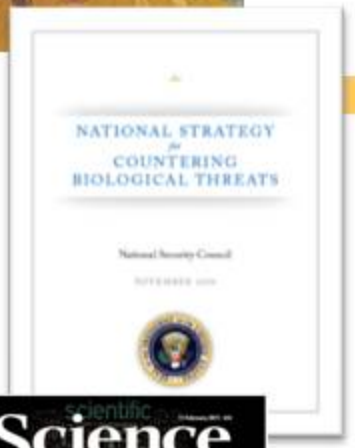

Research and Biosurveillance Data

Analysis and Characterization

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University of Missouri
April 12, 2011

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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

Trust

- 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

Biosurveillance Data and Analysis

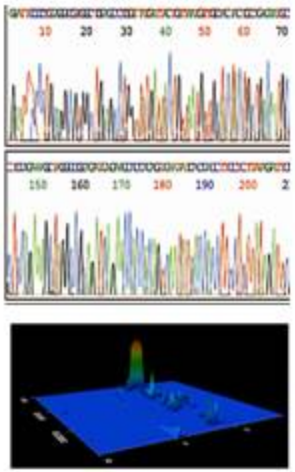
Inform/define data stream collection

Data Streams

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

Data stream

Information Management



Knowledge Management

Tailored results

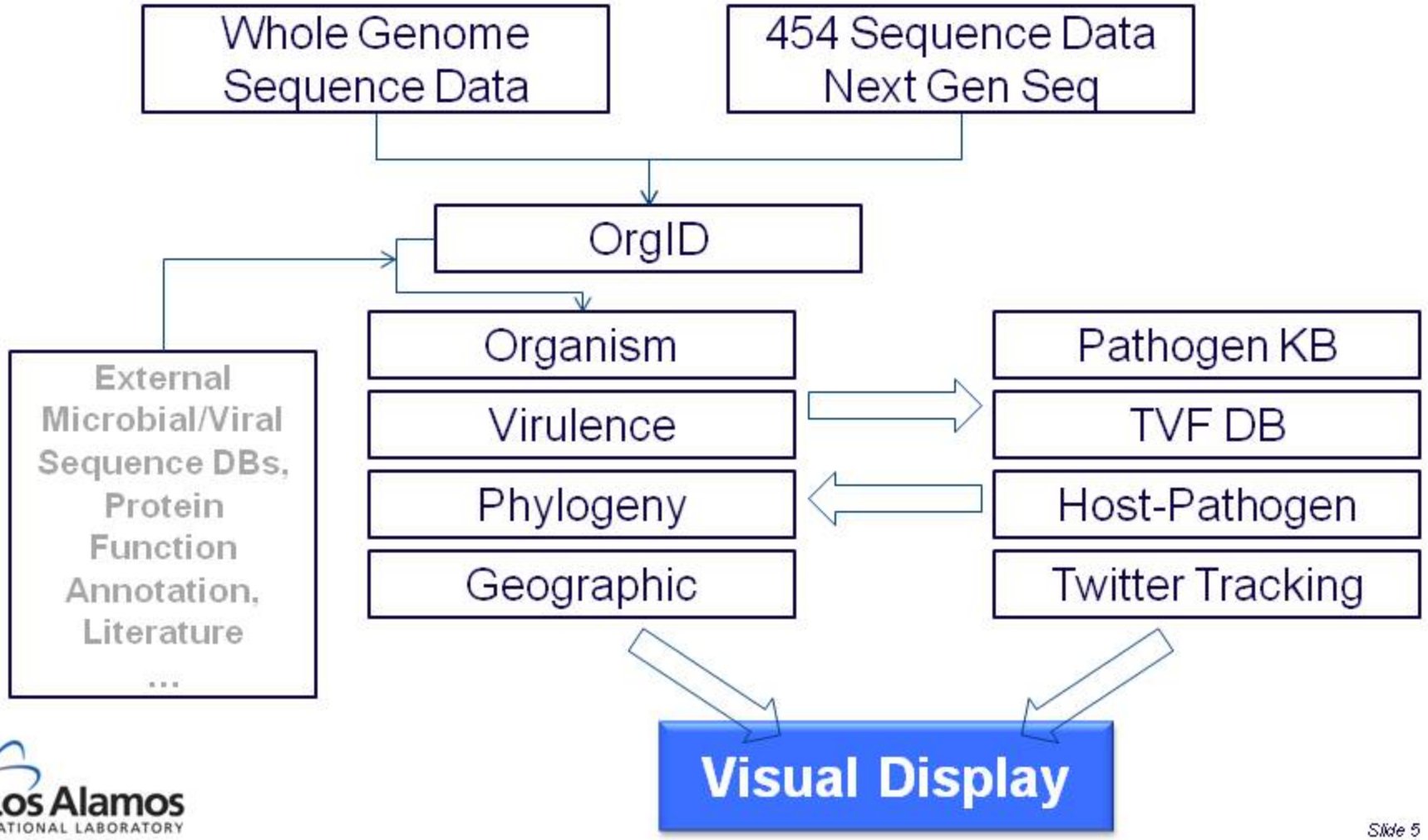
Applications

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

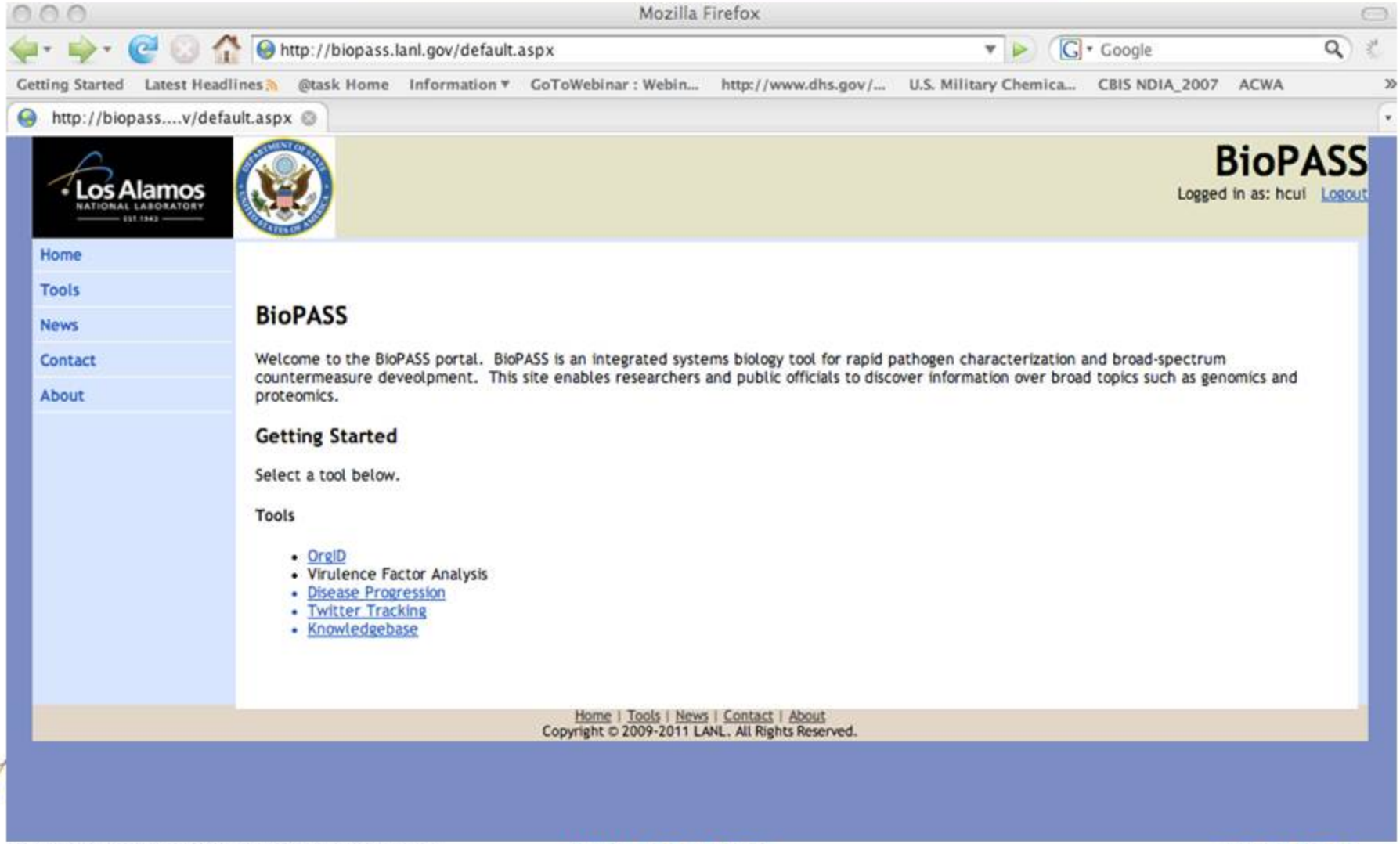
Toward Sustained GBSV:

