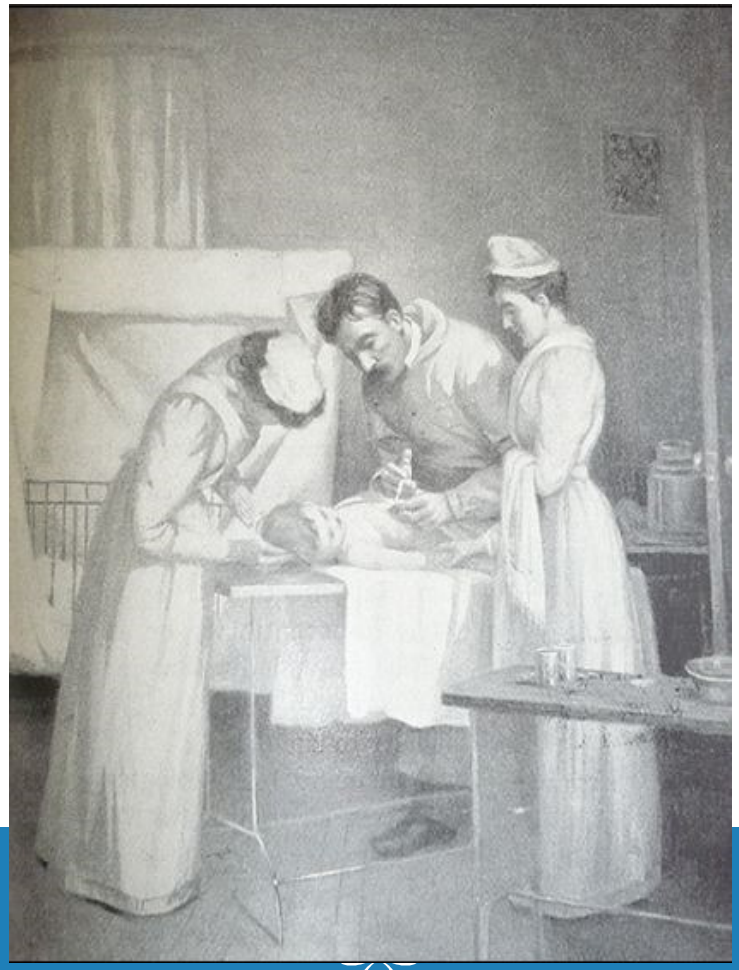
Monoclonal antibodies for infectious diseases

Martin Friede

1890: Emil von Behring and Shibasaburo Kitasato

- From anti-toxin to the serotherapy of diptheria, tetanus
- Nobel prize for von Behring in 1901

The birth of anti-infectives



A century of trials and success

Diptheria

Tetanus

Rabies

Hepatitis A & B

Varicella

RSV

Pneumococcus

Meningococcus

Influenza (pandemic)

Haemophilus influenza

Pseudomonas

Malaria

Polio

Hemorhagic fever

Ebola (?)

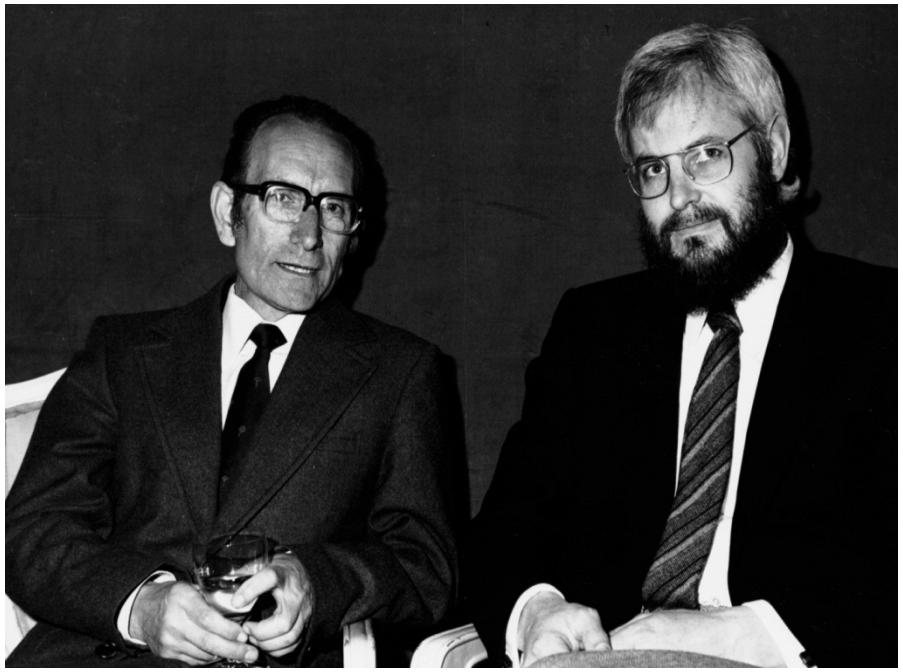
…. And others

And still a strong demand

Procurement by PAHO revolving fund (doses)

