Crucell

human monoclonal antibody cocktail for post-exposure prophylaxis against rabies

Lex Bakker
Program Director
12th, March 2008
London

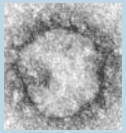
Products and pipeline

offering excellent scope for long-term growth

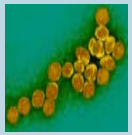
Product	Development stage					Comment
	Pre-clinic	Phase I	Phase II	Phase III	Marketed	
Quinvaxem™						Fully liquid vaccine for protection against five childhood diseases
Hepavax-Gene®						Recombinant hepatitis B vaccine
MoRuViraten®						Vaccine for protection against measles and rubella (all age groups)
Epaxal® Junior						Unique aluminum-free hepatitis A pediatric vaccine (0.25 ml)
Epaxal®						Unique aluminum-free hepatitis A vaccine
Vivotif®						Unique oral anti-typhoid vaccine
Dukarol®						Internationally licensed oral vaccine against cholera (and ETEC)
Inflexal V®						Virosomal adjuvanted influenza (all age groups)
Flavimun®						Yellow Fever vaccine; priority given to production MoRuViraten®
Influenza seasonal						Partnered with sanofi pasteur; planned submission in 2010
H9N2 (influenza pandemic)						Trial completed; findings expected first half 2008
Rabies antibody cocktail			Fast Track			Partnered with sanofi pasteur; Phase II US trial to start in 1H 2008
Malaria						Phase I trial in US on two sites; initial findings expected in 2008
Tuberculosis						Partnered with Aeras Foundation; well tolerated, response to TB antigens
Ebola						Partnered with VRC of NIAID; initial indication suggest safety & immunogenicity
H7N1/Flupan (influenza pandemic)						Developed by sanofi pasteur using Crucell's technology
Factor $V^{L/C}$						Blood coagulation Factor $V^{L/C}$
HIV						Partnered with Harvard; Phase I trial expected to start in Q1 2008
Antibodies against H5N1						Results demonstrating potential pandemic preparedness

PER.C6® derived

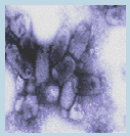
human monoclonal antibodies to fight infectious diseases



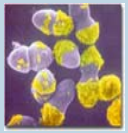
SARS



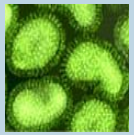
WNV



Rabies



Gram positive bacteria



H5N1

Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets

Jan ter Meulen, Alexander B H Bakker, Edward N van den Brink, Gerrit J Weverling, Byron E E Martina, Bart L Haagmans, Thijs Kuiken, John de Kruif, Wolfgang Preiser, Willy Spaan, ...

THE LANCET • Vol 363 • June 26, 2004 • www.thelancet.com

OPEN ACCESS Freely available online PLoS MEDICINE

Human Monoclonal Antibody Combination against SARS Coronavirus: Synergy and Coverage of Escape Mutants

Jan ter Meulen[1¤*], Edward N. van den Brink[1¤], Leo L. M. Poon[2], Wilfred E. Marissen[1], Cynthia S. W. Leung[2], Freek Cox[1], Chung Y. Cheung[2], Arjen Q. Bakker[1], Johannes A. Bogaards[1], Els van Deventer[1], Wolfgang Preiser[3], Hans Wilhelm Doerr[3], Vincent T. Chow[4], John de Kruif[1], Joseph S. M. Peiris[2], Jaap Goudsmit[1]

JOURNAL OF VIROLOGY, Apr. 2005, p. 4672–4678 Vol. 79, No. 8

Novel Rabies Virus-Neutralizing Epitope Recognized by Human Monoclonal Antibody: Fine Mapping and Escape Mutant Analysis†

Wilfred E. Marissen,[1] R. Arjen Kramer,[1] Amy Rice,[2] William C. Weldon,[3] Michael Niezgoda,[3] Milosz Faber,[2] Jerry W. Slootstra,[4] Rob H. Meloen,[4] Marieke Clijsters-van der Horst,[1] Therese J. Visser,[1] Mandy Jongeneelen,[1] Sandra Thijsse,[1] Mark Throsby,[1] John de Kruif,[1] Charles E. Rupprecht,[3] Bernhard Dietzschold,[2] Jaap Goudsmit,[1] and Alexander B. H. Bakker[1]*

Isolation and Characterization of Human Monoclonal Antibodies from Individuals Infected with West Nile Virus§

Mark Throsby,[1]* Cecile Geuijen,[1] Jaap Goudsmit,[1] Arjen Q. Bakker,[1] Jehanara Korimbocus,[2] R. Arjen Kramer,[1] Marieke Clijsters-van der Horst,[1] Maureen de Jong,[1] Mandy Jongeneelen,[1] Sandra Thijsse,[1] Renate Smit,[1] Therese J. Visser,[1] Nora Bijl,[1]† Wilfred E. Marissen,[1] Mark Loeb,[3] David J. Kelvin,[4] Wolfgang Preiser,[5]‡ Jan ter Meulen,[1] and John de Kruif[1]

