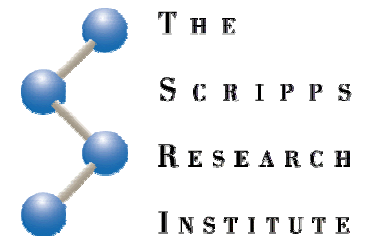




Project Checkmate

The Scripps Research Institute & IBM
Institutional Consortium



Ajay Royyuru
Computational Biology Center
IBM Research
ajayr@us.ibm.com

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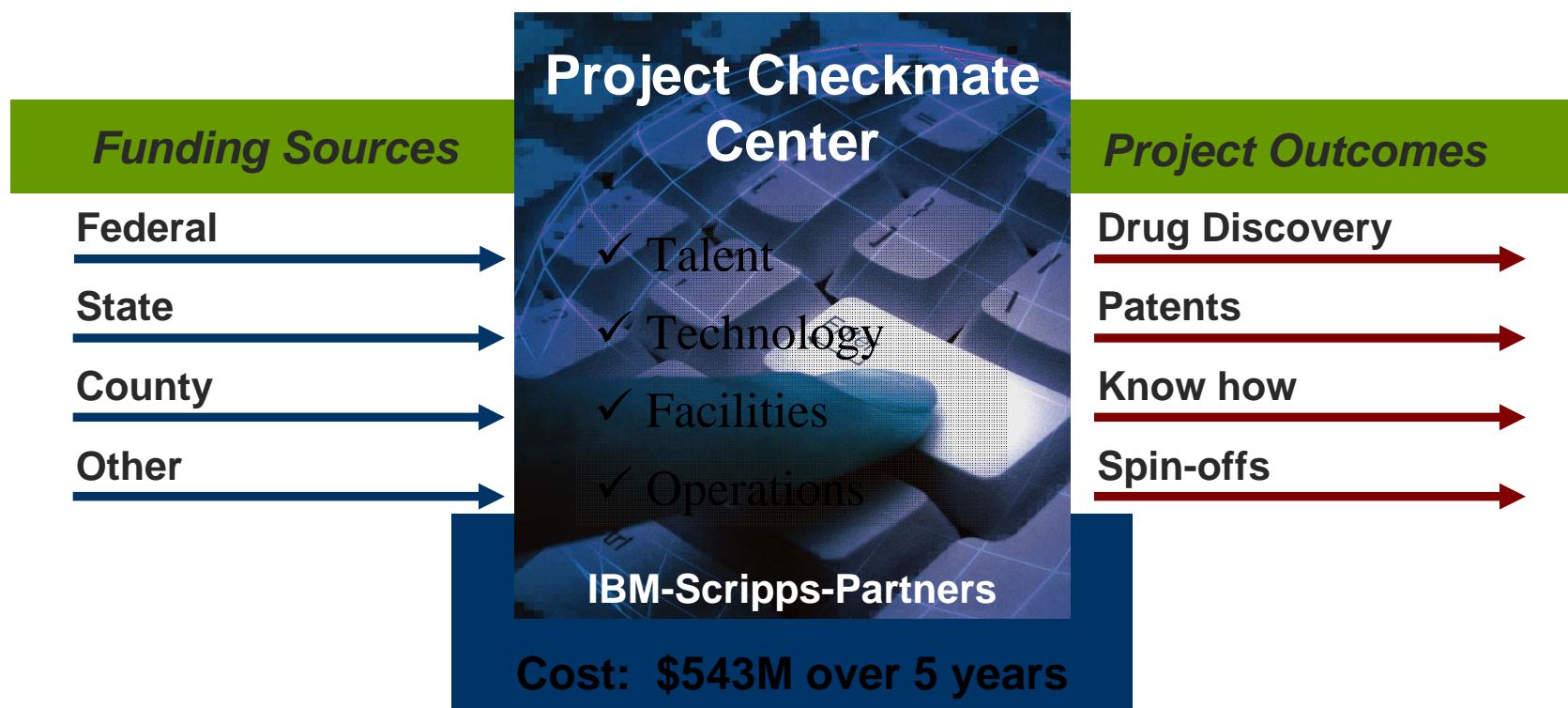
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Background

Date	Event
November 2005	President Bush announces National Strategy for Pandemic Influenza
December 2005	IBM and TSRI evaluate combining expertise to support the federal strategy for the pandemic threat
February 2006	IBM and TSRI announce collaborative initiative called Project Checkmate
April 2006	Inaugural meeting of Project Checkmate scientists
May 2006	IBM announces global pandemic initiative
June/July 2006	Project Checkmate introduced to county and state officials
August 2006	Initial meeting with Chief Scientist at Office of Public Health and Emergency Preparedness
September 2006	Initial Meeting with Director NIAID
October 2006	Meeting with Special Assistant to the President for Biodefense White House Homeland Security Council

