

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

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The Social, Economic and Political Impact of Epidemic and Epizootic Disease

Plague of Athens

First described in *Greek*,
By *THUCYDIDES*;
Then in *Latin*
By *LUCRETIVS*.
Since attempted in *English*
By the Right Reverend Father in God,
THOMAS Lord Bishop of *Rocheſter*.
London: Printed and Sold by *H. Hills*, in *Black-friars*,
near the *Waterſide*. 1709.

Bubonic Plague



Small Pox



Pandemic Influenza



Foot and Mouth Disease



Rinderpest



African Swine Fever



Rabies



A Decade of New and Resurgent Viral Threats

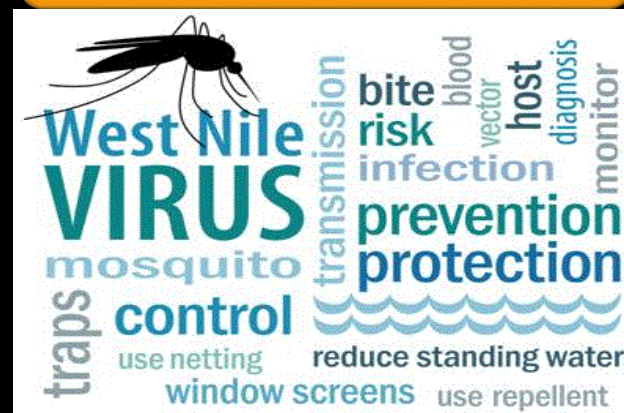
SARS-CoV



MERS-CoV



West Nile



Yellow Fever



Dengue



Chikungunya



Ebola



Zika

Expanded Horizons for Preparedness Against Infectious Disease

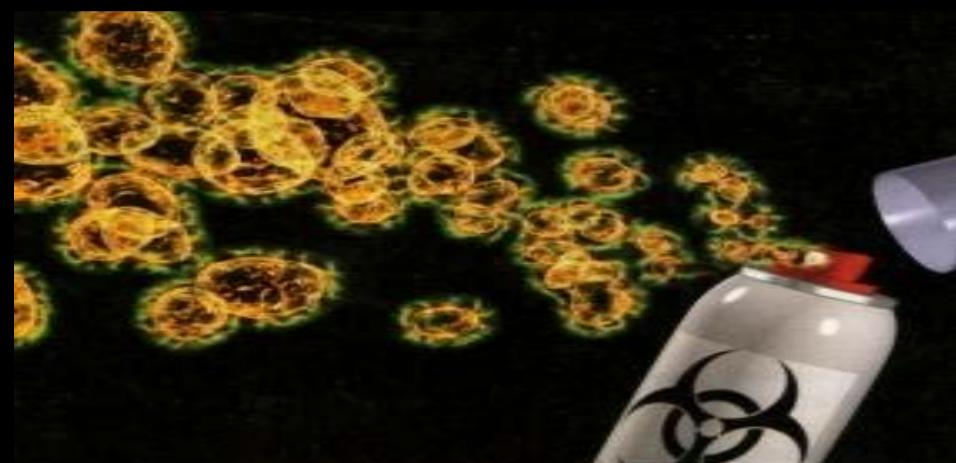
**global connectivities
and faster spread**



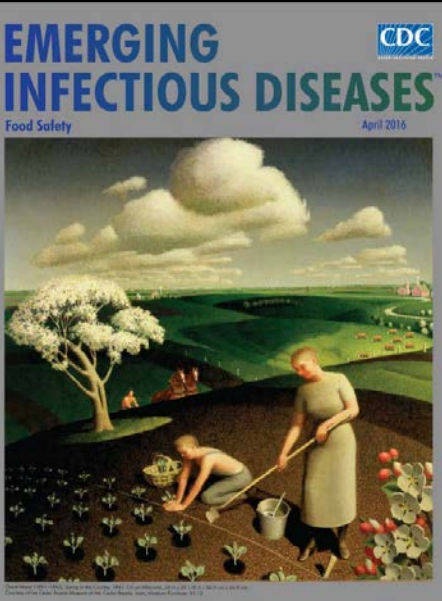
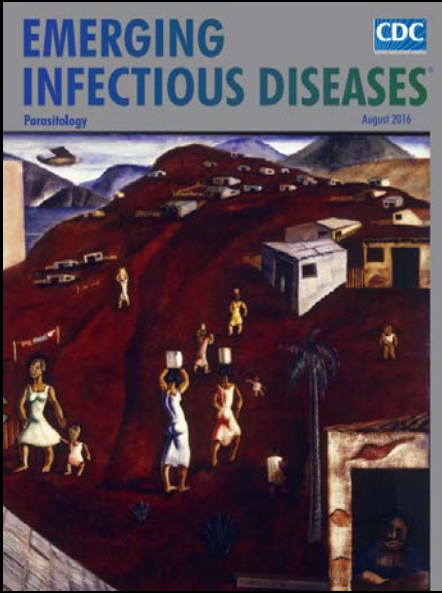
**new technologies: gene editing
and synthetic organisms**



**bioterrorism and
dual-use technologies**



WHAT'S NEXT?



