

Phase I Clinical evaluation of a Human Rabies mAb Cocktail for Post-Exposure Prophylaxis

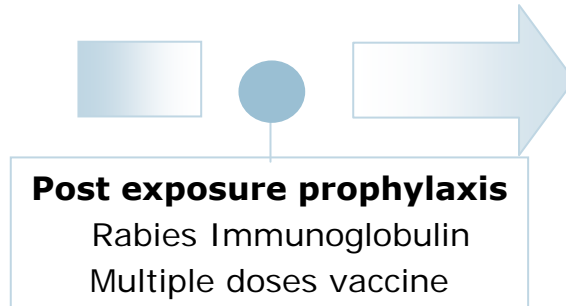
Demonstration of tolerability and neutralizing activity

RITA XVIII, Guanajuato, 03 October 2007

Lex Bakker



Post Exposure Prophylaxis (PEP) can be 100% effective in preventing rabies



Patient with rabies

Two types of RIG preparations

Human (HRIG)

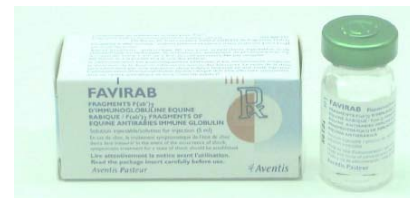


HyperRab
(Talecris)



Imogam Rabies HT
(Sanofi-Aventis)

Equine (ERIG)



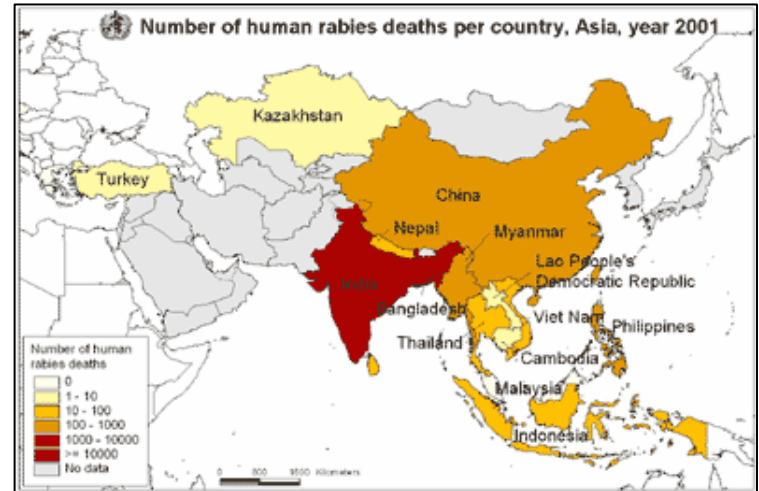
Favirab (Fab2)
Sanofi-Aventis

National productions
Asia and South America

Rabies prevention

Addressing a global unmet need

- Asia & Africa
 - 40.000-60.000 annual deaths due to rabies
 - Safe and efficacious rabies immunoglobulin often not available to the people in need
- North America & Europe
 - Limited supply of human rabies immunoglobulin
 - Current human serum-based treatment under scrutiny due to adventitious agents (HIV, hepatitis, vCJD)



Rationale to replace plasma-derived products with human rabies mAb product

- Improved safety
 - Eliminate risk of transmission of serum derived adventitious agents
 - Consistent product with well defined potency
- Expanded availability
 - Production capacity is unlimited
- Increased product concentration
 - Allows administration of full dose in the wound in majority of PEPs (High volume HRIG (10ml) complicates adherence to WHO/ACIP guidelines, i.e. all RIG in wound)
 - Less painful i.m. administration in absence of wound

The Rabies mAb cocktail CL184: its components and target product profile

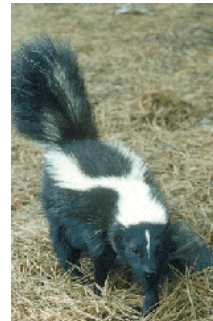
mAb	CR57	CR4098
isotype	IgG1, lambda	IgG1, kappa
Lyssavirus coverage	Genotype 1, 4-7	Genotype 1,7
epitope	linear	conformational
Potency (IU/mg)	937	924
Affinity (KD)	2.4 nM	4.5 nM
Production platform	Human PER.C6 cells	Human PER.C6 cells

