

CENTER FOR GENETIC ENGINEERING AND BIOTECHNOLOGY



CIGB CENTRO
DE INGENIERÍA GENÉTICA
Y BIOTECNOLOGÍA





BIOCUBAFARMA



32
Cuban Enterprises



80
Production Lines



+20000
Employees



+40
Exportations to countries



740
Marketing approvals in 53 countries





We focus on key areas of the sectors

BIOMEDICAL

Diagnosis, treatment and prevention of infectious, autoimmune, cardiovascular, cerebrovascular, oncological, dermatological, hematological, neurological and gastrointestinal diseases, diabetes and scarring

VETERINARIAN

Diagnosis, prevention, control and treatment of various infectious diseases, as well as in animal nutrition

AGRICULTURAL

Control of pests and fungal and viral diseases that affect plants

INDUSTRIAL

We have products for use in the food industry



CIGB CENTRO
DE INGENIERÍA GENÉTICA
Y BIOTECNOLOGÍA



MAIN PRODUCTS

VACCINES

Pentavalent vaccine
Rec. Hepatitis B vaccine
Conjugated Hib vaccine

PRODUCTS

Rec. IFN Alpha-2b
Rec. GCSF (Hebervital)
HeberNasvac
HeberFERON (IFN α and γ)
Heberprot-P
Rec. IFN gamma
Rec. Streptokinase
Proctokinase
Heberon
Diagnostic kits
Jusvinza
Abdala

PRODUCTS

Rec. tick vaccine
(GAVAC)
Bionematicide
Acuabio



1981



Casa 149

1982



CIB

1986



CIGB

1989



CIGB Cam

1990



CIGB SS

1991



HeberBiotech

2003

ChangHeber



2016

LukangHeber



2019



I+D Center
Yongzhou

2019



Liof-Pharma

2021

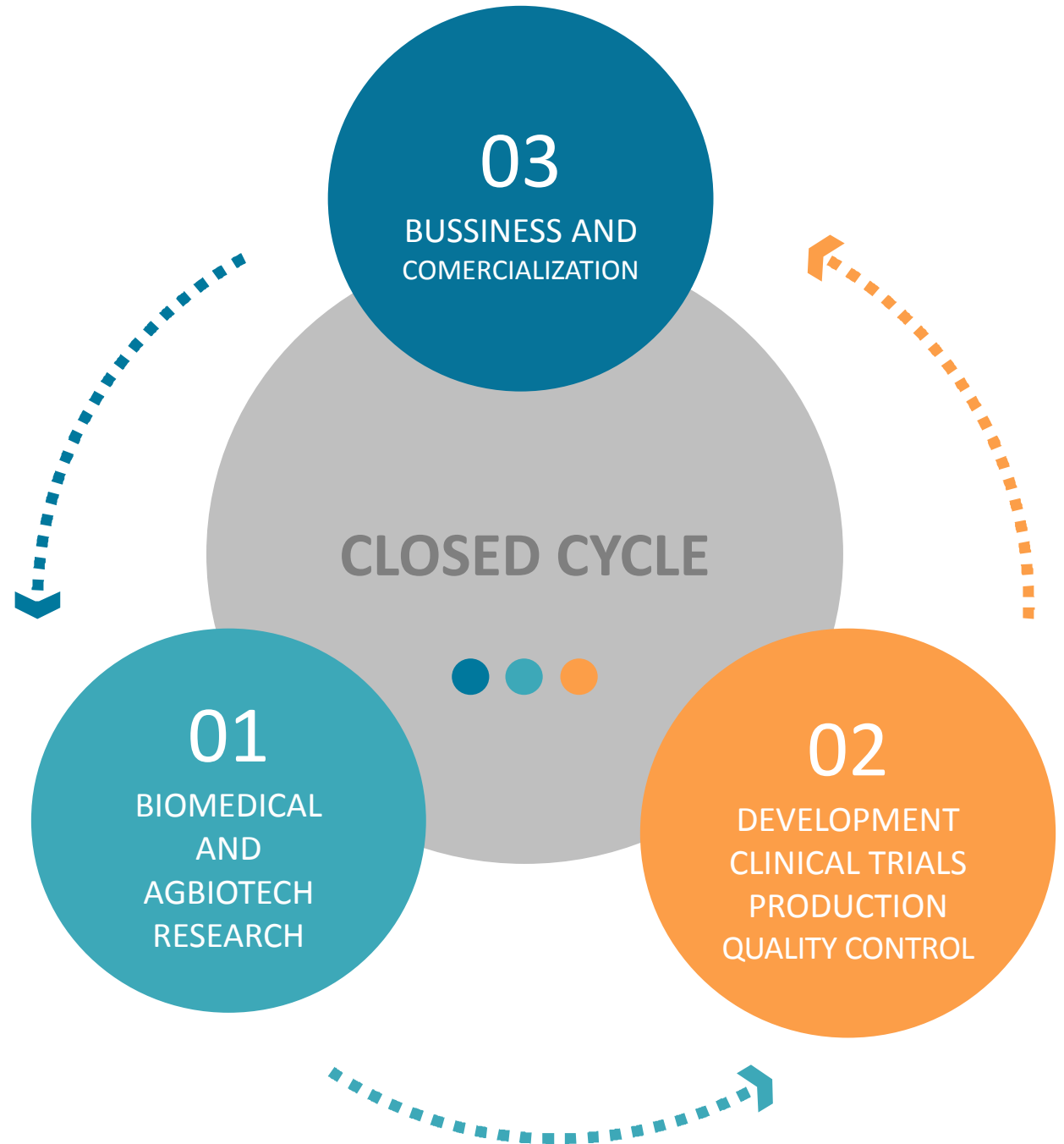


CIGB Mariel

CENTER FOR GENETIC ENGINEERING AND BIOTECHNOLOGY

It is dedicated to scientific research and innovation, development, production and marketing of **products, applications, medicines and vaccines** with high added value, for the biomedical, veterinary, agricultural, aquacultural and industrial sectors, for **one health**.

