



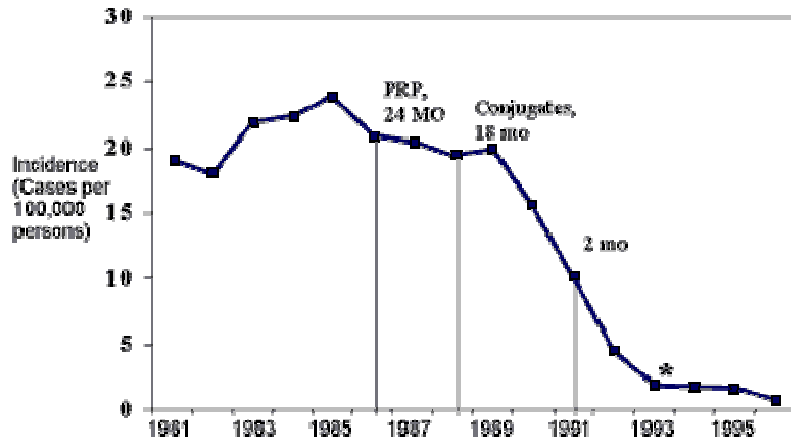
**Enabling technologies to induce T- cell responses  
and protective antibody responses:  
DNA-based vaccines—are they a disruptive vaccine  
technology?**

**David C. Kaslow, M.D.**

**Vaccines Integration and Pipeline Management  
Merck Research Laboratories**

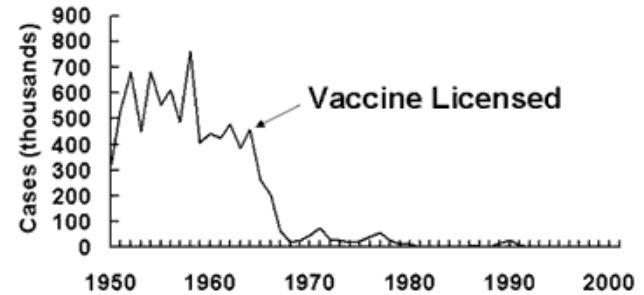
# 20<sup>th</sup> Century Vaccine Legacy

