The Microgravity Research Platform: Novel Insights into the Mechanisms and Treatment of Infectious Disease

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How does our lab use the spaceflight platform to benefit human health?
New Insights into Disease Mechanisms Not Observed using Traditional Culture

The pathogen

In-flight infections
Risk assessment/Countermeasures

SPACE ACT AGREEMENT

Fluidic environment relevant to conditions encountered by pathogens in human body

Physiologically relevant

Biomedical phenotypes not observed during conventional culture

Vaccines/Therapeutics/Tissue Engineering
Treatment and prevention

Why Infectious Disease?

Outpacing Infectious Disease!
Better understanding of the mechanisms of microbial pathogenesis leads to new strategies to combat infectious disease

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

Leading causes of death

63.9 million from all causes, worldwide, 1998

- Infectious diseases 26%
- Cardiovascular disease 17%
- Causes 13%
- Injuries 11%
- Neoplasms and digestive 9%
- Maternal 9%
- Other 6%

Note: Causes, cardiovascular and respiratory/obstructive deaths can also be caused by infectious and make the percentage of deaths due to infectious diseases even more.
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 holds tremendous promise to benefit infectious disease research

Commercial Development through Spaceflight

A unique environment for innovative discoveries to advance human health

Spaceflight culture induces novel changes in both human and microbial cells directly relevant to infectious disease development and its treatment

- Virulence
- Immune system function
- Antibiotic resistance
- Tissue engineering

Discovery of previously unknown molecular targets and mechanisms

Identify target mechanisms in space

Investigate target mechanisms on Earth

Commercial product development

Incremental decreases in cost of drugs/vaccines and time to clinical bedside
The Reality of Spaceflight Research

Advances U.S. efforts to maintain technological leadership against international competition with a lasting impact on our scientific capability, economy, and quality of life

- **Does** provide novel vaccine and therapeutic targets for future research investigations on Earth
- Potential acceleration and cost savings in the discovery process
- **Does** provide a platform to modify existing vaccines and therapeutics
- **Does not** create a manufacturing platform for vaccine production
- **Does not** bypass current federal regulations, including clinical trial timelines
  - Accelerated downstream vaccine approval should not be expected
  - FDA clinical trials ~8-10 years

We Must Communicate Realistic and Scientifically Accurate Goals and Expectations!
This platform has tremendous potential
We must reject unsubstantiated claims!
Microgravity Culture Uniquely Alters Gene Expression, Stress Resistance and Virulence in Major Human Pathogens

Virulence 

Stress resistance 

Biofilm 

Gene Expression 

+ Virulence genes down-regulated 
+ Hfq Master regulator

Modulating ion levels turns off virulence

Salmonella typhimurium 

Pseudomonas aeruginosa 

Virulence gene expression Quorum sensing, biofilm, adherence, cytotoxicity

Gene Expression 

+ Hfq Master regulator

Spaceflight

Hfq – Evolutionarily conserved master regulator of microgravity response in Salmonella and Pseudomonas


Our Recent Spaceflight Experiments

First study to profile the infection process in human cells during spaceflight

Characterization of the host-pathogen interaction when both host and pathogen are simultaneously exposed to the microgravity environment of spaceflight.

Spaceflight experiment to enhance (Recombinant Attenuated Salmonella Vaccine) strain against pneumococcal disease in human clinical trials

Flown under ASU’s Space Act Agreement with NASA

Our discoveries led us to hypothesize the spaceflight environment could be used to accelerate genetic engineering of RASV strains as immunizing vectors against infectious disease by maximizing their ability to induce a protective immune response.
**NASA funded SpaceX Experiment**

**MICRO-5/PHOENIX**

*Goal:* Investigate susceptibility and associated cellular, molecular and innate immune responses in the human surrogate host, *Caenorhabditis elegans*, to infection when both host and pathogen are simultaneously exposed to spaceflight culture.

**Utilization of ASU’s Space Act Agreement with NASA to use the ISS National Lab platform**

*Goal:* Identification of cellular and molecular responses to the microgravity environment with innovative biomedical and biotechnological applications to solve major human health challenges.

