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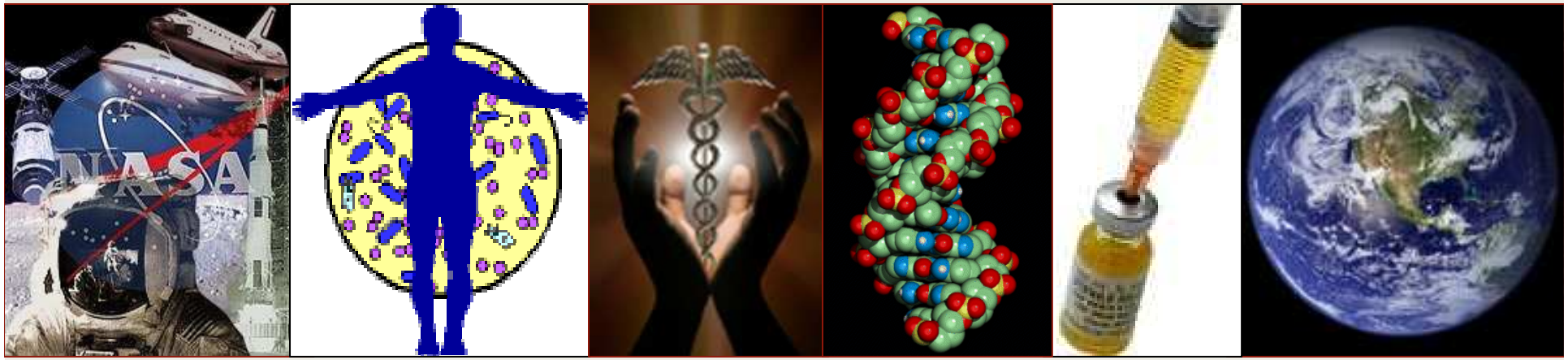
Center for Infectious Diseases and Vaccinology

Spaceflight Platforms Toward Innovations in Infectious Disease Control: *A Vision for Commercialization*

Cheryl A. Nickerson, Ph.D.