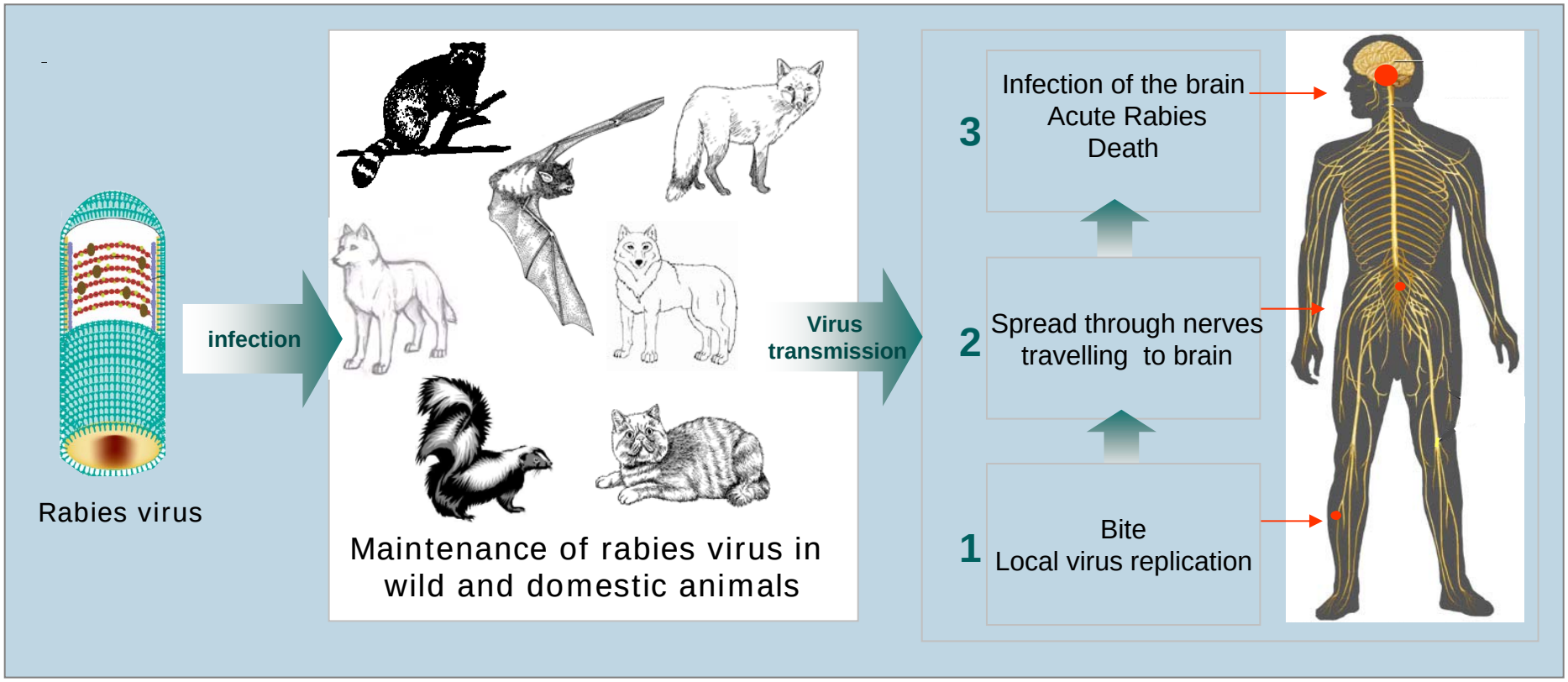
Crucell Holland B.V., Leiden, The Netherlands[1]; National Reference Centre for Arbovirus and Viral Hemorrhagic Fevers, Pasteur Institute, Lyon, France[2]; Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada[3]; Division of Experimental Therapeutics, University Health Network, Toronto, Canada[4]; and Institute of Medical Virology, W. Goethe-Universität, Frankfurt, Germany[5]

JOURNAL OF VIROLOGY, July 2006, p. 6982–6992

Crucell

Rabies virus

transmitted from animals to humans causing a fatal disease



http://www.virology.net/Big_Virology/Special/Rabies1/Rabies.htm

To date there are only six documented cases of human survival from clinical rabies

Rabies

causes over 50,000 deaths each year: over 90% in Asia and Africa

Almost half of all rabies deaths occur in children < age of 15 y

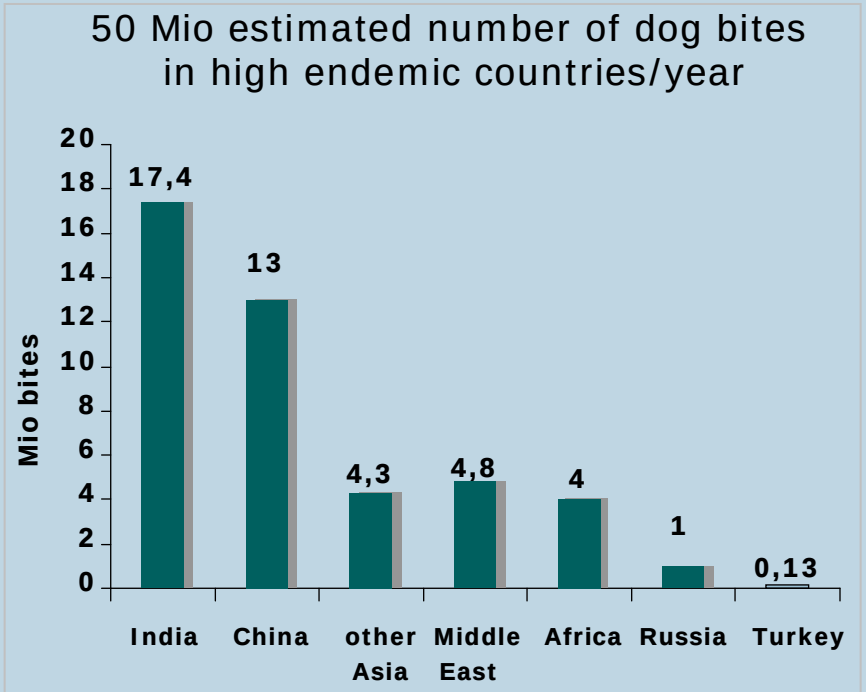
http://www.who.int/rabies/human/en/

Source: FX Meslin, WHO NECTM, Knobel and Tang et al EID, 2005; Zhang et al InFoRab 2005, APCRI data

Dog bites

cause over 95% of human deaths from rabies

Dog bites in children



Indian Journal of Community Medicine Vol.31, No1, January-March 2006

K.M. Kale, S.K. Wadhva, N.R. Aswar, N.D. Vasudeo

Post exposure prophylaxis

100 % effective in preventing rabies

Bite by rabid dog

PEP

Patient with fatal rabies

Administration of
Rabies Immunoglobulin
and multiple doses of rabies vaccine
blocks infection and prevents rabies

Crucell

Blood-derived products

used for PEP but need to be replaced

Human Rabies ImmunoGlobulin (**HRIG**)

