

Biodefense / Human Threats and Mass Spectrometry Applications

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CDC Biological Diseases/Agents List

Category A

Anthrax (*Bacillus anthracis*)
Botulism (*Clostridium botulinum* toxin)
Plague (*Yersinia pestis*)
Smallpox (*Variola major*)
Tularemia (*Francisella tularensis*)
Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])

Category B

Brucellosis (*Brucella* species)
Epsilon toxin (of *Clostridium perfringens*)
Food safety threats (e.g., *Salmonella* species, *Escherichia coli* O157:H7, *Shigella*)
Glanders (*Burkholderia mallei*)
Meliodosis (*Burkholderia pseudomallei*)
Psittacosis (*Chlamydia psittaci*)
Q fever (*Coxiella burnetii*)
Ricin toxin from *Ricinus communis* (castor beans)
Staphylococcal enterotoxin B
Typhus fever (*Rickettsia prowazekii*)
Viral encephalitis (alphaviruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis])
Water safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)

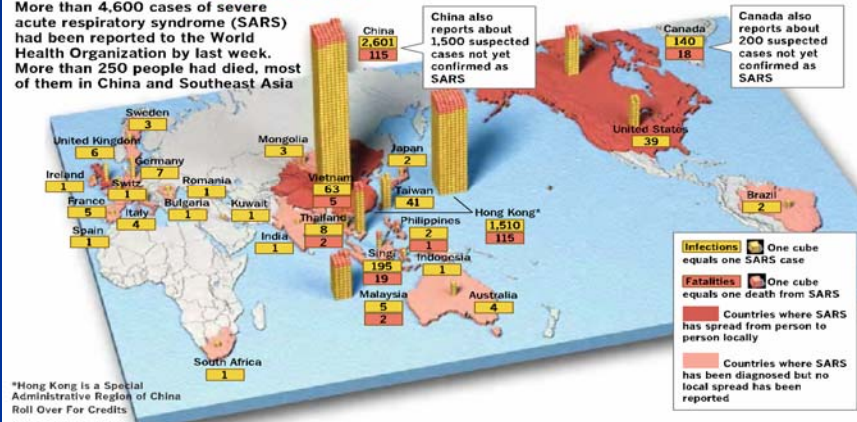
Category C

Emerging infectious disease threats such as Nipah virus and hantavirus.

SARS(Severe Acute Respiratory Syndrome)

GLOBAL REACH

More than 4,600 cases of severe acute respiratory syndrome (SARS) had been reported to the World Health Organization by last week. More than 250 people had died, most of them in China and Southeast Asia



Colera



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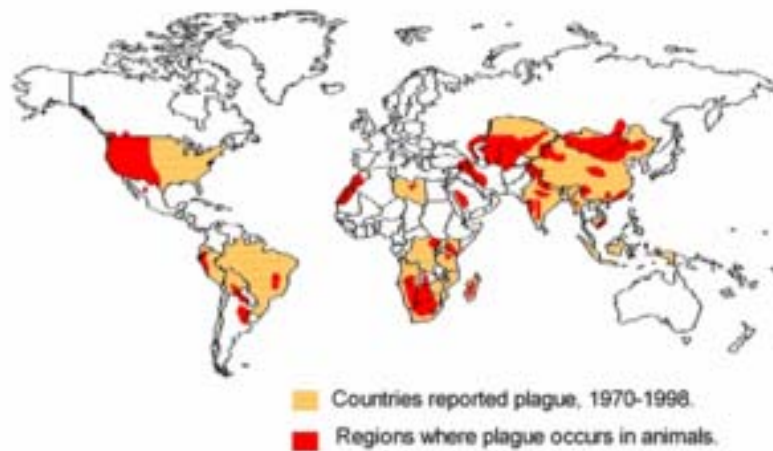
Colera

- Gram negative bacteria causes severe watery diarrhea.
- Severe dehydration.
- Incubation period 24 hours
- January 1991 to September 1994 - Outbreak in [South America](#), apparently initiated when a ship discharged ballast water. Beginning in [Peru](#) there were 1.04 million identified cases and almost 10,000 deaths.