Personnel: 1600
Facilities: 70 000 m²

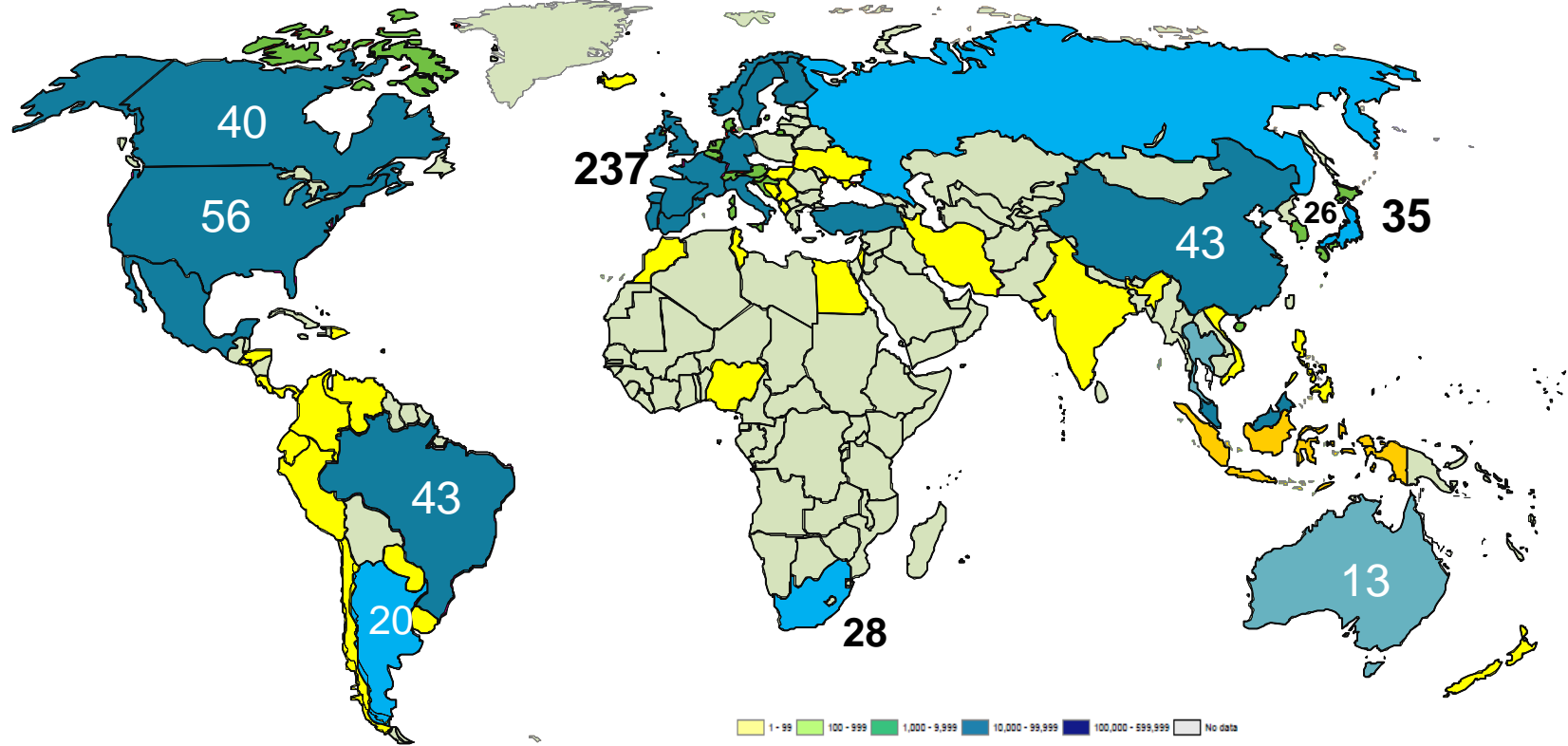


International Patent Status

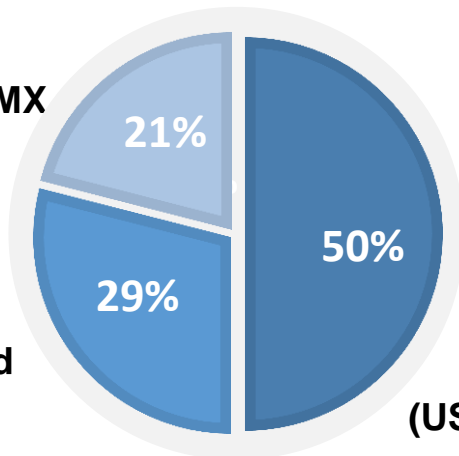
62 Inventions

768 Applications and total patents

75% Patents granted

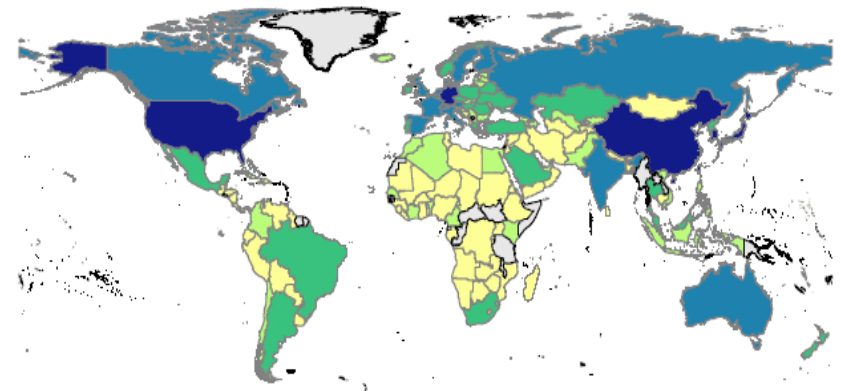


BRICS + AR + KR + MX

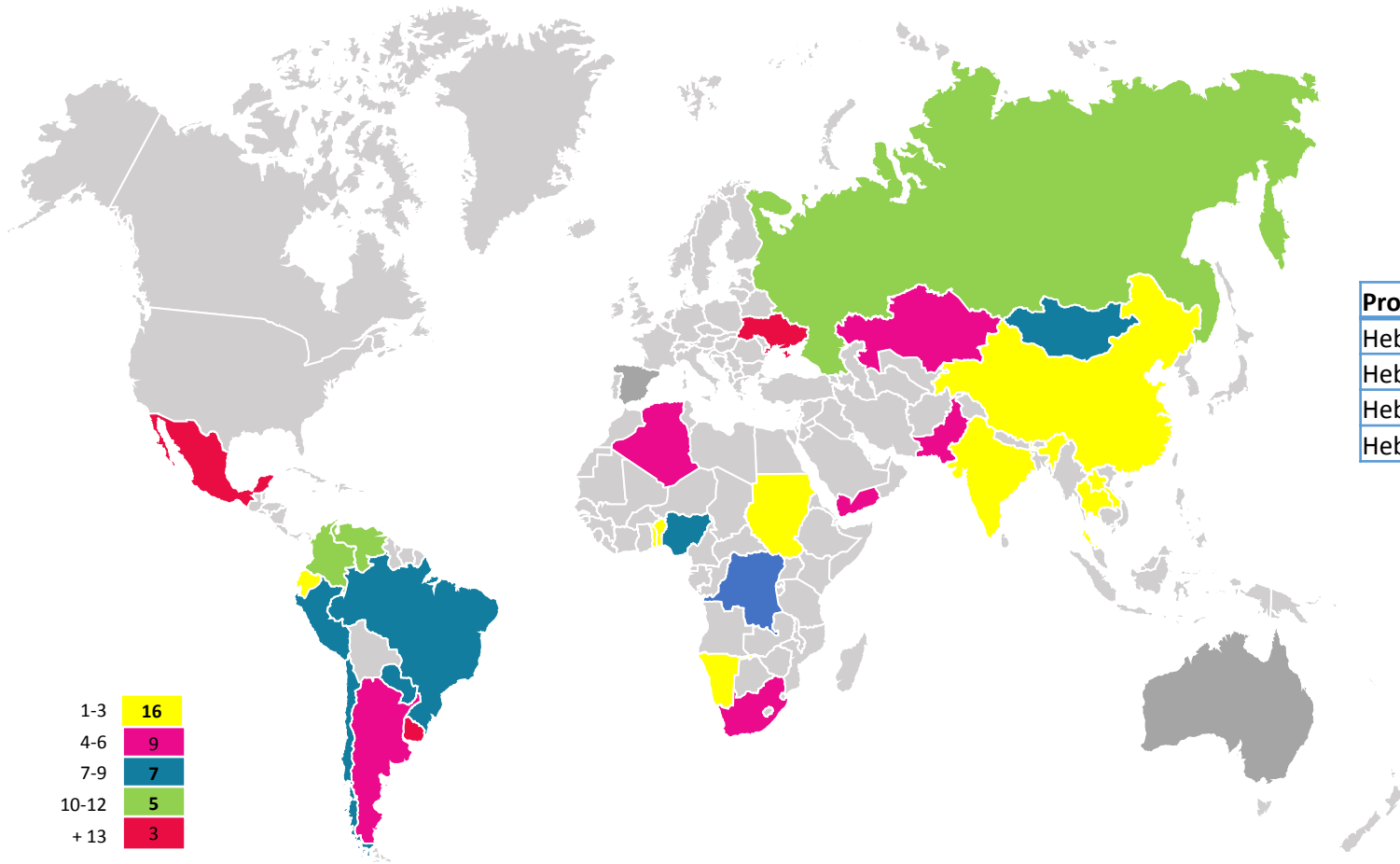


Rest of the world

First world (US, EP, CA, JP, AU)



Product Marketing Authorizations abroad



252 approvals products in 57 countries


Product	No. Reg.	Product	No. Reg.	Product	No. Reg.
Heberbiovac HB	67	Hebervital	11	Heberprot-P	24
Heberon Alfa R	61	Heberitro	7	Trivac HB	4
Heberkinasa	22	Quimi-Hib	16	Acuabio 1	1
Hebermin	14	Gavac	4	Heberprenta-L	4

Vaccines, drugs and other products commercialized




Range of Products Developed

Me too




Biosimilars

Innovative



Products

Innovative



Projects

Biopharmaceutical Projects

Project	Indication	Therapeutic Area	Laboratory	Development	Phase I	Phase II	Phase III
CIGB 300: Proapoptotic peptide that acts on phosphorylation mediated by CK2	Cervical Cancer	Oncology					
Heberprot-P: Recombinant human epidermal growth factor, for scarring	Diabetic foot ulcer	Diabetes and scarring					
Nasvac vaccine: Therapeutic recombinant vaccine	Chronic hepatitis B virus infection	Viral diseases					
CIGB 845: Neuroprotective agent	Neuroprotection	Neurology					
Heberprovac: Prostate Cancer Vaccine	Prostate cancer	Oncology					
Heberferon: Pharmaceutical formulation for parenteral use containing IFN alpha2b and gamma. Antiviral action.	COVID-19	Viral diseases					
Nasalferon: Nasal pharmaceutical solution, containing recombinant human interferon alpha 2b	Prophylaxis of SARS-CoV-2 virus infection	Viral diseases					
Heberferon: Pharmaceutical formulation for parenteral use containing IFN alfa2b and gamma. Anti-tumor action	Basal cell carcinoma	Oncology					
CIGB 247: Active Immunotherapy for Cancer Treatment	Ovarian cancer	Oncology					
CIGB 814: Deadly type of modified peptic ligament	Rheumatoid arthritis	Autoimmune diseases					

..... continued https://www.cigb.edu.cu/en/project_category/bioph_project

Innovative product

Heberprot-P®



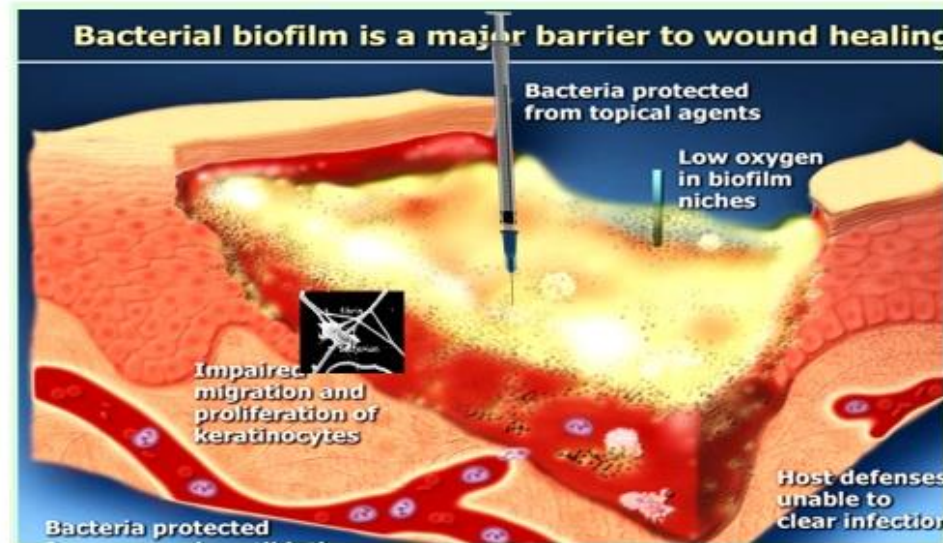
MACIGB CENTRO
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Recombinant human Epidermal Growth Factor (EGF)

Worldwide unique product for the treatment of patients with advanced diabetic foot ulcers with high risk of amputation.

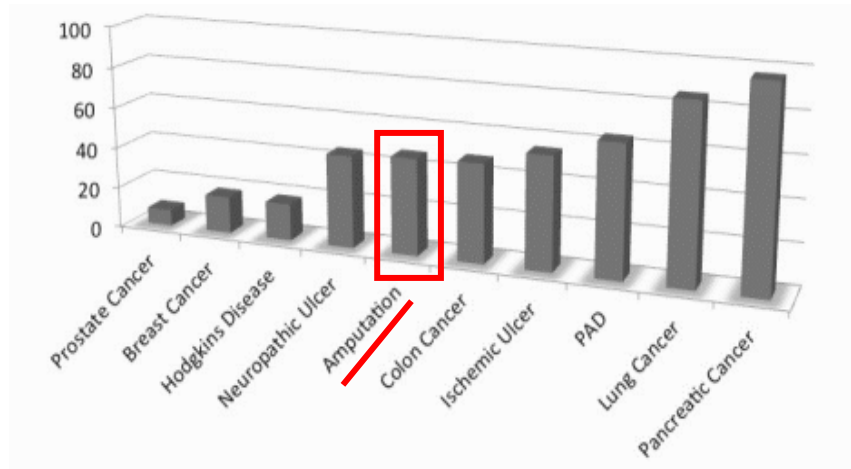
Patents Granted: United States, European Union, Australia, Hong Kong, Singapore, South Korea, South Africa, Russia, China, India, Indonesia, Ukraine, Mexico, Malaysia and Cuba.

