Agile Vaccine™ Development

Naval Industry Partnership for Transformational Vaccine Technology

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Director, ONR Agile Vaccinology Program

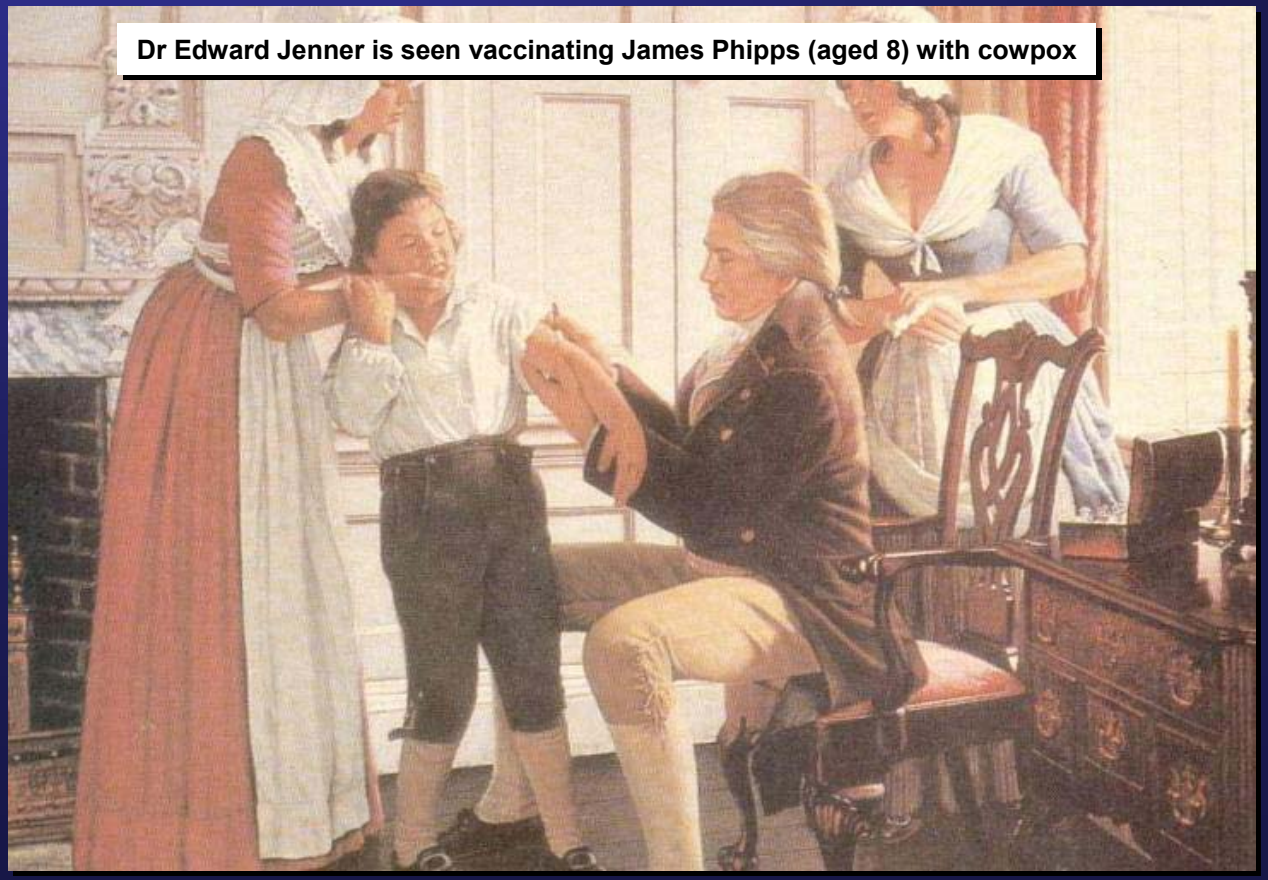
Director, NMRC Malaria Vaccine Program

Agile Vaccine™ panel participants

- **David C. Kaslow, MD**
  Chief Scientific Officer
  Vical, Inc, San Diego, CA
- **Robert S. Tenerowicz**
  Vice President, Process Development and Clinical Supplies
  GenVec, Gaithersburg, MD
- **Gary J. Nabel, MD, PhD**
  Director, Vaccine Research Center
  National Institutes of Health

Traditional Vaccines

All current licensed vaccines based on traditional technologies (Jenner, 1796)



