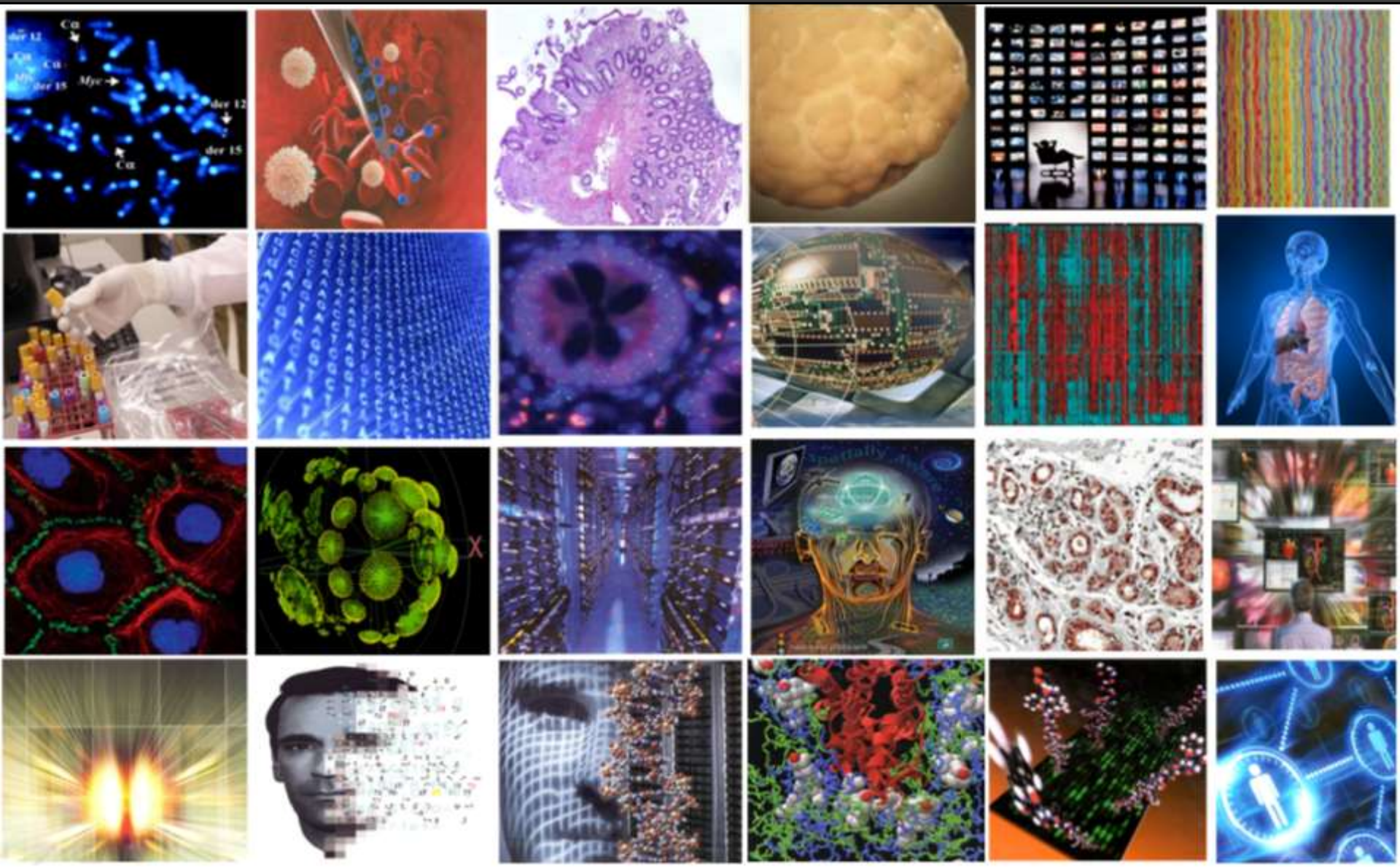
ASU COMPLEX ADAPTIVE SYSTEMS
ARIZONA STATE UNIVERSITY

Outpacing Infectious Diseases: Dynamic Foes and The Need for Innovation in Diagnostics, Drugs and Vaccines

Dr. George Poste
Chief Scientist, Complex Adaptive Systems
and Del E. Webb Chair in Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

Presentation at ASU General Biochemistry BCH462
Tempe, Arizona
10 September 2013

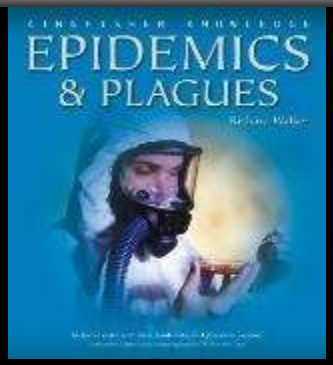
Slides available @ http://casi.asu.edu/

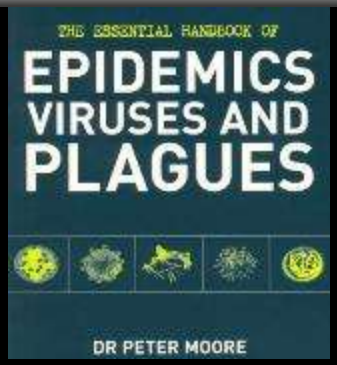


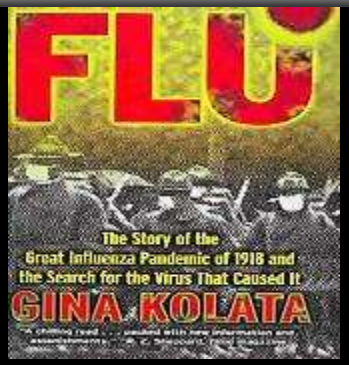
A Shared Global Risk:

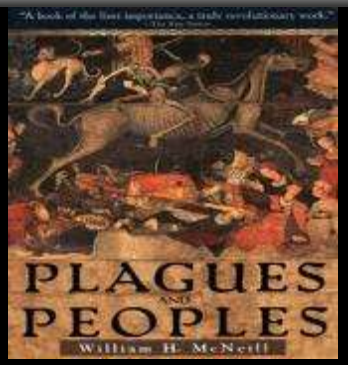
The Omnipresent Threat Posed By Microorganisms and Parasites

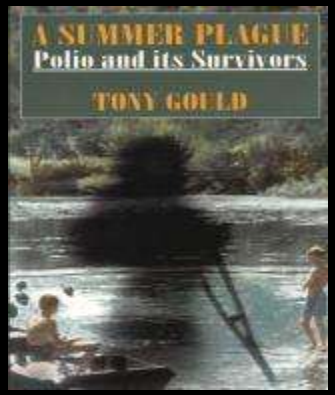
Infectious Disease: A Powerful Force in Human Evolution

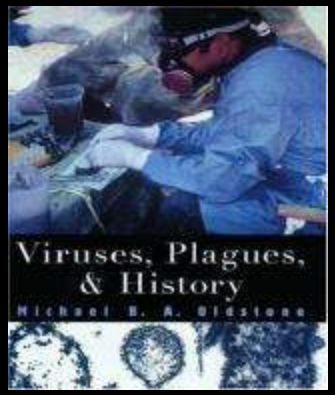


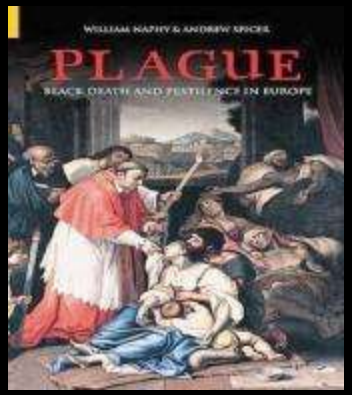


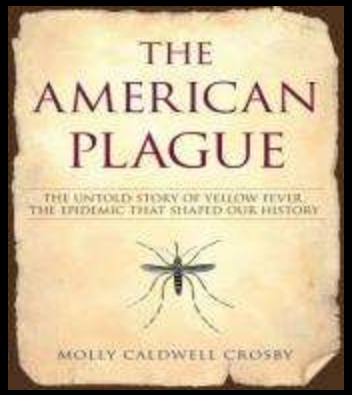


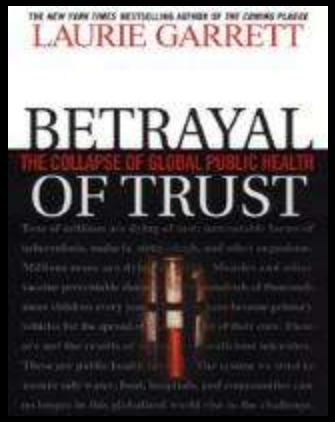


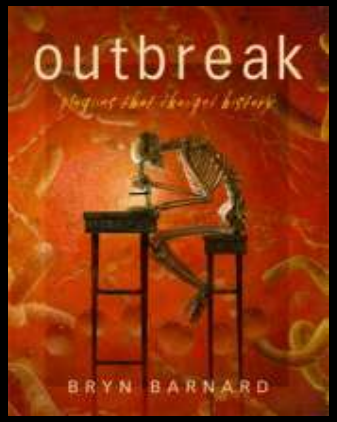


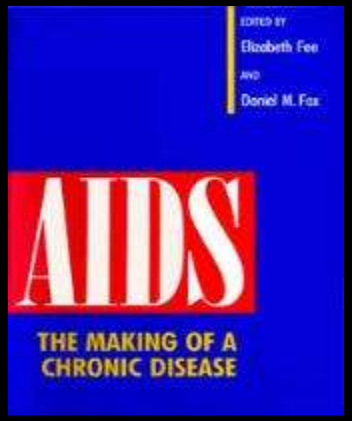


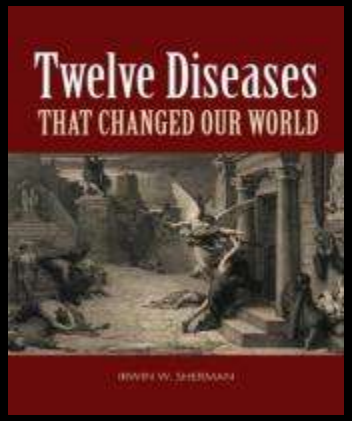












Microbial Life: Transmissible Diseases

Bacterial Phages

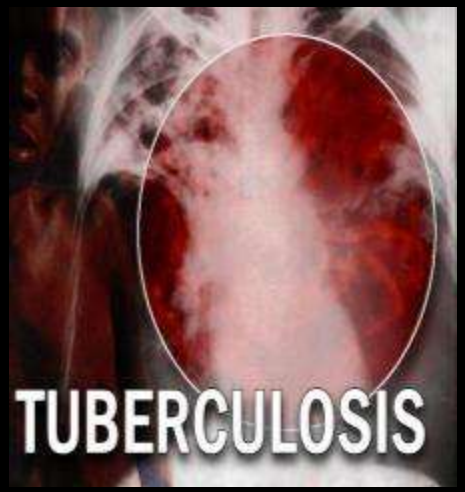
Plant Diseases

Animal Diseases

Ecosystem Disruption

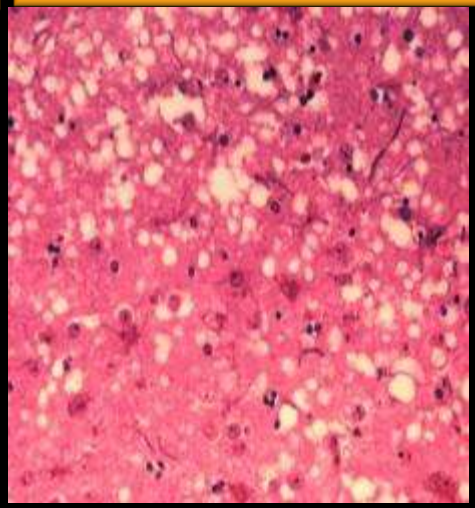
Acute Disease

Chronic Disease



Latent and Reactivated Disease

Slow Virus Infections



Infectious Diseases: A Shared Global Risk

#1

- cause of neonatal and maternal death worldwide
- economic impact of disease via premature death, disability and reduced productivity
- growing drug-resistance as most important clinical threat in both industrialized nations and DCs

