Extended Business Project
Portfolio

BIOCUBAFARMA
2016-2017
Introduction

The biotechnological and pharmaceutical industries group, BioCubaFarma, is a holding established in 2012 which integrates companies dedicated for more than 30 years to scientific development, research, production and marketing of biotechnology, pharmaceuticals, medical equipment and other medical products to supply to domestic and international markets.

Its objectives were defined from the outset: to maintain and raise the standards of health and quality of life in the Cuban population and to become a source of capital from the exportation of its products.

With 31 companies and 64 manufacturing facilities, the organization is dedicated to develop strategies, technologies, products and assistance for the prevention, diagnosis and treatment of multiple ailments, such as cancer, diabetes, cardiovascular, neurological, etc. We work closely with the Ministry of Public Health in complex interventions and performing therapeutic guidelines to apply to patients.

BioCubaFarma’s commercial pipeline encompasses more than 1000 products, which are sold in 48 countries and has more than 800 marketing approvals abroad.

Currently the Group has over 2000 patents granted in many countries, including United States, Europe and Japan.

Our specialized personnel have successfully performed Technology Transfer Agreements of biopharmaceutical products to Brazil, Vietnam, India, South Africa, Venezuela, Algeria, Iran and China, especially in the framework of South-South cooperation.

There are 16 foreign entities governed by BioCubaFarma through different modalities, such as joint ventures companies and wholly owned subsidiaries.

The biotechnology and pharmaceutical industries achieve exporting high value-added products and with higher technological level. Its strategic alliance with the company that commercializes Cuban Medical Services (SMC) refines these possibilities, because the benefits include medical services together with the drugs, reagents and equipments, in order to offer a comprehensive package.

The comprehensive Health Programs that BioCubaFarma offers to achieve a high social impact are the following:

1. Program for the prevention of infectious diseases with prophylactic vaccines.
2. Program for early diagnosis and treatment of different cancer pathologies.
3. Program for monitoring and treatment of diabetes and its complications, such as diabetic foot ulcers.
4. Program for the diagnosis and rehabilitation of cardiovascular diseases.
5. Care program for hearing impairment.
6. Program for the early detection of neurological development in infants.
7. Program for the massive pre and neonatal screening.
8. Program for the epidemiological surveillance.

The emergence of BioCubaFarma sets a milestone in terms of investment as it led the incursion of foreign capital in this area, mainly in the construction of manufacturing facilities to enhance the production capacity with high GMP standards of biopharmaceutical products, in the Mariel Special Development Zone (ZEDM) at the west of Havana city.
BioCubaFarma business model proposal for the foreign investment is to constitute Joint Venture Companies in ZEDM, in the spirit of sharing all the benefits with the foreign partner.

BioCubaFarma is pleased in sharing a set of projects and products open for international partnership with proper counterpart hoping in the near future the products that could be derived from this cooperation impact in the quality of life of millions of people and generate a profitable business model to all involved parts.

Bussines Portfolio Summary

BioCubaFarma is open to implement a coordinated and targeted alliance building earlier in the product’s life cycle. Thus immerse in this movement, you will find summaries of a selection of projects which we considered most attractive for negotiation with the international scientific sector. However while the main proposed focus is set within these propositions, discussions can be opened around other projects of mutual interest as well.

