Anti-Nipah/Hendra virus
Human monoclonal antibody m102.4

Workshop on Research Roadmap for Nipah Virus Disease for India & Nipah Treatment Protocol Team Meeting
New Delhi, India

The opinions or assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the DOD or the Uniformed Services University
Nipah and Hendra viruses
Paramyxoviruses (Henipavirus)

Transcriptase complex
L (Large polymerase protein)
N (Nucleocapsid protein)
P (Phosphoprotein)

Virion RNA
M (matrix protein)
F (fusion protein)
G (attachment protein)

Lipid bilayer

- Zoonotic and highly pathogenic
- Broad species tropism
- BSL-4 restricted, select agents
Nipah & Hendra Infection - Summary

- Widespread **multisystemic vasculitis**
  --thrombosis, ischemia and necrosis
  --severe in the **brain, lungs, and spleen**

Severe respiratory disease: pneumonitis/multi-organ failure and/or **Acute Encephalitis**
Hendra and Nipah virus membrane fusion and infection

Ephrin-B2 and Ephrin-B3 are henipavirus receptors

Nipah and Hendra virus Countermeasures

- **Attachment (G)**
- **Fusion (F)**

2001
- **Subunit vaccine**
  - sG

2006
- **Naive human antibody phage library**
- **Fab**
- **m102.4 (IgG)**

**Passive Immunization**
Exceptionally potent and cross-reactive neutralization against Nipah and Hendra

human mAb m102.4

~IC$_{50}$ values

0.04ug/ml (NiV)
0.6ug/ml (HeV)

Comparison of G-protein binding loop between ephrin and mAb m102.4

m102.4 utilizes the same hydrophobic pockets for G binding as ephrin

A Neutralizing Human Monoclonal Antibody Protects against Lethal Disease in a New Ferret Model of Acute Nipah Virus Infection

Katharine N. Bossart\textsuperscript{1*}, Zhongyu Zhu\textsuperscript{2,3}, Deborah Middleton\textsuperscript{1}, Jessica Klippel\textsuperscript{1}, Gary Crameri\textsuperscript{1}, John Bingham\textsuperscript{1}, Jennifer A. McEachern\textsuperscript{1}, Diane Green\textsuperscript{1}, Timothy J. Hancock\textsuperscript{1}, Yee-Peng Chan\textsuperscript{4}, Andrew C. Hickey\textsuperscript{4}, Dimiter S. Dimitrov\textsuperscript{2}, Lin-Fa Wang\textsuperscript{1}, Christopher C. Broder\textsuperscript{4*}

Post-Exposure Passive Immunotherapy

Human mAb m102.4

Complete protection (10hrs after infection)
A Neutralizing Human Monoclonal Antibody Protects African Green Monkeys from Hendra Virus Challenge

Katharine N. Bossart, Thomas W. Geisbert, Heinz Feldmann, Zhongyu Zhu, Friederike Feldmann, Joan B. Geisbert, Lianying Yan, Yan-Ru Feng, Doug Brining, Dana Scott, Yanping Wang, Antony S. Dimitrov, Julie Callison, Yee-Peng Chan, Andrew C. Hickey, Dimitar S. Dimitrov, Christopher C. Broder, Barry Rockx

FOCUS

Containing the Contagion: Treating the Virus That Inspired the Film
Benhur Lee

Postexposure passive immunotherapy protects African green monkeys from lethal challenge with Contagion-related Hendra virus.
Hendra virus challenge - African Green Monkeys

Geisbert & Broder

Human mAb 102.4 protects African Green monkeys from Hendra virus challenge

Two 100mg doses: (~15mg/Kg):
First dose at 10, 24 or 72 hrs after challenge,
Second dose 48hrs after the first dose.

Bossart et al., Science Translational Medicine, 2011 Oct 19;3(105):105ra103

4x10^5 (Hendra) Intratracheal
Human mAb m102.4 (Nipah virus)
Nipah virus challenge—African green monkey

Sanguinous Fluid/Froth

Day 8

Day 9

Lungs—“ARDS-Like” Disease

Therapeutic Treatment of Nipah Virus Infection in Nonhuman Primates with Human Monoclonal Antibody (m102.4)

First dose Day 5
second dose day 7

100% survival

Challenge: ~ 5x10^5 pfu of NiV

40x
bar = 50 μm.
The therapeutic window of m102.4 treatment is shorter in Nipah Bangladesh infection.

