**Studying pathogens at the genomic level**

*An introduction to pathogenomics*

Although interest and experimentation to understand pathogenicity had existed long before, the publication of the *Haemophilius influenza* genome was the first true investigation into pathogenomics. Researchers in this new field of pathogenomics aim to understand how changes in the genomic architecture of pathogens result in changes in the virulence to host organisms. This is accomplished by the integration of tools of microbial research with the insights available from sequence information. Through this combination, researchers are able to cross-reference the phenomic results from genomic changes in vitally important microbial pathogens. From this foundation, researchers are able to describe, in fascinating detail, how a particular collection of genes within a particular organism can cause disease, increase pathogen fitness, and modulate the host-pathogen interface. This genome-wide view of pathogenicity subsumes genetic changes in single virulence genes into a model of genome-wide genetic alterations and chromosomal dynamics. This level of analysis proves additional context necessary to fully articulate the complex relationships that exist between hosts, pathogens, and the ecosystem at large.

Now, used to identify specific pathotypes associated with genomic organization.

*Genomic pathoadaption*

While the concepts of pathoadaptation, genetic or genomic alterations that results from specialization to new niches, and virulence factors, microbial products that cause damage or disease, specific definition of these concepts are difficult to articulate. These difficulties come about, in part, due to the lack of clear delimiters between pathogenic and non-pathogenic strains of microbes. For instance, uropathogenic *Escherichia coli* (UPEC) function as commensal

* 1. What are pathoadaptive mutations
     1. Definition of pathoadaptive mutations
     2. How are they investigated
  2. How do bacteria gain pathoadaptive mutations
     1. HGT
        1. Importance of HGT, especially in Enterobacteriacaea in gaining new functions
           1. Innovation paper, Koonin paper
           2. Introduction of pan-genome versus core genome.
           3. Size of pan-genome
        2. Types of HGT
           1. Plasmids
           2. Pathogenicity islands

Dobrindt 2011

* + - * 1. Prophage regions

Canchaya 2005

* + 1. Other types of pathoadaptive mutations
       1. SNPs responsible for changes in fitness
          1. Chen positive selection paper
       2. Genome reduction in ABU
          1. ABU to UTI genomic comparison paper
  1. Importance of pathogenomic analysis
     1. Why assign pathotypes to genotypes?
        1. Microbial ecology
           1. Probably that virulent pathotypes compete with commensals for space
        2. Susceptibility
           1. Why do we get sick? How can we prevent it?
        3. Drug-discovery
           1. How do we cure sick? Can we cure it?  Dobrindt paper 2005 Pathogenomics leads to drug discovery

1. Introduction to E. coli genomics
   1. What is E. coli
   2. Serogroups
   3. Commensal versus Pathogen
   4. Types of pathogenic E. coli
   5. Genomic structure of commensals and pathogens.
      1. Genomes of commensals and pathogens share core genome and a variable outer envelope genes
      2. Where is the difference?  Most differences are associated with mobile genetic elements Dobrindt 2005 paper.
   6. What is upec (strains, ect.)
   7. What makes UPEC good model organism for studying facultative pathogen, professional pathogen, and commensal Dobrindt 2005 paper
2. Introduction to UTI's
   1. What are UTI's
   2. Types of UTI's (clinical microbiology)
   3. Occurences of UTI's
   4. Genetic factors that predispose to UTIs?
   5. Costs of UTIs
   6. Bring back to general infection models
   7. Model organism used to study ExPEC infections is UPEC
3. UTI maturation and UPEC population dynamics during infection
   1. Initial explanation of UTI by UPEC
   2. Steps
      1. Adherence
      2. Invasion
      3. IBC formation
      4. Fluxing
      5. Formation of QIR
      6. Chronic Infection
   3. Clearance
   4. Population bottleneck affects genetic diversity of population
   5. Origin of UPEC for UTI
4. History of genomic analysis of UPEC
   1. Previous genetic analysis of UPEC
   2. Genomic analysis of UPEC introduction
   3. first genome sequence
   4. Comparison of virulence factors
   5. Comparison of HGT
   6. Genomic Structure of UPEC
   7. Gaps or criticisms of genomic analysis
5. Population dynamic
   1. Source-Sink model
      1. Explanation of model
      2. Reasoning for application to UTIs
      3. Flaws in application
         1. Existence of Urogenital-Oral or Fecal-Oral transmission
         2. Preliminary evidence showing high abundance in both habitats
         3. Preliminary evidence showing high-rates of turnover in sink habitat
   2. Alternative models - Gut UPEC bloom leads to uropathogenic E. coli
      1. Explanation of model
         1. Dysbiosis leads to increased abundance of *E. coli* and other proteobacteria
            1. Ab therapy paper, cancer-microbiome paper, pregnant women paper
      2. Reasoning
         1. Prelim data shows disruption of microbiota leads to increased susceptibility to UTIs
         2. Preliminary data shows a recurrence of same strain in the bladder, rather than recent mutants that repeatedly colonize bladder
         3. Preliminary data shows that strains that are more fit in the gut ALSO outcompete previous strain in the bladder.