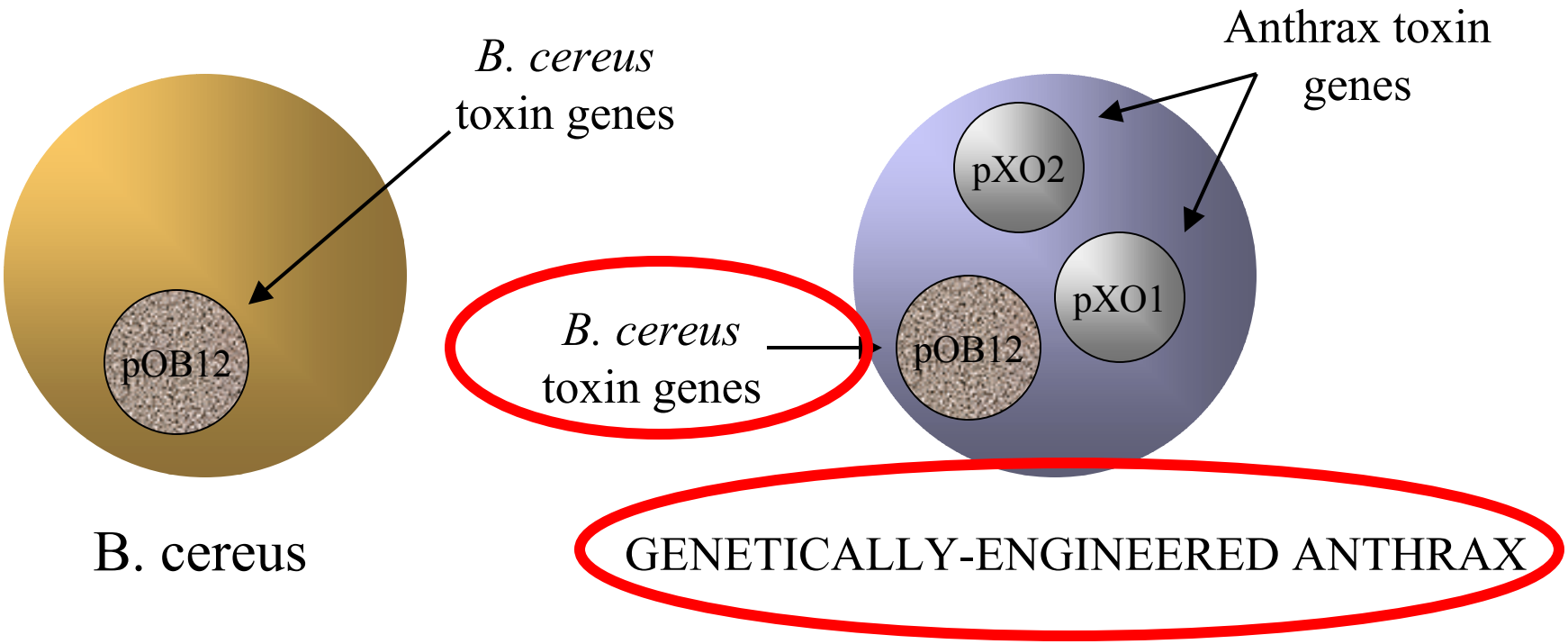
Limitations of Traditional Vaccines

- Time (years) required to develop new vaccines or to modify current vaccines
- Difficulty and cost in manufacturing, purification and production
- Need for maintenance of a cold chain
- Inability to induce a multi-armed immune response
- Potential for toxic side effects.

Need for modern vaccines

- Traditional vaccines may be adequate for some current threats (smallpox).
- Probably inadequate for others (anthrax, tularemia, ebola)
- New vaccine technology needed to address potentially new bio-warfare threats (emerging, genetically-modified organisms, toxins)

Genetically-engineered Anthrax overcomes protection of Anthrax vaccine in mice



Pomerantsev AP, et al. Expression of cereolysine AB genes in Bacillus anthracis vaccine strain ensures protection against experimental hemolytic anthrax infection. Vaccine 1997 Dec;15(17-18):1846-50