	2009	2010	2011	2012
Tetanus	14000	5000	17000	32000
Rabies	15000	16000	31000	40000
Hepatitis B	47000	48000	5000	72000
Varicella	12000	15000	23000	21000

The Birth of Monoclonal antibodies



1975 Cesar Milstein and Georges Köhler develop technique for making monoclonal antibodies

Nobel prize: 1982

"Developed as a "research tool…"

Currently $140,000,000,000 / year market

The pros and cons of monoclonal antibodies for infectious diseases

- Safety theoretically easy to predict (but not always…)
- Functions rapidly (unlike vaccines)
- Quicker to develop than vaccines

- Supply: limited !
- Cost: !!!!! Especially when grams of product needed !
- Time to development !!

mAbs in infectious disease

- Palivizumab: anti-RSV mAb (Medimmune 1998)
  - First monoclonal approved for prophylaxis of infectious disease (RSV).
  - For premature infants (<29 weeks), CHF, bronchopulmonary dysplasia.
  - $7000-10,000 per treatment course (4-5 months).
- Raxibacumab: anti-anthrax mAb (GSK 2012)
  - Approved using animal rule
  - For treatment of inhalation anthrax.

Improved production systems

- Murine myeloma NS0 cells
- CHO cells
- PerC6
- Tobacco plants

Variable glycosylation patterns -> immunogenicity, function

- Yield 0.1g/l →10g/l
- Cost of goods: $10,000/g → $100g

Technical skills barrier, Technology access barrier, CAPEX barrier.

Addressing cost and supply issues

- WHO technology transfer centre at Utrecht University.
- Palivizumab anti-RSV mAb. Target price $500 (compared to current $7000).
- There is a competitor that may make this redundant…

'Lunamab' can prevent death of tens of thousands of premature infants

First consortium of local manufacturers to make affordable biosimilars available for low income countries

Press release March 9 2016

Zmapp: Anti-Ebola mAb cocktail

Plant-based monoclonal antibodies reach the headlines

- If Zmapp had been made in CHO cells it would NOT have been ready for clinical testing in 2014 !

