Research and Biosurveillance Data

Analysis and Characterization

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2011 GBSV Conference Objectives

- Identify, with Supporting Rationale, Opportunities for:
  - Integration of existing biosurveillance systems
  - Near term technology advancements
  - Priority future R&D areas

- Required Technical Infrastructure
  - Methodology for technology evaluation, validation and transition
  - Standards (data, information technology)

- Opportunities for Partnerships & Collaborations
  - Interagency, Public Health, National Security
  - Government, Academia, National Labs, DoD Labs, Private Industry
  - Operational and R&D communities
  - Information S&T
  - Global Network

Development of a Technology Road Map for Comprehensive Global Biosurveillance
Principal Observations

- Participants were all passionate about and committed to pursuing biosurveillance and its potential impacts.
- Several communities have long successful histories of practicing biosurveillance.
- Biosurveillance is extremely complex from numerous perspectives.
- Great desire is expressed for high level leadership and direction.
- Many believe integration should first occur at practitioner level, then system and technology levels.
- Information science and technology will be a critical force for integration.
- Zoonotic diseases are most critical source of novel high impact human diseases, need to focus on the human-animal interface (zoonotics).
- Sustainable operations require rapid, simple, easy to use, affordable and market driven technologies.
- GBSV is an important component for international engagement.
- Building trust is critical and focusing on host nation needs is necessary for sustainability.

Trust
Biosurveillance Data and Analysis

Inform/define data stream collection

Data Streams
- Genomics
- Metagenomics
- Transcriptomics
- Proteomics
- Molecular Structure
- Syndromic
- Clinical
- Public Health
- Climate
- Vegetation

Information Management

Knowledge Management

Applications
- Biodetection
- Bioforensics
- Vaccine Design
- Therapeutic Design
- Virulence Prediction
- Epi Modeling
- Tactical/Strategic Planning
- Unusual Disease Analysis
- Agriculture
- Environmental Mgt

Theory & Simulation

Tailored results

Toward Sustained GBSV:
- Integration of components & systems
- Compression of time from innovation/discovery to application
- Targeted R&D innovation to overcome barriers of cost & effectiveness
BioPASS Homepage:

Welcome to the BioPASS portal. BioPASS is an integrated systems biology tool for rapid pathogen characterization and broad-spectrum countermeasure development. This site enables researchers and public officials to discover information over broad topics such as genomics and proteomics.

Getting Started
Select a tool below.

Tools
- OrgID
- Virulence Factor Analysis
- Disease Progression
- Twitter Tracking
- Knowledgebase
Initial Result Display:

Results

- Show Analysis Details [Bacteria]
- Show Analysis Details [Virus]
- Show Analysis Details [Toxin]
- Generate Expert List [Uses smart PubMed (and other resources) search to identify experts on identified organism]
- More About [Organism] [Shows selected manually edited material on identified organism]
- Assess Risk [Analyzes related organisms to further refine risk assessment]
Phylogeny Analysis of the New Org:

Bacterial Results

- Bacteria (193 assemblies)
  - Bacteroidetes (1 assembly)
  - Flavobacteria (1 assembly)
  - Flavobacteriales (1 assembly)
  - Flavobacteriaceae (1 assembly)
  - Flavobacterium (1 assembly)
  - Flavobacterium atlanticum HTCC2559 (1 assembly)
- Firmaceae (42 assemblies)
- Firmicutes (24 assemblies)
- Bacillales (18 assemblies)
- Bacillus (10 assemblies)
- Bacillus cereus group (18 assemblies)
- Bacillus anthracis TeaAncestor-l (1 assembly)
- Bacillus anthracis TeaAncestor (1 assembly)
- Bacillus anthracis str. "Ames Ancestor" (1 assembly)
- Bacillus anthracis str. 2107 (1 assembly)
- Bacillus anthracis str. CstAvA-9065 (1 assembly)
- Bacillus anthracis str. CstAvA-9066 (1 assembly)
- Bacillus anthracis str. CSU96 (1 assembly)
- Bacillus anthracis str. CSU97 (1 assembly)
- Bacillus anthracis str. Kinga B (1 assembly)
- Bacillus anthracis str. Voldus (1 assembly)
- Bacillus anthracis Western North America USA6153 (1 assembly)
- Bacillus cereus 93B11 (1 assembly)
- Bacillus cereus AH1134 (1 assembly)
- Bacillus cereus AH1135 (1 assembly)
- Bacillus cereus AH1136 (1 assembly)
- Bacillus cereus AH1138 (1 assembly)
- Bacillus cereus G2424 (1 assembly)
- Bacillus cereus G2424 (1 assembly)
- Bacillus cereus G9244 (1 assembly)
- Bacillus cereus G9245 (1 assembly)
- Bacillus cereus MS180197 (1 assembly)
- Bacillus cereus TN1059 (1 assembly)
- Bacillus cereus V (1 assembly)
- Listeria (3 assemblies)
- Listeria (3 assemblies)
- Listeria (3 assemblies)
- Listeria (3 assemblies)
- Clostridiales (14 assemblies)
- Lactobacillales (8 assemblies)
- Streptococcales (4 assemblies)
- Streptococcus (4 assemblies)
- Proteobacteria (116 assemblies)
## Similarity Returns, Virulence Factor Hits:

<table>
<thead>
<tr>
<th>Category</th>
<th>Lysinibacillus sphaericus</th>
<th>Bacillus cereus ATCC 10987</th>
<th>Bacillus anthracis</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Bacterial hits</td>
<td>84</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>% Firmicutes</td>
<td>66</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>% Bacilli (class)</td>
<td>54</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>% Bacillales (order)</td>
<td>50</td>
<td>85</td>
<td>92</td>
</tr>
<tr>
<td>% Bacillus (genus)</td>
<td>26</td>
<td>82</td>
<td>91</td>
</tr>
<tr>
<td>% <em>B. cereus</em> (~5 species)</td>
<td>6</td>
<td>76</td>
<td>83</td>
</tr>
<tr>
<td>% <em>Bacillus anthracis</em></td>
<td>2</td>
<td>36</td>
<td>61</td>
</tr>
<tr>
<td># hits Lethal factor</td>
<td>20</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td># hits Protective antigen</td>
<td>13</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td># hits Edema factor</td>
<td>11</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td># hits Cap A, B, C</td>
<td>28</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td># hits Drug resistance transporters</td>
<td>36</td>
<td>142</td>
<td>139</td>
</tr>
<tr>
<td># hits Penicillin-binding protein</td>
<td>19</td>
<td>144</td>
<td>136</td>
</tr>
<tr>
<td># Total Toxin, Virulence factor, Ab hits</td>
<td>220</td>
<td>825</td>
<td>865</td>
</tr>
</tbody>
</table>
### Potential Virulence Related Factors:

<table>
<thead>
<tr>
<th>Accession</th>
<th>Entry name</th>
<th>Status</th>
<th>Protein names</th>
<th>Gene names</th>
<th>Organism</th>
<th>Length</th>
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<tbody>
<tr>
<td>Q51639</td>
<td>CAPD_BACAN</td>
<td>Capsule biosynthesis protein capD</td>
<td>capD</td>
<td>Bacillus anthracis</td>
<td>528</td>
<td></td>
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<tr>
<td>Q44636</td>
<td>ATXA_BACAN</td>
<td>Anthrax toxin expression trans-acting positive regulator</td>
<td>atxA</td>
<td>Bacillus anthracis</td>
<td>475</td>
<td></td>
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<tr>
<td>Q44643</td>
<td>ACPA_BACAN</td>
<td>Capsule synthesis positive regulator acpA</td>
<td>acpA</td>
<td>Bacillus anthracis</td>
<td>483</td>
<td></td>
</tr>
<tr>
<td>Q9RMX9</td>
<td>ACBP_BACAN</td>
<td>Capsule synthesis positive regulator acpB</td>
<td>acpB</td>
<td>Bacillus anthracis</td>
<td>482</td>
<td></td>
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<tr>
<td>P19579</td>
<td>CAPA_BACAN</td>
<td>Capsule biosynthesis protein capA</td>
<td>capA</td>
<td>Bacillus anthracis</td>
<td>411</td>
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<td>P19580</td>
<td>CAPB_BACAN</td>
<td>Capsule biosynthesis protein capB</td>
<td>capB</td>
<td>Bacillus anthracis</td>
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<tr>
<td>P19581</td>
<td>CAPC_BACAN</td>
<td>Capsule biosynthesis protein capC</td>
<td>capC</td>
<td>Bacillus anthracis</td>
<td>149</td>
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</tr>
<tr>
<td>P15917</td>
<td>LEF_BACAN</td>
<td>Lethal factor</td>
<td>lef</td>
<td>Bacillus anthracis</td>
<td>809</td>
<td></td>
</tr>
<tr>
<td>P13423</td>
<td>PAG_BACAN</td>
<td>Protective antigen</td>
<td>pagA</td>
<td>Bacillus anthracis</td>
<td>764</td>
<td></td>
</tr>
<tr>
<td>P40114</td>
<td>TOPI_BACAN</td>
<td>DNA topoisomerase 1</td>
<td>topX</td>
<td>Bacillus anthracis</td>
<td>870</td>
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</tr>
<tr>
<td>Q9ZFB4</td>
<td>GERXA_BACAN</td>
<td>Spore germination protein XA</td>
<td>gerXA</td>
<td>Bacillus anthracis</td>
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<tr>
<td>Q9ZFB5</td>
<td>GERXB_BACAN</td>
<td>Spore germination protein XB</td>
<td>gerXB</td>
<td>Bacillus anthracis</td>
<td>355</td>
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<tr>
<td>Q9ZFB3</td>
<td>GERXC_BACAN</td>
<td>Potential Spore germination protein XC</td>
<td>gerXC</td>
<td>Bacillus anthracis</td>
<td>317</td>
<td></td>
</tr>
<tr>
<td>P40136</td>
<td>CYAA_BACAN</td>
<td>Calmodulin-sensitive adenylate cyclase</td>
<td>cya</td>
<td>Bacillus anthracis</td>
<td>800</td>
<td></td>
</tr>
</tbody>
</table>