#2

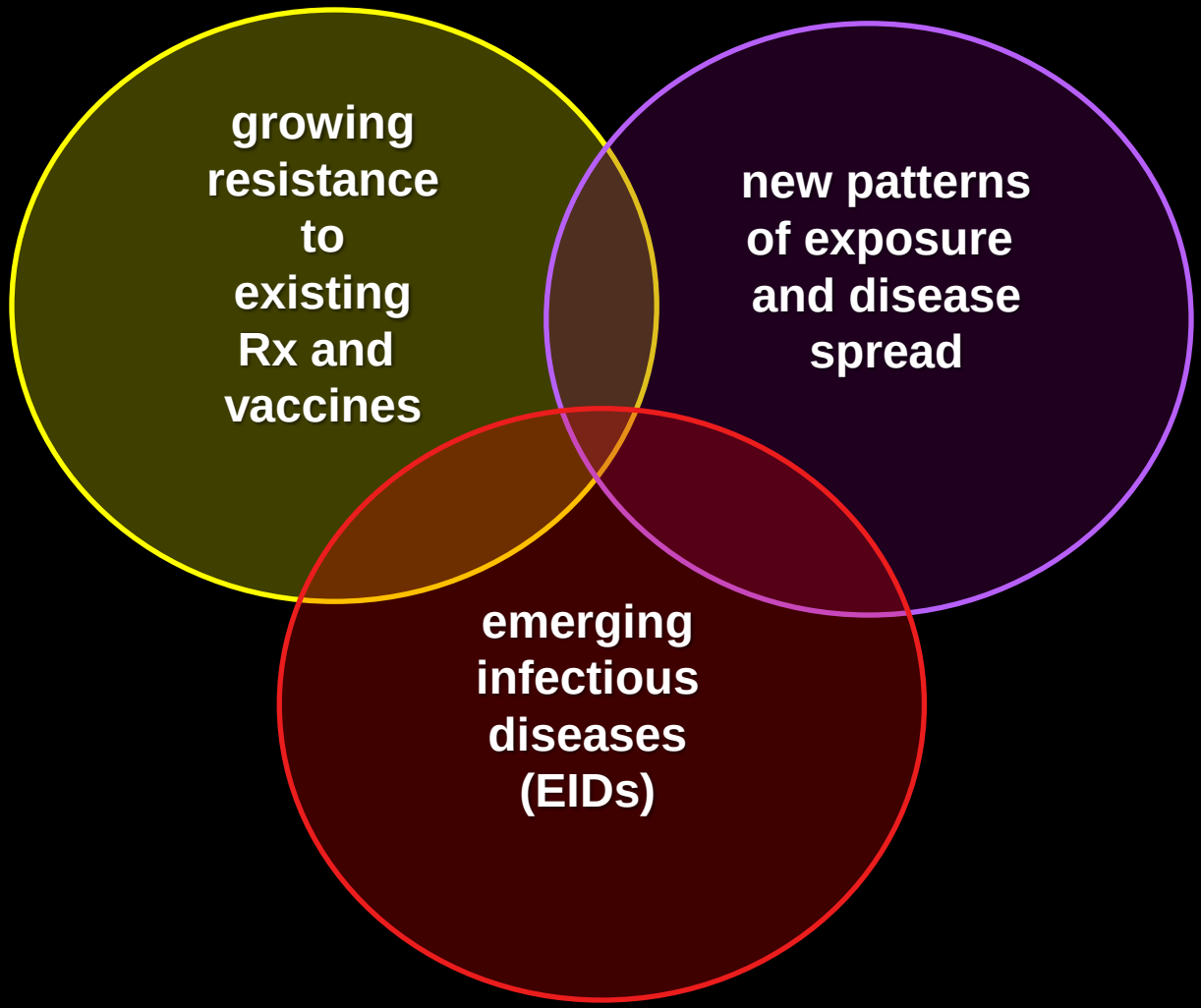
- cause of death worldwide

#3

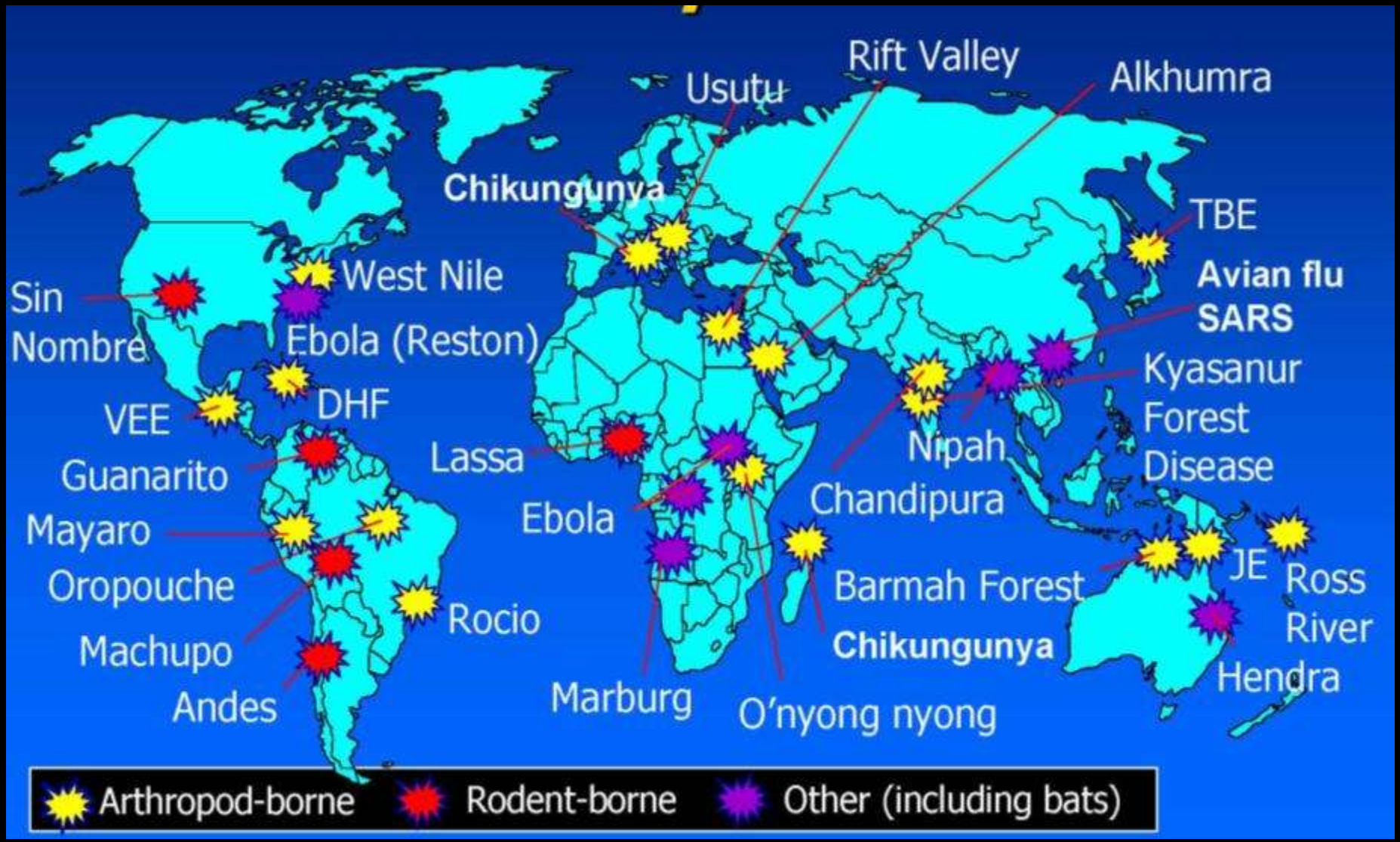
- cause of death in US and Europe

The Imperative for new R&D Strategies and Investments in Diagnostics, Drugs and Vaccines

Outpacing Infectious Diseases



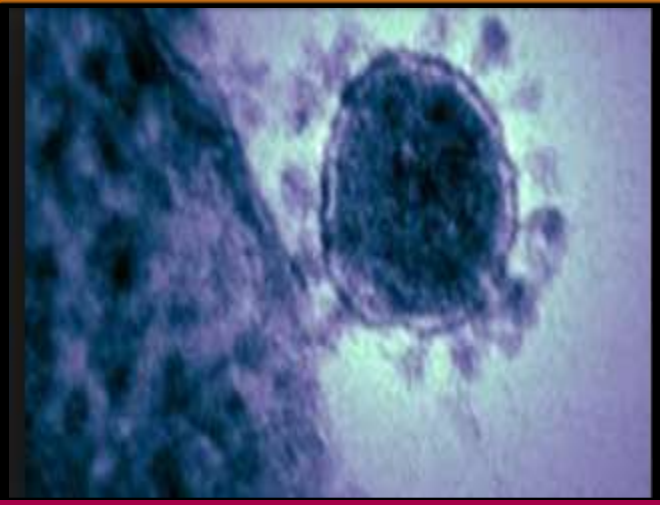
Emerging Infectious Diseases (EIDs)

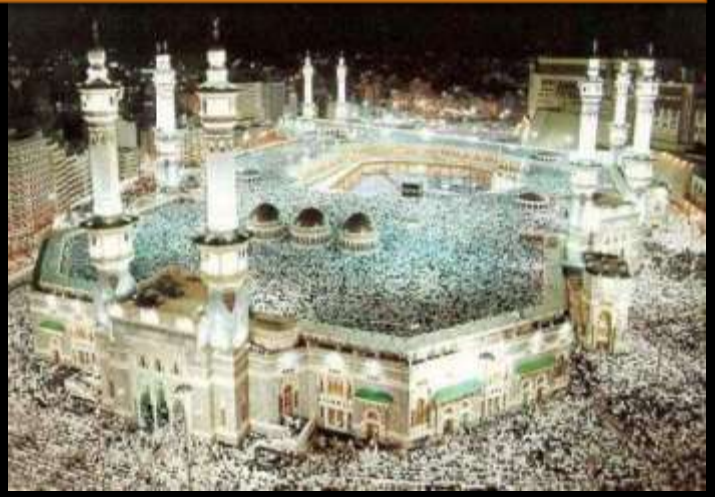


Human Coronaviruses

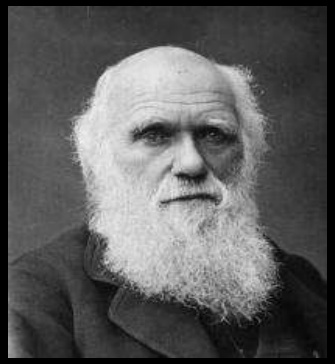
Emergence of SARS-CoV (PRC 2003)

Emergence of MERS-CoV (KSA 2012)





Microbe: Host Interactions
A Complex Ecosystem and Evolutionary Co-dynamics



Darwinian Evolution

- selection by variation
- adaptation
- evolvability

"Nothing in biology makes sense, except in the light of evolution."

Theodosius Dobzhansky

"The future of humanity and microbes will likely evolve as episodes of our wits versus their genes"

Dr. Joshua Lederberg, Nobel Laureate
Science (2000) 6, 427-30

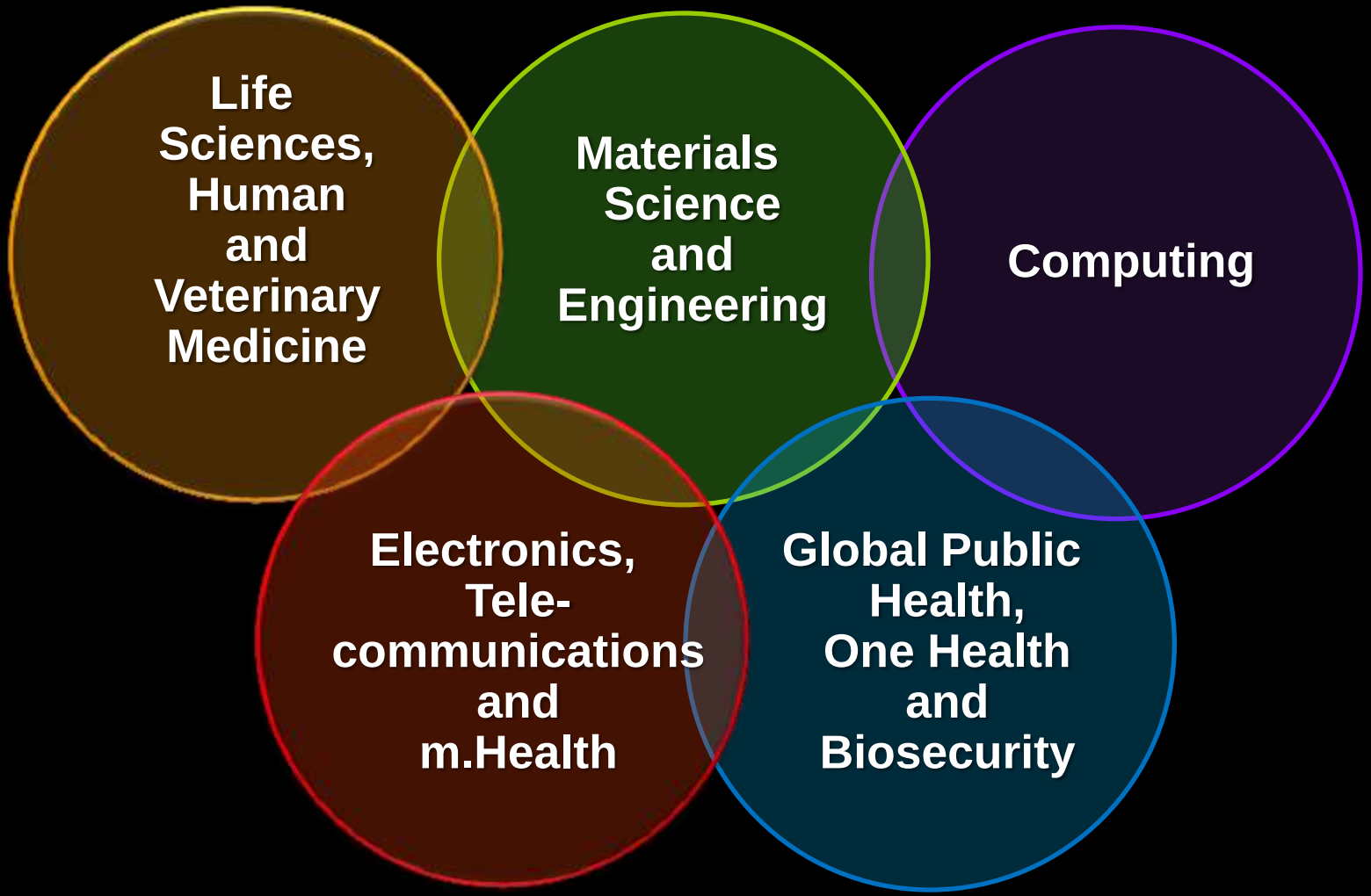
Building Resilient and Agile Systems for Biosecurity

