



Research and Developments in Smallpox Vaccine LC16m8

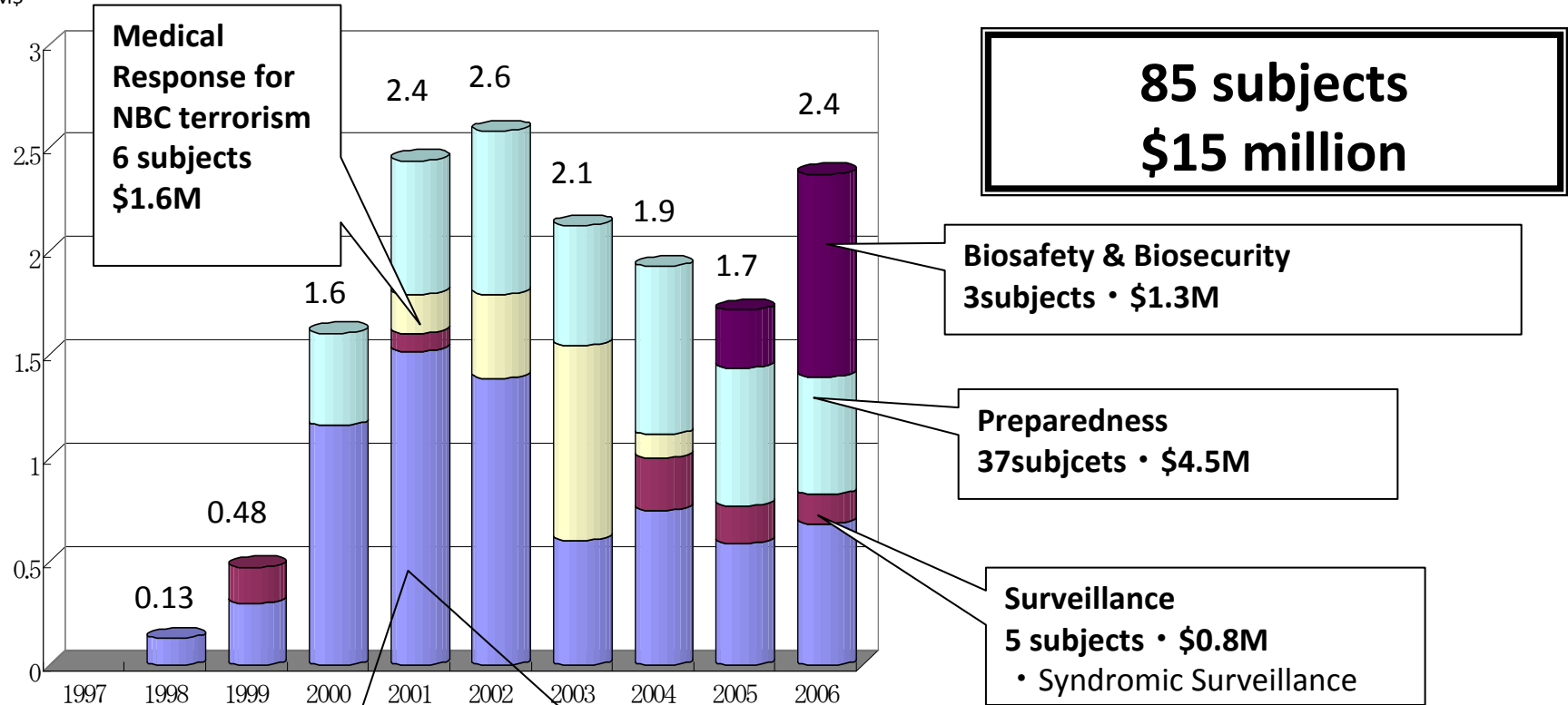
Tomoya Saito, M.D., Ph.D.

