Vaccines in Brazil: the role of Butantan in Research, Development and Production

Luciana C.C. Leite

Laboratório de Desenvolvimento de Vacinas
Centro de Biotecnologia
Instituto Butantan

Vaccination begins in Brazil

The history of vaccines in Brazil begins in 1804 with the arrival of the smallpox vaccine.

In 1904, vaccination became mandatory and generated the episode known as the Vaccine Revolt, in Rio de Janeiro. Smallpox was eradicated in 1973.

The early 20th century is a turning point in the history of vaccines in Brazil, with the foundation of Instituto Butantan and Fiocruz.

In 1901 Butantan was established to produce serum against the bubonic plague.

In 1927, vaccination against tuberculosis began in Brazil. Butantan began producing the BCG vaccine in 1971.



Vaccination in Brazil matures

The National immunization plan was created in the 70's, together with the first vaccination calendar.

Vaccination with the oral Polio vaccine, began in 1979 and in 1986, was born "Zé Gotinha", a friendly character who symbolizes vaccination campaigns.
Polio was erradicated from Brazil in 1989.

The Federal Constitution of 1988 determined the creation of the Unified Health System (SUS), that guarantees free vaccination to the whole Brazilian population.

In the same year, the National institute for quality control laboratory (INCQS) was established.

Our national regulatory agency, Anvisa, was created in 1999.

In the years that followed, Brazil continued to advance in vaccinating its people.

Diseases such as tetanus, diphtheria, whooping cough, hepatitis B, measles, chickenpox, among others, are now prevented.
Butantan produced for many years, DTP and Hep B.



Vaccine production renovated at Butantan

The National Program for Self-Sufficiency in Immunobiologics was launched in 1985.

In the same year the Center of Biotechnology was created in Butantan, to establish a bridge between research and production.

The production of vaccines and anti-sera was renovated: 50-year-old technologies were substituted for modern self-contained processes.

Production of tetanus, diphtheria and whooping cough (DPT) vaccine facilities were totally remodeled and hepatitis B production was established.

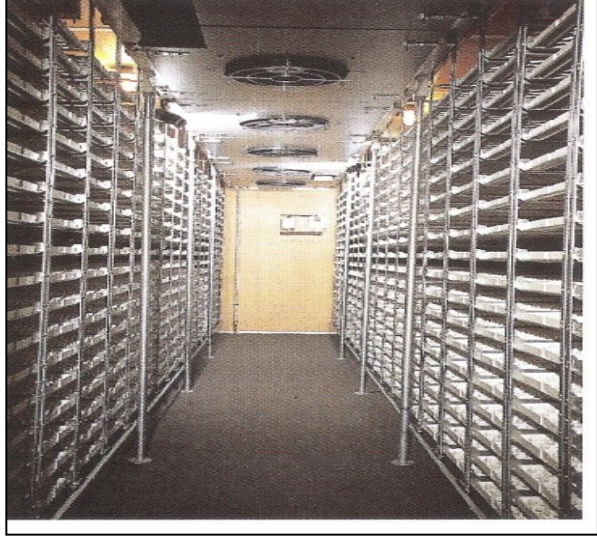




Technology transfer at Butantan

Influenza vaccine production
TT with Sanofi-Aventis

Butantan - Sanofi agreement signed in 1999 and with the MoH for Influenza vaccine production signed in 2003
Construction of Industrial Plant started in 2006
H5N1 Avain Influenza Pandemic
Pilot Influenza Laboratory – Influenza Preparedness
A/H5N1 and A/H3N2 pilot production
Currently producing over 80 Mi doses of seasonal Flu vaccine



Dengue vaccine development agreement with NIH

Currently completed successfully the phase III clinical trial
Production plant ready to start



Sars-CoV-2 vaccine production agreement with Sinovac

Coronavac was the first vaccine to be used in Brazil
Over 100 Mi doses of Coronavac were administered in Brazil



The Center of Biotechnology

Development of new products and technologies to be transferred to the Production Division.