RATIONALE OF HEBERPROT-P INFILTRATION METHOD



Severe DFU is also a life-threatening problem, greater than some types of cancer

- 15% of diabetic patients would be affected by DFU
- 30% of DFU patients never healing the ulcer with standard therapy
- 15% of DFU patients would be amputated as consequence of the DFU
- 50% of amputee patients died in 5-year, one of the most severe conditions



Heberprot-P®

CIGB CENTRO DE INGENIERÍA GENÉTICA Y BIOTECNOLOGÍA

For effective healing of diabetic foot ulcers (DFU)

LESIONS TREATED WITH HEBERPROT-P®



Market Authorization in 28 countries.
More than 390,000 patients treated in Cuba and abroad.

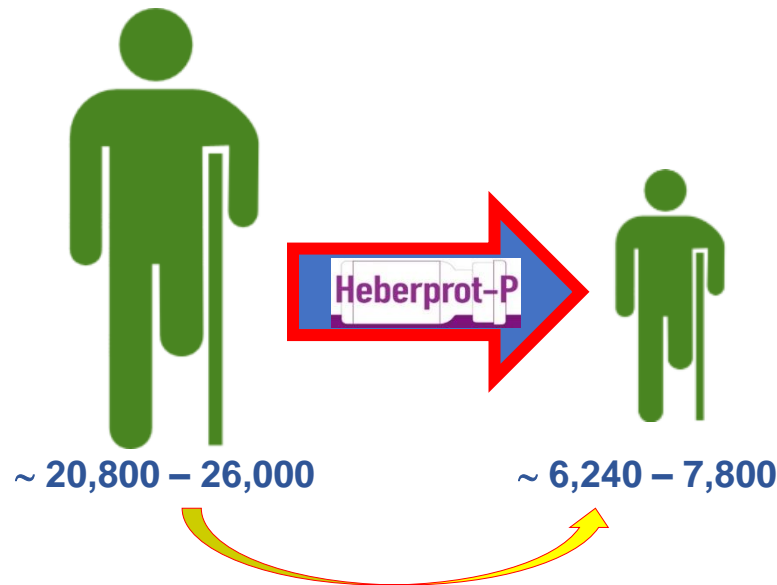
Diabetes and Diabetic Foot Ulcer



IRAN

	Population	Diabetic Adults	Amputations	Rate
USA	320,000,000	33,000,000	153,000	0.005
France	68,000,000	2,331,123	8,509	0.004
Italy	60,000,000	2,450,000	8,943	0.004
Greece	11,000,000	405,000	1,478	0.004
Iran	85,000,000	5,200,000 [★]	20,800 [*]	0.005
			26,000 [*]	0.004
		DFU-related deaths	2,080 – 2,600 [*]	

~ **57 – 71 DFU amputations/day** in Iran



[★] *Diabetes in Iran: Prospective Analysis from First Nationwide Diabetes Report of National Program for Prevention and Control of Diabetes:*
<https://www.nature.com/articles/s41598-017-13379-z>

^{*} *Estimated*

An national **Heberprot-P** program covering the whole population of advanced DFU patients in Iran might putatively save every year:

- ~ 14,000 – 20,000 lower limbs
- ~ 1,450 - 1,820 lives

Innovative product



HeberFERON

Treatment for non-melanoma skin cancer



HEBERFERON induces complete responses in advanced BCC and SCC

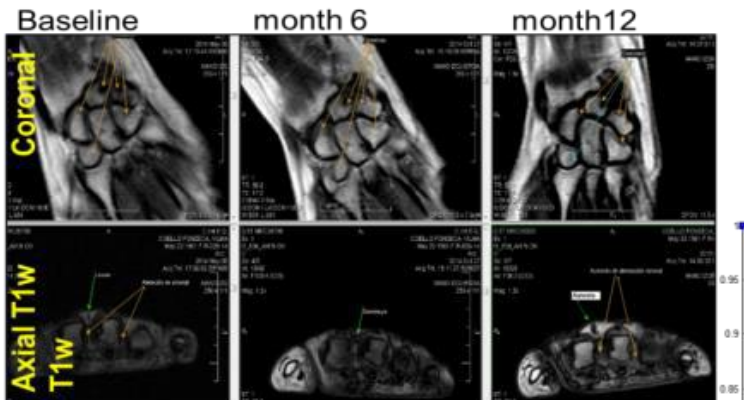


Innovative project

CIGB 814

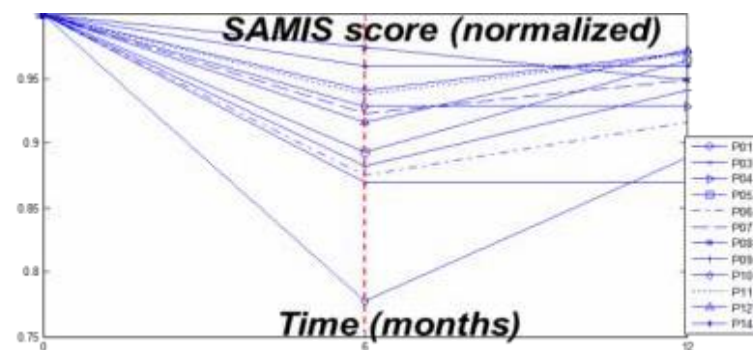
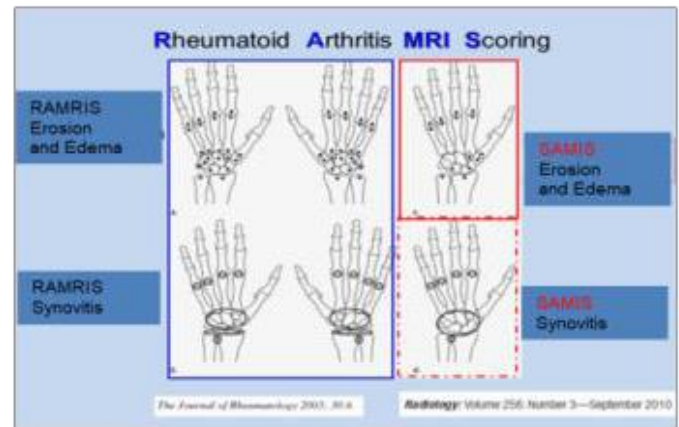
For rheumatoid arthritis treatment
Current status: clinical trial phase II

Clinical Trial assisted by Magnetic resonance imaging



Finding	T_o	%	T_f	%
Edema	10	58.8	5	29.4

13 patients out of 18 improve their score

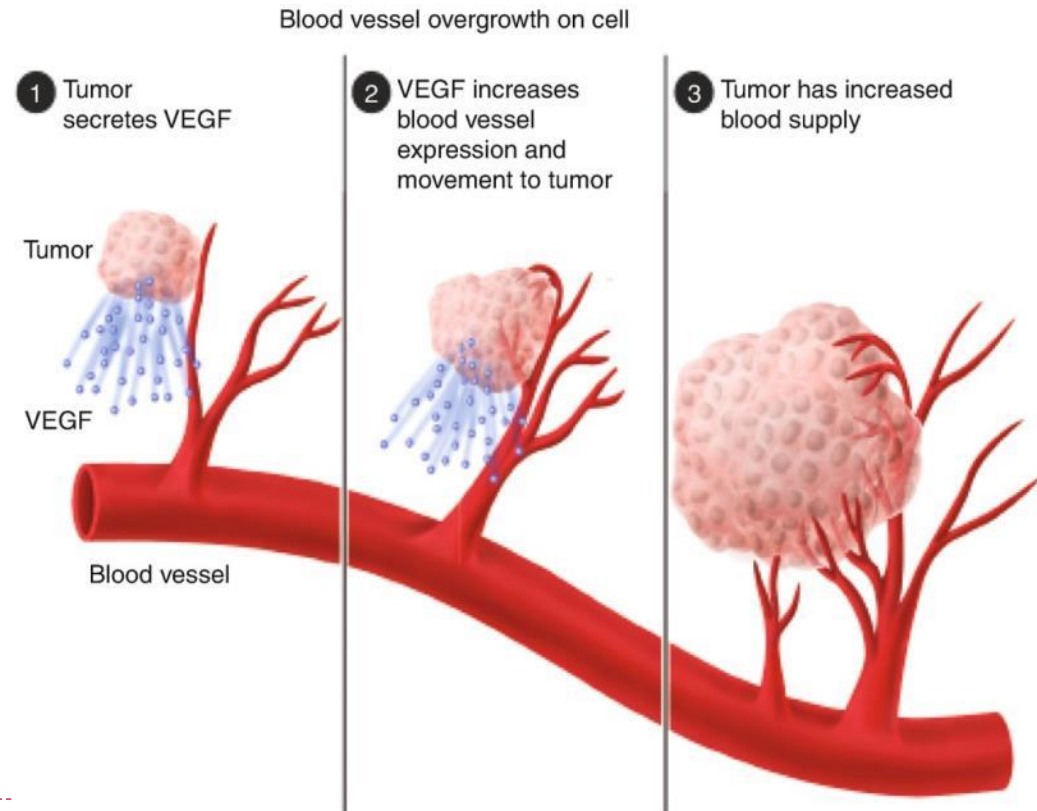


Innovative project

HeberSaVax

mediates humoral and cellular responses in cancer indications

Current status: Clinical trial phase II



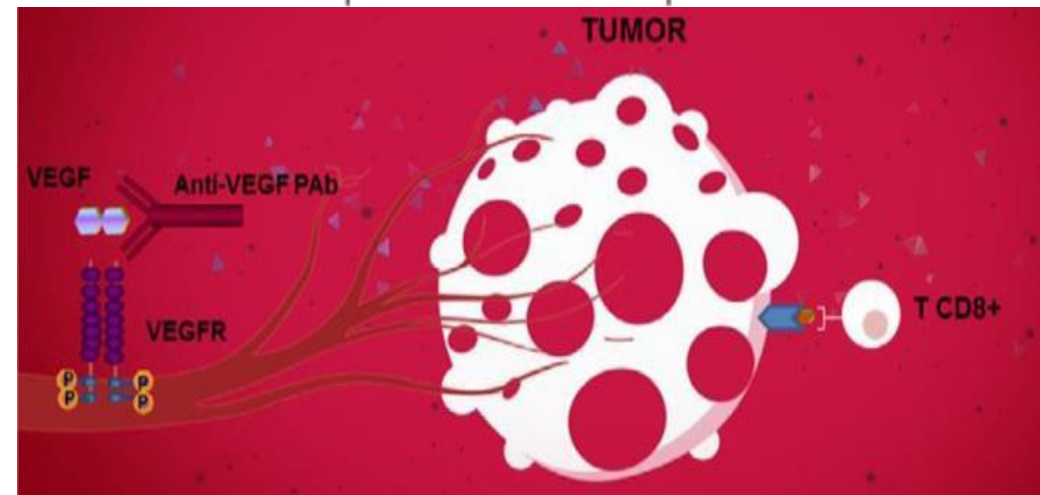
VEGF is overexpressed through the whole tumor “life cycle” and metastasis appearance and with bad patient prognosis.