Plague : The Black Death

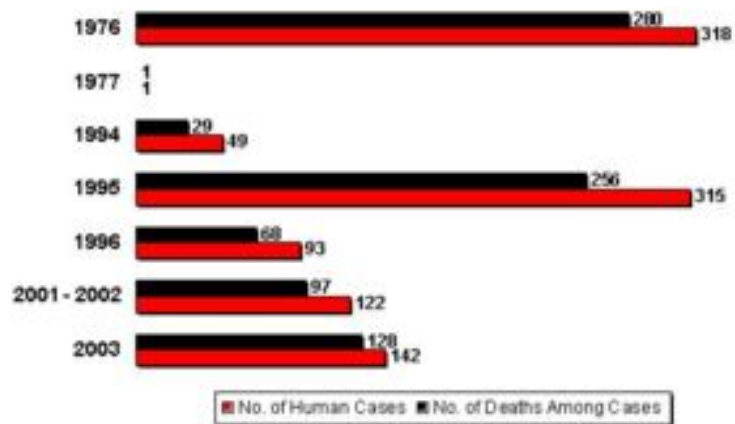
World Distribution of Plague, 1998





Ebola /Marburg

Cases And Deaths From the Ebola-Zaire Virus, 1976-2003

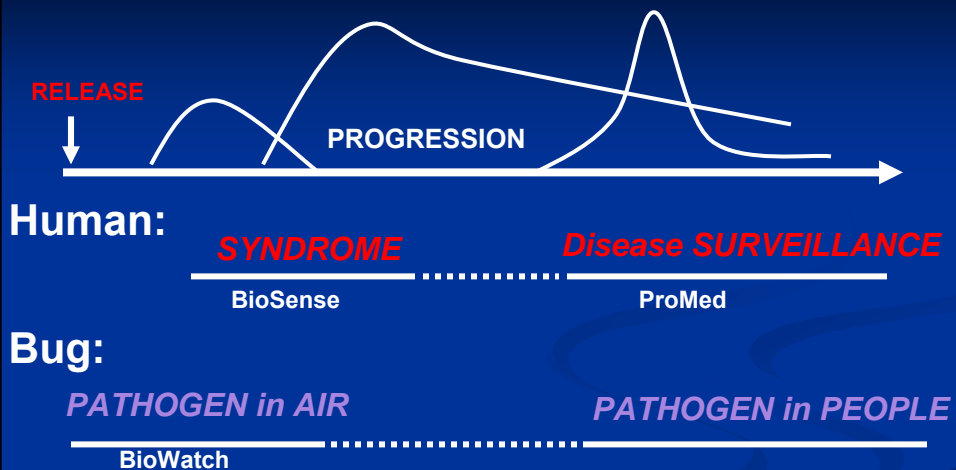


Smallpox

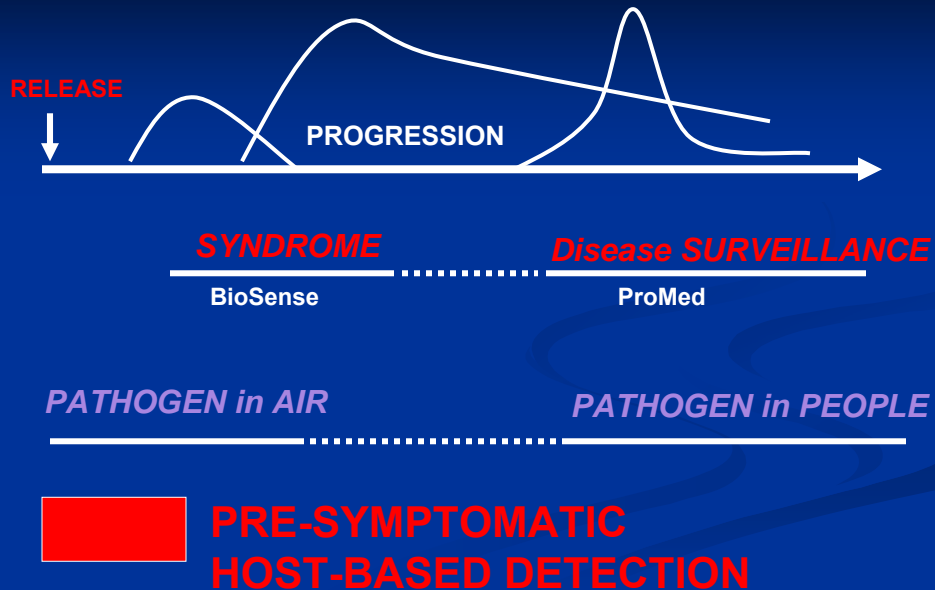
- Eradicated ; 05/1980
- Last case Birmingham , England after which all isolates were sent to reference labs for destruction.
- In 2003 Smallpox scabs found in Civil War Medicine book in Santa Fe, New Mexico, no cases reported.
- ? used as biological weapon in French and Indian wars, American Revolutionary war and perhaps World War II (research).
- Incubation period 10 days , if severe disease death may happen in 3-5 days.
- Vaccine available but hypothesized that virus might be genetically modified for use as bioweapon.



DETECTION OF BIOATTACK OR OUTBREAK



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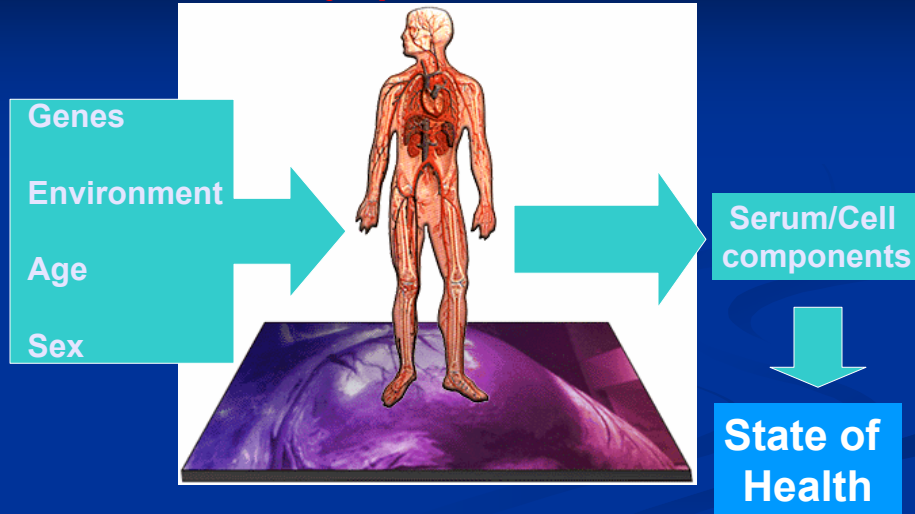


Advantages of Host-Based Pre-Symptomatic Detection

- Treat to Prevent
- Containment of Outbreak
- Triage Based on Diagnosis
- Solution to AGENT X Problem
- **DUAL USE TECHNOLOGY**

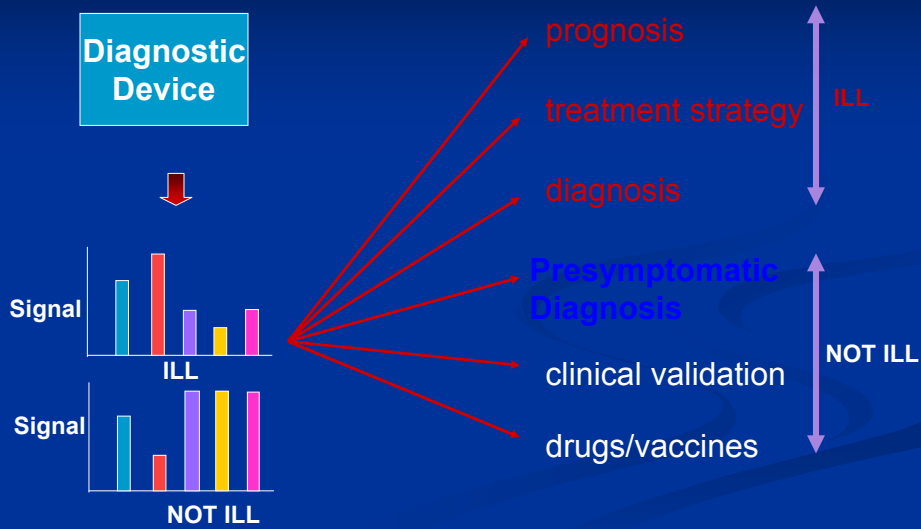
Biosignature Pattern Recognition in Human Diseases

Host-based Presymptomatic Detection of Events



Center for Innovations in Medicine

Doc In Box: BioSignatures



Center for Innovations in Medicine



Medical Countermeasures Against Advanced Bio Threats

Today's Threats

- Anthrax*
- Smallpox*
- Botulinum*
- Plague*
- Tularemia*
- Ebola/Filo*
- Hemorrhagic Fever*
- Encephalitis*
- SARS*
- Influenza*
- Ricin/SEB, others*

Modes of Action

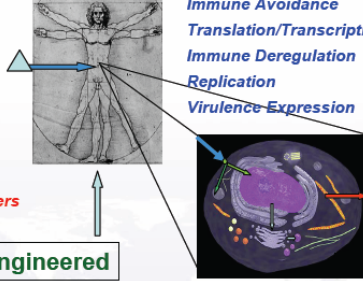
- Receptor Binding*
- Signal Transduction*
- Decoys*
- Immune Avoidance*
- Translation/Transcription*
- Immune Deregulation*
- Replication*
- Virulence Expression*

Parallel Systems Approach

Solutions

Target Agent Commonalities

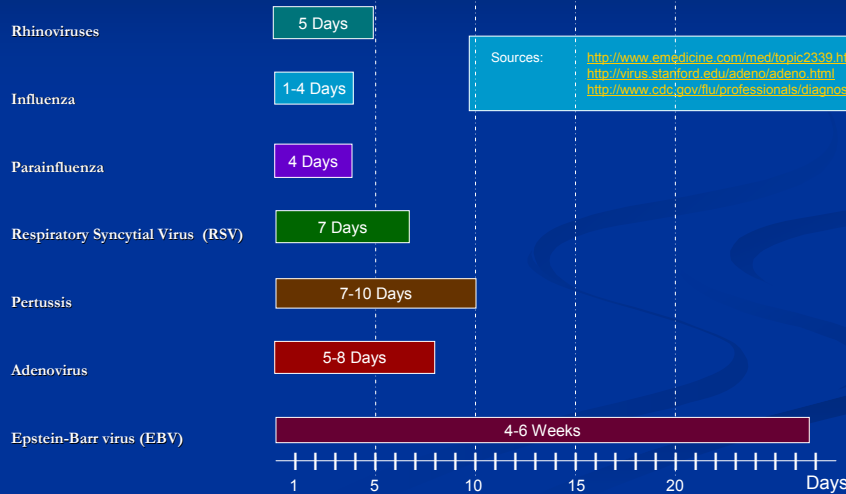
- Block Key Receptors
- Inhibition by Small Molecules
- Modulate Immunity
- Change Gene Expression
- Block Protein Actions
- Modulate Physiologic Impacts



Bioengineered

One **PIECE** at a time → Process Analysis → Broad Spectrum

Upper Respiratory Disease Incubation Periods



Proteomics Research Centers

Goal:

Characterize the pathogen and/or host cell proteome, identifying proteins associated with biology of microbes, mechanisms of microbial pathogenesis, and host response to infection.