Project Checkmate business model

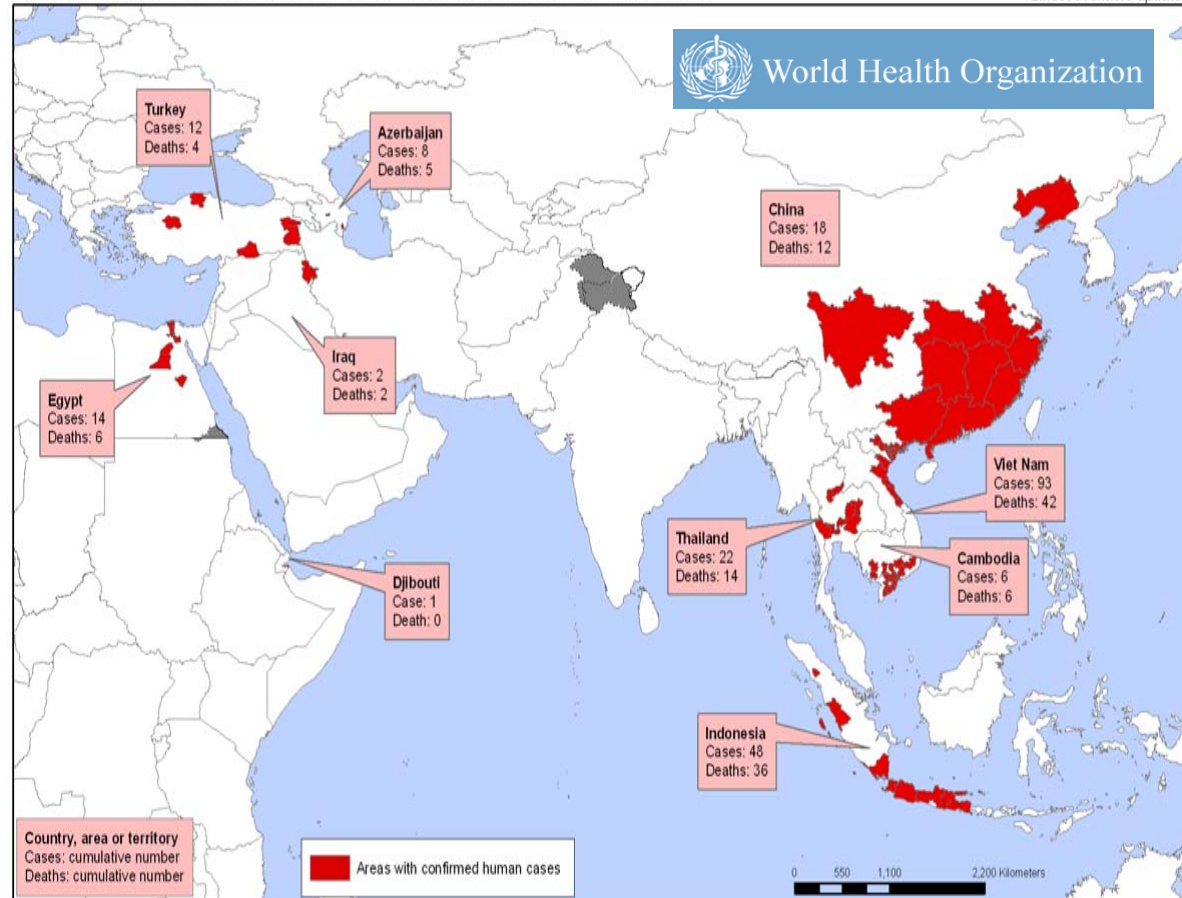
- Project specific funding for Avian Influenza
- IBM/Scripps partnership model
 - Joint funding request, research, intellectual capital & go-to-market plan
- Scripps ownership of technology
 - IBM solution partner; build, operate, maintain



Avian Influenza: The next Pandemic Flu?

Affected areas with confirmed human cases of H5N1 avian influenza since 2003

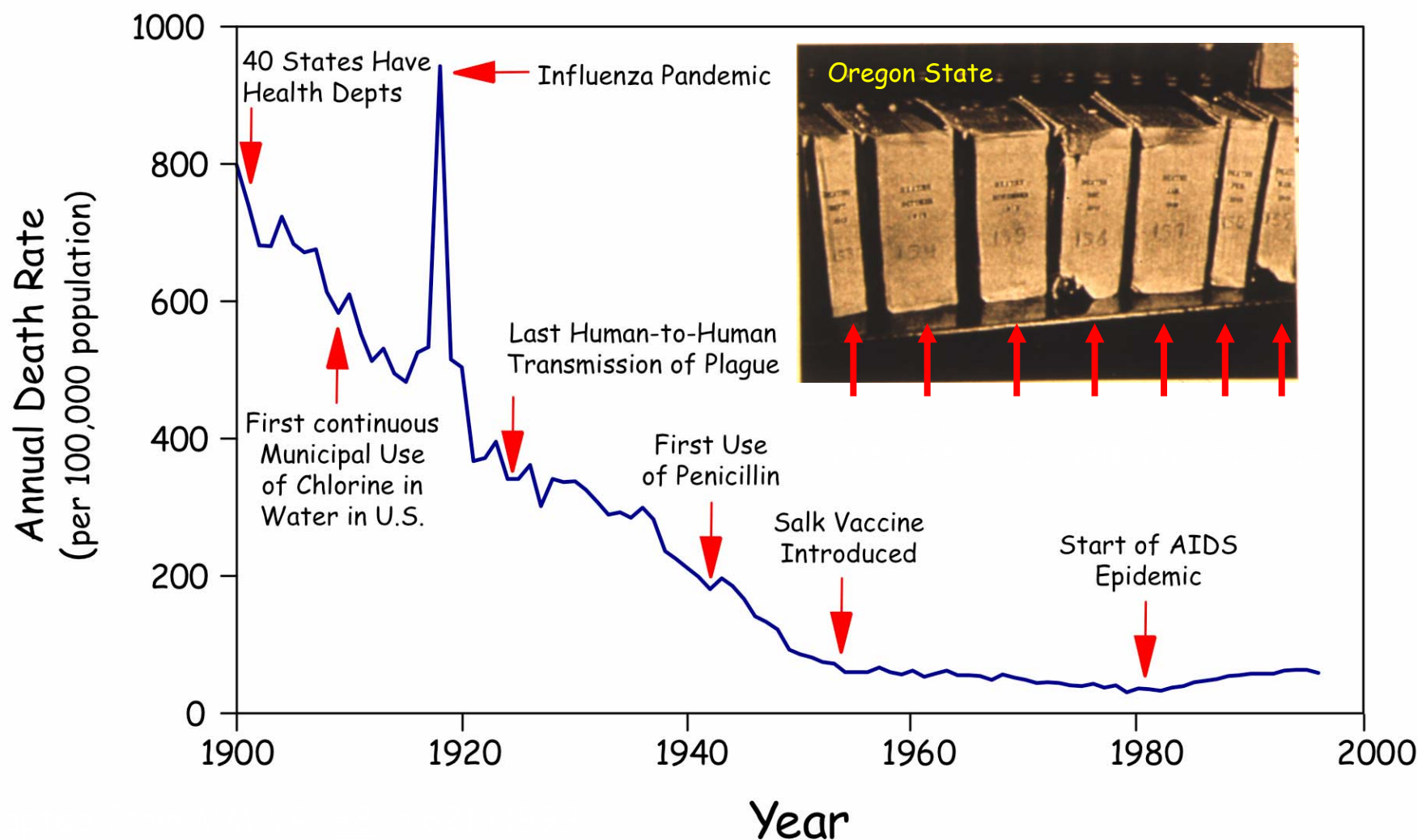
Status as of 30 May 2006
Latest available update



