

MAIN PROJECTS

PORTFOLIO 2018

Group of the Biotechnological and Pharmaceutical Industries of Cuba.

The pharmaceutical and biotechnology sectors in Cuba have a worldwide reputation thanks to their high standards of innovation and quality. BioCubaFarma, the business group that represents the sector, is made up of 34 companies, which in turn have 61 production lines and more than 20,000 employees. BioCubaFarma has a consolidated international presence, with exports to more than 40 countries.

The main products in its portfolio are biopharmaceuticals for the prevention and treatment of different diseases, such as cancer, infectious diseases, cardiovascular diseases, diabetes, as well as diagnostic reagents and medical equipment. In addition, it has a wide portfolio of projects in different stages of development, both for human health, as well as animal and agricultural use. The high scientific level of human resources in the Cuban biopharmaceutical industry guarantees the quality and competitiveness of its projects.

The Mariel Special Development Zone (ZEDM) is contributing significantly to the growth of the sector through its regulatory framework, favorable for those international companies wishing to invest in research-production facilities with high added value. The Portfolio of Opportunities for Investment offers several options to be inserted as an investor in the companies of the new biopharmaceutical hub of that Special Zone.

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HEBERPROT-P

A UNIQUE PRODUCT FOR THE TREATMENT OF DIABETIC FOOT ULCER AND REDUCTION OF THE RISK OF LIMB AMPUTATION.

HOST INSTITUTION: Centro de Ingeniería Genética y Biotecnología (CIGB).

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THERAPEUTIC AREA:

Cicatrización

GOAL

Development of a product for the treatment of DFU and reduction of the risk of limb amputation.

DESCRIPTION

Heberprot-P product is a pharmaceutical composition containing human recombinant epidermal growth factor (hrecEGF) in an injectable formulation, used by intralesional administration, locally into the wound, for the treatment of diabetic foot ulcer, to accelerate the healing of deep and complex ulcers, either neuropathic or ischemic.

Previous preclinical evidences showing efficacy in the neurogenic ischemia and protection of peripheral tissue have been demonstrated. On the rationale that EGF can enhance healing of chronic wounds following repeated local infiltrations, between 2000 and 2008 various clinical trials, including clinical trials phase I, II and III were conducted in Cuba with proven safety and efficacy in more than 300 patients.

Heberprot-P is registered in Cuba since 2006, and included within the National Medical Formulary since 2007 and approved for commercialization. Upon starting the national extension, the product has been applied to more than 270,000 DFU patients among Cuban and foreign people to date; 120,000 in a National Program of Comprehensive Care to the patient with diabetic foot ulcer in Venezuela.

So far, Heberprot-P has been registered in 23 territories all over the world. Commercial Agreements have been signed with foreign companies for the European Union, Colombia, Brazil, Algeria, Mexico, China, Russia and the Gulf and Middle East, among others. Clinical trial phase I for the DFU (Wagner's classification I & II) under European good clinical practices finished in Cuba with very good results. In addition, a clinical trial phase II finished in Spain, in patients with diabetic foot ulcers in compliance with European GCPs.

PATENT STATUS

"Use of a novel formulation and a method of treatment to prevent amputations due to diabetic foot ulcers". Granted in: Australia, China, South Korea, Cuba, Europe, United States, Hong Kong, India, Mexico, Russia, Singapore, South Africa, Malaysia, Ukraine, Indonesia, Argentina, Canada and Japan. Filed in Brazil, Thailand and Chile.

PROJECT STATUS

Registry in Cuba and other 23 country around the world.

TYPE OF COLLABORATION REQUESTED

Corporate partnership for trademark and patent license to specific territories.

COMPETITIVE ADVANTAGES -MILESTONES

Heberprot-P is a first in class product, unique worldwide, for the treatment of DFU and reduction of the risk of limb amputation. It is the only therapeutic choice available for the most advanced and complex DFU, reluctant to healing (grades 3, 4 & 5 of Wagner's classification) to avoid amputation.

DESCRIPTION

The following project invites you to establish partnership towards the development of a unique product for the treatment of DFU and reduction of the risk of limb amputation. Heberprot-P is a first in class product, unique worldwide, for the treatment of DFU and reduction of the risk of limb amputation until now was registered in Cuba and 23 countries more around the world. It is the

only therapeutic choice available for the most advanced and complex DFU, reluctant to healing (grades 3, 4 & 5 of Wagner's classification) to avoid amputation. The partnership is welcome to conduct either registry or Phase IV actions (Pharmacovigilance study). Corporate partnership for trademark and patent license to specific territories is open to analysis as well.

PATENT

"Use of a novel formulation and a method of treatment to prevent amputations due to diabetic foot ulcers" which has been granted in: Australia, China, South Korea, Cuba, Europe, United States, Hong Kong, India, Mexico, Russia, Singapore, South Africa, Malaysia, Ukraine, Indonesia, Argentina, Canada and Japan and filed in Brazil, Thailand and Chile.



FIGURE 1. Bone exposed: With Heberprot-P: Granulation achieved after 18 infiltrations (6 weeks) and wound closure after 51 days. ($\geq 95\%$ efficacy of treated cases).



FIGURE 2. Tendon exposed: With Heberprot-P: Granulation achieved in 4 weeks and wound closure after 52 days. ($\geq 95\%$ efficacy of treated cases).

PUBLICATIONS

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CIGB 500: A peptide with cardiac cyto-protective effects.

HOST INSTITUTION: Centro de Ingeniería Genética y Biotecnología (CIGB).
E-mail: merardo.pujol@cigb.edu.cu / Web site: <http://gndp.cigb.edu.cu>

THERAPEUTIC AREA:
Cardiology

DESCRIPTION

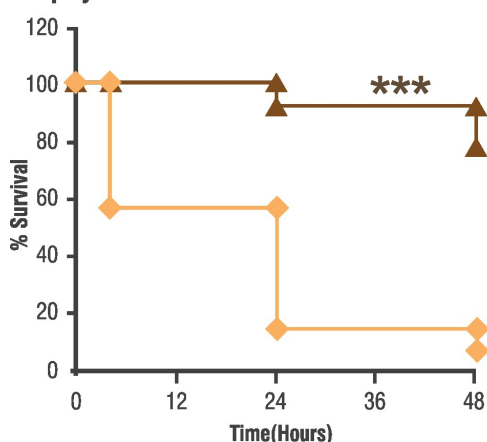
CIGB-500 is a six aminoacids synthetic peptide with a substantial safety profile. CIGB 500 belongs to the heterogeneous group of synthetic peptides that act as potent GH secretagogues on specific G-protein-coupled receptors in the hypothalamus and pituitary. The pharmacological effects induced by CIGB 500 and other cognate agents could result from the agonistic activation of the GPCR and the CD 36.

Different experiments have shown that a single pre-conditioning or multiple CIGB 500 administrations amplify cellular cyto-protective mechanisms preventing single or multiple organs demise. In hepatic ischemia, CIGB 500 prevents hepatocytes death and transforms the placebo-submassive necrotic pattern into a hepatocytes' individual one. Similarly, in a porcine,

surgically induced model of acute myocardial infarction, necrosis was reduced by more than 70% as compared to untreated pigs. In dilated cardiomyopathy modelos CIGB 500 could prevent heart failure and other toxic systemic complications when concomitantly administered to (DX). Therapeutically administered-CIGB 500 restored myocardial damages and failure.



