Combating Agent X:
Accelerating Global Vaccine Production Against New Pandemic Threats

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

From ‘Omics to Action: Exponential Medicine 2016 Conference
October 9, 2016
Hotel del Coronado, San Diego
The Social, Economic and Political Impact of Epidemic and Epizootic Disease

- Plague of Athens
- Bubonic Plague
- Small Pox
- Pandemic Influenza
- Foot and Mouth Disease
- Rinderpest
- African Swine Fever
- Rabies
A Decade of New and Resurgent Viral Threats

- SARS-CoV
- MERS-CoV
- West Nile
- Yellow Fever
- Dengue
- Chikungunya
- Ebola
- Zika
Expanded Horizons for Preparedness Against Infectious Disease

- Global connectivities and faster spread
- New technologies: gene editing and synthetic organisms
- Bioterrorism and dual-use technologies
WHAT’S NEXT?
Recognition of the Importance of Zoonotic Diseases as Human Health Threats

- Pandemic (avian) influenza
- HIV
- West Nile virus
- MERS
- Ebola virus
- Bush meat food chain
- Zika virus
- What's out there?
Urbanization and Mega-Cities in Developing Countries and the Increased Threat of Exotic Zoonotic Diseases

High Population Density With Inadequate Biosurveillance

Major Gaps in Health Infrastructure and Disease Reporting

Expanded Eco-niches and New Zoonotic Exposures/Risks
Anthropogenic Effects on Ecosystem Stability and Altered Patterns of Infectious Diseases

- famine
- contaminated water
- desertification
- depletion of natural resources
- climate change and new vector ranges
- new vulnerabilities
Phylogenetic Maps of Viral Evolution
Understanding ‘Drift and Shift’ in Immunogenic Proteins

Influenza Virus

Zika
The Core Triad in Combating Infectious Diseases

- global biosurveillance
- preparedness
- protection

**Threat Spectrum**
- monitoring
- detection
- dynamics

**Robust Public Health Capabilities**
- resources
- training
- infrastructure
- investment

**Counter-Measures**
- drugs
- vaccines
- quarantine/vector control
Ebola in West Africa 2013: Underinvestment and Bureaucratic Sclerosis of International Public Health Responses to New Threats

- **26 December 2013**
  - index case zero
  - Emile Ouamouno (Meliandou, Guinea)

- **21 March 2014**
  - first report by WHO-AFRO region

- **8 August 2014**
  - WHO declaration of Public Health Emergency of International Concern
Notice the Resemblance? 
Hygiene and Quarantine as the Only Protection 
Absent Drugs or Vaccines
Combating Agent X:
Speed Saves Lives

● the imperative for faster detection and accelerated protection counter-measures

● current R&D cycles are too slow to counter global epidemic/pandemic threats
  – diagnostic tests (Dx): 3-12 months
  – vaccines (Vx): 3-10 years
  – therapeutics (Rx) 8-15 years

● the greatest good for the largest number of people
  – production volume and access
  – cost
  – vaccines trump drugs
Limitations and Challenges in Current Vaccine Production

- **Efficacy**
  - Lengthy R&D cycles (years)

- **Safety**

- **Speed**
  - Extended production cycles (months)

- **Scale**

- **Access**
  - Constrained production volumes (millions vs billions for global population of doses)

- **Affordability**

Identification of Immunizing Antigen(s) | Manufacture | Distribution
---|---|---
- Efficacy
- Safety
- Speed
- Scale
- Access
- Affordability
The Three Eras of Vaccine Production

- **Pasteurian Era**
  - intact organisms
    - killed
    - live, attenuated

- **Recombinant DNA Era**
  - rDNA expression/purification of immunizing antigens

- **Engineered Vector Era**
  - live DNA and RNA viral vectors for in vivo expression of immunizing antigens
Combating Agent X: The Urgent Need for Faster, Larger Scale Vaccine Production

Convert 19th Century Pasteurian-Derivative Biological Production Methods to 21st Century Predictive Computational Design and Chemical Synthesis of Immunizing Antigens
Elucidation of the Molecular Design ‘Rules’ for Immune Recognition of Peptides and Proteins

“self”

“non-self”

Vaccinomics: The convergence of microbiology, genomics, immunology, computational analytics and synthetic chemistry
Mapping the Universe of 3-D Protein Structures: Linking Structure and Composition With Immunogenicity
Immune Recognition of Foreign Peptides and Proteins at the Molecular Level: Mapping Epitopes

Immunogenicity of Non-Self Molecules
Recognition of Specific Molecular Domains (epitopes) by the Immune System
Excision and Processing of Epitopes by Dendritic Cells and Presentation to B and T Cells

B lymphocyte antibody-mediated immunity
Cytotoxic T lymphocyte-mediated immunity
The Quest for Pan-Vaccines

- effective against multiple strains of the same virus
  - HIV
  - Influenza
  - Zika
- cross-protection against related viruses
  - dengue, Zika, Chikungunya

A Crucial Clue:

- formation of broad neutralizing antibodies that protect against multiple strains
The Quest for a Universal Influenza Vaccine: Identification of Broad- (Multi-Strain) Neutralizing Antibodies
Overlapping Epitopes in the Hemagglutinin (HA) Stem Domain for Antibodies Neutralizing Group 1 and 2 Influenza A Viruses

From: K. J.L. Jackson and S. D. Boyd (2016) Cell 166, 532
Understanding Commonalities in Epitope Design and Identification of “Rules” for Epitope Recognition by the Immune System