Pandemic Influenza: Critical Issues

1. The world is on the brink of a pandemic influenza due to the threat from H5N1 Avian Influenza
2. Widespread illness and death rates will occur due to inadequate vaccines & antiviral drugs
3. International economic and social disruption will occur
4. June 2006 - World Health Organization reports 225 human cases of avian influenza; 128 were fatal

Crude Death Rate for Infectious Diseases 1900-2000



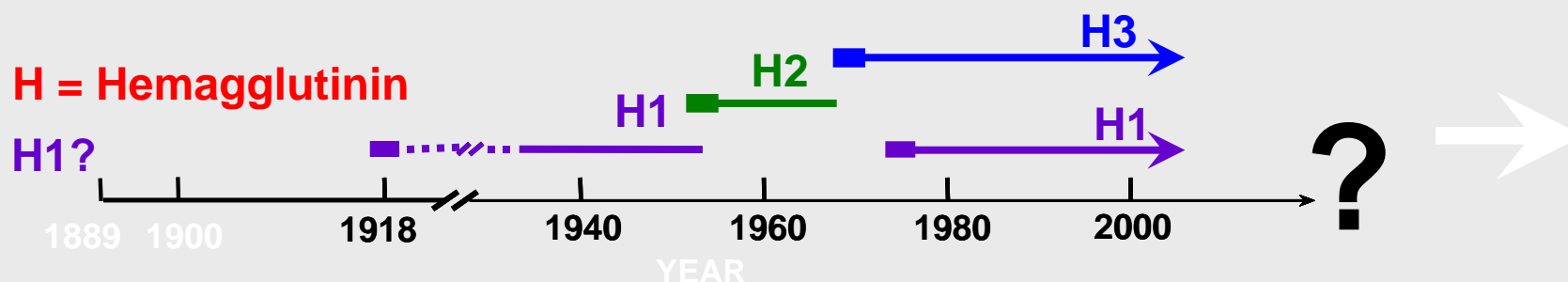
National Strategy for Pandemic Influenza is reactive

Challenges addressed by current US Pandemic Influenza Implementation Plan:

- **Detect** major disease pathogens
- **React** to real time outbreak detection
- **Contain** disease spread, collaborating with public health agencies

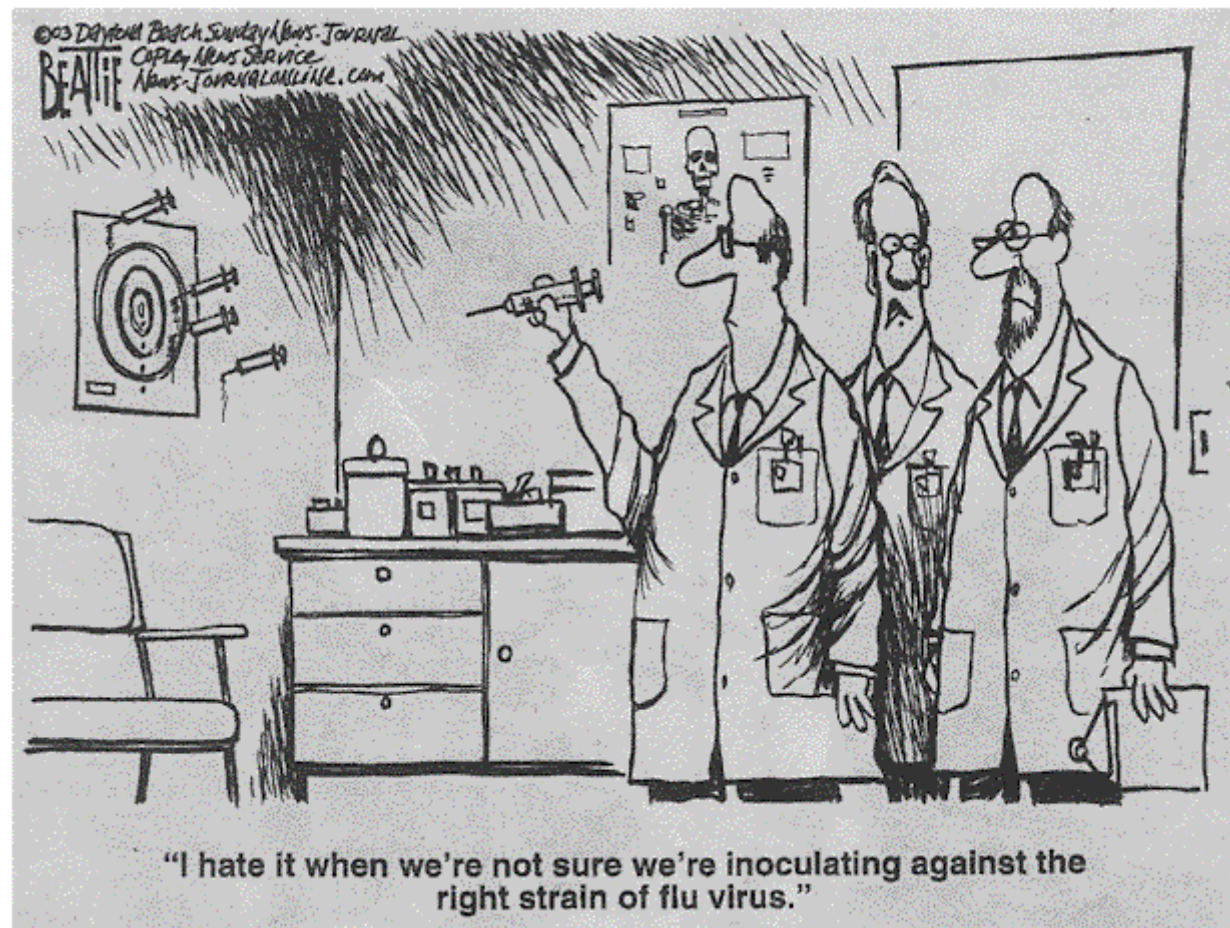
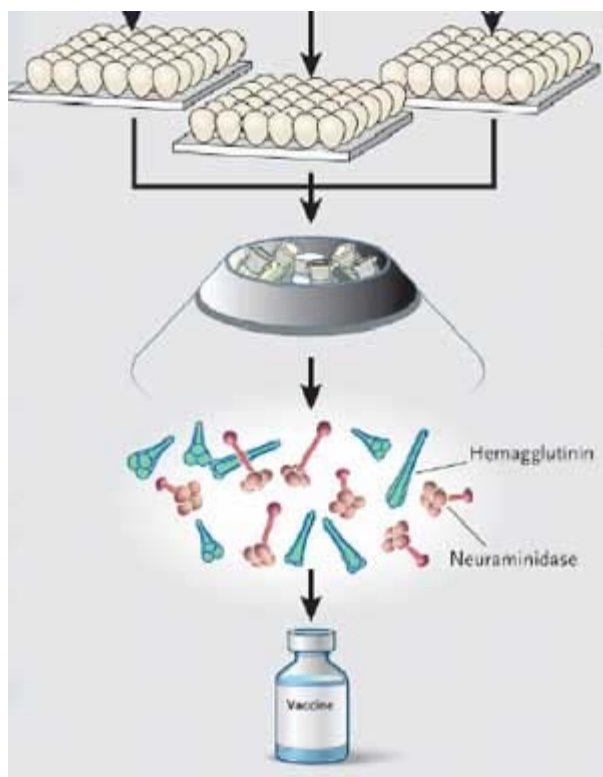
However...
rapid virus evolution makes any pandemic plan a reactive challenge and vaccination efforts difficult