Enteroviruses D68, A71

Crimean-Congo
Hemorrhagic Fever

Hantavirus

Hepatitis E

Marburg

Rift Valley
Fever

Lassa Fever

Arenaviruses

Parechovirus

Japanese
Encephalitis

Lujo Virus

Pegivirus

O'nyong-Nyong

Monkeypox

Poliovirus

Norovirus

Mayaro
Virus

Henipavirus

Measles

Polyoma Virus

Venezuelan Equine
Encephalitis

Chatanga Virus

Senecavirus A

Phleboviruses

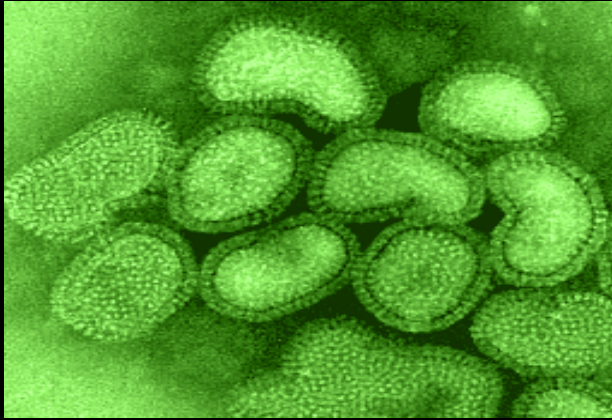
Bunyaviruses

Inkoo Virus

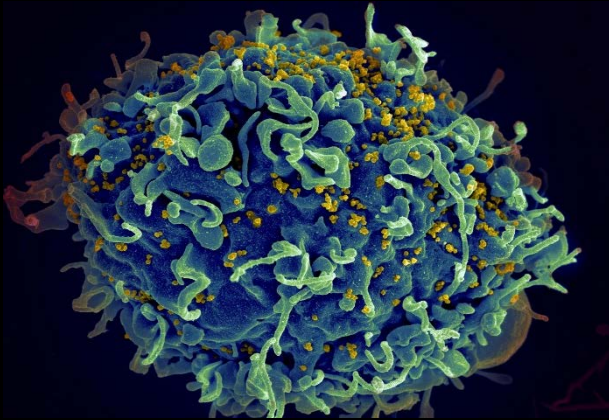
Thogotovirus

Recognition of the Importance of Zoonotic Diseases as Human Health Threats

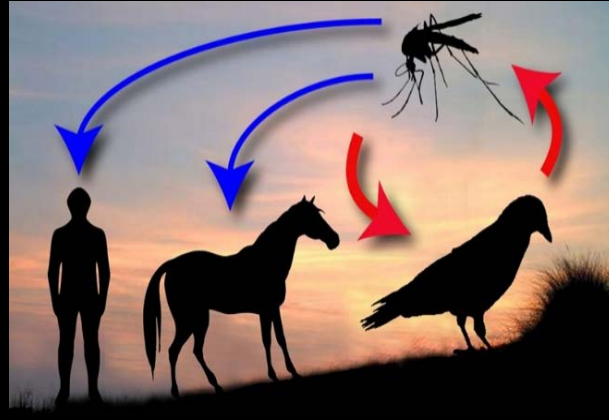
**pandemic (avian)
influenza**



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



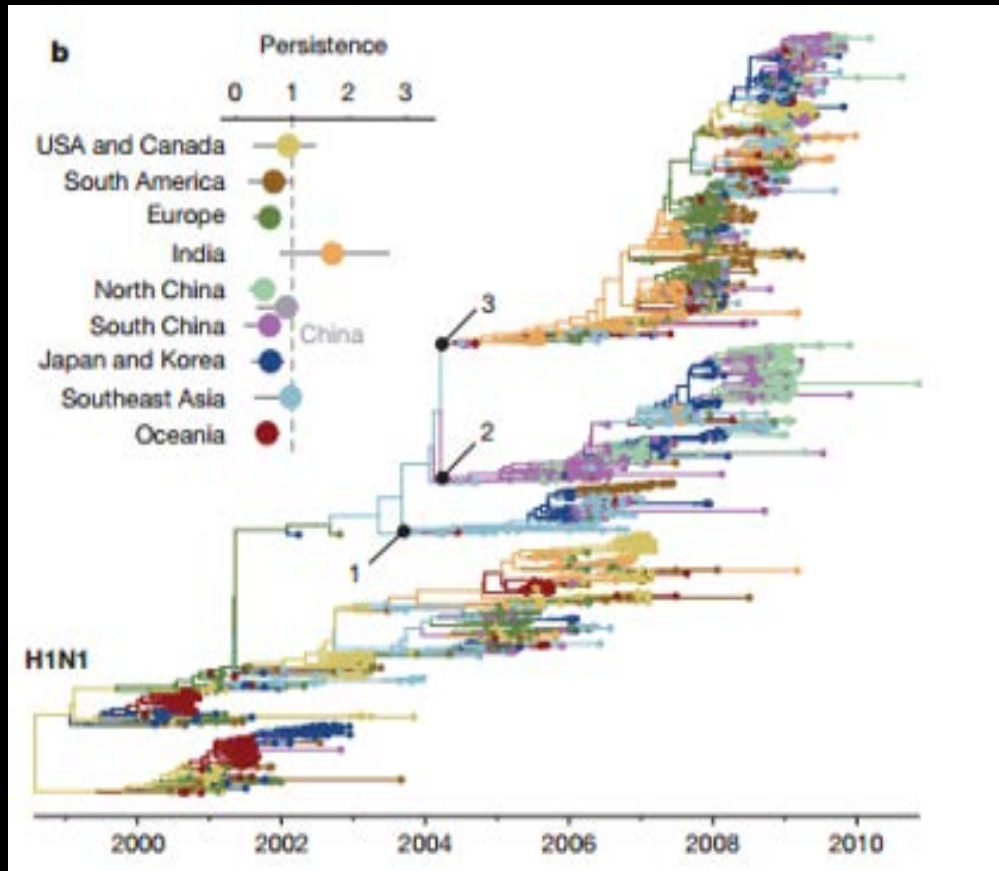
**climate change and
new vector ranges**