Infectious Diseases of Natural Origin

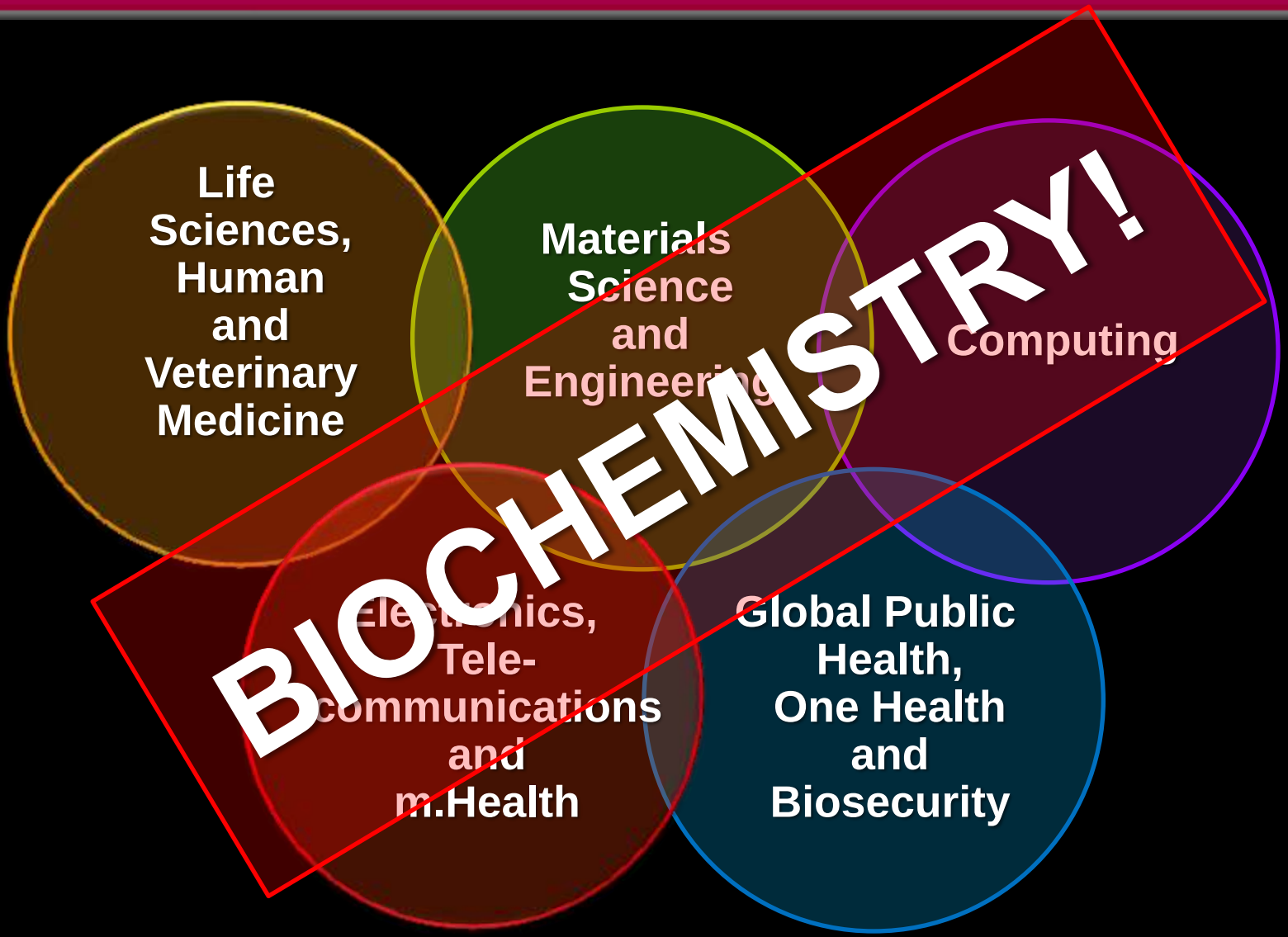
Environmental and Ecological Impacts on Disease Emergence

Bioterrorism

Technology Convergence in the Detection and Control of Infectious and Parasitic Diseases



Technology Convergence in the Detection and Control of Infectious and Parasitic Diseases



The Global Public Health Challenge Posed by Rapid Urbanization in Developing Countries

High Disease Transmission

Lack of Safe Water

Bush Meat Food Chain

Major Deficits in Health Infrastructure

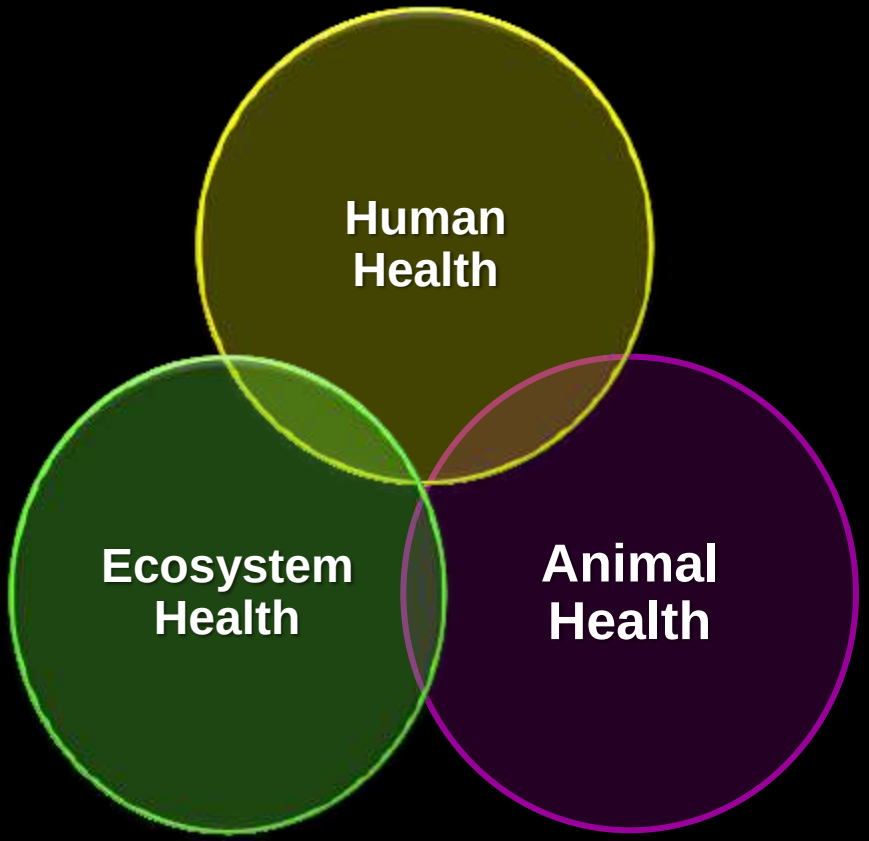
Expanded Eco-niches and Increased Zoonotic Risks

The Evolving Nature of Human Infectious and Parasitic Diseases

1407 species of human pathogens

- 538 bacteria
- 208 viruses
- 317 fungi
- 57 protozoa
- 287 helminth worms
- 60% are zoonoses
- over 70% zoonoses arise from interactions with wildlife
- Emerging Infectious Diseases (EIDs)
  - 58 in last 25 years
  - viruses significantly over-represented
  - RNA viruses most variable and rapidly changing
  - helminths under-represented

"One Health": The Rationale for Integration of Historically Separate Domains and Responsibilities



- urbanization of DCs and emergence of new zoonotic threats
- food chain as increasing source of disease risks
- enhanced agricultural productivity to support global population growth
- economic impact of agricultural disease on trade, development and resources/production footprints

Detection of Large Scale Incidents: Epi-Pandemics/(Zootics) or Bioterrorism

Not A Hazmat or Wide Area Sensor Network Solution

Emergency Rooms and Farms Will be the Front Line

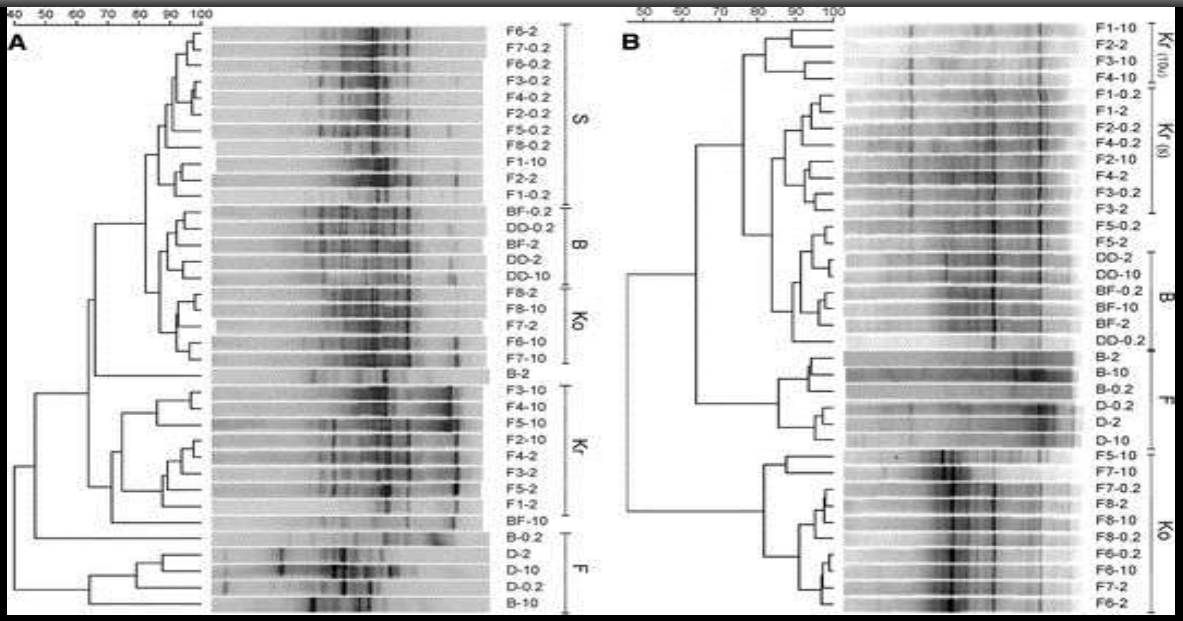
Technology Platforms for Infectious Disease Diagnostics

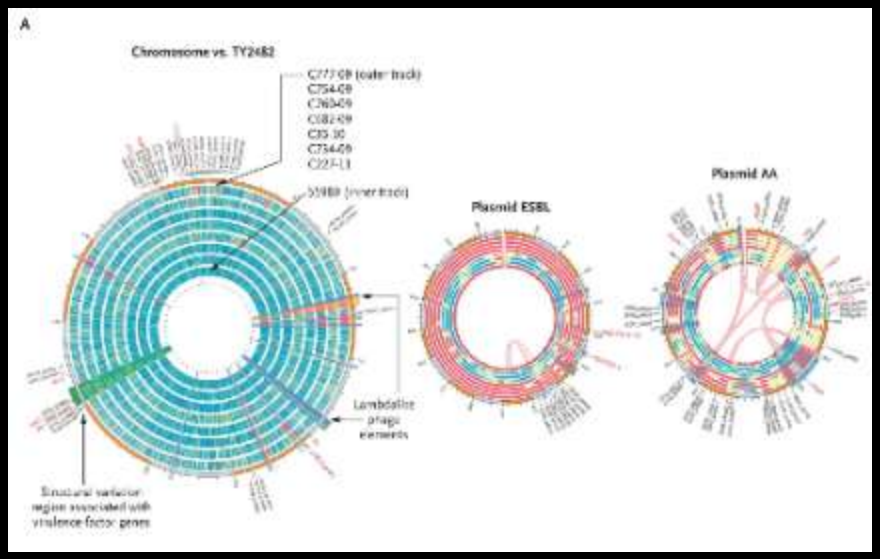
profile the organism

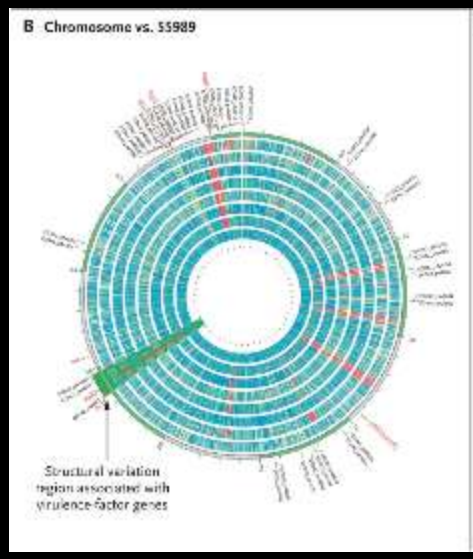
versus

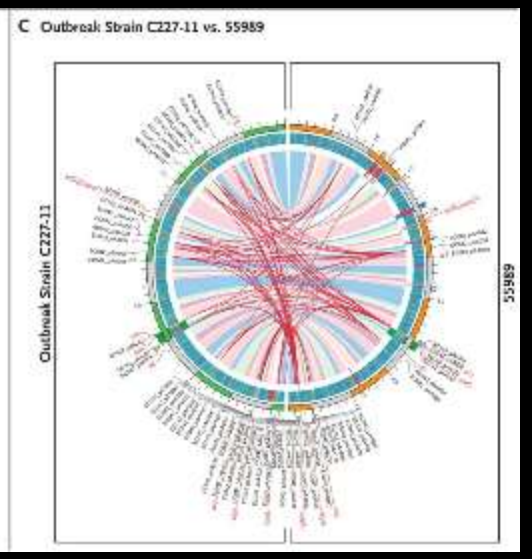
profile the host

Genome Sequencing, Microbial Identification and Epidemiology
E. Coli Strain STEC 0104: H4 (Germany 2011)

