Rabies Immunoprophylaxis in Humans:
Current Recommendations and Experience with Modern Immunobiologicals

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- Rabies Prevention:
  - Pre-Exposure Prophylaxis (PrEP)
  - Post-Exposure Prophylaxis (PEP)

- Sanofi Pasteur’ Clinical Experience with Rabies Immunobiologicals:
  - Verorab™ – purified Vero cell rabies vaccine (PVRV)
  - Favirab™ – purified equine rabies immunoglobulin (pERIG)

- Prospects on passive immunization development
  - CL184: a combination of rabies monoclonal antibodies (mAb)
RABIES Prevention

Pre-Exposure Prophylaxis (PrEP)

Post-Exposure Prophylaxis (PEP)

100% fatal disease
BUT...
100% preventable

According to WHO, PrEP is recommended for anyone at increased risk of exposure to rabies virus

PrEP: Rationale

1. To protect
   - Persons with unrecognized exposure or those for whom PEP might be delayed

2. To simplify
   - Eventual PEP by decreasing the number of doses of vaccine required

3. To eliminate
   - The need for RIG


PrEP: Target populations (1/3)

Subjects at permanent risk must be vaccinated
- Diagnostic, research and production, laboratory staff

Subjects at frequent risk should be vaccinated
- Nurses, medical staff, animal handlers and veterinarians
PrEP: Target populations (2/3)

IN PARTICULAR CHILDREN SHOULD BE VACCINATED

- Children are at higher risk of animal bites
  - Their small size makes them less intimidating to animals
  - They fail to recognize and avoid threatening behavior
  - They are less able to shelter themselves or escape when attacked
  - Their stature make them especially vulnerable to severe facial and head bites, which carry the highest risk of disease

- Children have a faster development of rabies disease than do adults

- Unapparent, unrecognized or unreported exposure increases the risk for children to be untreated

PrEP: Target populations (3/3)

TRAVELERS ARE PARTICULARLY LIKELY TO BE EXPOSED

- Travelers are at higher risk of rabies exposure
  - Outdoor activities such as camping, bicycling, hiking etc. increase the risk for travelers to be exposed to rabies, even if the trip is brief

- Travelers have an increase risk of developing rabies
  - Risk of delay in rabies PEP
  - Risk of no access to medical services and PEP abroad
  - Risk of unapparent or unrecognized exposure to rabies virus

- WHO recommends PrEP:
  - LOW risk areas: For people likely to get in contact with bats
  - MEDIUM risk areas: Travelers/people likely to get in contact with bats and other wildlife
  - HIGH risk areas: Travelers/people likely to get in contact with domestic animals and other rabies vectors

PrEP: vaccination schedule

- **Primary course:**
  - IM route
    - In the deltoid muscle in adults and children
    - In anterolateral part of the thigh in infants and toddlers
  - Alternatively ID route (0.1 mL)
    - In countries where ID route for vaccine administration is approved by Health Authorities
    - For vaccines that are recommended by WHO for intradermal use

* D38 injection may also be given at D21


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RABIES Prophylaxis

- **Post- Exposure Prophylaxis (PEP)**
PEP: Principle

1. To remove free virus from tissues by both washing and neutralizing
2. To induce a rabies virus-specific immune response in the exposed individual before rabies virus can replicate in the central nervous system

PEP: WHO’ categorization of contacts

<table>
<thead>
<tr>
<th>Category</th>
<th>Type of contact</th>
<th>Recommended immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Touching or feeding of animals, licks on intact skin, contact of intact skin with secretions or excretions of a rabid animal or human</td>
<td>None, if reliable case history is available</td>
</tr>
<tr>
<td>II</td>
<td>Nibbling of uncovered skin, minor scratches or abrasions without bleeding</td>
<td>Administer vaccine as soon as possible *</td>
</tr>
<tr>
<td>III</td>
<td>Single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks, exposure to bats **</td>
<td>Administer rabies immunoglobulin and vaccine at distant sites as soon as possible. Immunoglobulin can be administered up to day 7 after injection of the first dose of vaccine. *</td>
</tr>
</tbody>
</table>