Prophylactic CIGB-500 administration



Therapeutic CIGB-500 administration

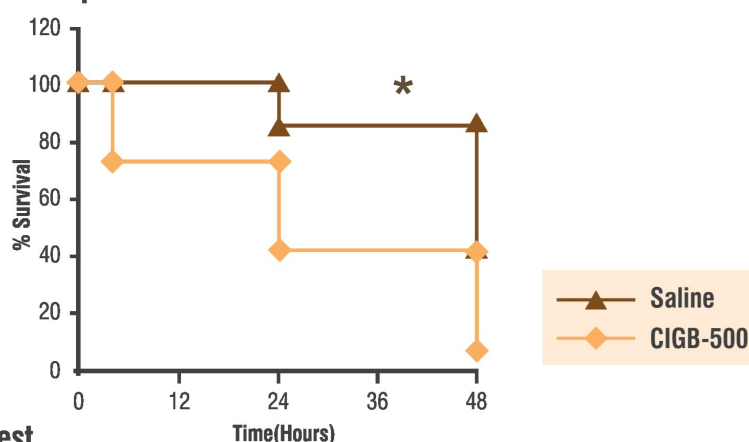


FIGURE 1. Kaplan-Meier survival analysis.

1. As a prove-of-concept for a cyto-protective agent we examined whether CIGB 500 could reduce mortality associated to multiple organ failure (MOF) induced by full-thickness scalds in rodents as a robust multi-organ challenge. Both prophylactic and preconditioning schemes were assayed
2. CIGB 500 reduced necrosis upon an ischemia/reperfusion event in a porcine model of acute myocardial infarction (AMI).

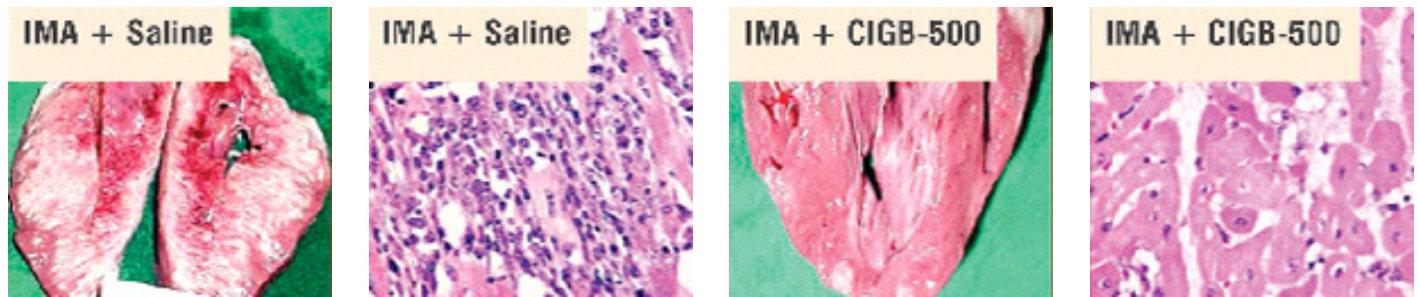
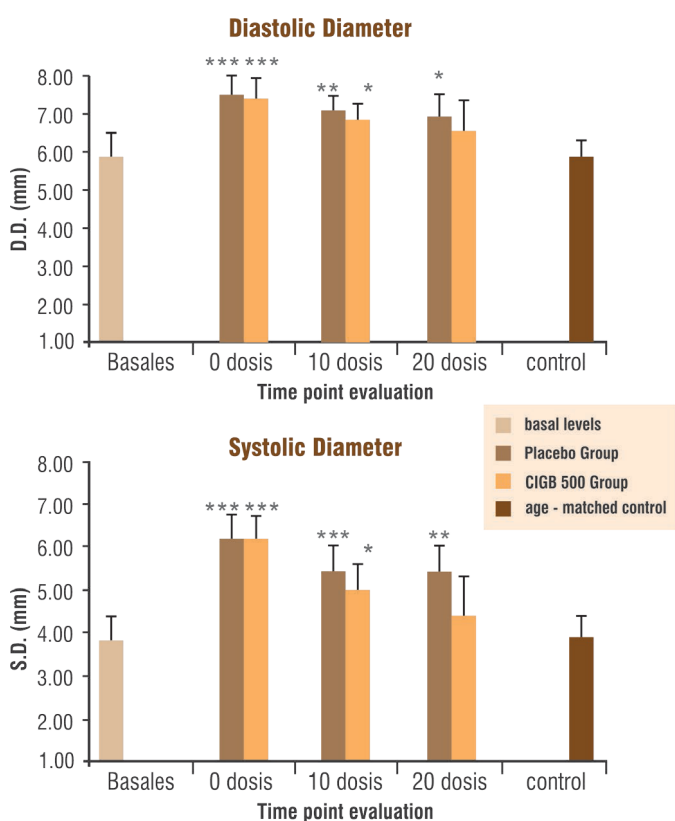
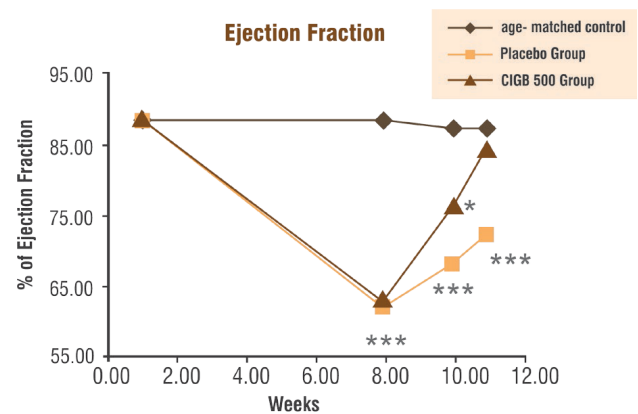


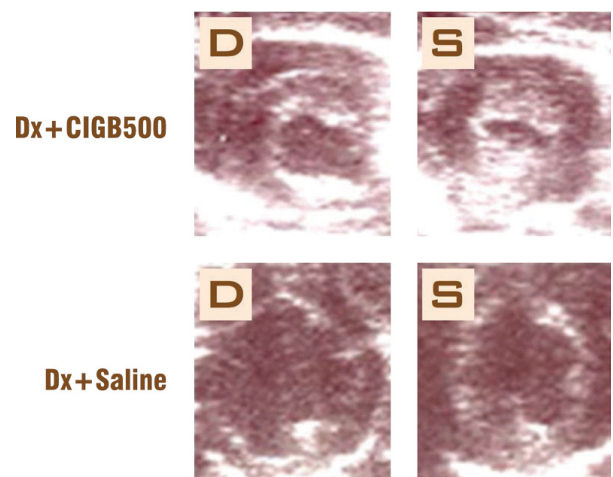
FIGURE 2. Macroscopic and microscopic aspect representative of hearts from saline control group and CIGB 500 treated group..