*Note: The table entries are placeholders for demonstration purposes.*
Infectious Disease Progression:

-- 7 disease model available
Twitter Disease Tracking:
**Infectious Disease Knowledgebase:**

-- 28 agents/diseases available

### Transmission

<table>
<thead>
<tr>
<th>Environment-to-Human</th>
<th>B. anthracis spores can live in the soil for many years (696)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal-to-Human</td>
<td>Virtually all warm-blooded species susceptible, although herbivores are most commonly infected; bison, buffalo, cattle, sheep, goats, horses and swine, wildlife, occasionally dogs (698)</td>
</tr>
<tr>
<td></td>
<td>Even if not many people are infected following a deliberate release, infected animals may serve as a source of new human infection (691)</td>
</tr>
<tr>
<td></td>
<td>Carcasses of infected animals pose a hazard to humans and other animals both in the vicinity and at a distance through their meat, hides, hair, wool or bones; hides, hair, wool and bones may be transported large distances for use in industries, feedlots or handicrafts (697)</td>
</tr>
<tr>
<td></td>
<td>Following naturally occurring anthrax among livestock, cutaneous and rarely (in the US) gastrointestinal exposures among humans are possible, but inhalation anthrax has not been reported (695)</td>
</tr>
<tr>
<td></td>
<td>Humans can be infected upon contact with infected animals or animal products; hair, wool, hides, bone, meat contact with soil; ingestion (under-cooked meat), skin abrasion, inhalation (691/674)</td>
</tr>
<tr>
<td>Human-to-Human</td>
<td>Rarely person-to-person transmission (672)</td>
</tr>
<tr>
<td></td>
<td>Person-to-person transmission is extremely unlikely and only reported with cutaneous anthrax where discharges from cutaneous lesions are potentially infectious (699)</td>
</tr>
<tr>
<td></td>
<td>Anthrax does not spread from person to person (691)</td>
</tr>
<tr>
<td>Vectors</td>
<td>All mammals are susceptible, although herbivores are most commonly infected; bison, buffalo, cattle, sheep, goats, horses and swine, wildlife, occasionally dogs and other carnivores infected by scavenging anthrax-infected carcasses (699)</td>
</tr>
<tr>
<td></td>
<td>B. anthracis spores can survive for 2 years in pond water (692)</td>
</tr>
<tr>
<td></td>
<td>Spores survive for &gt;40 years in soil (294)</td>
</tr>
<tr>
<td></td>
<td>Animal products including carcasses, hides, hair, wool, meat, and bone meal (699)</td>
</tr>
<tr>
<td></td>
<td>Dogs and other carnivores from scavenging on anthrax-infected carcasses; workers infected from hides, wool, hair etc from infected animals imported to barns and mills (699)</td>
</tr>
<tr>
<td></td>
<td>Animal-to-animal greatest risk to humans exposed to an aerosol of B. anthracis spores occurs when spores first are made airborne (primary aerosolization) (674)</td>
</tr>
<tr>
<td>Routes of Infection</td>
<td>Rarely person-to-person cutaneous transmission (672)</td>
</tr>
</tbody>
</table>
TVFac (ToxinVirulence Factor DB)

TVFac Hierarchy:
- Adhesins
- Type IV Pili
  - Phase-related
  - Transport and secretion systems
- Type II secretion system