Discover targets for potential candidates for the next generation of vaccines, therapeutics, and diagnostics.

Proteomic Technology Development

Proteomics Research Centers

- **Albert Einstein College of Medicine**
 PI: Ruth Angeletti
 Pathogens: *Toxoplasma gondii*, *Cryptosporidium parvum*
- **Harvard Medical School**
 PI: Joshua LaBaer
 Pathogens: *Bacillus anthracis*, *Vibrio cholerae*
- **Myriad Genetics, Inc**
 PI: Jerry Lanchbury
 Pathogens: *Bacillus anthracis*, *Yersinia pestis*, *Francisella tularensis*, *vaccinia*, *variola*
- **Caprion Pharmaceuticals, Inc**
 PI: Eustache Paramithiotis
 Pathogen: *Brucella abortus*
- **The Scripps Research Institute**
 PI: Peter Kuhn
 Pathogens: SARS-CoV
- **Pacific Northwest National Laboratory**
 PI: Richard Smith
 Pathogens: Orthopox (vaccinia and monkeypox), *Salmonella typhimurium* and *Salmonella typhi*
- **University of Michigan**
 PI: Phillip Hanna
 Pathogen: *Bacillus anthracis*
- **Administrative Resource Center**
 PI: Margaret Moore



Proteomics Research Centers

Overall Summary-May 2006

Proteins Identified:

- ✓ 6 structures solved for SARS-CoV; 282 human proteins that interact with *Y. pestis*(60), *B. anthracis*(50), and vaccinia(172) proteins; 176 novel proteins identified from *B. abortus*, and 360 from *T. gondii*.

Genes Identified:

- ✓ 493 differentially expressed murine macrophage genes found upon infection with anthrax

Reagents Generated

- ✓ 2983 *V. cholerae* Gateway entry clones made and deposited in an NIAID repository for use by the community



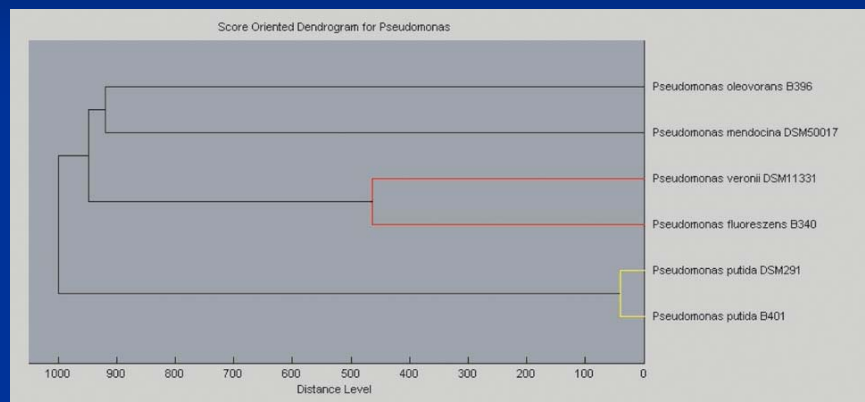
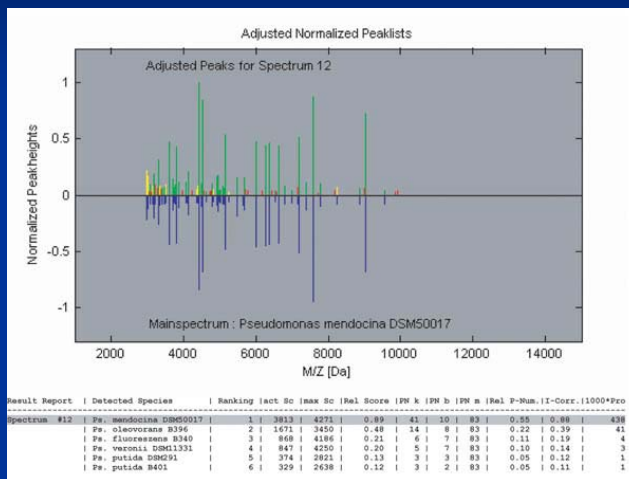
Proteomics Research Centers

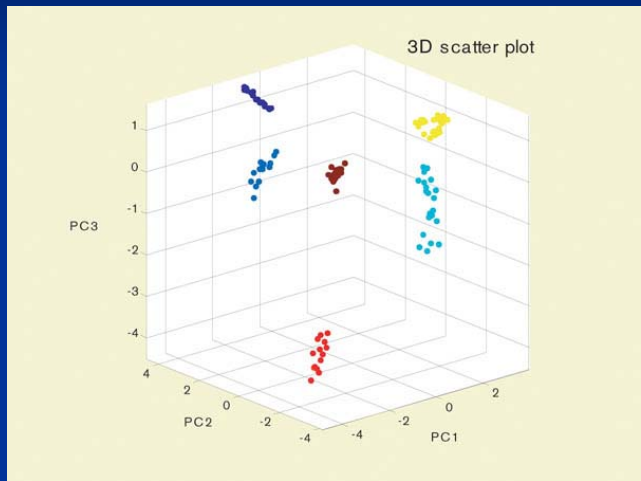
Progress Achieved –May 2006

Proteins Identified

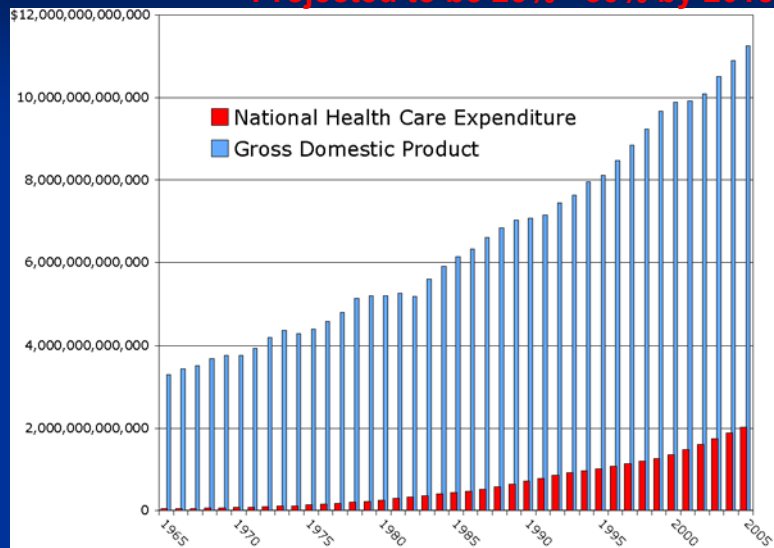
- > 360 membrane and cytoskeletal proteins identified in *T. gondii*
- > 176 outer membrane proteins associated with virulence identified in *B. abortus*
- > 282 human proteins found to interact with vaccinia (172), *B. anthracis* (50), and *Y. pestis*(60) proteins
- > 6 SARS-CoV structures solved
- > 2121/2343 proteins identified in virulent/avirulent *S. typhimurium*
- > 263 early response and 329 late response proteins identified in murine macrophages infected with anthrax