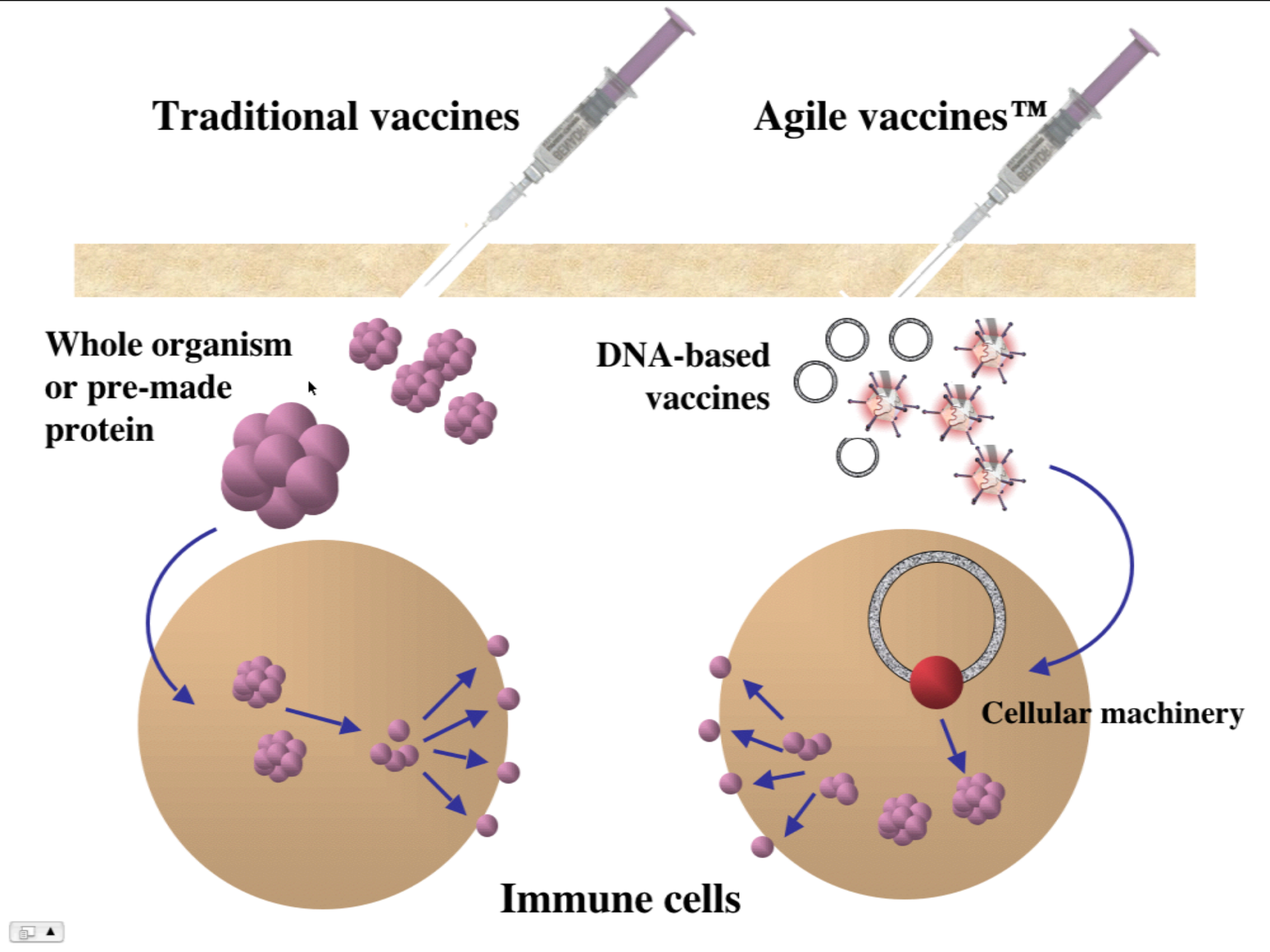
State Research Centre for Applied Microbiology, Obolensk, Moscow Region, Russia.