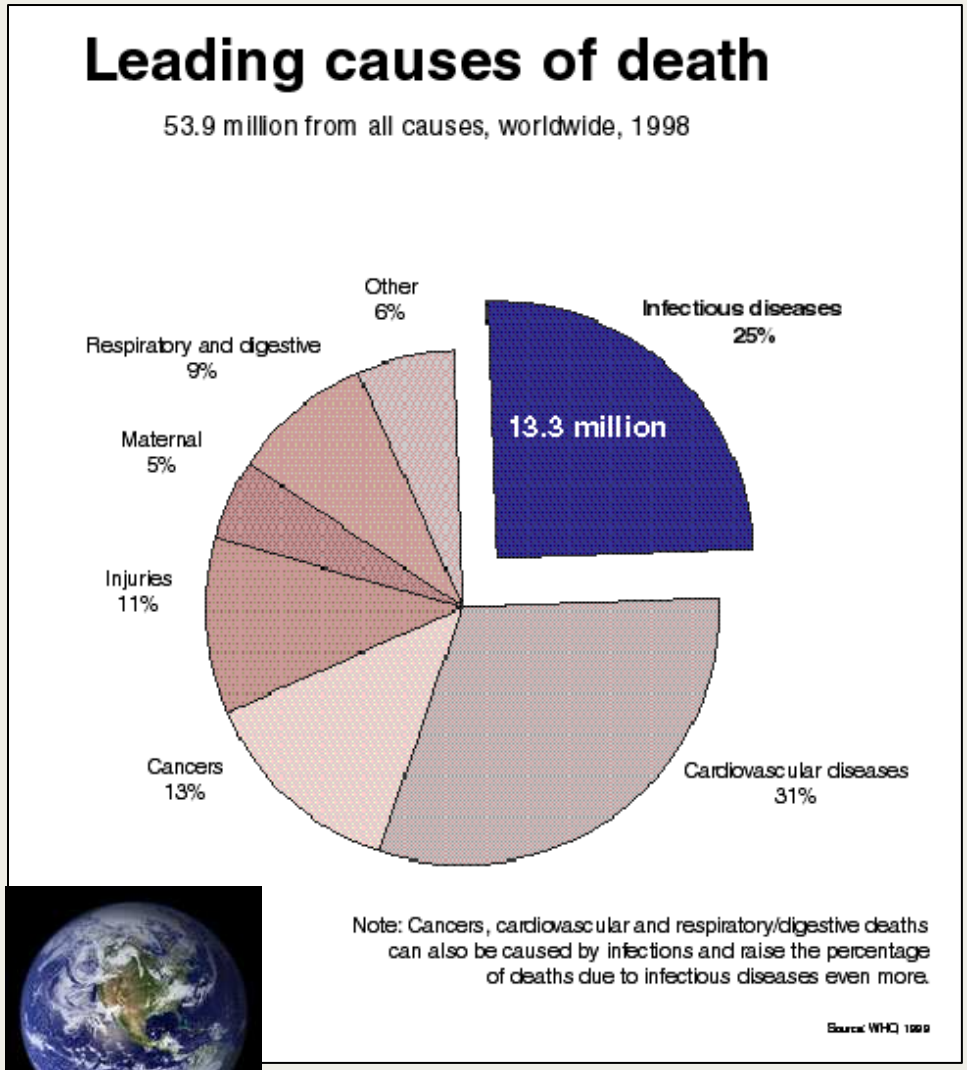
Associate Professor

Center for Infectious Diseases and Vaccinology



Why Infectious Disease?

- Infectious disease is a leading cause of death world-wide
- National and global social, economic, political, and security impact
- Total cost in the US exceeds $120 billion annually due to direct medical and lost productivity costs. Globally staggering costs.
- New and re-emerging infectious disease, antibiotic resistance, bioterrorism threat



Outpacing infectious disease!

Investing in Infectious Disease Research

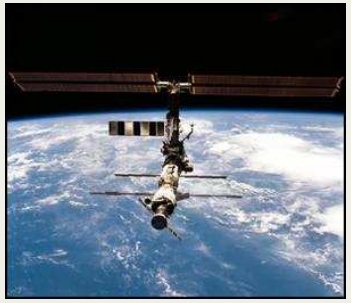
- Current estimates of bringing a new drug to market ~ $1 billion and requires extended development times of over a decade before it reaches patients
- Even incremental decreases in this cost and time are of tremendous importance
- *Spaceflight hold tremendous promise to benefit infectious disease research*

Infectious Disease Research and Spaceflight

- **Major advances in our knowledge about biological systems have come by studying their responses to *extreme* environments - (ex. temp, pH, etc) which have led to major advances in global human health breakthroughs**
- **Spaceflight is another extreme environment which offers tremendous potential to provide new insight into biological responses - including *infectious disease***
- **Spaceflight produces an environment that is relevant to conditions encountered by the pathogen during infection in the human host**

Commercial Development through Spaceflight

Spaceflight shown to induce novel changes in both human and microbial cells directly relevant to infectious disease; Immune system function, Antibiotic resistance, and Virulence