**School of Medicine, Keio University
& Smallpox Vaccine Research Group**

Biodefense Research in Japan, 1997~2006

Research Grant from MHLW

単位
M\$

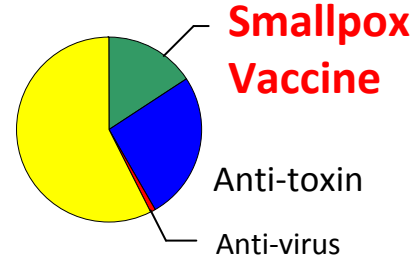


Medical Countermeasures

34 subjects • \$7.1M

- Smallpox Vaccine (1998~)
- Anti-toxin (2000~)
- Detection, Lab Dx (1999~)
- Anti-virus (2004~)

Detection
Lab Dx



**Smallpox
Vaccine**

Anti-toxin

Anti-virus

Biosafety & Biosecurity
3 subjects • \$1.3M

Preparedness
37 subjects • \$4.5M

Surveillance
5 subjects • \$0.8M
• Syndromic Surveillance

**85 subjects
\$15 million**

**Medical
Response for
NBC terrorism**
6 subjects
\$1.6M

1\$=115 Yen

T Saito, unpublished

The History of Smallpox Vaccine Preparedness in Japan

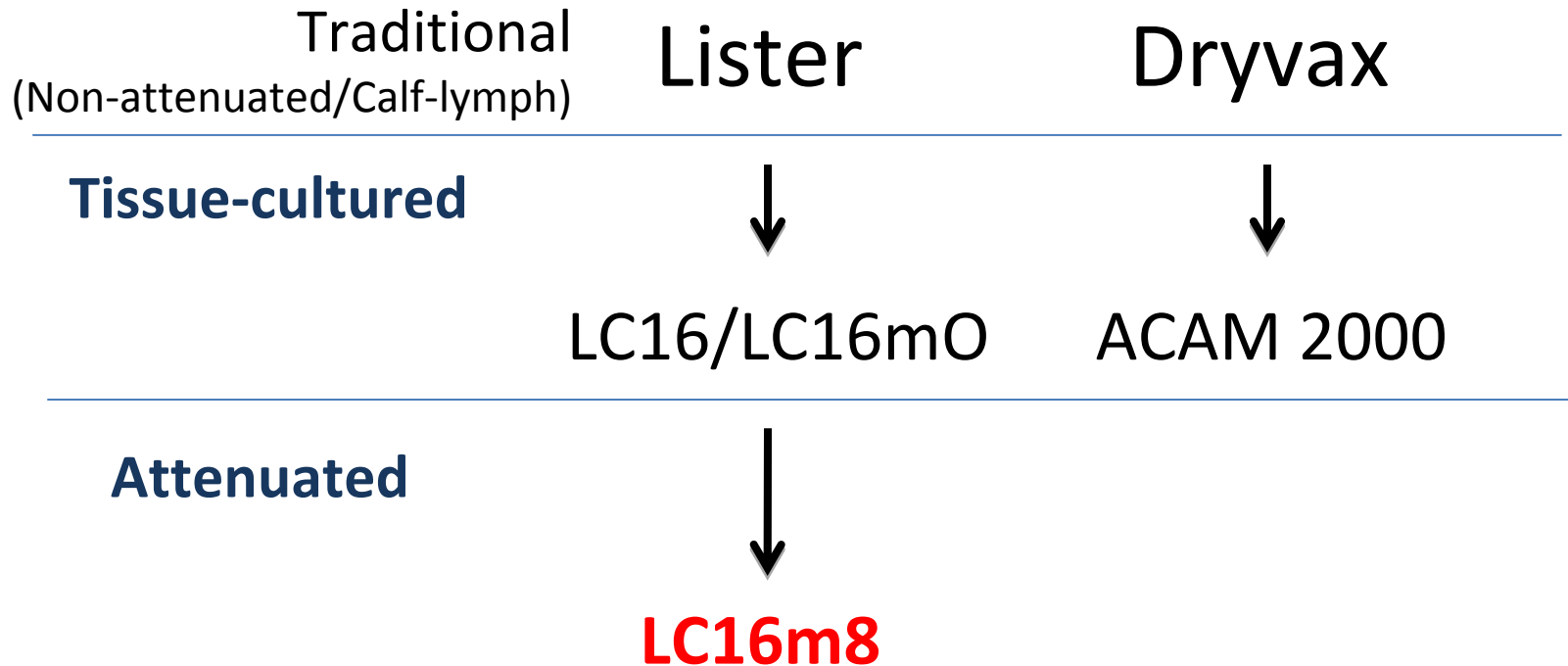
- 1976 Regular vaccination ceased
- 1980 Vaccine production ceased, 1.3m doses stockpiled
- 1998 SVRG re-established
Test Production of 10,000 doses for Lab workers
- 2001 Govt. contracted for 2.5m dose (Nov.)
- 2002 2.5m dose delivered (Mar.)
Manufacturer Chiba Serum Institute closed
: Vaccine Seed moved to KAKETSUKEN
Armed Forces (SDF) started vaccination for Selected Personnel
- 2003 7.5m doses delivered
- 2005 Task Force recommended 56m doses for stockpile
- 2006 Shelf-life extended: 3 yrs --> **4 yrs**

