CSIR Biosciences

Rabies antibodies for Passive Post-exposure prophylaxis

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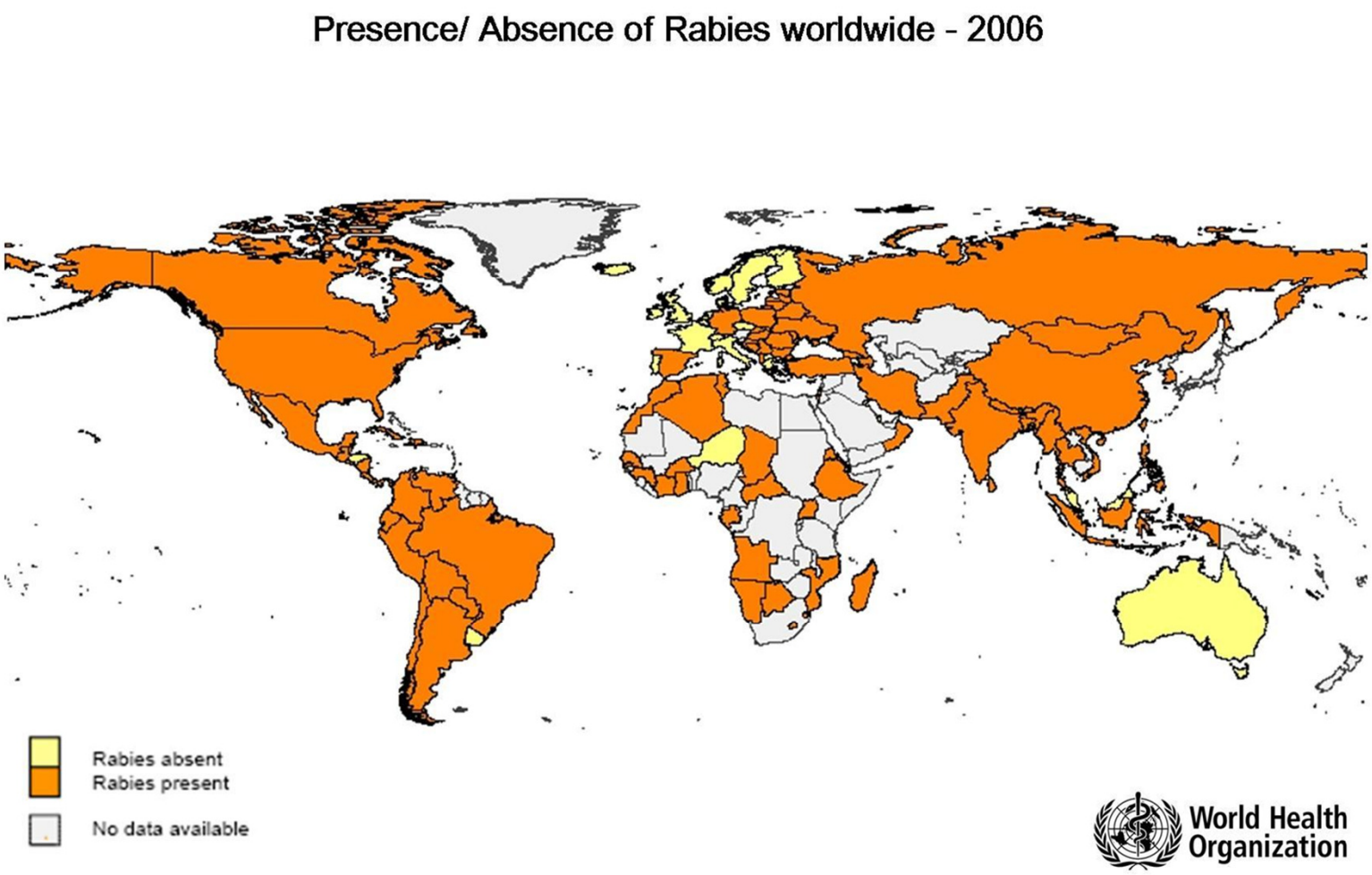
Global Vaccine and Immunization Research Forum
Sandton, South Africa

Rabies virus: Widespread zoonotic disease found across the globe



Rabies virus: Some background

- Rabies was the first of several lyssavirus species to be identified.
- Has 100% fatality rate if left untreated
- 55,000 to 70,000 people die of the disease each year, mainly in Africa, China and India
- Disproportionately affects children: 50% of cases of rabies worldwide are in children
- About 10 million people receive plasma-derived Rabies Immunoglobulin (RIG) as part of post-exposure prophylaxis (PEP)
- A therapy for symptomatic rabies is not available
- Vaccination and post-exposure prophylaxis (PEP) are effective if administered promptly after infection