HiB-United States, 1981-1995

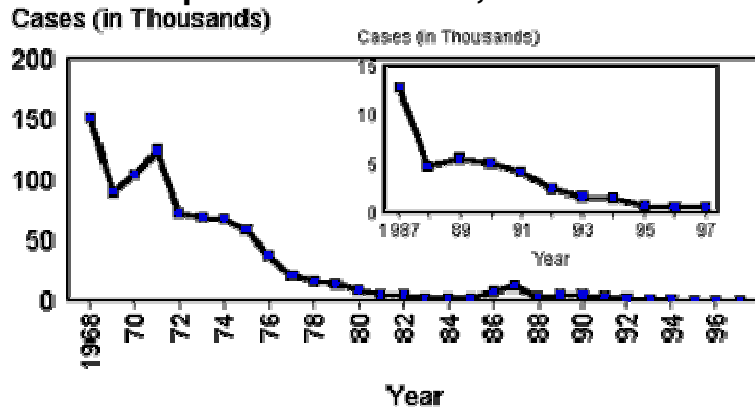


<http://www.hhs.gov/nvpo/concepts/intro6.htm>

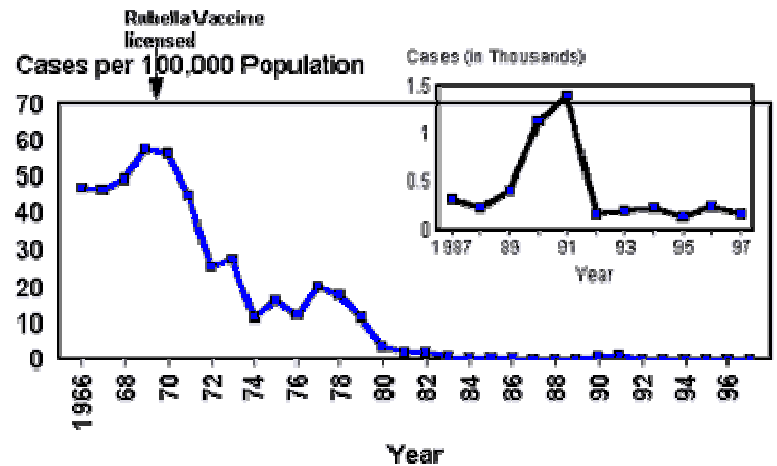
Measles-United States, 1950-2001



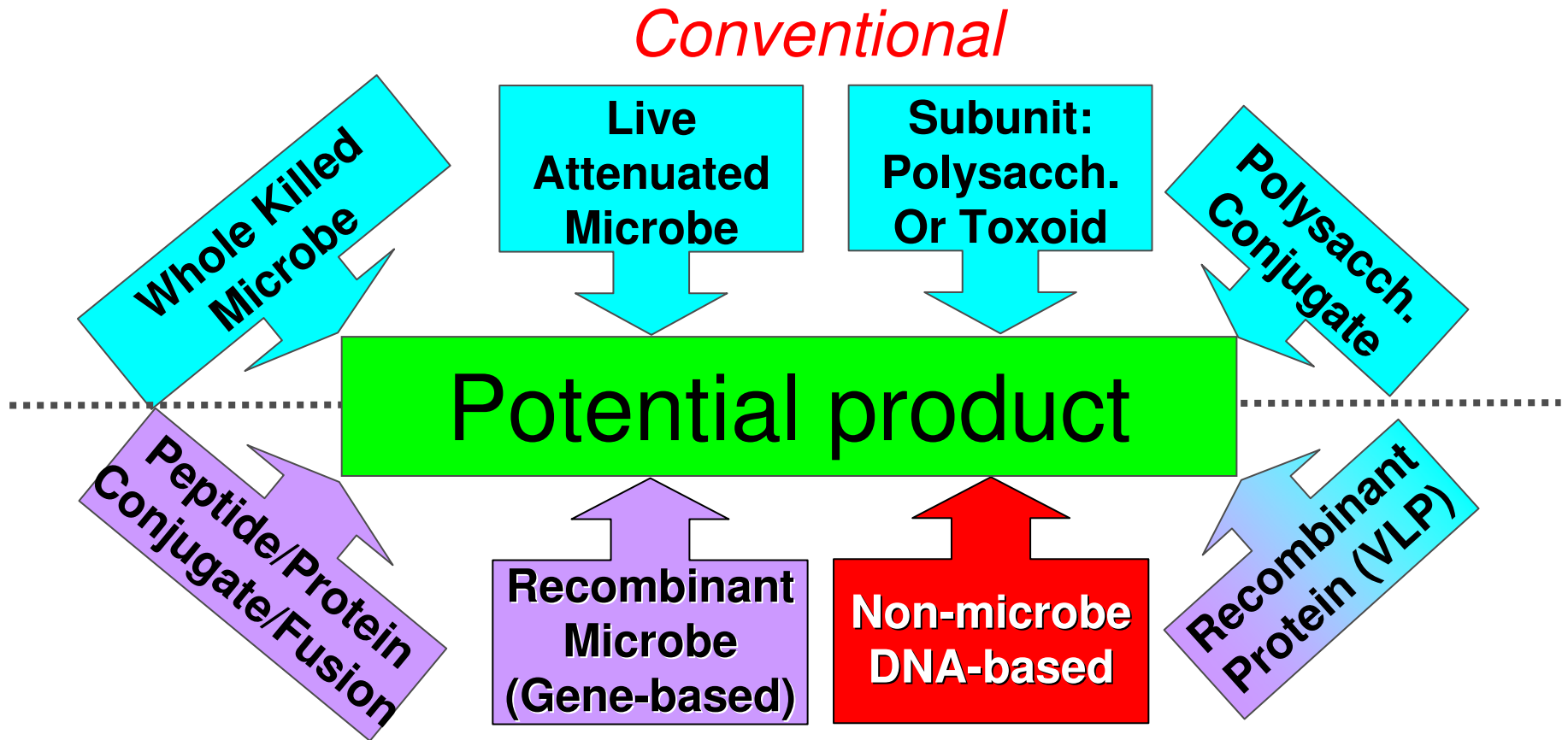
Mumps-United States, 1968-1996



Rubella-United States, 1966-1996



# Right Vaccine Technology for the Right Vaccine Target



+/- adjuvant & delivery systems

*Incremental v Disruptive*

# DNA-based Vaccines: A Disruptive Technology?

- What is a disruptive technology?
- Do DNA-based vaccines have the potential to be disruptive vaccine technologies?
- Do DNA-based vaccines work?
- Are DNA-based vaccines safe and effective for use in humans?
- If so, which targets should be sought first?

# What is a disruptive technology?

Disruptive technologies are *not* incremental or even radical improvements in conventional technologies

Disruptive technologies bring completely new approaches that allow completely new products to emerge

*Innovator's Dilemma*

Clayton Christensen

# Characteristics of 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... ..because they are able to deliver sufficient performance... and they add some new ones.”

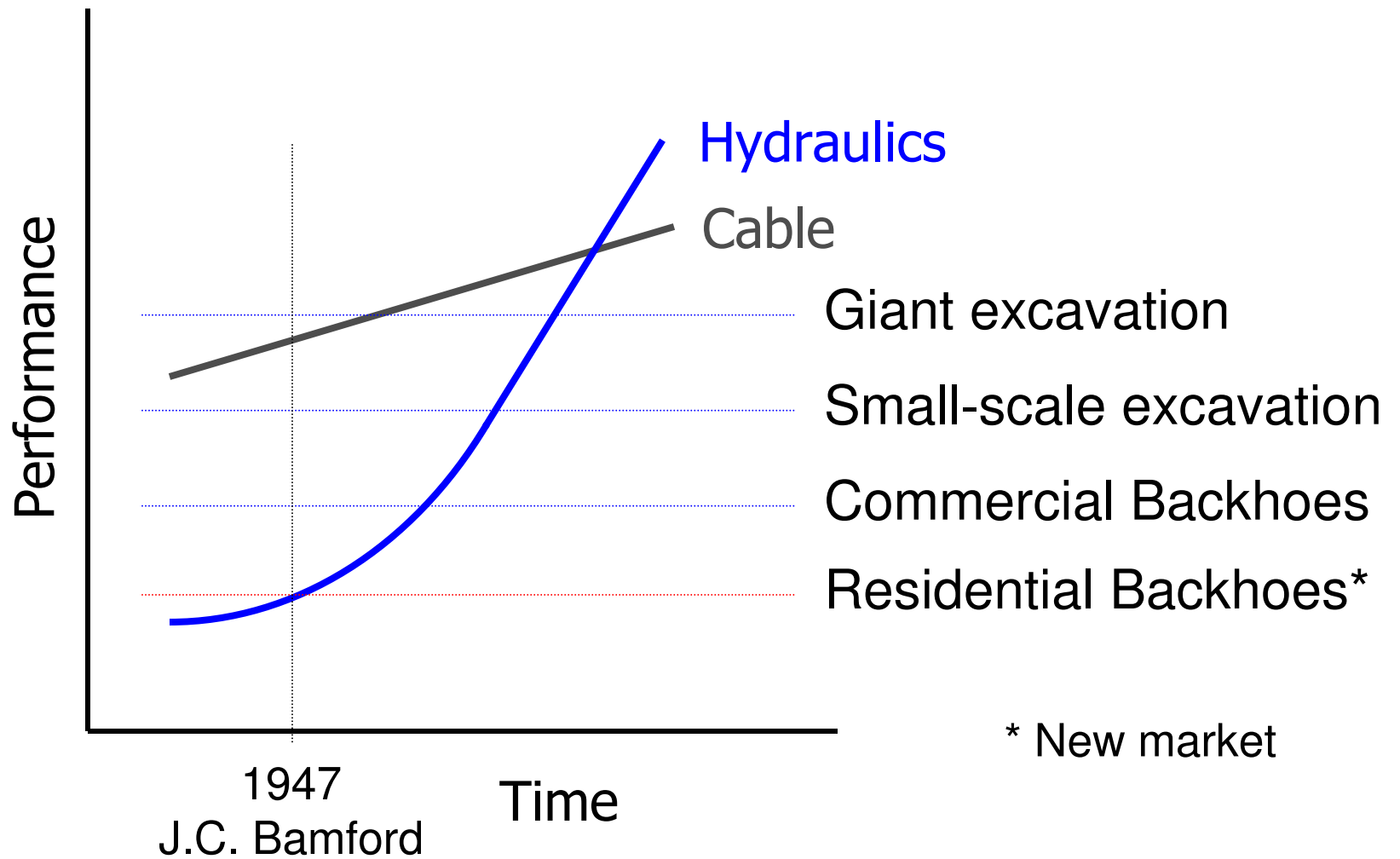
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Clayton Christensen