Smallpox Vaccine Preparedness in Japan: Current Activities

- Govt is still contracting for stockpiling LC16m8 vaccine.
- Production Capacity:
80 million doses/year in KAKETSUKEN
- Smallpox Vaccine Research Group has been working since 1998 for
 - Maintenance of the stockpile (potency, stability)
 - Re-evaluation of LC16m8 vaccine for bioterrorism preparedness

Smallpox Vaccine LC16m8

- Developed and **licensed** in Japan in 1970's



Smallpox Vaccine LC16m8

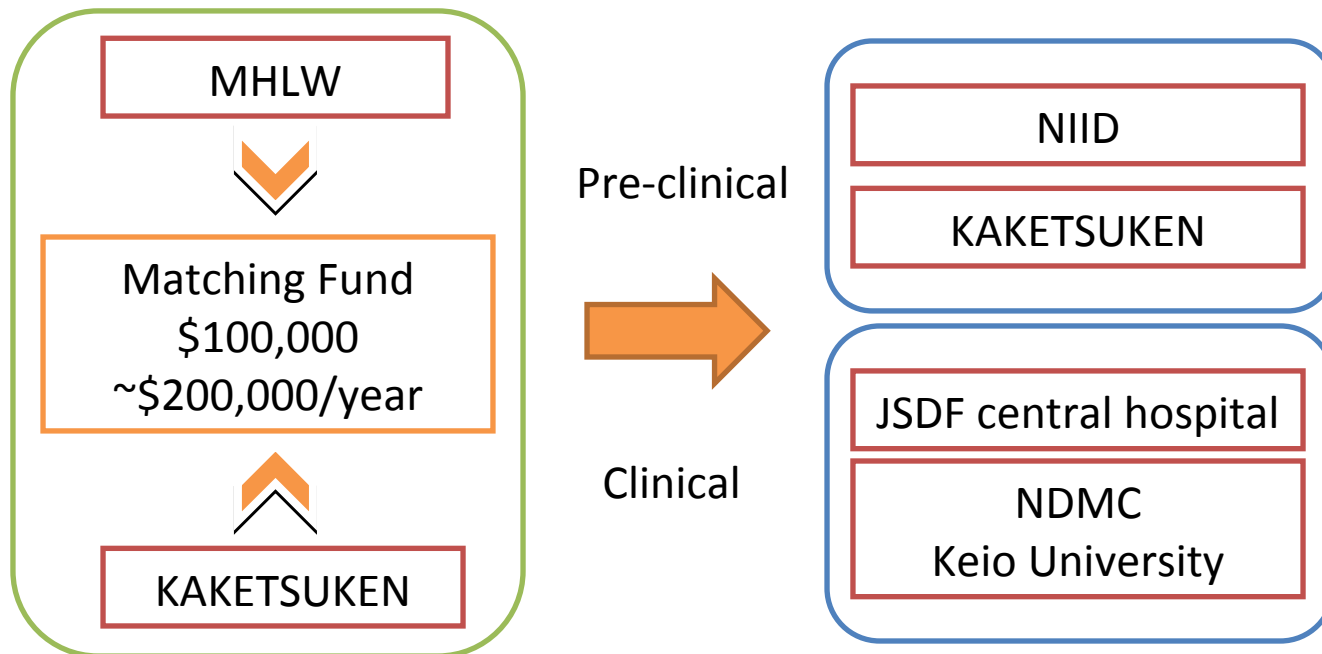
- Experience in 1970's
 - Pre-Clinical Experience
 - **Lower dermal reaction** in rabbits
 - **Lower neuro-virulence** in rabbits and monkeys
 - **Comparable Ab titer** in rabbits to that of non-attenuated strain
 - Clinical Experience
 - Clinical trial in ~10,000 children
 - Take%: **95.2%**
 - No severe adverse events reported
 - ~100,000 infants until the end of regular vaccination
 - **no severe adverse events** reported.