Mastering new technologies while developing new products - Establishing competence

New developments in pertussis vaccines with appropriate technologies

Hemoderivatives Purification from Human Placenta/Plasma:
Albumin, IgG, Factor VIII

Monoclonal antibodies production

Vaccines against encapsulated bacteria: *N. meningitidis, Haemophilus influenzae b, S. pneumoniae:* polysaccharide production and conjugation



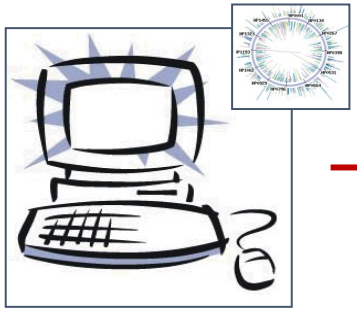




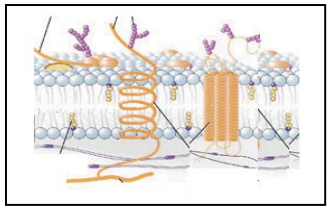
Molecular Biotechnology at the Center of Biotechnology

The Center of Biotechnology was involved in the first Brazilian Genome Projects – *Xylella fastidiosa* and Human Cancer

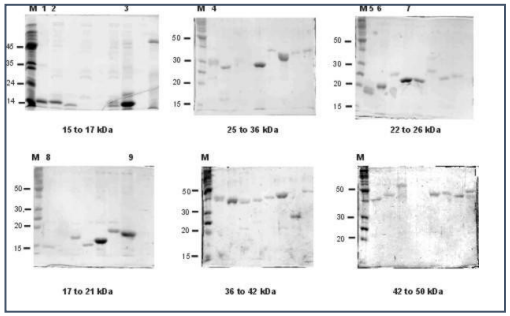
Genomics/transcriptomics/functional genomics: Schistosoma and Leptospira – Reversed vaccinology



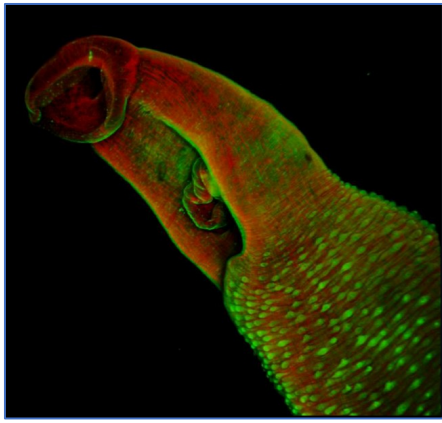
Search for antigens by bioinformatics



In silico identification of vaccine candidates



High throughput cloning, expression and purification

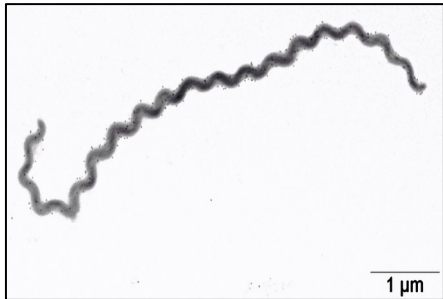




Immunogenicity



Vaccine development





Recombinant BCG Laboratory

An improved Onco rBCG for bladder cancer treatment

Decreased tumor size in animals treated with Onco rBCG

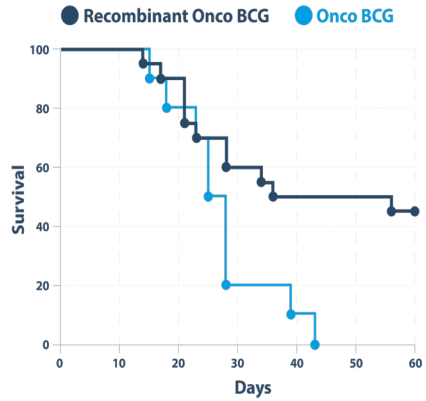
Improved survival of animals treated with Onco rBCG

Normal Bladder

Bladder with tumour (BwT)

BwT treated with Onco BCG

BwT treated with Onco recombinant BCG



Improved treatment

The new Onco rBCG has genetic modifications that increases the immune response and reduces the tumors



Currently in GMP production – Clinical trial planned for 2025



Genetic Engineering



BCG



Recombinant BCG

Onco rBCG was produced under GLP conditions and evaluated in preclinical toxicology studies

Recombinant Onco BCG

- Quality Control
- Stability (6 Mo – 2 Yr)
- Pre-clinical toxicology (6 i.v. instillations))

A repeated dose toxicity study via i.v. instillations to rabbits
No adverse events and was considered well-tolerated





Currently in GMP production – Clinical trial planned for 2025

Advancing innovation through partnership with Spin-offs/Start-ups

Instituto Butantan has a robust innovation program

Many potential products in early stage development

Butantan also has many urgent Epidemic/Pandemic demands

Therefore, a program for Spin-offs / Start-ups in partnership with Butantan is now in place to advance the many innovations that cannot be absorved by Butantan



bcgene

A partnership with Instituto Butantan

Pioneering in recombinant BCG technology

Advanced technology for development of products based on recombinant BCG as Vaccines and Cancer Therapy