Evolution of Influenza A Virus Subtypes in the Human Population



- Evolving virus strains are more aggressive and tolerant
- Vaccines may become ineffective unless you stay ahead of the strain

Influenza Vaccine Development



Project Checkmate secures the missing link for a proactive plan

Project Checkmate changes focus from reactive disease control to proactive pandemic prevention

By partnering the world's best research science & supercomputing technology, Project Checkmate provides a means to:

- **Anticipate** genetic variation and disease evolution to develop effective vaccines
- **Develop** prophylactics and therapeutics for potential future pandemics
- **Apply** this strategy to other emerging infectious diseases

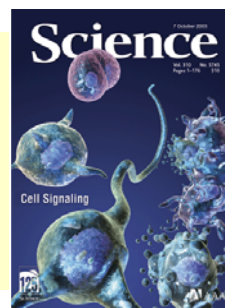
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Project Checkmate leverages proven scientific experience to study avian influenza

Biological analysis:

Reconstructed 1918 pandemic virus to study disease properties



Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus
Tumpey et al., Science: Vol. 310, Page 77, Published 2005

Structural analysis:

Completed Hemagglutinin from 1918 pandemic & H5N1 avian viruses



Structure and Receptor Specificity of the Hemagglutinin from an H5N1 Influenza Virus
Stevens, et al., Science: Vol. 312, Page 404, Published 2006

Blue Gene technology:

World-renowned high capacity computational power

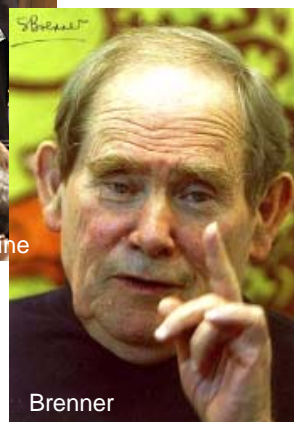
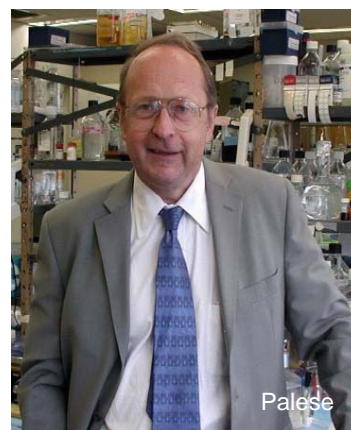
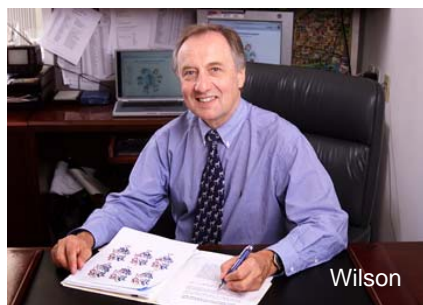
IBM
ranks #1 & #3