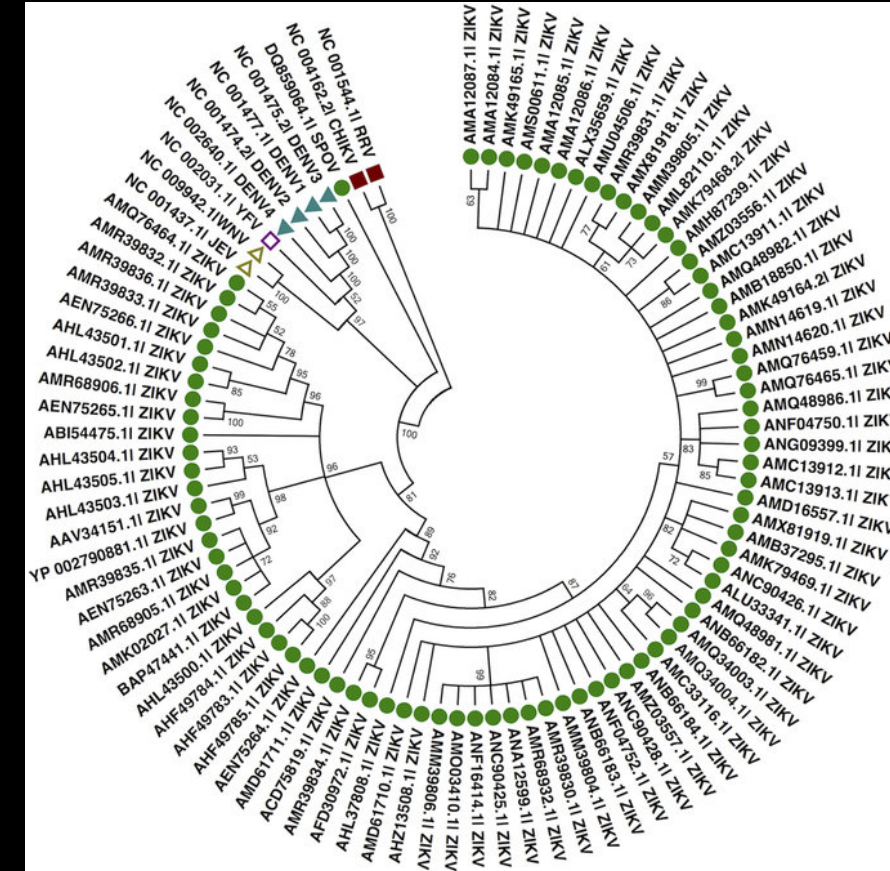
new vulnerabilities

Phylogenetic Maps of Viral Evolution

Understanding 'Drift and Shift' in Immunogenic Proteins



Influenza Virus



Zika

The Core Triad in Combating Infectious Diseases



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

**Bubonic Plague
Physician 15th Century**



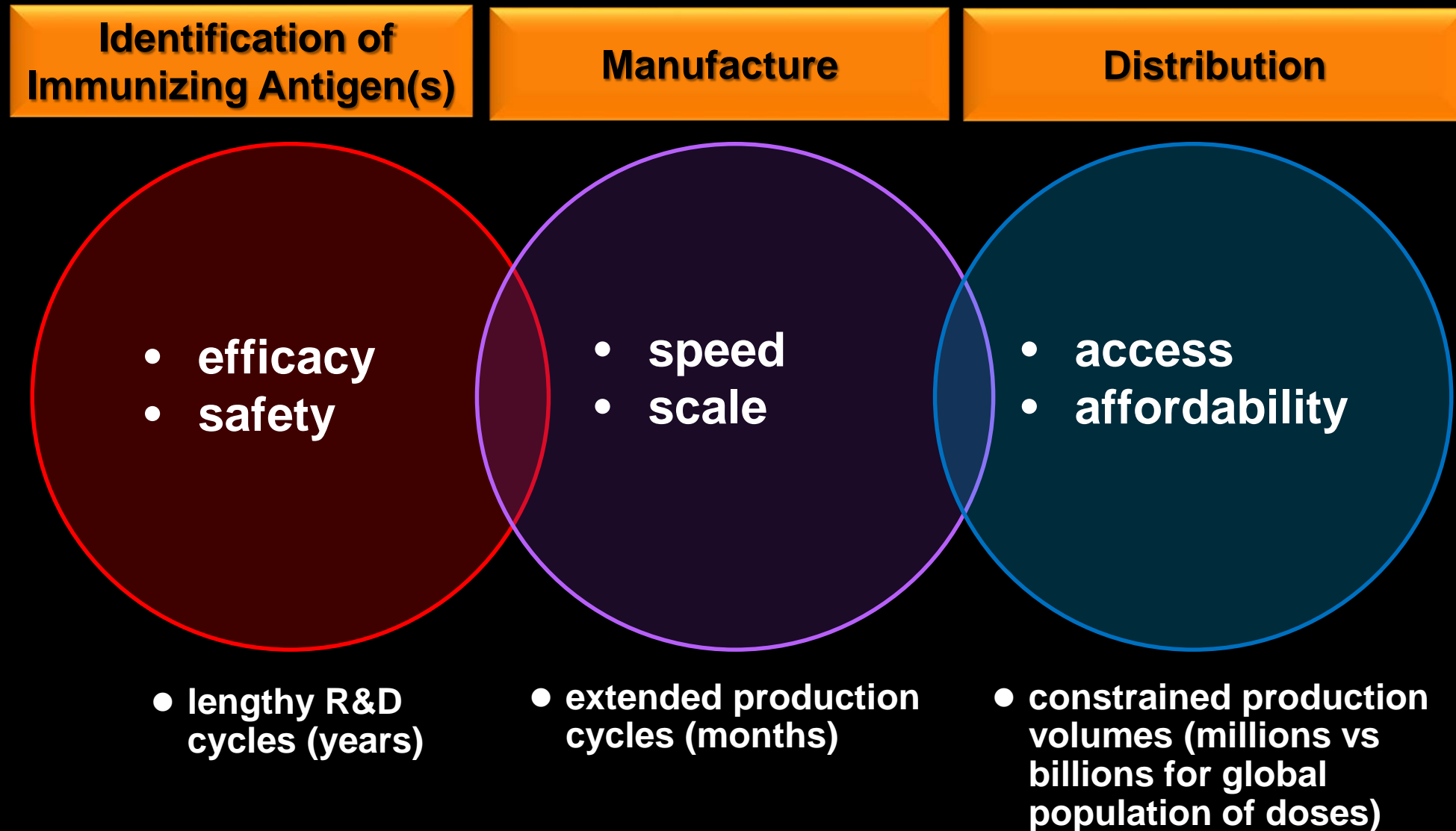
**Ebola, Liberia
21st Century**



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



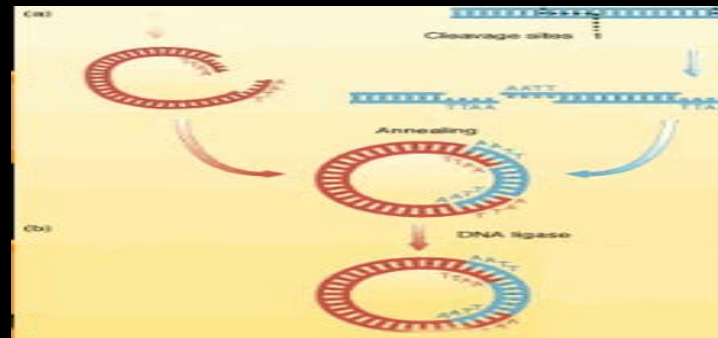
The Three Eras of Vaccine Production

Pasteurian Era



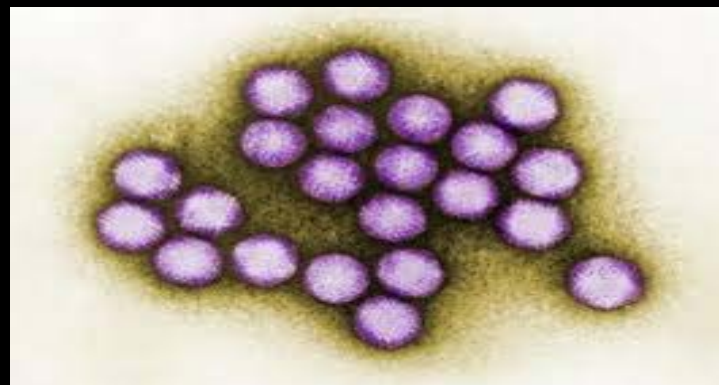
- intact organisms
 - killed
 - live, attenuated

Recombinant DNA Era



- rDNA expression/
purification of
immunizing antigens

Engineered Vector Era

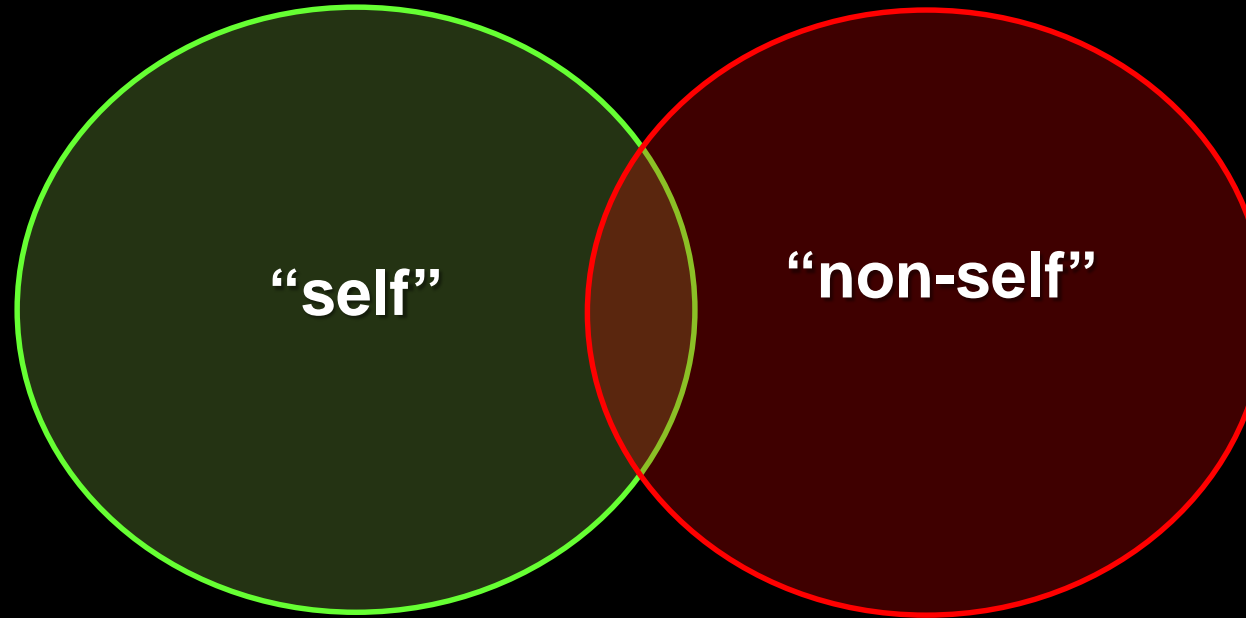


- live DNA and RNA viral
vectors for in vivo
expression of
immunizing antigens

Combating Agent X: The Urgent Need for Faster, Larger Scale Vaccine Production

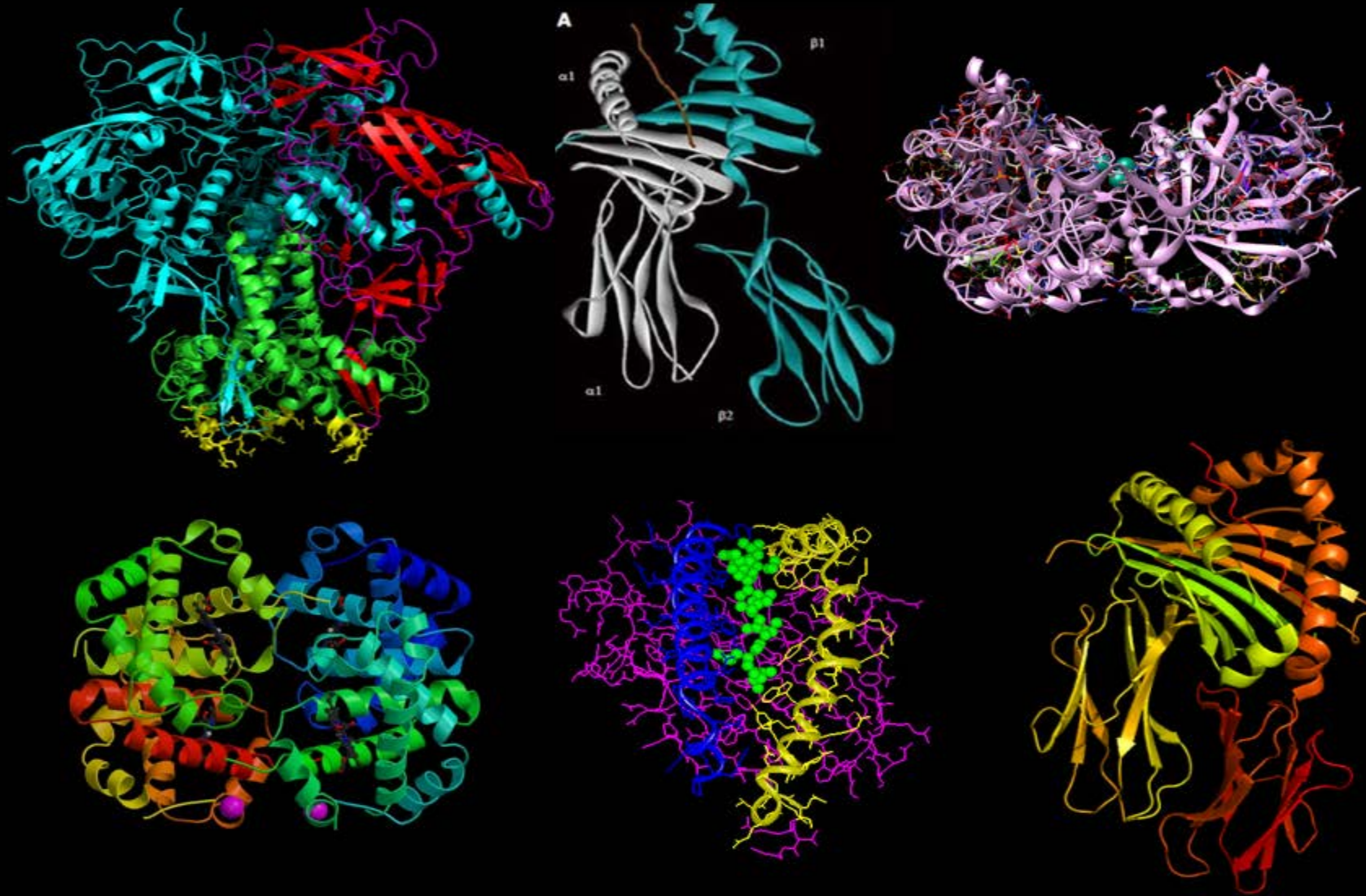
**Convert 19th Century Pasteurian-Derivative
Biological Production Methods
to
21st Century Predictive Computational Design
and Chemical Synthesis of Immunizing Antigens**