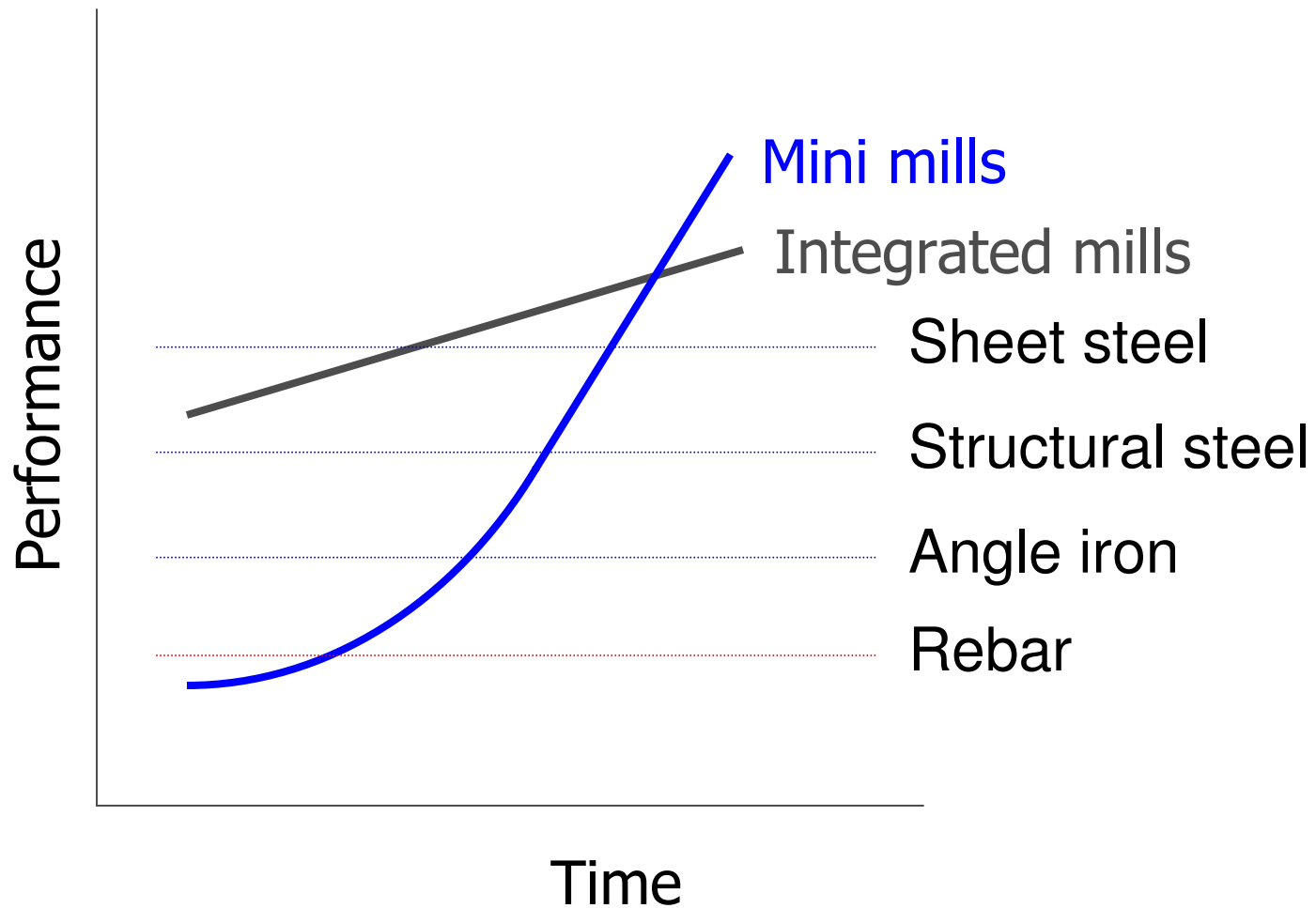
# Examples of disruptive technologies

<b>Field of use</b>	<b>Conventional technology</b>	<b>Disruptive technology</b>
<b>Electronics</b>	Vacuum tubes	Transistors
<b>Excavation</b>	Cable-actuated Steam-powered	Hydraulics Internal combustion
<b>Steel production</b>	Blast furnace integrated mills	Electric arc mini mills
<b>Read-write memory</b>	50 X 24 inch random access memory disk	Flash memory