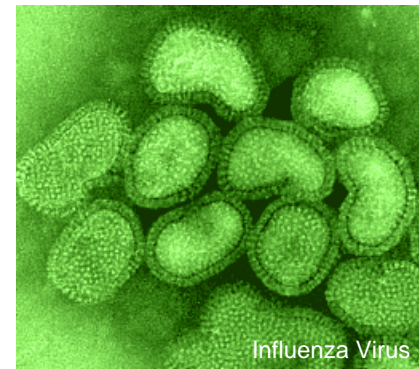
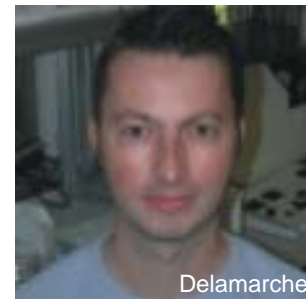
Observation of a dewetting transition in the collapse of the melittin tetramer
P. Liu, et al., Nature: Vol. 435, Page 159, Published 2005

Result is ability to proactively predict disease evolution

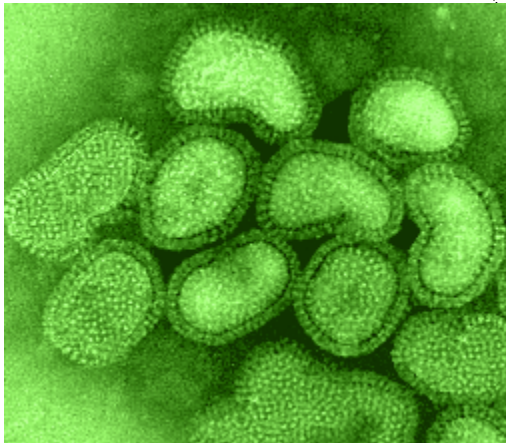
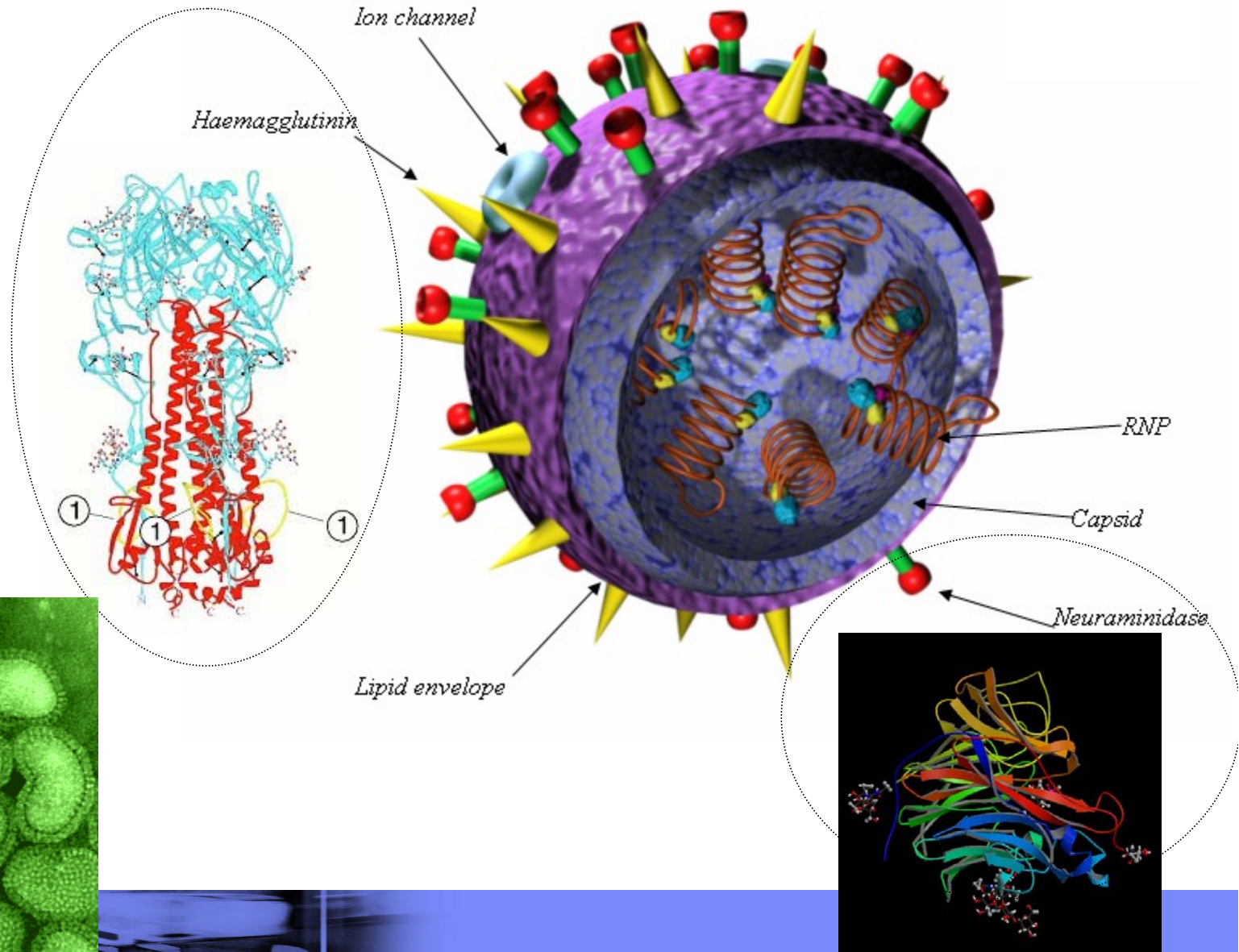
Cast of Characters