Identify target mechanisms in space

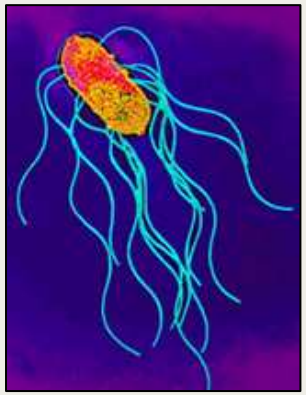
Investigate target mechanisms on Earth

Discovery of previously unknown molecular targets and mechanisms

Commercial product development

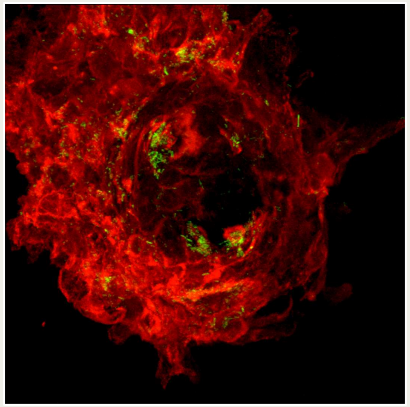
Incremental decreases in cost of drugs/vaccines and time to clinical bedside

Our Research Interests



The pathogen

In-flight infections
Risk assessment/ Countermeasures

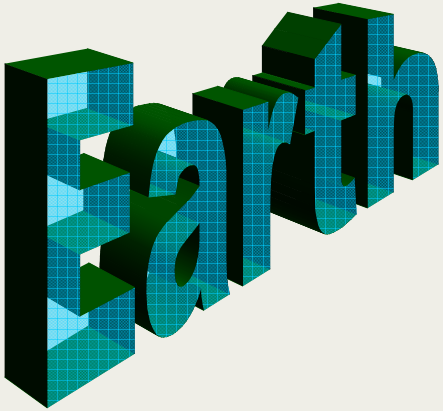


The host

Low fluid shear culture environment

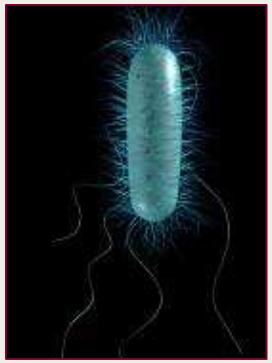
Physiologically relevant

Medically important phenotypes not observed during conventional culture



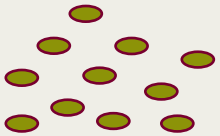
Vaccines/Therapeutics
for treatment and prevention

Model Intestinal Pathogen - Salmonella typhimurium



- Common food-borne pathogen >2,000,000 cases annually in U.S.
- A leading cause of death from foodborne illness in U.S.
- Responsible for pre-flight ISS food disqualification
- Gastroenteritis, secretory diarrhea in healthy individuals
- Serious/fatal infections in immuno-compromised
- Best characterized bacterial pathogen

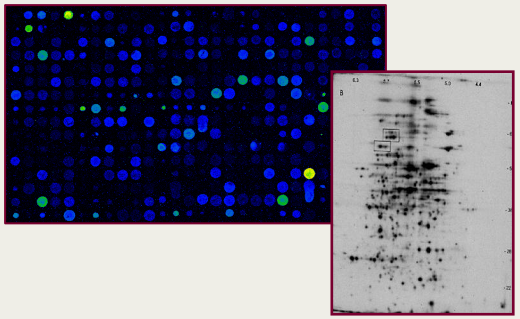
Spaceflight analogue studies demonstrate global changes in microbial pathogen responses



Salmonella typhimurium

Rotating Wall Vessel bioreactor

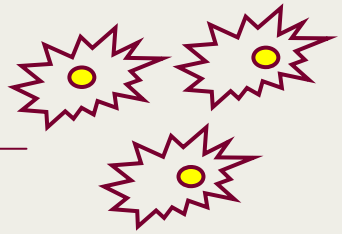
Virulence



Gene expression

*** Classic virulence genes down-regulated**

**** Ion response genes/pathways!***



Stress Resistance

(Macrophage, acid, thermal, osmotic, oxidative)

Nickerson et. al., 2000, Infect. Immun. 68:3147-3152; Wilson, et al., 2002, Proc. Natl. Acad. Sci. USA. 99:13807-13812; Wilson, et al., 2002, Appl. Environ. Microbiol. 68:5408-5416; Nickerson, et al., 2004, Microbiol Mol Biol Rev, 68:345-361; Wilson et al, 2008, PLoS ONE, Accepted.

