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Vaccine Research Center
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Product Development: Moving from the Bench to the Clinic

Introduction to the Principles and Practice of Clinical Research

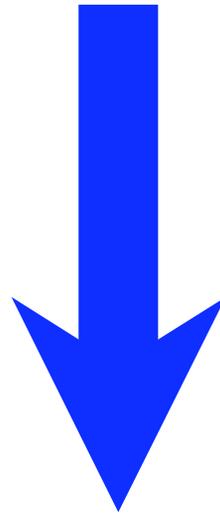
Phillip L. Gomez III, Ph.D., M.B.A.
Director, Vaccine Production

Product Development

- **Product Development**
- **Costs of Product Development**
- **Example: H5 Influenza Vaccine from Bench to Clinic**

Product Development

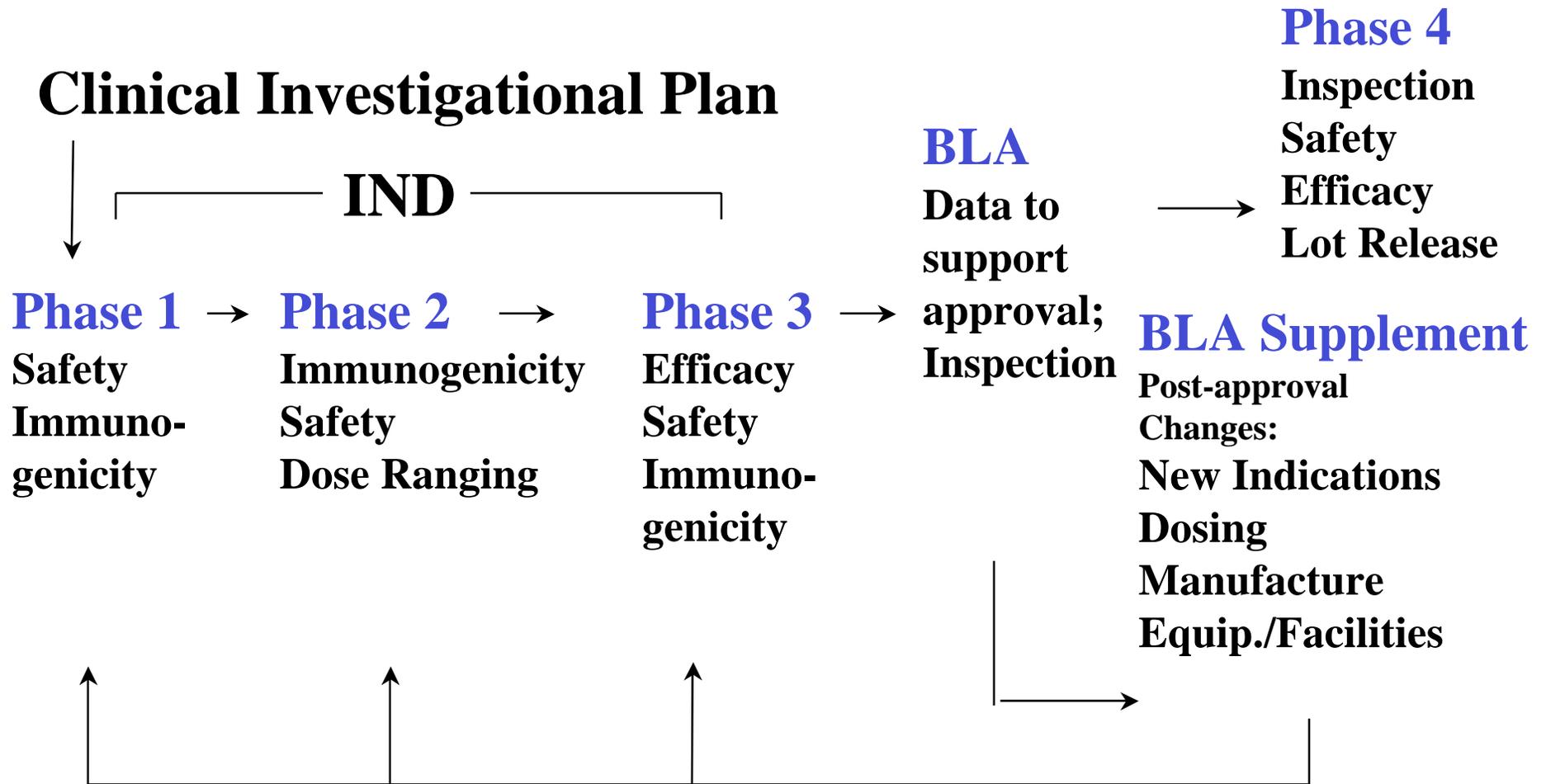
1967. Dr. Hunein Maassab of the University of Michigan develops a live, cold-adapted flu virus for use in a vaccine.