Cast of Characters

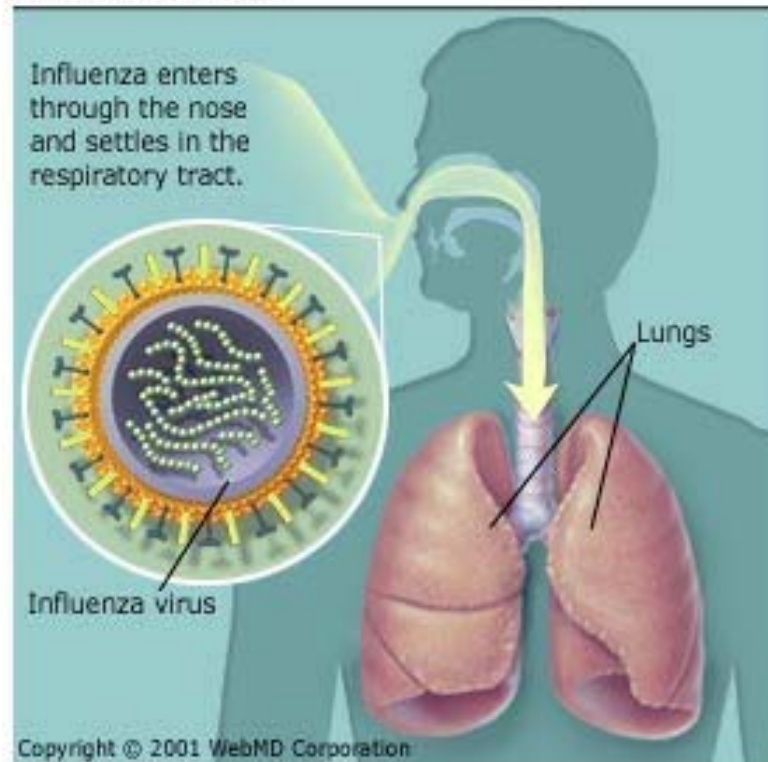


Influenza Virus

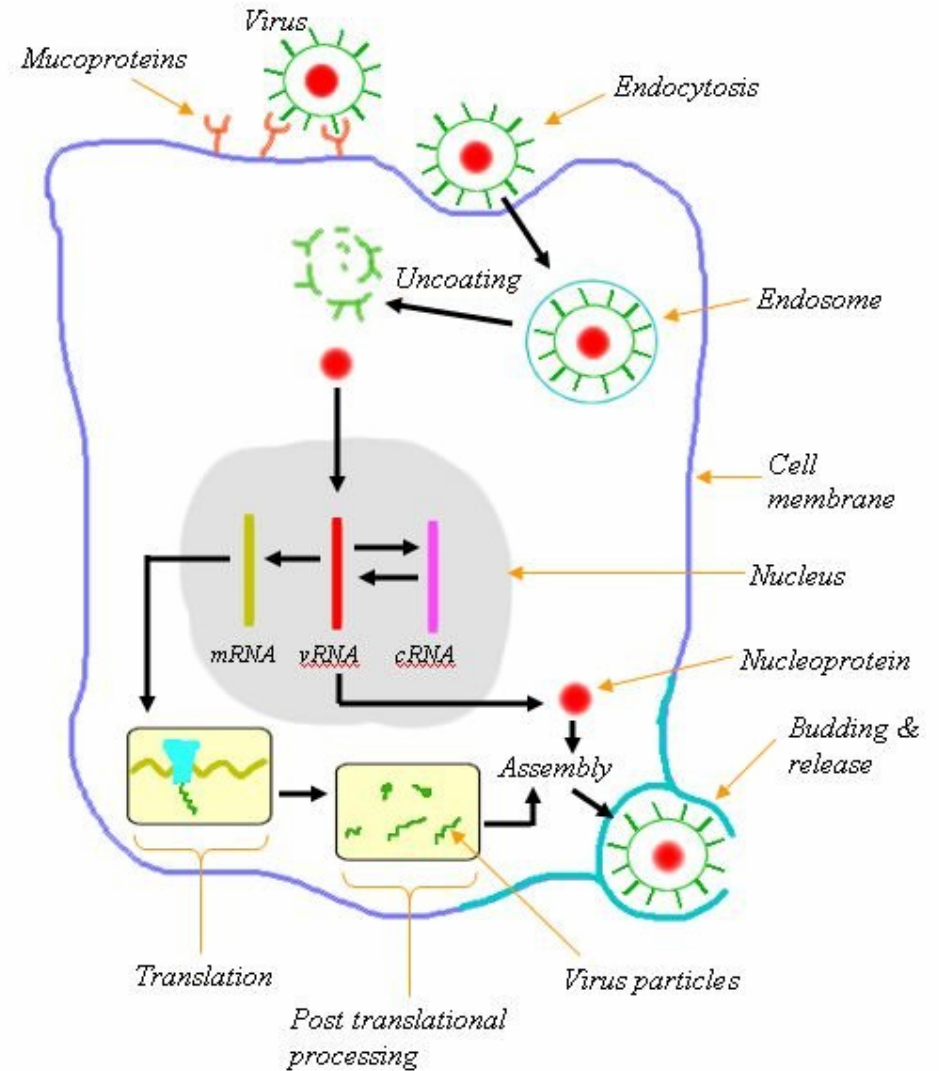


Influenza Infection and Life Cycle

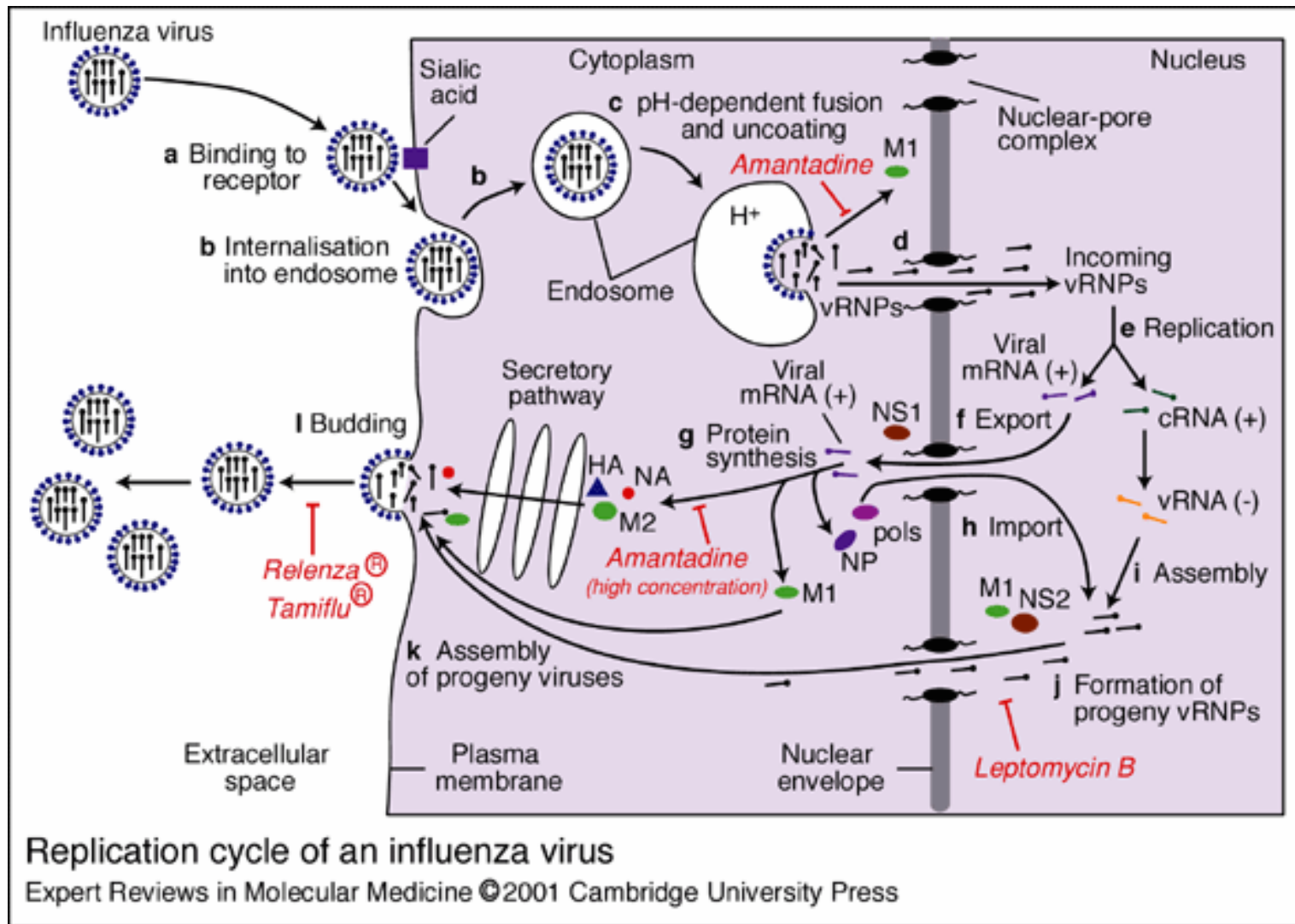
Influenza Virus