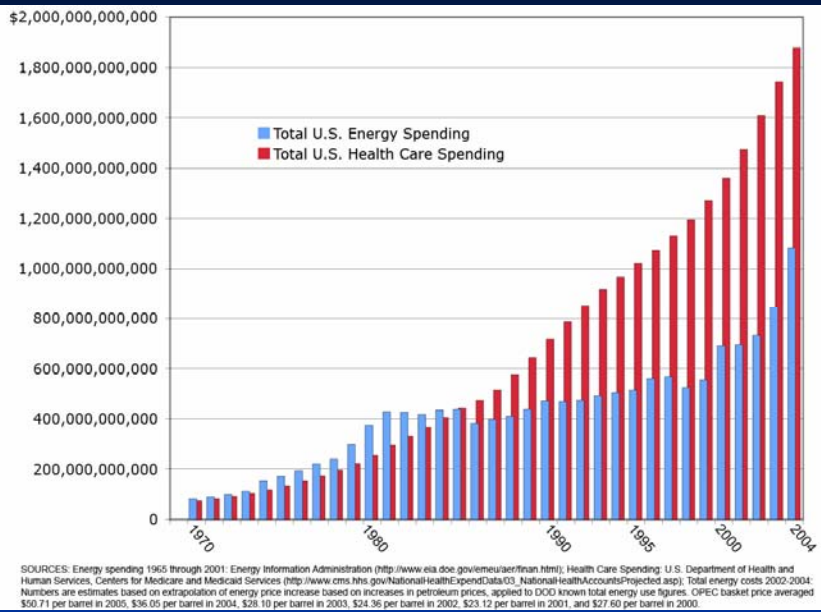
Speciation/Identification



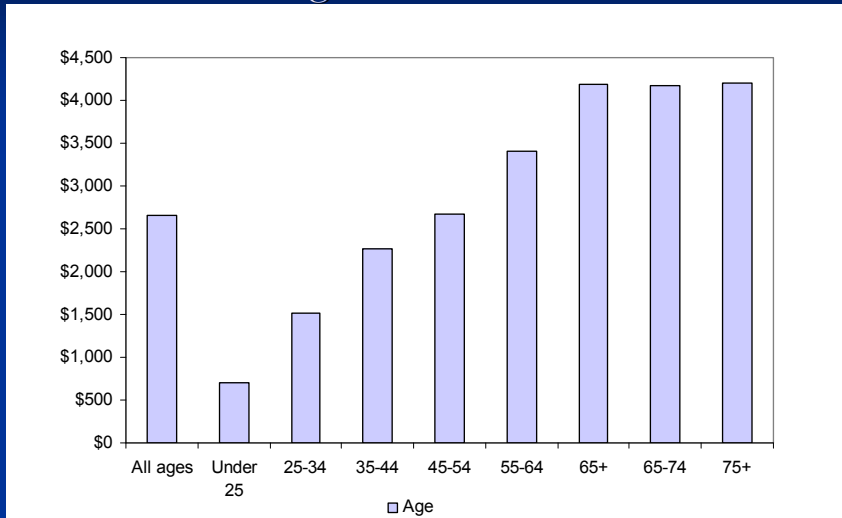


**18% of GNP on Health Care in 2006
Projected to be 25% - 30% by 2015**



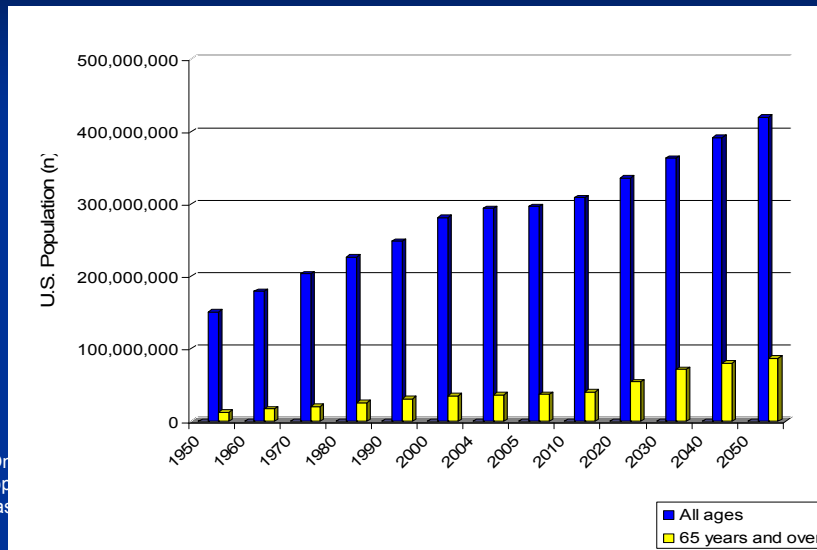


Average annual healthcare



Source: U.S. Bureau of Labor Statistics, U.S. Department of Labor. *Consumer Expenditures in 2005*. Report 998, Feb 2007.

Total Population vs. 65+ Population, 1950-2050



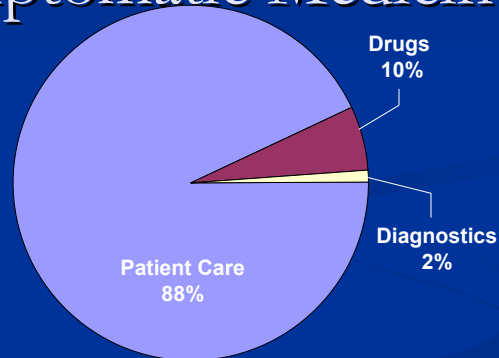
What are the Costs of Medicine?

\$2.26T/Year*
Drugs
Diagnostics
Care

**Estimated health expenditures for 2007*

Source: Centers for Medicare & Medicaid Services, Office of the Actuary, 2007. Healthcare spending projections are based on the 2005 version of the National Healthcare Expenditure data released by the CMS in January 2007.
 Borger C, et al. "Health spending projections through 2015: changes on the horizon." *Health Affairs*. March/April 2006; 25(2): 61-73.

The Cost of Post-symptomatic Medicine



~\$2 Trillion in Direct Medical Costs per Year

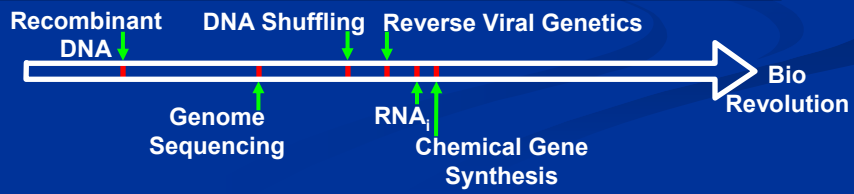
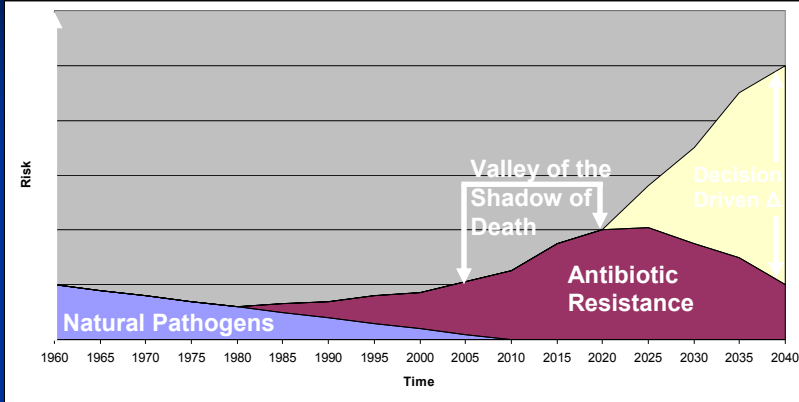
Two Options to Solve HC Crisis

