111 years producing immunobiologics: New challenges

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THE EFFORTS OF A PUBLIC INSTITUTE TO DEVELOP NEW VACCINES

Prof. Jorge Kalil

Portugal, 2012
AGENDA

- Overview of Immunization Program in Brazil and Instituto Butantan
- Butantan Developments
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- Butantan Developments
**THE IMPACTS OF VACCINATION IN BRAZIL**

*Children vaccination coverage by type of vaccination*

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**Vaccination coverage in Brazil**

(2000 to 2010)

- Over 70 million children successfully vaccinated in two decades

Implementation of the MMR vaccine and DTP + Hib vaccine (tetravalent) in 100% municipalities

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**Graph Legend:**
- BCG
- MMR
- Hepatitis B
- Oral Polio
- Tetravalent (DTP+Hib)
- Rotavirus
THE IMPACTS OF VACCINATION IN BRAZIL

Number of cases for tetanus – accidental and neonatal

Number of cases – Accidental and neonatal Tetanus

Accidental (1990 – 2010)


Incidence per 100K inhabitants

Number of accidental tetanus per year

I Incidence per 100K inhabitants

Number of neonatal tetanus per year

Emergency Plan for high-risk counties

Elimination Plan

Source: Sinan/SVS/MS, data in 25/08/11Ministry of Health, Brazil, 2010.
The impacts of vaccination in Brazil

The number of severe cases and deaths due to influenza A H1N1 has been falling since March 2010

Number of severe cases and deaths due to influenza A H1N1
Brazil (2010)

Source: Sinan/SVS, Ministry of Health, Brazil, 2010.
BRAZIL HAS BECOME AN INTERNATIONAL REFERENCE IN IMMUNIZATION

**Strategy**
Brazil decided in the mid 80's to become self-sufficient in vaccines and immunization programs

**Decision**
This was a State decision rather than a government decision

**Why**
Too important to depend on availability and pricing
NATIONAL IMMUNIZATION PROGRAM (PNI) IN BRAZIL

PNI – Founded in 1973

Eradication
- Smallpox
- Poliomyelitis
- Measles (autocne transmission)

Under Control
- Neonatal tetanus
- Accidental tetanus
- Tuberculosis
- Diphtheria
- Pertussis
- Hepatite B
- Influenza
- Pneumococcus

PNI – General Information of Brazil (2011)
- 194 MM inhabitants
- 43 types of immunobiological
  - 26 Vaccines
  - 13 sera from animal
  - 4 sera from human
- 77% produced in Brazil
- ~ 300 MM doses of vaccines per year
- 30 K vaccination rooms
- Expansion of national self-sufficiency

Source: SVS/Ministry of Health, National Immunization Program, Brazil, 2011.
In 1901 Butantan was established to produce serum against the bubonic plague

- Vital Brazil, the first director, investigated antivenoms against snake bites

Currently, Butantan is the main public producer of vaccines, antivenoms, antitoxins in Latin America

- Fully dedicated to develop scientific research and production of immunobiological products for public health
RESEARCH & DEVELOPMENT LABORATORIES

- ~21 scientific labs
- ~180 Researchers
  - 85% are PhD
- 1 Biotechnology Center
  - Multiple laboratories
- 1 Hospital (10 hospital beds)
- 1 Central Animal Facility

- Training programs (PAP)
- Graduate studies in Toxicology
- Masters and PhDs
SCREENING OF BIOACTIVE COMPOUNDS OF ANIMAL VENOMS

Pharmacological Activities

- ANALGESIC
- ANTI-INFLAMMATORY
- ANTI-MICROBIOLOGICAL
- ANTI-COAGULANT
- ANTI-TUMORAL
- NERVOUS SYSTEM ACTION
- ANTI-VENOMS REACTIVITY
- ANTI-HYPERTENSION

Venom Composition by Transcriptomics and Proteomics
Plasma fractioning by chromatography
INDUSTRIAL COMPLEX

