CSIR Biosciences
Rabies antibodies for Passive Post-exposure prophylaxis

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Rabies virus: Widespread zoonotic disease found across the globe

Presence/ Absence of Rabies worldwide - 2006

- Rabies absent
- Rabies present
- No data available
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
### Rabies Immunoglobulins and monoclonal antibodies for Rabies PEP

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

#### Phase 1 – selection & evaluation

<table>
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<tr>
<th>Year</th>
<th>Event</th>
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<tr>
<td>2002</td>
<td><strong>WHO consultation held</strong> - recommends cocktails ≥ 2 mAbs, set criteria for mAbs evaluation, mapped the way forward</td>
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<tr>
<td>2003</td>
<td><strong>Phase I begins</strong> - selection and evaluation of candidate murine anti-G mAb panels from WHO CCs</td>
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<td>2005</td>
<td>MTAs finalized, 5 mAbs donated to WHO (WI 11-12-1; CDC 62-713; ADRI M727-5-1 &amp; M777-16-3; FLI E559), further evaluation of 5 mAbs</td>
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<tr>
<td>2006</td>
<td>Master cell banking of 5 candidates, cDNA for 62-713 &amp; E559</td>
</tr>
<tr>
<td>2011</td>
<td>Humanized sequence for mAbs E559 and 62-713</td>
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</tbody>
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*Slides courtesy: Martin Friede, WHO*
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

Slides courtesy: Martin Friede, WHO
International pipeline of Rabies PEP products

**RIG Products (Licensed)**

- **HRIG products**
  - Imogam (Sanofi Pasteur)
  - Hyperrab

- **ERIG products**
  - Favirab (Sanofi Pasteur)
  - 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

Transiently expressed in Nicotiana plant transiently or stably transformed virus vector

<table>
<thead>
<tr>
<th>Name</th>
<th>GnGn</th>
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<tr>
<td>E559 (HC)</td>
<td>95 %</td>
</tr>
<tr>
<td>62-71-3 (HC)</td>
<td>95 %</td>
</tr>
<tr>
<td>E559 (LC)</td>
<td></td>
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- Mannose
- GlcNAc

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

Slides courtesy: Martin Friede, WHO
How can we balance?

- **Risk** to the individual to participate in the trial

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

Slides courtesy: Martin Friede, WHO
Historical clinical development of RIG

- Never evaluated in "phase III" clinical studies¹
  - 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 patients²
  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


Slides courtesy: Martin Friede, WHO
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.
  

- Post market surveillance to:
  - Ensure cross protective across genotypes

Slides courtesy: Martin Friede, WHO
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
CSIR Plant-made E559/62-71-3 Rabies mAbs
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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