- Target indication
 - Post-exposure prophylactic treatment of subjects suspected to be exposed to a rabid animal
- Administration and use
 - Single administration in conjunction with the first dose of rabies vaccine according to WHO/ACIP guidelines. Dosage on the basis of IU/kg bodyweight
- Pharmaceutical presentation
 - Liquid formulation with can be diluted with saline, storage at 2-8°C, shelf life minimally 2 years

Rabies mAb cocktail CL184 provides global coverage of canine and bat rabies isolates

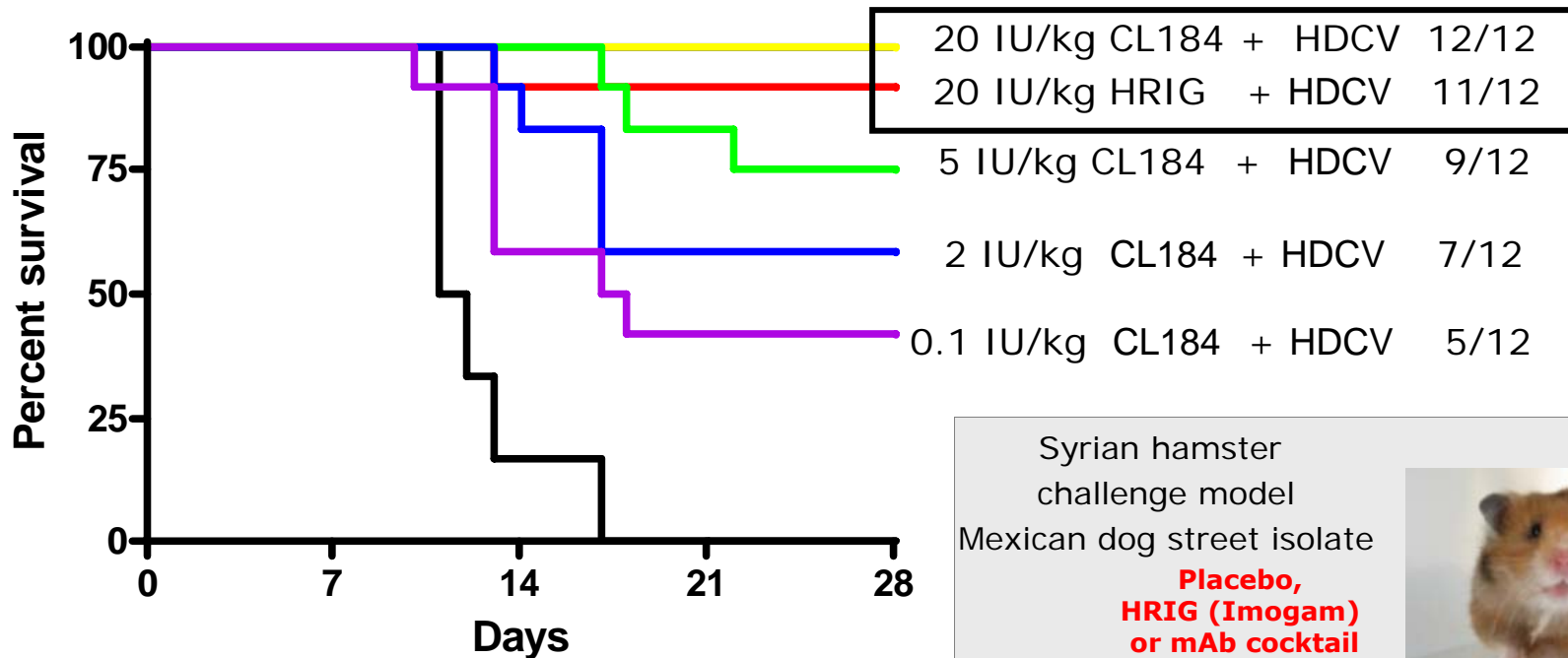
Rabies virus terrestrial mammals	SRIG	CR57	CR4098
Arctic fox, AK	+	+	+
Coyote, TX	+	+	+
Cow/dog Sri Lanka	+	-	+
Dog/Coyote, TX	+	+	+
Dog, Argentina	+	+	+
Dog, China	+	+	+
Dog, China (RV342)	+	+	+
Dog, Gabon	+	+	+
Dog, Phillipines	+	+	+
Dog, Phillipines (231)	+	+	+
Dog, Sonora	+	+	+
Dog, Thailand	+	+	+
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	+	+	+