# Excavation

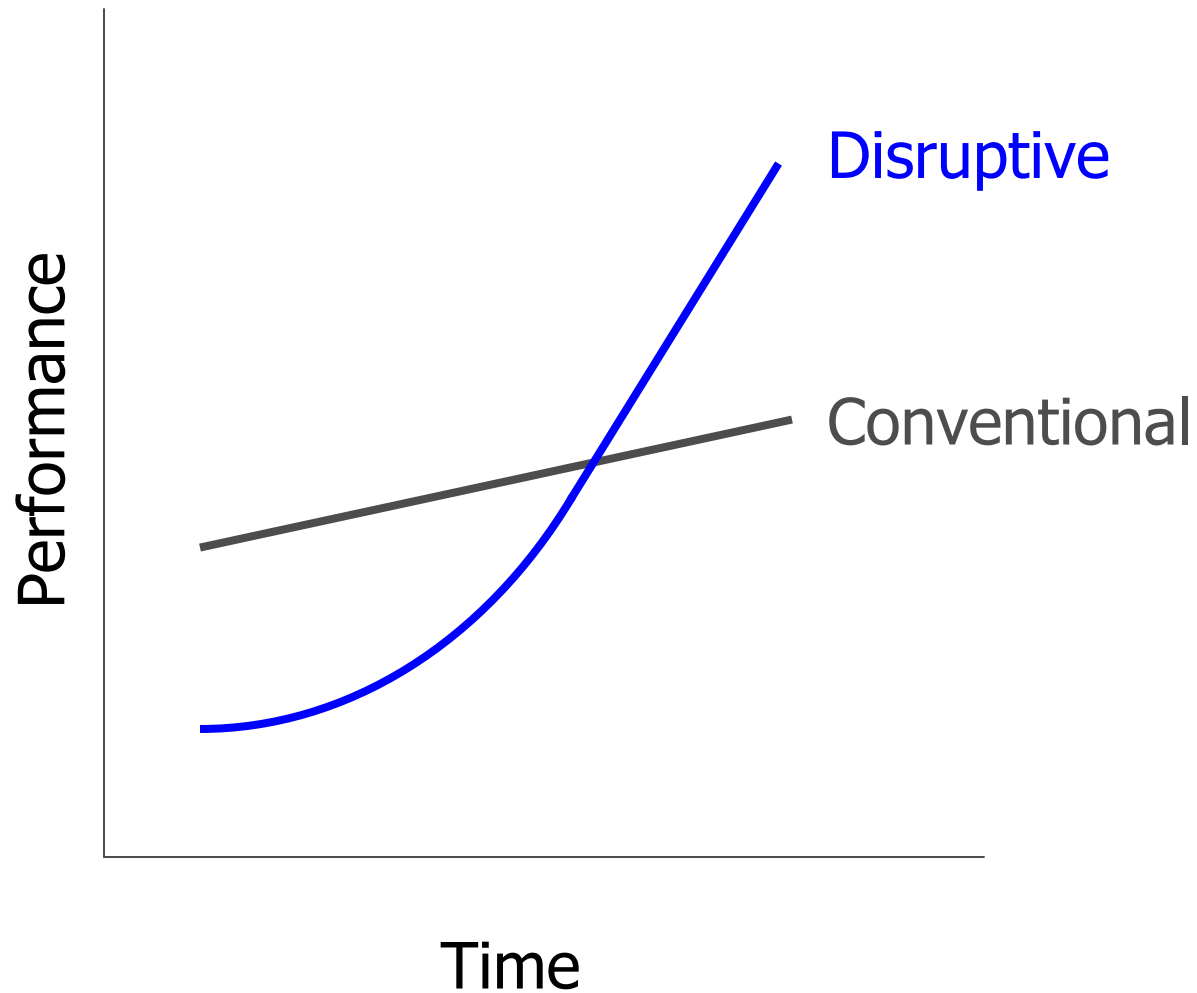


# Steel Production



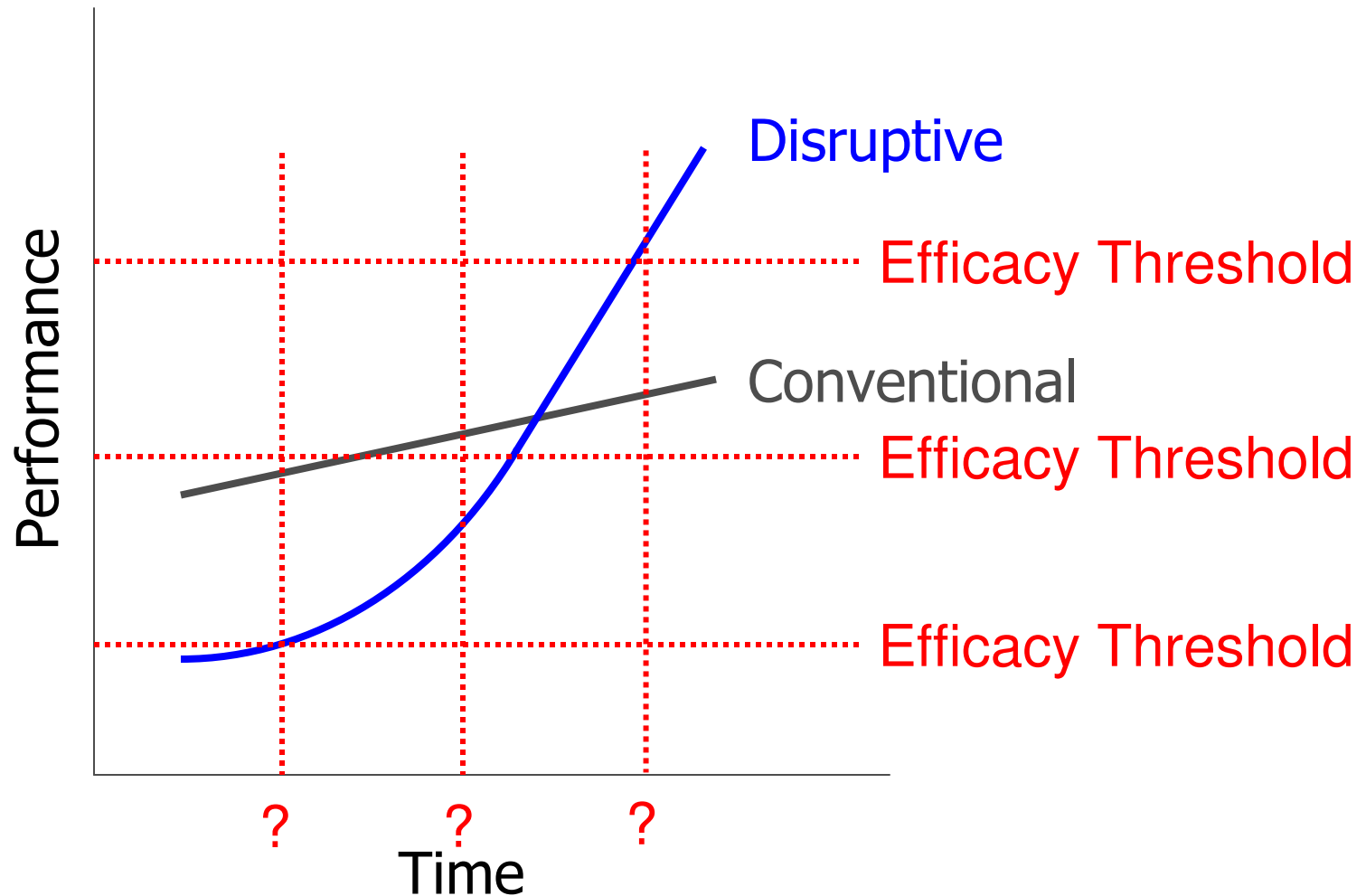
# Are DNA-based vaccines a disruptive technology?

*Where are they in development?*



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*Where are they in development?*