Re-evaluation of LC16m8 vaccine for bioterrorism preparedness

- Not field-tested
- Long-term efficacy
- Efficacy and Safety in immunocompromised
- Post-exposure prophylaxis
- Quality assurance for a long-term storage
- Limited experience in adults

Re-evaluation of LC16m8 vaccine for bioterrorism preparedness

- Smallpox Vaccine Research Group (SVRG)



MHLW: Ministry of Health, Labour and Welfare
NIID: National Institute of Infectious Diseases
JSDF: Japan Self Defense Forces
NDMC: National Defense Medical College

KAKETSUKEN

(The Chemo-Sero-Therapeutic Research Institute)

- Established in 1945
- Non-profit juridical foundation
- Provides vaccines and anti-toxins such as:
 - Seasonal/Pandemic Flu vaccines
 - DTaP, JE, HBV, HAV, Rabies vaccines
 - anti-venom, anti-botulinus toxin and toxoids, etc.
 - Animal Vaccines

Re-evaluation of LC16m8 Vaccine

- Not field tested
 - > Challenge studies in animal models (Animal rules)
 - Mouse (J Virol., 2005; PNAS, 2005; Vaccine, 2006)
 - Rabbit (Vaccine, 2006)
 - Monkey (ASM Biodefense meeting, 2006, J Virol., 2006)
- Long-term Efficacy
 - > Mouse (~1.5 yrs) (ASM Biodefense meeting, 2009)
 - > Monkey (1 yr) (J Virol., 2006; 12th meeting of J Society for Vaccinology, 2008)
- Efficacy and Safety in immunocompromised
 - > Murine atopic dermatitis model (55th meeting of J Society for Virology, 2007)
 - > Immunodeficient mouse model (Sci. Rep. Chemo-Sero-Therap.Res. Inst., 2007)
- Post-exposure prophylaxis
 - > Early phase challenge after vaccination model in Mouse/Monkey (ASM Biodefense meeting, 2007; 13th Int'l Congress on Inf Dis, 2008)
- Quality Assurance for a long-term storage
- Limited experience in adults

Re-evaluation of LC16m8 Vaccine

- Quality Assurance for a long-term storage
 - Stable for at least 5 years at -20°C
 - Stable moisture content for 4 years
 - Shelf life extended to 4 years in 2006
 - Potency can be easily evaluated by the virus titer, however, how the stability might affect vaccine safety cannot be predicted.
 - We are looking for an indicator for safety in a long-term storage