Elucidation of the Molecular Design 'Rules' for Immune Recognition of Peptides and Proteins

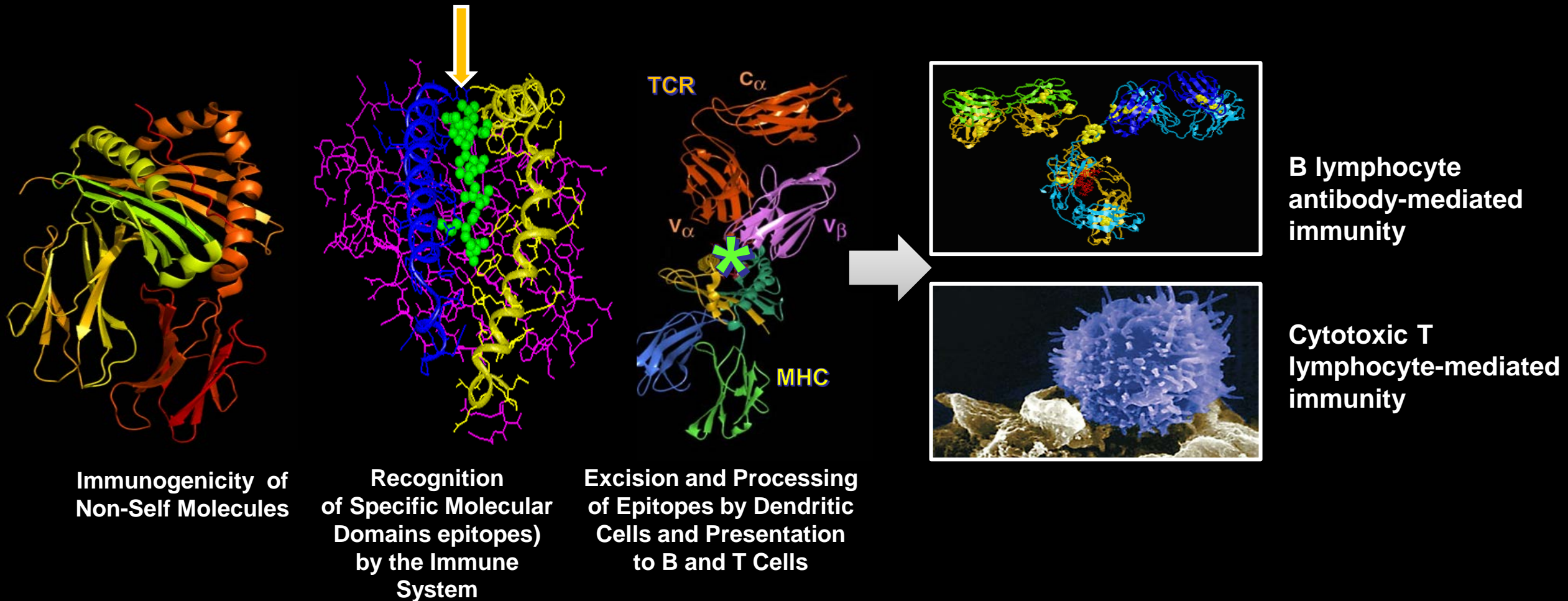


Vaccinomics:
The convergence of microbiology, genomics,
immunology, computational analytics and synthetic chemistry

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



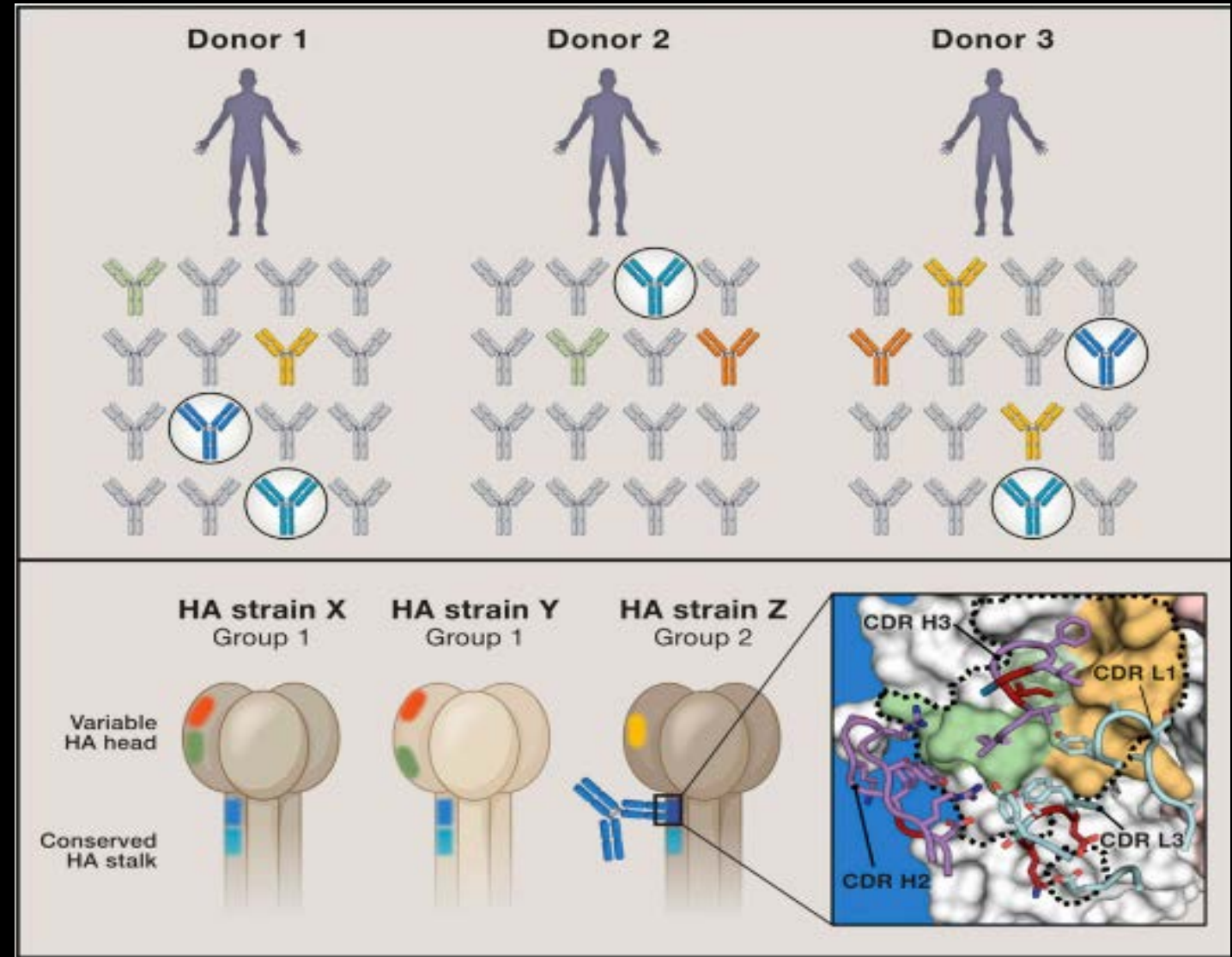
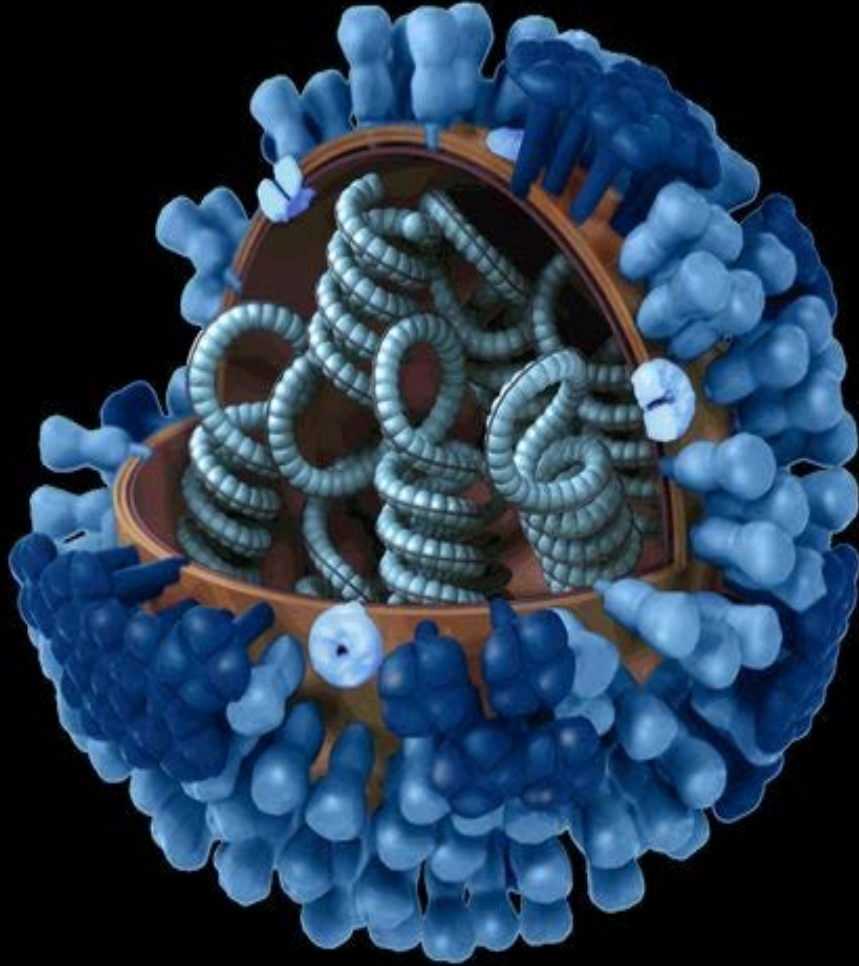
The Quest for Pan-Vaccines