Epitope ‘Design Rules’ as the Foundation For Chemical Production of Synthetic Vaccines

Application of ‘Design Rules’ to Predict Epitopes in Agent X
Complementary In Silico and In Vivo Analysis of Virus Epitopes

- application of large scale computational and machine learning analytics to characterize commonalities in the structure and composition of epitopes in different viruses

- profiling of virus epitope peptides recognized by high affinity antibodies or T cell receptors
Combating Agent X:
Conversion of Vaccine Technology From Biological Production to Synthetic Chemistry

Master Reference Databank of Peptide and Protein Composition, 3-D Structure and Immunogenicity
Large Scale Computational and Machine Intelligence Analytics of Epitope Composition: Structure ‘Rules’ for Immune Recognition

<table>
<thead>
<tr>
<th>Taxonomy of Design Rules for Epitope Recognition</th>
<th>Stimulation of Adaptive Immunity</th>
<th>Stimulation of Autoimmunity and Adverse Events</th>
<th>Non-Immunogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Structure</td>
<td>B Cells</td>
<td>T Cells</td>
</tr>
<tr>
<td>RREDSEGDESLS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RREDSEGDESLS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPPAMGNPK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPPAMGNPK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKAKGKYYC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKAKGKYYC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVTALWCKKN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVTALWCKKN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLVLVPWTQQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLVLVPWTQQ</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Image of table and structures]
Combating Agent X: Predictive Design Rules for Recognition of Foreign Peptides and Proteins by the Immune System

- Identification of structural proteins and strain variation
- Machine learning prediction of most likely immunogenic epitopes
- Assay immunogenic safety/efficacy
Parallel Insights Into Epitope Structure By High Throughput Screening of Antibody Binding to Peptide Arrays
Immunosignatures: Comprehensive Profiling of Antibody Repertoires
Profiling Differential Patterns of Peptide Recognition by Antibodies Elicited by Different Infectious Agents

Known Agent A

Known Agent B

Agent X
Sequencing of Immunosignature Peptides Recognized by High Affinity Antibodies and Synthesis as Candidate Vaccines

**Immunosignature of Agent X**

**Sequence Cognate Peptides**

**Synthesize Cognate Peptides and Assay Immunogenicity**

- TFLCNLGFATLGTGLALWLSLVLAILFSYVYVC
- SFLCLWTSLTVLCTASIETLCLVIAEDLYLAI
- NEXTFLSTLTVLCTASIETLCLVIAEDLYLAI
- RVCLVTLYTVLVMCTAS1VWNLCAISVDYTAIVV
- PFLCWLSMYYASTASIFSVFLCICRRYSVQG
- VVVFVWALYVVSNASVMNLLESFDYCTVE
- NVCLWLSINVASVNLVLSSIFTYCTVE
- VYVCFWSSLTVCTASIWCLVIAEDRYWATD
- LFLCFWSSLTVCTASIWCLVIAEDRYWATD
- GCGLFLACFVVLTVOS1FSLLAIAIDRYAI
- PAVWELLGSMFVALSASVSFLLAIAIDRYAIT
- HAGFTYIAACTYATANAVLAVYLAICT
- NFLDVYVITLYSVWLAFSILASYLAI
- NMTDORLTQTYFESISSLFIILTLRYRAV
- RLYVCLVLSIDYMNFSTFSTLTMSVRYIAVC
- NALCFTYAVIAIDYMNSTFSTLTAMSVRYIAVC
- TFLCKAVLSIDYMNFSTFSTLTMSVRYIAVC
- TFLCKAVLYIDYMNFSTFSTLTAMSVRYIAVC
- TFLCKAVLYIDYMNFSTFSTLTAMSVRYIAVC
- TFLCKAVLYIDYMNFSTFSTLTAMSVRYIAVC
- TFLCKAVLYIDYMNFSTFSTLTAMSVRYIAVC
- TFLCKAVLYIDYMNFSTFSTLTAMSVRYIAVC
- TFLCKAVLYIDYMNFSTFSTLTAMSVRYIAVC
- TFLCKAVLYIDYMNFSTFSTLTAMSVRYIAVC
- TFLCKAVLYIDYMNFSTFSTLTAMSVRYIAVC
Peptide and Protein Engineering for Rational Design and Chemical Synthesis of Vaccines

- cryo-EM technologies for rapid ID of 3-D structure
- backbone scaffolds and self-assembling structures to carry multiple epitopes
- optimize epitope presentation and recognition by MHC/HLA alleles
- incorporate additional peptide domains to stimulate release of immune-enhancing cytokines/lymphokines
The Global Landscape for Infectious and Parasitic Diseases

- society is ill-prepared to combat a novel pandemic threat (Agent X)
- inadequate threat surveillance: “what’s out there”
- major gaps in pandemic preparedness: from faster detection to robust counter-measures and control
- potential expansion of threat spectrum from new gene editing technologies and engineered organisms
- escalating vulnerabilities: “rude shocks await”
Conversion of Vaccine Technology from the Current Pasteurian-Pedigree of Biological Production to Chemical Production of Synthetic Epitope-Based Vaccines

- expand production volume to meet global protection needs
- expand production facilities via use of larger footprint of worldwide chemical facilities
- accelerated response for protection of global population or critical agricultural livestock economies against novel threats
A Philosophy for Robust Preparedness Against Existential Threats

“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)