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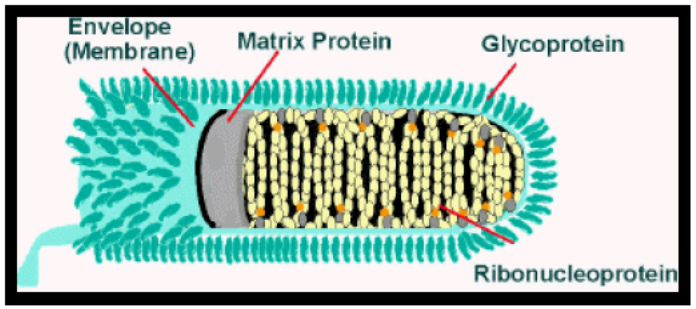
Rabies Immunoglobulins and monoclonal antibodies for Rabies PEP

RIG	mAbs
Supply constraints	Available in large quantities
Batch to batch inconsistency	Consistent product composition
Large volumes for effective dose	Purification and concentration to address bite wound infiltration
Safety concerns: Serum sickness, allergy, anaphylaxis	Safety relatively predictable
Cost and affordability	Can be cost-competitive (not always)
Limited breadth	Broader and predictable neutralisation pattern (may cover non-rabies lyssaviruses)
Polyclonal effect	Escape more likely

Neutralizing Abs to Rabies Virus

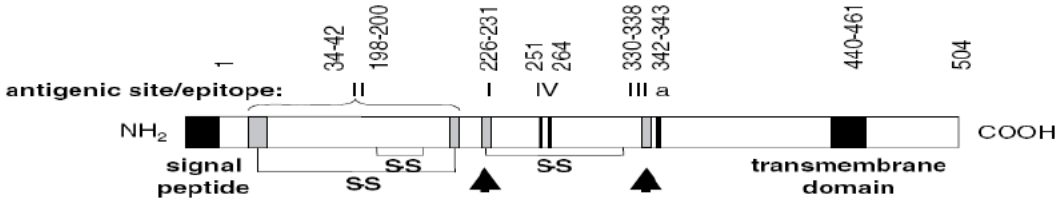


Glycoprotein (G)

- Major protein on virion surface
- Interacts with specific cell surface receptors

G protein

- Classified by Antigenic Domains
- Majority of neutralizing antibodies directed to antigenic sites II and III
- Changes in G-protein sequence influence virulence



WHO initiative to develop anti-rabies mAbs 2002-present

- **Phase 1** – Select and evaluate potential mAbs
- **Phase 2** – transfer the technology to developing country manufacturers
- **2002 Goal**: To make monoclonal antibody products to replace RIG which are available at the lowest possible price to the public sector of developing countries.

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WHO technology transfer of rabies mAbs
Phase 1 – selection & evaluation

2002
- **WHO consultation held -** recommends cocktails ≥ 2 mAbs, set criteria for mAbs evaluation, mapped the way forward

2003
- **Phase I begins** - selection and evaluation of candidate murine anti-G mAb panels from WHO CCs

2005
- MTAs finalized, 5 mAbs donated to WHO (WI 11-12-1; CDC 62-713; ADRI M727-5-1 & M777-16-3; FLI E559), further evaluation of 5 mAbs

2006
- Master cell banking of 5 candidates, cDNA for 62-713 & E559

2011
- Humanized sequence for mAbs E559 and 62-713

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WHO technology transfer of rabies mAbs Phase 2 – tech transfer

2008	• **Zydus Cadila**, India joins the programme – MTA signed – begins work on a cocktail comprising 62-71-3 and M777-16-3
2009	• CSIR, South Africa joins the programme – MTA signed – begins work on a cocktail of 62-71-3 and E559 using tobacco expression system.
2011	• **Span Diagnostics**, India joins the programme – MTA signed – begins work on a cocktail of 62-71-3 and E559
2012	• Phase I for Zydus Cadila candidate begins
2012	• Informal consultation with industry in Sep 2012 to discuss clinical pathway and issues

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International pipeline of Rabies PEP products

RIG Products (Licensed)

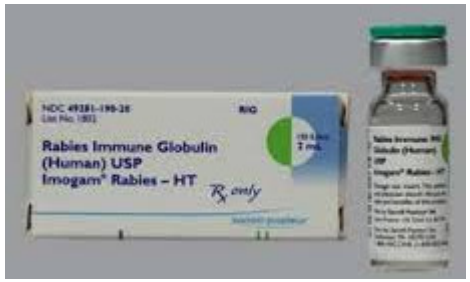
- HRIG products
  - Imogam (Sanofi Pasteur)
  - Hyperrab