- Integration of components & systems
- Compression of time from innovation/discovery to application
- Targeted R&D innovation to overcome barriers of cost & effectiveness

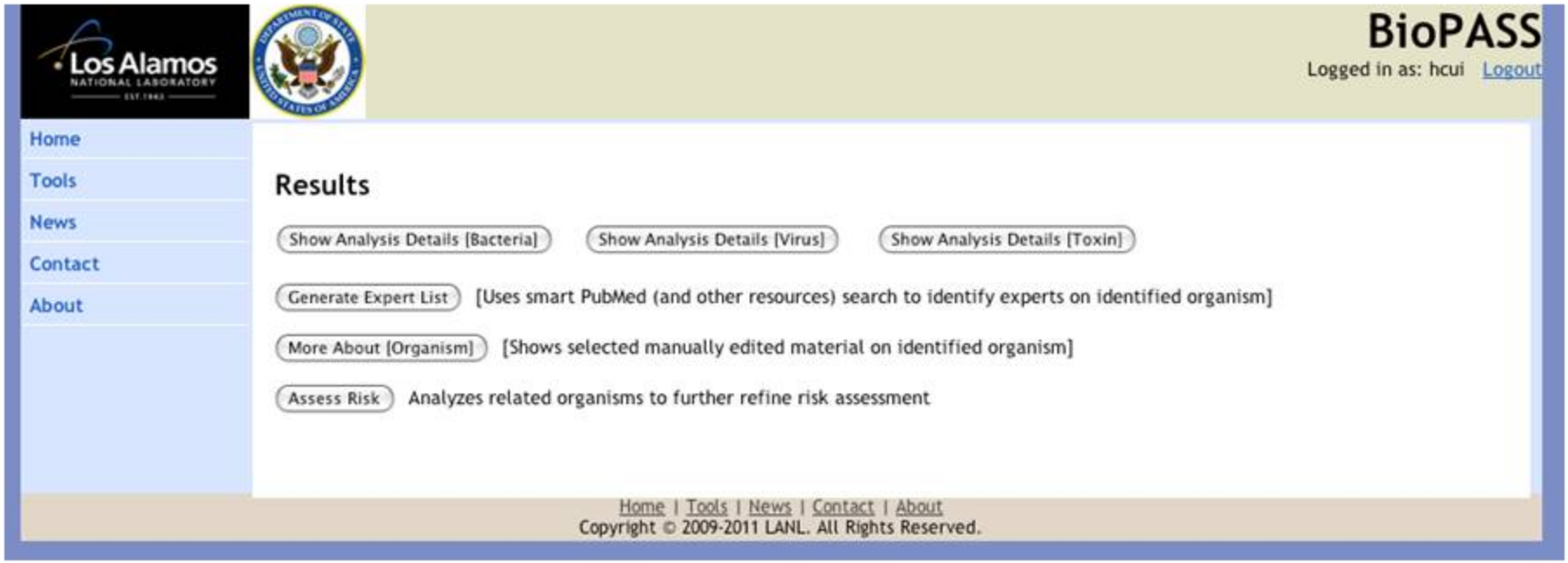
System Concept:



BioPASS Homepage:



Initial Result Display:



Phylogeny Analysis of the New Org:

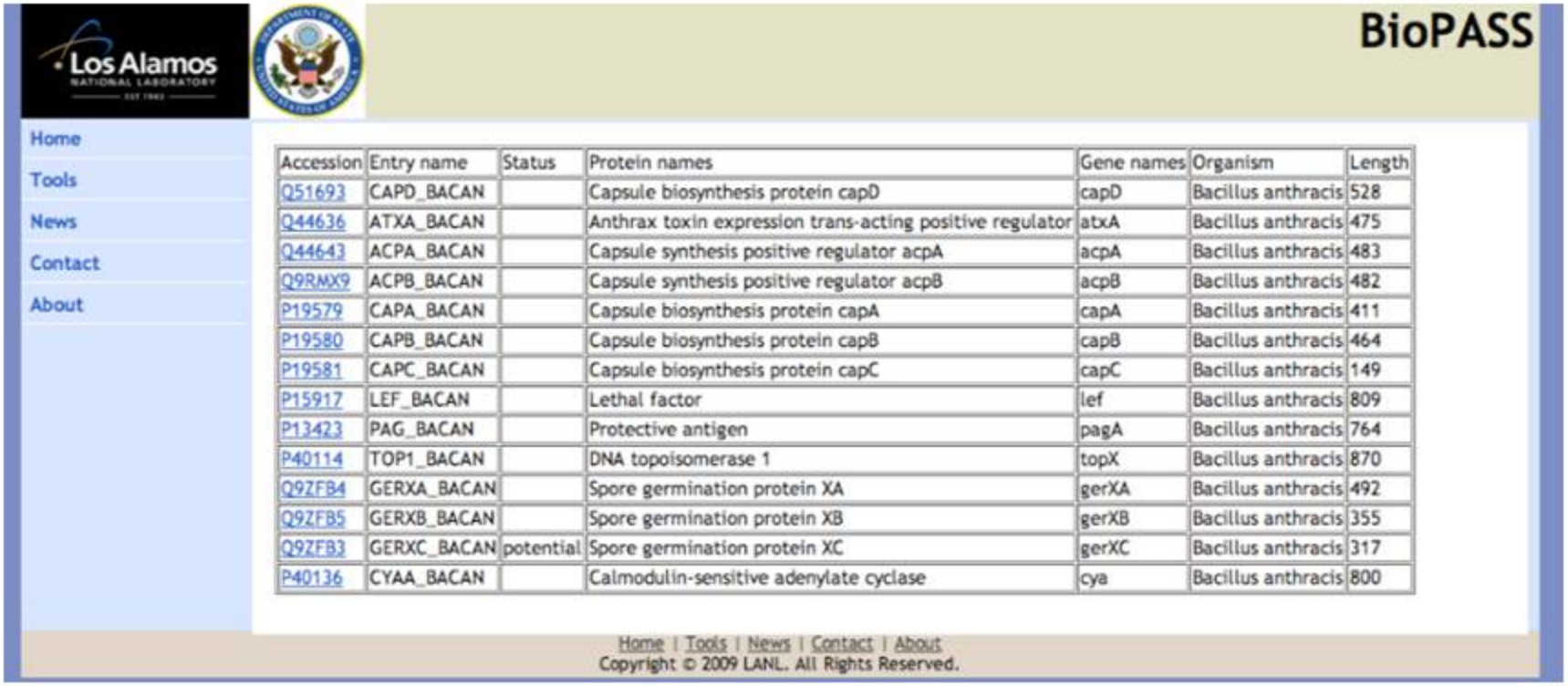
Similarity Returns, Virulence Factor Hits:

Contact

About

Category	*Lysinibacillus sphaericus*	*Bacillus cereus* ATCC 10987	*Bacillus anth* Sterne
% Bacterial hits	84	95	97
% Firmicutes	66	90	94
% Bacilli (class)	54	86	92
% Bacillales (order)	50	85	92
% Bacillus (genus)	26	82	91
% *B. cereus* (~5 species)	6	76	83
% *Bacillus anthracis*	2	36	61
# hits Lethal factor	20	25	0
# hits Protective antigen	13	24	0
# hits Edema factor	11	22	0
# hits Cap A, B, C	28	28	0
# hits Drug resistance transporters	36	142	139
# hits Penicillin-binding protein	19	144	136
# Total Toxin, Virulence factor, Ab hits	339	935	965

Potential Virulence Related Factors:



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BioPASS

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Accession	Entry name	Status	Protein names	Gene names	Organism	Length
Q51693	CAPD_BACAN		Capsule biosynthesis protein capD	capD	Bacillus anthracis	528
Q44636	ATXA_BACAN		Anthrax toxin expression trans-acting positive regulator	atxA	Bacillus anthracis	475
Q44643	ACPA_BACAN		Capsule synthesis positive regulator acpA	acpA	Bacillus anthracis	483
Q9RMX9	ACPB_BACAN		Capsule synthesis positive regulator acpB	acpB	Bacillus anthracis	482
P19579	CAPA_BACAN		Capsule biosynthesis protein capA	capA	Bacillus anthracis	411
P19580	CAPB_BACAN		Capsule biosynthesis protein capB	capB	Bacillus anthracis	464
P19581	CAPC_BACAN		Capsule biosynthesis protein capC	capC	Bacillus anthracis	149
P15917	LEF_BACAN		Lethal factor	lef	Bacillus anthracis	809
P13423	PAG_BACAN		Protective antigen	pagA	Bacillus anthracis	764
P40114	TOP1_BACAN		DNA topoisomerase 1	topX	Bacillus anthracis	870
Q9ZFB4	GERXA_BACAN		Spore germination protein XA	gerXA	Bacillus anthracis	492
Q9ZFB5	GERXB_BACAN		Spore germination protein XB	gerXB	Bacillus anthracis	355
Q9ZFB3	GERXC_BACAN	potential	Spore germination protein XC	gerXC	Bacillus anthracis	317
P40136	CYAA_BACAN		Calmodulin-sensitive adenylate cyclase	cya	Bacillus anthracis	800

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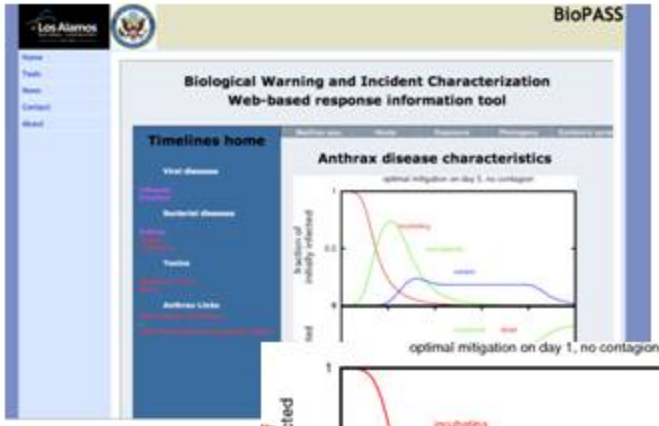
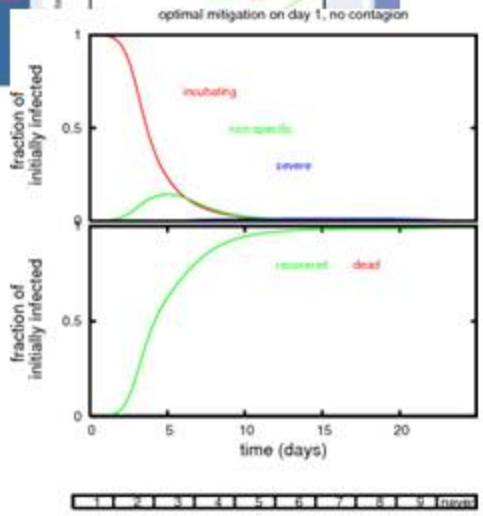
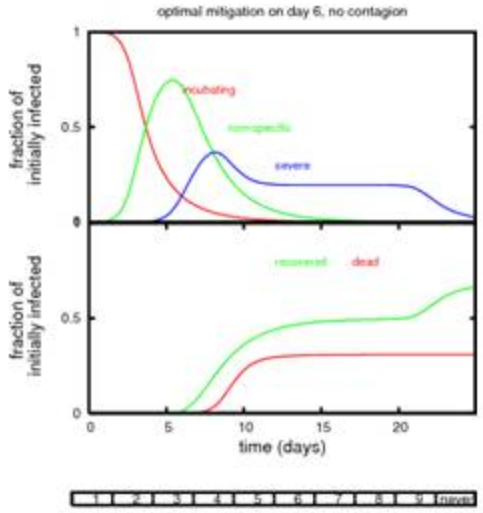
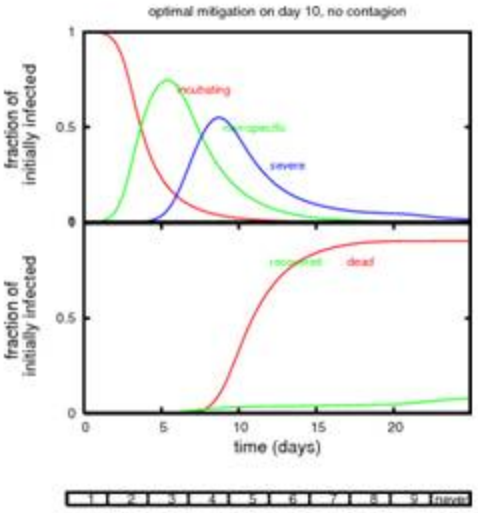
Infectious Disease Progression:



-- 7 disease model available







Twitter Disease Tracking:

Infectious Disease Knowledgebase:

-- 28 agents/disease available

Next Gen Knowledge Representation:

Transmission

Transmission Information

Environment-to-Human	B. anthracis spores can live in the soil for many years (668)
Animal-to-Human	virtually all warm-blooded species susceptible, although herbivores a buffalo, cattle, sheep, goats, horses and swine, wildlife, occasionally
	even if not many people are infected following a deliberate release, t new human infection (661)
	carcasses of infected animals pose a hazard to humans and other a distance through their meat, hides, hair, wool or bones; hides, hair, s distances for use in industries, foodstuffs or handicrafts (666)
	following naturally occurring anthrax among livestock, cutaneous an exposures among humans are possible, but inhalation anthrax has n
	humans can be infected upon: contact with infected animals or anima contact with soil; ingestion (under-cooked meat); skin abrasion; inha
Human-to-Human	rarely person-to-person cutaneous transmission (672)
	person-to-person transmission is extremely unlikely and only reporte discharges from cutaneous lesions are potentially infectious (669)
	anthrax does not spread from person to person (691)
Vectors	
animals	all mammals are susceptible, although herbivores are most common goats, horses and swine, wildlife, occasionally dogs and other carniv anthrax-infected carcasses. (666)
insects	biting fly can transmit B. anthracis after biting a terminally infected animal (666)
environment	B. anthracis spores can survive for 2 years in pond water (662)
	spores survive for >40 years in soil (294)
	animal products including carcasses, hides, hair, wool, meat, and bone meal (666)
fomites	dogs and other carnivores from scavenging on anthrax infected carcasses; workers infected from hides, wool hair etc from infected animals imported to tanneries and mills (666)
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)
Routes of Infection	rarely person-to-person cutaneous transmission (672)