BioCubaFarma strategy holds a high level of coherence with the global oriented commercial strategy of the Cuban Ministry of Foreign Trade and the Cuban Trade Chamber. BioCubaFarma develops scientific and production activities in close collaboration with other institutions mainly from the Health and Agriculture Ministries. The commercial strategy involves the expansion of sales into new markets while maintaining current established positions working on the introduction of novel products into the most regulated markets such a US, Europe, Canada and Japan, promoting early stage partnership for development and sharing commercial opportunities with players.
<table>
<thead>
<tr>
<th>PROJECT TITLE</th>
<th>FIELD</th>
<th>CENTER</th>
<th>pag.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CIGB 500, a cardiac cyto-protective peptide</td>
<td>Cardiology</td>
<td>CIGB</td>
<td>8</td>
</tr>
<tr>
<td>2 Proctokinase, a suppository to treat hemorrhoids</td>
<td>Gastroenterology</td>
<td>CIGB</td>
<td>12</td>
</tr>
<tr>
<td>3 CIGB 128 against non melanoma skin cancer</td>
<td>Oncology</td>
<td>CIGB</td>
<td>14</td>
</tr>
<tr>
<td>4 CIGB 300, a pro-apoptotic peptide</td>
<td>Oncology</td>
<td>CIGB</td>
<td>16</td>
</tr>
<tr>
<td>5 CIGB 247, a cancer therapeutic vaccine</td>
<td>Oncology</td>
<td>CIGB</td>
<td>18</td>
</tr>
<tr>
<td>6 CIGB 247, an anti VEGF therapy for macular degeneration</td>
<td>Ophthalmology</td>
<td>CIGB</td>
<td>20</td>
</tr>
<tr>
<td>7 CIGB 552, anticancer peptide able to inhibit NFKB in tumoral cells</td>
<td>Oncology</td>
<td>CIGB</td>
<td>22</td>
</tr>
<tr>
<td>8 CIGB 845, a therapeutic tool towards neurological diseases</td>
<td>Neurology</td>
<td>CIGB</td>
<td>24</td>
</tr>
<tr>
<td>9 CIGB 814, a peptide for treating autoimmune diseases</td>
<td>Autoimmunity</td>
<td>CIGB</td>
<td>28</td>
</tr>
<tr>
<td>10 PO, anti ticks vaccine</td>
<td>Veterinary</td>
<td>CIGB</td>
<td>30</td>
</tr>
<tr>
<td>11 Classical Swine Fever (rec. vaccine and diagnosis kit) project</td>
<td>Veterinary</td>
<td>CIGB</td>
<td>32</td>
</tr>
<tr>
<td>12 Soybean improvement through biotech tools</td>
<td>Agriculture</td>
<td>CIGB</td>
<td>34</td>
</tr>
<tr>
<td>13 Hebernem, an effective biological nematocide</td>
<td>Agriculture</td>
<td>CIGB</td>
<td>36</td>
</tr>
<tr>
<td>14 CIGB 42 for citrus Huanglongbing (HLB) control</td>
<td>Agriculture</td>
<td>CIGB</td>
<td>38</td>
</tr>
<tr>
<td>15 CIMAvax-EGF new therapeutic vaccine against non small lung cancer</td>
<td>Oncology</td>
<td>CIM</td>
<td>40</td>
</tr>
<tr>
<td>16 Family of human IL2-muteins with anticancer properties</td>
<td>Oncology</td>
<td>CIM</td>
<td>42</td>
</tr>
<tr>
<td>17 Bivalent vaccine HER1 + HER 2</td>
<td>Oncology</td>
<td>CIM</td>
<td>44</td>
</tr>
<tr>
<td>18 Immunotherapy using mabs to treat atherosclerosis</td>
<td>Neurology</td>
<td>CIM</td>
<td>46</td>
</tr>
<tr>
<td>19 NeuroEPO to treat several brain inflammatory diseases</td>
<td>Neurology</td>
<td>CIM</td>
<td>49</td>
</tr>
<tr>
<td>20 CIDEM 161 a new chemical entity for treating cerebral ischemia</td>
<td>Neurology</td>
<td>CIDEM</td>
<td>52</td>
</tr>
<tr>
<td>21 CIDEM 162 a molecule to treat dementia, Parkinson and neurophatic pain</td>
<td>Neurology</td>
<td>CIDEM</td>
<td>54</td>
</tr>
<tr>
<td>22 AMYLOVIS. New molecules for early imaging diagnosis of Alzheimer</td>
<td>Neurology</td>
<td>CNeuro</td>
<td>58</td>
</tr>
<tr>
<td>23 AMYLOVIS. New molecules for treating Alzheimer disease</td>
<td>Neurology</td>
<td>CNeuro</td>
<td>60</td>
</tr>
</tbody>
</table>
CIGB 500: A Peptide with Cardiac Cyto-Protective Effects

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

Therapeutic Area: Cardiology.

Goal: To further characterize the molecular pharmacology of the CIGB-500 cyto-protective effects toward its clinical use as a cardio-protective and/or cardio-restorative agent.

Business proposal: Corporate partnership for out-licensing and co-development.

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, CIGB500 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 myocardiopathy modelos CIG 500 could prevent heart failure and other toxic systemic complications when concomitantly administered to (DX). Therapeutically administered- CIGB 500 restored myocardial damages and failure.