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

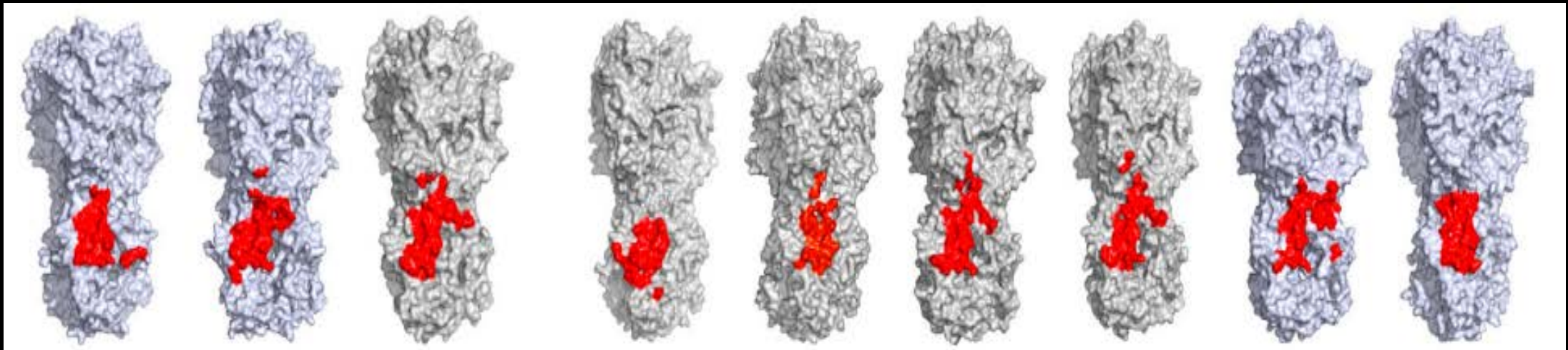
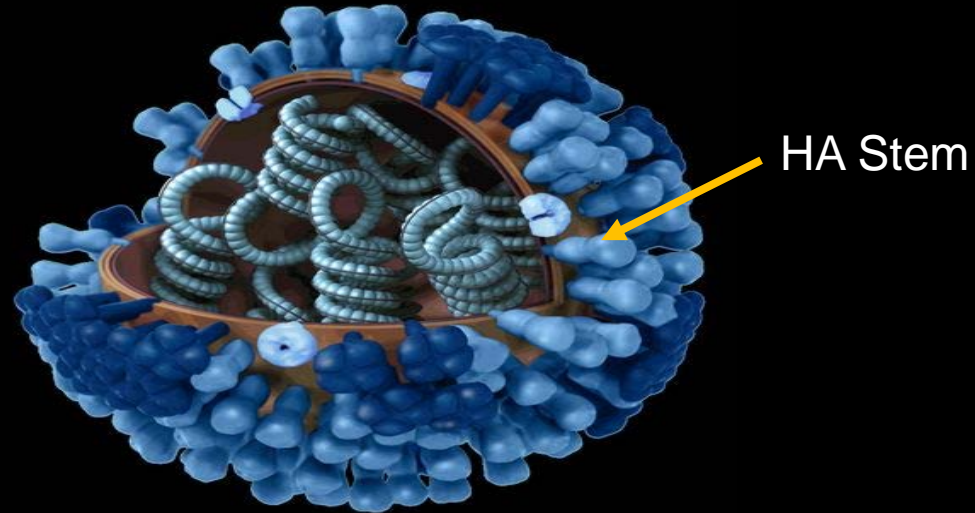
A Crucial Clue:

- **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



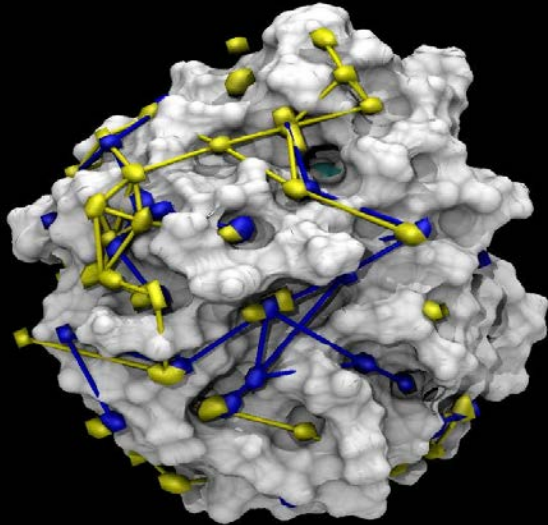
From: K. J.L. Jackson and S. D. Boyd (2016) Cell 166, 532

**Understanding Commonalities in Epitope Design and
Identification of “Rules” for Epitope Recognition by
the Immune System**

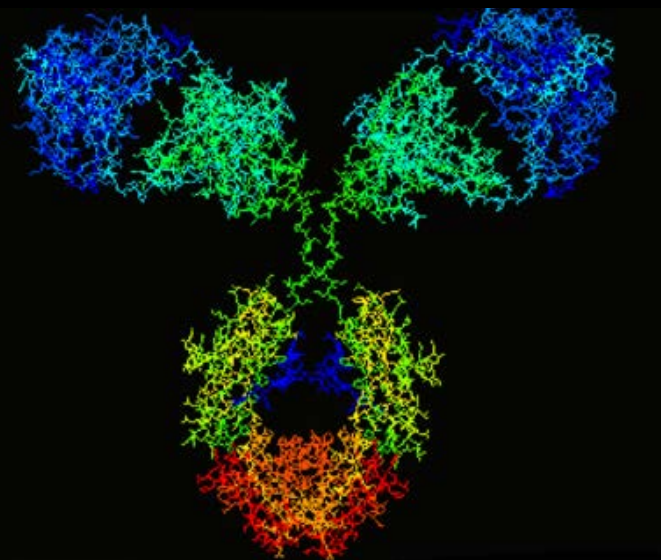
**Epitope ‘Design Rules’ as the Foundation
For Chemical Production of Synthetic Vaccines**

