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
gorge.poste@asu.edu
www.casi.asu.edu

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

TUBERCULOSIS
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

- growing resistance to existing Rx and vaccines
- new patterns of exposure and disease spread
- emerging infectious diseases (EIDs)
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

Life Sciences, Human and Veterinary Medicine

Materials Science and Engineering

Computing

Electronics, Telecommunications and m.Health

Global Public Health, One Health and Biosecurity
Technology Convergence in the Detection and Control of Infectious and Parasitic Diseases

- Life Sciences, Human and Veterinary Medicine
- Materials Science and Engineering
- Computing
- Electronics, Telecommunications and m.Health
- Global Public Health, One Health and Biosecurity

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

<table>
<thead>
<tr>
<th>High Disease Transmission</th>
<th>Lack of Safe Water</th>
<th>Bush Meat Food Chain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Deficits in Health Infrastructure</td>
<td>Expanded Eco-niches and Increased Zoonotic Risks</td>
<td></td>
</tr>
</tbody>
</table>
The Evolving Nature of Human Infectious and Parasitic Diseases

1407 species of human pathogens

- 538 bacteria
- 57 protozoa
- 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

- 317 fungi
- 287 helminth worms
- 208 viruses
“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
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

- 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)
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 Dilemma 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

<table>
<thead>
<tr>
<th>Anomaly Detection and Early Alert</th>
<th>Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Anomaly Detection Map" /></td>
<td><img src="image2.png" alt="Disease Progression Map" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Satellite Surveillance" /></td>
<td><img src="image4.png" alt="Predictive Modeling" /></td>
</tr>
</tbody>
</table>

## 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)
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
increasing resistance in G+ and G- pathogens in hospital and community settings

the ESKAPE pathogens

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumanii*
- *Pseudomonas aeruginosa*
- *Enterobacter 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)
“Fewer countries have discovered, developed and registered drugs to an international standard, than have developed atomic bombs”

Chris Hentshel
Medicines for Malaria Venture
### Efficacy and Safety of Drugs and Vaccines in Special Populations

<table>
<thead>
<tr>
<th>Children</th>
<th>Pregnant</th>
<th>Aged</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Children Image]</td>
<td>![Pregnant Image]</td>
<td>![Aged Image]</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>Impaired Major Organ Function</td>
<td>ICU-Critical Care</td>
</tr>
<tr>
<td>![Immunosuppressed Image]</td>
<td>![Impaired Major Organ Function Image]</td>
<td>![ICU-Critical Care Image]</td>
</tr>
</tbody>
</table>
Molecular Targets for Antimicrobial Antibiotics

Mechanisms of Antibiotic Resistance and Tolerance

Molecule Screening

http://www.news.pitt.edu/news/molecule-scanner
Big Data in Drug Discovery

Chem2Bio2RDF

Mapping Large Scale Chemoinformatics Space

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

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

- Infectious Diseases of Natural Origin
- Environmental and Ecological Impacts on Disease Emergence
- Bioterrorism
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/