2003. FluMist is available for use for the first time to health adults and children ages 5 through 49.

Source: NIAID Website

Product Development



IND = Investigational New Drug Application; BLA=Biologics License Application

Drug Development Costs

J.A. DiMasi et al. / Journal of Health Economics 22 (2003) 151–185

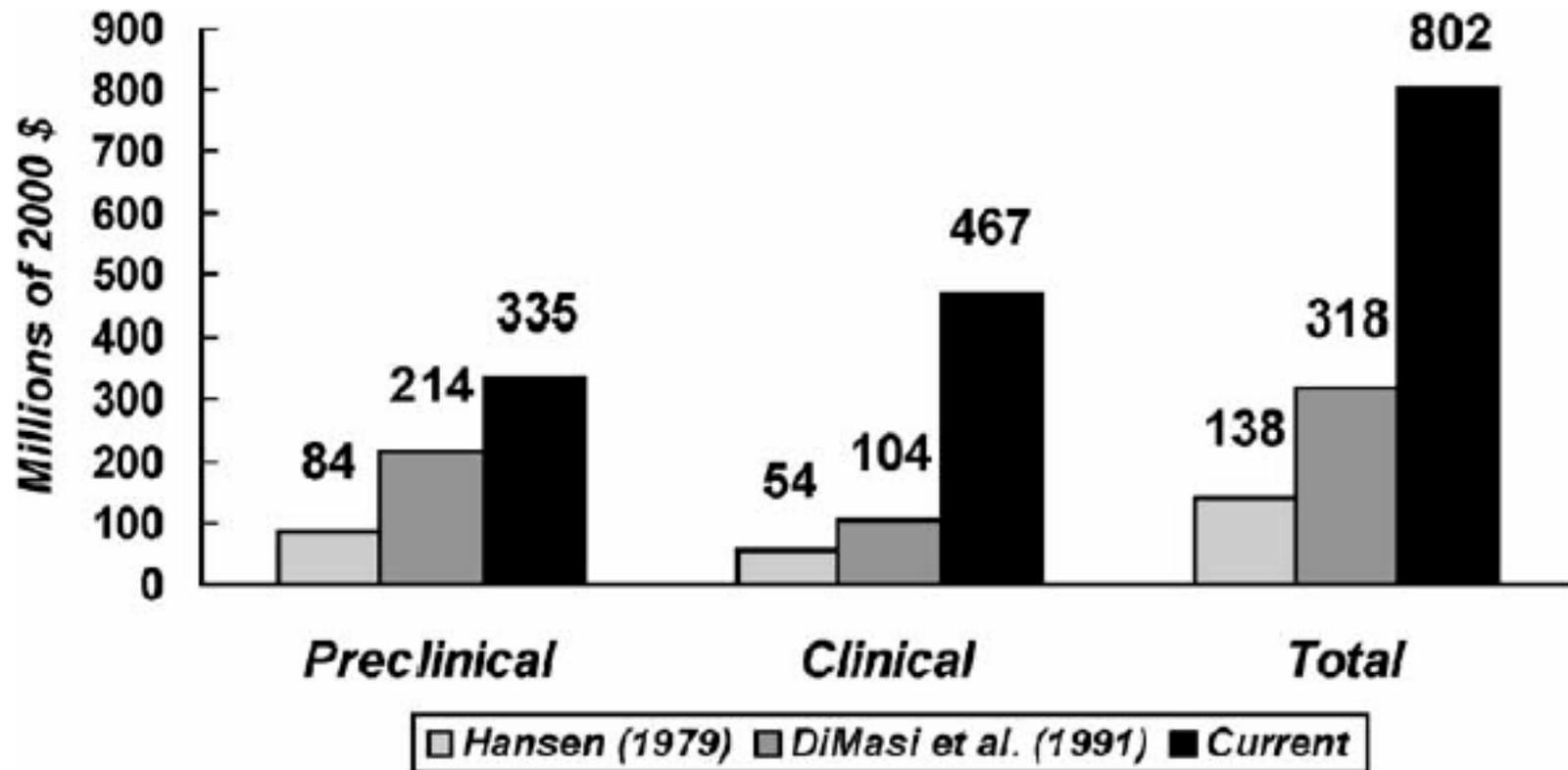


Fig. 2. Trends in capitalized preclinical, clinical and total cost per approved new drug.

Probability of Success

Table 1. Breakdown of vaccine projects per development stage.

Change in stage	Successful	Suspended	Discontinued
Preclinical to phase I	27	3	111
Phase I to phase II	17	3	32
Phase II to phase III	16	0	15
Phase III to preregistration	5	0	10
Preregistration to registration	2	0	2
Registration to launch	22	0	1

Table 2. Transition probabilities of vaccines compared to biopharmaceuticals.

Transition	Vaccine	Biopharmaceutical
Preclinical to phase I	0.57	0.57
Phase I to phase II	0.72	0.88
Phase II to phase III	0.79	0.86
Phase III to registration	0.71	0.93
Registration to launch	0.96	1.00

Vaccine Development at the VRC





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National Institutes of Health
Department of Health and Human Services