Agile Vaccines™

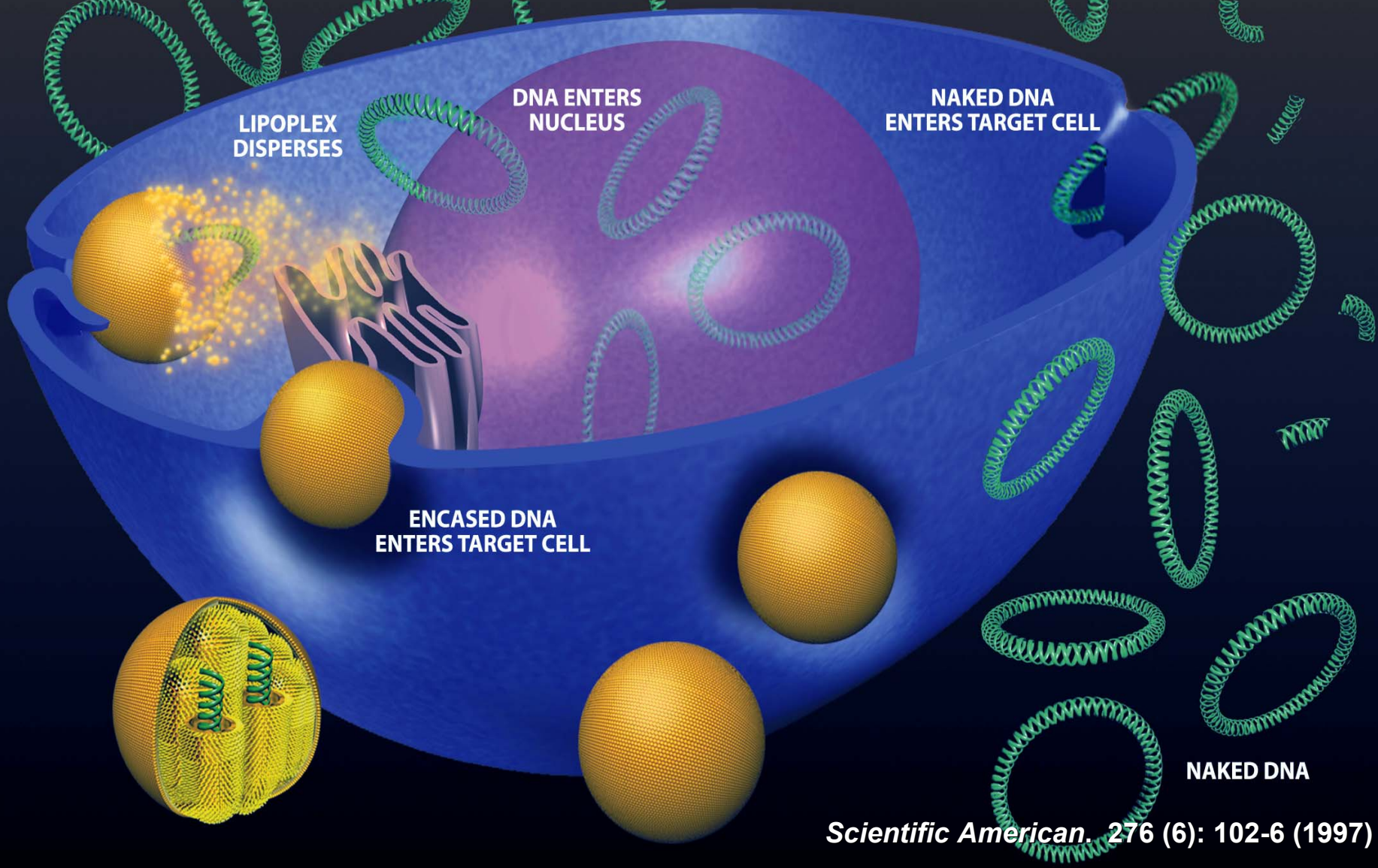
- Simple and rapid production
- Easy and rapid modification
- Capability to generate both strong antibody and cellular immune responses
- Ease of combination
- Stability (does not require cold chain)
- Simple administration

Agile Vaccine™ Technologies

- DNA-based vaccines
- Recombinant pox virus vaccine vectors
- Adenoviruses vaccine vectors
- Replicons (VEE particles)
- *Ex vivo* T cell stimulation (MaxVax)
- others