HeberSaVax induces anti-VEGF antibodies that block VEGF-VEGFR2 interaction and inhibit the pro-angiogenic and immune suppressive effects of this growth factor.



Activates cytotoxic T cells that kill tumor and other tumor stromal cells that produce VEGF. The effector CD8+ T cells recognize major histocompatibility complex (MHC) class I binding VEGF-peptides expressed in tumor cells.



HeberNASVAC

Novel therapeutic vaccine for **Chronic Hepatitis B**

Composition:

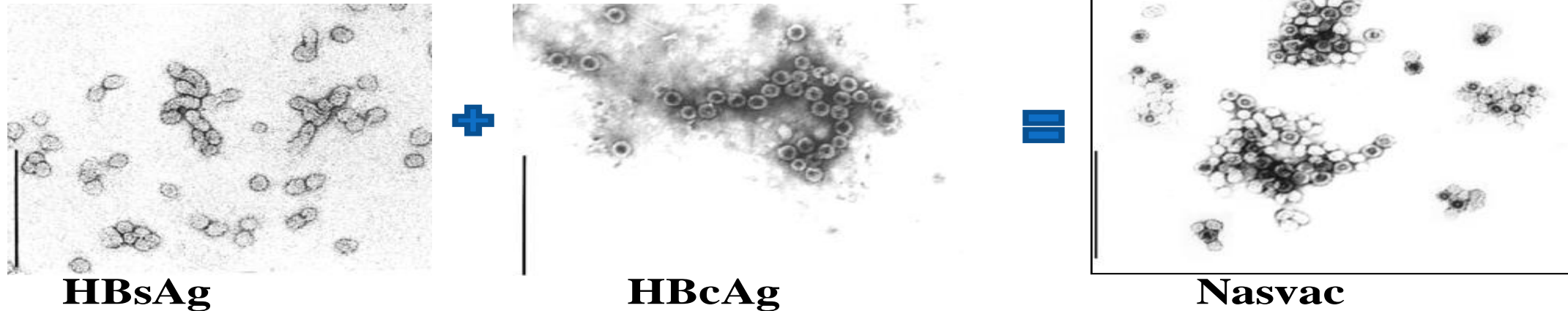
HBsAg (adw2 subtype, *Pichia pastoris* expressed recombinant antigen)

HBcAg (183 aa full antigen, produced in *E. coli*)

Simple mixture in saline phosphate buffer.



Immunol and Cell Biol (2004)



➤ Both Nasvac antigens are VLP

HBsAg: high lipid content

HBcAg: super-antigen, containing bacterial nucleid acid (ARN)

➤ Both antigens form aggregates, that are in the range from 20 to 120 nm, with a mean size of 55 ± 5 nm.

➤ This vaccine is for intranasal administration exploiting the immune resources presented at mucosal tissues.

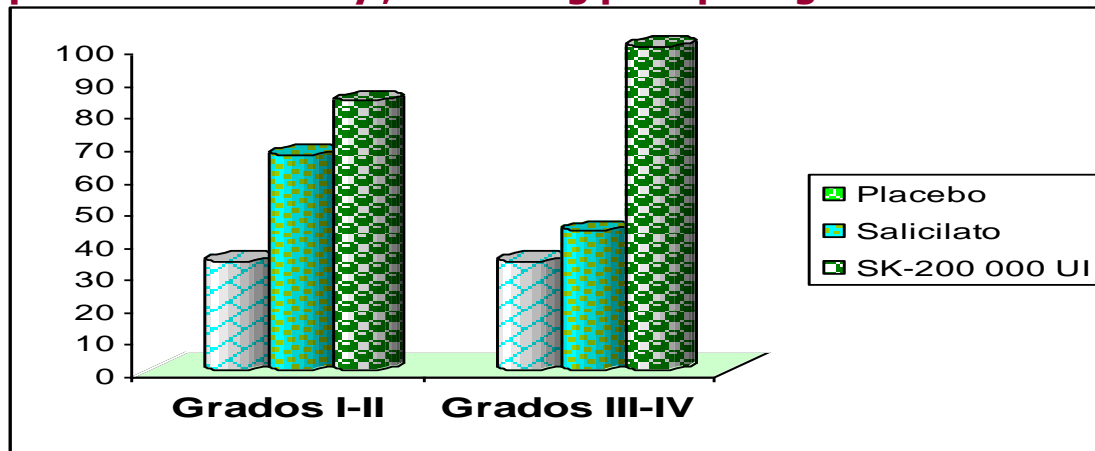
Granted Marketing Authorization in Cuba

Proctokinase

Treatment of Hemorrhoids with Recombinant Streptokinase Suppository

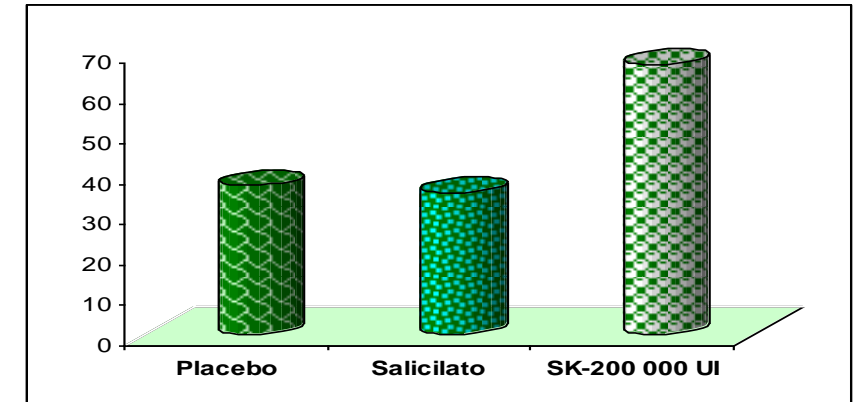
Hemorrhoids are one of the rectal pathologies with the highest worldwide incidence, 50 % of people with more than 50 years old will develop hemorrhoids.

Total response after 5th day , according prolapsus grade



Differences between Proctoquinasa (SK 200 000 UI) vs. Placebo, in III-IV Grades.

Total response at day 5th



Difference between Proctoquinasa (SK 200 000 UI) vs. Placebo.

Streptokinase
suppositories



COVID-19 Therapeutic products



Injectable recombinant interferon alpha

Covid positive patients, early stage.



Combination of recombinant human interferon alpha 2b and gamma

Covid positive patients, early stage.



Nasal recombinant interferon alpha

Persons in risk, and COVID-19 positive patients, early stage.



Anti-inflammatory peptide

Persons with COVID-19 in serious/critical condition.

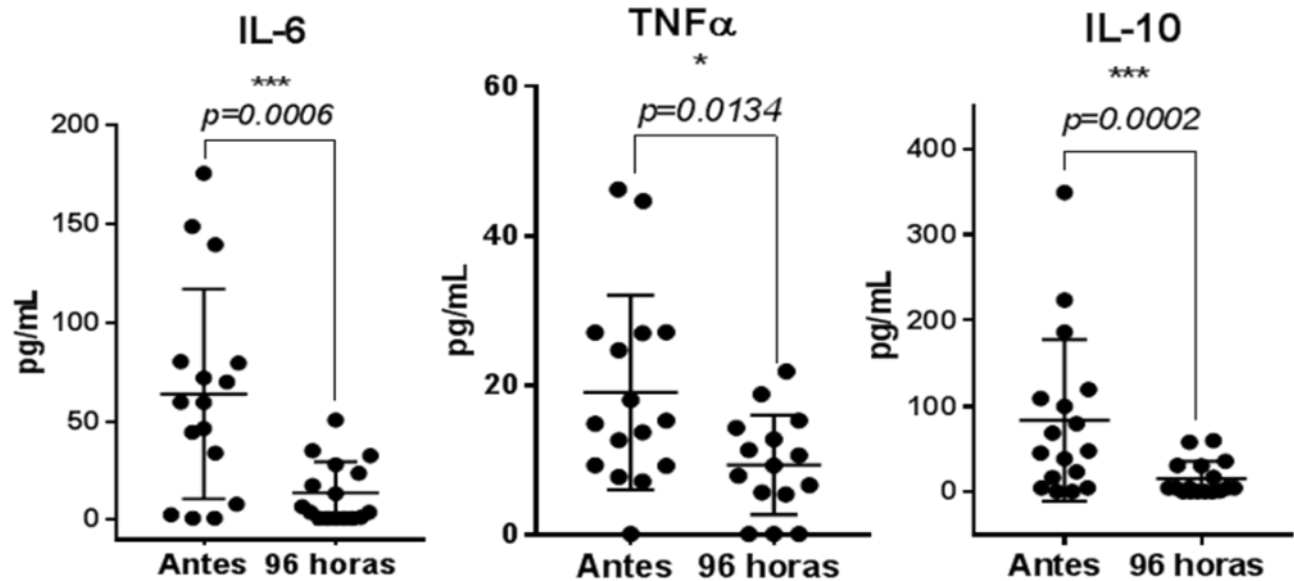
Anti-inflammatory peptide for the treatment of COVID-19 patients in serious/critical condition



Jusvinza reduces citoquine levels associated with hyperinflammation in COVID-19 patients

Granted **Emergency Use Authorization** in Covid-19 by the Cuban Regulatory Agency (CECMED)

Molecular and cellular characterization molecular of Jusvinza effect on COVID-19 patients



Anti-inflammatory peptide for the treatment of COVID-19 patients in serious/critical condition



- The use of Jusvinza in the national COVID protocol has been crucial in mortality reduction
- More than 6,000 COVID patients treated

Data from the Ministry of Health (January – August 2021)