Equine Rabies ImmunoGlobulin (**ERIG**)

(Talecris)

(sanofi-pasteur)

(sanofi-pasteur)

(HRIG & ERIG)
Asia and South America

(National productions)

- Expand product availability
- Increase product concentration

- Improve safety
- Expand product availability
- Increase product concentration

Crucell

Human monoclonal antibodies

highly suitable to replace HRIG and ERIG

- Safe product
- Available in unlimited quantity
- Consistent and concentrated product

Estimated market opportunity

peak annual sales exceeding $300 million

	PEP need (dog bites)	PEP Vaccine only	PEP Vaccine + HRIG
India	**17 million**	**3 million**	**>0.1 million**
China	**13 million**	**10 million**	**>0.5 million**

Asia is a high volume market, currently HRIG supply constraint

	PEP need (treatments)	PEP Vaccine + HRIG
USA	**45,000**	**45,000**

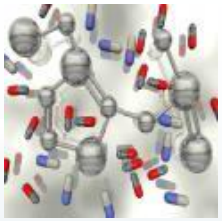
USA is a high price / low volume market

Crucell

First rabies virus neutralizing antibody

CR57 came from known DNA sequence

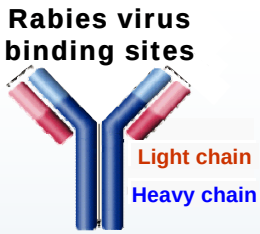
Licensed DNA Sequence of rabies antibody



Synthesis of optimized genes

PER.C6®

Transfer of genes to human PER.C6 cells



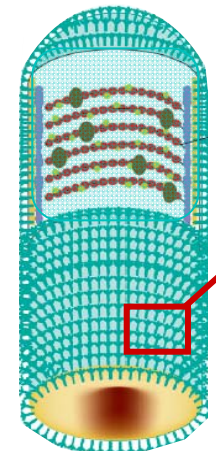
Fully human antibody CR57

- Does antibody CR57 bind to rabies virus?
- Does antibody CR57 neutralize rabies virus isolates?

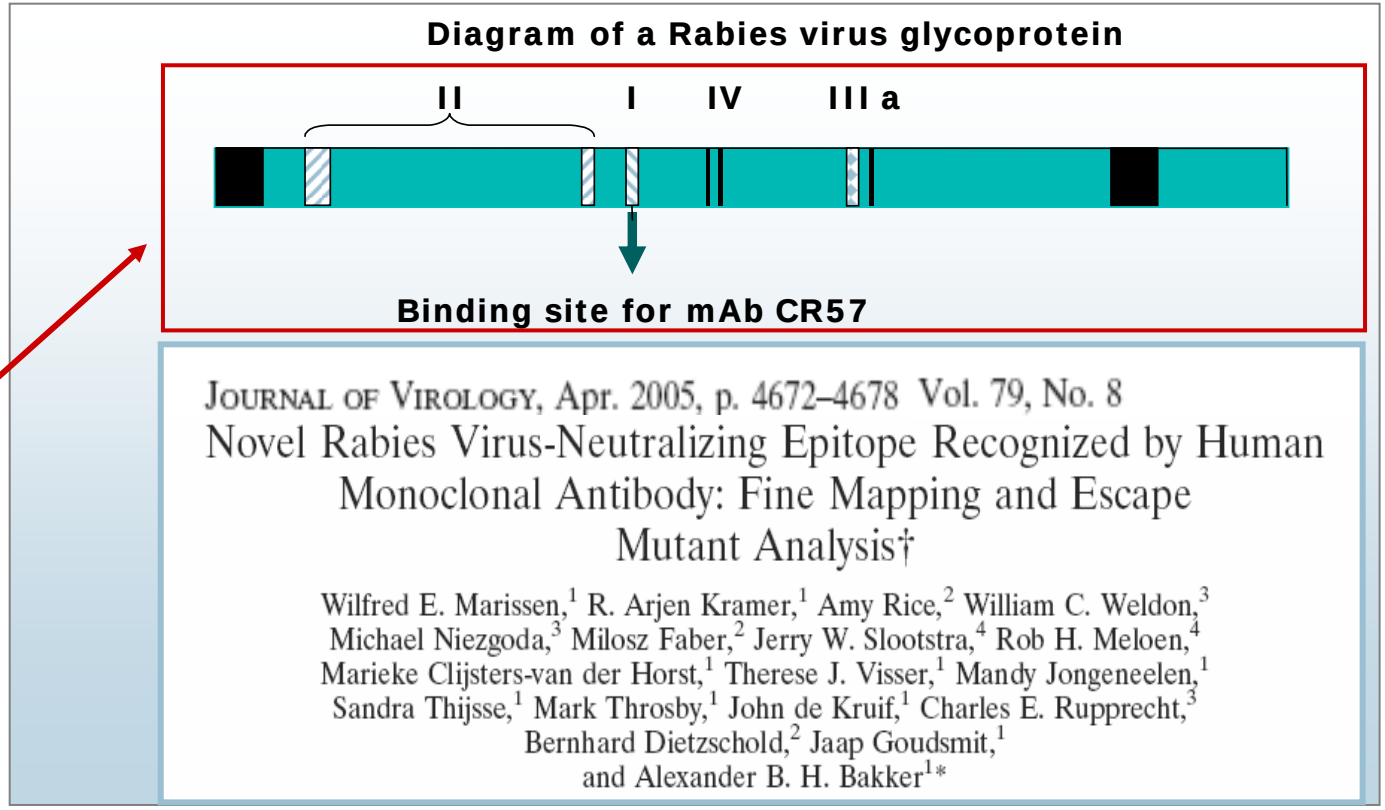
Crucell

Antibody CR57

binds on the rabies virus glycoprotein and neutralizes the virus



Rabies virus



JOURNAL OF VIROLOGY, Apr. 2005, p. 4672–4678 Vol. 79, No. 8

Novel Rabies Virus-Neutralizing Epitope Recognized by Human Monoclonal Antibody: Fine Mapping and Escape Mutant Analysis†