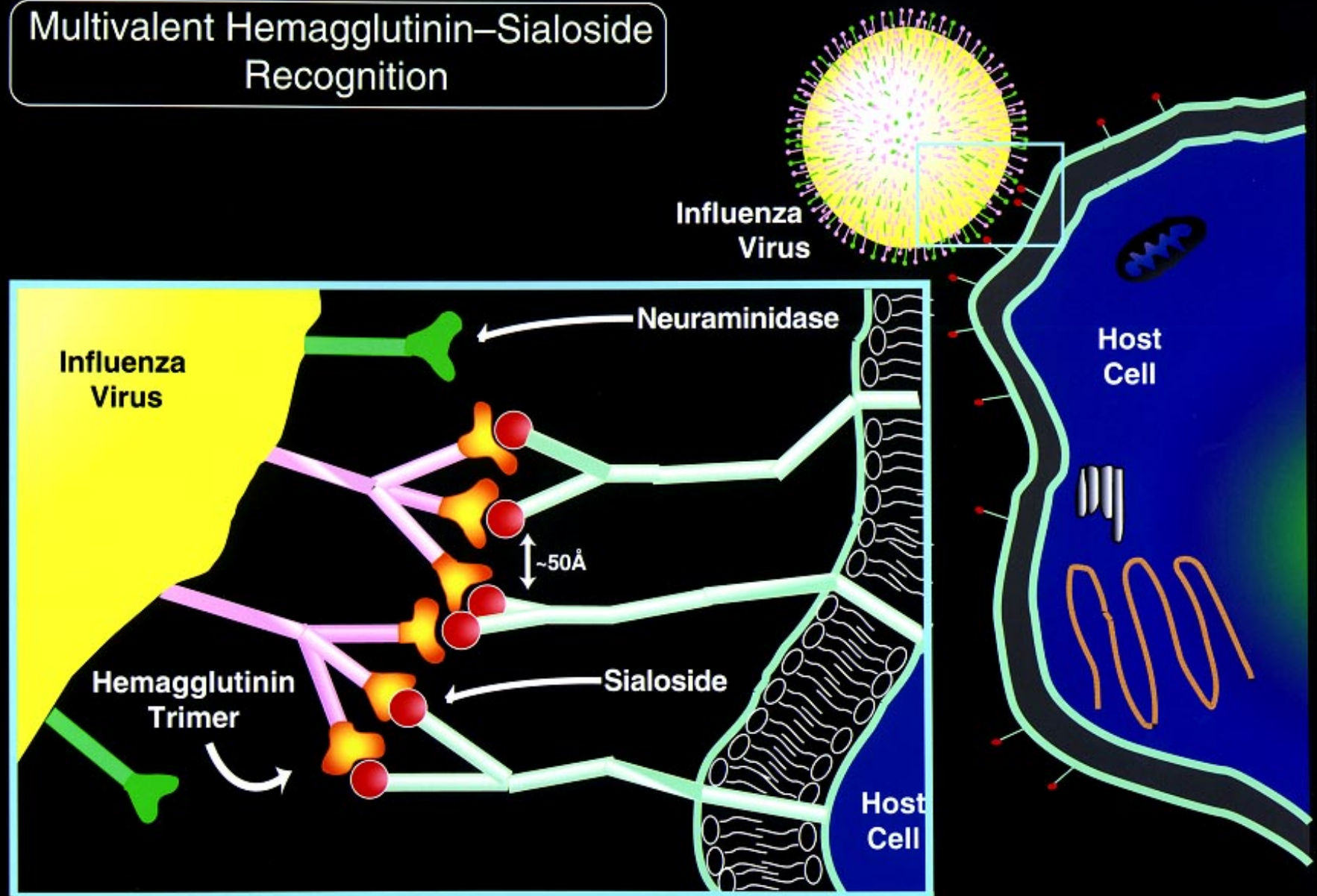
Influenza virus replication



Influenza Therapeutics



Multivalent Hemagglutinin–Sialoside Recognition



Antigenic evolution of avian influenza A (H5N1) virus from 1997 to 200?