- 7 Main Industrial Plants (Buildings)
  - Anaerobic vaccines (tetanus and botulinic) and Anatoxin Purification
  - Biological control
  - Aerobic Vaccine (Diphtheria and Pertussis)
  - Hepatitis
  - Influenza
  - Rabies
  - Blood Products (under construction)
  - Control, Serums, Formulation and Filling

- 6 Pilot Plants
  - Dengue / Rotavirus (Under Construction)
  - Recombinant (BCG)
  - Monoclonal Antibodies
  - Influenza
  - Blood Products
WHAT DO WE DO?
NATIONAL SUPPLIERS OF VACCINES FOR THE MINISTRY OF HEALTH

‘Market Share’ per Suppliers\(^{(1)}\)
(2010)

Butantan
51%

Biomanguinhos
42%

FAP
4%

FUNED
3%

Products (Vaccines)

- DTP
- DT
- dT
- Rabies
- Hepatitis B
- Influenza (Flu)

Note: Part of Butantan’s production was sent to other Institutes, such as Biomanguinhos. Not computed in the analysis

\(^{1}\)Source: Ministry of Health, 2010
WHAT DO WE DO?
NATIONAL SUPPLIERS OF ANTIVENOMS AND ANTITOXINS FOR THE MINISTRY OF HEALTH

‘Market Share’ per Suppliers (1)
(2010)

- IVB 25%
- Butantan 56%
- FUNED 19%

Note: Part of Butantan’s production was sent to other Institutes, such as FUNED and CPPI. Not computed in the analysis.

Products (Sera)
- Snakes AV
- Scorpion AV
- Spider AV
- Caterpillar AV
- Tetanus AT
- Diphtheria AT
- AntiRabies
- Botulism AB & E

1Source: Ministry of Health, 2010
## Vaccines with External Cooperation

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AGENDA

- OVERVIEW OF IMMUNIZATION PROGRAM IN BRAZIL AND INSTITUTO BUTANTAN

- BUTANTAN DEVELOPMENTS
## What do we want to do?

*Presentation and discussion of vaccines projects*

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<th>Area</th>
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<td><strong>Vaccines – Basics R&amp;D</strong></td>
<td>Leptospira</td>
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<td><strong>Techtransfer</strong></td>
<td>Several vaccines under negociation</td>
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¹ *Not exhaustive*
**Pertussis\textsubscript{low} vaccine**

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**Product - Pertussis\textsubscript{low} vaccine**

- **Composition**
  - *B.pertussis* whole cell with lower content of LPS

- **Production Technology**
  - Organic extraction of the cells to reduce LPS content
    - \checkmark \textasciitilde 70\% reduction of LPS
    - “in line” process without additional costs

- **Phase of Development**
  - Pre-clinical studies performed in Butantan and in the Netherlands Institute Vaccine (NIV)
  - **Phase I (2012) – Brazil**

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**Butantan –**

- **Challenges:**
  - Scale-up

- **Objectives:**
  - To make available an alternative vaccine for immunization of children, adolescent, pregnant women and adults

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Whole Cell Pertussis Vaccine

B. pertussis fermentation

WCP

Tangential filtration

Organic extraction

Whole Cell Pertussis Low LPS content

~ 70% reduction of LPS
Less reactogenic
Low cost

WCP_{low}®

Chromatography

Acellular Pertussis Vaccine

MPLA Adjuvant

Recombinant BCG-Pertussis

Neonatal immunization

® = Patents

Pertussis_{low} vaccine - technical and scientific aspects
New developments in Pertussis Vaccines with Appropriate technologies

Pertussis vaccine before and after organic extraction of LPS (P_{Low})

Before

After

Figure 1- Electron microscopy: negatively stained whole cell pertussis vaccine before (wP) and after solvent treatment (P_{low}). The dimensions of the cells were measured in micrometers.
Adjuvant – Monophosphoryl lipid A (BpMPLA)