*** Basal levels vs Placebo and CIGB-500 - 0 dose, $p < 0.0001$
 */*** Placebo and CIGB-500 - 10 dose vs basal, $p = 0.0185/p = 0.0005$
 ** Placebo - 20 dose vs age-matched control, $p = 0.0012$. Unpaired t-Test



8th week: placebo and CIGB-500 vs age-matched control, $p < 0.001$
 10ma y 12va weeks: placebo vs control, $p < 0.001$
 10ma week: CIGB-500 vs age-matched control, $p < 0.05$. Unpaired t-Test



3. CIGB500 prevented and reversed Doxorubicin-induced Dilated Miocardiopathy in rats.

The main biological properties of CIGB 500 which mechanistically support its mechanism of action can be summarized as:

1. Inotropic. It seems to be mediated by an elevation of Ca^{2+} influx via PLC/DAG/PKC, through the voltage-gated calcium channel, triggering Ca^{2+} release from thapsigargin-sensitive intracellular stores, which translated in a positive inotropic response without a chronotropic effect.
2. Anti-fibrotic. According to our data, CIGB 500 upregulated PPAR- gamma which is followed by a TGF-beta, CTGF and PDGF downregulation.
3. Anti-inflammatory. Blunts NF.kB expression and activation and the ensued
4. Cyto-protective. It involves the phosphatidil inositol-3 kinase /protein kinase B (PI-3K/PKB), Akt pathway, as the induction of the hypoxia-inducible factor-1 alpha (HIF-1) all committed in cellular survival.
5. Cardio-protective. It involves different biological actions which converge to enhance cardiomyocytes survival. I.E., reduction of ROS and NEP cyto-toxicity, reduction of neurohormones, etc.
6. Vasodilatory. It seems to involve and endothelin activity reduction and an e-NOS up-regulation.

The paramount significance of CIGB 500 in acute myocardial infarction is summarized below. Significantly, CIGB 500 bounties are supported by its ability to cut off the pathophysiological damage cascade by different target points.

CIGB is currently running a phase I/II clinical trial in myocardial infarction-affected patients. This clinical trial will aim to: (1) Reduce myocardial infarct extension. (2) Reduce acute morbidity including re-infarction. (3) Prevent ventricular remodeling. (4) Reduce acute ventricular mechanical failure.

PATENTS

Berlanga J et al. Pharmaceutical combination for the treatment of tissue damage owing to an arterial irrigation defect. United States Patent 7361638. European patent 1 354 597 B.

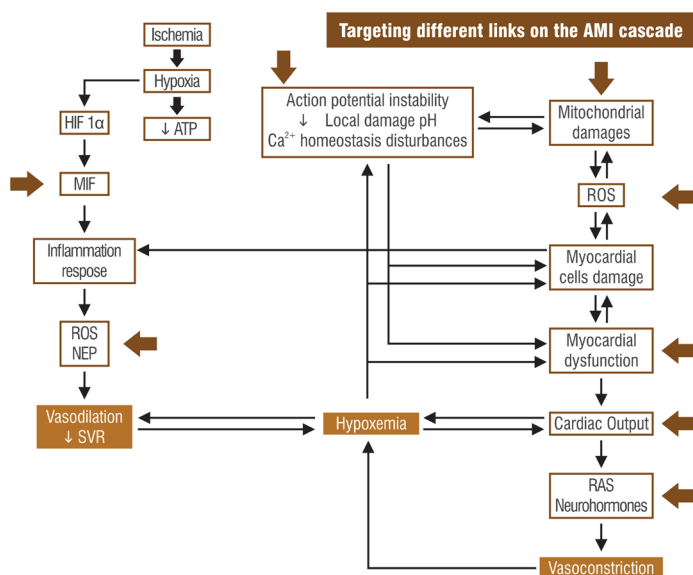


FIGURE 3. CIGB 500 metabolic impact on intact, healthy-hearts in rats.

4. Summary of study conclusions of CIGB 500 in healthy human volunteers
 - CIGB 500 has long since proved to be safe. The scale up was safely and successfully completed.
 - A total of 66.7% of the subjects exhibited moderate adverse effects (sweating, and bradychardia) with spontaneous remission.
 - CIGB 500 showed a biphasic plasmatic concentration with a rapid biodistribution phase ensued by a second slower phase. AUC increased in relation to the dose.
 - CIGB 500 administration did not disturb the homeostasis of the REDOX system and temporarily stimulated the release of GH / IGF-I / IGFBP3.

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CIMAVAX-EGF®: New Therapeutic Vaccine for Advanced Non- Small Cell Lung Cancer

HOST INSTITUTION: Centro de Inmunología Molecular (CIM).

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GOAL

To benefit patients diagnosed of advanced Non- small cell lung cancer in term of improve-ment survival, quality of life, together with a very good safety profile by active imunotherapy against to epidermal growth factor (EGF).

BUSINESS PROPOSAL

Creation of a GMP facility in the Special Zone from Development in Mariel with foreign capital.

DESCRIPTION

Lung cancer is the most common cause of death from cancer worldwide, estimated to be responsible for nearly 1.59 million

deaths, 19.4% of the total. Because of its high fatality and the relative lack of variability in survival in different world regions, the geographical patterns in mortality closely follow those in incidence. The incidence rates are generally lower and the geographical pattern is a little different, mainly reflecting different historical exposure to tobacco smoking. Thus the highest estimated rates are in Northern America (33.8) and Northern Europe (23.7) with a relatively high rate in Eastern Asia (19.2) and the lowest rates again in Western and Middle Africa (1.1 and 0.8 respectively).

At the time of diagnosis, most patients with lung cancer have disease advanced, inoperable, which is associated with poor prognosis. Despite of standard treatment options based to radiations, chemo-therapy and targeted therapies, NSCLC remain as unmet medical need. So, the active immunotherapy approach has interesting space to involve use of relevant antigen expressed in NSCLC and reverse the fatal evolution to become a chronic and controlled disease.

The Center of Molecular Immunology (CIM) has patented and developed a therapeutic cancer vaccine named CIMAvax-EGF®. It is vaccine composed of human recombinant EGF coupled to a carrier protein, recombinant P64. The vaccine is emulsified in Montanide ISA51, an oily adjuvant from Seppic, France. P64 is one of the most immunogenic proteins of the meningitis B bacteria. The carrier protein and the adjuvant are aimed to break the tolerance against EGF, a self-protein in humans (Figure 1).

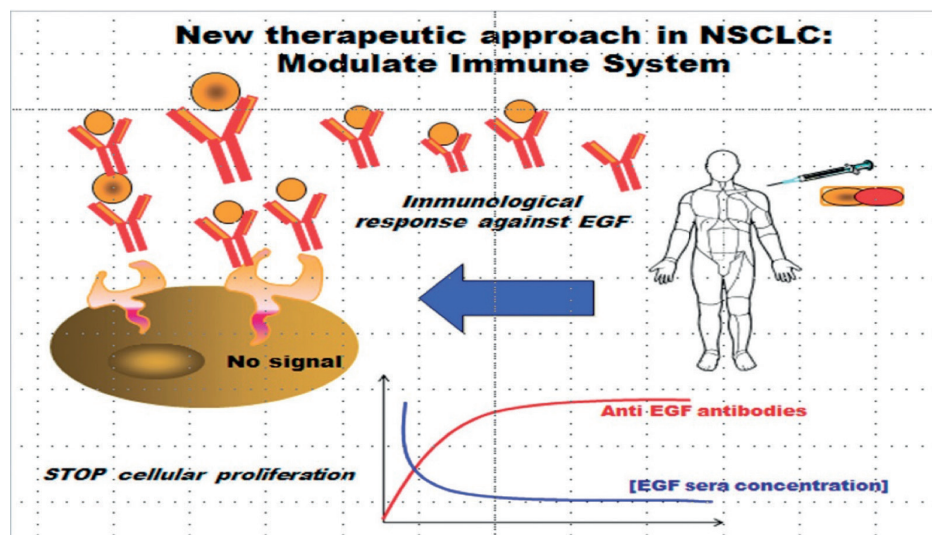


FIGURE 1. CIMAvax- EGF, mechanism of action.