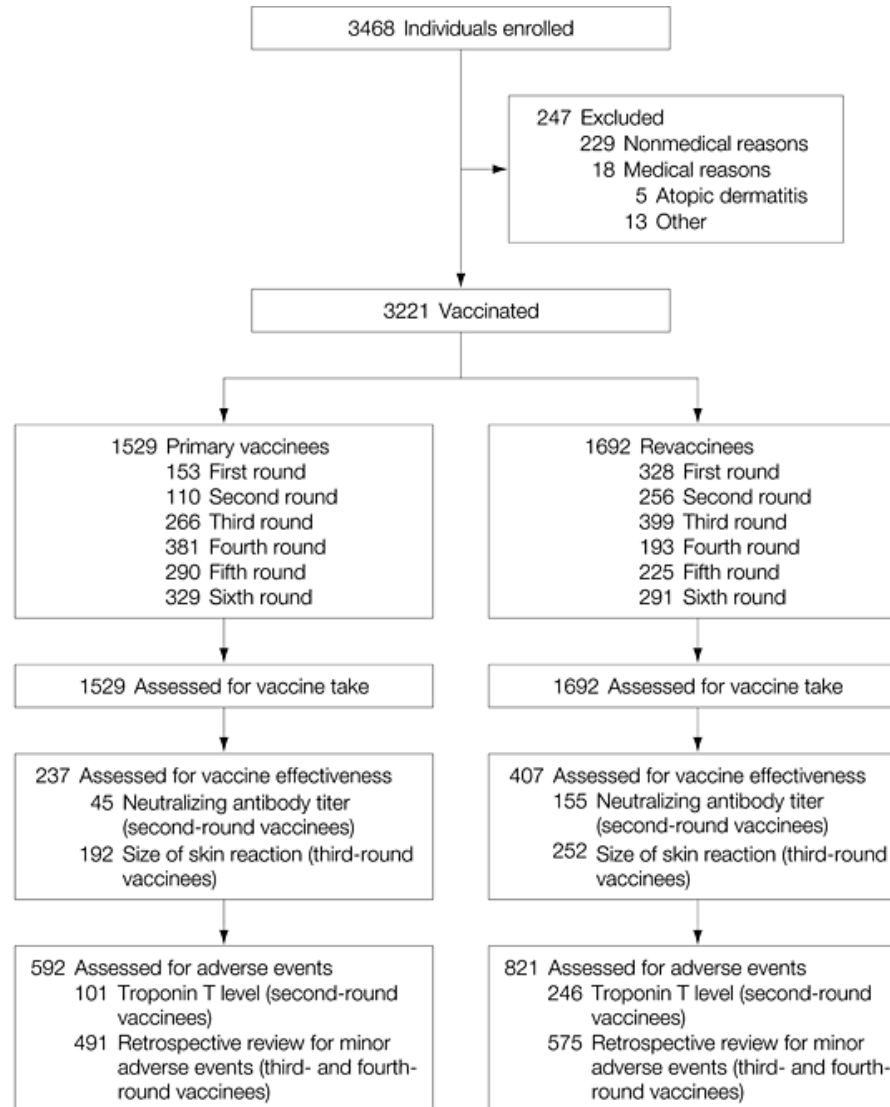
Re-evaluation of LC16m8 Vaccine

- Limited experience in adults
 - > Clinical study in Japanese Armed Forces
 - Immunogenicity in vaccinia-naïve adults and re-vaccinees

Study Design

- Place/Time: Japan Self Defense Force Central Hospital, 2002-2006
- Subjects: Healthy adults, 18-55 y/o
- Vaccine: LC16m8 (KAKETSUKEN, Japan), 10^8 pfu/mL
- Vaccination: Scarification by bifurcated needle
 - 5 strokes for vaccinia-naïve, 10 strokes for previously vaccinated
- Immunogenicity: Clinical Take
 - Plaque Reduction Neutralization Test (PRNT)
 - (Challenge virus: LC16m8, Dryvax®)