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MICROBE launches on board Shuttle Atlantis September 9, 2006

Astronaut Heidi Stefanyshyn-Piper activates MICROBE on orbit

MDRV launches on board Shuttle Endeavour March 11, 2008

Commander Dom Gorie activates MDRV on orbit

The MICROBE Flight Experiment

While ground based research provides excellent insight into microbial responses, *only spaceflight provides conclusive information!*

MICROBE Experimental Design

Effect of Spaceflight on Microbial Gene Expression and Virulence

SPECIFIC AIMS:

1) Global gene expression profiling (transcriptomic/proteomic) of *S. typhimurium, P. aeruginosa, and C. albicans,* in response to spaceflight as compared to synchronous identical ground controls.

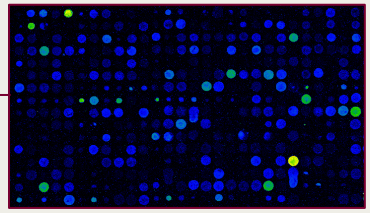
2) Determination of the effect of spaceflight on the virulence potential of these microorganisms immediately following their return from spaceflight.

MICROBE

Shuttle Atlantis, STS-115, launch Sept 9, 2006

Results:

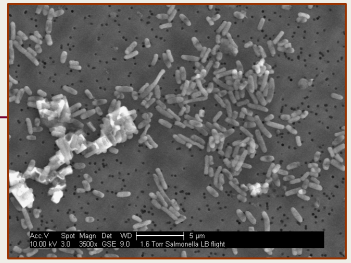
In-flight hardware



Gene expression → ***Spaceflight Globally Alters Microbial Gene Expression (167 genes)***
Ion response pathways

Identification of global molecular regulator ("master switch") of spaceflight induced cellular responses!

Disease potential → ***Spaceflight Alters Microbial Virulence***
(Increased disease potential for Salmonella in rich media)



Cellular morphology → **Spaceflight alters microbial morphology (biofilm production)**

* ***Synchronous ground controls maintained under identical conditions as those on-board Shuttle*** - *ground and in-flight hardware loaded with same sample.*

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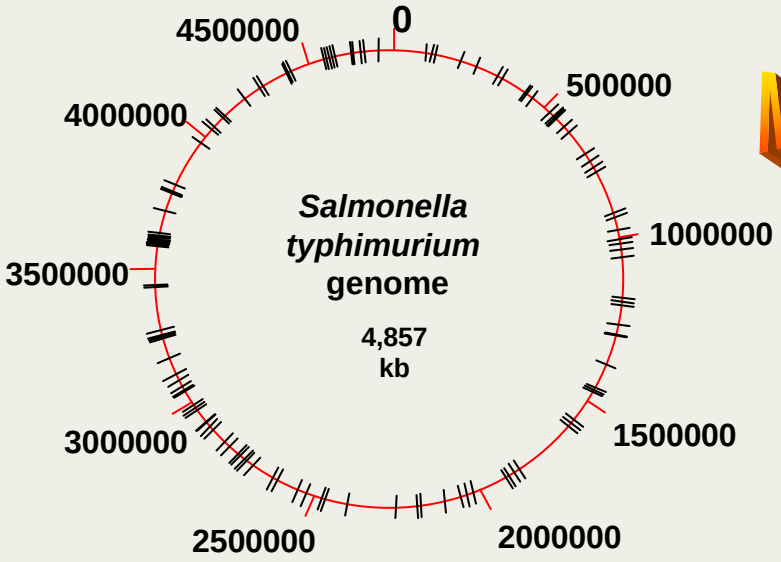
Global gene expression profiling