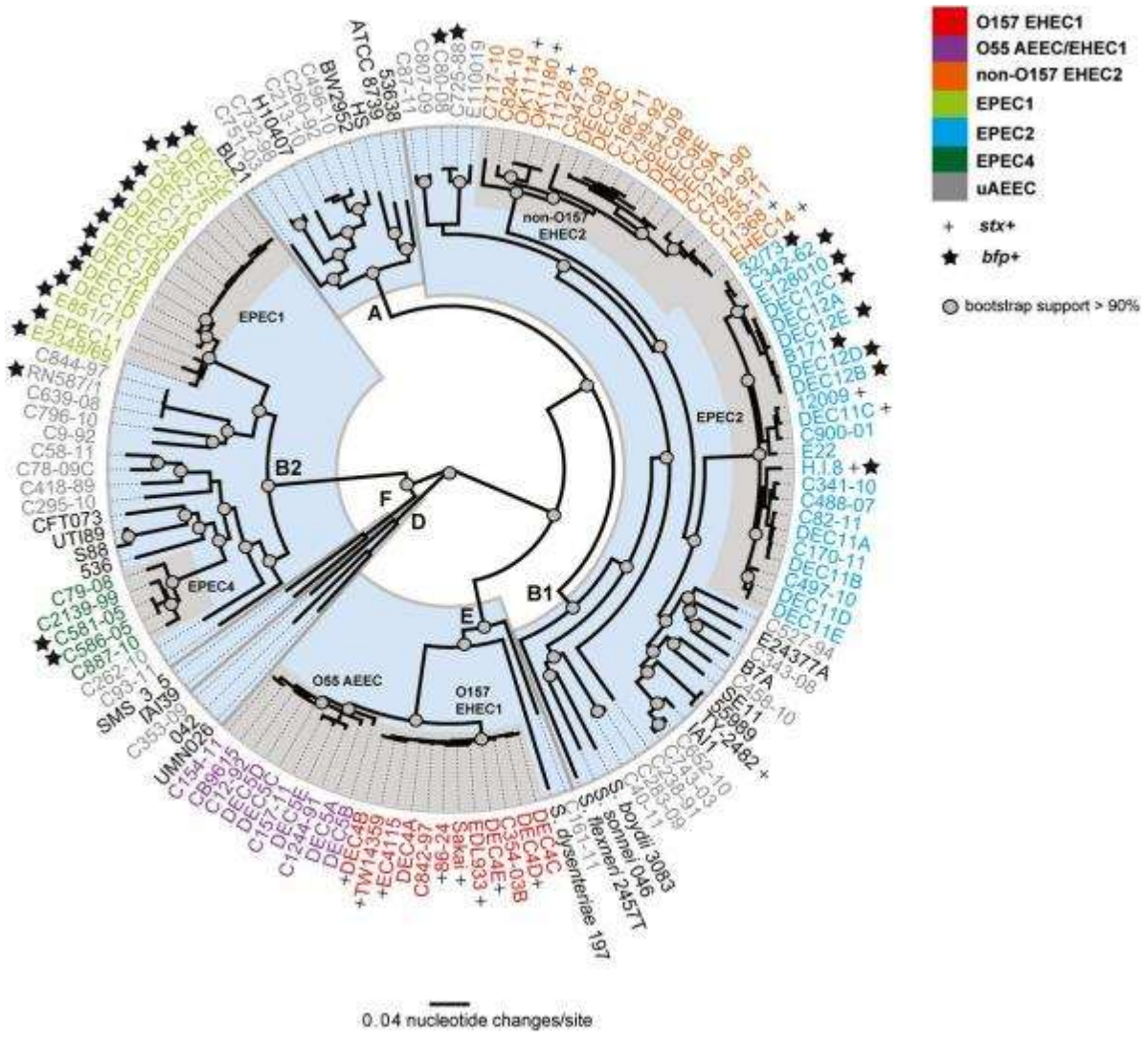








Phylogenomic Analysis of Pathovar *E. coli*



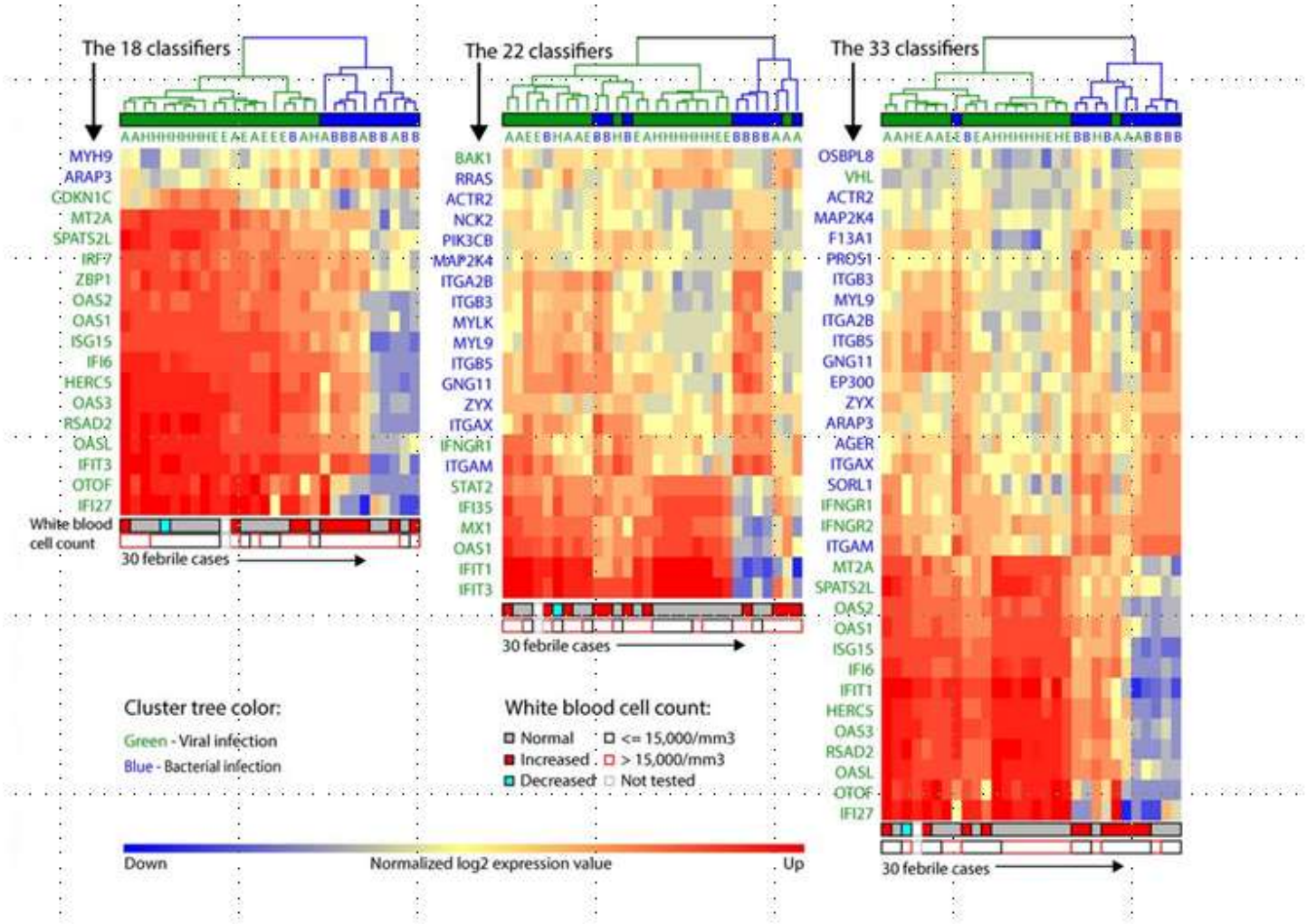
From: T. H. Hazen et al. (2013) PNAS 110:12810

Design of Technology Platforms for Microbial Diagnostics

profile the host

- body defense systems as exquisite sentinel of exposure
- not limited to ‘known’ pathogens
- need for facile, rapid profiling from easily obtained samples (blood, saliva)
  - rapid triage in bioincident
  - population-based biosurveillance

Heat Map Transcriptional Profiles of Febrile Children in Viral (Green) and Bacterial (Blue) Infections

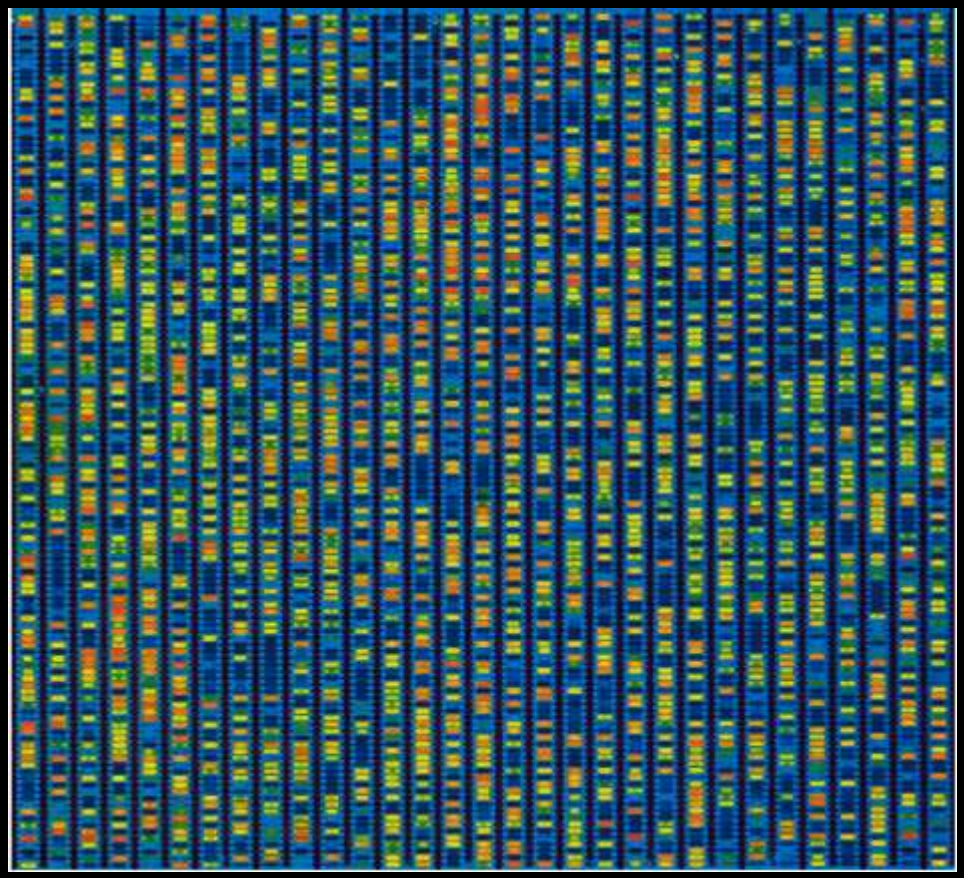


From: Hu X et al. (2013) PNAS 110:12795

IFN-pathways activated in viral infections and integrin pathways in bacterial infections

Immunosignatures

ASU BIODESIGN INSTITUTE
ARIZONA STATE UNIVERSITY



- approx. 10^9 different IgG antibodies in healthy adult
- new analytical thresholds reveal faster adaptive immune response than believed previously (pre-symptomatic)
- isotype profiling of dynamic response to infection
- IgG species with long life-time persistence and stable in prolonged specimen storage
- detection of both known and previously unknown agents

From: Drs. S. Johnston and N. Woodbury (ASU)

Global Surveillance Against Infectious Disease Outbreaks
E.H. Chen et. al. (2010) PNAS 107, 21701

- 398 WHO-verified outbreaks 1996-2009
- median times
  - 23 days for event detection
  - 32 days for public communication
  - 35 days for official laboratory confirmation
  - 48 days for inclusion in WHO Disease Outbreak News

No Ambiguity - No Error: No Problem!
The Omnipresent Dillema of Uncertainty When Political Leaders Want Certainty

"Insufficient data, Captain"

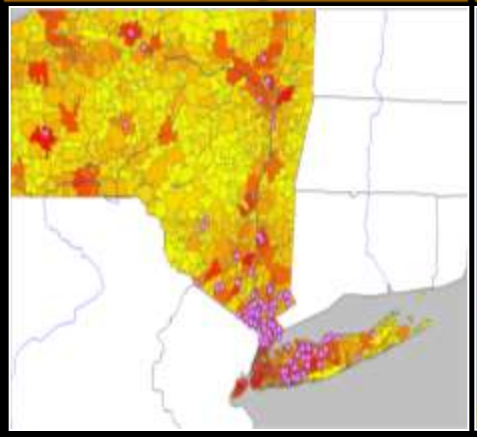
"Insufficient data is not sufficient,
Mr. Spock.
You're the Science Officer.
You're supposed to have sufficient data all the time"

Star Trek
The Immunity Syndrome

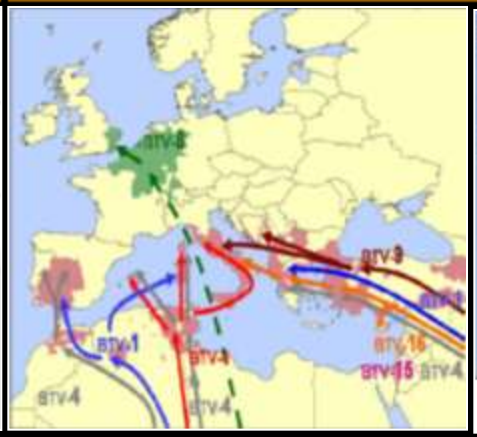
Geodemographic Information Systems (GIS): Real-Time, Front Line, Ground Zero Data from Field Sampling and Sentinels

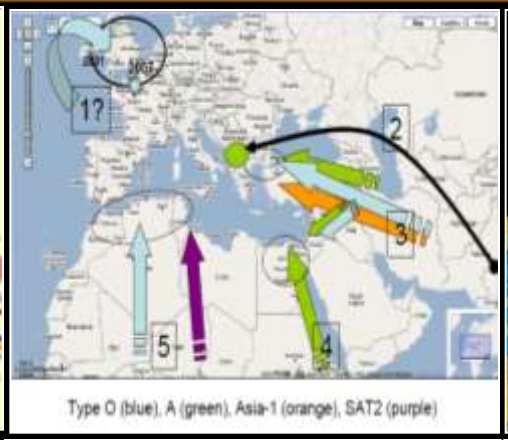
Geodemographic Information Systems: Mapping Disease Patterns and Modeling Trends

Anomaly Detection and Early Alert

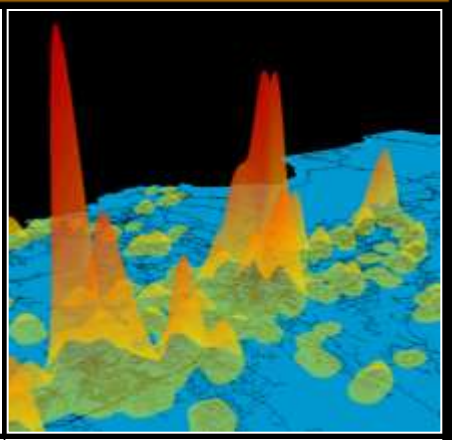


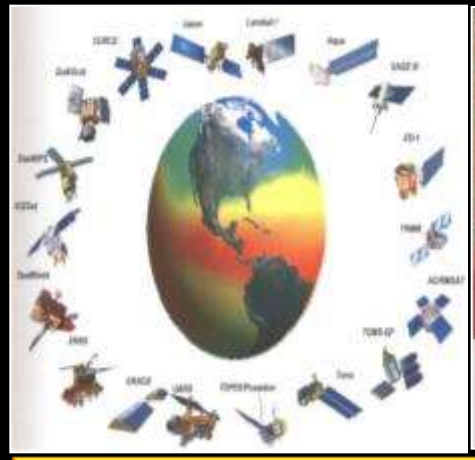
Disease Progression

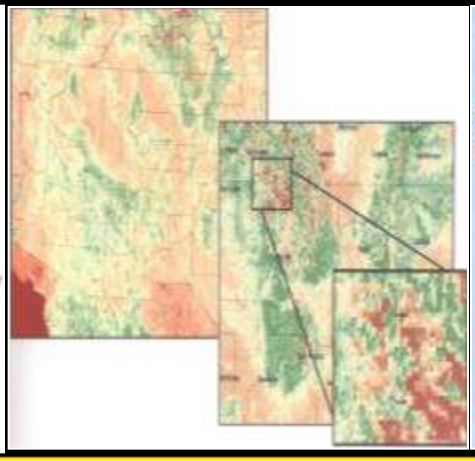


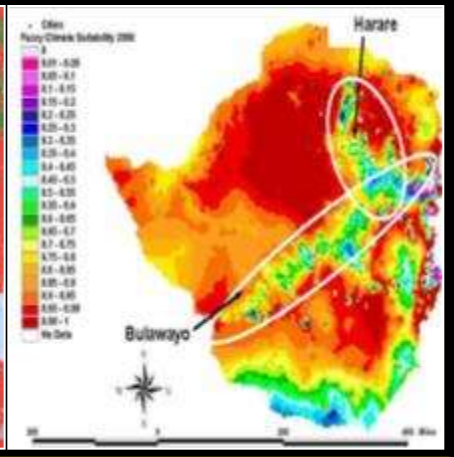


Type O (blue), A (green), Asia-1 (orange), SAT2 (purple)