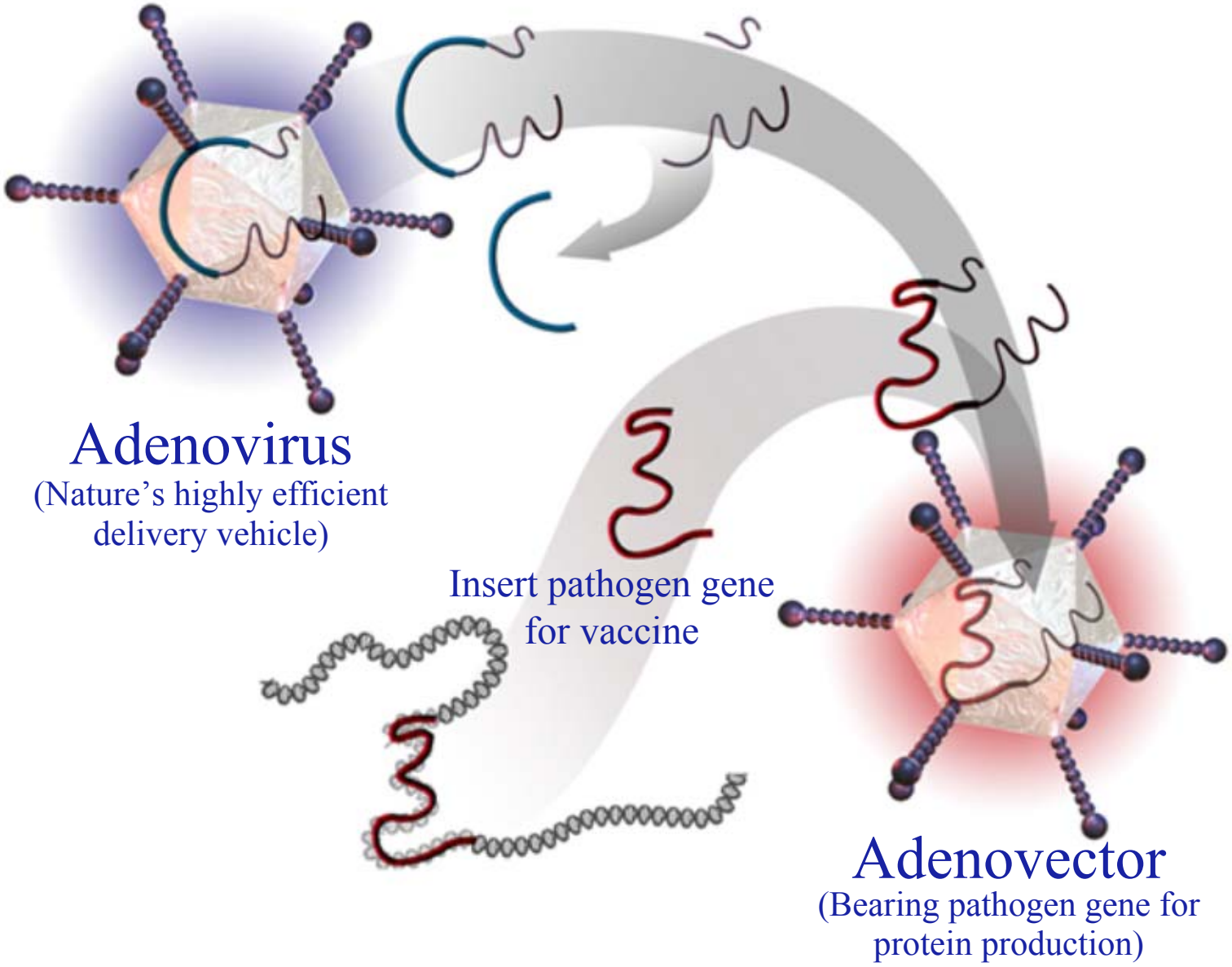

Traditional vaccines
Agile vaccines™
Whole organism or pre-made protein
DNA-based vaccines
Cellular machinery
Immune cells

Vical's Naked DNA Technology



Scientific American. 276 (6): 102-6 (1997)