* Stop treatment if dogs or cats remain healthy throughout an observation period of 10 days or if animal is euthanized and found to be negative for rabies by appropriate laboratory techniques

** PEP should be considered when contact between a human and a bat occurred unless the exposed person can rule out a bite or scratch, or exposure to mucous membrane

Management of WHO category III contacts: Full Post-Exposure Prophylaxis course

As soon as possible

Local wound treatment
First: Immediate washing with copious soap and water (15 min)
Then: Disinfecting with 70% ethanol or any other suitable disinfectant after all traces of soap have been removed

Appropriate administration of RIG
First: Instillation deep into and around the wound
Then: the remainder of the dose to be injected intramuscularly at a site distant from the vaccine injection site

Administration of a potent cell culture vaccine following recommended schedule


PEP: Passive immunization

How
Infiltration of RIG at the site of the wound (virus inoculation site) puts them in close contact with the rabies virus

Why
To fill the gap between virus inoculation and first appearance of rabies virus-neutralizing antibodies, produced in response to vaccination

Result
Prevents virus diffusion through nerves toward the CNS
**PEP: Passive immunization**

Administer rabies immunoglobulin (RIG)

- Local infiltration with RIG as much as anatomically possible into and around the wound site to immediately neutralize virus

- If any remainder of RIG is left after all wounds have been infiltrated, it should be administered slowly by intramuscular route in a single injection at a site distant from the vaccine injection site

- HRIG: 20 IU/kg of body weight (recommended by WHO)
- ERIG: 40 IU/kg of body weight (recommended by WHO)


**PEP: Active immunization**

Recommended for the WHO category II & III contacts

- IMMEDIATELY

Administer potent rabies vaccine as per the recommended protocols

PEP: WHO-recommended vaccination schedules for non-immunized subjects (1/2)

**Intramuscular (IM) schedules:**

- **Essen regimen** *
  *(Standard 5-dose IM schedule)*

- **Zagreb regimen** *(4-dose “2-1-1” IM schedule)*

* An alternative for healthy, fully immunocompetent, exposed people who receive wound care plus high quality rabies immunoglobulin plus WHO-prequalified rabies vaccines, is a post-exposure regimen consisting of 4 doses administered intramuscularly on days 0, 3, 7 and 14.


PEP: WHO-recommended vaccination schedules for non-immunized subjects (2/2)

**Intradermal (ID) schedule:**

- **2-site TRC regimen** *(the updated Thai Red Cross “2-2-0-2” ID schedule)*

Each vaccine dose is 0.1 mL.

WHO recommends ID vaccine administration in areas where rabies vaccines are in short supply and resources are limited.

Management of PEP vaccination protocol deviations: ACIP recommendations

- For most minor deviations from the schedule, vaccination can be resumed as though the patient were on schedule
  - For example, if a patient misses the dose scheduled for day 7 and presents for vaccination on day 10, the day 7 dose should be administered that day and the schedule resumed, maintaining the same interval between doses. In this scenario, the remaining doses would be administered on days 17 and 31

- When substantial deviations from the schedule occur, immune status should be assessed by performing serologic testing 7–14 days after administration of the final dose in the series.

PEP: WHO-recommended vaccination schedules for previously immunized subjects (1/2)

- Fully immunized subjects:
  - Those who have previously undergone complete pre-exposure vaccination or post-exposure prophylaxis with potent rabies vaccines
  - Those who have been vaccinated against rabies and demonstrated neutralizing antibody titers of at least 0.5 IU/mL

- ‘2 visits’ PEP booster schedule*: two vaccine doses (IM or ID) without RIG

* As an alternative to the standard ‘2 visits’ booster PEP schedule the patient may be offered a ‘single-visit 4-site’ID booster PEP regimen consisting of 4 injections of 0.1 mL.
PEP: WHO-recommended vaccination schedules for previously immunized subjects (2/2)

- A full PEP regimen (including use of RIG for Category III contacts) is indicated if:
  - Vaccination was not documented or incomplete
  - Person was vaccinated with vaccines of unproven potency
  - Person was vaccinated with nerve tissue rabies vaccine and the neutralizing antibody titers were less than 0.5 IU/mL
  - It is an immunocompromised person

Sanofi Pasteur Company Core Data Sheet 084 RABIES (VERO) VACCINE, CCDS version 4.0, July 31, 2008. Sanofi Pasteur internal data.