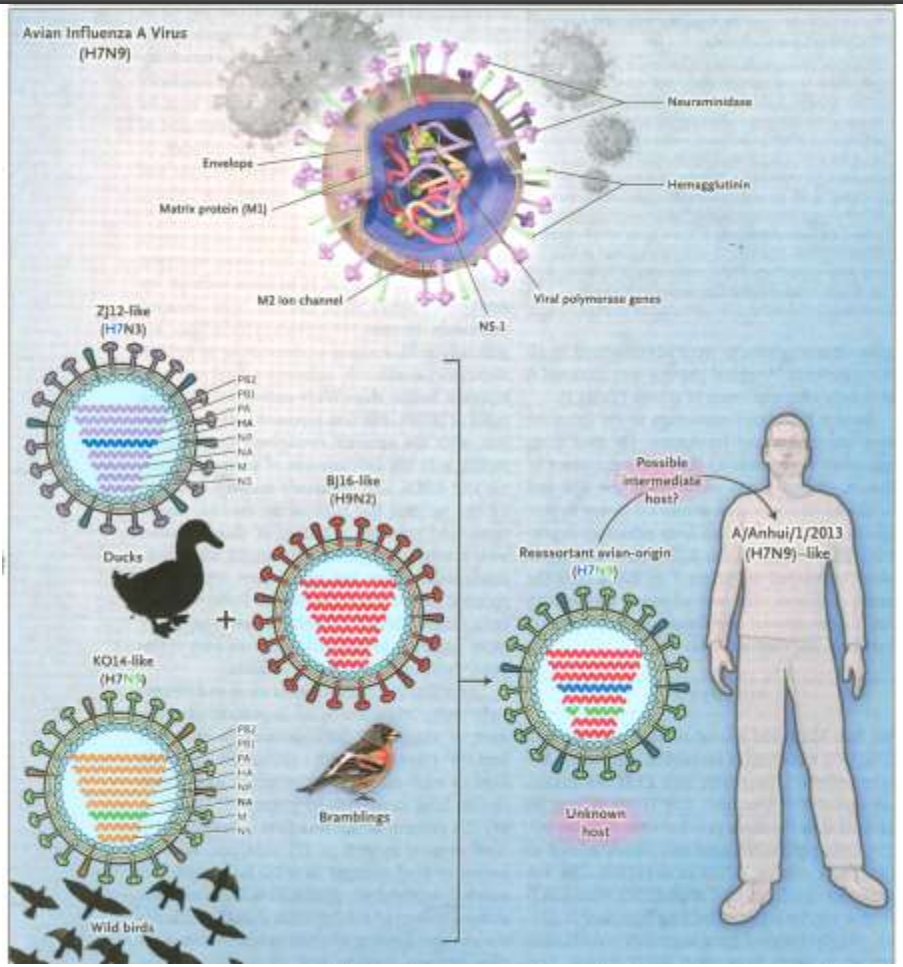
Satellite Surveillance and Predictive Modeling of Disease Trends

mHealth: Rapid Reporting of Atypical Events and Faster Identification of Disease Outbreaks

- geolocation data (where)
- temporal information (when)
- contextual information (what)
- improved decision support (action)

Understanding Animal to Human Transmission

Model of Potential Hosts and Lineage Origins of Novel Reassortant Human H7N9 Influenza A Viruses



From: Gao et al. (2013) NEJM 368, 1895

GJ16 = A/brambling/Beijing/16/2012; K014A/wild bird/Korea A4/2011; ZJ12 A /duck/Zhejiang/12/201

Maintaining Global Preparedness for a High Virulence Pandemic

- H1N1: high transmissibility - low virulence/mortality
- H5N1: low transmissibility – high virulence/mortality
- H5N1 x (H1N1) or (X): potential for devastating pandemic

Bad Bugs and Few New Drugs

NO ESKAPE!

NO ESKAPE!: Resistant Bugs and Few New Drugs

- increasing resistance in G^+ and G^- pathogens in hospital and community settings
- the **ESKAPE** pathogens
  - ***E**nterococcus faecium*
  - ***S**taphylococcus aureus*
  - ***K**lebsiella pneumoniae*
  - ***A**cinetobacter baumanii*
  - ***P**seudomonas aeruginosa*
  - ***E**nterobacter species*

Tuberculosis

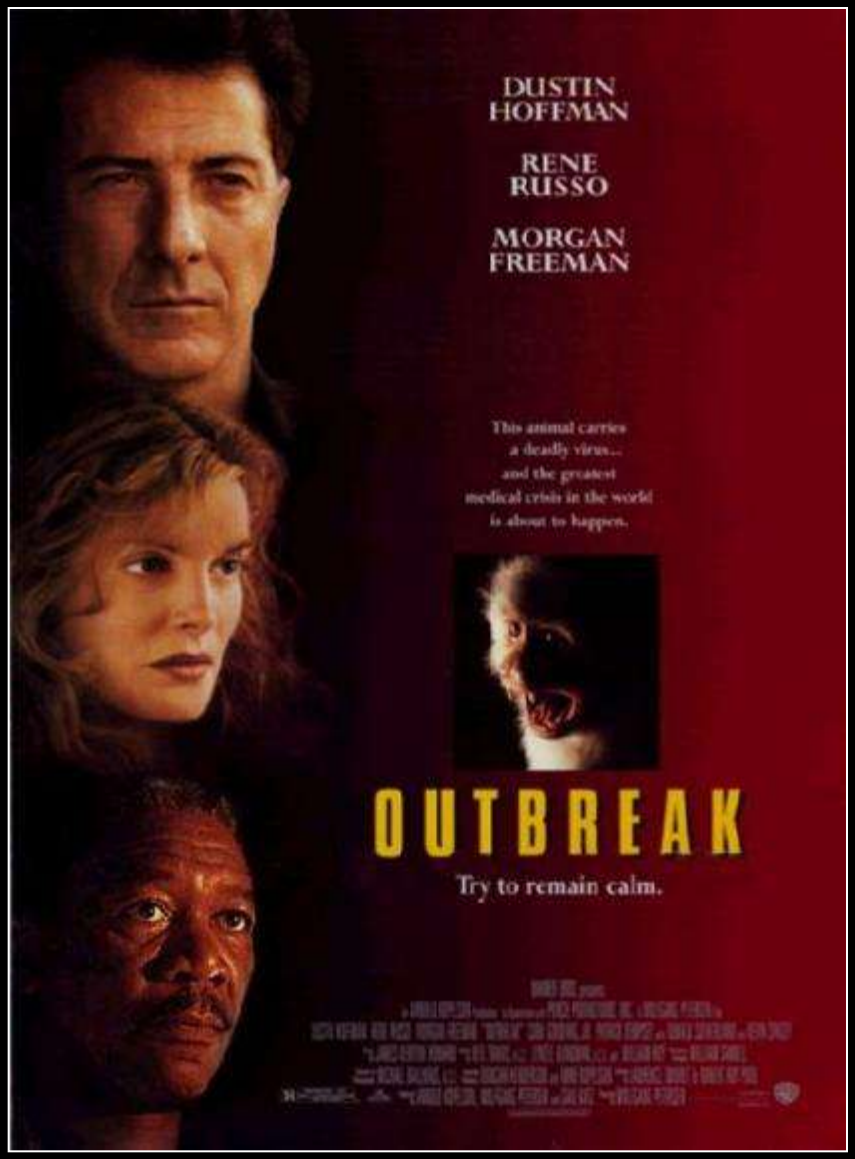
- 2.2 billion people infected
- every 20 seconds a person dies from TB (1.77 million/year)
- second leading infectious cause of adult death
- #1 infectious killer for individuals with HIV/AIDS
- kills more women than all other maternal mortality causes combined
- emergence of multi-(MDR) and extreme-(XDR) resistant strains

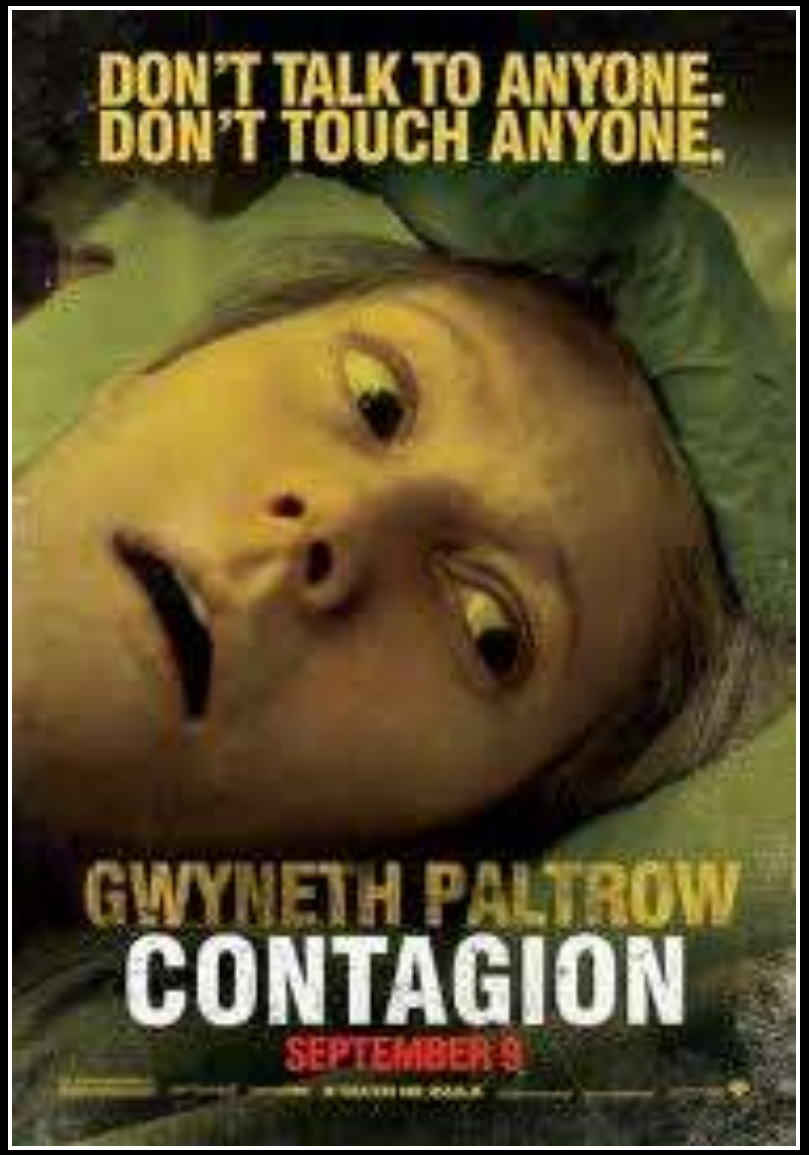
No New TB Drug for 40 Years

The Valley of Dearth:
The Consequence of Declining R&D Investment in Antibiotic Discovery*

- 75% decrease in antibacterials approved from 1983 to 2011
- only 16 agents currently in Phase II / III clinical trials
  - only 3 as new ‘classes’ with novel mechanisms of action
  - absence of new agents for therapy of G^- bacilli
  - lack of systemic agents in advanced development for organisms resistant to all current antibacterials

….. and then a technical miracle cure occurs with dramatic rapidity
….. and always created by an individual scientific genius





Drug Discovery and Development: One of the Most Complex Intellectual and Logistical Exercises Undertaken by Industry

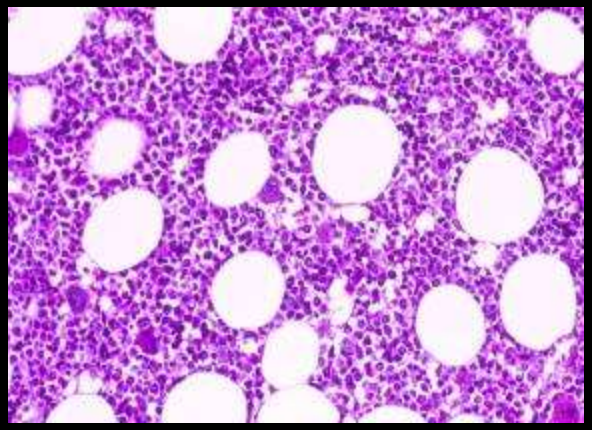
- $750 million to $2 billion R&D cost/drug
- 9-15 year R&D cycle
- efficacy
- safety
- cost-effectiveness and outcomes (non-US)