Removal of DNA to prevent viral replication

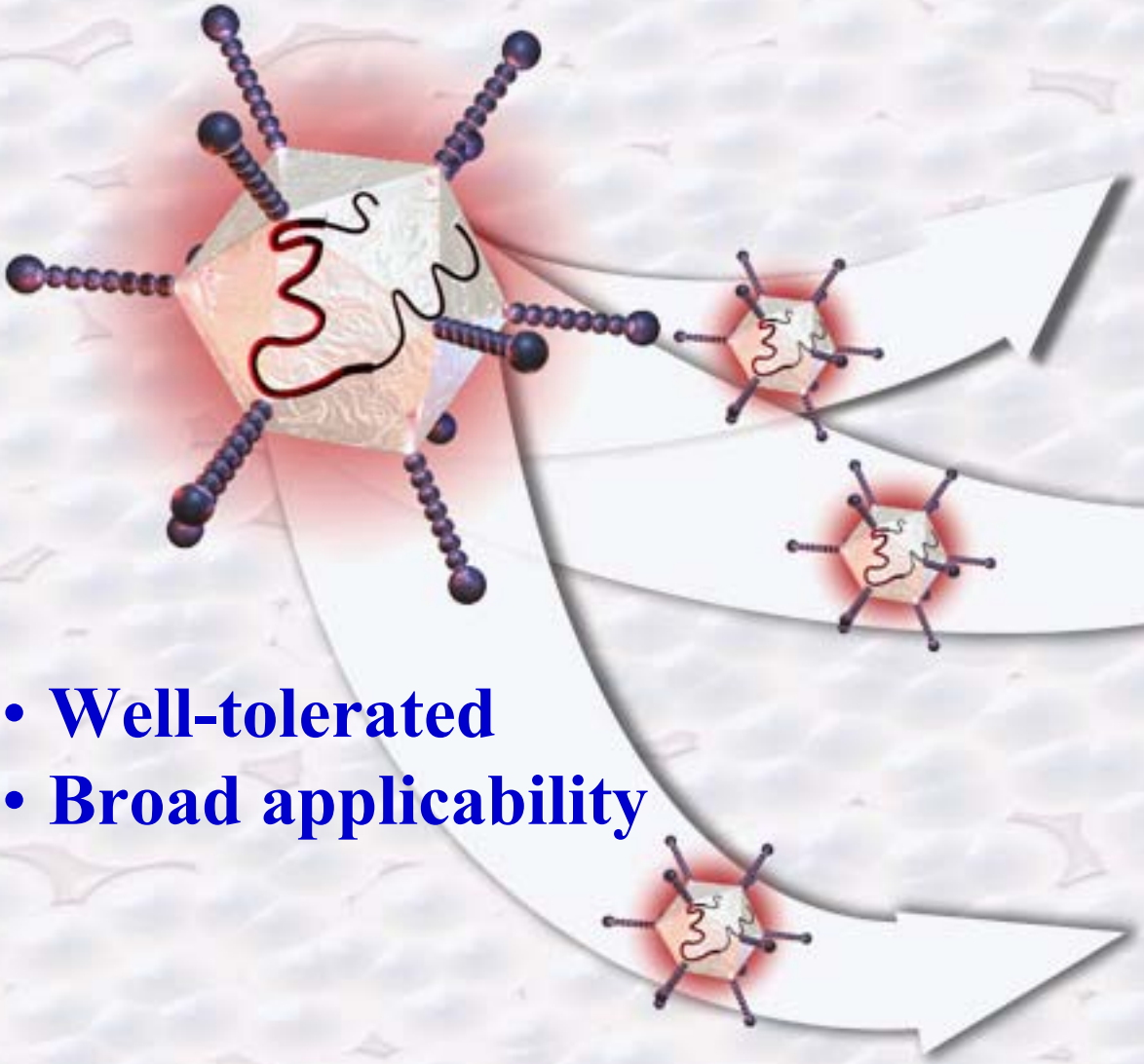


Adenovirus
(Nature's highly efficient delivery vehicle)

Insert pathogen gene for vaccine

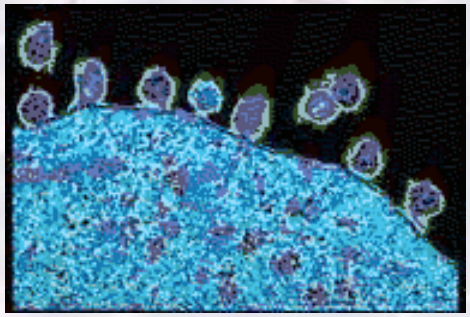
Adenovector
(Bearing pathogen gene for protein production)

Highly Versatile Vaccine Platform



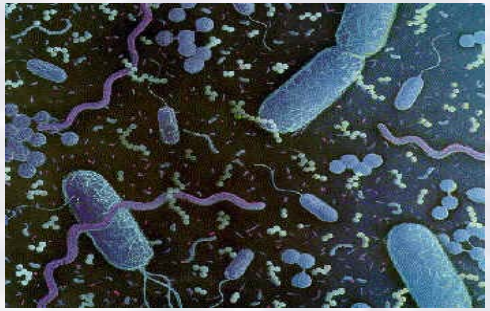
- Well-tolerated
- Broad applicability

Viral Diseases



Parasitic Diseases

Bacterial Diseases



Proven efficacy of Agile Vaccines™ in animal studies

- Agile vaccines™ proven in animal studies
  - rodents, rabbits, chickens, cattle and monkeys
- Viruses
  - bovine herpes virus 1, cytomegalovirus, St Louis encephalitis virus, hepatitis B, hepatitis C, herpes simplex virus, human immunodeficiency virus, influenza virus, lymphocytic choriomenigitis virus, rabies, rotavirus and simian immunodeficiency virus
- Bacteria
  - Lyme disease, Mycobacterium tuberculosis, Bacillus anthracis
- Parasites
  - malaria, leishmania
- Toxins
  - tetanus toxin, anthrax toxin

Agile Vaccines™ in Humans

- Phase 1 and 2a (influenza, HIV, HBV, malaria, cancer, immunotherapeutics) human clinical trials
- Agile vaccines™ safe, well-tolerated and immunogenic in humans

Navy is a world-leader in Agile Vaccine™ technologies

- Advanced technology Demonstration (ATD) FY98 - 01: "Development of DNA vaccines for Complex Multi-stage Pathogens and Against Multiple Pathogens of Military Importance”
- Four human clinical trials of DNA vaccines in healthy humans (malaria as model) established safety and immunogenicity.
- Awarded US patent on DNA vaccines against malaria.
- First DNA-based vaccine against malaria (in development).
- First DNA-based vaccine against anthrax (in development).
- First DNA-based vaccine against dengue virus (in development).
- Fully embraced in genomic approaches to vaccine development.
- Established “biotech-style” approach to high-tech vaccine development
- Partnerships (CRADAs/cooperative agreements/MTA) with NIH, Vical, GenVec, Aventis-Pasteur, Alphavax, Chiron, Vaxin, others.