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

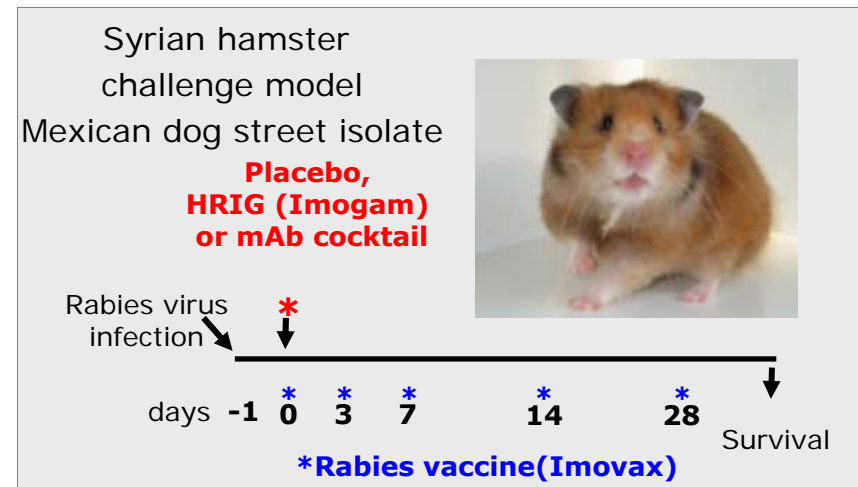


Eight additional US skunk and bat isolates and African and, Asian dog rabies isolates were efficiently neutralised

Full protection against lethal challenge by Rabies mAb cocktail CL184 and vaccine



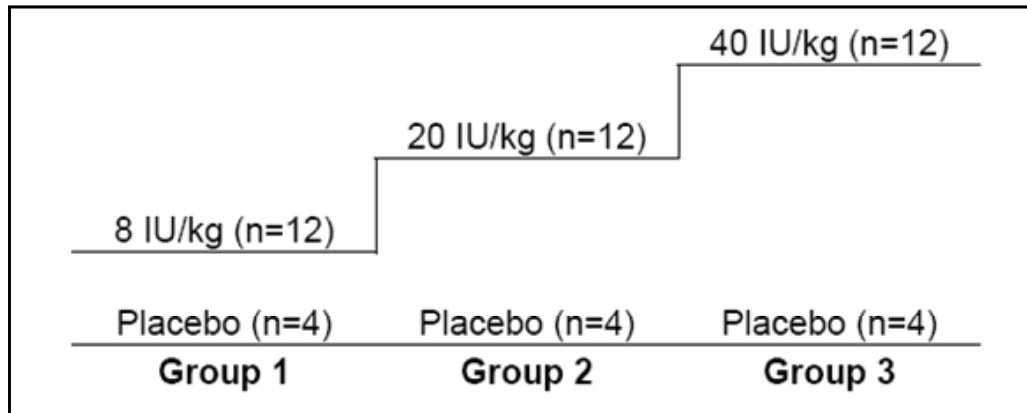
Rabies MAb cocktail CL184, in dose of 20 IU/KG, provides comparable survival to HRIG



Phase I First-in-Man clinical study design

- RAB-M-A001 (start Dec 2006)
 - Part 1 Randomized, double-blind, placebo-controlled study in healthy volunteers, dose escalation mAb cocktail (8, 20, 40 IU/kg)
 - N=12/group
 - Part 2 Administration of mAb cocktail in combination with vaccine
 - N=12/group

Part 1



Part 2



Study Parameters

- Safety:
 - Unsolicited Adverse Events
 - Solicited injection site reactions
 - Safety laboratory panel
 - Blood chemistry and urine analysis
 - ECG
 - Human anti-human antibodies
 - Vital signs
- Rabies virus neutralizing activity (RFFIT)
- PK of CR57 and CR4098