As a prove-of-concept for a cyto-protective agent we examined whether CIGB500 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.

Figure 1. Kaplan-Meier survival analysis.
2. CIGB500 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.

3. CIGB 500 prevented and reversed Doxorubicin-induced Dilated Myocardopathy in rats.
The main biological properties of CIGB 500 which mechanistically support its mechanism of action can be summarized as:

1- **Inotropic**. Its seems to be mediated by an elevation of Ca2+ influx via PLC/DAG/PKC, through the voltage-gated calcium channel, triggering Ca2+ 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 downstream pro-inflammatory cascade. Reduces ROS, NEP and activates SOD expression and activity.

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-1α) 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.

**Figure 6.** 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.

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.

**Patent**


**Publications**


**PROCTOKINASE®**: Recombinant Streptokinase Suppository for the Treatment of Hemorrhoids Disease

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

*Therapeutic area*: Gastroenterology.

*Goal*: Clinical evaluation and registration of a Formulation based on recombinant streptokinase suppository for the treatment of fluxion and/or thrombus hemorrhoidal disease.

*Business proposal*: Corporate partnership for out-licensing to specific territories.

**Description**

The CIGB has developed a therapeutic formulation based on the recombinant streptokinase suppository for the treatment of hemorrhoids disease.

Hemorrhoids are one of the rectal pathologies with the highest worldwide incidence in which the venous plexus of the rectum and the anus become inflamed. Approximately from 10 to 25% of the adult population suffers hemorrhoids, it appears in any age but the incidence is increased after 30 years. To treat the disease different formulations with local application are used and the main action is the diminution of the inflammation and the pain, but sometimes surgical treatment is necessary because its can protrude or thromboses and the conventional treatments do not solve this pathology.

Streptokinase suppository is a novel product with Cuban patent and is the unique product that has demonstrated the capacity to eliminate the thrombus, micro thrombus, thus it permit the reduction of the hemorrhoid lesion, evolution of edema and anal pain.

A Phase I, II, III, IV clinical trials had been conducted in Cuba proven safety and efficacy in 1500 patients. Sanitary registration was granted in Cuba in August 2012.

• The recombinant streptokinase suppository (Proctokinasa®) is a non-invasive effective treatment for the acute hemorrhoids, with a suitable safety profile.
  • It eliminates pain and inflammation.
  • It does not imply any complications to the patient taking into account its capacity of eliminating thrombus and diminishing inflammation of the affected zone in a short period of time.
  • It avoids invasive or surgical treatments, such as thrombectomy that requires specialized personnel, equipment and obligatory attention in specialized health centers.
  • It is a new save therapeutic alternative for a very frequent pathological condition.
  • There are not antecedents on the use of a thrombolytic agent for this purpose.

**Patent**

*PCT number*: PCT/CU2003/000020. Publication date Mar 30, 2010. Filing date Dec 22, 2003. Patent granted in Cuba, Europe, Canada, India, South Korea, Australia, China, Mexico, Malaysia, and South Africa. It has been applied for in the USA, Brazil, Argentina, Thailand.
Publications


Cigb 128 (Heberferon): Development of New Pharmaceutical Formulation Containing Ifns Alpha and Gamma against Non-Melanoma Skin Cancer

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

Therapeutic Area: Oncology.

Goal: To develop a new pharmaceutical formulation containing IFNs alpha and gamma in synergistic proportions, based on anti-proliferative properties, for the treatment of patients with non-melanoma skin cancer.

Business Proposal: Corporate partnership for out-licensing and co-development.

Description

The formulation CIGB 128 (HeberFERON) is an investigational pharmaceutical formulation designed to have more potent anti-tumoral effect. The formulation consisted of the combination of recombinant IFN alpha and gamma in selected proportions to have synergistic anti-proliferative effects against several tumour cells (non-melanoma skin cancer, malignant glioma, colon carcinoma, lung carcinoma and others. The animal models on tumour cells have been demonstrated that some of the mechanism of action of the CIGB-128 formulations consisted on anti-proliferative and anti-angiogenic actions.

During clinical trials on non-melanoma skin cancer it was demonstrated a more potent therapeutic effect: more rapid complete and prolonged clinical response.

Figure 1. Clinical results after treatment with CIGB-128 of advanced non-melanoma skin cancer (BCC, top picture; SCC, bottom picture).