- **REDUCE CARE PROVIDED**

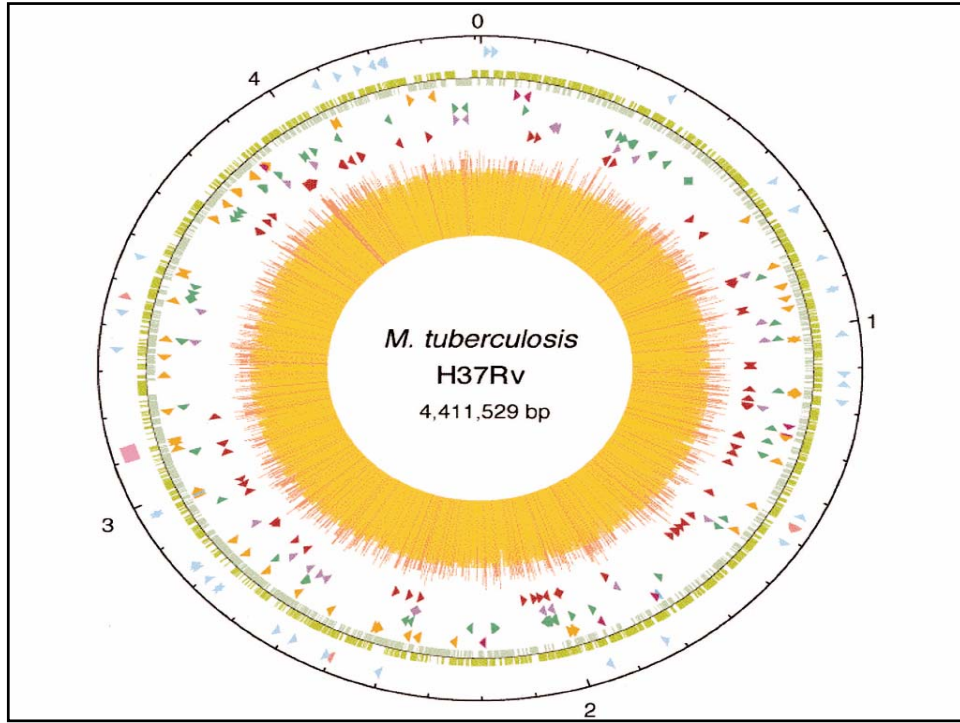
or

- **TRANSITION TO PRE-SYMPTOMATIC DIAGNOSIS AND PREVENTATIVE MEDICINE**

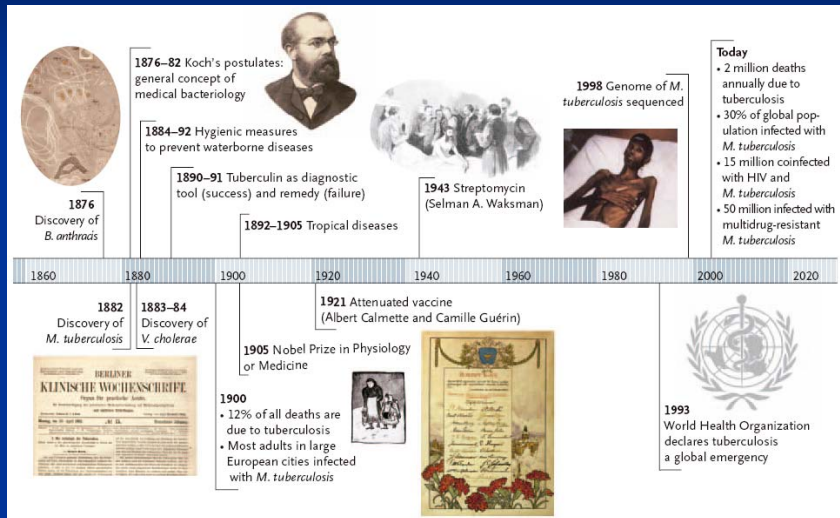
Changing Spectrum of BioThreat Risk



Tuberculosis



TB Timeline

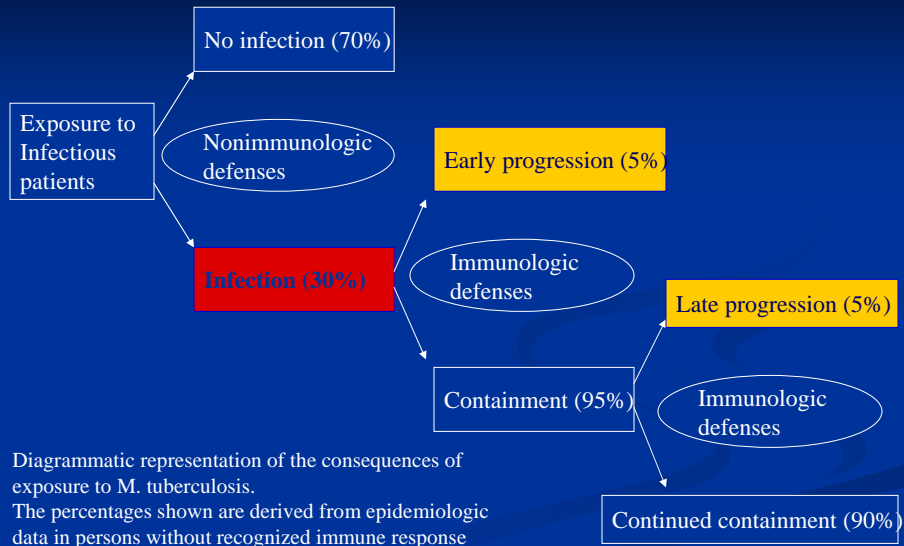


TB kills

1.6 million people
every year

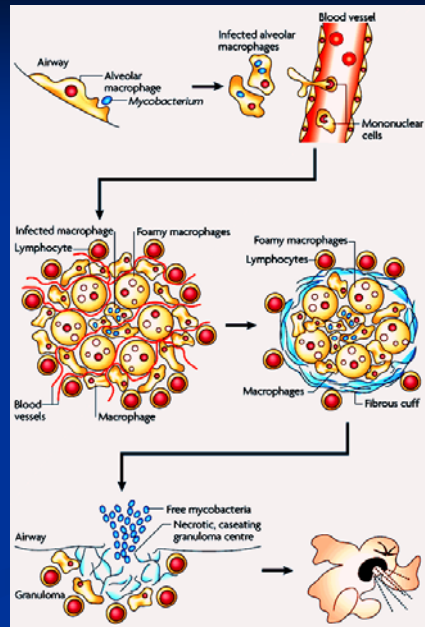
4,400 people
every day

one person
every 20 seconds

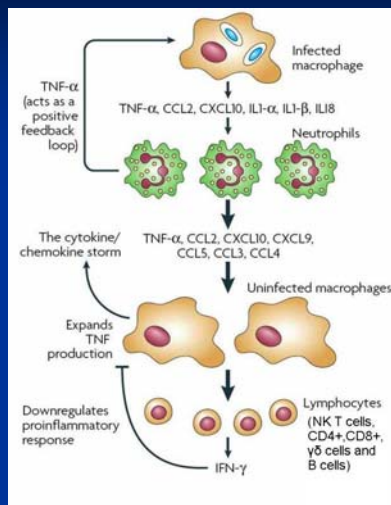


TB Pathogenesis in a "Nutshell"