Subject Disposition

	Part 1				Part 2
	Placebo	CL184 8 IU/kg	CL184 20 IU/kg	CL184 40 IU/kg	CL184 Rabavert
Received medication	11	12	11	12	11
Completed study	10	12	11	9	10
Discontinued study	1	0	0	3	1
Positive RFFIT at baseline	0	1	0	2	0

Unsolicited Adverse Events

	Part 1				Part 2
	Placebo	CL184 8 IU/kg	CL184 20 IU/kg	CL184 40 IU/kg	CL184 Rabavert
Subjects dosed	11	12	11	12	11
Subjects with ≥ 1 AE (%)	9 (82)	11 (92)	10 (91)	9 (75)	11 (100)
Total # AE's	37	61	53	31	68
Severe AE's	2	4	0	0	0
Subjects ≥ 1 AE related to study drug (%)	5 (45)	6 (50)	4 (36)	4 (33)	5 (42)
# AE's related to study drug	8	8	5	11	13

Serious Adverse Events

Not related to CL184

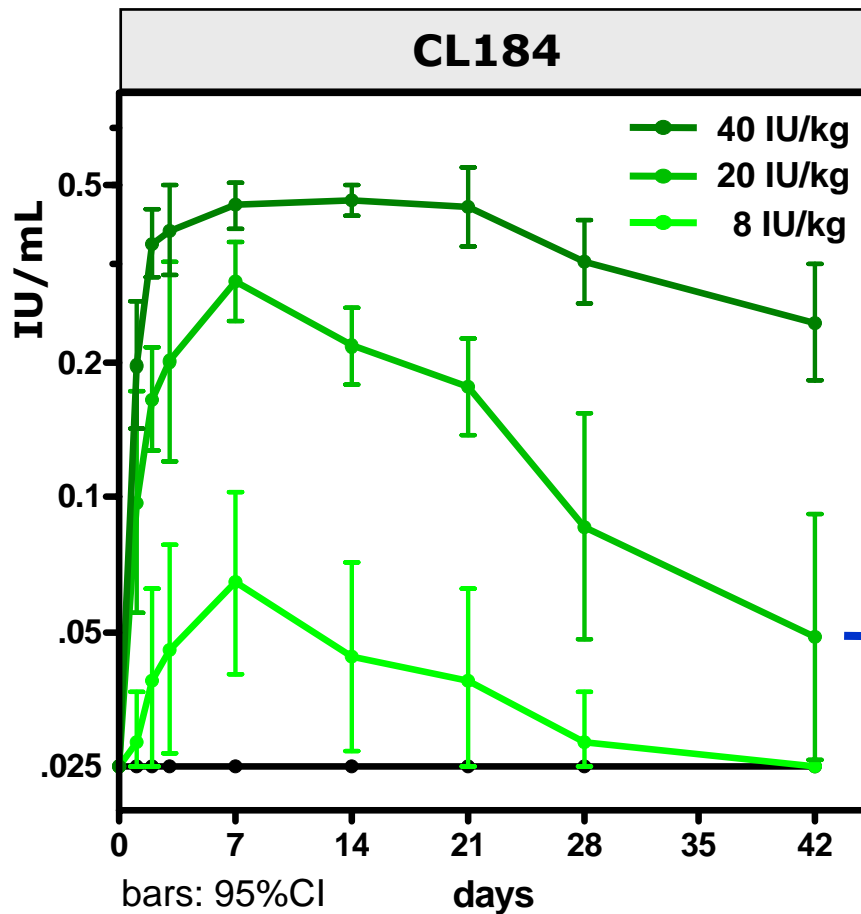
- One subject (40 IU/kg) reported being hospitalized for the mild SAEs of back pain and muscle strain due to a motor vehicle accident during a non-confinement period
- One subject (40 IU/kg) experienced suicidal ideation and worsening of post-traumatic stress disorder beginning prior to dosing. This subject failed to disclose his full medical history and discontinued concomitant psychiatric medication during screening

Solicited injection site reactions:

CL184 is well tolerated

	Part 1				Part 2
	Placebo	CL184 8 IU/kg	CL184 20 IU/kg	CL184 40 IU/kg	CL184 Rabavert
Subjects dosed	11	12	11	12	11
Redness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Swelling	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Induration	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pain	1 (9%)	1 (7%)	4 (36%)	3 (25%)	1 (9%)