Drug Discovery and Development

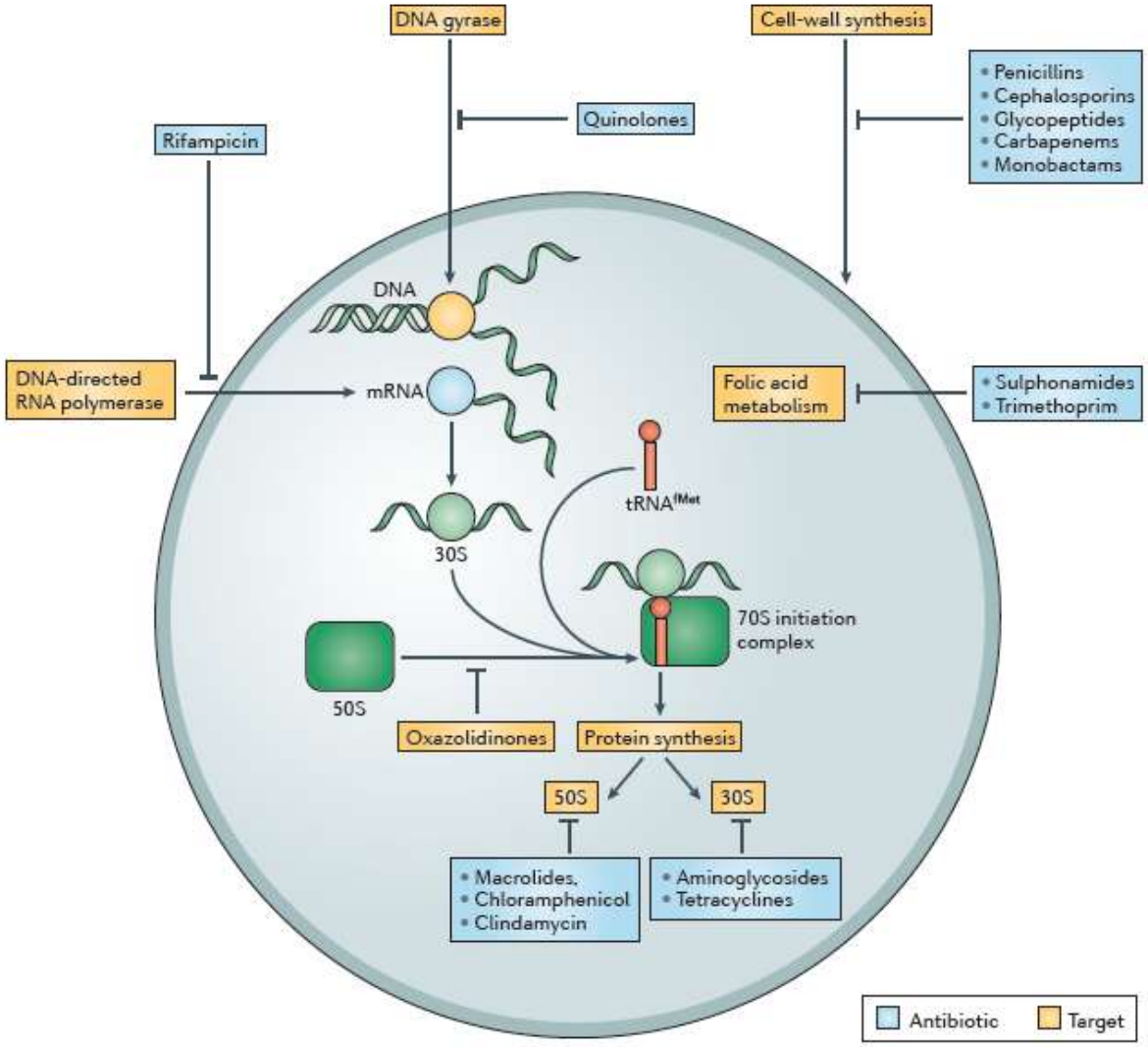
"Fewer countries have discovered,
developed and registered drugs
to an international standard,
than have developed atomic bombs"

Chris Hentshel
Medicines for Malaria Venture
Lancet (2004) 363, 2198

Efficacy and Safety of Drugs and Vaccines in Special Populations

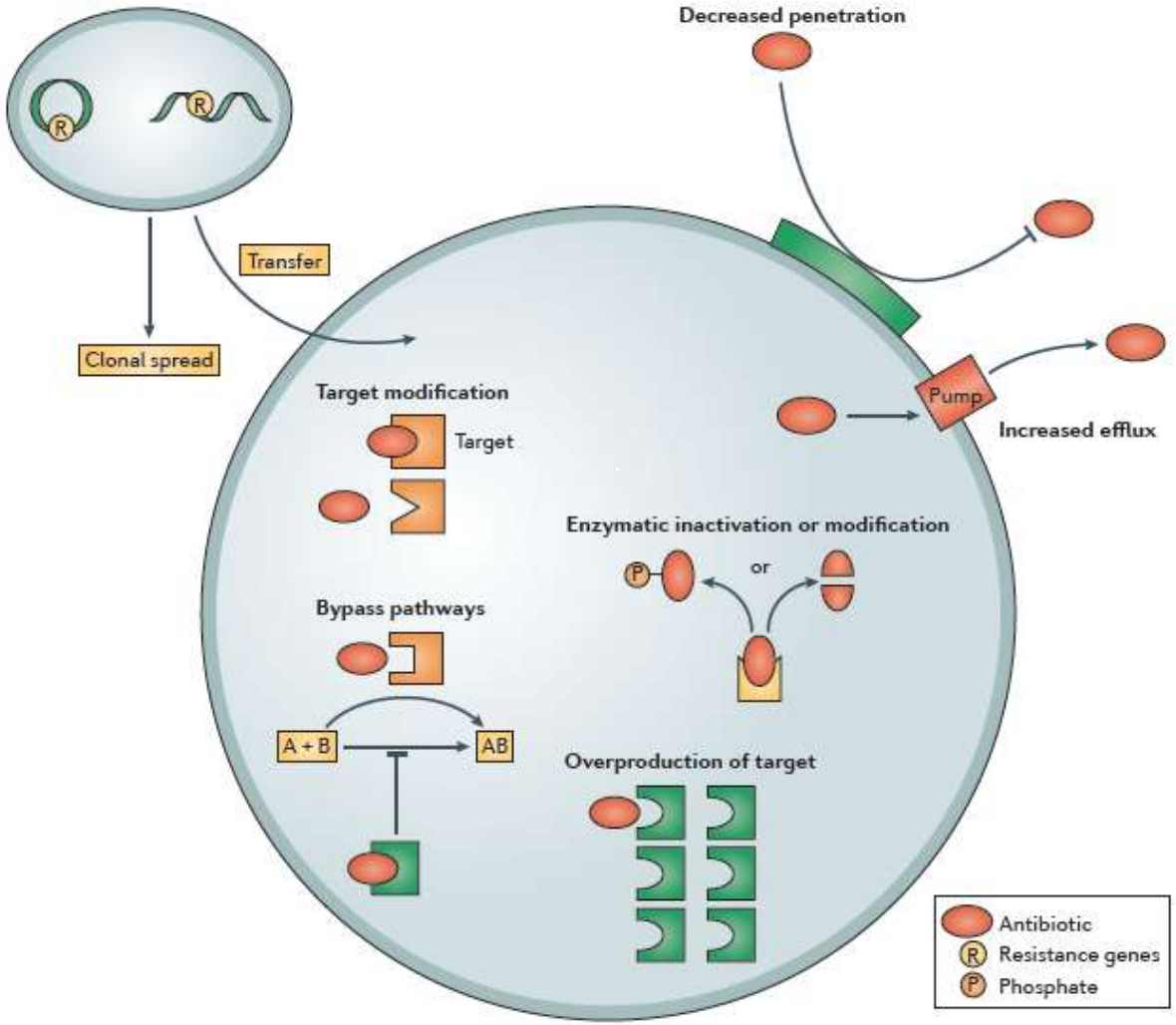
Children	Pregnant	Aged
		
		
Immunosuppressed	**Impaired Major Organ Function**	**ICU-Critical Care**

Molecular Targets for Antimicrobial Antibiotics



From: K. Lewis (2013) Nature Rev. Drug Disc. 12, 371

Mechanisms of Antibiotic Resistance and Tolerance



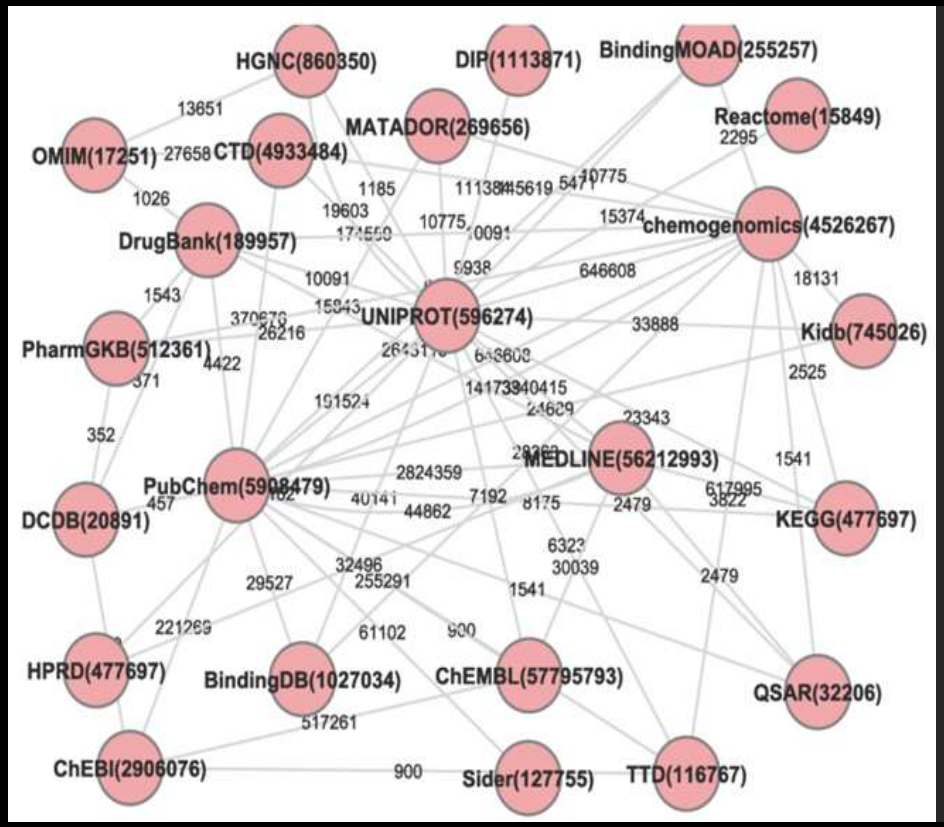
From: K. Lewis (2013) Nature Rev. Drug Disc. 12, 371

Molecule Screening

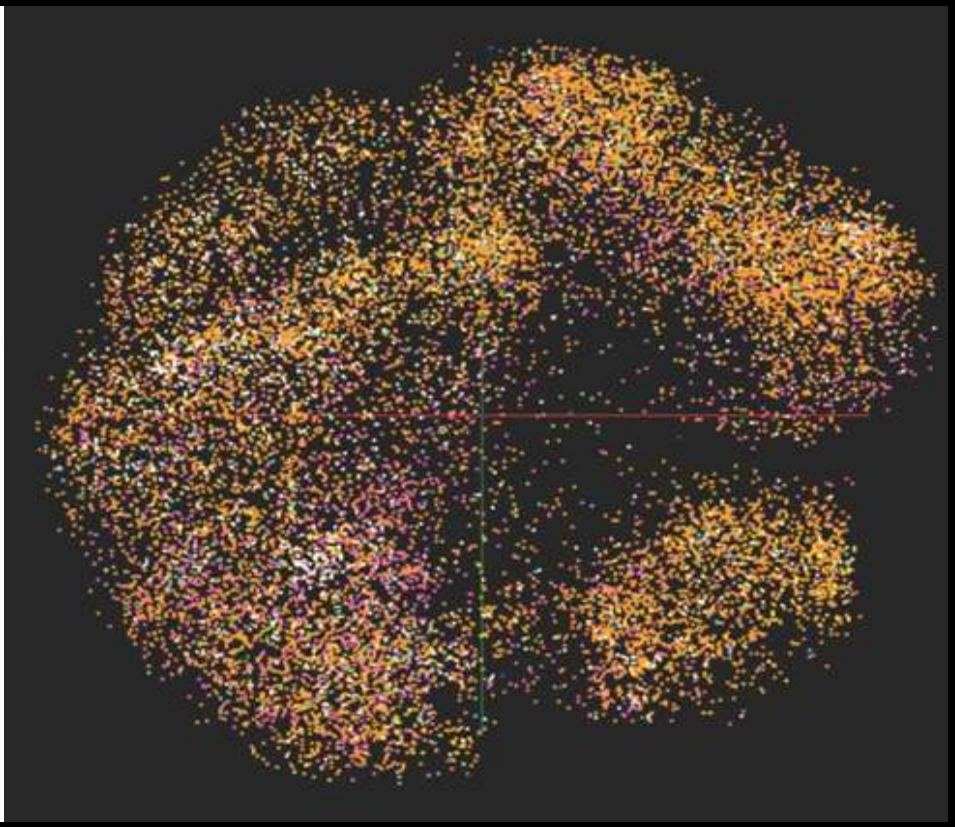
http://www.news.pitt.edu/news/molecule-scanner

Big Data in Drug Discovery

Chem2Bio2RDF



Mapping Large Scale Chemoinformatics Space



D. J. Wild (2010) Indiana Univ.

Defining SAR for Rx Candidates

- computational screening of ‘chemical space’ to enrich hits for ‘biological’ screening
- structural complexity of ‘pharmacophore’ domain
- combinatorial chemistry and fragment-based lead discovery
  - low Mr compounds < 250-300Da
  - more synthetically tractable targets for medicinal chemistry?
  - insufficient structural complexity for ligand mimicry?
  - weak affinities (high micro- to millimolar range) as obstacle to detection of biologically relevant interaction?