Human Tuberculosis

10.3 Mi

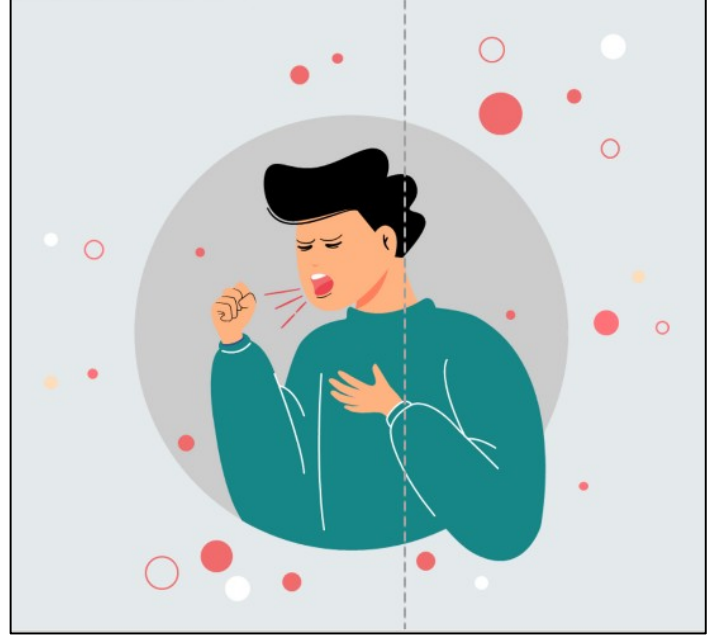
New cases/year

1.5 Mi

Deaths/year

A vaccine is available but protection wanes over time

Treatments are available but long and debilitating
Drop-outs lead to mycobacterial resistance