Scope of VRC Activities

Pre-clinical Phase I Phase II Phase III

HIV



Ebola



SARS



West Nile Virus



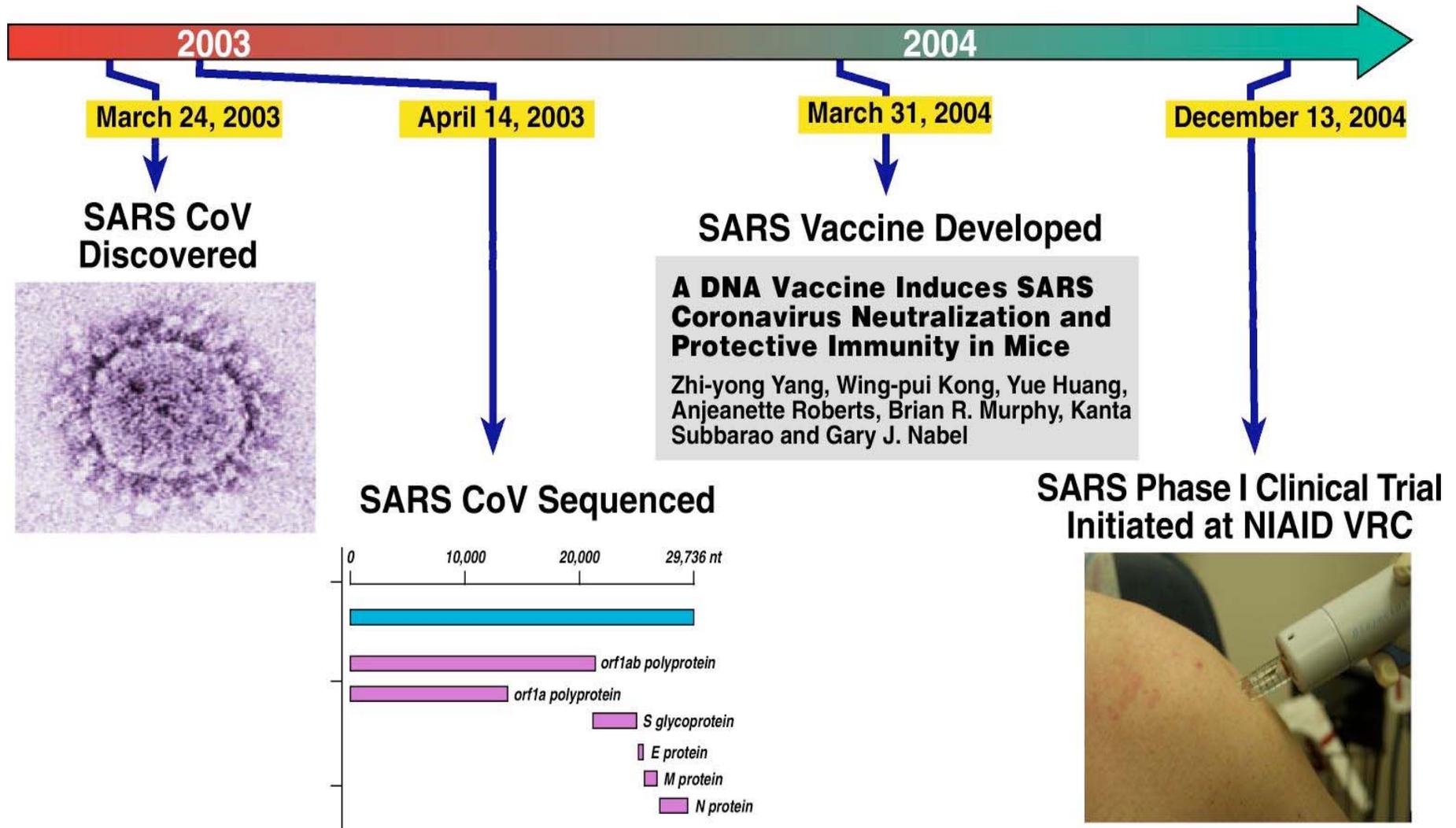
Marburg



Influenza



SARS Characterization and Vaccine Development



Bench to Clinic

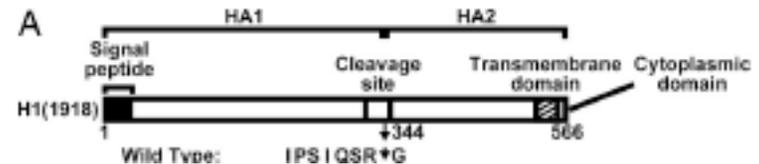
Protective immunity to lethal challenge of the 1918 pandemic influenza virus by vaccination

Wing-pui Kong*, Chantelle Hood*, Zhi-yong Yang*, Chih-Jen Wei*, Ling Xu*, Adolfo García-Sastre†, Terrence M. Tumpey‡, and Gary J. Nabel*[§]

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Communicated by Robert M. Chanock, National Institutes of Health, Bethesda, MD, September 5, 2006 (received for review May 16, 2006)

The remarkable infectivity and virulence of the 1918 influenza virus resulted in an unprecedented pandemic, raising the question of whether it is possible to develop protective immunity to this virus and whether immune evasion may have contributed to its spread. Here, we report that the highly lethal 1918 virus is susceptible to



Bench to Clinic



[National Institute of Allergy and
Infectious Diseases \(NIAID\)](#)

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NIAID DNA Vaccine for H5N1 Avian Influenza Enters Human Trial

The first human trial of a DNA vaccine designed to prevent H5N1 avian influenza infection began on December 21, 2006, when the vaccine was administered to the first volunteer at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD. Scientists from the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID), one of the NIH Institutes, designed the vaccine. The vaccine does not contain any infectious material from the influenza virus.

Vaccine Production Program

Goal: Efficiently translate candidate research vaccines into materials for proof of concept clinical trials and enable advanced development and licensure by partners.

Projects:



Process Research



**Assay
Development**



cGMP Production



**Pre-clinical
Safety**

**Regulatory
Science**



DNA Plasmid Fermentation



DNA Plasmid Purification



DNA Assay Development



Engineering Controls

- **HVAC design**
 - Air handlers
 - Airlock setup and room pressurizations
 - Room Classifications
- **WFI system**
- **Disposable fluid path solution preparation**
- **Liquid and solid biowaste systems**
- **Uniflow building layout**

Airlock Setup and Room Pressurizations

- **Separate air handlers for each area**
- **Separation between production areas is maintained by a system of negative pressure airlocks protecting both entry and return corridors**
- **All airlock functions and room pressure differentials are individually monitored and alarmed**