- Equirab

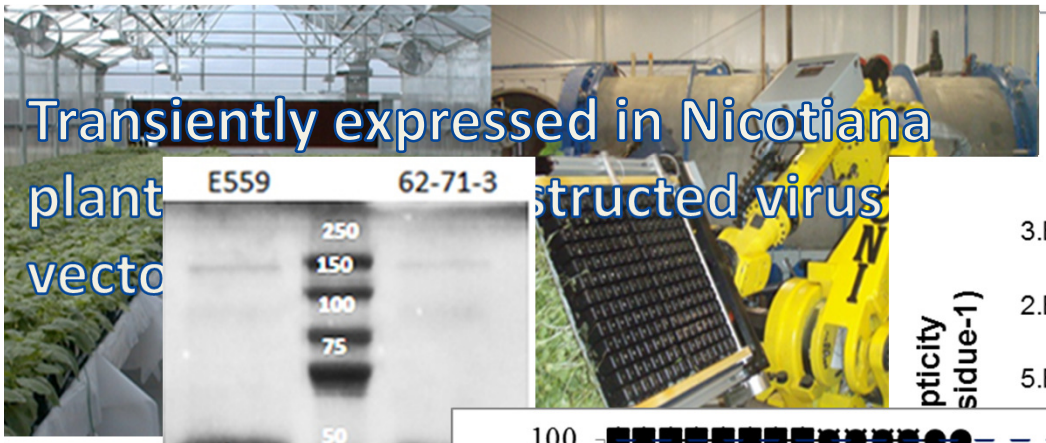
- Regional preparations of HRIG and ERIG
  - Asia, South America and Africa
  - South Africa: National Bioproducts Institute

Antibody-based Products

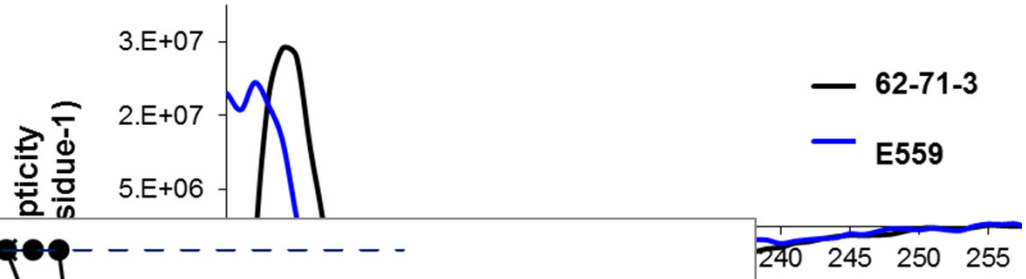
- Serum Institute of India (Phase III Clinical Trials complete)
- Crucell (Phase II Complete)
- Zydus (Phase I/II)
- MTTI/NCPC (Phase I)
- **CSIR (R&D/Preclinical)**
- HUMAbs (Switzerland)
- Fraunhofer (Germany)