Agile Vaccine™ Goals/Payoff

- A technological leap forward.
- A coordinated program of partners (federal government, academia and industry) that will leverage respective technologies, capabilities and infrastructure.
- Identify and optimize critical vaccine technologies.
- Overcome limitations of current manufacturing processes.
- Develop plans for sustainable vaccine manufacturing.
- Definitive solutions for vaccines against agents of bio-terrorism, emerging and genetically-modified threats

Agile Vaccine™ Technical Potential

- Agile Vaccines™ vaccines are fundamentally different
  - Instead of administering foreign material against which human immune system reacts, DNA or virus encoding foreign material is administered. Human cells produce the foreign material using the DNA or virus as a template.
- Advantages of Agile Vaccines™ over conventional vaccines
  - Easy to produce and purify.
  - Can be combined (multivalency)
  - Relatively inexpensive.
  - Easy to modify.
  - May not require a cold chain.
  - Highly immunogenic, especially for CD8+ T cells.

☑ Provides potential for RAPID production of new vaccines.

- Ideal for emerging infectious diseases.

- No other existing vaccine delivery system provides all potential advantages of Agile Vaccines™ .

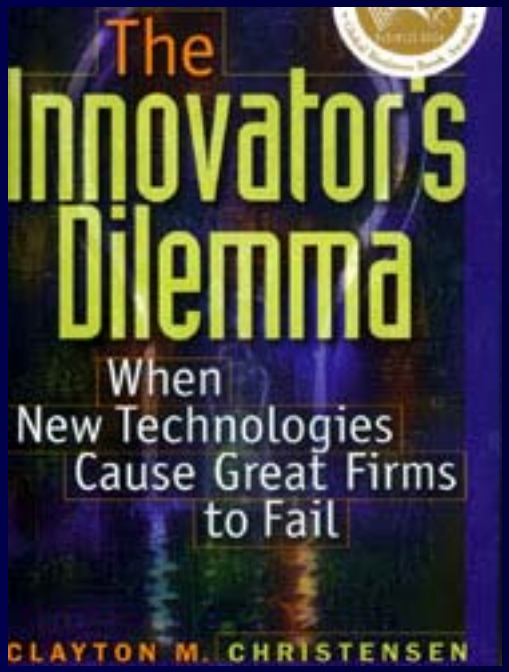
Agile Vaccines™: An Emerging Disruptive Technology

Disruptive technologies:

"typically cheaper, simpler, and more convenient-to-use…"