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**An Additional Research Area for our Future Spaceflight Investigations:**

**GOAL:** *In vitro* models of human tissues which better approximate *in vivo* to study host-microbe interactions, drugs and therapeutics.

- **Explore**
  Better models = more relevant research outcomes

- **Validate**
  Reduce, Replace, Refine

- **Translate**
  Disease mechanisms, drug discovery, environmental health, organ generation

*Benefit human health*
OUR 3-D CELL CULTURE MODELS DEVELOPED FOR INFECTION STUDIES

Neuronal tissue
Small intestine - *Immunocompetent
Lung - *Immunocompetent
Colon - *Immunocompetent
Placental tissue
Vaginal tissue

Engineering state-of-the-art 3-D tissue models under physiological low fluid shear: Mimicking immune response and underlying tissue microenvironment

Bamila et al. 2010, Nat Rev Microbiol; Radtke et al. 2010, PLoS ONE; Crabbe et al. 2011, Cellular Microbiology

Pathogens Establish Infection of 3-D Cells in Ways that Model Important Aspects of an *in vivo* Infection

*In vivo*-like validation of infectious disease mechanisms not mimicked by conventional cell culture models

- Tissue Pathology
- Adherence, invasion, apoptosis
- Innate immune responses
- Host biosignatures – transcriptomics, proteomics, metabolomics
- Microbial virulence mechanisms
- Growth of pathogens not previously culturable
- Mimic human responses to antimicrobial therapeutics

What Does the ISS Microgravity Research Platform Offer?

A unique environment for innovative discoveries to advance human health

- Novel environment offers insight into fundamental biological response parameters from both the host and pathogen perspective that are directly relevant to infectious disease - and which cannot be observed using traditional experimental approaches
- Scientific advances and commercial potential for innovative solutions toward treatment and control of infectious disease.

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• Objective

To characterize the host-pathogen interaction when both host and pathogen are simultaneously exposed to the microgravity environment of spaceflight.

Implications for understanding how human cells function normally - how physical forces and mechanical stress influence balance between normal tissue homeostasis and disease progression

- Profiling cellular responses of human intestinal cells before and after infection with S. typhimurium during spaceflight
  - Changes in immune function and cellular stress responses
  - Changes in cellular differentiation
  - Targeted gene expression profiling

*First study to profile the infection process in human cells during spaceflight*
Summary Part 1

Lessons Learned from Spaceflight Culture of Microbial Pathogens

- Spaceflight culture alters molecular genetic and phenotypic characteristics of pathogens, including virulence in novel ways not observed using traditional experimental approaches on Earth.

- Genes differentially expressed during spaceflight can be targeted for vaccine development.

- Modulation of different ion concentrations to counteract/inhibit the enhanced virulence of pathogens in spaceflight.

- Hfq is a conserved global molecular regulator that may be used by other bacterial pathogens (in addition to Salmonella and Pseudomonas) to respond to microgravity conditions.

Importance for both Earth- and spaceflight-based studies for new strategies to combat infectious disease.
Infectious Disease Research and Spaceflight

- Major advances in our knowledge about biological systems - studying their responses to extreme environments - (ex. temp, pH, etc) - 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 – but gravity masks key cellular responses on Earth.

WHY STUDY BACTERIAL PATHOGEN RESPONSES TO FLUID SHEAR?

- Pathogens experience wide fluctuations in fluid shear in vivo during infection.

- Most studies have not cultured bacteria under physiological fluid shear conditions encountered during infection.

- Fluid shear affects bacterial gene expression, physiology, pathogenesis - but mechanism(s) not well understood.

- Entire classes of microbial genes/proteins involved in host interactions not previously identified during growth under conventional culture conditions.

- New targets for vaccine/therapeutic development.
A Comparison of Cell Culture Environments

Gravity

Laminar fluid flow

Microgravity

Physical forces play a central role in dictating both normal cell/tissue function and disease progression.

Cells sense and respond to mechanical force

Physical basis of disease

- Infectious Disease, Immune Disorders, Cardiovascular Disease, Cancer
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