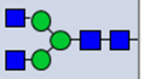


CSIR Plant-made E559/62-71-3 Rabies mAbs

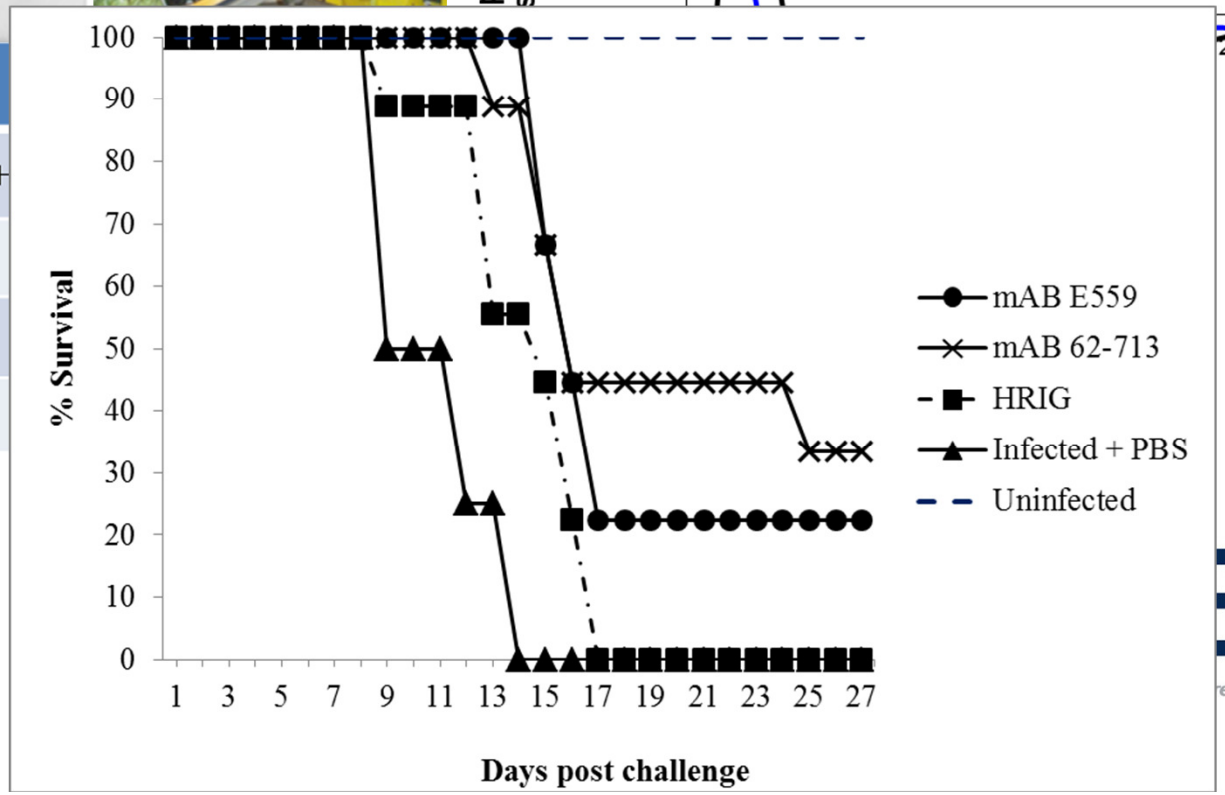


Tsekoa et al., accepted for publication.
Plos (2016)



Name	GnGn
	
E559 (HC)	95 %
62-71-3 (HC)	95 %
E559 (LC)	

Mannose GlcNAc



Licensing rabies mAbs

- Preclinical and phase I/II pathway known
  - In vivo, in vitro animal studies, hamster challenge, phI/II safety, PK, sera neutralization across broad range of isolates
- Phase III efficacy challenging (not clear what is required)
  - Placebo controlled not ethical
  - head to head with RIG required?
  - Large numbers to power trials (rabies confirmed through dog brain analysis)
  - Achieving informed consent and enrolment
  - RIG is 100% effective, so superiority cannot be established (i.e what is the benefit?)

Slides courtesy: Martin Friede, WHO

If your child was bitten by a rabid dog…

Would you give informed consent to enter into a clinical trial?

RIG
100% efficacy
proved in
humans

mAb efficacy
in humans
not yet
determined

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How can we balance?

Risk to the individual to participate in the trial

Benefit to the masses *(*safer, cheaper, increased availability)

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Historical clinical development of RIG

- Never evaluated in "phase III" clinical studies[1]
  - 1954: Iran, 29 ppl bitten by a rabid wolf, treatment started within 30h, 2 treatment groups, vaccine alone or combination of serum & vaccine.
  - Excluding those with less severe wounds, in the 18 severe: 3 of 5 who received vaccine alone died, of the 13 individuals given both vaccine & serum, only 1 died

- Highly purified ERIG F(ab´)2 fragments (Favirab), Sanofi Pasteur: 2 studies conducted in 1990s, no rabies exposed patients[2]
  1. Compared safety & serum concentrations of either Favirab or Pasteur Anti Rabies Serum in healthy adults.
  2. Simulated PEP in healthy volunteers using rabies vaccine and PARS or Favirab
  - Both studies completed in 1995, Favirab™ licensed in France in 2000

1. Both L et al, Passive immunity in the prevention of rabies, Lancet Infect Dis 2012; 12: 397–407
2. Lang J et al, Evaluation of the safety, immunogenicity, and pharmacokinetic profile of a new, highly purified, heat treated equine rabies immunoglobulin, administered either alone or in association with a purified, Vero-cell rabies vaccine, Acta Tropica 70 (1998) 317–333

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Alternative approaches

- Animal rule (FDA)?
- Conditional MA (EMA)?
- SII approach for phase III – head to head with RIG, risk and age de-escalation, limited number of dog bite victims (N=200), lack of rabies verification.

  http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=4191
- Post market surveillance to:
  - Ensure cross protective across genoytpes

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Challenges of uptake

- Switching from RIG to mAbs?
  - Decision by policy makers
  - Cost effectiveness needed
  - Treatment guidelines needed
  - Training of HCWs
  - Procurement/supply
  - WHO model essential medicines list
  - Shelf-life and stockpiling

Slides courtesy: Martin Friede, WHO

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Next Steps and Challenges

IND-enabling pre-clinical studies followed by phase I

- Funding chasm
- Clinical grade pilot manufacturing capacity

Regulatory path

- Ethical considerations
- “Unfamiliar” plant-based manufacturing for a lethal indication coupled with an existing 100% efficacious alternative (RIG)
- How do you adequately show non-inferiority to existing RIG?

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