Flow of Participants Through the Study



Immunogenicity

“Take” at 14 Days Following Vaccination With LC16m8 Vaccine



	Vaccinia-naïve (n=1,529) [95%CI]	Previously-vaccinated (n=1,692) [95%CI]
%Take	94% [93%, 96%]	87% [85%, 88%]
%Seroconversion	90% [81%, 99%]	60% [52%, 67%]

Severe Adverse Events

- 5 hospitalized within 30 days after vaccination
 - 2 were suspected to be related to the vaccination
 - Allergic dermatitis
 - Erythema multiforme
- No case of
 - Auto/contact-inoculation, Eczema vaccinatum, Progressive vaccinia, Generalized vaccinia, Encephalitis, Death
 - Myopericarditis
 - No symptomatic myopericarditis
 - 347 subjects were further reviewed for asymptomatic myopericarditis.
 - All the subjects were under detection limit (0.01 ng/ml) for Troponin T before and after the vaccination (Day28).
 - None of the subjects had abnormality in ECG on day 28.
- VIG/Drug were not used for any vaccinee.

Prevalence of Adverse Events by Previous Vaccination History With LC16m8 Vaccine

Table 4. Prevalence of Adverse Events by Previous Vaccination History With LC16m8 Vaccine

Adverse Events (%)	No. of Events (%)		
	Primary Vaccinees (n = 491)	Revaccinees (n = 575)	Total (N = 1066)
Swelling of axillary lymph node	76 (15.5)	20 (3.5)	96 (9.0)
Low-grade fever (>37.5°C)	13 (2.6)	8 (1.4)	21 (2.0)
Skin itching/urticaria	4 (0.8)	3 (0.5)	7 (0.7)
Influenza-like symptom	5 (1.0)	1 (0.2)	6 (0.6)
Headache	5 (1.0)	0	5 (0.5)
Myalgia of neck, breast, upper arm	3 (0.6)	1 (0.2)	4 (0.4)
Swelling of cervical lymph node	2 (0.4)	1 (0.2)	3 (0.3)
Diarrhea	1 (0.1)	1 (0.2)	2 (0.2)
Acute sensorineural deafness	1 (0.2)	0	1 (0.1)
Dizziness	0	1 (0.2)	1 (0.1)
Swelling around orbital area	0	1 (0.2)	1 (0.1)
Arthralgia	0	1 (0.2)	1 (0.1)
Total	110 (22.4)	38 (6.6)	148 (13.9)

Summary of clinical study in adults

- The present study proved the **immunogenicity** of LC16m8 vaccine in vaccinia-naïve adults **by a single scarification**.
- LC16m8 vaccine also induces a **good booster** response in previously vaccinated individuals.
- Our study also offers supportive evidence for the **safety** of LC16m8 vaccine **in adults**.
- LC16m8 vaccine is a **viable alternative** to first, second and other third generation vaccines in the global smallpox preparedness program.

Key Issues in Smallpox Vaccine Preparedness in Japan

- Governmental Support
 - Long-term purchase contract to KAKETSUKEN
 - Research grant for SVRG
 - \$100,000~\$200,000/year since 1998
- Smallpox Vaccine Research Group (SVRG)
 - has been working for 10 years since 1998
& established tight Gov/Industry/Academia partnerships
 - Addressing concerns in LC16m8 for biopreparedness
 - Long-term storage
 - Usage in the contraindicated, etc.
 - Model for “sustainable” MCM preparedness

Issues to be addressed for CBRN MCM Preparedness in Japan

- Development of well-balanced portfolio for CBRN medical countermeasures
 - unbalanced attention to smallpox vaccine & anti-toxins
- “Research Group on Medical Countermeasures for Health Crisis” (2009-) funded by MHLW PI: Tsutomu Takeuchi (Keio Univ.)
 - Gap analysis on availability of anti-CBRN medical countermeasures between Japan and US/EU
 - Development of portfolio for CBRN MCM
 - Addressing emergency use of unlicensed products



THANK YOU