Hynetics System



- **Dual capacity at 100 – 750 Liters and 750 – 3,000 Liters**
- **Completely disposable fluid path to single use final containers**
- **Final containers are sterile, disposable bags in mobile transports**

Utilities



- Flexible delivery of 19 utility systems
- Approximately 9 miles of pipe
- Over 180 miles of cable

Bioreactor Capacity

- Dual use (prokaryotic/eukaryotic)
- 15L - 2000L



Downstream Processing

- ISO 8 and ISO 7 rooms in each train
- Open design for maximum flexibility



Fill / Package / Finish Operations



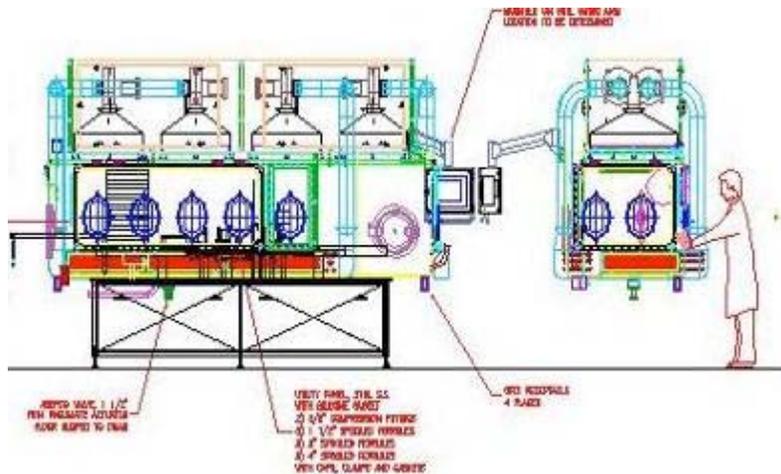
Fill Range and Line Capacity:

- **Vial Sizes:** 2 mL to 5 mL vials
- **Manual Filling** - < 100 to 5000 vials
- **Semi-Automatic Small Scale** - 2000 to 5000 vials/shift
- **Continuous Large Scale** - 5000 to 50,000 vials/shift

Barrier Isolator Technology

utilized to allow both viral and non-viral filling capabilities

- Validated cleaning between vaccine types
- High quality Class 100 filling environment
- Limits product exposure to contamination



Full range of operation: component preparation; sterilization; formulation; filling; inspection; labeling and packaging

Biowaste

■ Liquid

- Dedicated validated plumbing leading to dual tank batch heat inactivation system
- Inactivated waste is transferred to neutralization tanks then to sanitary sewer

■ Solid

- All solid waste from the processing areas is transferred to a sterilizing macerator
- Resulting waste is dried and disposed in regular trash



cGMP Compliance

*Over 1 million pages of
QA documentation to date in validated
electronic document control system*

Preclinical Safety Studies

	Repeat-Dose Toxicity 	Biodistribution 	Integration 
Test System			
# animals	5/sex/time	5/sex/time	9 L <u>or</u> R quadriceps pooled
# neg. controls (PBS)	5/sex/time	3/sex/time	4 L + R pairs pooled
# plasmid controls	n/a	5/sex/time	n/a
Dose	8 mg* (4 X 0.5 mL)	2 mg (0.5 mL)	100 µg
Regimen	0,1,2 Months**	Day 1	Day 1
Route 	I.M.* Biojector®	I.M.* Biojector®	I.M. Needle & syringe
Endpoints	48 hr & 2 wk post-last dose	8, 30 & 60 days qPCR	30 day Integ. qPCR (thigh)

* Maximum dose/ same route of administration in trial

** Later studies used n+1 trial dosing

Toxicological Safety Evaluation of DNA Plasmid Vaccines against HIV-1, Ebola, Severe Acute Respiratory Syndrome, or West Nile Virus Is Similar Despite Differing Plasmid Backbones or Gene-Inserts

Rebecca L. Sheets,^{*,1} Judith Stein,[†] T. Scott Manetz,[‡] Charla Andrews,[§] Robert Bailer,[¶]
John Rathmann,[¶] and Phillip L. Gomez^{||}