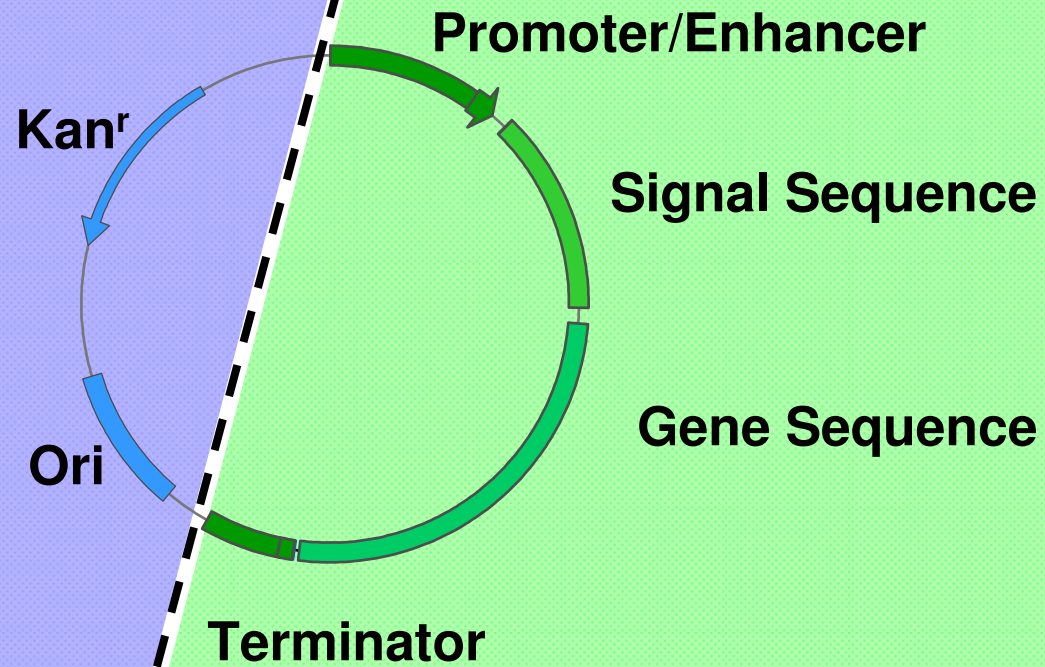
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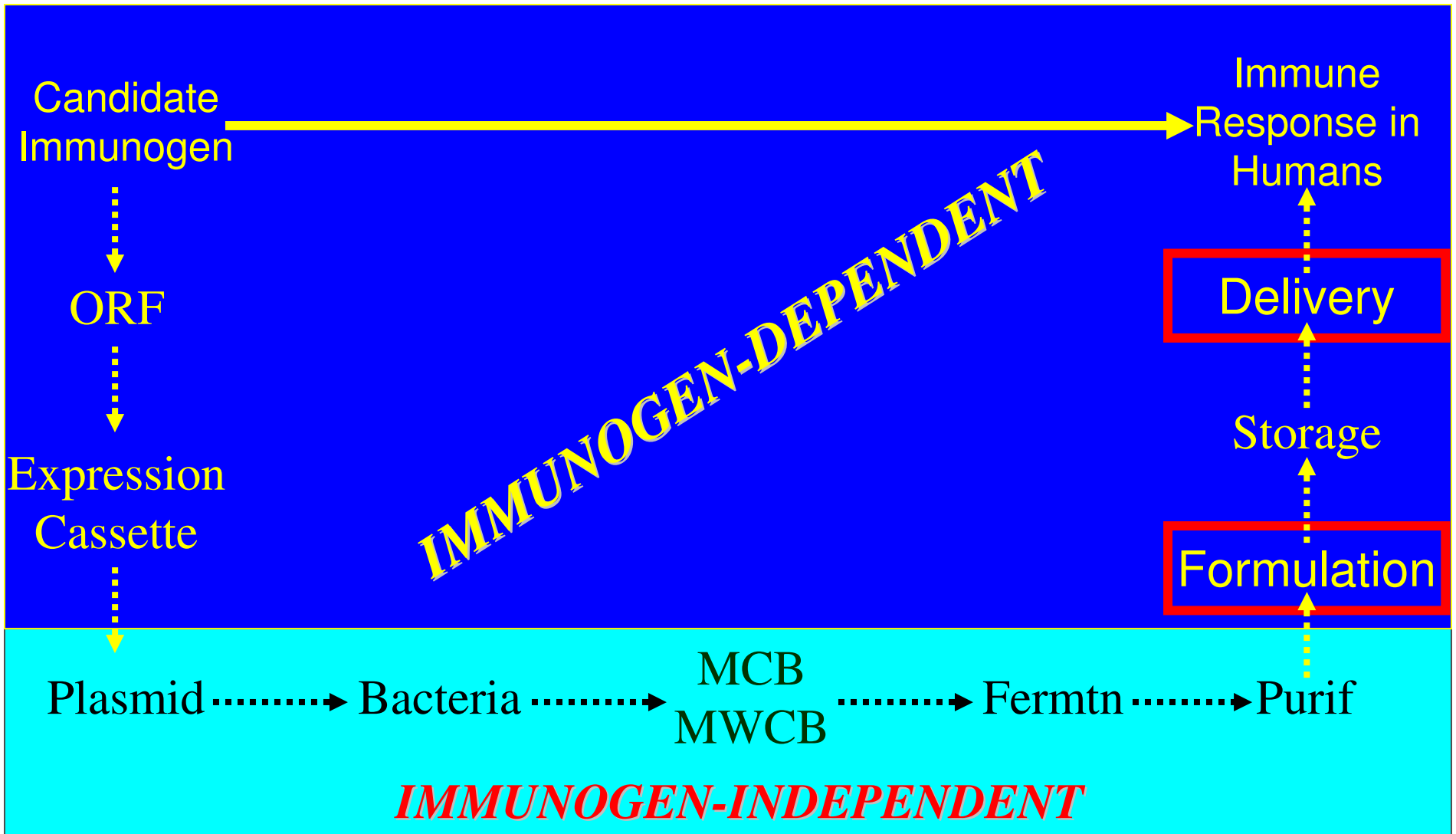
# Plasmid

Required for manufacturing

Required for *in vivo* expression



# Unit Operational Analysis



= cheaper, simpler, faster, more convenient (including regulatory)

# Characteristics of disruptive technologies

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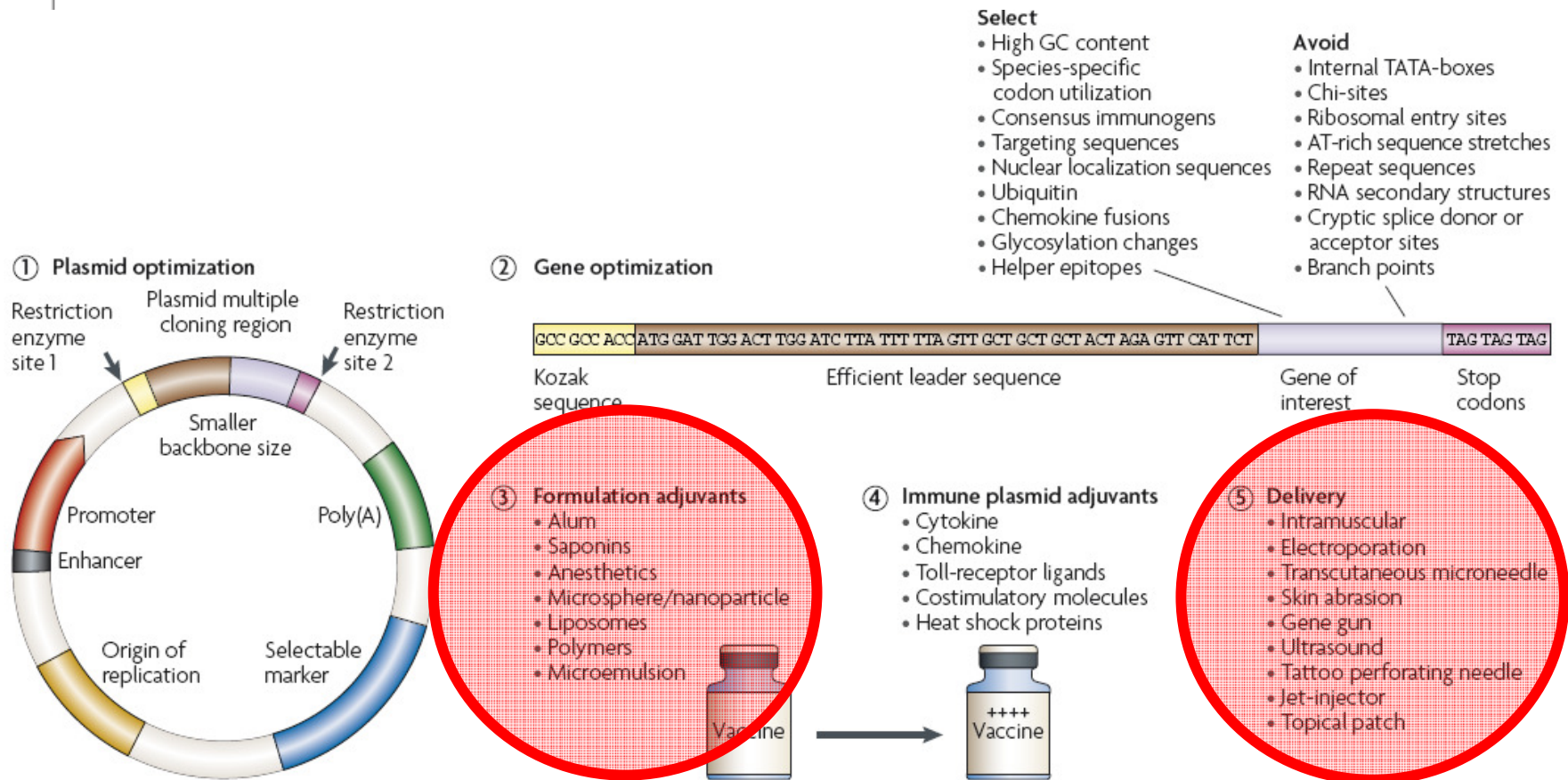
“always improve in performance (and) eventually are able to take over older markets... ..because they are able to deliver sufficient performance... and they add some new ones.”