CIMAvax-EGF® induces antibodies against EGF, which is a potent growth factor for EGFR positive neoplastic cells. EGF-EGFR interaction activates a signal transduction cascade that results in cellular proliferation, angiogenesis and survival. The goal of vaccination is to induce neutralizing antibodies against EGF that can 'sequester' soluble EGF and hamper the EGF-EGFR interaction.

CURRENT STATUS

- Phase III Clinical trial ongoing in Europe in patients with advance lung cancer by Bioven enterprise.
- Its requested a phase I/III clinical trial in USA with Roswell Park Cancer Institute based in formalities realized by Cancervax years ago.
- Phase II/III, intercurrent with chemotherapy in Cuba,
- Phase /III, after first-line chemotherapy and second-line in Europe.
- Phase /III in China.
- Phase IV post registration, for its extension to the primary health care level in Cuba.
- All vaccinated patients survive significantly more than a concurrent historical control.
- In patients with ages of 60 years an effect of vaccination with CIMAvax-EGF® showed a significant increase in survival of vaccinated patients as compared with controls.
- There is a direct correlation between the percentage of binding inhibition capacity of sera and patient's survival.
- Switch maintenance with CIMAvax-EGF® is well tolerated and significantly increased survival of patients that completed induction vaccination.

Phase III trial showed a Survival benefit significant (HR 0.77; $p=0.036$) in the per-protocol setting (patients receiving at least 4 vaccine doses): median survival time (MST) was 12.43 months for the vaccine arm vs. 9.43 months for the control arm. Median survival time (MST) was larger (14.66 months) for vaccinated patients with high EGF concentration at baseline in comparison with control (8.63 months), while high EGF concentration at day 0. (Figure 3 and 4).

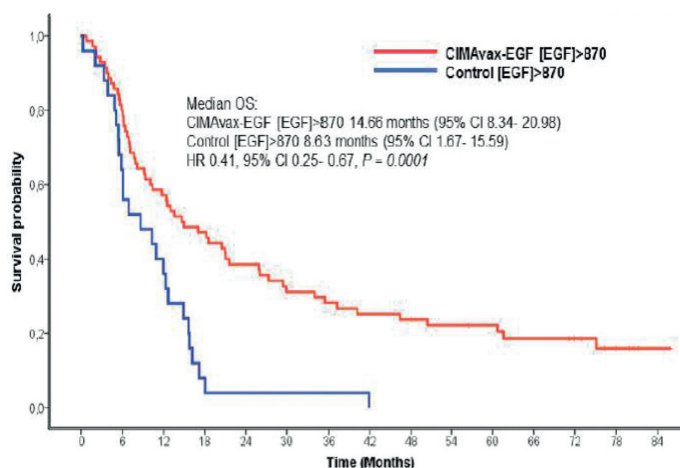


FIGURE 2. Kaplan Meier curve in patients with high [EGF] at day 0.

PATENT STATUS

- The Intellectual property of CIMAvax-EGF® protect the vaccine composition and those derived from the priority CU 154/2007, protect the method of obtaining the vaccine composition and product obtained by this method.
- Vaccine composition comprising autologous epidermal growth factor or a fragment or a derivative thereof having anti-tumor activity and use thereof in the therapy of malignant diseases. Granted in USA (1999/2014), Canada, EPO, Japan and China.
- Patents granted in Europe (EP 1 350 521 B1 with priority date 2001, EP 2 184 072 B1 with priority date 2008); in USA (USA 7 744 871 B2 with priority date 2001, USA 8 778 879 B2 with priority date 2008, y USA 8 841 251 B2 with priority date 2008).

MAIN REFERENCES

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2. CIMAvax EGF (EGF-P64K) vaccine for the treatment of non-small-cell lung cancer. Crombet Ramos T et al. Expert Rev Vaccines. 2015;14(10):1303-11.
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SAVAX: A cancer immunotherapy vaccine with human VEGF as antigen.

HOST INSTITUTION: Centro de Ingeniería Genética y Biotecnología (CIGB).
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THERAPEUTIC AREA:
Oncology

GOAL

Applied Research Project, aimed to obtain a new product with Intellectual Property. This candidate could be used mainly in the treatment of solid tumors and may have possible implications in chronic diseases of importance for men including among others age related macular degeneration.

DESCRIPTION

SaVax is a novel cancer therapeutic vaccine candidate based on a bacterial recombinant antigen CIGB-247 representative of human VEGF-A, and a suitable adjuvant. Preclinical results in mice and nonhuman primates indicates that the use of SaVax in adjuvants like Alum phosphate or VSSP, produces high titers of anti-VEGF IgG blocking antibodies able to neutralize VEGF binding to VEGFR2. A relevant cytotoxic response specific for VEGF expressing cells including tumoral and tumor stroma cells is also achieving after the immunization procedures. Anti-tumoral and anti-metastatic effects were characterized in several tumor models. For all tested species the immunological effects were obtained

without impairing the healing of deep skin wounds or inducing any other of the common side effect attributed to VEGF /VEGFR2 neutralizing drugs in the market.

The Project completed a Phase I clinical trial in 2012), and a Phase Ib in 2014. Safety and immunogenicity were extensively demonstrated during the trials and after 4 years of continuous administrations. A clinical benefit was associated with a relevant immune response in the trial (Figure 1). In particular eight of the thirty patients enrolled in trial are still alive, three with complete response, one with a partial response and the rest with stable disease. All of these patients continue to respond to monthly boosters by increasing VEGF specific titer, VEGFR2 neutralization or IFN-gamma secretion (un-published results).

PATENT STATUS

CU 2002/0076; PCT/CU 03/00004. Granted in Cuba, Iran, the European Patent Convention, USA, Russia, Canada, Australia, Japan, India, South Africa, China and South Korea.

PROJECT STATUS

The Project completed a Phase I clinical trial in 2012 (CENTAURO), and a Phase Ib in 2014 (CENTAURO-2). Safety and immunogenicity were extensively demonstrated during the trials and after 5 years of continuous administrations in patients. A clinical benefit was associated with a relevant immune response. In preparation four Phase II clinical trials against different tumors.

TYPE OF COLLABORATION REQUESTED

Search of corporate association to bring clinical development to registration and marketing from the granting of Patent and trademark license and distribution and marketing rights.

Collaboration in order to develop studies related to the characterization of the anti-tumor potential of different vaccine formulations, evaluating other possible adjuvant substances, as well as combinations with other anti-tumor agents, using animal models and human trials. To evaluate the potential of the vaccine for other non-tumoral diseases which are associated with pathological angiogenesis and an excess production of VEGF.