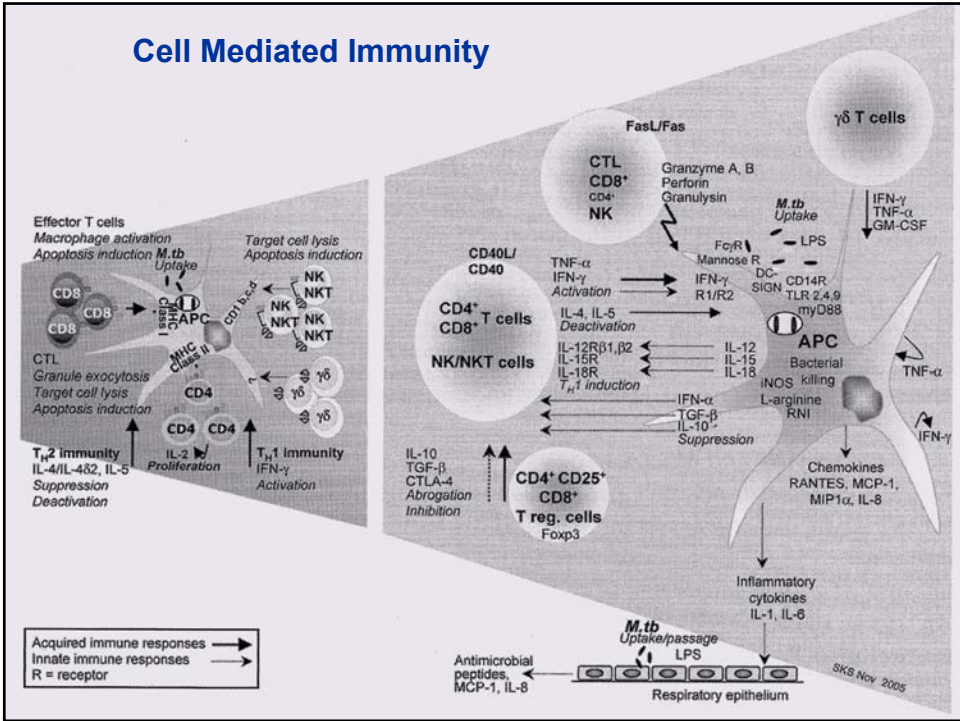
- Three important steps:
 - Phagosome formation
 - Granuloma formation
 - Failure of containment



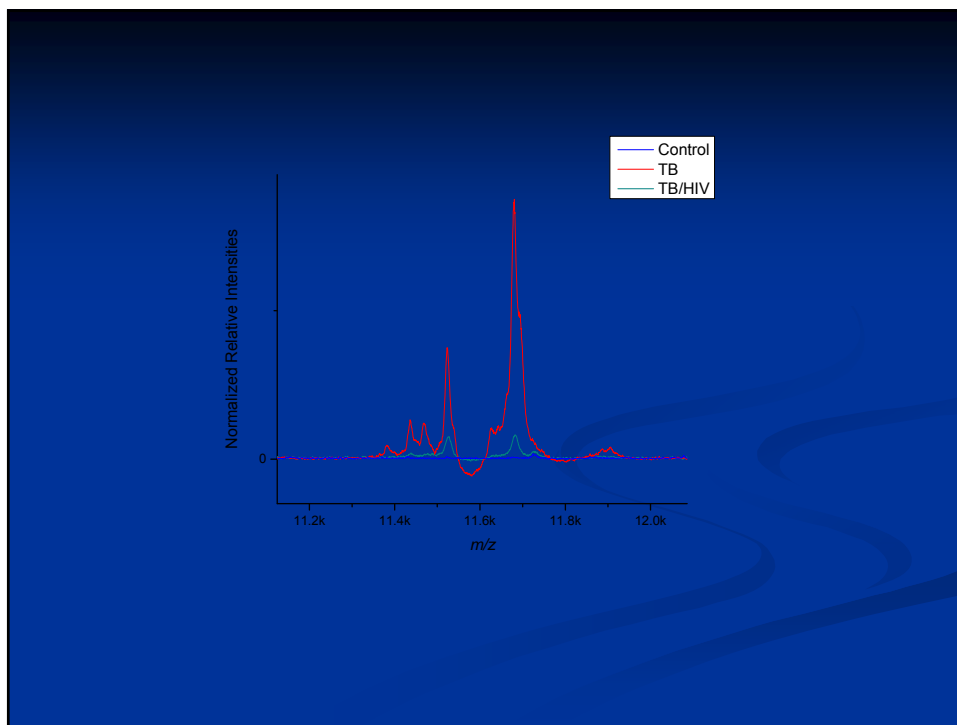
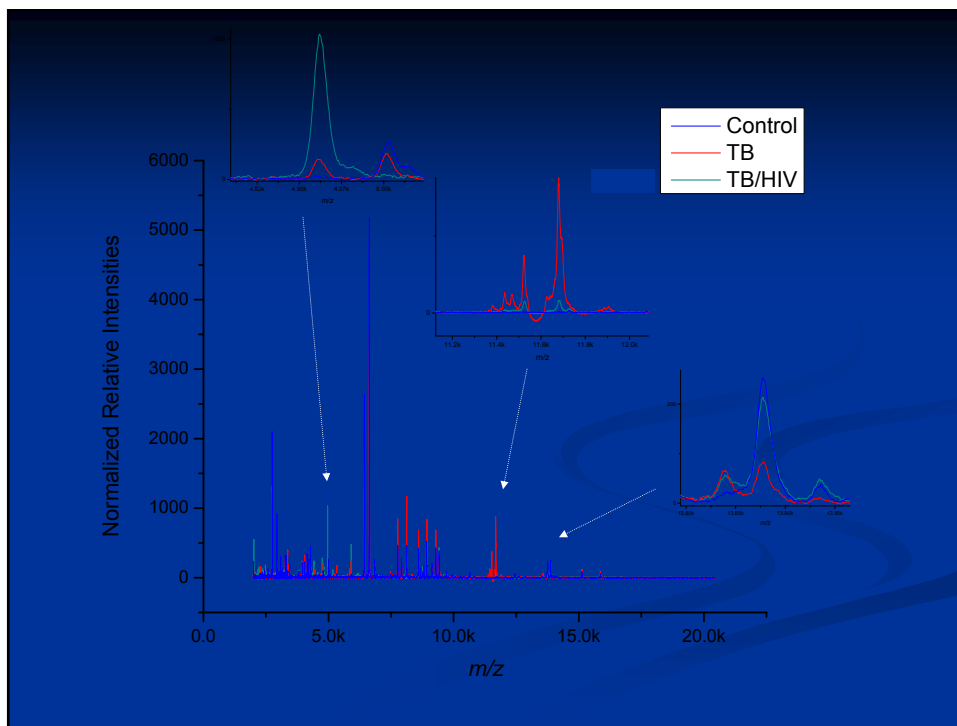
Cytokine / Chemokine Storm