*Innovator's Dilemma*  
Clayton Christensen

# DNA-based vaccines: optimization strategies to enhance immunogenicity

## DNA vaccines: ready for prime time?

Michele A. Kutzler\* and David B. Weiner†



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# Pathogen-animal models demonstrating efficacy

- Fish: Infectious hematopoietic necrosis virus  
(Corbeil et al., *Dis. Aquat. Organ.* 39:29, 1999)
- Birds: West Nile Virus  
(Turell et al., *Emerg. Infect. Dis.* 9:1077, 2003)
- Rabbits: Anthrax  
(G. Hermanson et al., *Proc Natl Acad Sci U S A.* 101:13601, 2004)
- Dogs: Canine distemper virus  
(Fischer et al., *Vaccine* 21:1099, 2003)
- Non-human primates: Rabies  
(Lodmell et al., *Nat. Med.* 4:949, 1998)
- Horses: West Nile Virus  
(Davis et al., *J Virol.* 75:4040, 2001)

# West Nile Virus Recombinant DNA Vaccine Protects Mouse and Horse from Virus Challenge and Expresses In Vitro a Noninfectious Recombinant Antigen That Can Be Used in Enzyme-Linked Immunosorbent Assays

BRENT S. DAVIS,<sup>1</sup> GWONG-JEN J. CHANG,<sup>1\*</sup> BRUCE CROPP,<sup>1</sup> JOHN T. ROEHRIG,<sup>1</sup> DENISE A. MARTIN,<sup>1</sup>  
CARL J. MITCHELL,<sup>1</sup> RICHARD BOWEN,<sup>2</sup> AND MICHEL L. BUNNING<sup>1</sup>

JOURNAL OF VIROLOGY, May 2001, p. 4040–4047

TABLE 4. Serum Nt antibody titers and protective immunity elicited by a single i.m. injection of WN virus DNA vaccine in horses

Sample (day)	Titer							
	Vaccinated horse no.				Unvaccinated control horse no.			
	5	6	7	8	9	10	14	15
<b>Postvaccination</b>								
12	<1:10	<1:10	<1:10	<1:10				
14	1:10	<1:10	<1:10	<1:10				
16	1:10	<1:10	<1:10	<1:10				
18	1:40	<1:10	<1:10	<1:10				
20	1:40	<1:10	<1:10	<1:10				
22	1:40	<1:10	1:10	<1:10				
28	1:40	<1:10	1:20	1:10				
31	1:40	1:5	1:20	1:10				
37	1:40	1:5	1:20	1:20				
<b>Postchallenge Day 39</b>								
2	1:40	1:5	1:20	1:20	<1:2	<1:2	<1:2	<1:2
4	1:40	1:10	1:20	1:40	<1:2	<1:2	<1:2	<1:2
6	1:40	1:10	1:40	1:40	<1:2	<1:2	<1:2	<1:2
8	1:80	1:20	1:40	1:40	1:80	<1:10	<1:10	<1:10
10	1:80	1:20	1:40	1:80	>1:320	<1:10	<1:10	1:160
12	1:160	1:40	1:80	1:160	>1:320	1:20	1:20	>1:320
14	>1:320	1:40	1:160	1:160	>1:320	1:160	1:10	1:160
<b>Viremia titer<sup>a</sup> range (day)</b>					1.3–2.4 (4)	1.0–1.6 (6)		1.3–2.2 (2)

<sup>a</sup> Viremia titer was expressed as log<sub>10</sub> Vero cell PFU/ml of serum.

0/4 vaccinated v 7/8 control horses viremic

# Market-approved DNA-based Vaccines



## USDA ISSUES CONDITIONAL LICENSE FOR CANINE MELANOMA VACCINE

WASHINGTON, March 26, 2007--The U.S. Department of Agriculture's Animal and Plant Health Inspection Service today announced that it has issued a conditional license to Merial, Inc., of Athens, Ga., for a melanoma vaccine to aid in the treatment of oral cancer in dogs.