PEP: Intervention Failures

- Delay in starting PEP
- Inappropriate wound care, or wound suture prior to immunoglobulin injection
- Non-usage of immunoglobulin, or it was injected only intramuscularly and not into wounds, or not all bite wounds have been infiltrated
- Application of immunoglobulin or vaccine of low potency
- Exposure in immunocompromised patient
- Introduction of an exceptionally large viral load
- Atypical virus strain that might not be neutralized by immunoglobulin or by natural antibodies resulting from vaccination.
- Injuries in highly innervated regions of the body, such as hands or face

The issue is not a failure of cell/tissue culture vaccines or RIGs, but a deviation from WHO-recommended PEP protocol

Therapy of human rabies?

The recovery of 3 children [Hattwick 1972, Willoughby 2005, Taylor 2011] in the USA raised the question of a possible cure:

- The “Wisconsin Protocol”: induced deep anesthesia and use of multiple antiviral drugs;
- These patients had high serum and spinal fluid antibody titers on admission, and no virus could be detected throughout their hospital courses;
- These patients had developed an endogenous early immune response that, with good intensive care management, resulted in their recovery.

However:

- After 20 repeat unsuccessful efforts to repeat “Wisconsin Protocol” at centers in USA, Canada, Thailand, India, Europe, South America and Africa, this protocol is no longer recommended by some experts [Wilde 2011, Jackson 2011];
- There were at least 2 documented recovery of patients who received only basic intensive care without induced-coma and no antivirals.

The important lessons learned [Wilde 2011]:

- The patients who have neutralizing antibodies and spinal fluid antibody early on admission, deserve to be placed in intensive care with full respiratory and circulatory support.
- There are no proven rabies effective antiviral drugs known at this time, and the induced deep anesthesia only adds further risks and should be avoided.

Effective, readily available and affordable PEP remains an essential emergency intervention.

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**PEP: Active immunization**

Sanofi Pasteur’ Clinical Experience
Sanofi Pasteur rabies legacy
From Louis Pasteur’ 1st rabies vaccine to the next generation of PVRV

Cell culture vaccines
- Vaccine prepared from primary animal cells
  - 1960 Fenje et al  Primary Hamster kidney Cell vaccine (PHKC)
  - 1965 Kondo et al  Chicken Embryo Cell Vaccine (PCECV)
- Vaccine prepared from human diploid cell
  - 1977 Wiktor et al  Human Diploid Cell Vaccine (HDCV)
- Vaccine prepared from continuous cell line
  - 1985 Montagnon et al  VERORAB® from the vero cell line

VERORAB®: In practice

- Pre-qualified by WHO and approved for PrEP, and PEP using Essen-IM, Zagreb-IM, and TRC-ID [WHO, 2005]
- At least as immunogenic as the reference HDCV
VERORAB®: In practice

Clinical trials confirm the persistence of protection, with rapid and strong anamnestic response to booster. These findings include data from use in:

- **Pregnancy** [Chutivongse, 1989; Chutivongse, 1995; Sudarshan, 1999]
- **Childhood** [Chutivongse, 1988; Thongcharoen, 1989; Lang, 1997; Chanthavanhich, 1997; Seghal, 1997; Sabchareon, 1998; Lang, J Trop Pediatr 1999; Lang, Trans R Soc Trop Med Hyg 1999; Sabchareon, 2004; Shanbag, 2008; Vien, 2008; Lang, 2009]
- **Individuals with severe and high risk injuries** [Dureux, 1986; Suntharasamai, Lancet, 1986; Chutivongse, 1988; Chutivongse, 1995; Thongcharoen, 1989; Chutivongse, 1991; Sehgal, 1994; Chutivongse, 1995; Seghal, 1997; Jaiiaroensup, 1998; Sudarshan, 1999; Wang, 2000; Quiambao, PLoS Negl Trop Dis 2008; Quiambao, 2009]

VERORAB®: In practice

The combined study population of about 18,000 subjects includes:

- 260 pregnant women
- 1,400 children under 18 years of age
- About 1,000 patients severely bitten by a confirmed rabid animal
**VERORAB®**

**Pre-Exposure Prophylaxis: Immunogenicity**

Comparative trials with HDCV in seronegative adults in: **France** [Ajian, 1989; Strady, 1986], **Croatia** [Vodopija, 1986], **Kenya** [Kitala, 1990] and **Turkey** [Hacibektasoglu, 1992] (IM doses at D0, D7, D21/D28):

100% of subjects achieved RVNA levels ≥0.5 IU/mL at D21/D28 or earlier

[Ajian, 1989]: 21 months follow-up (no booster): 98% of PVRV and 94% of HDCV vaccinees with RVNA ≥0.5 IU/mL.

![Kinetics of antibody titers following pre-exposure rabies vaccination with VERORAB® and HDCV.](image)


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**VERORAB®**

**Post-Exposure Prophylaxis: Immunogenicity**

- Rapidly and consistently elicits RVNA levels detectable after 7 days in all PEP regimens
- 25 clinical trials demonstrated RVNA titers achieved WHO min level (≥0.5 IU/mL) at D14:
  - Svjatzko, 1985
  - Vodopija, 1986
  - Suntharasamai, Lancet 1986
  - Suntharasamai, 1987
  - Kletzmann, 1988
  - Waa, 1988
  - Chutivongse, 1990
  - Phanuphak, 1990
  - Chutivongse, 1991
  - Chanthawanchai, 1997
  - Lang, Acta Tropica 1999
  - Sudanhan, 1999
  - Briggs, 2000
  - Wang, 2000
  - Ambrozaitis, 2006
  - Khaaiploot, 2006
  - Madhusudana, 2006
  - Costa, 2007
  - Quiambao, APCRI 2008
  - Warrel, 2008
  - Ashwathnarayana, 2010
  - Sampath, 2010
  - Shrivastava-rinkiku, 2010
  - Wang, 2010

171 patients with WHO cat III received VERORAB™ at D0, D3, D7, D14, D28 (Essen-M) + ERIG (40 IU/mL) at D0

VERORAB®

PEP: Effectiveness

Survival of patients with Cat III exposure to proven rabid animals, after PEP

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Number of subjects</th>
<th>Vaccination schedule</th>
<th>Follow-up period</th>
<th>Survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Suntharasamai, 1986]</td>
<td>106</td>
<td>Essen-IM +/- HRI</td>
<td>1 year</td>
<td>100%</td>
</tr>
<tr>
<td>[Chutivongse, 1988]</td>
<td>309</td>
<td>Essen-IM +/- RIG or TRC-ID +/- RIG</td>
<td>3 months</td>
<td>100%</td>
</tr>
<tr>
<td>[Chutivongse, 1990]</td>
<td>100</td>
<td>TRC-ID +/- RIG</td>
<td>1 year</td>
<td>100%</td>
</tr>
<tr>
<td>[Sehgal, 1994]</td>
<td>55</td>
<td>Essen-IM +/- RIG</td>
<td>7 to 25 months</td>
<td>100%</td>
</tr>
<tr>
<td>[Jaigaroonsup, 1998]</td>
<td>84</td>
<td>Essen-IM +/- RIG or TRC-ID +/- RIG</td>
<td>3 years</td>
<td>100%</td>
</tr>
<tr>
<td>[Quiambao, 2008]</td>
<td>143*</td>
<td>Essen-IM +/- pERIG</td>
<td>6 to 29 months</td>
<td>100%</td>
</tr>
<tr>
<td>[Quiambao, 2009]</td>
<td>191*</td>
<td>TRC-ID +/- pERIG or Essen-IM +/- pERIG</td>
<td>1 year</td>
<td>100%</td>
</tr>
</tbody>
</table>

* The number of patients who received post-exposure prophylaxis strictly in accordance to WHO protocol.