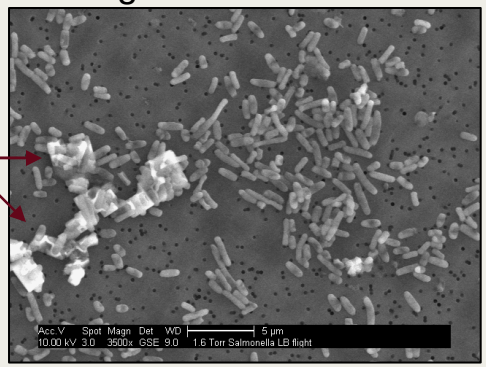
Microarrays

- Protein secretion
- Outer membrane proteins
- Iron metabolism and storage
- Ion response pathways
- Plasmid transfer functions
- Energy and metabolism
- Biofilm formation
- Transcriptional regulators
- Ribosomal proteins
- Unknown function

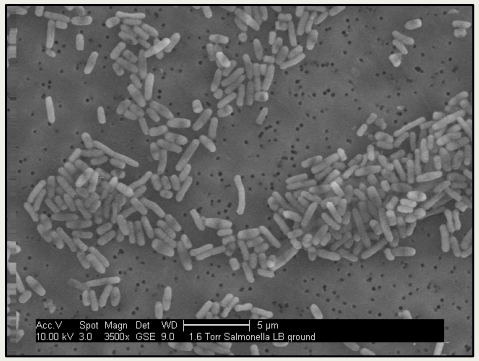
MudPIT proteomic analysis

Hfq = Master genetic regulator identified

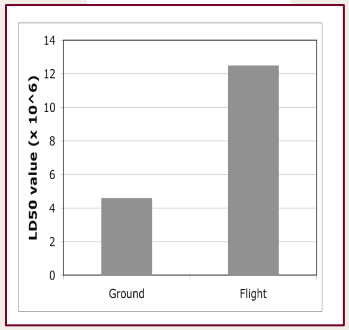
Flight

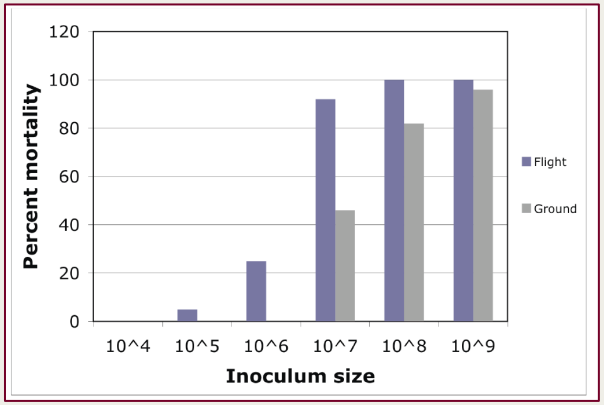


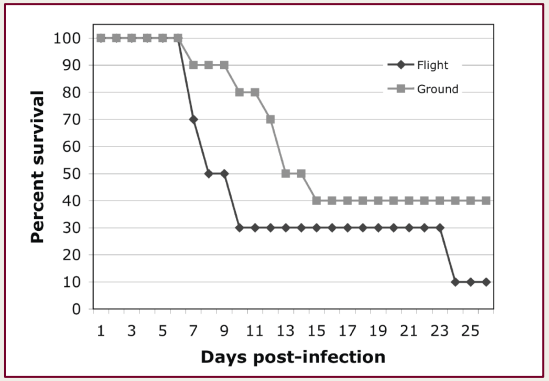
Ground



Flight Ground







Wilson et al., 2007, Proc. Natl. Acad. Sci. USA. **104**(41):16299-304

The MDRV Flight Experiment

STS-123, March, 2008

A follow-up to MICROBE:

SPECIFIC AIMS:

- **Independent validation of the effect of spaceflight on *Salmonella* virulence in rich and minimal media** ✓
- **Determine if modulation of different ion concentrations can be used as novel way to counteract or block spaceflight-associated increase in disease-causing potential observed in *Salmonella* in rich media** ✓
- **Determine common spaceflight responses that are conserved/shared between different pathogenic microbes (*multiple investigator effort*)** ✓