Wilfred E. Marissen,[1] R. Arjen Kramer,[1] Amy Rice,[2] William C. Weldon,[3] Michael Niezgoda,[3] Milosz Faber,[2] Jerry W. Slootstra,[4] Rob H. Meloen,[4] Marieke Clijsters-van der Horst,[1] Therese J. Visser,[1] Mandy Jongeneelen,[1] Sandra Thijsse,[1] Mark Throsby,[1] John de Kruif,[1] Charles E. Rupprecht,[3] Bernhard Dietzschold,[2] Jaap Goudsmit,[1] and Alexander B. H. Bakker[1]*

Antibody CR57

neutralizes most, but not all representative rabies street viruses

Rabies virus terrestrial mammals	SRIG	CR57
Arctic fox, AK	+	+
Coyote, TX	+	+
Cow/dog Sri Lanka	+	—
Dog/Coyote, TX	+	+
Dog, Argentina	+	+
Dog, China	+	+
Dog, China (RV342)	+	+
Dog, Gabon	+	+
Dog, Phillipines	+	+
Dog, Phillipines (231)	+	+
Dog, Sonora	+	+
Dog, Thailand	+	+
Dog, Tunesia	+	+
Gray fox, AZ	+	+
Gray fox, TX	+	+
Mongoose NY/PR	+	+
Raccoon SE US	+	+
Raccoon Dog, Russia	+	+
Skunk, CA	+	+
Skunk north central	+	+
Skunk south central	+	—
Wolf siberia	+	+

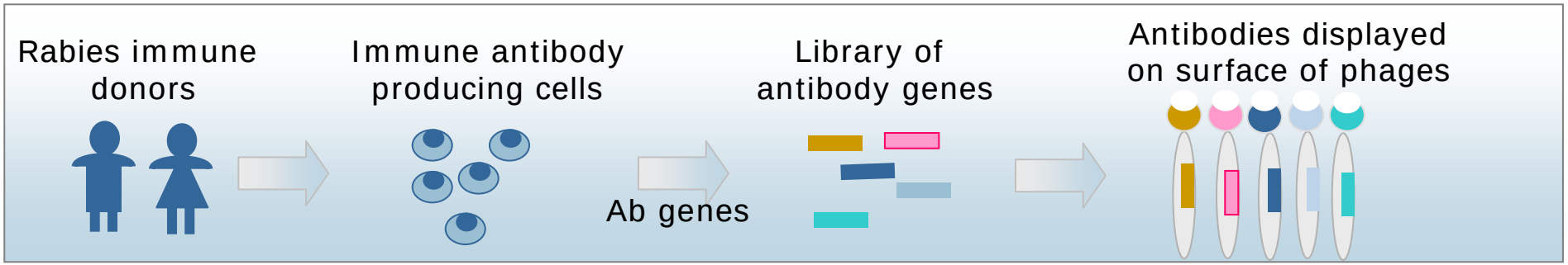
Rabies virus (Bat origin)	SRIG	CR57
Bat, *Desmodus rotundus*, Brazil	+	+
Bat, *Desmodus rotundus* , TN/MX	+	+
Bat, *Eptesicus fuscus* , PA	+	+
Bat, *Eptesicus fuscus-Myotis spp.*, CO	+	—
Bat, *Lasionycteris noctivagans,* WA	+	+
Bat, *Lasiurus borealis*, TN	+	+
Bat, *Lasiurus cinereus* , AZ	+	+
Bat, *Lasiurus cinereus* , NY	+	+
Bat, *Myotis spp.*, WA	+	+
Bat, *Pipistrellus hesperus* , CA	+	+
Bat, *Pipistrellus subflavus* , AL	+	+
Bat, *Tadarida brasiliensis* , AL	+	+

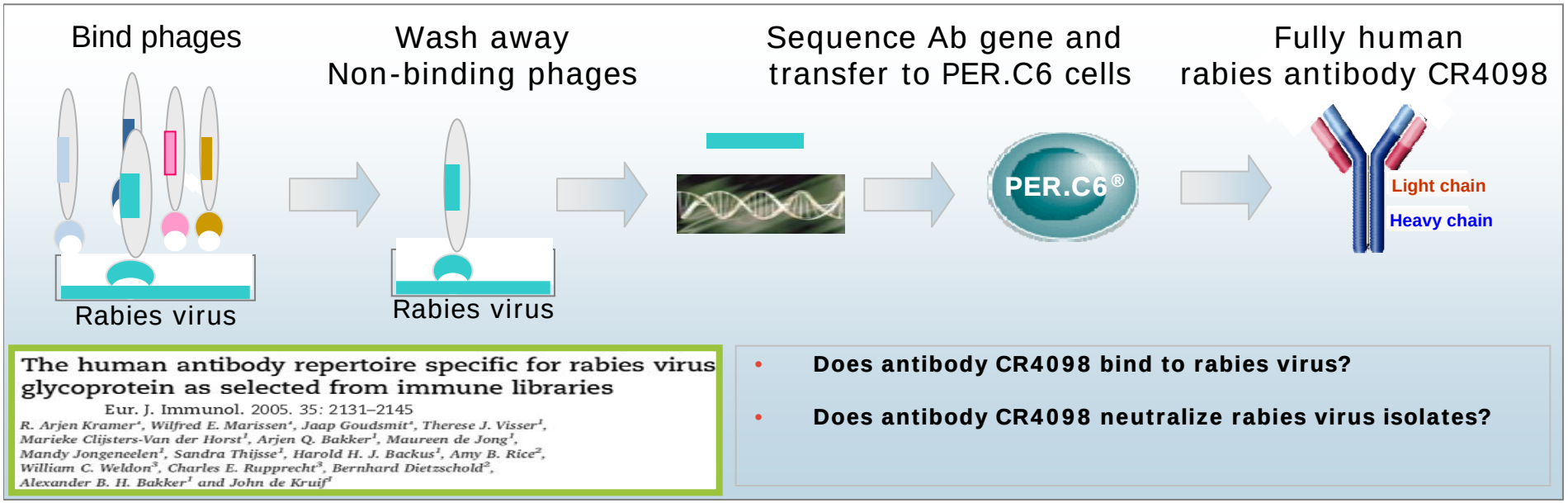
A second antibody is required to obtain full neutralization of all viruses