VERORAB®

Long-term immunogenicity

Survival of rabies virus-neutralizing antibody in previously vaccinated subjects: long-lasting immunity

VERORAB®
Safety profile in PrEP and PEP

Studies showed that VERORAB™ can be safely used in different groups, including children (n=1,400) and pregnant (n=260)

- Mild local or systemic adverse events
  - Local: pain (<61%), erythema (<31%), induration (<25%)
  - Systemic: mild fever (<18%), lymphadenopathy (<3%), headache (<15%)

- No immune complex-like adverse reactions after booster

Studies showed that VERORAB™ can be safely used in both IM and ID route


VERORAB™:
Conclusions (1)

- Verorab is pre-qualified by WHO for PrEP & PEP.
- During extensive experience safety and efficacy of Verorab were widely documented in different ages (infants, toddlers, children, and adults) and situations (pregnancy) in many areas, including rabies enzootic.
- In PEP, Verorab safety and immunogenicity were demonstrated with Essen and Zagreb IM regimens, as well as with Thai Red Cross and innovative “one-week” ID regimens.
- Verorab reliably induces rabies virus neutralizing antibody at concentrations above the WHO threshold 0.5 IU/mL in up to 100% vaccinees at day 14 after PEP initiation.
- Clinical trials confirm long-term persistence of RVNA and immune memory up to 20 years after primary immunization.
VERORAB™: Conclusions (2)

The combined study population includes about 1,000 patients bitten by a confirmed rabid animal. In these field studies in rabies enzootic areas Verorab provided 100% survival rate (6 months – 3 years follow-up period) in patients with appropriate PEP according to WHO protocol.

In 44 studies conducted with the assessment of safety profile (total number >14,000 subjects) the most frequently reported reactions were pain, erythema and induration at injection site, fever, lymphadenopathy, and headache. Virtually all have been characterized as mild and did not provoke any change in vaccination schedule.

During 3 decades of extensive usage more than 100 million vials were distributed in over 100 countries throughout Europe, Asia, Africa, and Latin America.

PEP: Passive immunization

Sanofi Pasteur’ Clinical Experience
Sanofi Pasteur ERIG portfolio: Evolution from PARS™ to Favirab™

- **1972**: Exportation license of Pasteur Antirabies Serum™ (PARS) ERIG
  - Hyper-immunized with an absorbed and inactivated rabies vaccine (PM strain)
  - Protein discard (albumin)
  - Virus elimination

- **1977**: French license for SAR Pasteur™ (800 IU / 5 mL)
  - IgG and IgA are removed
  - Elimination of albumin, IgG, IgA, and non-specific Ig
  - Cleavage Fc / F(ab)2
  - Virus inactivation

- **1996**: Modification of French license (1000 IU / 5 mL)
  - Heat treatment >60°C 10h
  - IgG/mIgG extraction
  - Purified, mF(ab')2

- **2000**: French license for FAVIRAB™, highly purified, heat-treated ERIG
  - Purified, heat-treated F(ab')2
  - Virus inactivation
  - Elimination of aggregates, peptidase, Fc fragments

Favirab™: F(ab')2 Fragments of Equine Antirabies Immunoglobulin

The active ingredient consists of F(ab')2 fragments of equine antirabies immune globulin
Favirab™: Chromatographic Profile

Chromatography allows:
- Selective extraction of specific rabies IgG
- Improved purification of F(ab’)2 fragments
- F(ab’)2 fraction increased to 86.9%
- Fc fragments are eliminated