Figure 2. Periocular use of CIGB-128. The treatment avoided the surgical reconstruction and mutilations, and preserves the aesthetic.
Advantages

• CIGB-128 promotes a more rapid and prolonged antitumoral responses than separated IFNs with excellent safety profile for basal cell carcinoma (BCC) of any localization, subtype and volume, and advanced recurrent non melanoma skin tumors.

• CIGB-128 is biologically more potent than separated IFNs and similar to pegylated IFNs based in the pharmacodinamic profile.

• CIGB-128 could be used pre-surgical to reduce tumor size, after surgery to avoid residive, or as primary therapeutic option in non-surgical or recurrent BCC as well as for cosmetic reasons.

• CIGB-128 prolongs the survival of patients with advanced renal cell carcinoma to 41 months.

• Excellent cosmetic effect.

• Very low rate of recidive.

Patent


Publications

• Claudia Bello, Dania Vázquez-Blomquist, Jamilet Miranda y col. Regulation by IFN-α/IFN-α Co-Formulation (HerberPAG®) of Genes Involved in Interferon-STAT-Pathways and Apoptosis in U87MG. Current Topics in Medicinal Chemistry, 2014, 14, 351-358.


CIGB-300: A Novel Pro-Apoptotic Peptide that Impairs the Ck2-Mediated Phosphorylation and Exhibits Antitumor Properties, Both in Animal Models and in Cancer Patients

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

Therapeutic area: Oncology.

Goal: Development of a potential drug targeting the CK2-mediated phosphorylation for treating different malignancies.

Business Proposal: Corporate partnership for out-licensing and co-development.

Description

CIGB-300 is a First-in-Class antineoplastic synthetic peptide that inhibits the CK2-mediated phosphorylation, induces apoptosis in vitro and in vivo and is under clinical research in cancer patients. Of note, CIGB-300 modulates a diverse array of proteins involved in apoptosis, cell proliferation, ribosomal biogenesis, anti-cancer drug resistance and angiogenesis. Accordingly, CIGB-300 not only affects cell viability and proliferation, but also exhibits an antiangiogenic effect and synergizes with standard anticancer drugs, such as Paclitaxel, Cisplatin and the anti-Epidermal Growth Factor Receptor (EGFR) like Erlotinib. Remarkably, CIGB-300 can be delivered either by the systemic route or by local intratumoral administration, highlighting promising features of this investigational drug for cancer therapy. The available clinical data for CIGB-300 not only demonstrate its safety, tolerability and efficacy signs, but also provide important clues for designing later phase clinical trials focusing on its therapeutic efficacy. Overall, CIGB-300 meets several important requirements as an anticancer targeted agent that may serve as an adjuvant tool to improve the therapeutic index of current chemoradiotherapy.

Figure 1. A Antiangiogenic effect of CIGB-300 in tumor-bearing mice implanted in matrigel plus. B Antimetastasic effect of CIGB-300 in spontaneous metastasis model based on 3LL tumors in C57BL6 mice.
Patents

1. Peptides for the treatment of Cancer associated with the Human Papillomavirus and other epithelial tumors. WO 03/054002. Granted in: Europe, United States, Russia, China, Malaysia, Australia, South Africa, South Korea, Japan, India, New Zealand, Ukraine, Peru, Morocco, Lebanon, Mexico, Tunisia, Argentina, Chile, Norway, and Hong Kong.


Publications


---

**Figure 2.** A Magnetic Resonance Images from a cervical cancer patient before and after treatment with CIGB-300 + chemoradiotherapy. B Survival curve after intravenous delivery of CIGB-300 in advanced cancer patients.
CIGB-247: a Cancer Therapeutic Vaccine with Human Vegf as Antigen

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

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.

Business proposal: Corporate partnership for out-licensing and co-development. 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.

Description

CIGB-247 is a novel cancer therapeutic vaccine candidate based on a bacterial recombinant antigen representative of human VEGF-A, and a suitable adjuvant. Preclinical results in mice and non-human primates indicates that the use of CIGB-247 in adjuvants like Alum phosphate (CIGB-247 A) or VSSP (CIGB-247 V), 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).

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.
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 γ-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.

Patents

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

Publications


**CIGB-247: Anti VEGF Therapy for Age Related Macular Degeneration**

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

*Therapeutic area:* Ophthalmology.