Survived

Succumbed

Australia

 Authorities seek supply of Hendra antiserum
Rebecca Day and her daughter, Mollie, 12, opted to take an experimental drug to ward off the deadly Hendra virus ----as authorities make longer-term plans to combat the virus.

"The drug has successfully prevented Hendra virus in animals when given before symptoms develop and was flown in from the United States". (7pm TV News QLD)

mother and daughter received a 19mg/kg dose of m102.4 by intravenous infusion.

Both have remained well; no evidence of Hendra virus infection.

2010: m102.4 CHO-K1 cell line given to Queensland Health.
Monoclonal antibody m102.4 emergency use protocols 2009-2017

Therapeutic doses (19-20mg/kg)

2010: 2 horse owners (one was a child)
2012: 1 horse owner
2013: 1 BSL-4 lab worker in the USA, GNL, UTMB, exposed to Nipah-B virus; (received two 20mg/kg doses)
2014: 6 horse owners
2015: 1 BSL-4 lab worker in Australia, AAHL, exposed to Hendra virus
2017: 3 horse owners (2 were children)

Total 14 individuals (13 in Australia, 1 in the United States) received high dose therapy

None of the people since 2010 have had any serious adverse reactions.
Queensland Health has conducted a successful early phase clinical trial of monoclonal antibody against the Hendra virus in humans.

Dr. Jeanette Young, Queensland Health’s chief medical officer, told The Courier Mail that all 40 participants of the year-long trial were well and had not suffered any negative impact from the treatment.

The trial cohort comprised five groups of eight people each. Six people were given the antibody and two were given a placebo. The subjects ranged from 18 to 65 years of age.

Randomized, double blind, placebo controlled study. Dose escalation,

5 cohorts (4 are single dose, one is a two dose at day 1 and 3)

1 1mg/kg
2 3mg/kg
3 10mg/kg
4 20mg/kg
5 (two dose, 20mg/kg)
m102.4 mAb trial, Queensland, Australia

Half-life averages m102.4 for cohorts 2,3,4 ~14 days (13.75 to 15.75 days); a maximum in one subject 18.6 days, minimum 10.6 days was also observed.

Data from UTMB (emergency protocol) of two 20mg/kg doses days 1 and 3 of m102.4 was reported at >100µg/ml in serum at 26 days post infusion, well higher than a calculated IC50 in vitro of <0.04µg/ml.

*2 doses are better than one dose. Single 20mg/kg yields 17ug/ml mAb at 42 days post in NHPs

Overall, mAb m102.4 single doses and repeated dosing of up to two doses, separated by 3 days, appeared to be safe and well tolerated when administered to healthy volunteers in the trial.

There were no immunogenicity findings of concern associated with the mAb m102.4 treatment regimen.

No subject withdrawals

Conclusion:

As a result of this trial, there is now available safety data to support the use of a m102.4 mAb in humans with high level exposure to HeV/NiV.

The data from the healthy volunteer study will inform future dosing regimens for mAb m102.4 and it is expected that safe use of the mAb m102.4 should result in improved health outcomes for people who are a risk of severe disease following exposure to HeV or NiV.
Active vaccination strategy

Hendra sG recombinant subunit vaccine

Potent polyclonal Hendra/Nipah neutralizing antibody responses generated in mice, rabbits, cats, ferrets, monkeys, horses… and people.

Complete protection against (Hendra or Nipah)

In:

- Cats
- Ferrets
- Horses
- Monkeys
A Hendra Virus G Glycoprotein Subunit Vaccine Protects African Green Monkeys from Nipah Virus Challenge

Katharine N. Bossart, Barry Rockx, Friederike Feldmann, Doug Brining, Dana Scott, Rachel LaCasse, Joan B. Geisbert, Yan-Ru Feng, Yee-Peng Chan, Andrew C. Hickey, Christopher C. Broder, Heinz Feldmann, Thomas W. Geisbert

A Henipavirus Vaccine in Sight

Veronika von Messling and Roberto Cattaneo

Hendra-sG
Hendra-sG subunit vaccination of African green monkeys

Vaccination and Nipah challenge schedule

-42
0
21
35
42
45
48
50
52
56
63
70

prime
boost
intratracheal NiV challenge
10^5 TCID_{50}
euthanasia

100 µg doses:
- AGM 9
- AGM 10
- AGM 11
- AGM 12
50 µg doses:
- AGM 13
- AGM 14
- AGM 15
10 µg doses:
- AGM 16
- AGM 17
- AGM 18

% survival

0
25
50
75
100

days post-infection

controls
10 µg
50 µg
100 µg

Australian horse industry: > 8 billion dollars/yr.