Product - Monophosphoryl lipid A (BpMPLA)
- Composition
  - BpMPLA derived from LPS of B.pertussis

- Production Technology
  - Purification of B.pertussis followed by LPS hydrolises

- Phase of Development
  - Scale-up

Butantan –
- Challenges:
  - Scale-up

- Objectives:
  - To optimize immunological response of pre-existing and new vaccines
  - To increase production capacity

**BpMPLA**
- Clinical trial
  - Pandemic H1N1 + BpMPLA
- Pre-clinical
  - Human rabies
- Animal Study
  - Dog Leishimania
- In development
  - Hepatites B + BpMPLA
  - Seazonal Influenza + BpMPLA
Recombinant BCG-Pertussis

Neonate vaccine / Onco BCG for Bladder cancer

Product - Recombinant BCG – Pertussis

- Composition
  - Recombinant BCG strain expressing the S1 subunit 1 of Pertussis toxin

- Production Technology
  - The rBCG-Pertussis strain was produced without antibiotic resistance gene
  - Appropriate for use in humans

- Phase of Development
  - Production of GMP lots

Butantan –

- Challenges:
  - To produce the vaccine by fermentation or static culture
  - To perform the clinical trials

- Objectives:
  - To immunize infants 0 – 2 months of age
  - To make available a new vaccine for bladder cancer

Nota: ¹ Auxotrophic strain for lysine is complemented with a plasmid that expresses the deleted gene plus the heterologous gene – S1PT
Recombinant BCG-Pertussis - technical and scientific aspects
Protection of neonate mice immunized with rBCG-S1PT against intracerebral challenge with *B. pertussis*

**ONE DOSE AT DAY 5**

- **Challenge dose at day 21: 10^6 CFU**
- **Challenge dose at day 21: 3x10^7 CFU**

Silica (SBA-15)

**Immunogenic complex formed by vaccinal antigens encapsulated by nanostructured mesoporous silica**

**Features**

- The SBA-15 possesses hexagonal porous uniformity (3.1 – 6.5 nm)
- Thermal and hydrothermal stability
- Exhibits potential applications for selective adsorption and catalysis
Rotavirus Vaccine

Product – Pentavelent Rotavirus Vaccine

- Composition
  - Attenuated virus
  - Sorotypes: G1, G2, G3, G4 e G9

- Technology of Production
  - Cell substrate: Vero cells
  - Reassortment – Human/bovine
  - Nº lots produced: 09 (6 K doses)

- Phase of Development
  - Phase I: 2010
    - Results: safe and immunogenic
  - Phase II: 2013

- Partnership
  - NIH / PATH / BNDES

Butantan –

- Challenges:
  - To perform Phase II and III - non-inferiority study
  - To find funding for:
    - Clinical Trial and laboratory assay – Phase II / III

- Objective:
  - Pentavalent low cost vaccine
Dengue Vaccine

Product – Tetravalent Dengue Vaccine

- Composition
  - Attenuated virus
  - Sorotypes: DEN1, DEN2, DEN3, DEN4

- Technology of Production
  - Cell substrate: Vero cells
  - Recombinant DNA technology
  - Chimeric
  - Nº lots produced: 06 (17 K doses)

- Phase of Development
  - Phase I and II: 2012/2013

- Partnership
  - NIH - DVI (Dr. Steve Whitehead)
  - BNDES / FAPESP

Butantan –

- Challenges:
  - To speed up Phase I, II, and III – (to avoid non-inferiority study)
  - To find funding for:
    - Clinical Trial and Laboratory assay – Phase III
    - Equipment
    - Plant
    - Maintenance of “The Global Solutions for Infectious Disease” support
  - To define target population for immunization
  - Production capacity x national and international demand

- Objective:
  - Tetravalent low cost vaccine
Obrigado
Thank you