- Risk assessment
  - Cases
    - Agent Character Related Estimate
    - Definition for Susceptible Population
    - Scenario Related Estimate
  - Decontamination
    - Ease of Decontamination
      - sensitivity to chemical inactivation
      - sensitivity to heat inactivation
    - Persistence in Vectors/Reservoirs
    - Survival Following Aerosol Dispersion
      - length of time
      - percent detectable at specific temperature
      - percent detectable of viable particles
      - sensitivity to light
  - Diagnostics
    - Characteristics of Infections
      - incubation period
      - infectious dose
      - infectivity after incubation period
      - infectivity during incubation period
      - initial symptoms
      - severity of disease
    - Clinical Signs and Symptoms
      - diagnostic value
      - differential
      - signs and symptoms
    - Epidemiology
      - ease of tracking contacts
    - Lab detection
      - culture
      - immunoassay
      - microscopy
      - PCR
    - Surveillance
      - deliberate vs. accident
      - effectiveness of environmental surveillance
      - historical evidence of effectiveness
      - recent advancement in integrated system
  - Interdiction
    - Food Handling laws
    - Import/Export
      - bans
      - laws
    - Laboratory Handling laws
    - Production laws
    - Transfer laws
- Mitigation
  - Drug considerations
    - age difference
    - allergy/adverse effect
    - naturally acquired resistance of agent
  - Economic impacts
    - agricultural losses
    - cost of therapy
    - loss of lives
  - Physical Protection
    - effectiveness of personal protective equipme
    - suggested personal protective equipment
  - Post-Exposure Prophylaxis
    - availability of prophylaxis
    - effectiveness of prophylaxis
  - Post-Exposure Therapy
    - agent susceptibility
    - availability of second line of defense
    - availability of therapy
    - dose/route of administration
    - effectiveness of single therapeutic agent
    - empiric therapeutic first choice
    - value of synergistic combination
  - Public Health Response System
    - emergency response protocols
    - global plans
    - local plans
    - national pharmaceutical stockpile
    - national plans
    - state plans
  - Social Isolation
    - effectiveness of quarantine
    - effectiveness of voluntary isolation
  - Supportive Care
    - effectiveness of care
    - suggested therapies
  - Vaccination
    - effectiveness of vaccination
    - existence of vaccinated population
    - immune status of previously vaccinated popu
    - immunity from previous infection
    - passive immunization availability
    - usefulness post-exposure
- Prevention
  - Medical countermeasures
  - Pre-exposure Prohyloaxis
    - availability of prophylaxis
    - effectiveness of prophylaxis
  - Preventative measures
- Prognosis
  - Long-Term Sequelae
    - Economic sequelae
    - Medical sequelae
  - Medical outcomes
    - immunocompromised hosts
    - morbidity
    - mortality
    - time to resolution of disease
  - Potential of becoming endemic
  - Potential of becoming pandemic
- Transmission
  - Animal-to-Animal
  - Animal-to-Human
  - Environment-to-Human
  - Human-to-Human
  - Routes of Exposure
  - Routes of Infection
  - Vectors
    - animals
    - environment
    - fomites
    - insects
- Weaponization
  - Availability of strain
    - collections/repositories
    - natural sources
  - Forms of Delivery
  - Genetic Engineering
    - resistance to antibiotic/antiviral
    - resistance to vaccine
  - Handling
    - laboratory facilities
    - personal protection equipment
  - Large-scale Production
    - growth limitations
    - growth requirements
  - Stability and Storage
    - air
    - humidity
    - light
    - pH
    - pressure
    - radiation
    - salt
    - soil
    - temperature
    - water

TVFac (ToxinVirulence Factor DB)

Toxin & Virulence Factor Database

- Annotation
  - Insert Record
  - Delete Record
  - Edit Record
- Browse
  - By Organisms
  - By Functional Classes
- Search Tools
  - Predefined Search
  - Basic Search
  - Advanced Search
- Pathogenicity Islands
- Analysis Tools
- Documentation

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Comments

MySQL

TVFac Hierarchies:

Adhesins
Type IV Fili
Phage-related
Transport and secretion systems
Type II secretion system

Name:
Type IV pili (N-methyl-phenylalanine pili) (fibriae)

Description:
Type IV pili (fimbriae) are filamentous polar organelle found in Pseudomonas aeruginosa and in a wide variety of other pathogenic bacrteria including Neisseria gonohoeae, Neisseria meningitidis, Dichelobacter nodosus, Moraxella bovis, Eikenella corrodas, Aeromonas hydrophila and Myxococcus xanthus. 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 mutation analysis in Pseudomonas aeruginosa. These genes fall into two broad categories: (1) those encoding regulatory networks that control the production and function of these fimbriae (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 fimbriae have also been identified in E. coli (bundle-forming pili; Bfp) and Vibrio cholerae (toxin-coreguated 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 fimbrial adherence and aided by production of a protease enzyme tha degrades fibronectin in order to expose the underlying fimbrial receptors on epethelial cell surface.

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

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

Counter Measure:
Pseudomonas aeruginosa is the major infectious agent of concern for cystic fibrosis patients. Production of exopolylysaccharide alginate and intrinsic resistance to most of the known antibiotics make it very difficult to control. So stragies to prevent colonization of P. aeruginosa and/or neutralize its toxins are needed. Hertle, et al. (2001) reported the development a dual-functional protein vaccine for P. aeruginosa. The vaccine is a chimeric protein containing the key sequence of type IV pilin and nontoxic version of exotoxin A. The chimeric protein (PE64Delta553pil), when injected into rabbits, produced antibodies that reduced bacterial adherence and neutralized the cell-killing activitiy of exotoxin A.