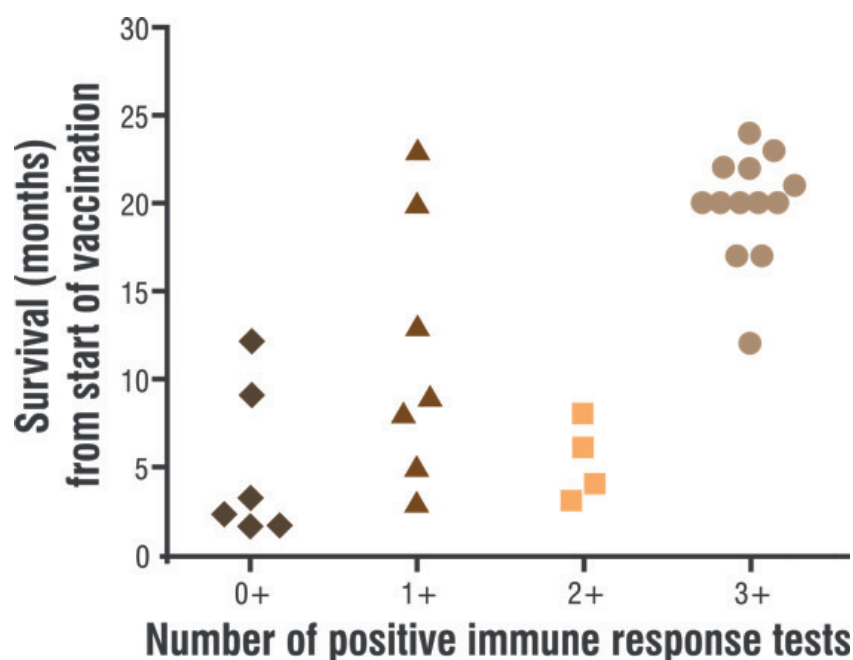


FIGURE 1. Survival and number of positive immune response tests per patient. Symbols stand for individual subjects. X-axis classifies patients according to the number of different immune response tests for which they were classified positive, at any time point during vaccination: (0+) patient negative for all tests, (1+) patient positive in one test, (2+) patient positive in two tests, and (3+) patients positive in the three tests.

COMPETITIVE ADVANTAGES - MILESTONES

- Possible use in many oncological disorders because their target, VEGF is expressed in over 90% of tumors.
- Unlike other antiangiogenic drug has a dual action mechanism: depletes the VEGF ligand and eliminates tumor and stromal cells that produce it.
- Active immunization induces an immune response against a self antigen self-regulating body and the toxicity is much lower than for antiangiogenic drugs classic.
- Possible combination with other anti-cancer agents or treatments as angiogenic not contributes additional toxicity.
- The route of administration is subcutaneous, which facilitates outpatient administration with lower costs due care and inpatient hospitalization.

VACCINE ADVANTAGES

Due to the controlled (regulated) nature of the immune response against self-antigens, intensity of the response to the vaccine should be moderate, with three main consequences:

- Vaccination with CIGB-247 is safe. Toxicity due to antibodies and/or T-cells should be minor or milder, compared to classic anti-angiogenic drugs.
- Immunization produces specific IgG antibodies, able to block VEGF/KDR interaction, and g-IFN secreting T-cells. There is a positive effect of increasing antigen dose in terms of the number of patients that develop a specific immune response.
- The use of different adjuvants/immunization regimes can be seen as ways to fine-tune the desired immune response.

- Combination with other anti-cancer or anti-angiogenic agents should be possible due to lack of overlapping toxicity.
- Seems that booster inoculations sustain the immune response and clinical benefit.

PUBLICATIONS

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Nanoparticulated adjuvants (VSSP) for the specific stimulation of humoral or cellular effectors in immuno compromised hosts.

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THERAPEUTIC AREA:
Oncology

GOAL

Introduction of specialized adjuvants in potential partners' therapeutic vaccines for the treatment of individuals with immune disfunctions associated to cancer and chronic viral infections.

DESCRIPTION

VSSP (very small size proteoliposomes) are nanoparticles derived from the association of hydrophobic proteins, extracted from *Neisseria meningitidis* bacteria, with synthetic variants of GM3 ganglioside, containing distinct fatty acids in the ceramide portion. Depending upon the fatty acid present in GM3, VSSP will act as an adjuvant for stimulating the humoral response or the cellular response. The peculiar particle size of VSSP and their negative charge simulate viral particles, inducing antigen presenting cells (APC) to secrete type 1 IFN. This property, in addition to VSSP capacity to reduce MDSC action at the

tumor microenvironment and in periphery, allows this unique adjuvant to stimulate the specific immune response even in an immunosuppressive context, which is not the case of other several known adjuvants.

PATENT STATUS

A patent claiming a former composition of VSSP as adjuvant has been granted in USA, Japan, Europe, China, Rusia, India, South Africa etc. and expires in 2021.

A patent application with new superior VSSP compositions as adjuvants has been requested in Cuba in 2017.

PROJECT STATUS

VSSP is a clinical stage adjuvant already produced in GMP conditions. Its safety and tolerability have been demonstrated in several clinical studies. Phase II/III clinical trials of 3 different cancer vaccines containing VSSP are ongoing. Other two vaccines are in preclinical stage.

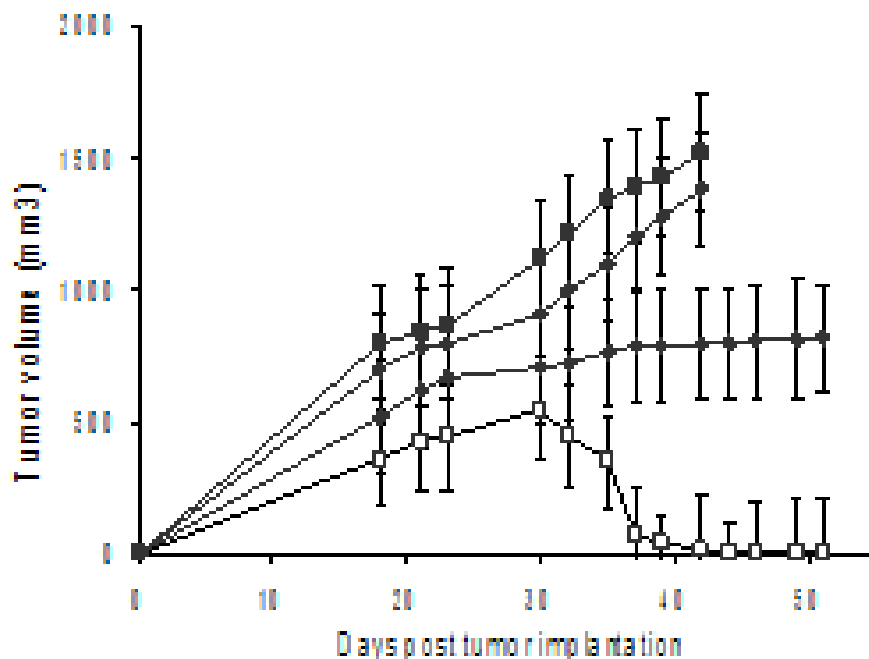


FIGURE 1. Therapeutic immunization with a HPV E7 peptide antigen plus VSSP vaccine induced TC-1 tumour regression. On the contrary, mice immunized with the same peptide in Incomplete Freund's adjuvant showed a discrete effect.

TYPE OF BUSINESS REQUESTED

Nonexclusive licensing to companies active in the fields of therapeutic cancer vaccines or new adjuvants development.

COMPETITIVE ADVANTAGES AND MILESTONES

Different clinical trials have demonstrated the safety and efficacy of VSSP as adjuvant. These nanoparticles naturally contains TLR2 and TLR4 ligands and contrary to the majority of the competitors' adjuvants, stimulate potent cellular responses even in immune dysfunctional individuals suffering advanced cancer. A unique feature of VSSP as adjuvant is the simultaneous mobilization

of the antiviral response vs the antigen together with a potent effect against MDSCs. VSSP exists in specialized variants for inducing humoral response or cellular response, allowing the implementation of alternated immunization

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CIGB-814: Peptide as drug for the treatment of autoimmune diseases.

HOST INSTITUTION: Centro de Ingeniería Genética y Biotecnología (CIGB).
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THERAPEUTIC AREA:
Autoimmunity

DESCRIPTION

CIGB 814 is an Altered Peptide Ligand (APL) derived from one of the main autoantigens involved in the pathogenesis of Rheumatoid arthritis (RA) Hsp60.