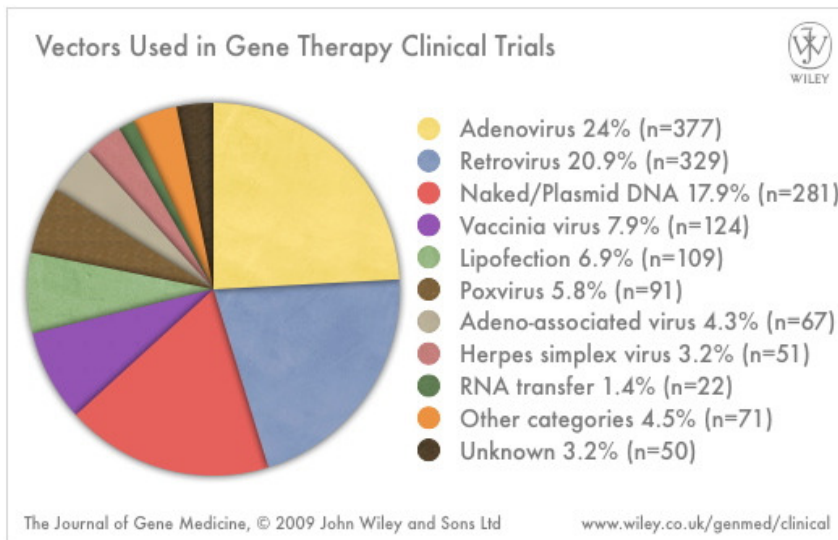


Infectious Haematopoietic  
Necrosis Virus *Vaccine*,  
*DNA Vaccine*

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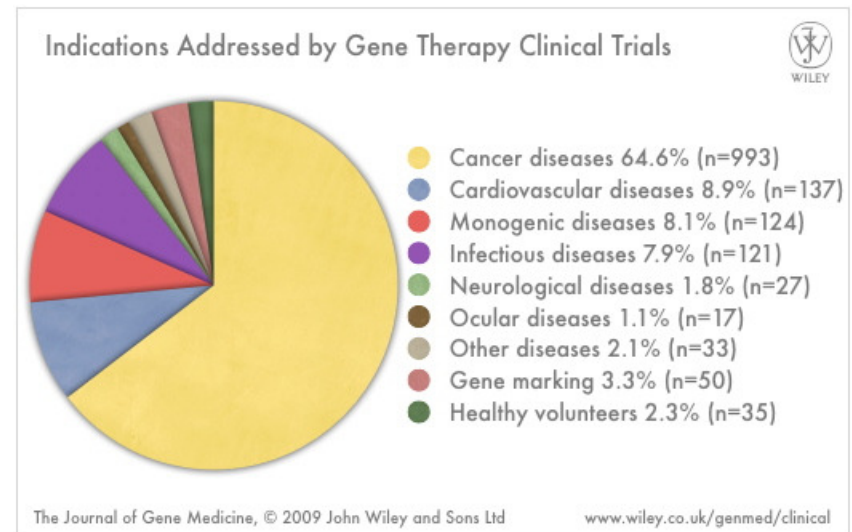
# DNA-based vaccines in humans



- >100 clinical trials with DNA-based vaccines for infectious disease indications
- “Naked” plasmid DNA vaccines generally well-tolerated
- Local reactogenicity mainly associated with formulation and/or delivery vehicle

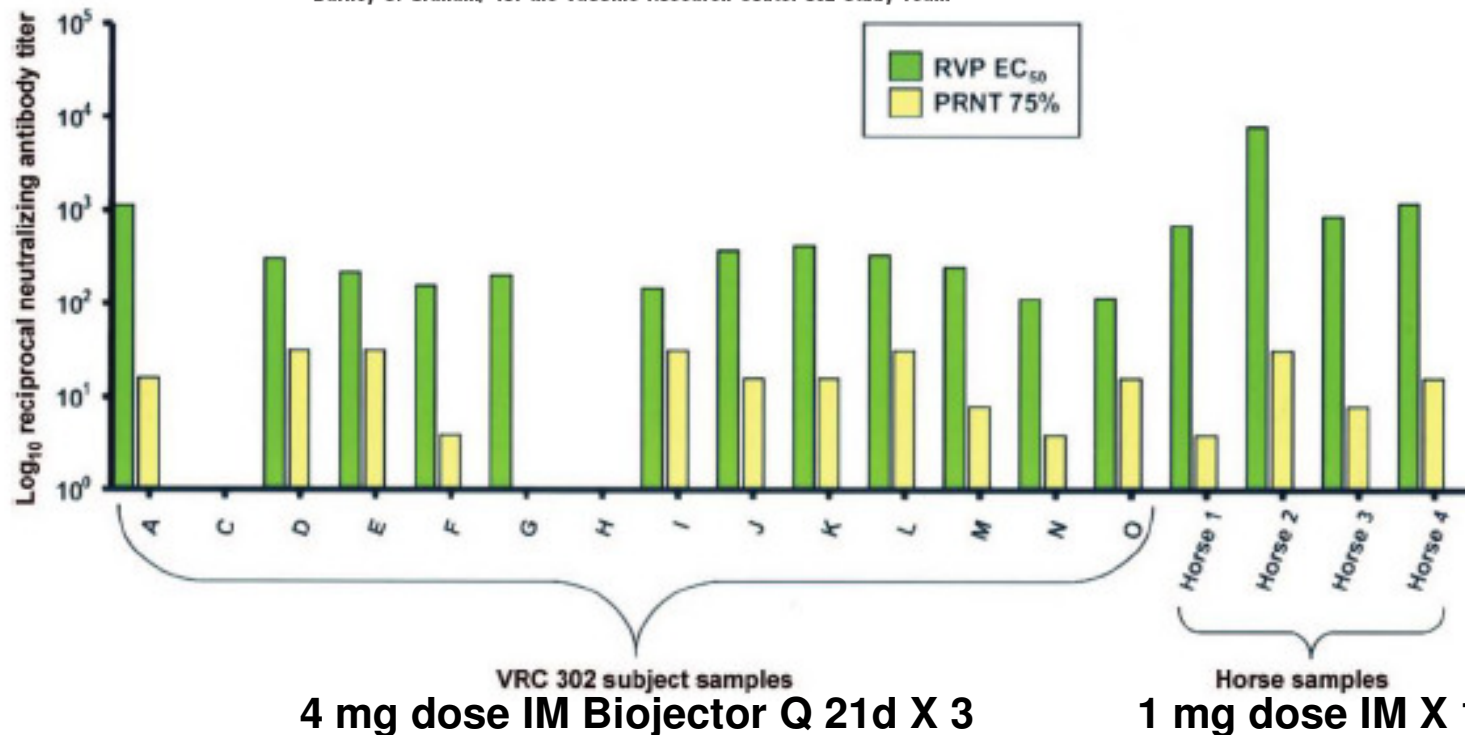
Target pathogens include:

- HIV
- Malaria
- Influenza
- Hepatitis B
- CMV
- WNV
- Ebola
- SARS
- Anthrax
- HPV (Rx)



# A West Nile Virus DNA Vaccine Induces Neutralizing Antibody in Healthy Adults during a Phase 1 Clinical Trial

Julie E. Martin,<sup>1</sup> Theodore C. Pierson,<sup>2</sup> Sarah Hubka,<sup>1</sup> Steve Rucker,<sup>1</sup> Ingelise J. Gordon,<sup>1</sup> Mary E. Enama,<sup>1</sup> Charla A. Andrews,<sup>1</sup> Qing Xu,<sup>2</sup> Brent S. Davis,<sup>3</sup> Martha C. Nason,<sup>1</sup> Michael P. Fay,<sup>1</sup> Richard A. Koup,<sup>1</sup> Mario Roederer,<sup>1</sup> Robert T. Bailer,<sup>1</sup> Phillip L. Gomez,<sup>1</sup> John R. Mascola,<sup>1</sup> Gwong-Jen J. Chang,<sup>3</sup> Gary J. Nabel,<sup>1</sup> and Barney S. Graham,<sup>1</sup> for the Vaccine Research Center 302 Study Team<sup>a</sup>



**Figure 2.** Serum samples from vaccinees at week 12 (4 weeks after the third vaccination) and serum samples from horses 3 weeks after receipt of a 1-mg dose of pCBWN West Nile virus (WNV) DNA vaccine, assessed by WNV reporter-virus particles (RVP) neutralization assay and by plaque reduction neutralization (PRNT). The X-axis shows individual vaccine clinical trial subjects or horse samples, and the Y-axis shows the log<sub>10</sub> reciprocal antibody titer. Subject B was not assessed at the week 12 time point because of visit noncompliance. Subjects G and H received 2 doses of vaccine. Subject C received 1 dose of vaccine. VRC, Vaccine Research Center.