ICU patients	Treated with Jusvinza	Recovered
871	676	575

Obstetric

In ICU N = 124

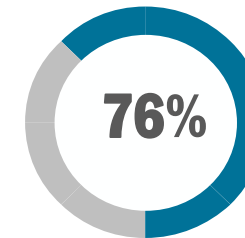
- Critical condition: 60
- Serious condition: 64
- Death : 16

Recovered: 108 (87,09 %)

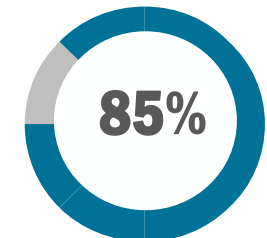
Pediatric

In ICU N = 118

- Death: 4 (3 PCR -)



Patients treated with Jusvinza



Patients recovered



**Nasal recombinant interferon alpha,
for persons in risk and early stage COVID-19 positive patients**



Nasalferon



**More than 1 million
units delivered to the
Ministry of Health**

AVCIGB CENTRO
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Abdala the first Latin American vaccine against COVID-19



 **CIGB** CENTRO
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Y BIOTECNOLOGÍA

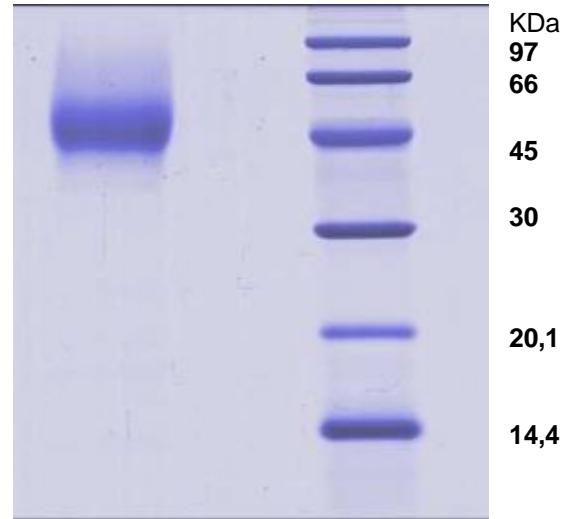
- CIGB has wide experience in the production of vaccines, including those based on subunit proteins (VPs).
- VPs are safe, non-toxic, without risk of pathogenicity.
- VPs are very stable, storage and cold chain during vaccination do not need freezing.



Abdala

COVID-19 vaccines

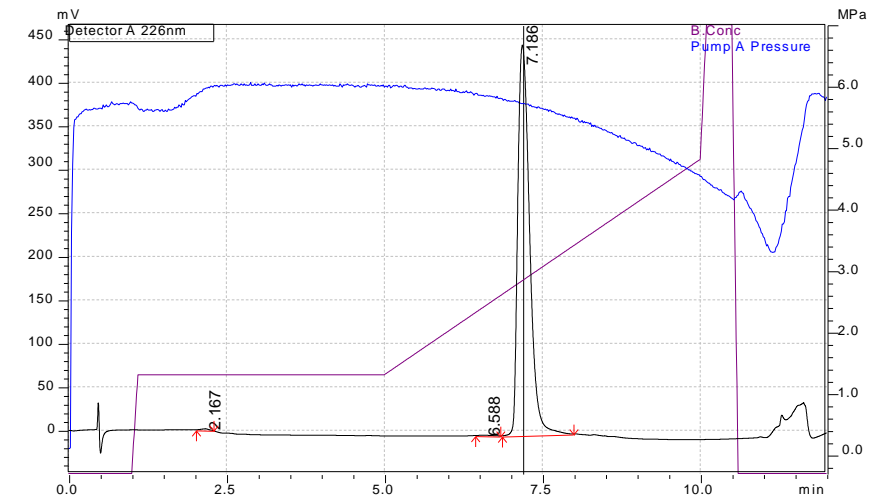
- **Abdala** is based on the receptor binding domain (RBD) of the spike protein of the SARS-CoV-2 virus. Abdala's production platform is based on *Pichia pastoris* yeast, which has been used in the Heberbiovac HB[®] preventive recombinant vaccine against the hepatitis B virus, registered in more than 30 countries and certified by the WHO.
- **Patent Number:** CU 2020-0081 "Proteína quimérica que comprende el dominio de unión al receptor de la proteína de la espiga de coronavirus y composiciones que la comprenden". Submission Date: 4.11.2020



RBD-API

MW

Datafile Name:EluBut 21006 1_5_1302021_001.lcd
Sample Name:EluBut 21006 1_5
Sample ID:1en5



Abdala: Three doses, efficacy 92.28%

EMERGENCY USE AUTHORIZATION (EUA)

Product with **Emergency Use Authorization** granted by the Center for State Control Of Medicines, Equipments and Medical Devices (Cuban Regulatory Authority, CECMED).
Date of issue: July 9, 2021.

Pediatric application extended use from 2 years old.

Date of issue: October 27, 2021.

BOOSTER DOSE

Authorization for the administration as a **booster dose**, starting 6 months after completing the immunization scheme against COVID-19 approved in Cuba.

EFFICACY

92.28 % against symptomatic COVID-19.

100 % at preventing the severe systemic disease.

100 % at preventing death in immunized patients.

Safety, Immunogenicity and Efficacy

Phase III clinical trial, multicenter, placebo-controlled, randomized and double-blind in order to evaluate the efficacy.
More than 48,000 subjects enrolled.



Summary of Clinical Trials

Study Name Trial Registration	Phase Type (primary outcome)*	Location	Participants & Ages eligible	Groups of study	Schedule	Start day/ Status
Abdala Phase I/II RPCEC 00000346	Phase I/II Randomized, double blinded, placebo controlled trial Safety and immunogenicity	Cuba (Santiago Cuba province)	Phase 1: 132 healthy participants 18- 54 years	6 groups of 22 volunteers receiving 25 µg/50 µg/placebo in two immunization schedules (1:1:1:1:1:1)	Three groups receiving 3 dose at 0-14-28 days and the 3 other at 0-28-56 days	Started: Dec 7, 2020 Complete
Abdala Phase III RPCEC 00000359	Phase III Multicenter, randomized, double blinded, placebo controlled trial Safety and efficacy	Cuba (Santiago Cuba/ Granma /Guantanamo provinces)	48 290 participants 18-80 years	2 groups of volunteers receiving 50 µg/ placebo (1:1)	3 doses at 0-14-28 days	Started: March 22, 2021 Complete***
Ismaelillo RPCEC 00000381	Phase I/II Multicenter randomized, double blinded, Safety and immunogenicity	Cuba (Camaguey province)	Phase I: 88 healthy children 3-18 years Phase II: 504 healthy children 3-18 years	2 groups of volunteers receiving 25 µg/ 50 µg (1:1) 2 groups of volunteers receiving 25 µg/ 50 µg (1:1)	3 doses at 0-14-28 days 3 doses at 0-14-28 days	Started: July 15, 2021 Complete Started: July 26, 2021 Complete

Emergency Use Authorization on July 9th, granted by Cuban NRA: CECMED



LA FUERZA DE UN PAÍS | más protegido
más inmune
más feliz

**Vacuna Abdala
recibe Autorizo
de Uso de Emergencia**

VACIGB CENTRO DE INGENIERIA GENETICA Y BIOTECNOLOGIA | **BIOCUBAFARMA** | **Cuba**



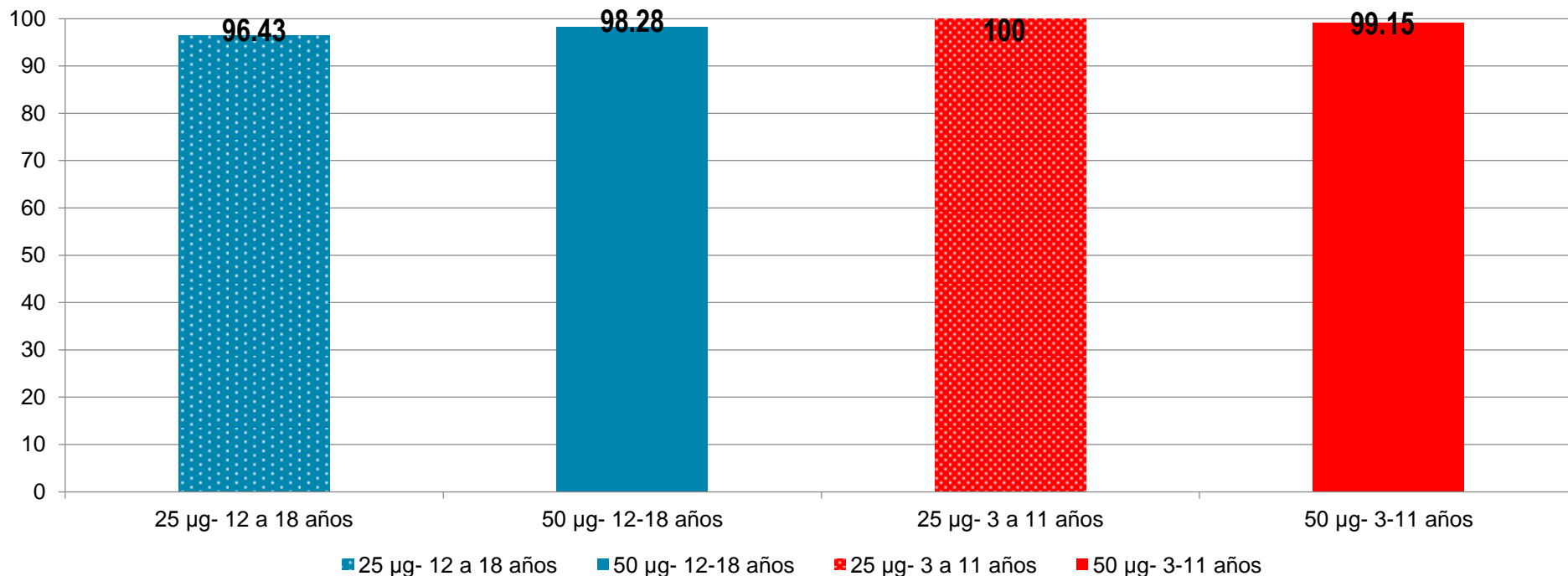
✓ **More than 30 million doses had been delivery to MOH**



- ✓ Studies of interventions in high risk cohorts such as pregnancy woman
- ✓ Population intervention in groups and territories of risk
- ✓ Massive vaccination