The APLs are similar to original epitopes but with one or several substitutions in the essential contact positions with the TCR or with the HLA class II molecule interfering with the cascade of necessary events for activation of T cells. These peptides can block the response of autoreactive T cells by different mechanisms in the control of autoimmune diseases.

CIGB 814 was designed using bioinformatics tools and obtained by chemical synthesis. Starting from human Hsp60 sequence, a novel region was identified as T-cell epitope, which was modified to increase its affinity with the HLA class II molecules frequently expressed by RA patients.

The therapeutic potentialities of CIGB-814 were evaluated in two animal models: adjuvant induced arthritis (AA) in Lewis rats and collagen induced arthritis (CIA) using DBA/1 mice. Clinical and histopathological analysis of the animals in

both cases demonstrated that CIGB-814 efficiently inhibits the course of RA (Figure 1). CIGB-814 induced a substantial increment of CD4+CD25+Foxp3+ regulatory T cells in ex vivo assays using PBMC and synovial cells from RA patients and in PBMC isolated from patients with Crohn's disease and with juvenile idiopathic arthritis.

In addition, this peptide increases the proportions of Treg cells in the draining lymph nodes (dLN) in mice (Figure 2). Toxicology evaluation of CIGB-814 in rats was carried out satisfactorily.

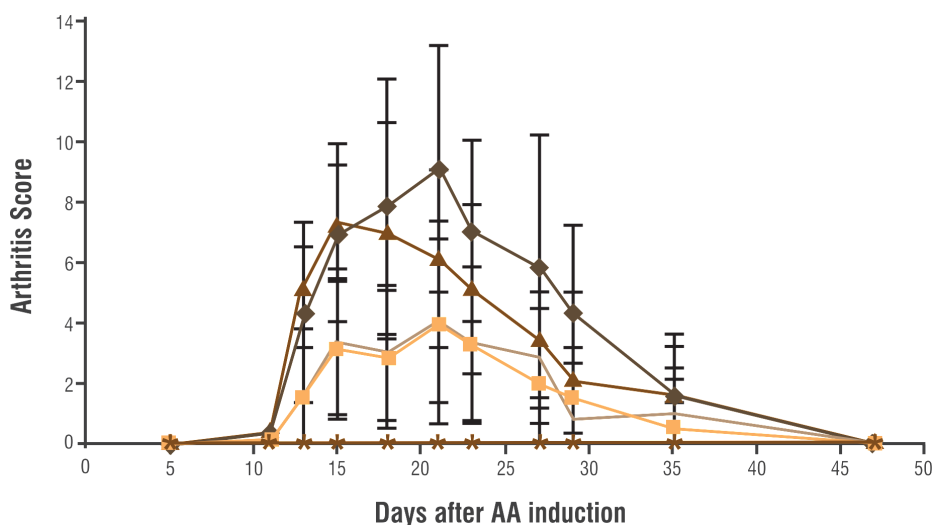


FIGURE 1. Treatment with APL-1 caused significant reduction of Adjuvant Arthritis (AA) in ill rats. Arthritis was induced on day 0 by immunization with MT in Incomplete Freund Adjuvant. On day 10, rats were randomly divided into five groups: Group I: rats inoculated with wild type peptide by intradermal route, Group II: rats inoculated with APL-1 by intradermal route, Group III: rats inoculated with APL-1 by subcutaneous route, Group IV: non-treated rats. Group V: healthy rats. Arthritis scores were assessed every other day from day 5 onward. N=12 rats per group.

Our results indicate that the modification in the CIGB-814 was efficient for inducing regulatory T cells and reinforce the therapeutic possibilities of this peptide in the treatment of RA patients, because the regulatory T cells are capable of reducing the inflammatory response by suppressive mechanisms.

The impact of these results is based on the evidence that CIGB-814: – Inhibits efficiently the course of arthritis in two animal models for RA.- This peptide can induce immunological tolerance mediated by activation of regulatory T cells. These results indicate the therapeutic potential of CIGB-814 as

candidate drug for treatment of RA and other autoimmune diseases. At the present -Phase I clinical trial in patients with rheumatoid arthritis was finished. In this study the safety of CIGB-814 was demonstrated. We have preliminary evidences of clinical efficacy. CIGB-814 therapy reduced IL-17 and IFN γ in the sera from patients. CIGB-814 pharmacokinetic profile was good as therapeutic candidate.

These results are being published. This approach is under evaluation on other autoimmune diseases where the HSP60 is an autoantigen as type I diabetes, Crohn’s disease and juvenile idiopathic arthritis.

PATENT:

PEPTIDES AND THEIR DERIVED TYPE APL OF THE HSP60 AND PHARMACEUTICAL COMPOSITIONS. PCT/ CU2005/000008. Granted in EEUU, Europe, China, Japan, Korea, Argentina, Rusia, Mexico.

USE OF AN APL PEPTIDE FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE AND TYPE 1 DIABETES. PCT/ CU2009/000009. Granted in EEUU, Europe, Rusia, Mexico.

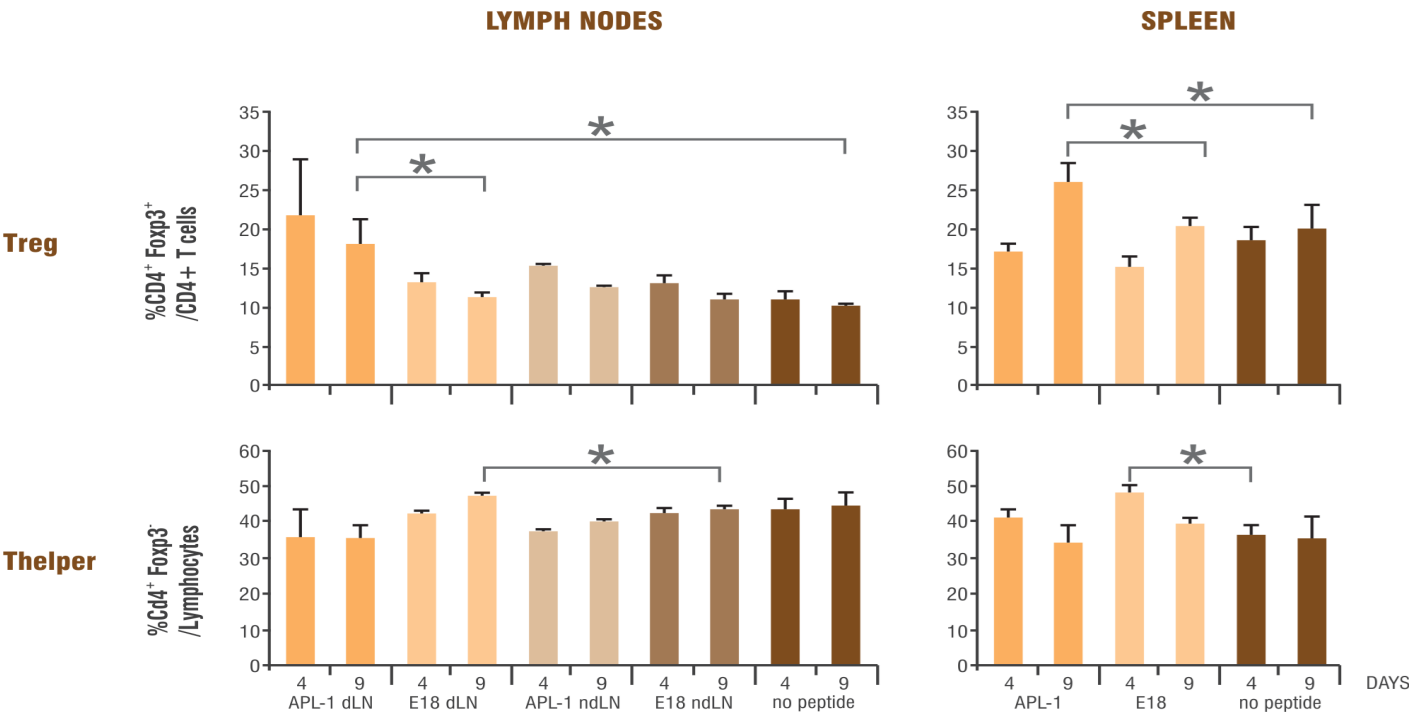


FIGURE 2. Treatment with APL-1 induced an increase of the proportions of CD4+FoxP3+ Treg cells in mice. Four animals of each group were sacrificed on days 4 and 9 after subcutaneous immunization with wild type peptide or APL1. Treg proportion was evaluated in draining (dLN), non-draining lymphnodes (ndLN) and spleen by Flow Cytometric Analysis. (*) Mean statistically significant differences $p<0.05$.