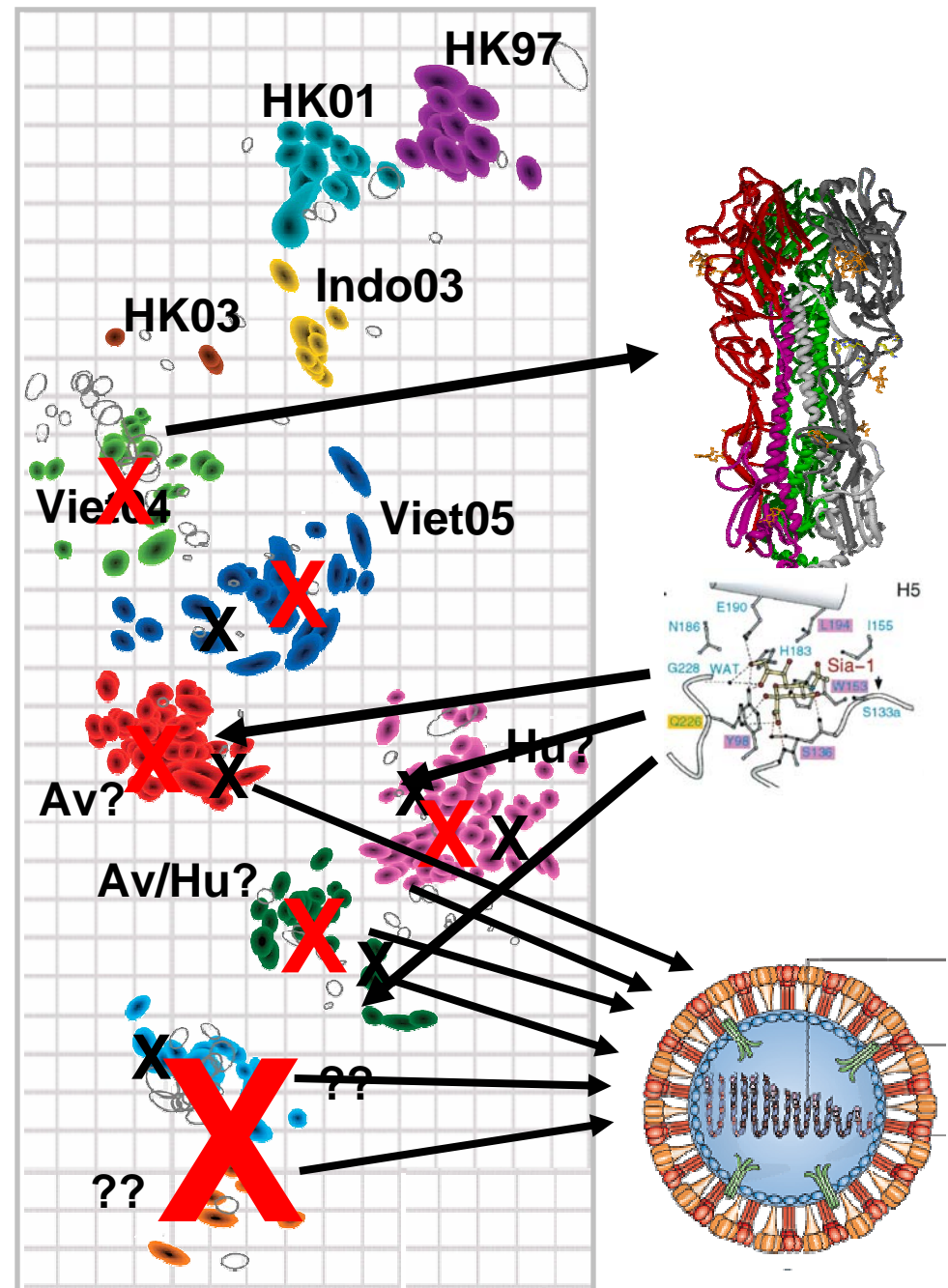
Team 1: Rapid in vitro Evolution:
Developing a methodology to identify and neutralize future virulent strains (Janda)

Team 2: Computer Modeling and Structural Prediction of Influenza Virus Evolution (Wilson)

Team 3: Antibodies and Vaccines:
Finding and Targeting Influenza's Achilles' Heel (Burton)

Team 4: Small molecule inhibitors:
targeting HA Attachment (Wong)

Team 5: Computational prediction of antigenic variation and biological validation: Reverse genetics to reconstruct influenza viruses to test computation and experimental predictions of antigenic variation (Palese)



Summary

Project Checkmate provides a strategic integration of:

- **Scientific expertise**
- **Proven technologies**
 - **Biological analysis:**
 - Reconstructed 1918 pandemic virus to study disease properties
 - Phage/yeast display of antigens and antibodies
 - **Structural analysis:** Completed Hemagglutinin from 1918 pandemic & H5N1 avian viruses
 - **Blue Gene technology:** World-renowned high capacity computational power applied to structural modeling

to anticipate virulent genetic changes in the virus that will enable preparation of effective vaccines and therapeutics in advance of those changes



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