In children high percentages of SEROCONVERSION (main variable of the study)



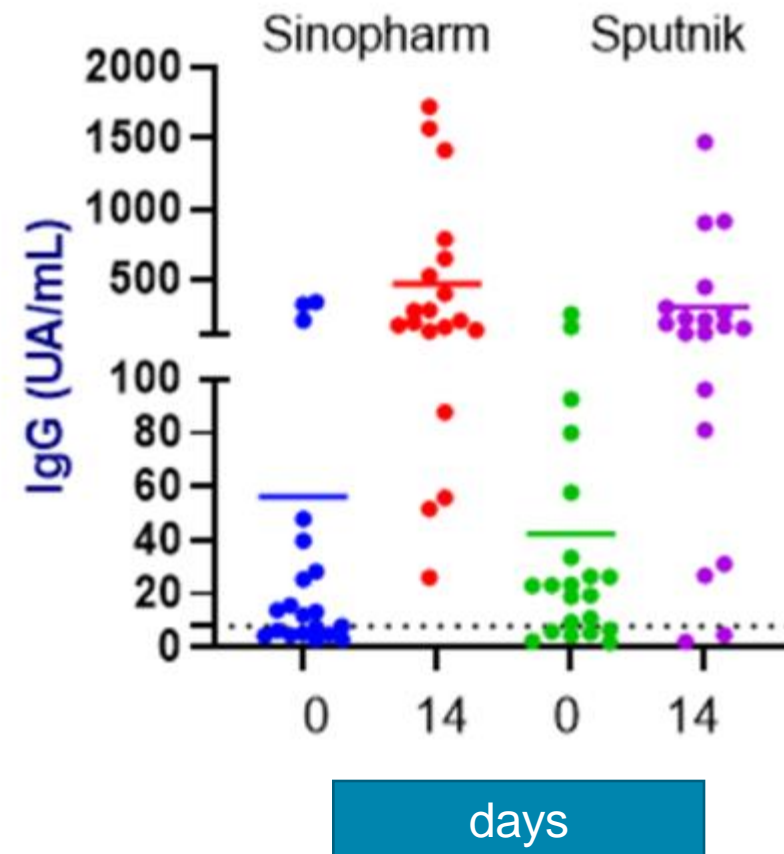
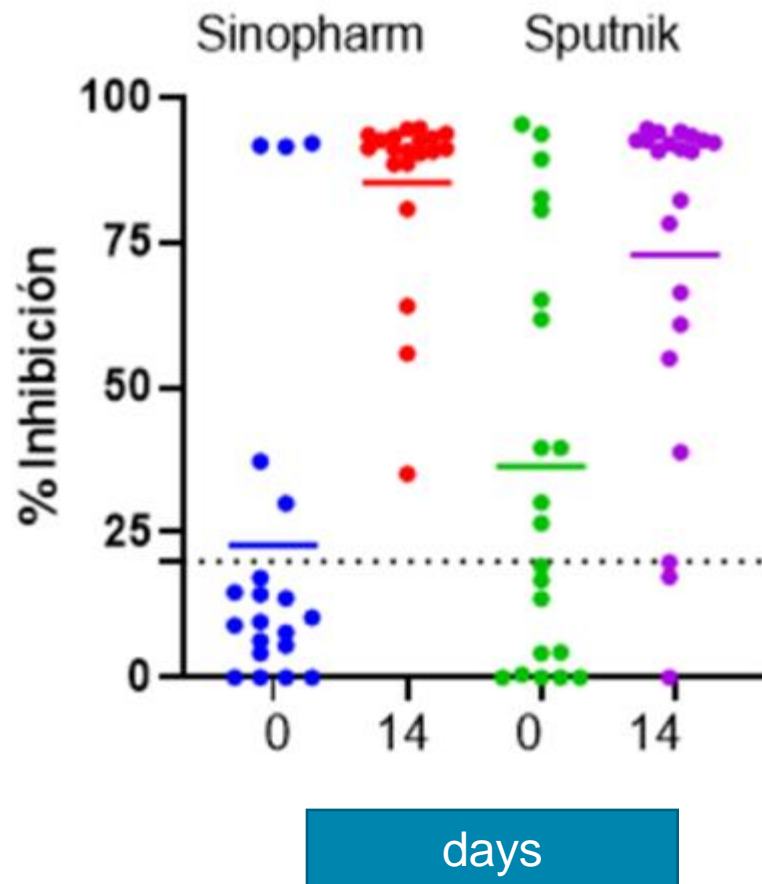
Seroconversion: Increase in anti-RBD IgG antibody titers 4 or more times from baseline before vaccination

✓ The hypothesis for the main variable of immunogenicity is fulfilled in both strata, with no significant differences between the study groups in this variable.



Abdala response durability and as a booster to others vaccines

Abdala as a booster of subjects immunized with Sputnik and Sinopharm vaccines



ABDALA Covid-19 Vaccine Timeline

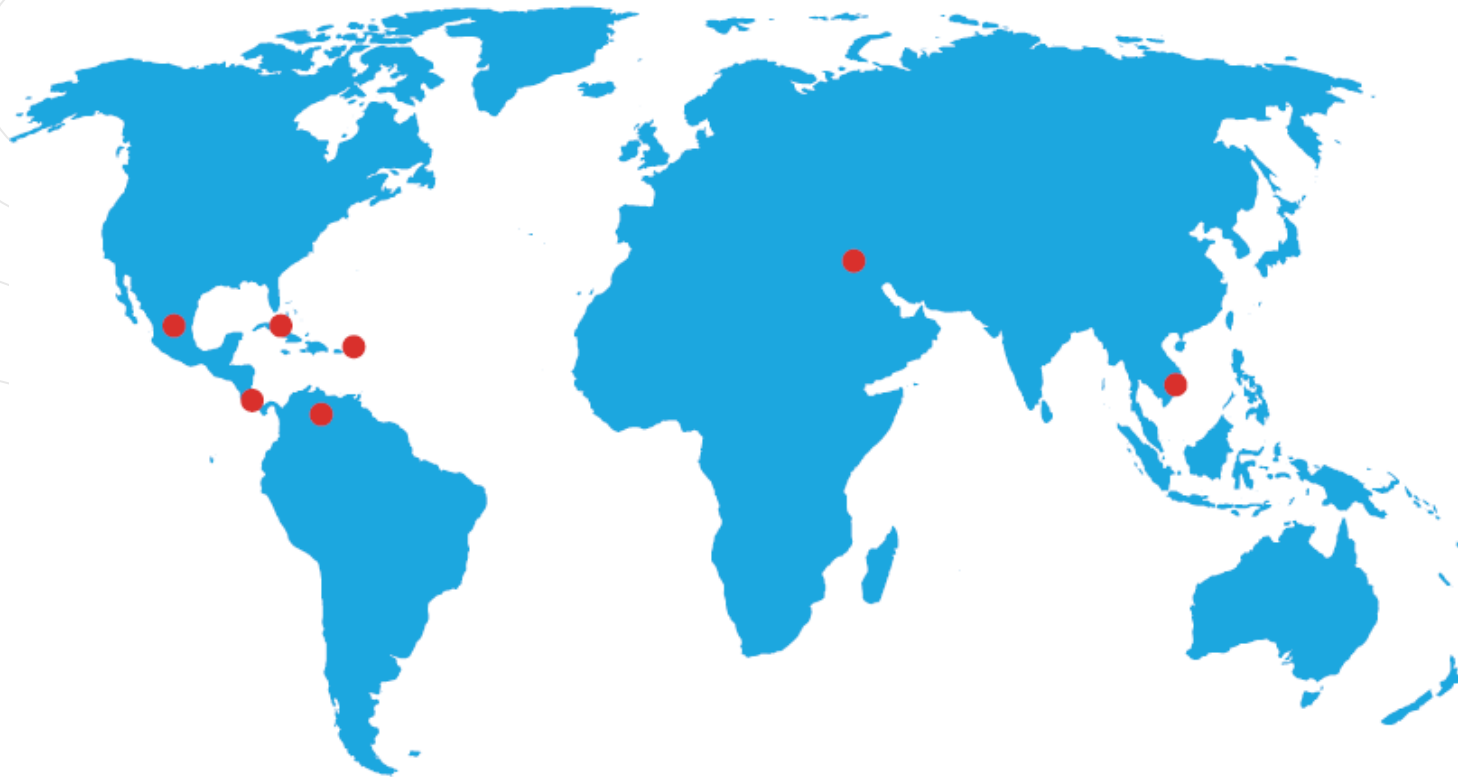


Effectiveness study, Havana
August 5 – 31
 (1,665,228 persons)

Abdala		Serious, Critical	Death
EFFECTIVENESS AGAINST SERIOUS/CRITICAL DISEASE AND DEATH	CI 95%	92,0	90,7
		(88,4-93,5)	(88,4-93,5)
		Siempre por la vida	

CIGB CENTRO DE INGENIERÍA GENÉTICA Y BIOTECNOLOGÍA

Abdala: Granted emergency use authorization in several countries and massively used in vaccination campaigns abroad.



-  Cuba
-  Venezuela
-  Nicaragua
-  San Vicente y las Granadinas
-  México
-  Vietnam
-  Siria





 **Abdala**

Mambisa

First nasally-administered COVID-19 vaccine candidate

- Recent publications in important scientific journals in the world, as well as relevant international immunology specialists, have pointed out the great prospects and potential advantages of nasal vaccines to combat the COVID-19 pandemic. However, currently there are only 11 vaccine candidates in clinical research phases with the intention of being used by nasal administration, among which **Mambisa** has been recognized.
- **Mambisa** vaccine candidate is one of the immunogens for nasal use against COVID-19 with the most advanced research at this time in the world, endorsed of high security because it is based on protein antigens produced on a platform with a history of safe and effective use for over 25 years.