TOXICOLOGICAL SCIENCES **91**(2), 620–630 (2006)

TABLE 2
Clinical Pathology Parameters

TABLE 3
Organs Collected and Weighed

TABLE 5
Organs Examined Histopathologically

Chemistries			Adrenal glands ^a	Brain	Esophagus ^b	Adrenals	Aorta (thoracic)	Brain
A/G ratio	Alanine aminotransferase	Albumin	Eyes ^b	Gonads	Heart	Cecum	Cervix ^a	Colon
Alkaline phosphatase	Aspartate aminotransferase	Calcium	Kidneys	Liver (with drained gallbladder)	Lungs with main bronchii	Duodenum	Epididymes	Esophagus
Carbon dioxide (CO ₂) ^a	Cholesterol	Chloride	Parathyroids/thyroids ^a	Pituitary ^{a,c}	Prostate ^b	Eyes	Femur	Gallbladder
Creatinine	Creatinine kinase	Gamma Glutamyl transpeptidase (GGT)	Spleen	Thymus ^c	Uterus	Gonads	Harderian glands ^b	Heart
Globulin	Glucose	Lactate dehydrogenase	^a In studies III, V, VI, and VII, not weighed in studies I, II, or IV. ^b In study I only. ^c In all studies except study I.			Injection sites (including underlying muscle and overlying subcutis)	Ileum	Jejunum
Phosphorase	Potassium	Sodium				Kidneys ^c	Lacrimal glands	Liver
Total bilirubin	Total protein	Triglycerides				Lung with main stem bronchii	Mandibular or submandibular lymph nodes	Mandibular salivary glands
Urea nitrogen						Mesenteric lymph nodes	Mammary glands (♀, ♂)	Optic nerves ^d
Hematology						Pancreas	Parathyroids	Pituitary
Cellular morphology ^c	Erythrocyte count	Hematocrit				Prostate	Rectum	Seminal vesicles
Hemoglobin	Leukocytes	Leukocyte differential				Sciatic nerve	Skeletal muscle ^d	Skin
Mean cell hemoglobin	Mean cell hemoglobin concentration	Mean cell volume				Spinal cord (cervical, midthoracic, lumbar)	Spleen	Sternum ^e
Mean platelet volume ^d	Platelet count	Reticulocytes ^e				Stomach	Thymus	Thyroids
Coagulation			External surface of body	Injection sites	Orifices	Trachea	Tongue	Urinary bladder
Activated partial thromboplastin time ^a	Prothrombin time ^a		Cranial cavity and contents	Thoracic cavity and contents	Abdominal cavity contents	Uterus	Vagina	Gross lesions
						Animal ID ^f		

Repeated-Dose Toxicity Results

- **All animals survived to sacrifice**
- **Minimal to mild erythema & edema at injection sites in some controls and all treated animals**
- **Correlated with histopathology at injection sites**
- **Other sporadic findings considered incidental for species**
- **Measures included: Mortality, Morbidity, Clinical obs., Physicals, Inj. site Draize score, Body wt & Food consumption, Ophthalmoscopic exams, Clinical pathology, Organ weights, Gross & Histopathology**

Biodistribution of DNA Plasmid Vaccines against HIV-1, Ebola, Severe Acute Respiratory Syndrome, or West Nile Virus Is Similar, without Integration, despite Differing Plasmid Backbones or Gene Inserts

Rebecca L. Sheets,^{*,1} Judith Stein,[†] T. Scott Manetz,[‡] Chris Duffy,[§] Martha Nason,[¶] Charla Andrews,^{||}
Wing-Pui Kong,[†] Gary J. Nabel,[†] and Phillip L. Gomez^{||}