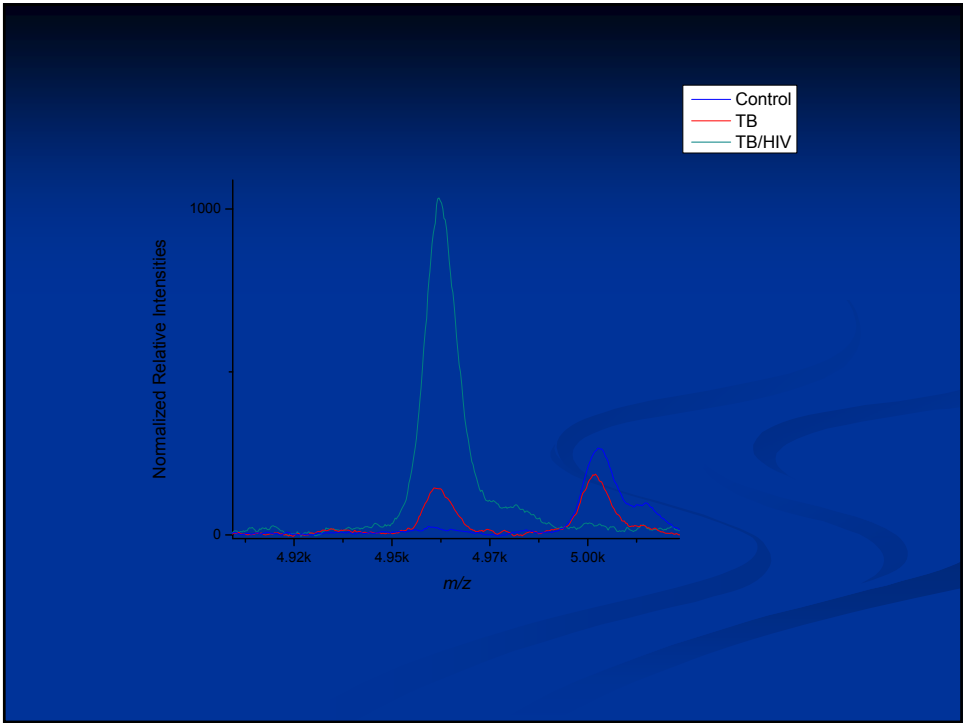
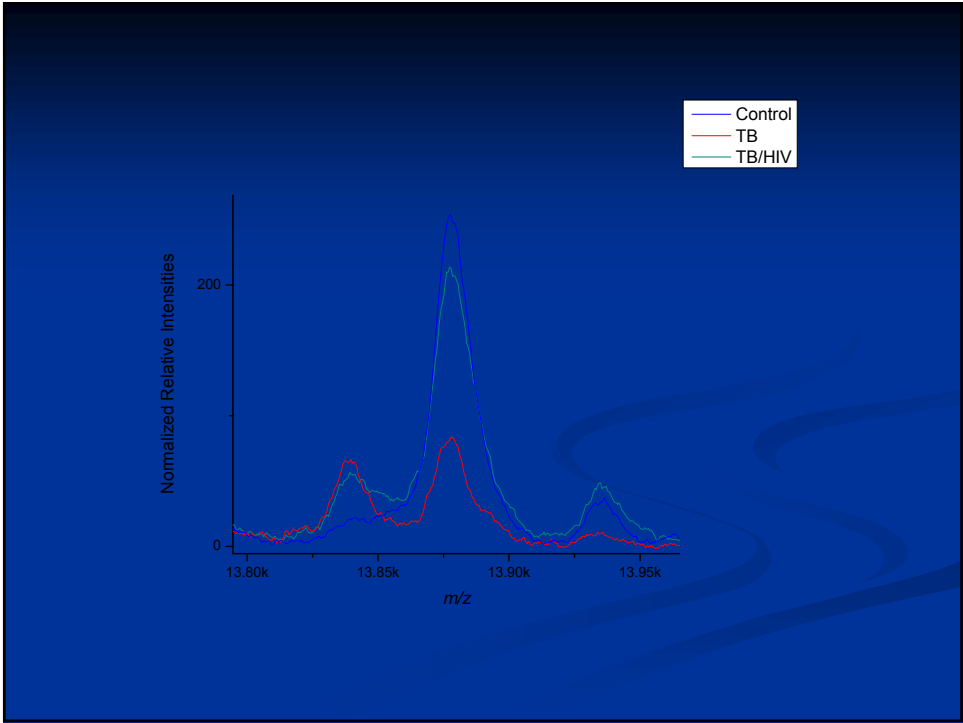


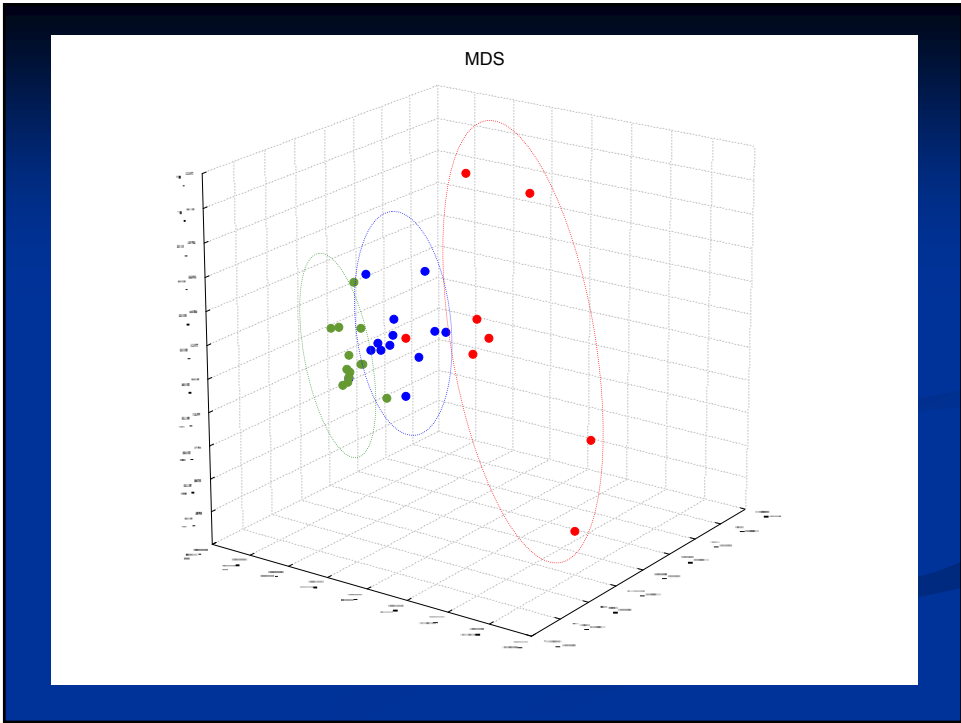
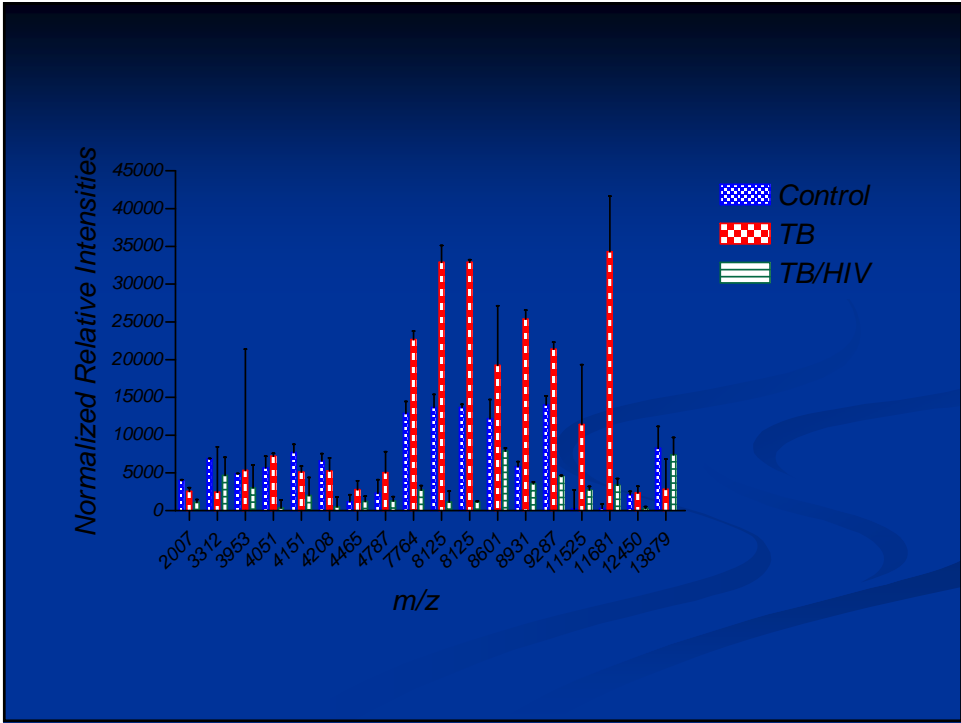
- Recruitment of cells induced by CC and CXC production.
- TNF-α dominant CC. Produced by infected macrophages and induced production of other CC and CXC.
- Subsequent recruitment of cells and production of IFN-γ