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6. Ariana Barberá, Noraylis Lorenzo, Peter van Kooten, Joel van Roon, Wilco de Jager, Dinorah Prada, Jorge Gómez, Gabriel Padrón, Willem van Eden, Femke Broere and María del Carmen Domínguez. APL1, an altered peptide ligand derived from human heat-shock protein 60, increases the frequency of Tregs and its suppressive capacity against antigen responding effector CD4+T cells from rheumatoid arthritis patients. *Cell Stress and Chaperones*. 2016, Jul; 21(4): 735–744.

CIGB-845: A therapeutic tool toward neurological diseases.

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THERAPEUTIC AREA:
Neurological diseases

GOAL

The aim of this project has been the assessment of combined therapy between EGF and GHRP6 to simultaneously target different nodes of the complex pathophysiology of the brain ischemia.

DESCRIPTION

CIGB 845 is a pharmacological combination between a synthetic peptide (Growth Hormone Releasing Peptide six) and a protein (Epidermal Growth Factor), endowed with neuroprotective and neurorestorative properties, both with a substantial safety profile. These effects relate to the recruitment of cell

survival mechanisms, providing protection against a broad range of pathologic processes. EGF and GHRP6 target a range of processes within the pathophysiological cascade of ischemic damage. These molecules share anti-apoptotic and anti-excitotoxic effects, while EGF promotes neurogenesis and remyelination and GHRP6 induces endogenous neuroprotective factors as exclusive effects. Thus, the combined administration of EGF and GHRP6 is likely to have beneficial consequences in stroke and other neurological diseases which share these pathophysiological

issues, like Amyotrophic Lateral Sclerosis and Multiple Sclerosis.

Different experiments have shown that a single pre-conditioning or multiple EGF+GHRP6 therapeutic administrations were able to protect the central nervous system and elicit neuro-protective mechanisms in different experimental models of neurological diseases: global brain ischemia, experimental autoimmune encephalitis and in vitro or in vivo models of amyotrophic lateral sclerosis.

In global brain ischemia experimental models, EGF+GHRP6 co-administration reduced mortality, neurological signs (Figure 1).

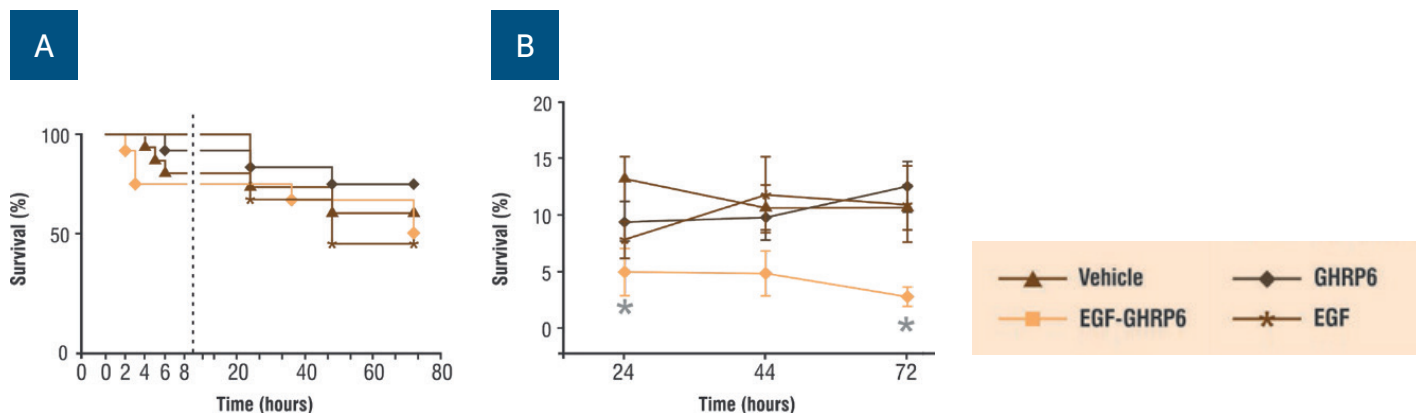


FIGURE 1. Neurological grade and pathology of the global brain ischemia experiment. A: Survival curves. Log-rank test. B: Clinical evolution. Kruskal-Wallis and Dunn tests. (García Del Barco-Herrera Restor Neurol Neurosci 2013;31(2):213-23).

The animals treated with EGF+GHRP6 had no infarcts in the cerebral cortex or in the hippocampus, and had only small infarcts in the caudate-putamen. The infarct volume calculated for the entire brain was significantly

lower in the EGF+GHRP6-treated group than in the group that received vehicle (Figure 2). Neuronal density was also preserved in brain cortex, caudate-putamen and hippocampus in the EGF+GHRP6-treated group.

The neuroprotective effect of EGF+GHRP6 co-administration is similar to that induced by hypothermia in terms of clinical signs, infarct volume and the preservation of neuronal density in CA1 hippocampus zone (Figure 3).



FIGURE 2. A: Infarct volume comparison between experimental groups. Kruskal-Wallis and Dunn tests. Asterisks indicate significant differences. B: Representative photographs of TTC-stained brain slides from false-operated, vehicle-treated and EGF+GHRP6-treated animals. (Garcia Del Barco-Herrera Restor Neurol 2013;31(2):213-23). 2013;31(2):213-23).