Application of ‘Design Rules’ to Predict Epitopes in Agent X

Complementary In Silico and In Vivo Analysis of Virus Epitopes



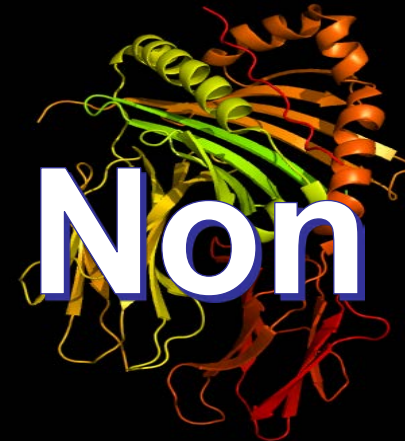
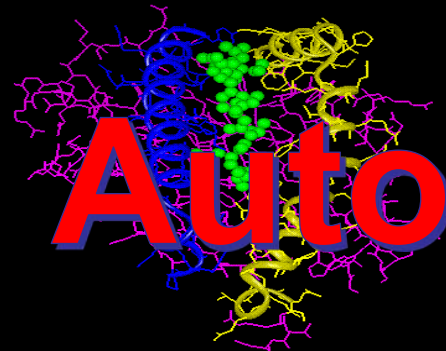
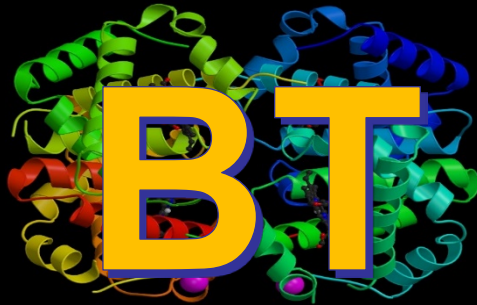
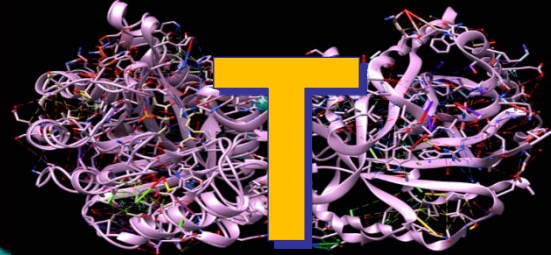
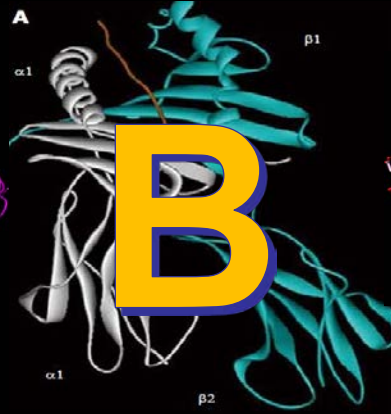
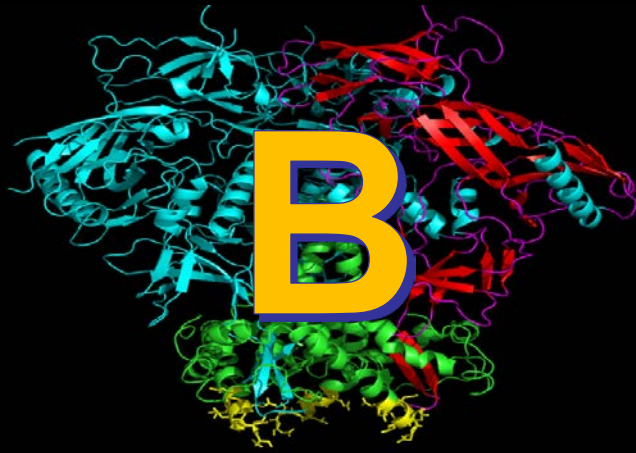
- application of large scale computational and machine learning analytics to characterize commonalities in the structure and composition of epitopes in different viruses



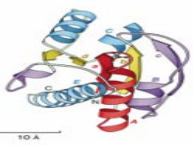


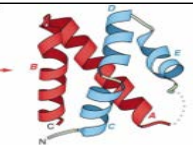




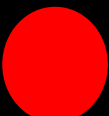


- profiling of virus epitope peptides recognized by high affinity antibodies or T cell receptors

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

Taxonomy of Design Rules for Epitope Recognition		Stimulation of Adaptive Immunity		Stimulation of Autoimmunity and Adverse Events	Non-Immunogenic
Composition	Structure	B Cells	T Cells		
<div><div>RFFDSFGDLS</div><div>RFFDSFGDLS</div><div>RFFESFGDLS</div><div>RFFESFGDLS</div><div>RFFESFGDLS</div></div>					
<div><div>SPDAVMGNPK</div><div>SPDAVMGNPK</div><div>SPDAVMGNPK</div><div>TPDAVMGNPK</div><div>TADAVMNNPK</div></div>					
<div><div>VKAHGKKVLN</div><div>VKAHGKKVLN</div><div>VKAHGKKVLG</div><div>VKAHGKKVLG</div><div>VKAHGSKVLN</div></div>					
<div><div>AVTALWGKVN</div><div>AVTALWGKVN</div><div>AVTTLWGKVN</div><div>AVTALWGKVN</div><div>AVHGLWSKVK</div></div>					
<div><div>RLLVVYPWTQ</div><div>RLLVVYPWTQ</div><div>RLLVVYPWTQ</div><div>RLLVVYPWTQ</div><div>RLLVVYPWTQ</div></div>					

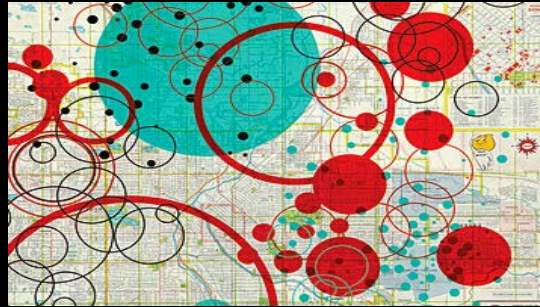
Combating Agent X: Predictive Design Rules for Recognition of Foreign Peptides and Proteins by the Immune System

Agent X
Genome
Sequence



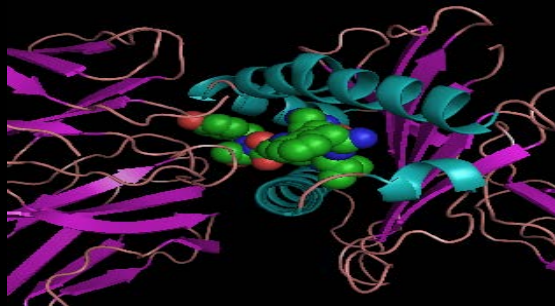
- identification of structural proteins and strain variation

