std indicates immune monitoring must be performed but does not define full scope
- Immune SMO is designed to develop this immune monitoring strategy
 - Will fill existing knowledge gap for immune changes during flight
 - Allow evidence-based risk prediction
- Immune SMO will also require improved clinical incidence tracking

Conclusion

- Critically need to close the knowledge gap of what happens to immune system during flight
- Immune SMO is required to do this
- Completion of SMO will support revision of standards and risk assessments
- Remaining time is very limited to accomplish this within life of ISS