Wagering alone on horses in Australia exceeds $20 billion per annum.

Break the chain of Hendra virus transmission through vaccination of horses.
2010
The Hendra horse vaccine project:
USU, HJF, CSIRO, Pfizer Animal Health
(Zoetis, Inc.)

Australian Animal Health Laboratory (AAHL)
CSIRO, Geelong, Australia
A One-Health Solution to a Transboundary Threat - Hendra virus

Welcome to
The Equivac HeV training presentation

Equivac® HeV - Pfizer Animal Health (Zoetis, Inc.)
The first licensed and commercially deployed vaccine against a BSL-4 agent- November 1st, 2012, Australia
2017

> 575,000 doses having been administered around Australia.

> 145,000 horses vaccinated.
More than 8,000 miles away, a deadly outbreak is occurring that has already claimed the lives of 17 people. The Nipah virus – which is typically hosted in fruit bats and can spread to people and other animals – is impacting India and quarantining more than 1,000 residents to their homes.

Kerala, India

May 21, 2018
CEPI: human Nipah vaccine development award: Profectus Bio & Emergent Bio

$25 million in vaccine funding
Meanwhile, CEPI today announced a collaboration with Profectus BioSciences and Emergent BioSolutions to develop and make a vaccine against Nipah virus, which is harbored in bats and can spread to humans and livestock.
Single Dose HeV-sG Subunit Vaccine Protects nonhuman primates from Lethal Nipah Virus or Hendra Virus Challenge

<table>
<thead>
<tr>
<th>Dosed group (count of AGMs)</th>
<th>Vaccine dose (day 1)</th>
<th>Vaccine dose (day 28)</th>
<th>Challenge (day 56)</th>
<th>Survival (day 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cntrl N (3 AGMs)</td>
<td>alhydrogel</td>
<td>alhydrogel</td>
<td>Nipah</td>
<td>All dead</td>
</tr>
<tr>
<td>Group 1 (6 AGMs)</td>
<td>100 µg</td>
<td>100 µg</td>
<td>Nipah</td>
<td>Visually healthy</td>
</tr>
<tr>
<td>Group 2 (3 AGMs)</td>
<td>300 µg</td>
<td>none</td>
<td>Nipah</td>
<td>Visually healthy</td>
</tr>
<tr>
<td>Cntrl H (3 AGMs)</td>
<td>alhydrogel</td>
<td>alhydrogel</td>
<td>Hendra</td>
<td>Two dead, one very sick, but survived</td>
</tr>
<tr>
<td>Group 3 (6 AGMs)</td>
<td>100 µg</td>
<td>100 µg</td>
<td>Hendra</td>
<td>Visually healthy</td>
</tr>
<tr>
<td>Group 4 (3 AGMs)</td>
<td>300 µg</td>
<td>none</td>
<td>Hendra</td>
<td>Visually healthy</td>
</tr>
</tbody>
</table>
Acknowledgements

Uniformed Services University
Katharine Bossart, Andrew Hickey, Yee-Peng Chan, Yanru Feng Lianying Yan

Australian Animal Health Laboratory
CSIRO, Geelong
Lin-Fa Wang (Duke-NUS, Singapore)
Deborah Middleton, Gary Crameri

NCI-Frederick, Frederick, MD
Dimiter S. Dimitrov and Zhongyu Zhu

Memorial Sloan-Kettering Cancer Center, New York
Dimitar B. Nikolov and Kai Xu

Profectus, Inc., Baltimore, MD
Anthony Dimitrov, Jeffrey Meshulam

Galveston National Laboratory, UTMB
Thomas Geisbert, Joan Geisbert, Chad Mire

University of Queensland and AIBN
Peter Gray and Team

Dept. of Health, Queensland Government
Jeannette Young and Team

Henry M. Jackson Foundation
Office of Technology Transfer
Mark Scher

Funding: NIAID/NIH; Intergovernmental Hendra Virus Taskforce (Australia); Zoetis, Inc.; Queensland Government; DTRA