Neutralizing activity of Rabies mAb cocktail CL184 detected at all dosages tested

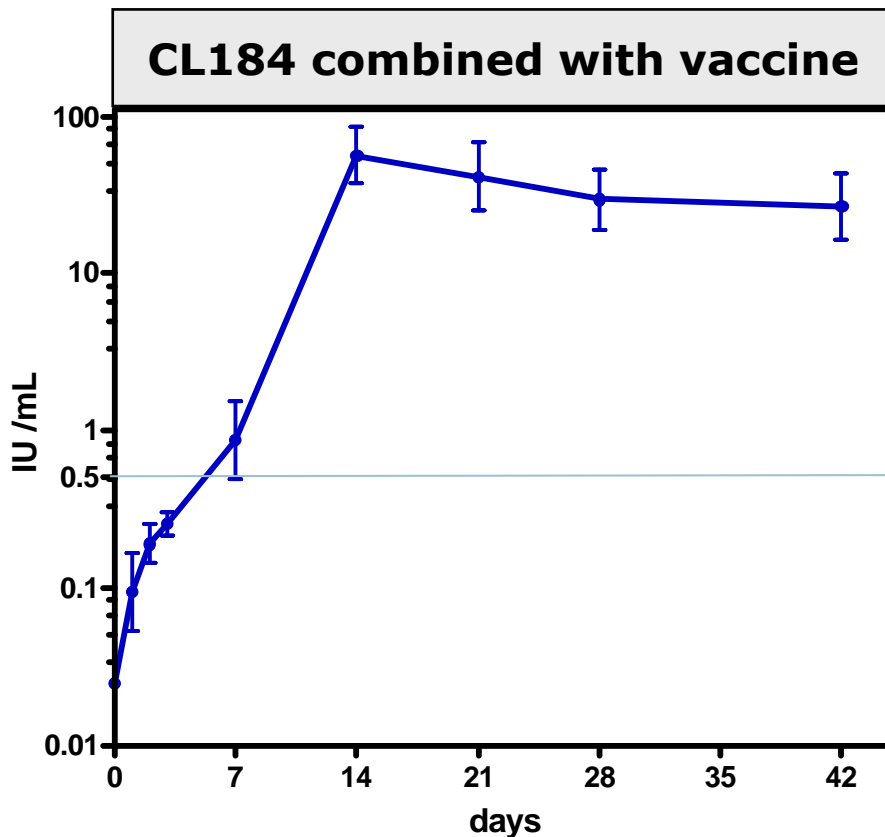


Dose of 20 IU/kg selected to test CL184 in combination with rabies vaccine in part 2 of RAB-M-A001

Fast onset of detectable neutralizing activity upon CL184 administration

Day	0	1	2	3	7	14	21	28	42
Placebo	0/11	0/11	0/11	0/11	0/11	0/11	0/10	0/10	0/10
CL184 8 IU/kg	0/11	1/11	3/11	4/11	7/11	4/11	3/11	1/11	0/11
CL184 20 IU/kg	0/11	8/11	11/11	10/11	11/11	11/11	11/11	8/11	4/11
CL184 40 IU/kg	0/11	10/10	10/10	10/10	9/9	8/8	8/8	8/8	8/8

Rabies mAb cocktail CL 184 combined with PCECV vaccine provides adequate neutralizing activity



% > 0.5 IU/mL	
Day 7	36 %
Day 14	100 %

0.5 IU/mL = rabies virus neutralizing activity that is considered to be adequate

RAB-M-A001

Conclusions

Safety

- CL184 was very well tolerated
- No human anti-human antibodies detected

Efficacy

- Neutralizing activity detected at all dose levels administered
- In combination with rabies vaccine, all subjects seroconverted at Day 14
- Neutralizing activity was comparable to historic Gold Standard HRIG data

RAB-M-A002

Phase I India

- Study design (start Apr 2007)
 - Part 1: Randomized, double-blind, placebo-controlled study in healthy Asian volunteers, dose escalation CL184 (20 and 40 IU/kg)
 - N=12/group
 - Part 2: Administration of mAb cocktail in combination with Rabipur vaccine
 - N=12/group
- Data to be presented November 2007 at JITMM conference in Bangkok