Next-Generation Vaccine Technologies

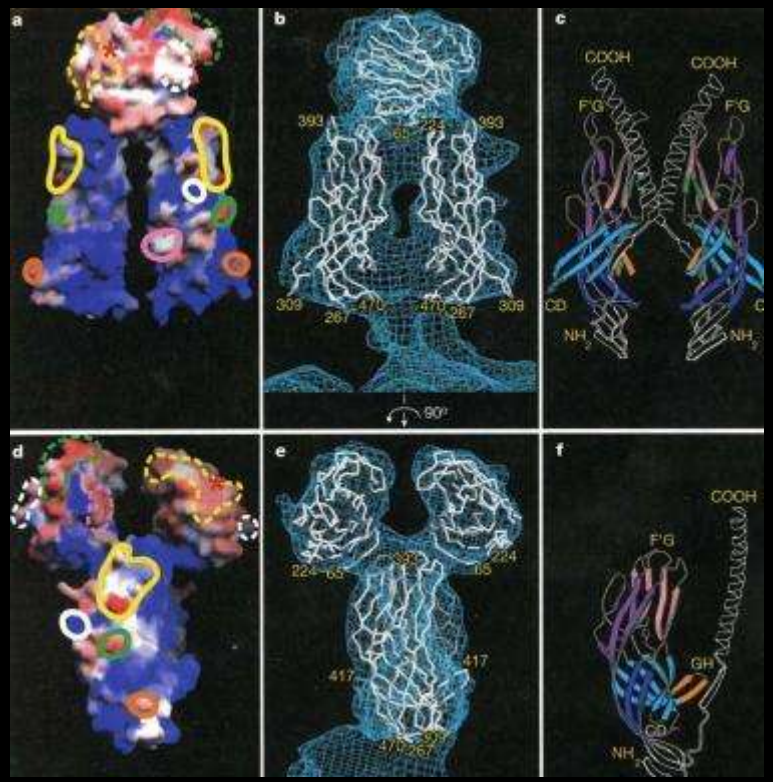
pan-vaccines

- protection against diverse strains of a pathogen
- protection against closely related classes of pathogens

combating “Agent-X”

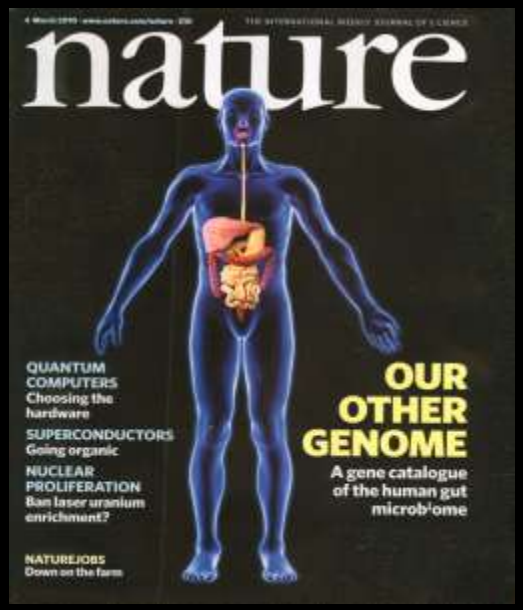
- rapid design and large scale production (weeks versus years) for protection against sudden emergence of an unprecedented pathogen (Agent-X)

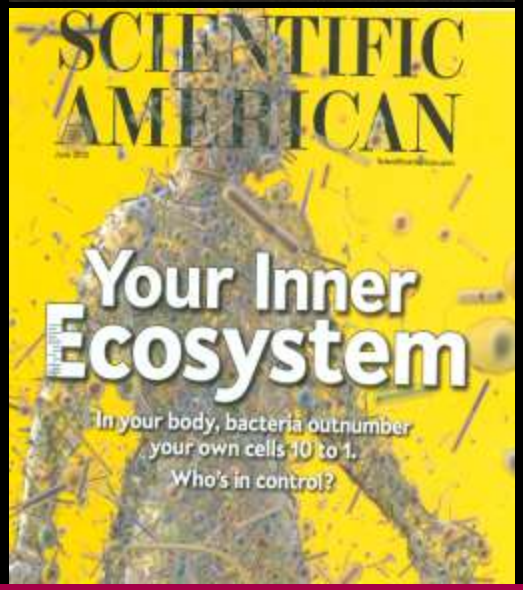
Accelerated Manufacture of Vaccines

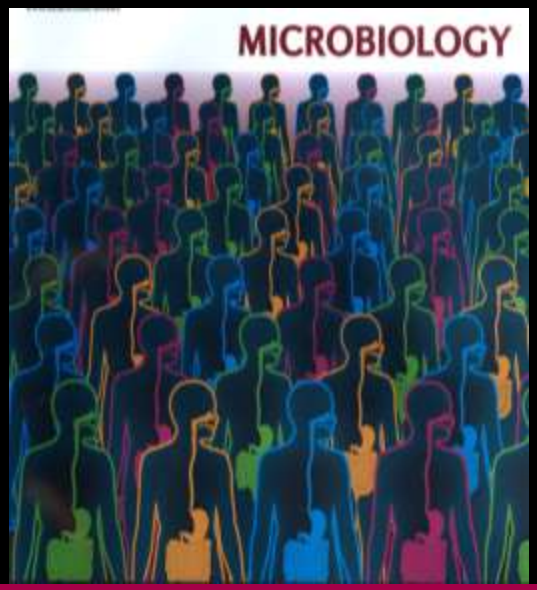


- convert vaccine production from a ‘biologics’ process to a ‘chemical’ manufacturing process
- reduce R&D cycle from 10-25 years to less than 1 year
- shorten production cycles run-time from 6-12 months to days/weeks

We Are Not Alone: The "Frenemy Within" Variation in the Human Microbiome as a Potential Factor in Health and Disease

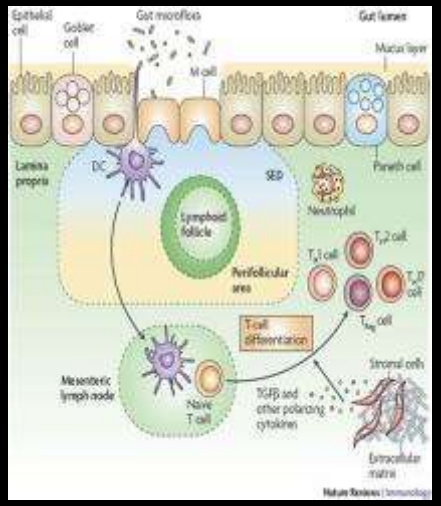


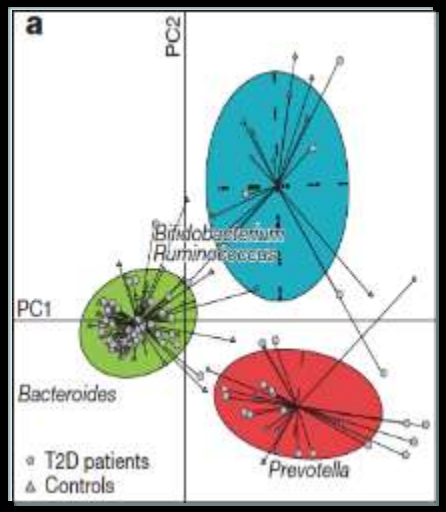


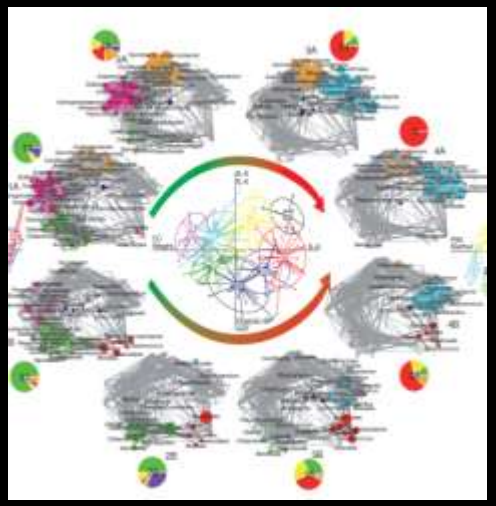


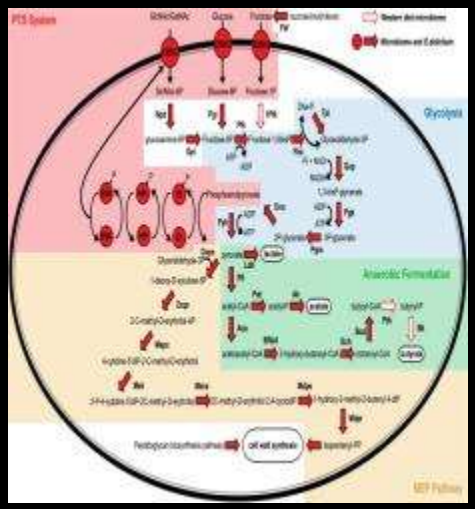
Commensal Microbiomes: The "Frenemy Within" An Additional Dimension to Biomarker Profiling

Metagenome-wide Association Studies (MGWAS)



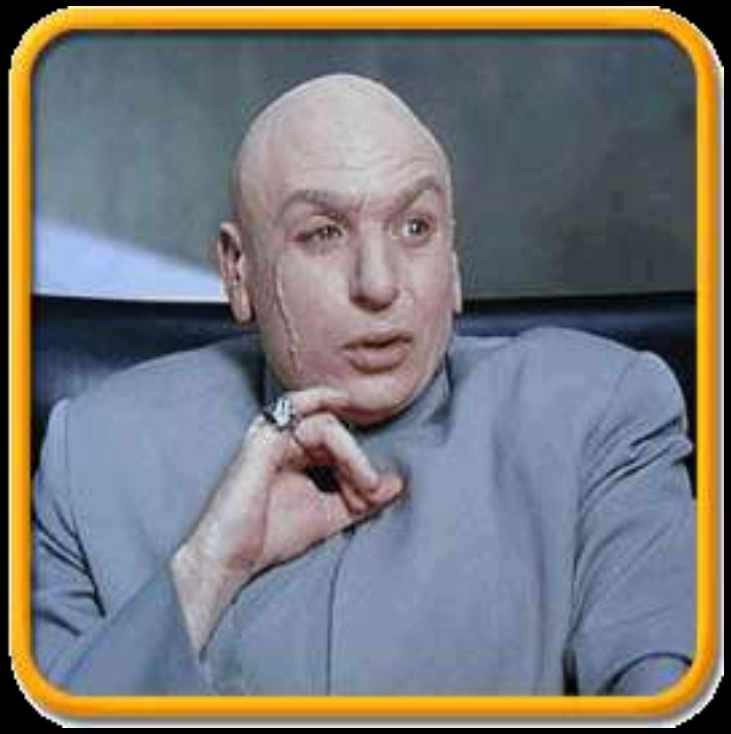






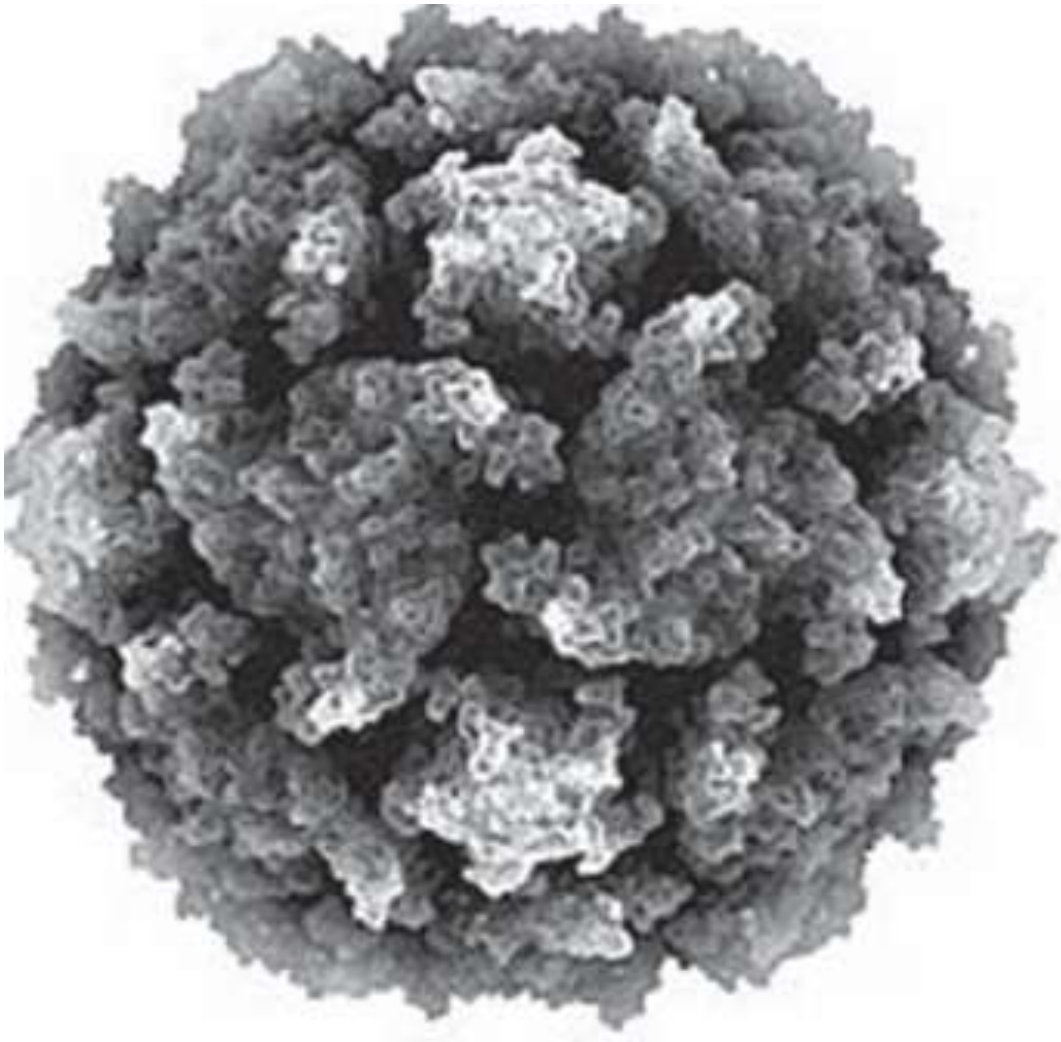
Immune-Mediated GI Diseases	Type 2 Diabetes Profile	Aging Metabolism and Fragility	Metabolic Activation of Carcinogens/ Pollutants

