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Labwork (Restricted)

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The only way I know how to make sense out of the last fifty years of molecular biology is to abandon the mechanistic and atomistic ideas of the pre-DNA era and embrace a more organic, cognitive and computational view of cells and genomes. There are no units, only interactive systems. Bacteria continually pick up and process information about the environment, internal conditions and other cells to decide on appropriate biochemical and biomechanical actions....The take-home lesson of more than half a century of molecular microbiology is to recognize that bacterial information processing is far more powerful than human technology.

from *Bacteria are small but not stupid: cognition, natural genetic engineering, and socio-bacteriology*

-James A. Shapiro PhD

*Everything touches everything*

-Jorge Luis Borges*
Our relationship with the microbial world is delicate and complicated. Our bodies are colonized with hundreds of micro-organisms that to a large extent play an important role in maintaining a state of health through contributions to digestion, metabolism, development and immune function. To that end, humans have been considered to be super-organisms, the sum of our own cells and the microbial communities we support. On the other hand, from these communities can emerge rogue players that can reek havoc on the human host through aggressive infection, tissue damage and even insidious disruption of key regulatory systems. Understanding the manner and contexts in which our microbial friends become foes has been the challenge of physicians and biologists for centuries. In the molecular age we have the highest resolution picture of what is going on, and still there is little in the way of new strategies to maintain health and prevent infection.

Our lab seeks to better understand the regulation of virulence expression among potential pathogens through investigating the characteristics of the microbial context, molecular machinery that senses that context, and ultimately the lethal combinations of virulence expression that leads to disease. The majority of our work has focused on the sense and response virulence mechanisms of Pseudomonas aeruginosa, a well characterized and clinically important pathogen. We have shown a remarkable potential for this organism to respond to host environmental cues related to stress, ischemia, immune activation and nutrient depletion. With this core model of environmental regulation of virulence expression, we are pursuing applications in intestinal transplantation, anastomotic and radiation physiology, necrotizing enterocolitis and ischemia/reperfusion injury. We are also investigating similar sense and response mechanisms in other clinically important organisms, including Staphylococcus aureus and Candida albicans. Finally, we are interested in developing virulence-based therapies to prevent virulence activation through modifications in microenvironment of the stressed host such as phosphate repletion and polymer-mediated mucosal replacement therapies.

The ultimate goal of understanding microbial virulence is to provide clinical tools to improve the care of patients. However the complexity of the host-pathogen interaction and the vast amounts of mechanistic information available constitutes a formidable barrier to translational research. Computational agent based modeling is a well suited to dynamically represent mechanistic detail in a modifiable context to recapitulate cellular behavior at the tissue, organ and patient levels.

Postulates of Surgical Infection

In order to appreciate the dynamic and complex relationship of microbe-host interactions, we have established postulates to guide our research endeavors as an evolution of the Koch's postulates.

Koch's Postulates

1. The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy animals.
2. The microorganism must be isolated from a diseased organism and grown in pure culture.
3. The cultured microorganism should cause disease when introduced into a healthy organism.
4. The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

Molecular Koch’s Postulates

1. The phenotype or property under investigation should be associated with pathogenic members of a genus or pathogenic strains of a species.” Additionally, the gene in question should be found in all pathogenic strains of the genus or species but be absent from nonpathogenic strains.
2. Specific inactivation of the gene(s) associated with the suspected virulence trait should lead to a measurable loss in pathogenicity or virulence. Virulence of the microorganism with the inactivated gene must be less than that of the unaltered microorganism in an appropriate animal model.
3. Reversion or allelic replacement of the mutated gene should lead to restoration of pathogenicity. In other words, reintroduction of the gene into the microbe should restore virulence in the animal model.

### Alverdy Lab Postulates of Surgical Infection

1. Under normal conditions there is an ongoing bi-directional chemical dialogue between host tissues and colonizing pathogens that establishes a dynamic equilibrium of molecular equipoise.

2. Under conditions of surgical stress, local micro-environmental cues are released by host tissues that shift the nature of host-pathogen dialogue.

3. Microbial pathogenicity (potential for harm) following surgical injury is governed by host tissue specific micro-environmental cues that activate the virulence machinery of colonizing bacteria to express a more invasive/aggressive phenotype.

4. The goal for surgeons is to minimize physiologic stress in order to suppress the release of environment cues that activate those pathogens known to colonize the most at risk patients. The goal for investigators is to develop strategies that can maintain environmental control at the site of the host-pathogen interaction.

### Pseudomonas aeruginosa

Gut derived sepsis is a complex process in which intestinal microbes participate to activate and sustain systemic inflammation leading to host damage and death. Over the past decade, my laboratory has created unique model systems and developed molecular tools to study gut-derived sepsis using the human opportunistic pathogen Pseudomonas aeruginosa. Virulence expression in P. aeruginosa is highly dynamic and is regulated by quorum sensing (QS), a hierarchical "sense and respond" system that uses secreted cell-cell communication molecules to synchronize bacterial community behavior and overcome the host. We discovered that host stress compounds (i.e. opioids, adenosine, interferon-) are released into the intestine during surgical injury that directly activate the QS system of P. aeruginosa, shifting its phenotype from harmless colonizer to lethal pathogen. Most importantly we also discovered that phosphate (Pi) depletion develops within the distal intestinal mucus layer following surgical injury. Decreased Pi levels further enhance the virulence output of P. aeruginosa to incoming host stress compounds via highly conserved membrane phospho-sensor kinases that communicate to the QS system. In a phosphate rich environment, intestinal P. aeruginosa becomes insensate to incoming host stress compounds and remains harmless.

These findings raise important questions. What gene expression changes and signaling circuits are specifically activated in P. aeruginosa in the intestine during surgical injury that confer a lethal phenotype? Are there specific sites within the intestine during surgical injury in which P. aeruginosa expresses a lethal gene signature? Can novel therapies that target fundamentally innate host responses, such as increasing the local concentration of phosphate, be used to block virulence activation and lethality? We hypothesize that there are conserved elements within the molecular circuitry of P. aeruginosa that detect host stress compounds in the gut in a site-specific manner that activate a lethal phenotype.

**Computational modeling**

**BIASE**

Bioengineering Institute for the Advancement of Surgery and Endoscopy

**Polymer therapies**
Necrotizing enterocolitis
Mike and Erica.

Anastomosis and Radiation
Andrea

Small bowel transplantation
Vesta and Testa

Staphylococcus aureus
Current collaboration with the lab of Dr. Robert Daum (University of Chicago Comer’s Children’s Hospitals).

Wiki Site
This wiki-site development is project of the Information Architecture and Modeling section of the lab. The site is designed to serve as a platform to consolidate the workflow of several initiatives within the lab and to facilitate collaborations within the university and larger research community. This prototype site is currently being managed by John Seal, a surgical research resident, and Gary An, a collaborator specializing in computational modeling. Please direct any questions, comments or suggestions to John.seal@uchospitals.edu