+ means the virus is neutralized by mAb CR57

Second rabies neutralizing antibody

CR4098 was obtained via phage display





The human antibody repertoire specific for rabies virus glycoprotein as selected from immune libraries

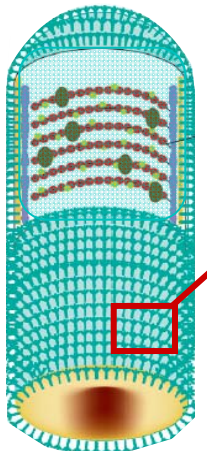
Eur. J. Immunol. 2005. 35: 2131–2145

R. Arjen Kramer[a], Wilfred E. Marissen[a], Jaap Goudsmit[a], Therese J. Visser[1], Marieke Clijsters-Van der Horst[1], Arjen Q. Bakker[1], Maureen de Jong[1], Mandy Jongeneelen[1], Sandra Thijsse[1], Harold H. J. Backus[1], Amy B. Rice[2], William C. Weldon[3], Charles E. Rupprecht[3], Bernhard Dietzschold[2], Alexander B. H. Bakker[1] and John de Kruif[1]

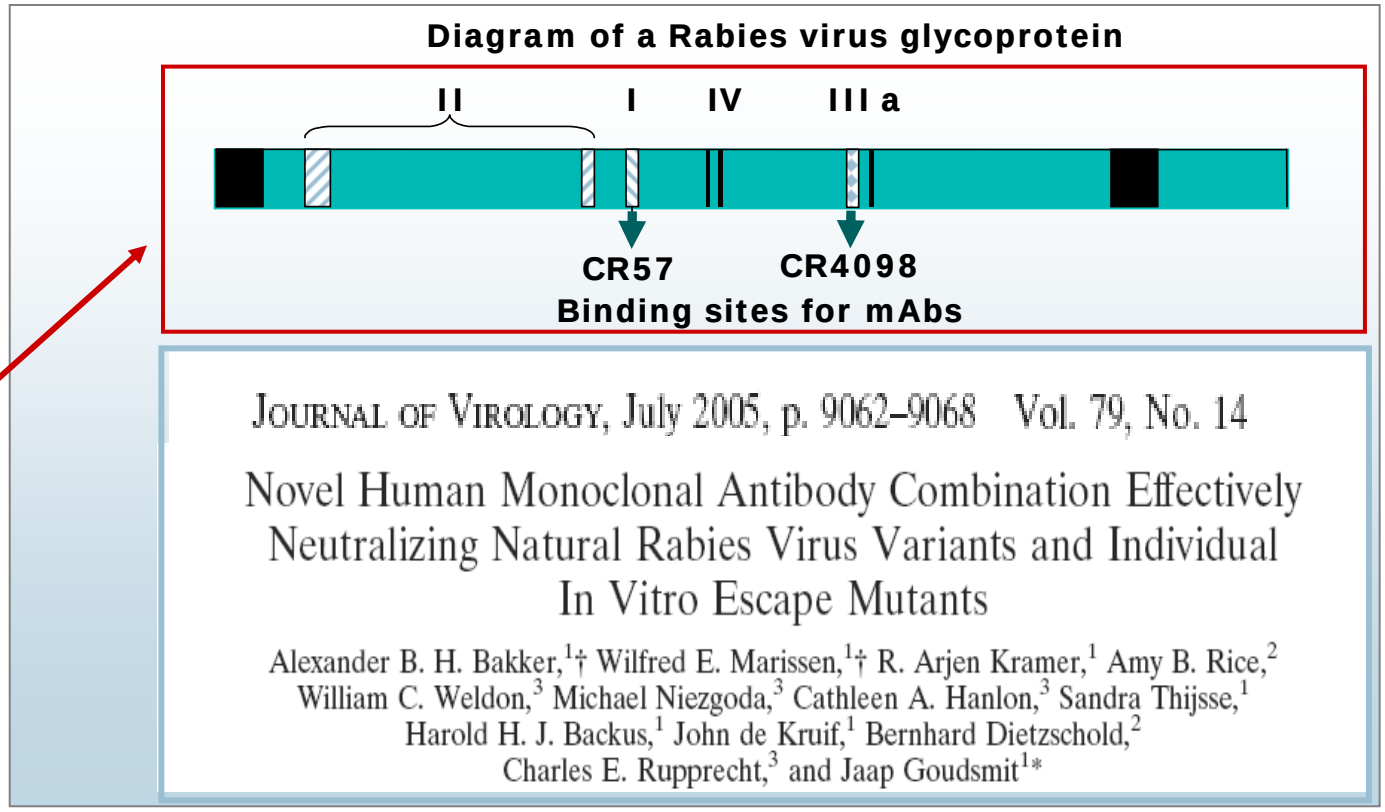
- **Does antibody CR4098 bind to rabies virus?**
- **Does antibody CR4098 neutralize rabies virus isolates?**

Antibody

CR4098 binds to a different site on the virus than CR57



Rabies virus



JOURNAL OF VIROLOGY, July 2005, p. 9062–9068 Vol. 79, No. 14

Novel Human Monoclonal Antibody Combination Effectively Neutralizing Natural Rabies Virus Variants and Individual In Vitro Escape Mutants

Alexander B. H. Bakker,[1]† Wilfred E. Marissen,[1]† R. Arjen Kramer,[1] Amy B. Rice,[2] William C. Weldon,[3] Michael Niezgoda,[3] Cathleen A. Hanlon,[3] Sandra Thijsse,[1] Harold H. J. Backus,[1] John de Kruif,[1] Bernhard Dietzschold,[2] Charles E. Rupprecht,[3] and Jaap Goudsmit[1]*