Agent X
Proteome



- machine learning prediction of most likely immunogenic epitopes

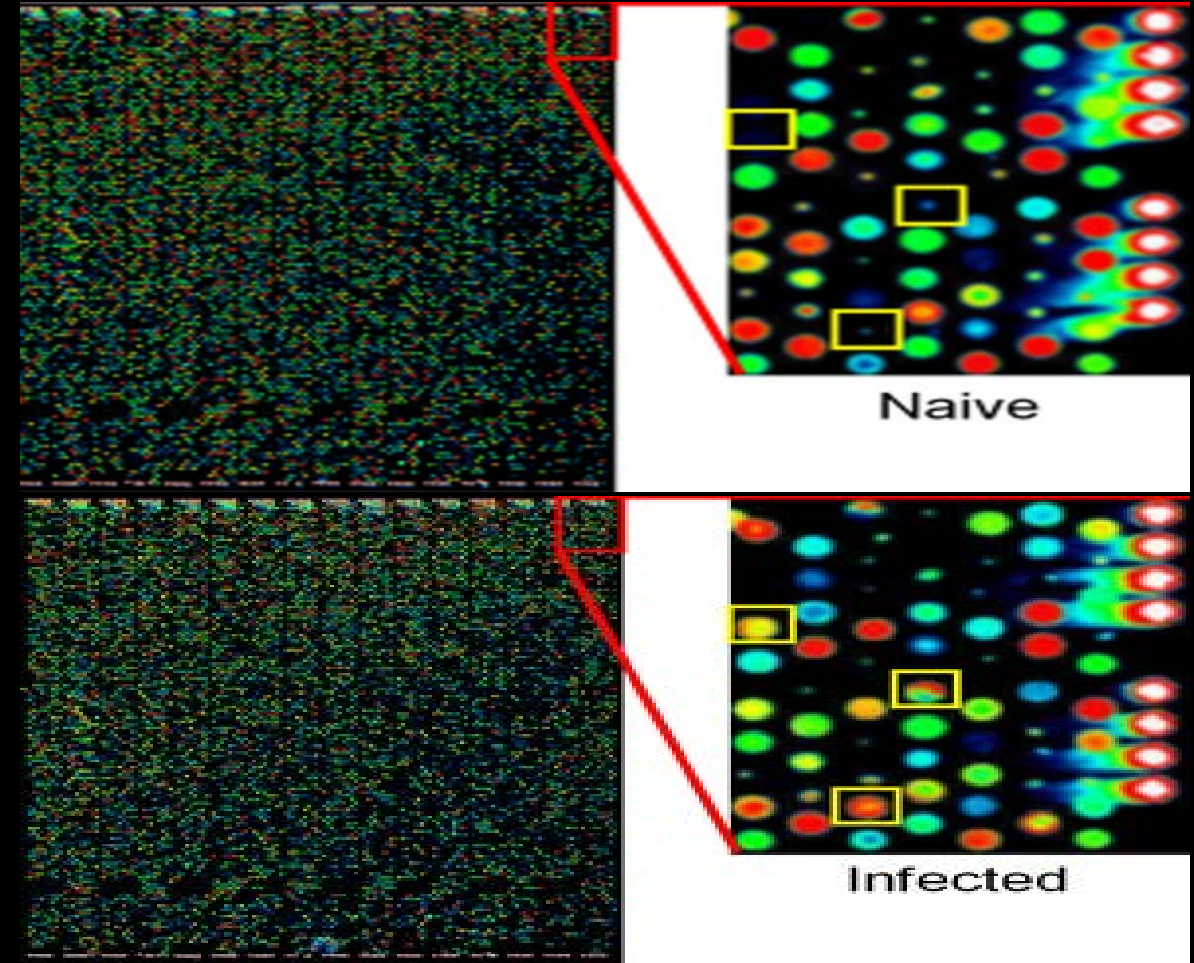
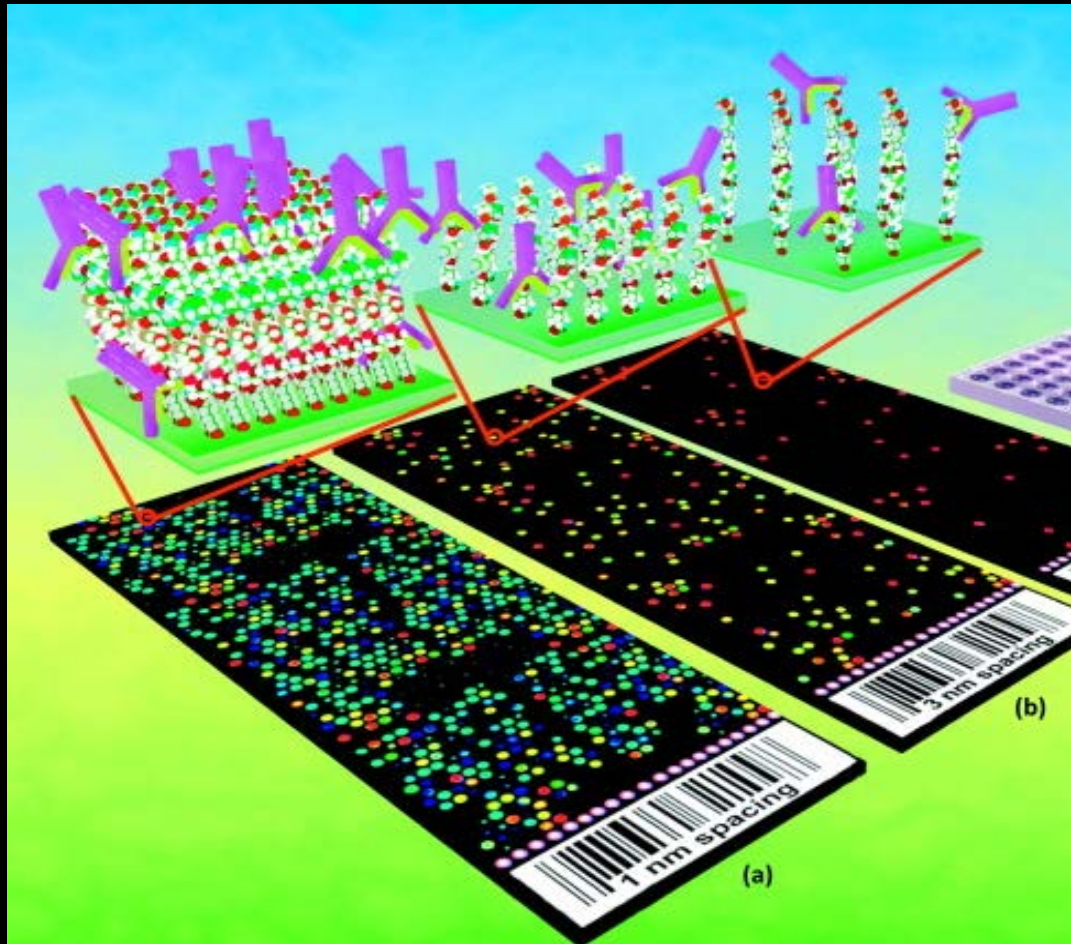
Chemical
Synthesis of
Candidate
Vaccine Epitopes



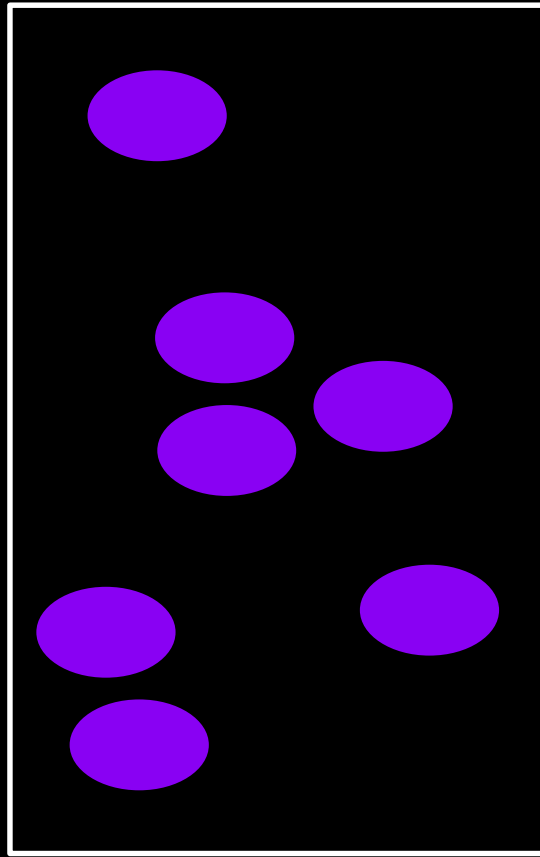
- assay immunogenic safety/efficacy

**Parallel Insights Into Epitope Structure By High Throughput
Screening of Antibody Binding to Peptide Arrays**

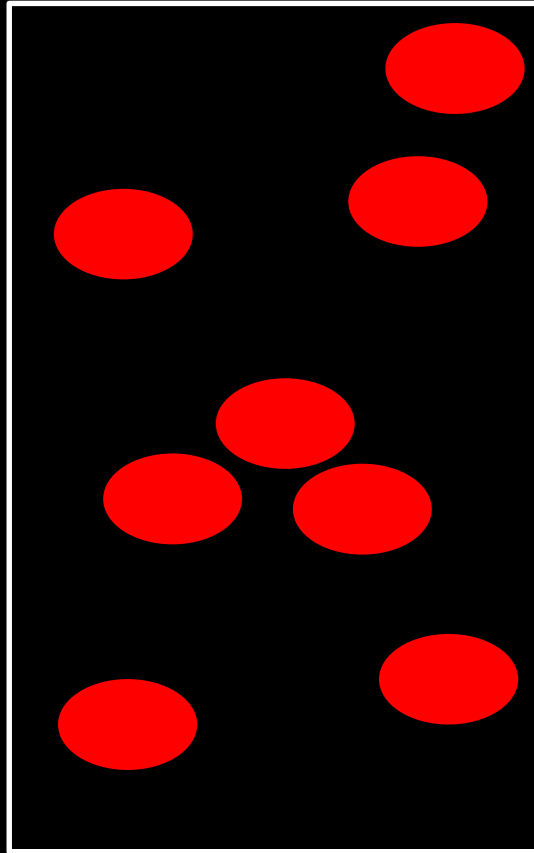
Immunosignatures: Comprehensive Profiling of Antibody Repertoires