  → Advantage: Speed of development

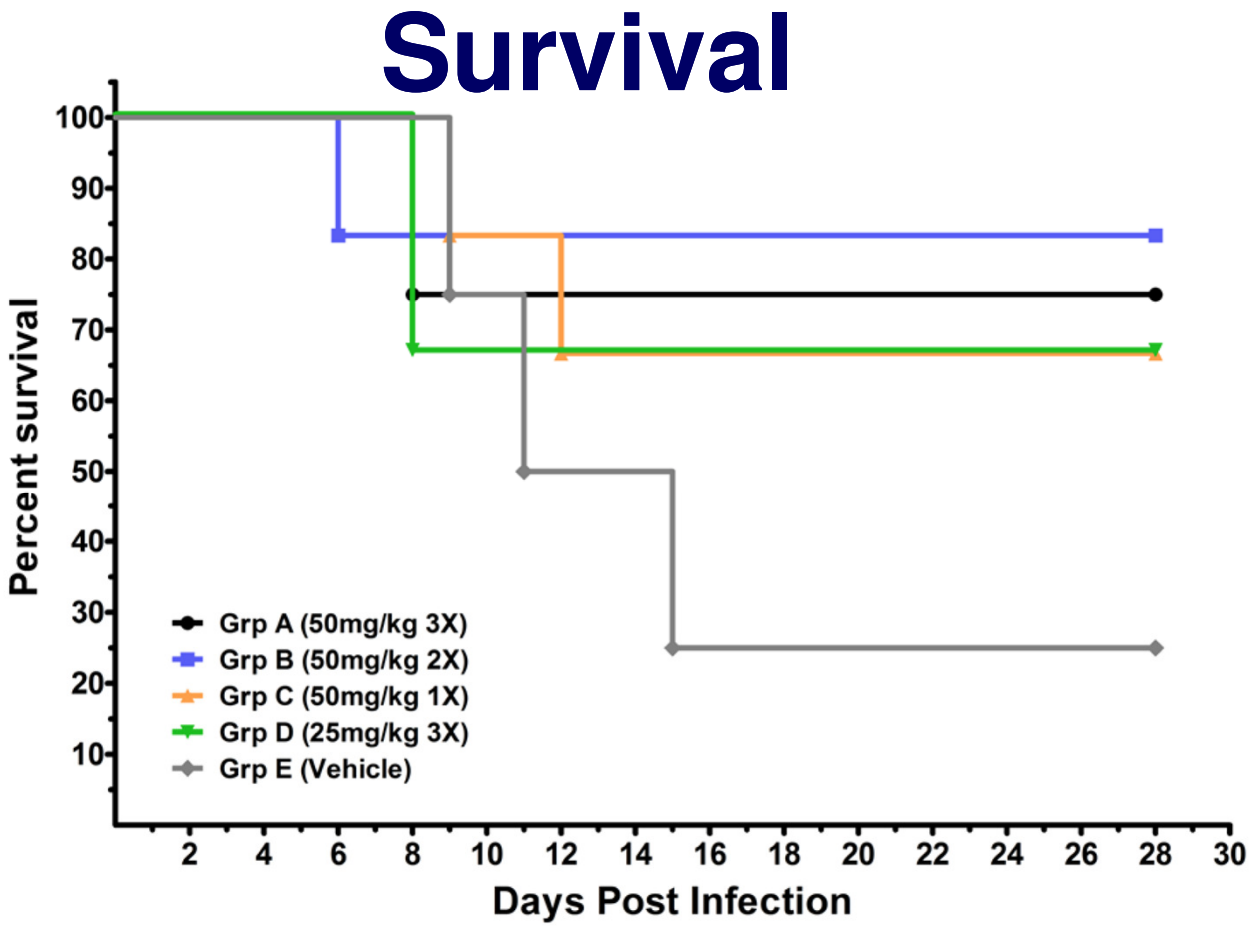
- Since Zmapp was being made in plants, supply was very limited (10 courses/month)

  → Disadvantage: production capacity

Clinical evaluation of Ebola Therapeutics

- >250 'therapeutic' products proposed
- Only 3 with evidence:
  - Zmapp: cures monkeys, 15 doses available
  - siRNA: cures monkeys if used early, 50 doses available
  - Favipiravir: 'kills' monkeys, but reduced viral load. Unlimited supply
  - Brincidofovir: inhibits virus in cells, no it doesn't, yet it does, no,…
  - Interferon: extends time to death (whoopee !)
- Clinical Testing:
  - 'compassionate use': everything plus the kitchen sink…
  - RCTs : "We don't want lotteries…"
  - Historical controls – but epidemic did not follow predicted curve

Zmapp preclinical data



Zmapp efficacy data: 28 day mortality

Deaths	Total	Control	Treatment
Overall	21/71 29.6%	13/35 37.1%	8/36 22.2 %
CT<22	16/30 53.3%	9/15 60%	7/15 46.7%
CT>22	5/41 12.2%	4/20 20%	1/21 4.8%

Data from Feb 23 Press release on PREVAIL trial http://bit.ly/1RkJ0yq

Bottom line…

- Zmapp: by time trial started in Liberia, epidemic nearly over.
  - Challenge to getting trial approved
  - Trial halted when no more patients available to enroll.
  - **Earlier supply of large doses could have changed this…**
  - Chinese CHO-derived MIL77 supply ?
  - Other CHO-derived products ?

- Is approval feasible ?

- Is animal rule feasible ?

Some of the Challenges to mAbs

- Regulatory :
  - Gathering adequate data for rare or emerging diseases
  - Trial design for highly lethal diseases
  - Switching from approved polyclonal to new monoclonal
- Economic viability
  - An antibody only works against a single disease target. If this disease is rare, or episodic is there a business model to support the continued production ?
- Pathogen escape
  - Polyclonal serum targeted multiple sites – will pathogens develop escape mutants to monoclonal products ?

Science will only fulfill its promises when the benefits are equally shared by the really poor of the world

—César Milstein, *Un Fueguito*

(nobel prize 1984 for discovery of the principle of production of monoclonal antibodies)