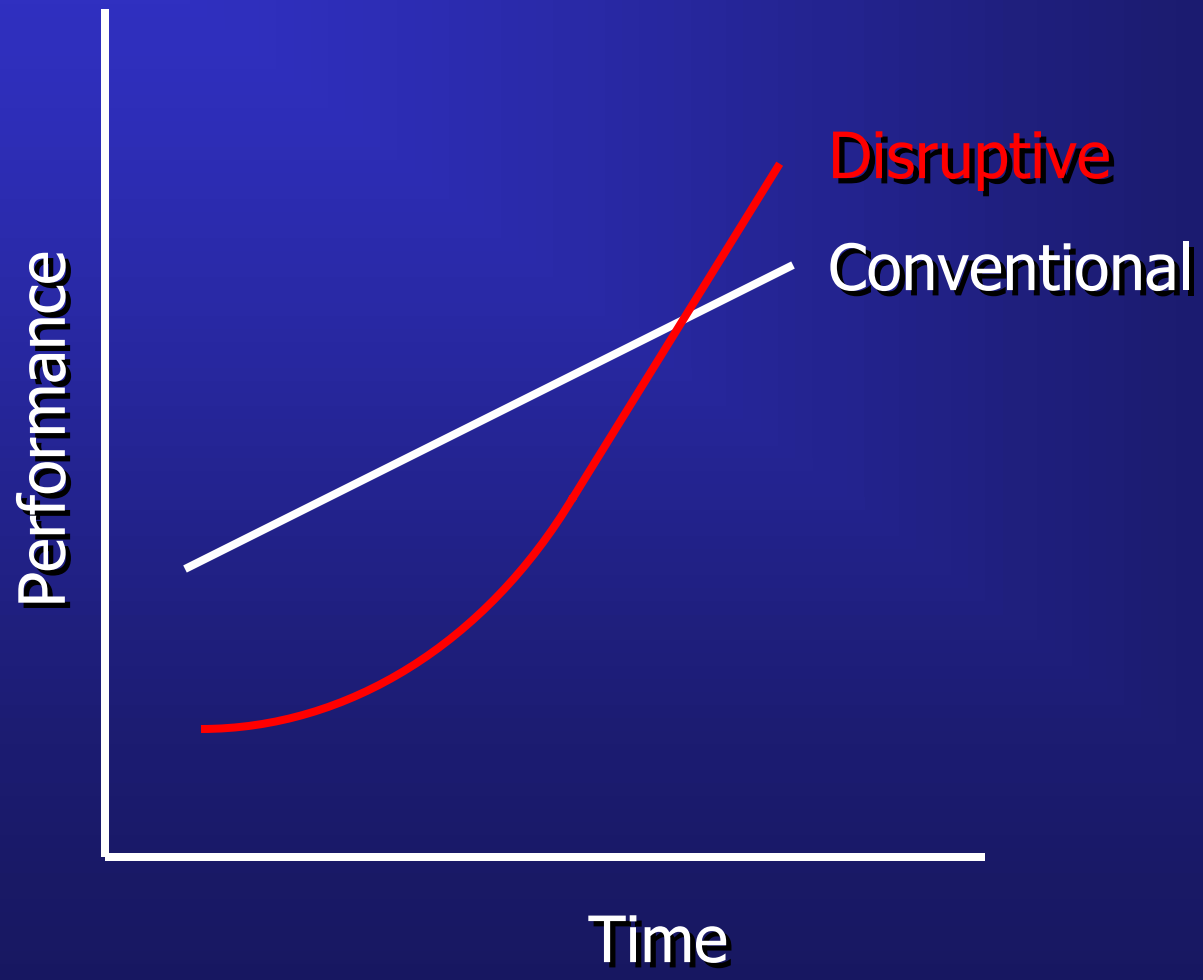
"when they first appear, they almost always offer lower performance…"

"always improve in performance (and) eventually are able to take over older markets…"



By Clayton M. Christensen
Harvard Business School Press
(C) 1997President and Fellows of Harvard College
ISBN: 0-87584-585-1

Evolution of technologies



Predictions:
The promise of Agile Vaccines™

- Innovative new universal vaccines
- More effective and safer vaccines to replace our current conventional vaccines
- Multivalent combination vaccines that are less complex to develop and manufacture, but are safer, requiring fewer injections

Key Challenges for Supply of Nationwide/ Worldwide Agile Vaccines™

Regulatory:

Strong partnership with FDA required for efficient development and approval

Capacity: Lack of capacity for manufacturing

Limited facilities for scales ≤ 100L

Few facilities for scales > 100L (pharma companies)

Leadtime for facilities ~3 years

Engineering: Scales required for therapeutics 100-500L; vaccines likely to require 1,000 – 10,000L scale. Time required to improve performance at the largest scale

Agile Vaccines™ Navy/Industry/Government Partnerships

- Vaccine development and in house scientific expertise, pathogen/animal model systems, human trials capabilities
- Naked DNA vaccines, process development, manufacturing, DNA vaccine regulatory expertise
- Recombinant adenovirus vaccines, process development, manufacturing
- Replicon particles, process development, manufacturing
- Immunology, primate studies, regulatory and licensing advisor, manufacturing capabilities

Agile Vaccines™: Transformational Vaccine Technology

- Agile vaccines™ represent 21st century vaccine development
- Only vaccine technology capable of rapidly responding to evolving infectious disease and bio-warfare threats
- Will require coordinated effort between DoD, NIH, CDC, academia and industry with close coordination with the FDA to produce licensable vaccines.
- Establishment of key partnerships with Agile Vaccine™ world leaders will ensure best chance for success.
- Requirement for sustained funding of 5 year Agile Vaccine™ Technology Development program

Agile Vaccines™: Breakout session

- Current status of agile vaccines
- How should efforts across government/academia and industry be coordinated?
- What is the potential role for the newly established Office of Homeland Defense in agile vaccine development?
- What are the technical, engineering, financial and regulatory hurdles and strategies to overcome them?
- What policy reforms are needed to bring this technology to deployable vaccines?