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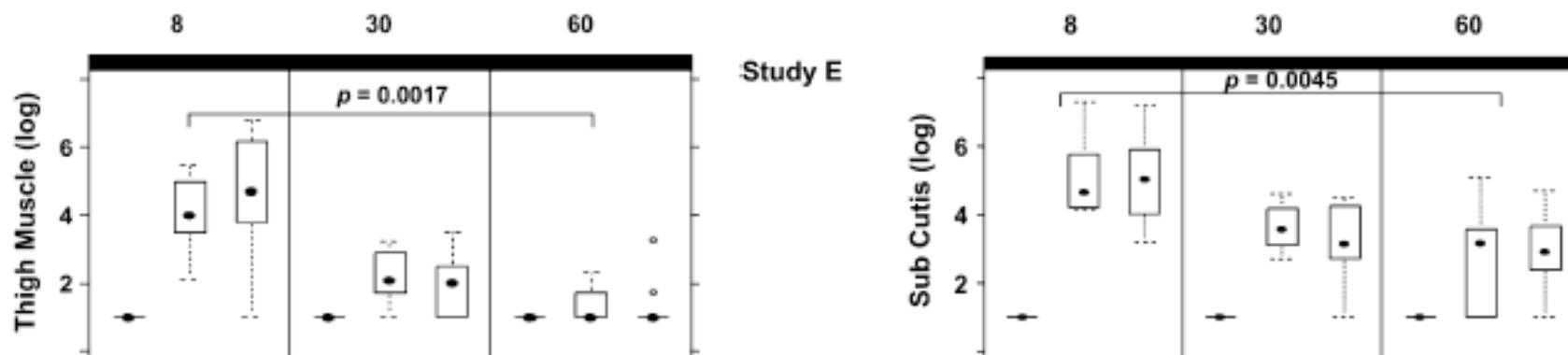


TABLE 2

Quantifiably positive PCR results in all tissues in all studies at the final study timepoint

		Injection site muscle	Injection site sub-cutis	Adrenal glands	Blood	Bone marrow	Brain	Gonads	Heart	Kidneys	Liver	Lungs	Lymph node—mesenteric	Lymph node—right popliteal	Lymph node—left popliteal	Spleen	Thymus
Study A	Placebo (n = 2)	0	*	*	0	0	0	0	0	0	0	0	0	*	*	*	*
	Test article (n = 10)	6	*	*	8	1	0	0	1	0	0	0	0	*	*	*	*
Study B	Placebo (n = 2)	0	*	*	0	0	0	0	0	0	0	0	0	*	*	*	*
	Test article (n = 10)	1	*	*	0	1	1	0	0	1	0	0	0	*	*	*	*
Study C	Placebo (n = 2)	0	*	*	0	0	0	0	0	0	0	0	0	*	*	*	*
	Test article (n = 10)	8	*	*	1	1	0	0	0	0	0	0	0	*	*	*	*
Study D	Placebo (n = 2)	0	0	*	0	0	0	0	0	0	0	0	*	*	0	0	*
	Test article 1 (n = 10)	0	7	*	0	1	0	0	0	1	0	0	*	*	0	0	*
	Test article 2 (n = 10)	2	7	*	1	0	0	0	0	0	0	0	*	*	0	0	*
	Comparator (n = 10)	2	8	*	0	0	0	0	0	0	0	0	*	*	0	0	*
Study E	Placebo (n = 2)	0	0	0	1	0	0	0	0	0	0	0	0	*	*	0	0
	Test article (n = 10)	2	7	0	0	0	0	0	0	0	0	0	0	*	*	0	0
	Comparator (n = 10)	1	9	0	0	0	0	0	0	0	0	0	1	*	*	0	0
Study F	Placebo (n = 2)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Test article (n = 10)	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Comparator (n = 10)	2	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Study G	Placebo (n = 2)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Test article (n = 10)	0	3	0	0	0	0	0	0	0	0	0	0	2	0	0	0
	Comparator (n = 10)	7	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0
VRC-4302	n = 40**	9 (23)	25 (83)	0	0	1 (3)	1 (3)	0	0	1 (3)	0	0	1 (3)	0	0	0	0

Final Release of Investigational Vaccine





Dale and Betty Bumpers

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National Institute of Allergy and Infectious Diseases

National Institutes of Health

Department of Health and Human Services

Vaccine Production

VPL

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Everyone At the VPP

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Woody Dubois
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Michelle Conan-Cibotti

VRC

Gary Nabel
John Mascola
Richard Koup
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