Safety and Efficacy Summary of Clinical Trials with Favirab™

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Completion year</th>
<th>Country</th>
<th>Trial description</th>
<th>Number of Subjects</th>
<th>Safety overview</th>
<th>Suspected lack of efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRC0114C</td>
<td>1995</td>
<td>Thailand</td>
<td>Phase III clinical trial prospective randomized controlled trial in healthy volunteers</td>
<td>15</td>
<td>No cases of hypersensitivity, no SAE</td>
<td>NA</td>
</tr>
<tr>
<td>SRC0209K</td>
<td>1995</td>
<td>Philippines</td>
<td>Phase III clinical trial prospective randomized controlled trial, comparison of immunogenicity of Favirab or PARS associated with PRRV in healthy volunteers</td>
<td>35</td>
<td>No cases of hypersensitivity, no SAE (&lt;20%)</td>
<td>NA</td>
</tr>
<tr>
<td>RAB67</td>
<td>2008</td>
<td>Philippines</td>
<td>Phase III efficacy clinical trial. Assessment of PEP with different route of vaccine administration in association with Favirab</td>
<td>102</td>
<td>No SAE</td>
<td>No case of rabies</td>
</tr>
<tr>
<td>RAB93</td>
<td>2006</td>
<td>India</td>
<td>Phase III randomized multi-center controlled clinical trial. Assessment of PEP with different route of vaccine administration in association with Favirab</td>
<td>405</td>
<td>No cases of hypersensitivity, no SAE</td>
<td>No case of rabies</td>
</tr>
<tr>
<td>FMC1</td>
<td>2004</td>
<td>Philippines</td>
<td>Phase IV Case series study in patients with category III exposure</td>
<td>7600</td>
<td>11 cases of hypersensitivity (0.14%)</td>
<td>2 cases of rabies</td>
</tr>
<tr>
<td>FMC2</td>
<td>2006</td>
<td>Philippines</td>
<td>Phase IV Prospective study in patients with category III exposures to a proven rabid animal</td>
<td>193</td>
<td>2 cases of hypersensitivity, 2 SAEs</td>
<td>1 case of rabies</td>
</tr>
<tr>
<td>FAV83</td>
<td>2008</td>
<td>Thailand</td>
<td>Phase IV Prospective-postexposure monitoring study 1-year follow up when used in rabies post-exposure treatment among patients with category III exposures to a proven rabid animal</td>
<td>178</td>
<td>No cases of hypersensitivity, no SAE (&lt;20%)</td>
<td>No case of rabies</td>
</tr>
<tr>
<td>RUBG</td>
<td>Ongoing</td>
<td>Philippines</td>
<td>Ongoing blinded, randomized, controlled multi-center, clinical trial Veronavir immunogenicity and safety after a one week, 4-site, intradermal (ID) post-exposure prophylaxis regimen followed by a one visit, 4-site, ID booster at five years</td>
<td>400</td>
<td>3 SAEs of hypersensitivity</td>
<td>No case of rabies</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
<td>8988</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Favirab™: Post-Marketing Experience**

- **Favirab™ has been marketed since May 2000**
  - Currently registered in more than 40 countries, including Asia, Eastern Europe, Middle East, and South America
  - About 1.8 million vials have been distributed worldwide since launch

- **Anaphylactic reaction considered as an important expected risk identified with the administration of the product due to the use of heterologous (non-human) proteins)** and is listed in section 4.8 of SmPC
  - A safety review of this type of event from Sanofi Pasteur's Global Pharmacovigilance database over the 2000-2013 period confirmed that anaphylactic reaction is very rare after the administration of Favirab™ (0.01% per dose distributed)
  - Additionally, this review showed that the time to onset of such events is from 10 minutes to 1 day after injection and that all patients recovered
  - No case of anaphylactic reaction with fatal outcome has been reported; no episodes of serum sickness or serum sickness-like reactions have been reported either

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**Favirab™: Key facts**

- **Favirab™, Sanofi Pasteur's pasteurized and purified ERIG [F(ab')2 fragments]** was shown to be comparable to ERIG containing whole immunoglobulin with regards to pharmacokinetic parameters, GMT profile, and evolution of GMT values.

- **The prospective post-licensure clinical trials with confirmed rabies exposure cases** confirmed the clinical efficacy of Favirab™ under real life conditions of routine practice when PEP is performed correctly: all of the patients who received PEP protocol in strict accordance with WHO recommendations survived.

- **Global Pharmacovigilance surveillance data** revealed that the reporting rate of anaphylactic type hypersensitivity after Favirab™ administration is very low and is in agreement with the good safety profile documented during clinical trials.

- **The results obtained during clinical development, along with post-marketing clinical experience, show that Favirab™ provides passive immunity against rabies virus after a single administration.**
PEP: Passive immunization

Prospects on monoclonal antibodies development

CL184: a combination of two human rabies monoclonal antibodies (mAb CR57 and mAb CR4098)

- CR57 and CR4098 mAbs bind to distinct non-overlapping epitopes on rabies virus glycoprotein
- CL184 provides complete coverage of natural rabies virus isolates of CDC panel (n=42)
Thank you