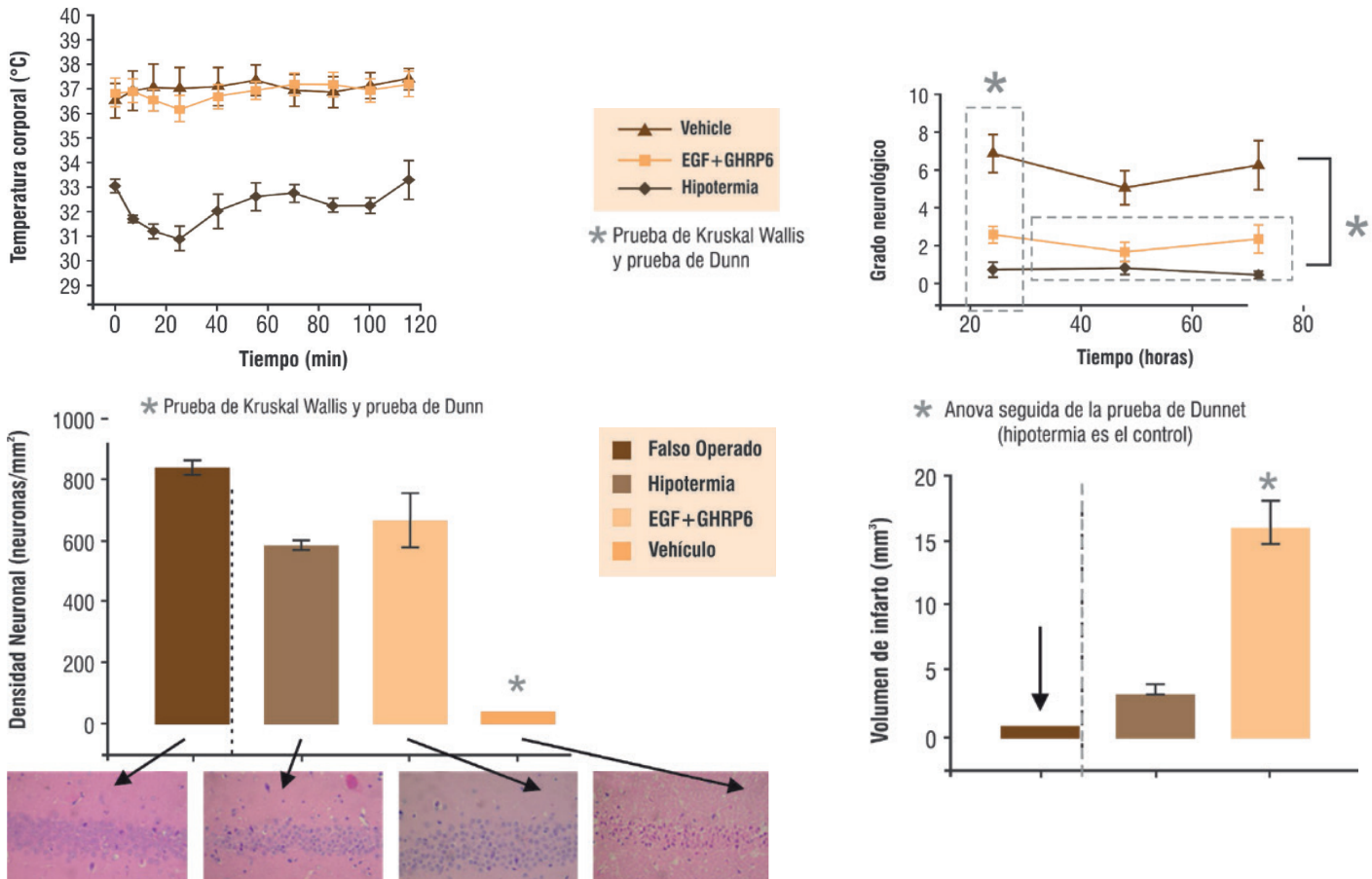


FIGURE 3. EGF+GHRP6 co-administration had a neuroprotective effect similar to hypothermia.

In these global-brain-ischemia models the therapeutic window for EGF+GHRP6 is four hours. The before mentioned results were also confirmed using a focal brain ischemia animal model. The neuroprotective effects of EGF+GHRP6 were again demonstrated associated to a reduction of neurological grade, mortality and infarct volume. Additionally, the effects of EGF+GHRP6 were similar to that induced by hypothermia.

Considering, there are not neuroprotective drugs effectively assessed in clinic, and the before evaluated neuroprotectant candidates have been designed to target only one element of the pathophysiology cascade of ischemia, the EGF+GHRP6 combined therapy (which is directed to multiples nodes of the such complex pathophysiology of stroke), could be a promissory First in Class therapeutic approach.

PATENT STATUS

1. Combination of EGF/GHRP-6 for neuroregeneration of central nervous system Pub. No.WO/2006/092106.
2. Pharmaceutical combination for the treatment of tissue damage owing to an arterial irrigation defect .Pub. No.WO/2002/053167.

The patents have been granted in several territories: Canada, Japan, Russia, China and others.

PROJECT STATUS

Phase I clinical study.

TYPE OF COLLABORATION REQUESTED

Corporate partnership for out-licensing and co-development.

COMPETITIVE ADVANTAGES - MILESTONES

Considering, there are not neuroprotective drugs effectively assessed in clinic, and the before evaluated neuroprotectant candidates have been designed to target only one element of the pathophysiology cascade of ischemia, the EGF+GHRP6 combined therapy (which is directed to multiples nodes of the such complex pathophysiology of stroke), could be a promissory First in Class therapeutic approach.

PUBLICATIONS

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NEUROEPO

PHARMACEUTICAL FORMULATION OF SELECTED GLYCOFORMS OF RECOMBINANT HUMAN ERYTHROPOIETIN WITH THERAPEUTIC POTENTIAL FOR SEVERAL BRAIN INFLAMMATORY DISEASES

HOST INSTITUTION: Centro de Inmunología Molecular (CIM).

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THERAPEUTIC AREA:

Neurological diseases

GOAL

Develop a pharmaceutical formulation of recombinant human erythropoietin with low sialic acid content for nasal administration for the treatment of several brain inflammatory diseases, like stroke and neurodegenerative diseases.

DESCRIPTION

It has been suggested that in some brain pathological processes EPO could have neuroprotective and/or neuroregenerative therapeutic effects. However the clinical evaluation of recombinant human erythropoietin (rhEPO) as a neuroprotective agent has been limited due to its hematological side effects. The intravenous administration of rhEPO has a very narrow therapeutic window because of the risk of thrombotic events. Two major technological improvements have been carried out in this project to face the drawback of current formulation of rhEPO approved by Pharmacopeia. First, the identification of rhEPO glycoforms (with low sialic acid content) obtained from a fermentation process, with a similar glycosylation profile to the natural human EPO produced into the

brain (rhEPOb). Second, the development of a pharmaceutical formulation for the nasal administration of rhEPOb, which takes advantage of the unique physiological and anatomic attributes of the olfactory region, provides extracellular and intracellular routes to the Central Nervous System (CNS) evading the Hemato-Encephalic Barrier (HEB). rhEPOb (NeuroEPO) could have pharmacological effects into the brain without erythropoiesis activity in patients with Ataxia Spinocerebellar type 2, stroke and Parkinson's disease, with positive results, opening new therapeutic possibilities to stimulate tissue regeneration and recovery of brain areas by using a safe and noninvasive therapy.

PATENT STATUS

(WO 2007/009404). Granted in: Mexico, MX/a/2008/000997; Cuba, CU 2758/2008; and Canada, 2,616,156. (CU- 1998-0023). Granted in: Cuba, CU 22709 A1; Colombia, 27642; Argentina, AR013022B1; Malaysia, MY-122336; Russia, 2215748; Chile, 46618; Mexico, 241665; Vietnam, 4772; and Algeria, 2783.

PROJECT STATUS

GMP production process at industrial scale has been set up. Phase I clinical trial in healthy people completed with positive results. Phase II/III clinical trial in Ataxia Spinocerebellar type 2 completed with positive results. Phase II/ III clinical trial in Stroke is ongoing. Phase I/II clinical trial in Parkinson's disease is ongoing. Pre-clinical study in genetic modified mice prone to develop Alzheimer's disease completed with positive results.

TYPE OF COLLABORATION REQUESTED

Corporate partnership for product co-development, registration and marketing in selected territories according to signed licensing agreements with pharmaceutical companies. In particular, investment for clinical development abroad is required.

COMPETITIVE ADVANTAGES MILESTONES

NeuroEPO could be considered a "best in class" product.



FOR US,
TO THE
WORLD