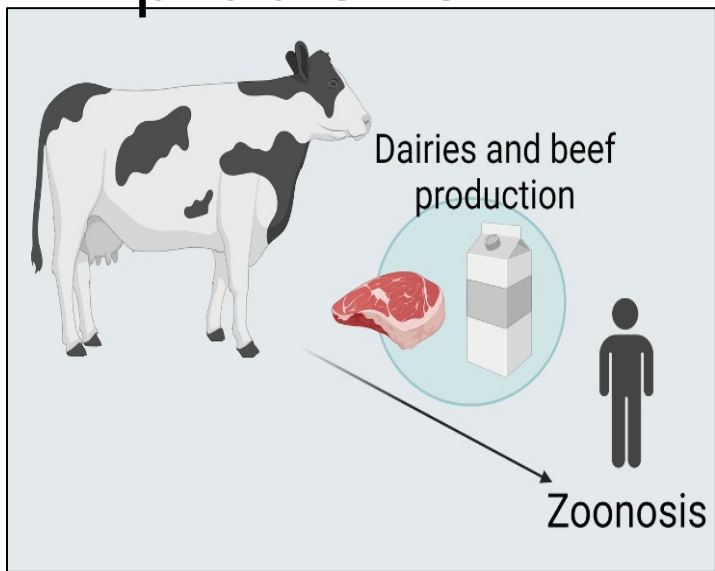
Bovine Tuberculosis

3 Bi US$

Global annual loss
An enormous econimic burden

No vaccine/No treatment
Control based on test and cull

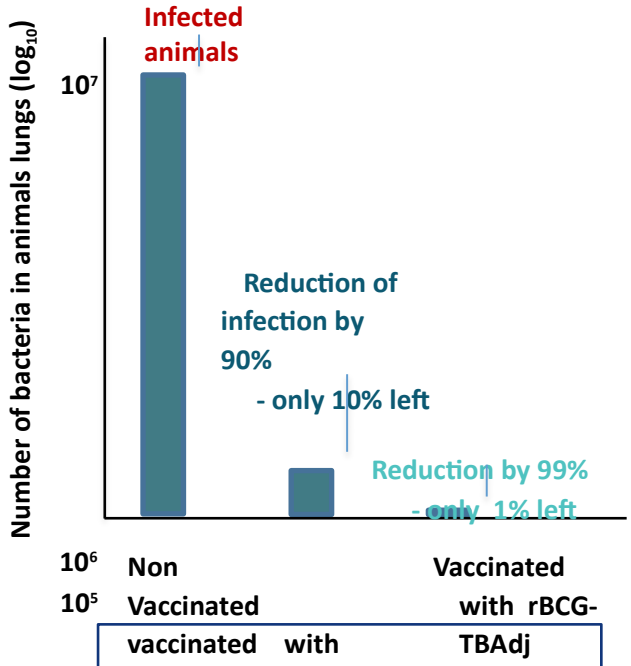
The problems



ONE VACCINE

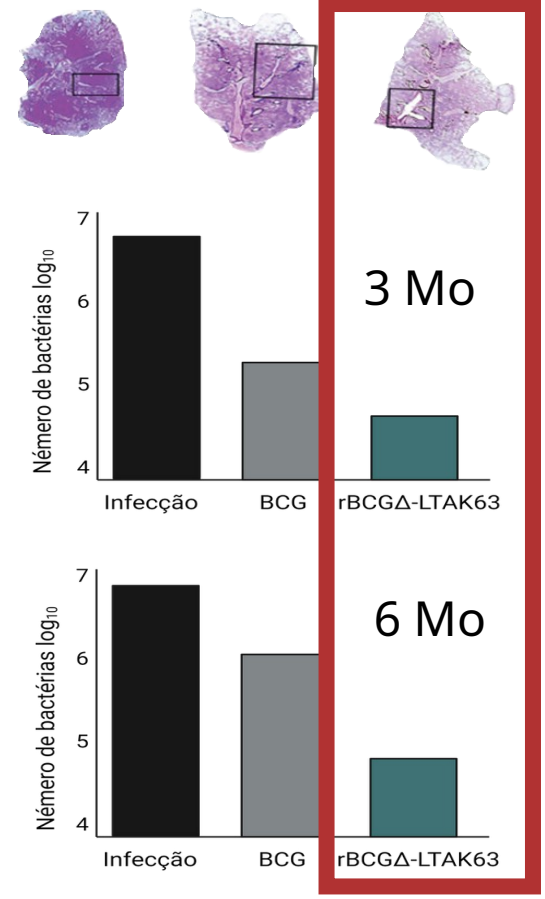
DUAL-TARGETS

Animals immunized with rBCG-TBAdj or BCG and infected with Mtb



Increased bacterial clearance in the lungs of infected animals

\+ –



Reduced Inflammation

Increased bacterial clearance

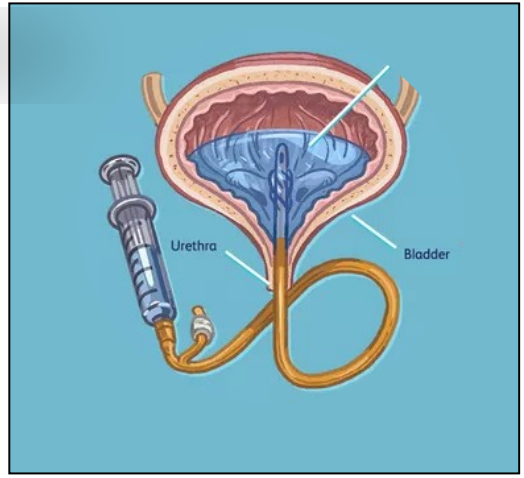
Increased duration

Improved treatment / efficacy / technology

DEMAND

Bladder cancer treatment

Improved TB vaccine



INNOVATION

Recombinant BCG strains:

More potent in the treatment of bladder cancer

More efficacious against TB



TECHNOLOGY

Robust production process by fermentation increases yields and compliance with GMP



INSTITUTO BUTANTAN

www.butantan.gov.br

Butantan and BCGene

have the expertise to take the product

through all stages of development,

to licensing for production

bcgene

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Our Group
Luciana CC Leite
Ivan P. Nascimento
Dunia Rodríguez
Alex Kanno
Carina Carvalho dos Santos
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Centro de Biotecnologia
Waldely O. Dias
Isaías Raw

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Diana Boraschi
Aldo Tagliabue

Trinity College Dublin
Kingston HG Mills

Albert Einstein College of Medicine
William R. Jacobs Jr
Glenn Fenelley

AERAS/IDT
Thomas Evans
Nathalie Cadieux

University of Surrey
Johnjoe McFadden

Institut Pasteur
Nathalie Winter
Brigitte Gicquel

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Rino Rappuoli
Mariagrazia Pizza

Urologia –Faculdade Medicina-USP
Miguel Srougi
Priscila Maria Andrade
Daher Cezar Chade
Ricardo Carneiro Borra

Universidade de São Paulo
Eduardo P. Amaral
Maria R. D'Império-Lima
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