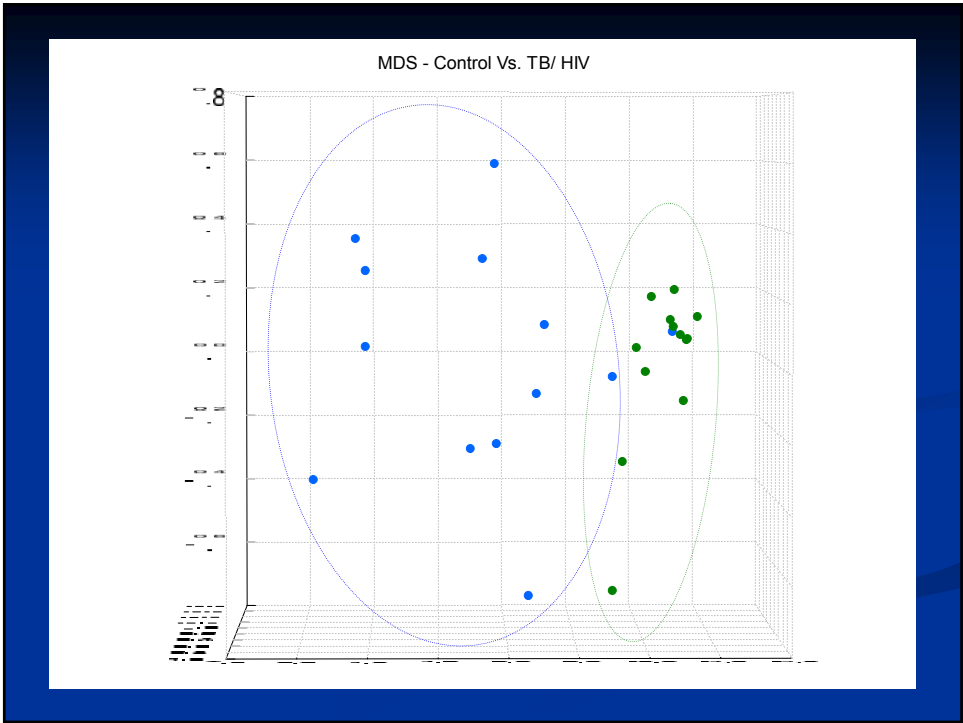
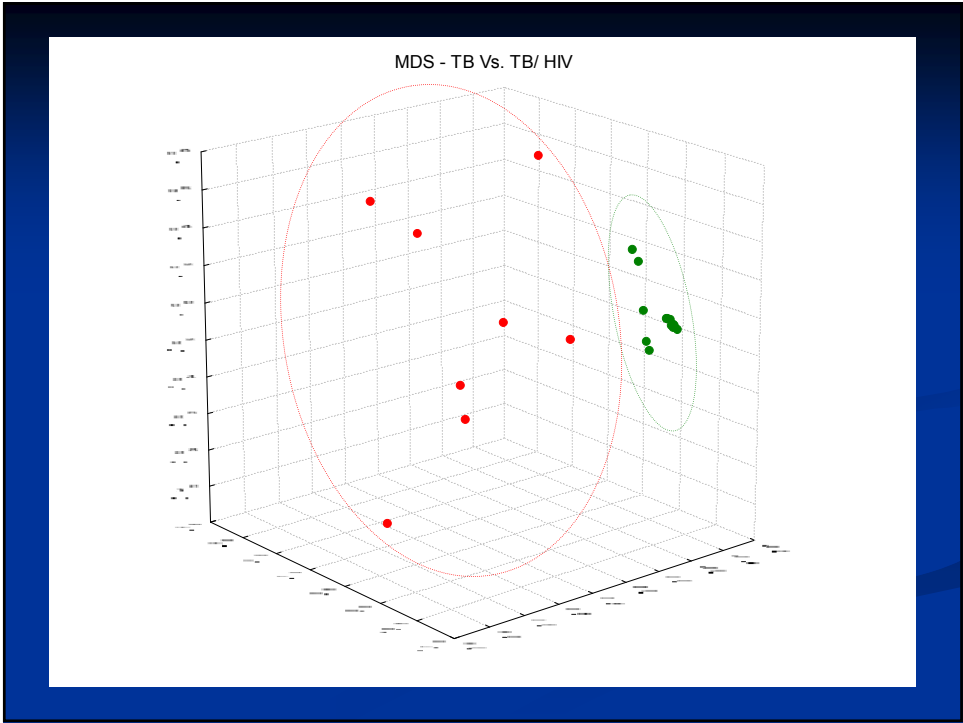


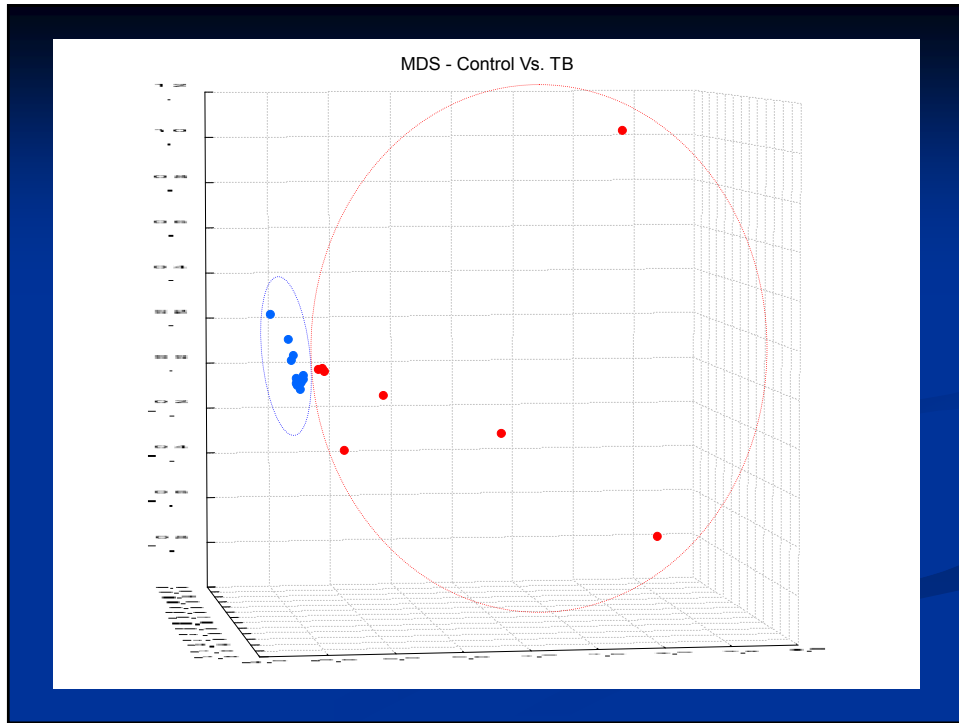
TUBERCULOSIS AND PROTEOMICS











Medicine: Art to Science

Sir William Osler 1892

“If it were not for the great variability among individuals, medicine might be a science, not an art”



Because of our new ability to measure variability among individuals, medicine now can become a science rather than an art.

Thank you