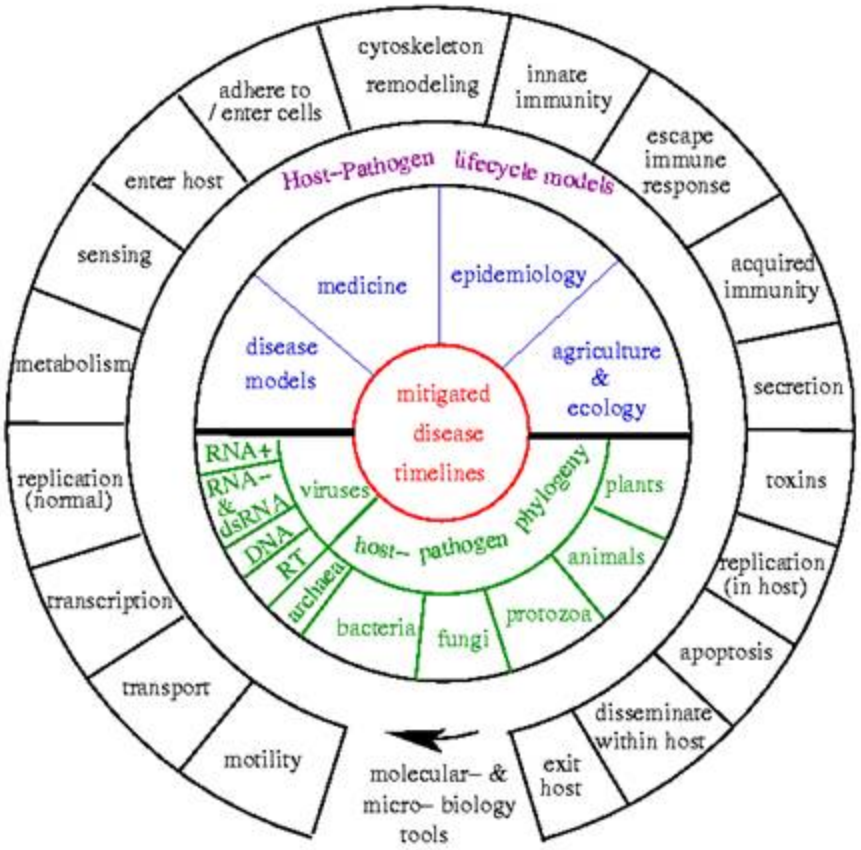
References:
Alm RA, Mattick JS.
Genes involved in the biogenesis and function of type-4 fimbriae in Pseudomonas aeruginosa.
Gene. 1997 Jun;192(1):89-98.
PMID: 9224878

Mattick JS.
Type IV pili and twitching motility.
Annu Rev Microbiol. 2002;56:289-314.
PMID: 12142488

Hertle R, Mrsny R, Fitzgerald DJ.
Dual-function vaccine for Pseudomonas aeruginosa: characterization of chimeric exotoxin A-pilin protein.
Infect Immun. 2001 Nov;69(11):6962-9.
PMID: 11598071

Comment:
Regulation of pilA -- The major fimbrial subunit gene pilA is transcriptionally regulated by a two-component sensor-regulator network encoded by pilSR. pilS encodes a sensor kinase, which is predicted to contain six transmembrane domains in its N-terminal region and the conserved kinase domain in its C-terminal region. pilR encodes a response regulator, which contains three domains: (1) a reponse domain, (2) C-terminal DNA-binding domain determining its target specificity, and (3) a central RpoN interaction domain. Experiments have shown that PilR binds to four sequences upstream from the pilA sigma-54 promoter and all of the four sites are absolutely required for PilR-mediated transscriptional activation, suggesting the PilR may bind the promoter regions as a multimers or bind cooperatively by PilR monomers. Sigma-54 (RpoN) is required for type IV pili biogenesis as rpoN mutants are non-fimbriated.

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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