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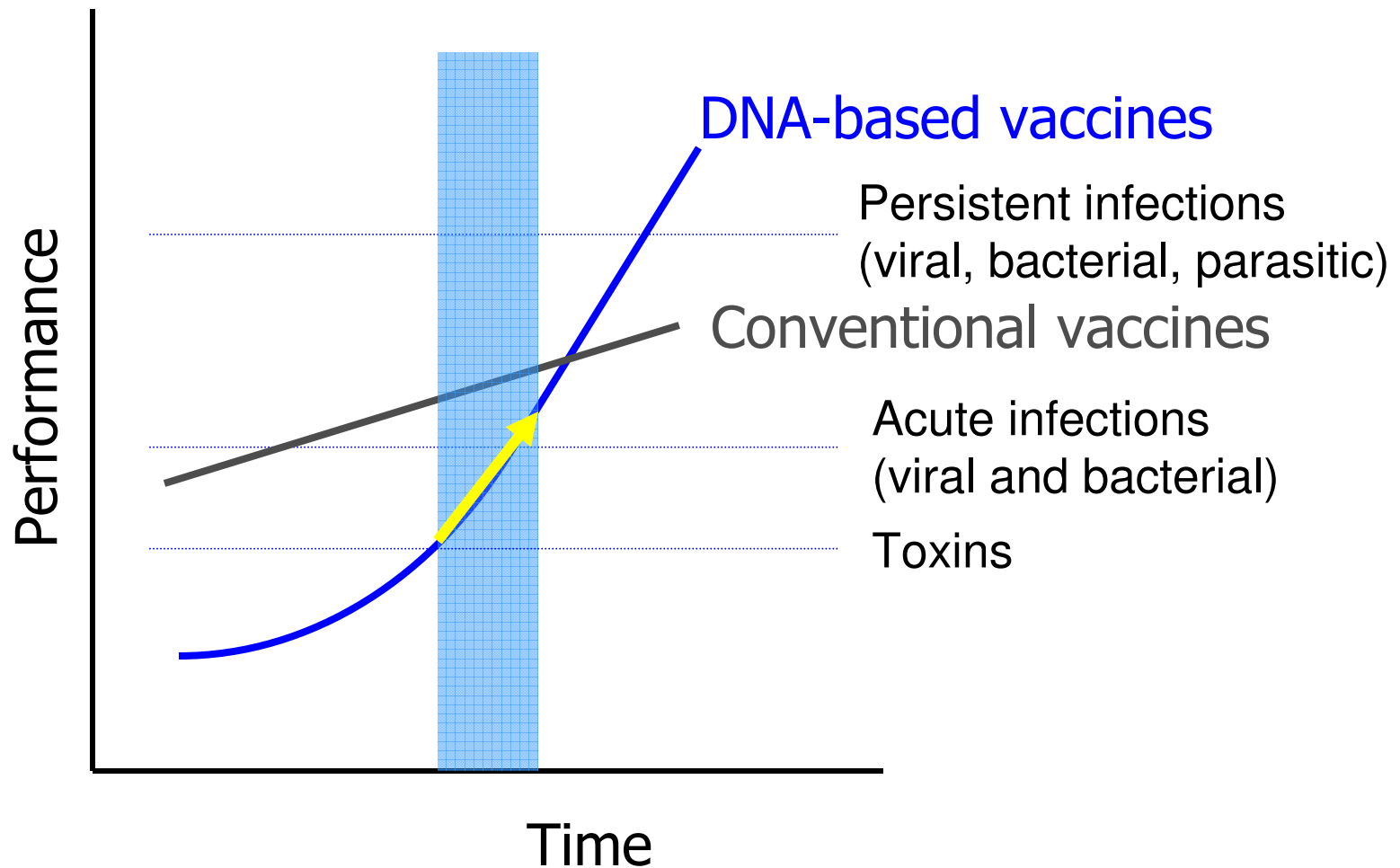
# Global infectious diseases for which there are not licensed vaccines

Pediatric	Adolescent	Adult/Elderly	Specialized
<p>B19 parvovirus Enterotoxigenic <i>E. coli</i> Flavivirus (Dengue, WNV) Group A Streptococci <i>Helicobacter pylori</i> HCV HSV-1 <i>Moraxella catarrhalis</i> <i>Mycobacterium tuberculosis</i> <i>Mycoplasma pneumoniae</i> <i>Neisseria meningitidis (type b)</i> Nontypeable <i>Haemophilus influenzae</i> Norovirus/Norwalk virus Picornaviridae (Rhino, Coxsackie, Echo) RSV, PIV, HMPV <i>Staphylococcus aureus / epidermidis</i></p>	<p>B19 parvovirus <i>Chlamydia trachomatis</i> Cytomegalovirus Epstein-Barr Virus Group B Streptococci HIV HSV-1 and -2 <i>Neisseria gonorrhoeae</i> <i>Neisseria meningitidis</i> <i>Treponema pallidum</i> (Syphilis)</p>	<p><i>Chlamydia pneumoniae</i> Flavivirus (Dengue, WNV) HBV Therapeutic HCV Therapeutic HPV Therapeutic <i>Helicobacter pylori</i> RSV <i>Legionella pneumophila</i> <i>Staphylococcus aureus</i></p>	<p><b>Immunocompromised/ Opportunistic</b> <i>Acinetobacter</i> <i>Aspergillus</i> <i>Candida</i> <i>Clostridium difficile</i> Cytomegalovirus <i>Enterococcus</i> Epstein-Barr Virus <i>Pseudomonas aeruginosa</i> Nosocomial: <i>E.coli/Klebsiella</i>, etc JC and BK virus <i>Staphylococcus aureus / epidermidis</i> Inactivated Varicella</p> <hr/> <p><b>Regional or Travelers</b> Arenavirus (Lassa Fever, Hantavirus) <i>Borrelia burgdorferi</i> (Lyme Disease) <i>Coxiella burnetii</i> (Q fever) Filovirus (Ebola virus, Marburg virus) Flavivirus (Dengue, WNV) Hepatitis E virus <i>Plasmodium spp</i> Norovirus/Norwalk virus <i>Salmonella typhi</i> SARS Shigella <i>Vibrio cholerae</i></p> <hr/> <p><b>Biowarfare</b> <i>Bacillus anthracis</i> <i>Francisella</i> (Tularemia)</p>

**Source:**

- Institute of Medicine: Vaccines for the 21<sup>st</sup> Century (2000)
- ASM Vaccine Development Report (2005)
- WHO: summary on new vaccines against infectious diseases (2005)
- NIH Jordan report (2002)

# Which targets should be sought first?



# Summary

- DNA-based technologies hold the promise of being:
  - cheaper, simpler, and more convenient-to-use
  - evidence that we can improve performance
- DNA-based vaccines have been market-approved for use in veterinary indications
- Data from human clinical trials are beginning to indicate where DNA-based vaccines are on the “performance curve”
- Stay tuned....