Antibody

CR4098 complements CR57 for rabies virus neutralizing activity

Rabies virus terrestrial mammals	SRIG	CR57	CR4098
Arctic fox, AK	+	+	+
Coyote, TX	+	+	+
Cow/dog Sri Lanka	+	—	+
Dog/Coyote, TX	+	+	+
Dog, Argentina	+	+	+
Dog, China	+	+	+
Dog, China (RV342)	+	+	+
Dog, Gabon	+	+	+
Dog, Phillipines	+	+	+
Dog, Phillipines (231)	+	+	+
Dog, Sonora	+	+	+
Dog, Thailand	+	+	+
Dog, Tunesia	+	+	+
Gray fox, AZ	+	+	+
Gray fox, TX	+	+	+
Mongoose NY/PR	+	+	+
Raccoon SE US	+	+	+
Raccoon Dog, Russia	+	+	+
Skunk, CA	+	+	+
Skunk north central	+	+	+
Skunk south central	+	—	+
Wolf siberia	+	+	+

Neutralisation in RFFIT

Rabies virus (Bat origin)	SRIG	CR57	CR4098
Bat, *Desmodus rotundus*, Brazil	+	+	+
Bat, *Desmodus rotundus* , TN/MX	+	+	+
Bat, *Eptesicus fuscus* , PA	+	+	–
Bat, *Eptesicus fuscus-Myotis spp.*, CO	+	—	+
Bat, *Lasionycteris noctivagans,* WA	+	+	+
Bat, *Lasiurus borealis*, TN	+	+	+
Bat, *Lasiurus cinereus* , AZ	+	+	+
Bat, *Lasiurus cinereus* , NY	+	+	+
Bat, *Myotis spp.*, WA	+	+	+
Bat, *Pipistrellus hesperus* , CA	+	+	–
Bat, *Pipistrellus subflavus* , AL	+	+	+
Bat, *Tadarida brasiliensis* , AL	+	+	+

Eight additional US skunk and bat isolates and African and, Asian dog rabies isolates were efficiently neutralised

Rabies antibody cocktail

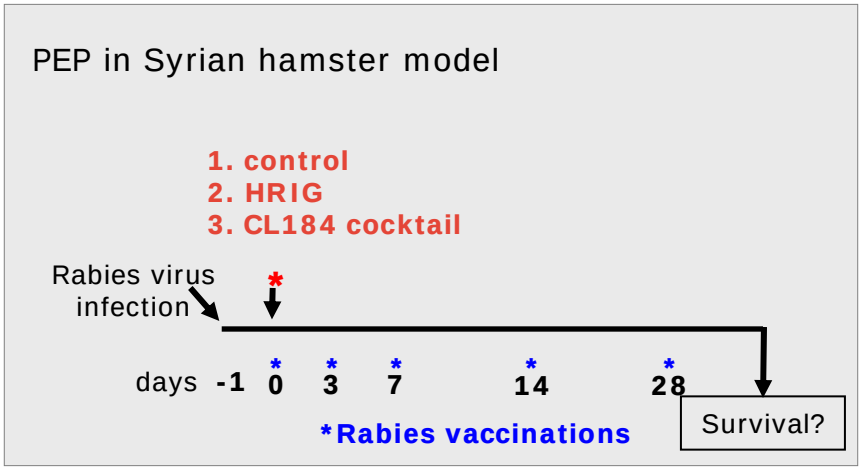
combined with vaccine fully protects against rabies in animal models

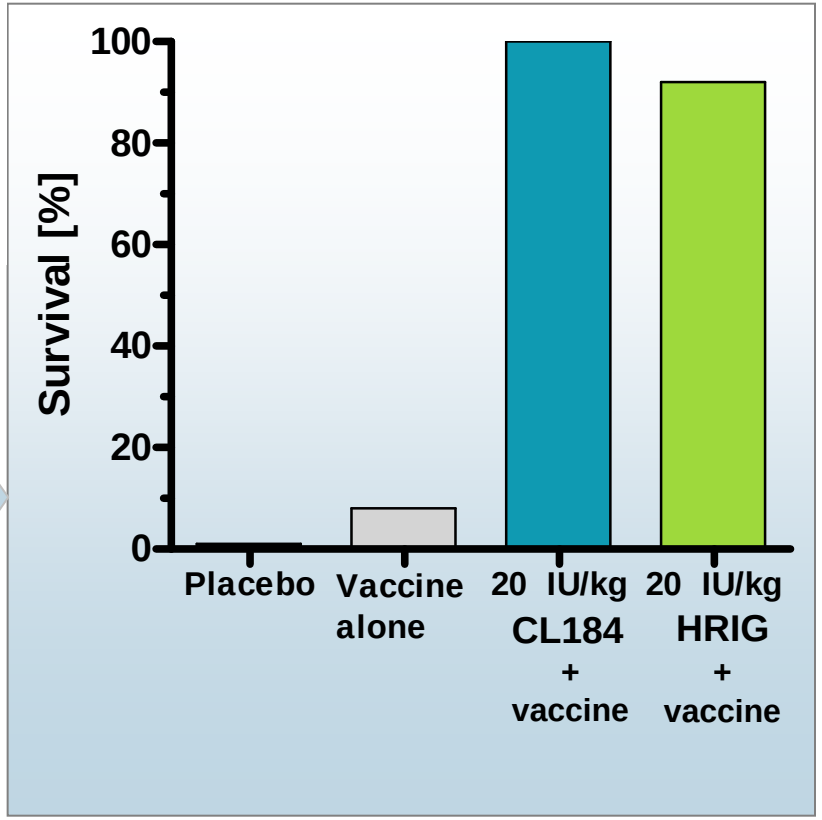
Comparison of an Anti-Rabies Human Monoclonal Antibody Combination with Human Polyclonal Anti-Rabies Immune Globulin

The Journal of Infectious Diseases 2006;193:796–801

Jaap Goudsmit,[1] Wilfred E. Marissen,[1] William C. Weldon,[3] Michael Niezgoda,[3] Cathleen A. Hanlon,[3] Amy B. Rice,[2] John de Kruif,[1] Bernhard Dietzschold,[2] Alexander B. H. Bakker,[1] and Charles E. Rupprecht[3]