Mambisa

FIRST ANTI-COVID-19 VACCINE CANDIDATE
FOR NASAL ADMINISTRATION

Always for life



ACIGB CENTRO
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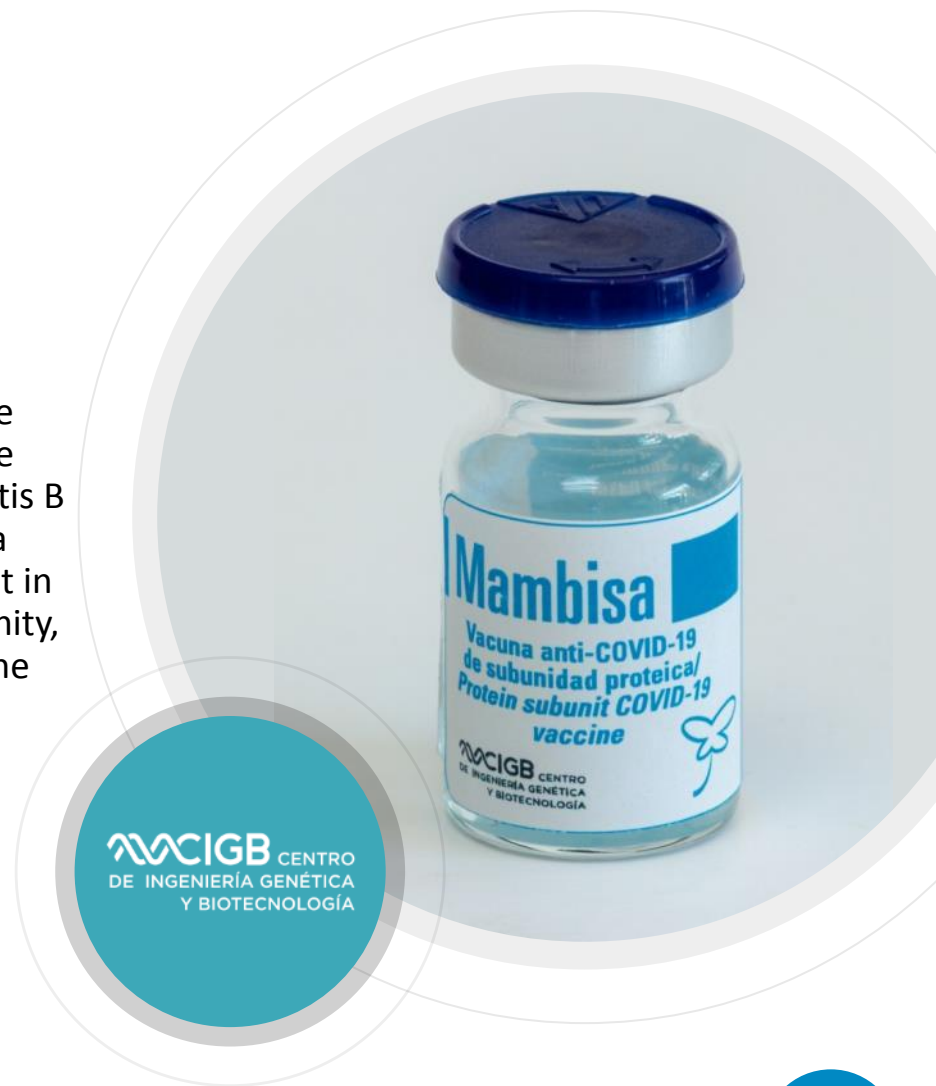
BIOCUBA
FARMA



Mambisa: nasally-administered COVID-19 vaccine candidate

RELEVANT FEATURES

- Stimulates immunity in the nasal passages, site of entry of SARS-CoV-2 virus.
- Based on recombinant proteins produced in a safe and effective technological platform in use for over 25 years.
- First protein vaccine candidate for nasal use against COVID-19 that began a phase of clinical studies in humans in the world.
- Induce immunological response both at mucosal and systemic level
- Booster for convalescent subjects only one dose.
- Booster dose for other vaccines.
- IMPD is already submitted to the NRA
- It is a combination of two recombinant proteins: the RBD protein from the spike of the SARS-CoV-2 virus, and the protein from the nucleocapsid of the hepatitis B virus.
- Previous research by the CIGB has shown that the protein from the hepatitis B virus nucleocapsid has a powerful adjuvant effect in stimulating nasal immunity, which led to its use in the production and sanitary registration of the HeberNasvac therapeutic vaccine against hepatitis B in 2015.



CIGB CENTRO
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Y BIOTECNOLOGÍA



Project portfolio, animal biotechnology



Project	Therapeutic Area	Research	Phase I	Phase II	Phase III	Record
CIGB-552vet	Veterinary	<div style="width: 80%;"></div>				
Acuabio IV	Aquaculture	<div style="width: 60%;"></div>				
Curvac: Recombinant vaccine candidate against rabbit haemorrhagic disease	Veterinary	<div style="width: 60%;"></div>				
Salvac: Vaccine candidate against sea lice, an ectoparasite of salmonids	Aquaculture	<div style="width: 20%;"></div>				
P0 vaccine: Protein-Based Tick Vaccine Candidate	Veterinary	<div style="width: 20%;"></div>				
Vaccine candidate for biological immunocastration	Veterinary	<div style="width: 20%;"></div>				
Antimicrobial peptides	Veterinary	<div style="width: 20%;"></div>				

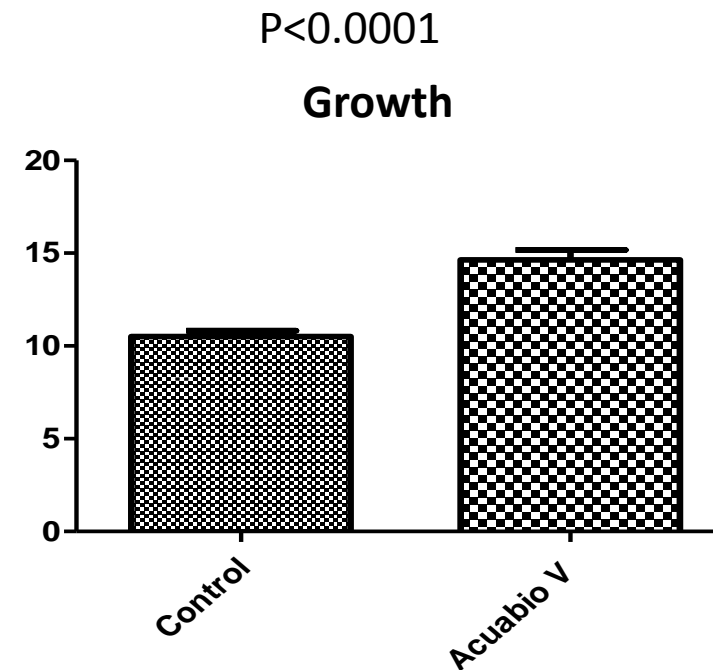
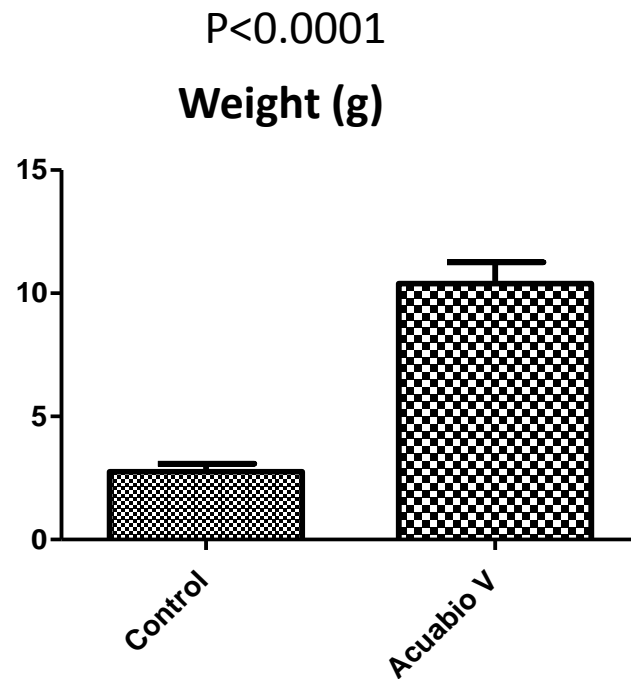
https://www.cigb.edu.cu/en/project_category/vet_project/

Acuabio V

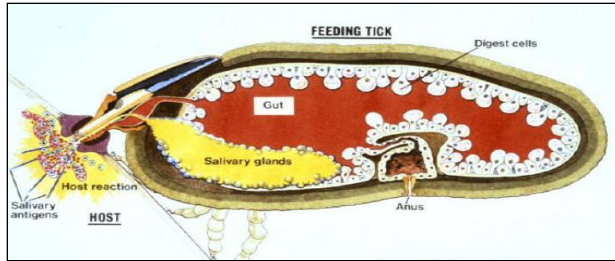
Aquatic species growth and health booster



Impact of Acuabio V application on shrimp post-larvae



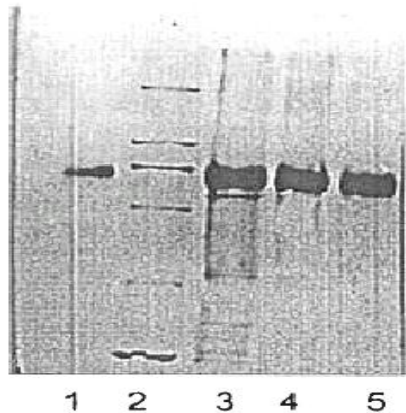
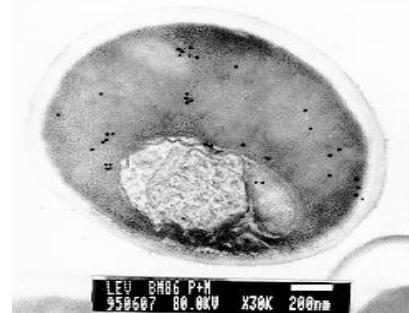
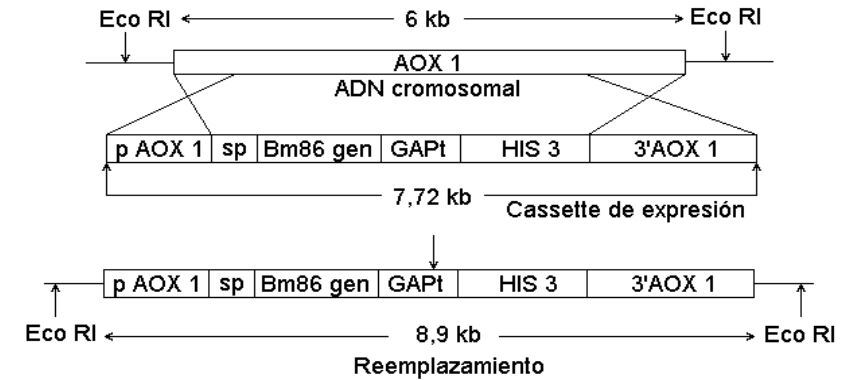
GAVAC: Vaccine against ticks