*Goal:* Evaluate an anti VEGF therapy to diminish age related macular degeneration.

*Business proposal:* Corporate partnership to conduct clinical trials and registration in specific territories.

**Description**

The key role played by Vascular Endothelial Growth Factor (VEGF) in the pathogenesis of neovascular eye diseases such as age related macular degeneration (AMD), proliferative diabetic retinopathy, diabetic macular edema, retinal vein occlusion, and retinopathy of the premature, has stimulated experimental and clinical research of anti-VEGF molecules in the treatment of these important diseases.

The preclinical studies conducted in mice using CIGB-247 V indicates that antibodies neutralizing VEGF binding to VEGFR2 are present in the retina blood circulation, and could neutralize in situ the neovascularization effect of VEGF. Definitely, CIGB-247-V vaccination in rabbits proved to effectively reduce retinal neovascularization caused by intravitreal VEGF injection. Based on anatomical parameters, CIGB-247-V immunization proved to effectively control retinal neovascularization induced by intra-vitreous injected VEGF; with respect to placebo-immunized animals, CIGB-247-V vaccinated rabbits showed reduced vascular dilatation and tortuosity, as well as leakage both at the disc and in the anterior chamber (AC). Even at the highest VEGF dose tested, some vaccinated animals almost completely abolished the effects of the locally injected growth factor (Figure 1).

These preclinical results and those of the recently finished Phase I clinical study of CIGB-247-V in patients with advanced solid tumors, concreted the way for possible human studies of the vaccine in neovascular eye syndromes and inform on the potential mechanisms involved in its effect. In particular, the clinical trial demonstrated that CIGB-247-V is safe and immunogenic in humans, and that anti-VEGF IgG antibodies with VEGF-VEGFR2 blocking activity are produced. The antibody responses in patients reached maximum levels by approximately after three months of immunization, and chronic maintenance vaccination has been possible for at least four years after trial entry, without significant adverse events.

A Phase I/II clinical trial on AMD patients aiming to reduce the number of intravitreal injections of Bevacizumab needed to sustain a clinical benefit in this disease. The hypothesis is that by immunizing with CIGB-247 V concomitantly with Bevacizumab administration is possible to reduce the need to apply the monthly injections needed during follow-up (after the administration of the first 3 weekly doses). The clinical trial is ongoing and results are expected early in 2017.
**Patents**

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

**Publications**


Figure 1. Representative FA images. Each row shows changes in FA of representative rabbits in each group performed within a week before the intravitreous injection of 5 mg of VEGF (Day 0) and follow-up examinations one week later (Day 7). There was leakage at disc and medullary wings and neovascular membrane at Day 7 in control rabbit A5. In the right eye of CIGB-247-V A7 accinated rabbit retinal vessels became slightly dilated, and tortuous and retinal capillaries are diminished but were not completely resolved. The left eye of CIGB-247-V vaccinated rabbit A6 showed normal FA. (Morera Y, et al. Exp Eye Res. 2014;122:102-9.)
Cigb-552: Anticancer Peptide that Inhibits the Inflammatory Activity of Nfkb in the Tumor Cells

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

Therapeutic Area: Oncology.

Goal: Development of a potential peptide-based drug capable of increasing COMMD1 to induce apoptosis in human cancer cells through inhibition of the transcription factor NFκB.

Business Proposal: Corporate partnership for out-licensing and co-development.

Description

CIGB-552 is a novel synthetic peptide derived from the antimicrobial peptide LALF 32-51 (Limulus sp) which has been shown to be a potential candidate for the anticancer therapy and one of its useful property is the cell-penetrating capacity. COMMD1 is a newly recognized pleotropic protein that plays an important role in inflammation, hypoxic response and cell survival. The recovery of COMMD1 protein by CIGB-552 inhibits NF-kB, a key factor involved in the survival, proliferation and dissemination of tumor cells (2). In addition, CIGB-552 inhibits the transcriptional activity of NFkB by TNFα and IL-1β in human colon cancer cells. The peptide CIGB-552 demonstrates potent in vivo efficacy against human colon and lung cancer with a considerable therapeutic window in murine xenograft models (3) (Figure 1). Besides, safety and tolerability of the therapy with the peptide CIGB-552 in a model of spontaneous tumor in dog was demonstrated.