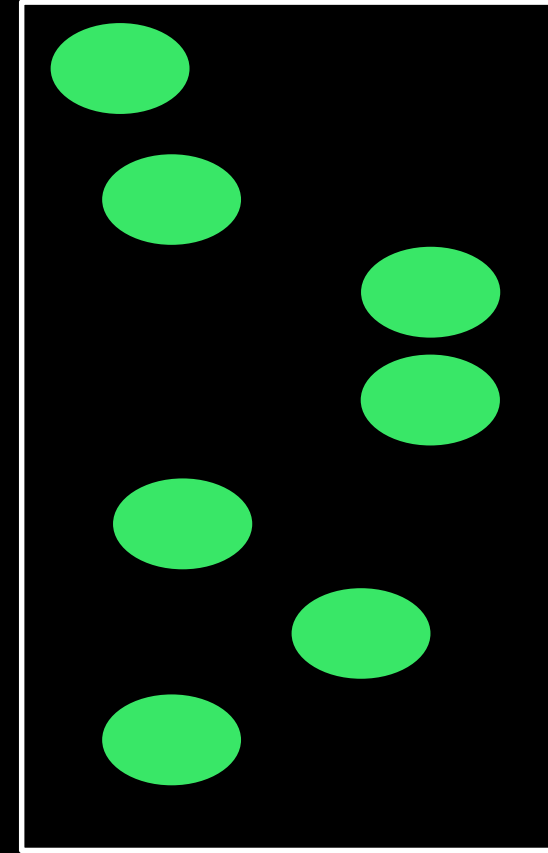
Profiling Differential Patterns of Peptide Recognition by Antibodies Elicited by Different Infectious Agents



Known
Agent A



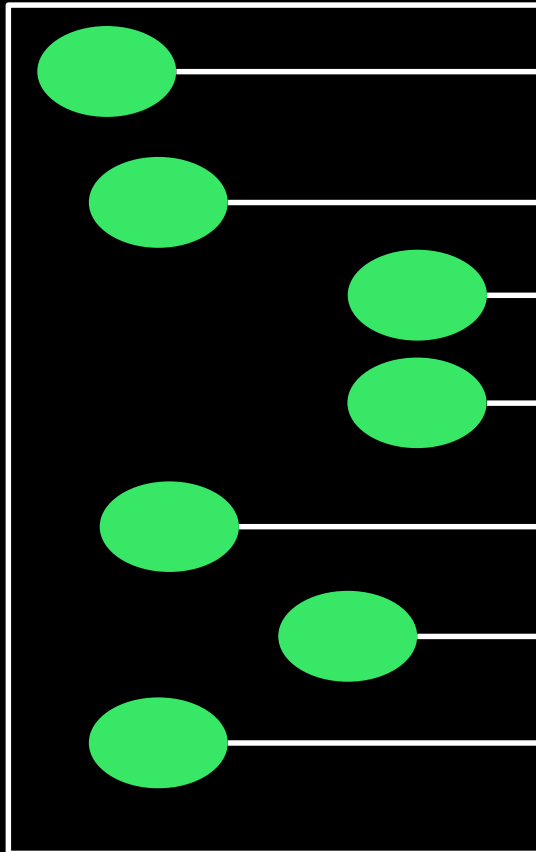
Known
Agent B



Agent X

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

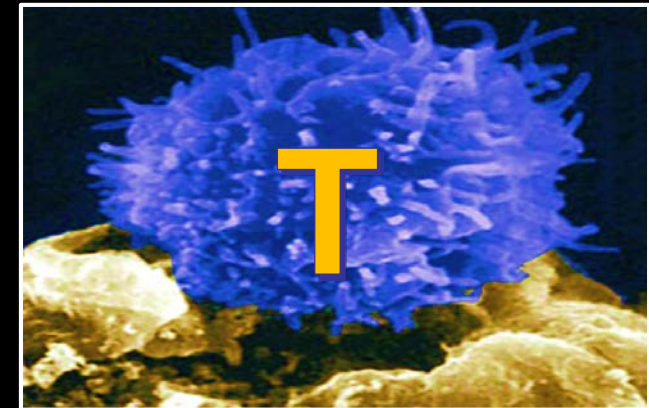
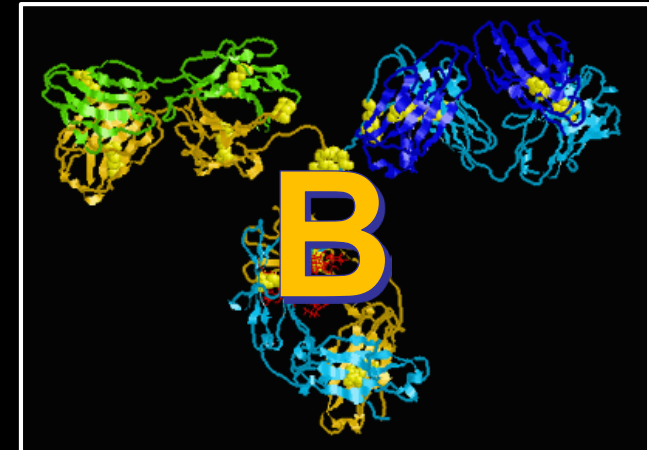
Immunosignature
of Agent X



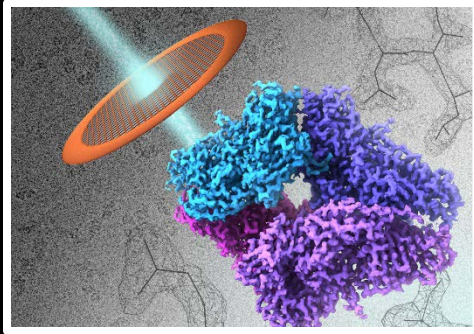
Sequence Cognate
Peptides

PTGCNLEGFATLGGEIALWSLVVLAIERVYVVCK
SFLCELWTSIDVLCVTASIEETLCVIAIDRYLAITS
NFWCEFWTSIDVLCVTASIEETLCVIAVDYFAITS
RICCDVFVTLVMMCTASIWNLCAISIDRYTAVVM
RPLCLFWLSMDYVASTASIFSVFILCIDRYRSVQ
PVVCILWLALDYVVSNASVMNLLISFDYFCVT
NLACDLWLSIDYVVSNASVMNLLVVSFDYFYSITR
QVVCDFWLSIDITCCTASIWHLCAIALDRIYWAITD
LYLCRAWLEIDVLFSTASIWHLCAISVDRIYIAIKK
CHGCLFIACFVLVLTQSSIFSLAIAIDRIYIAIRI
PAQWFLRECSMFVALSASVFSLLAIAIERYITMLK
TAACRCYYEIRDACTYATALNVASLSVARYLAICH
NFLCKAVHVIYTVNLYSSVWILAFISLDRIYLAIVH
NTMCQLLTGLYFICFFSIFFFIILLTIDRIYLAVVH
DVLCIKIVLSIDYYNMFTSIFTLTMMMSVDRIYAVCH
NIILCKIVISIDYYNMFTSIFTLTCTMSVDRIYAVCH
NALCKTVIAIDYYNMFTSTFTLTAMSVDRYVAICH
ELLCKAVLSIDYYNMFTSIFTLTMMMSVDRIYAVCH
SELCREVTAAFYCNMYASILLMTVISIDRFLAVVY
TFVCQVTSVIFYFTMYISISFLGLITIDRYQKTTT
VGWCRLVTAAYNYFHVNTFFWMFGCCYLHTAIVL
VAGCRVAAVEMQYGVANYCWLLVGLYLHNLLGL
TTSCYLQRLLVGLSSAMCYSALVTKTNRRIARILAG
QIYCYLQRIGIGLSPAMSYALVTKYRAARILAM
TLSCVIFVIVVYALMAGVVWFEVLTAWHTSEKA

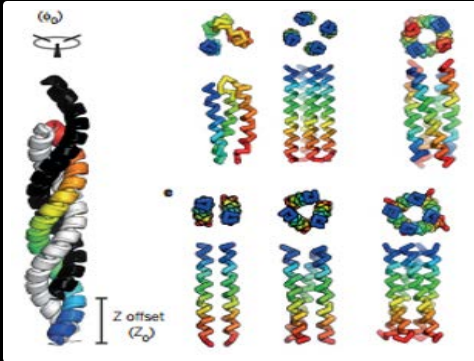
Synthesize Cognate
Peptides and
Assay Immunogenicity



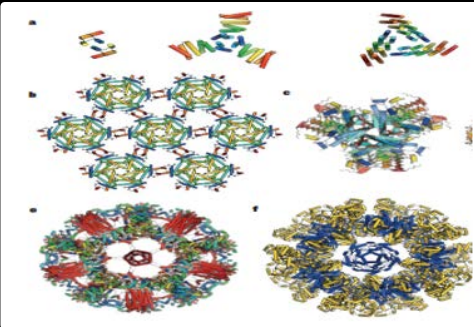
Peptide and Protein Engineering for Rational Design and Chemical Synthesis of Vaccines



- 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)**
- **comfort and complacency: “out-of-sight: out-of-mind”**
- **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)**