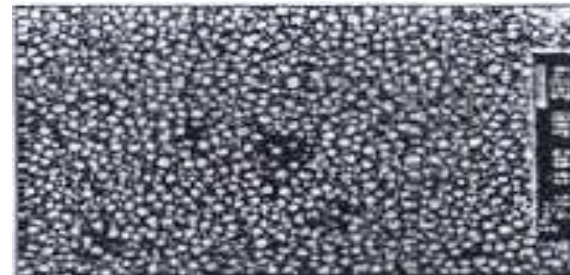
Bm86 gene obtained from gut of *Rhipicephalus microplus* tick



Inserted in *Pichia pastoris* strain



Bm86



GAVAC

Granted MA in Cuba and several countries

P0, a new antigen against ticks



Available online at www.sciencedirect.com

ScienceDirect

Veterinary Parasitology 151 (2008) 268–278

veterinary
parasitology

www.elsevier.com/locate/vetpar

Gene silencing of ribosomal protein P0 is lethal to the tick *Haemaphysalis longicornis*

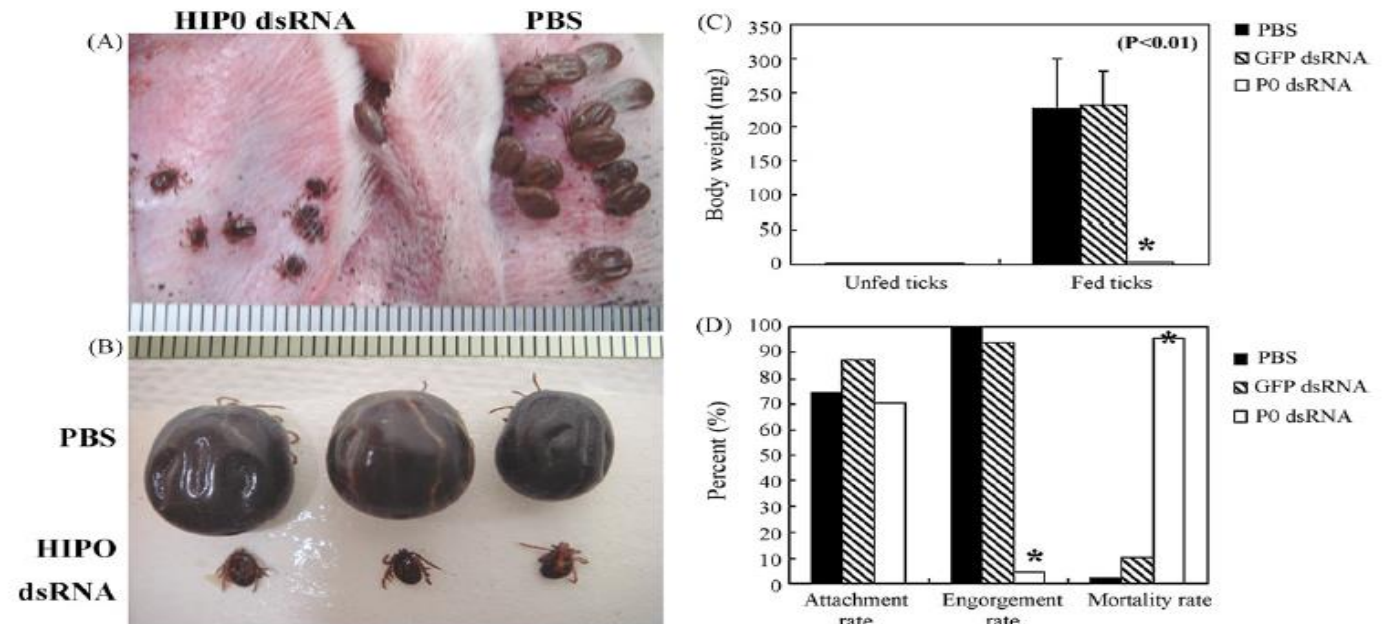
Haiyan Gong^a, Min Liao^b, Jinlin Zhou^a, Tekeshi Hatta^a, Penglong Huang^a,
Guohong Zhang^a, Hirotaka Kanuka^a, Yoshifumi Nishikawa^a,
Xuenan Xuan^a, Kozo Fujisaki^{a,b,*}

RNA interference in *Haemaphysalis longicornis* tick

P0 is a protein (a ribosome structural component), essential for cell viability, present in all organisms.

H. Gong et al. / Veterinary Parasitology 151 (2008) 268–278

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Project portfolio, plant biotechnology

Project	Therapeutic Area	Progress			
		Research	Pilot scale development	Field trials	Record
Genetic improvement of maize with biotechnological tools to sustainably increase yields in Cuba	Agriculture				
Highly thermostable biocatalyst enzymes for the production of invert syrup from sucrose	Industrial enzymes				
Obtaining soybean plants that carry the nmdef02 defensin gene and its evaluation against the Phakopsora pachyrhizi fungus	Agriculture				
Plants as bioreactors	Agriculture				
CIGB-42: for the control of infectious diseases in plants	Agriculture				
Control of geminivirus diseases in plants	Agriculture				
Transgenesis in plants	Agriculture				

https://www.cigb.edu.cu/en/project_category/agricultural_project/

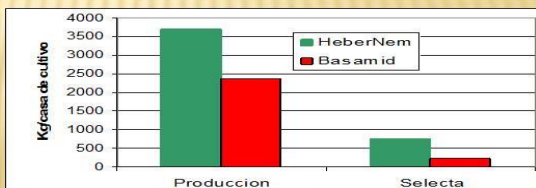
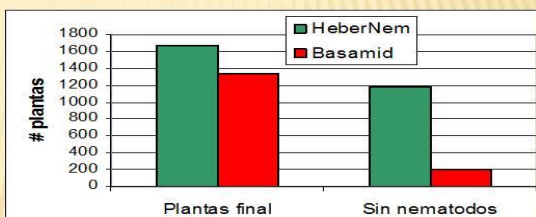
HeberNem

an effective biocontrol of nematodes and a biofertilizer



Biological Nematocide and Plant Growth Promotor

- Control of a wide range of species of plant nematodes.
- High efficacy.
- Environmentally friendly.

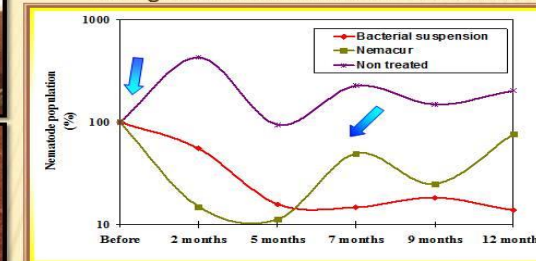


Non-treated control



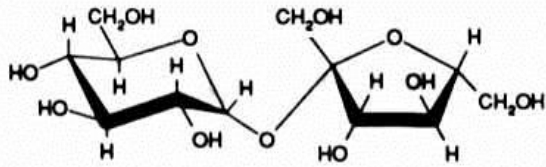
HeberNem

Biological Nematocide and Plant Growth Promotor

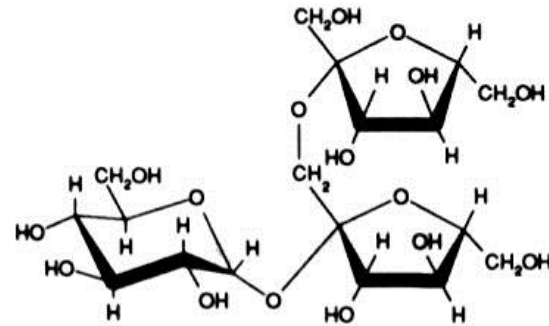
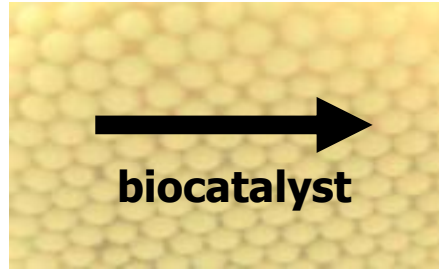


- Greater effectiveness than other biological control methods and comparable to chemical nematocides.
- Scalable for industrial production .
- Broad spectrum of action against nematode species and effective against larvae and eggs.
- Compatible with other biologicals and chemicals.
- Environmental friendly biological control and...
- Also a growth promoter.

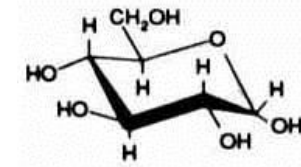
Enzymatic Technology for FOS* Production from Sucrose



sucrose + sucrose



**1-kestose
(natural prebiotic)**



glucose

*

FOS = fructo-oligosaccharides



Natural ways of FOS (inulin) consumption

Onion (2.8%), Garlic (1.0%), Barley (0.7%) Banana (0.3%), others

Vegetarian diet $\Rightarrow \leq 2$ g fructans / day

Alternative ways of FOS (inulin) consumption

1) Ingredients of functional foods (with/without probiotics) (yogurt, ice cream, confectionery, soft drinks, infant formulas, etc)



2) Dietary complement or medical treatment (w/o probiotics)

Humans

Minimal effective dose: 5 g/day
Average prebiotic dose: 5-10 g/day
Digestive tolerance: >40 g/day

100g \$7.05



140g \$15

1/2-1 tea spoon 2-4 times a day

The CIGB technology permits:

- High FOS yield ($GF_2 \geq 50\% + GF_3 \sim 5\%$)
- Concentrated reaction (initial sucrose 55-60°Bx)
- Conversion factor (0.55 kg FOS / kg sucrose)
- High specific activity ($\geq 1000,000$ u / L of culture)
- High productivity (275 kg FOS / L FT/day)
- Short-time reactions (20 h, 2 u/g de sucrose)
- Operation at 30-40°C, pH=6
- Large-scale supply of enzyme from JV.



FT Potential Applications

Fructosyltransferase (FT)

FOS production from sucrose

FOS-rich syrup production

Functional food production

Food additive

Mini-doses

Animal feed

Food industry

CIGB CENTRO DE INGENIERÍA GENÉTICA Y BIOTECNOLOGÍA

New CIGB production facilities in Mariel Special Development Zone

IB
Industrial
Biotecnológico
CIGB-MARIEL S.A.



New CIGB production facilities in Mariel Special Development Zone



THANKS!



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