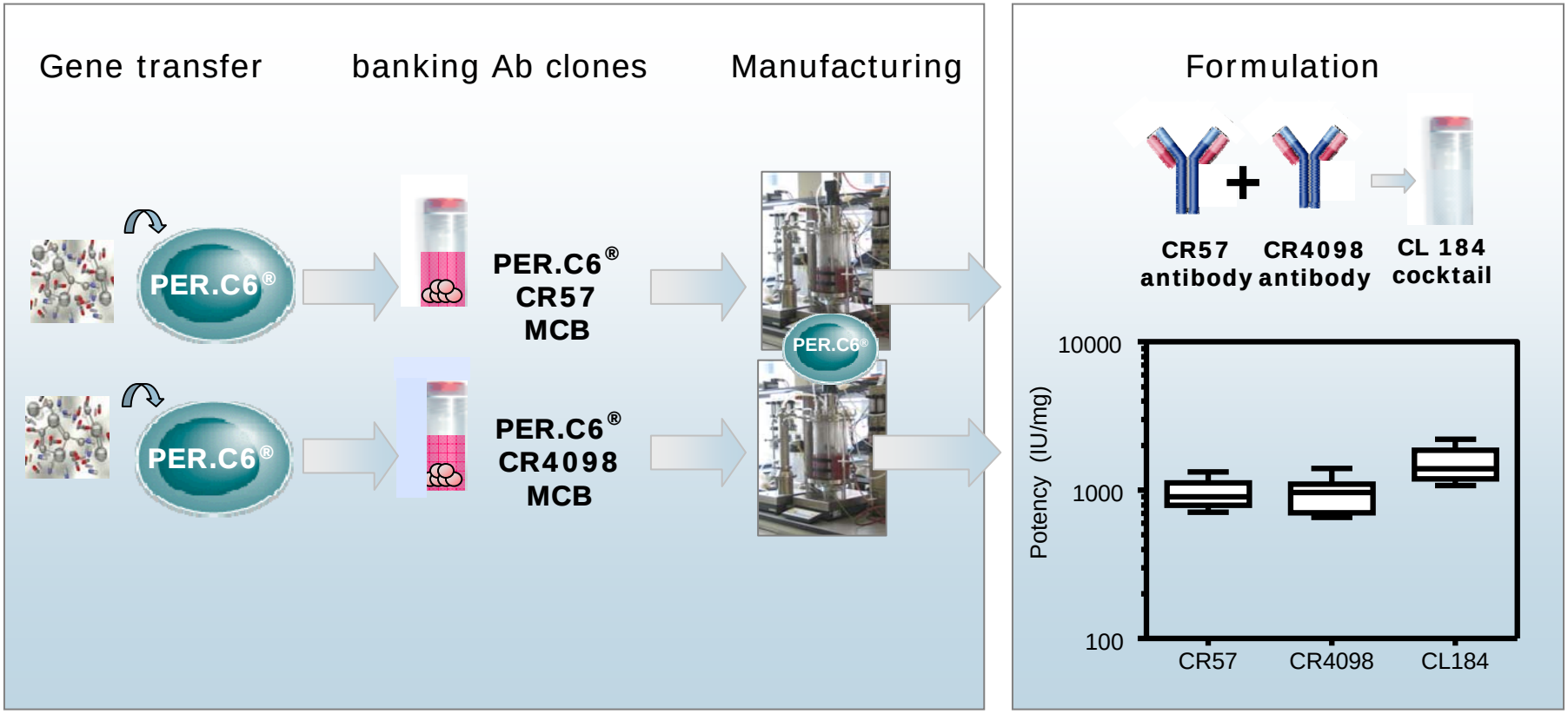
[1]Crucell Holland BV, Leiden, The Netherlands; [2]Department of Microbiology and Immunology, Thomas Jefferson University, Philadelphia, Pennsylvania; [3]Rabies Section, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia





Rabies antibody cocktail

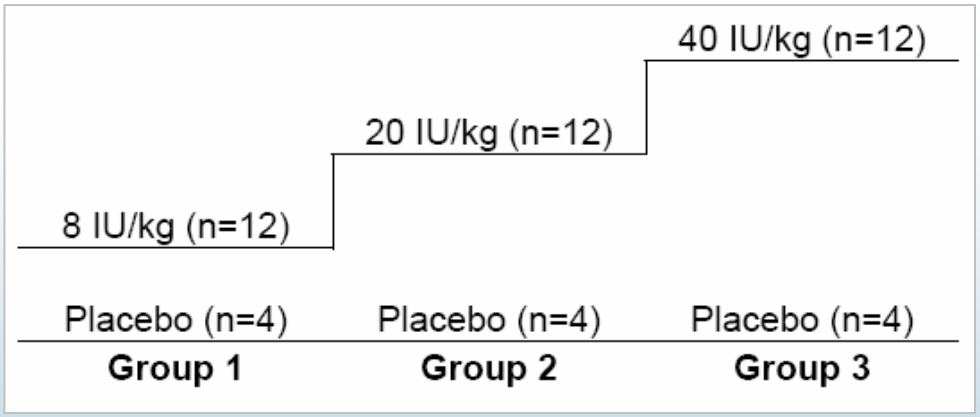
production and formulation



Rabies antibody cocktail CL184

phase I clinical study design

Part 1
Rabies antibody cocktail CL184
Different dosages



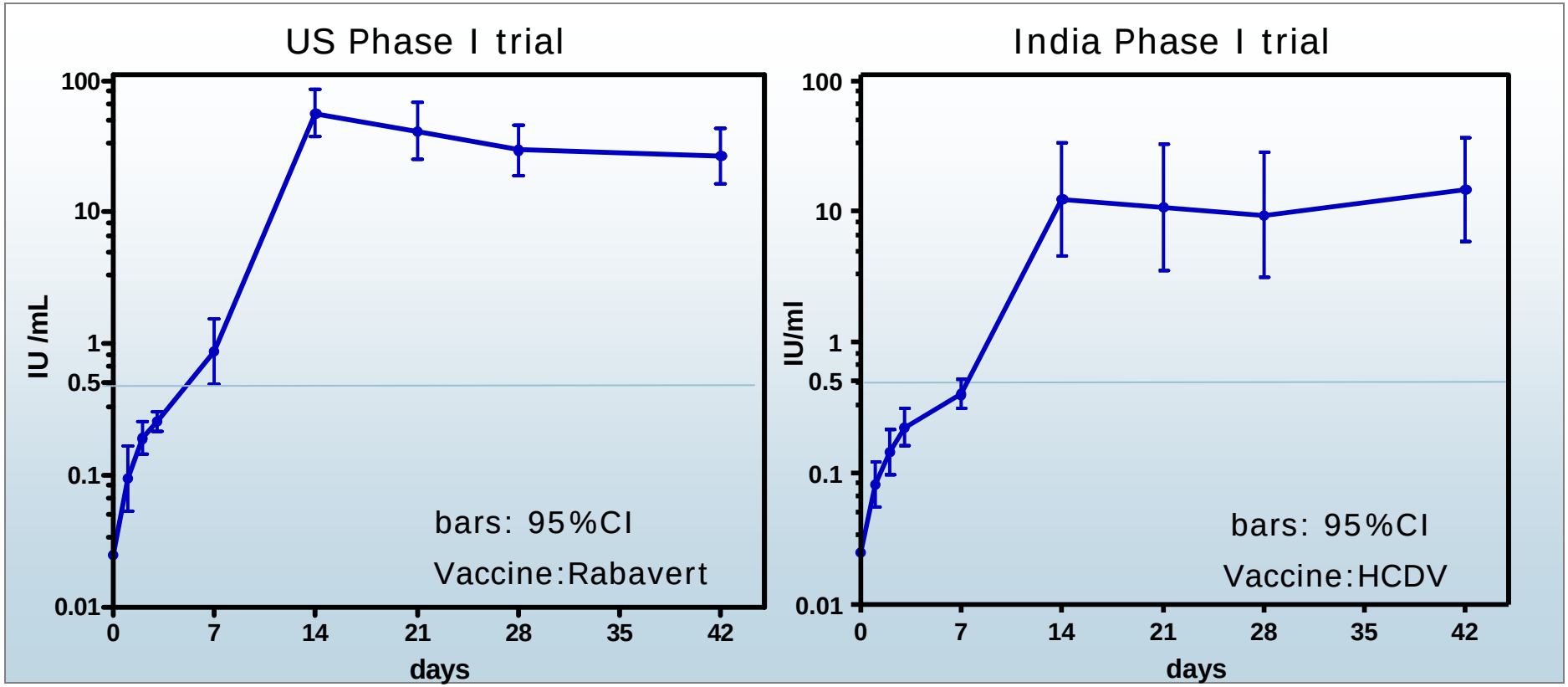
Part 2
Rabies antibody cocktail CL184
Defined dose + vaccine

- Primary endpoint: safety
  - Adverse events
  - Injection site reactions
- Secondary endpoint: efficacy
  - Rabies virus neutralizing activity (RFFIT)

Crucell

Rabies antibody cocktail CL 184

combined with vaccine shows adequate neutralization



0.5 IU/ml is the rabies virus neutralizing activity considered to be adequate by WHO

The rabies antibody cocktail is safe and well tolerated

Crucell

Rabies antibody cocktail CL184

clinical development

- ✓Phase I (US) (study completed)
  - ✓Healthy volunteers
- ✓Phase I (India) (study completed)
  - ✓Healthy volunteers
- Phase II (start 1H 2008)
  - Healthy volunteers and children
- Phase III (planning tbd with sanofi pasteur)
  - Exposed adults and children in endemic countries

Crucell

Human monoclonal antibody cocktail

post-exposure prophylaxis against rabies

- Preclinical studies
  - ✓ A combination of two mAbs with high potency
  - ✓ Neutralizes all representative rabies street viruses tested
  - ✓ PEP treatment protects hamsters against deathly rabies
- Clinical studies
  - ✓ Safe and well tolerated
  - ✓ Neutralizing activity comparable to HRIG
  - ✓ Efficacious in combination with vaccine

Crucell

Partnerships

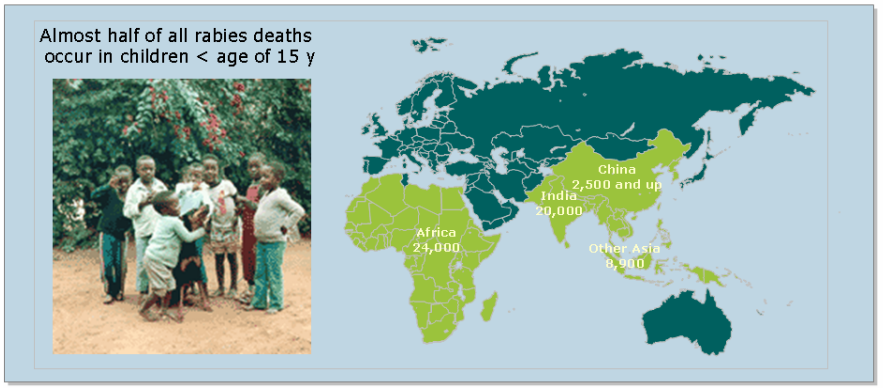
collaboration and commercialization

Sanofi pasteur

Antibodies

- Rabies Monoclonal Antibody Cocktail
- Fast Track status by the FDA
- Phase I US & Indian studies completed
- Safe and well tolerated
- Phase II US & Philippines start first half of 2008
- Upfront payment of €10 million in December 2007; milestones up to €66.5 million
- Estimated peak annual sales exceeding $300 million

Rabies causes over 50,000 deaths each year: over 90% in Asia and Africa



http://www.who.int/rabies/human/en/

Source: FX Meslin, WHO NECTM, Knobel and Tang et al EID, 2005; Zhang et al InFoRab 2005, APCRI data

For more information:

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