Future Trajectory Trends and Threat Expansion



New ‘Dual-Use’ Technologies

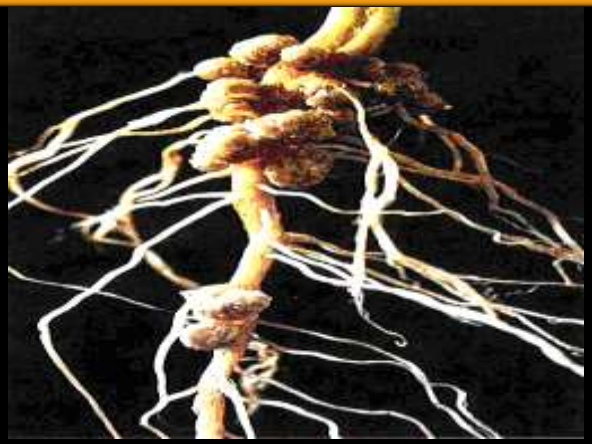
C332,652; H492, 388; N98, 245; O131, 196 P7, 501; S2,340 (a.k.a. poliovirus)



ATTGACTGCAA ……(design specifications)

Microbial Life:
Productive Applications of Microbial Biochemistry

Nitrogen Fixation

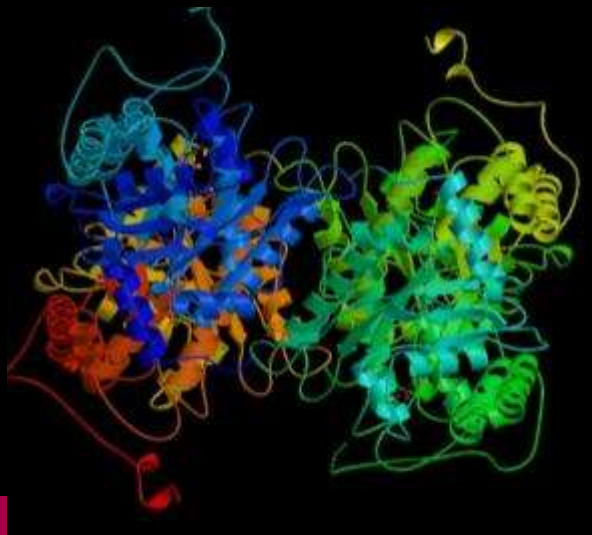


Food Production

Sewage Treatment

Biofuels

Enzyme and Chemical Synthesis

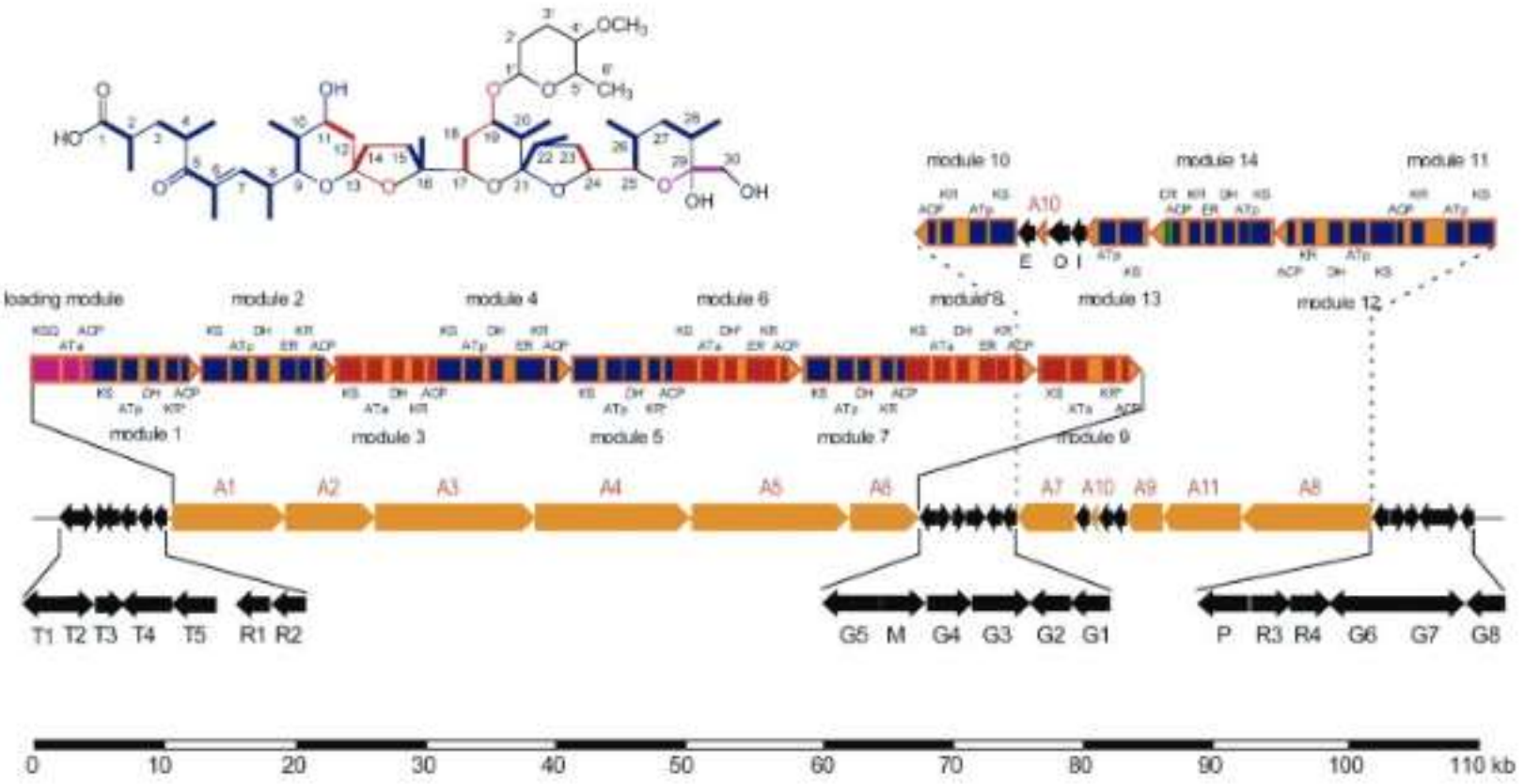


Essential Materials

Synthetic Biology and Novel Biosynthetic Capabilities

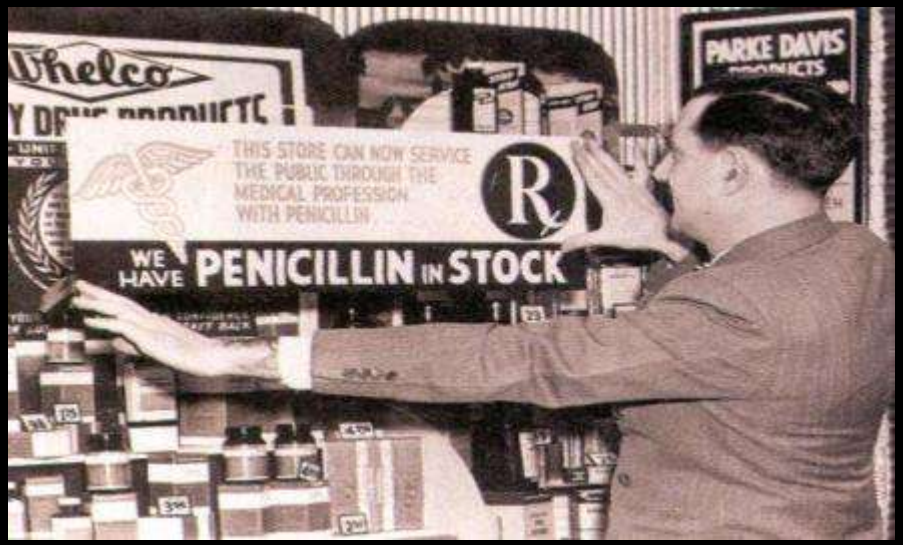
- manufacture of commodity and speciality chemicals plus (bio)pharmaceuticals
- complex syntheses (asymmetric syntheses) and single step synthesis to replace multi-step chemistry
- reduce VOC emission by switch from solvents to aqueous or aqueous-organic biphasic systems synthetic reactions
- reduced energy consumption and biodegradable waste products

Chemical Structure and Gene Synthesis Cluster for the Polyether Ionophore Antibiotic Nanchangmycin

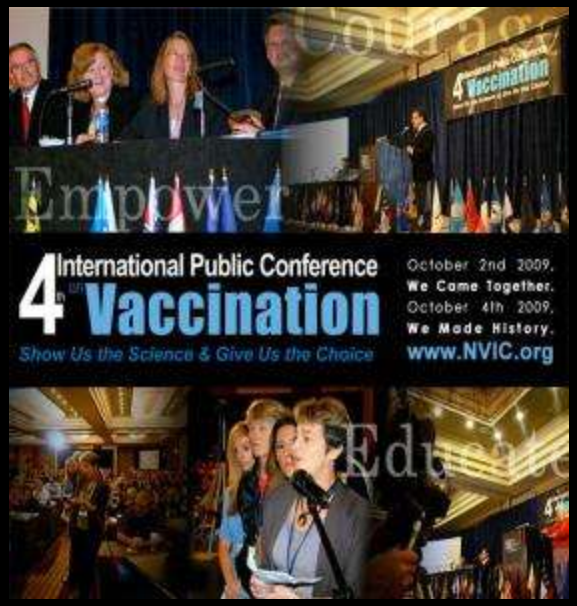


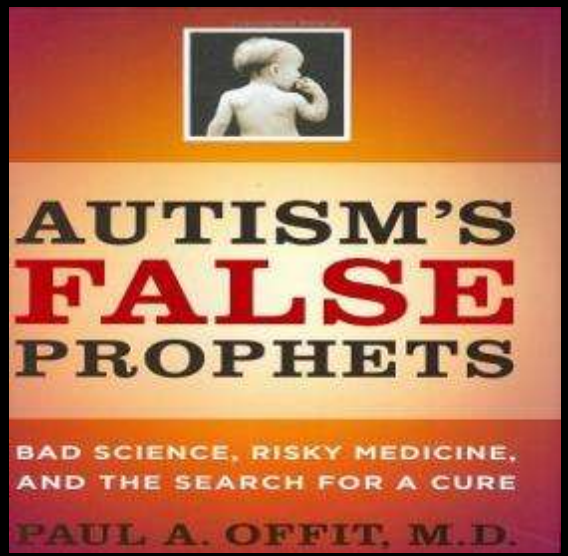
From: Y. Sun et al. (2003) Chem. Biol. 10, 431

Comfort and Complacency: The Enemies of Vigilance and Preparedness

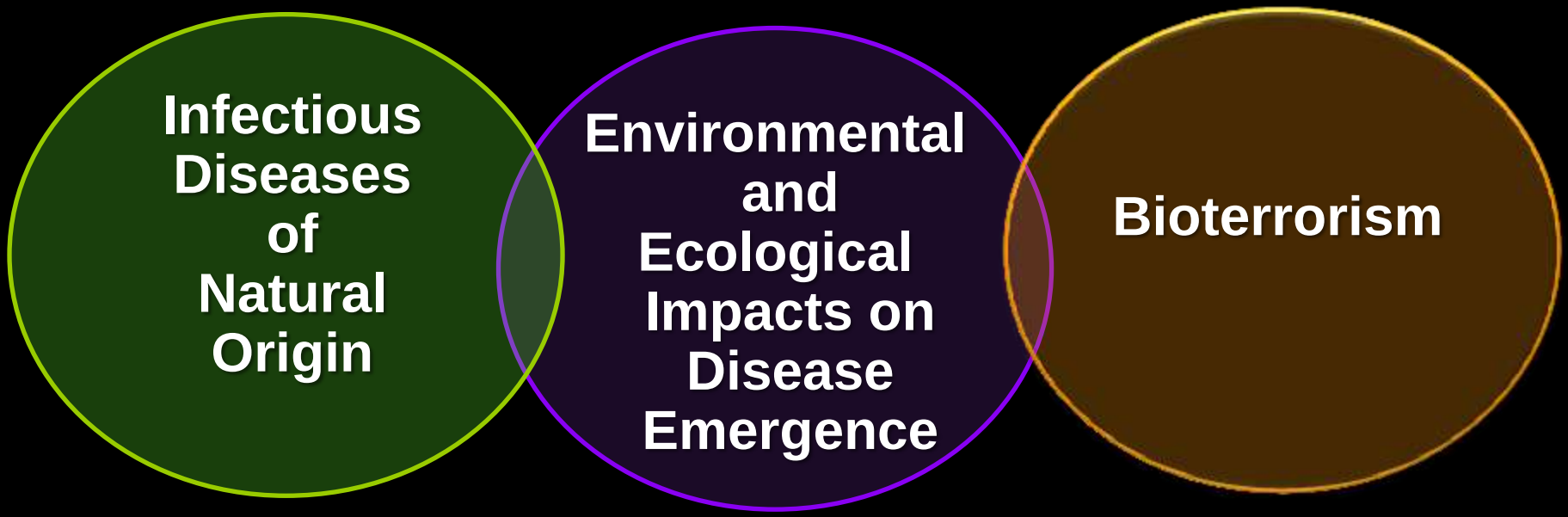


Vaccine Safety:
Media Sensationalism and Celebrity Quackery





Building Resilient and Agile Systems for Biosecurity Planning for the "All Hazards" Challenge



Biosecurity

one health:
humans
animals
ecosystems

urbanization,
environmental
sustainability
and
depletion of
non-renewable
resources

economic
and
political
instabilities
and
escalating
conflict risk

terrorism
and
international
security

**International Engagement,
Commitment and Political Resolve**

Meeting the Challenge(s) Posed by Global Infectious Diseases

- growing threat awareness as catalyst for action
- availability of powerful new genetic and biotechnology capabilities for discovery of diagnostics (Dx), drugs (Rx) and vaccines (Vax)
- building global surveillance networks using advances in sensor technologies, mobile devices, computing and telecommunications
- strengthening national public health and epidemic/pandemic management capabilities
- new financial incentives for R&D on Dx, Rx and Vax
- global political engagement and commitment

"Politics is the art of the possible,
the calculated science of survival"

Prince Otto von Bismarck

"Survival owes little to the art of politics,
but everything to the calculated application
of science".

Professor Rudolph Virchow
(in reply)

Slides available @ http://casi.asu.edu/