Type IV pili (O-methyl-phenylalanine pili) (fibriae)

**Description:**
Type IV pili (fibriae) are filamentous polar organelles found in Pseudomonas aeruginosa and in a wide variety of other pathogenic bacteria including Neisseria gonorrhoeae, Neisseria meningitidis, Bichelobacter nodosus, Moraxella bovis, Eikenella corrodens, Aeromonas hydrophila and Rpsnococcus azurescens. The biogenesis and function of type IV pili is controlled by a large number of genes, thus far about 40 of which have been identified by mutational analysis in Pseudomonas aeruginosa. These genes fall into two broad categories: (1) those encoding regulatory networks that control the production and function of these fibriae (and other virulence factors such as alginate biofilm) in response to alterations in the environment, and (2) those encoding proteins involved in export and assembly of these organelles. Many of the genes required for pili assembly are homologous to the genes involved in type II protein secretion and competence of DNA uptake, suggesting that these systems share a common architecture and evolutionarily related.

A group of related structures referred as type-4B fibriae have also been identified in E. coli (bundle-forming pili; Bfp) and Vibrio cholerae (toxin-coregulated pili; Tcp).

**Action:**
Type IV pili mediate attachment to host epithelial tissues and a form of surface translocation called twitching motility. These adhesins appear to bind to specific galactose or mannose or sialic acid receptors on epithelial cells. It has been shown that colonization of the respiratory track by Pseudomonas aeruginosa requires fibrial adherence and aided by production of a protease enzyme that degrades fibronectin in order to expose the underlying fibrial receptors on epithelial cell surface.

Tissues injury also play a role in Pseudomonas aeruginosa colonization of the respiratory tract as it was shown that P. aeruginosa will adhere to tracheal epithelial cells of mice infected with influenza virus but not normal tracheal epithelia.

In Pseudomonas aeruginosa, type IV pili also appear to function as receptors for fibrial-dependent bacteriophages.

**Counter Measure:**
Pseudomonas aeruginosa is the major infectious agent of concern for cystic fibrosis patients. Production of exopolysaccharide alginate and intrinsic resistance to most of the known antibiotics make it very difficult to control. So strategies to prevent colonization of P. aeruginosa and/or neutralize its toxins are needed. Hurts, et al. (2001) reported the development of a dual-functional protein vaccine for P. aeruginosa. The vaccine is a chimeric protein containing the key sequence of type IV pilin and non-toxic version of exotoxin A. The chimeric protein (FB64betaG3pilin), when injected into rabbits, produced antibodies that reduced bacterial adherence and neutralized the cell-killing activity of exotoxin A.

**References:**
FRED: 322697
FRED: 3212486

FRED: 11506071

**Comment:**
Regulation of pilA — The major fibrial subunit gene pilA is transcriptionally regulated by a two-component sensor-regulator network encoded by pilR. pilR encodes a sensor kinase, which is predicted to contain six transmembrane domains in its N-terminal portion. The pilR-encoded response regulator contains DNA-binding domains within the C-terminal domain and a C-terminal DNA-binding domain determining its target specificity, and (2) a central RpoE interaction domain. The FlrB protein and both of these sites are absolutely required for FlrB-mediated transcriptional activation, suggesting that the FlrB may bind the promoter regions as a dimer or bind cooperatively by FlrB monomers. Sigma-54 (RpoH) is required for type IV pilus biogenesis as rpoH mutants are non-fibriate.
Guiding Principles for Host-Pathogen Knowledge:

Lifecycle of the pathogen. The outer circle enumerates eighteen steps that most pathogens must solve in one way or another. These lifecycle steps can be interpreted both in terms of genes that can be searched for in genomic data and in terms of the patho-physiology. Hence, they serve as the glue that allows BioPASS to characterize potential outcomes from sequence data.
Team:

- **LANL Team:**
  - Helen Cui, PI
  - Craig Blackhart, systems
  - Bob Funkhouser, programming
  - Jennifer Harris, infectious diseases
  - Chris Stubben, pathogen virulence
  - Chen He, twitter map
  - Ben MacMahon, phylogeny
  - Carla Kuiken, sequence database
  - Jian Song, virulence factors
  - Patrick Chain: matagenomics
  - Amanda Minnich, pathogen knowledge
  - Nick Hangartner, proposal development
  - Julianna Fessenden, program development
  - Gary Resnick, biodefense, strategy

- **Sponsor:**
  - Brian Nordmann, Department of State
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