Wilson et. al., 2008, PLoS ONE, Accepted

MDRV

Shuttle Endeavour, STS-123, launch March, 2008

Experiment Design:

In-flight hardware

Disease potential ✓

- Independent validation of STS-115 results
- Test effect of media ion composition

Media Composition ✓

Common response conserved in other pathogens? ✓

* ***Synchronous ground controls maintained under identical conditions as those on-board Shuttle*** *- ground and in-flight hardware loaded with same sample.*

Wilson et. al., 2008, PLoS ONE, Accepted

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Moving Forward to Create Deliverable Biotechnologies to Combat Infectious Diseases:

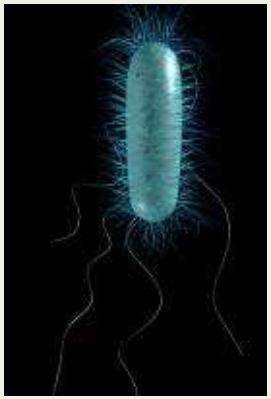
Spaceflight Vaccine and Therapeutic Development

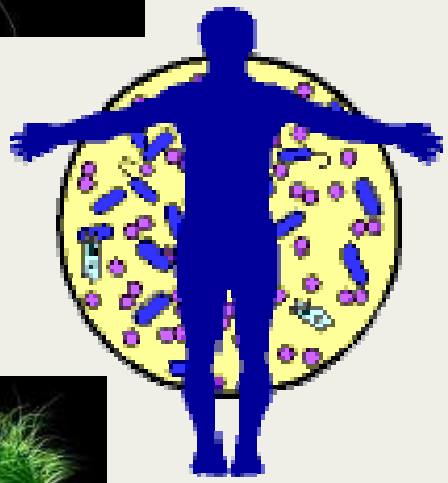
Collaboration with Dr. Roy Curtiss III; Pioneer and world leader in the development of vaccines against infectious diseases

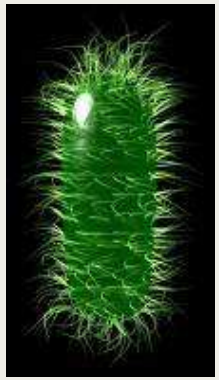
Combating infectious diseases through innovative and effective vaccine development using bacterial, viral and plant delivery methods

Successful in the distinct arenas of academic and commercial research

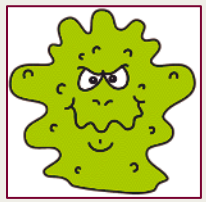
Lessons Learned from Flight Studies







- **Spaceflight alters microbial genotypic and phenotypic characteristics, including virulence *in novel ways***
- **Gene regulatory proteins identified during spaceflight can be targeted for vaccine development**
- **Modulation of different ion concentrations can be used to counteract/inhibit the enhanced virulence of pathogens in spaceflight – therapeutics**



Importance for both Earth-based and spaceflight studies for new strategies to combat infectious disease

What Does Spaceflight Offer?

A unique environment for innovative discoveries to advance human health

- **Novel environment offers insight into fundamental biological response parameters that are directly relevant to infectious disease - *and which cannot be observed using traditional experimental approaches***
- **Targets identified through spaceflight offer important direction into development of therapeutics against infectious disease**
- **This technology will have an impact on reducing the risk of infectious disease during spaceflight and on Earth.**

VISION FOR COMMERCIALIZATION FROM DISCOVERY TO THE CLINICAL BEDSIDE

FLIGHT EXPERIMENTS

↓

INTELLECTUAL PROPERTY

↓

INNOVATIVE SOLUTIONS TOWARD TREATMENT AND CONTROL OF INFECTIOUS DISEASE

↓

PATENTABLE VACCINES, THERAPEUTICS, AND DIAGNOSTICS

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