Figure 1 In vivo efficacy on a xenograft mouse model: colorectal (HT-29 human xenograft). Development by Experimental Pharmacology Oncology-Berlin

We have demonstrated that CIGB-552 mediated-estabilization of COMMD1 promotes RelA(p65) ubiquitination and subsequent repression of the NFκB activity, an event linked to the apoptosis of cancer cells.
The mechanism of action of CIGB-552 assumes a new targeted anticancer therapy to regulate oncogenic and inflammatory activity of NFkB in cancer cells, providing greater selectivity and specificity. This novel peptide presupposes a potential applicability in solid tumors and inflammation associated cancer including colorectal, breast, lung, melanoma, lymphomas and others.

**Patents**

1. A patent was filed claiming the anti-tumor activity of the novel peptide and their mimetics (PCT/CU2007/000006) Granted: Europe, China, India, Mexico, Australia, Rusia, USA. Expire: 2027

2. Cell penetrating peptides and its use fused to biomolecules with therapeutic action (PCT/CU2008/000006). Granted in USA, Canada, Mexico, China, Korea, Sudafrica. Expire: 2028

3. Cancer Therapy Method (PCT/CU2011/000003). The patent is claiming the sequence of the second generation peptide CIGB-552 and COMMD1 as a target for cancer therapy. Granted in USA, Mexico, China, Sudafrica, Australia, Japon, Ucrania. Expire: 2031

**Publications**


**CIGB-845: A Therapeutic Tool Toward Neurological Diseases**

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

*Therapeutic area:* Neurology.

*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.

*Business Proposal:* Corporate partnership for out-licensing and co-development.

**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 neurorestaurative 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](image-url)  
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 3). Neuronal density was also preserved in brain cortex, caudate-putamen and hippocampus in the EGF+GHRP6-treated group.

Figure 3A. 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 Neurosci 2013;31(2):213-23).
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 6).

**Figure 6.** 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.

**Patents**


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.


**CIGB-814:** Peptide as Drug for the Treatment of Autoimmune Diseases

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

**Therapeutic area:** Autoimmunity.

**Goal:** To demonstrate the potential usefulness of a peptide type Altered Peptide Ligand (APL) derived from an auto-antigen involved in the pathogenesis of Rheumatoid Arthritis for the treatment of this disease and other autoimmune pathologies.

**Business proposal:** Joint clinical development in order to register and commercialization. Joint clinical development to demonstrate the concept for the treatment of type I diabetes and juvenile idiopathic arthritis (JIA).

**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 IFNg 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.

**Patents**

- 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.

**Publications**

- Autoimmunity 2011; 44(6):471-482
**PO: Vaccine Candidate Against Ticks**

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

**Area:** Veterinary.

**Goal:** This is an applied research project, aimed to develop a vaccine preparation against ticks, based on a peptide of the ribosomal protein P0 of Rhipicephalus genus ticks.

**Business Proposal:** Coorporate partnership or sublicense to locate de veterinary vaccine.

**Description**

Ectoparasites are vectors for transmission of infectious agents causing diseases. The use of chemical pesticides is the traditional method for tick control. The intensive use of these acaricides contaminates food, environment, and develops resistant ticks. The vaccination is considered an alternative for tick infestation control. Although new tick proteins have been proposed as potential protective molecules, only a limited number of them have been evaluated as recombinant antigens in vaccination trials.

Ribosomal protein P0 of Rhipicephalus genus ticks is a promising vaccine candidate. A synthetic peptide of 20 amino acids of an immunogenic region of the protein that is not conserved with respect to their hosts, showed an efficacy of 90% and 89% as a vaccine against infestation of Rhipicephalus sanguineus in experiments in rabbits and dogs, respectively, causing a drastic decrease in the viability of the ticks. The same peptide used to immunize cattle showed an efficacy of 96% leading to a significant decrease in recovery and the weight of ticks Rhipicephalus Boophilus microplus and a significant reduction in the weight of egg masses and the hatch percent. These results suggest the promising possibilities of ribosomal protein P0 peptide for the effective control of ectoparasites. At the moment, research and proof of concept of peptide fused to carrier proteins using recombinant DNA techniques are ongoing. The objective is to obtain an immunogenic and effective variant of the candidate feasible for the production process.

![Figure 1. In red, the sequence of P0 peptide used as immunogen against ticks.](image)
• Experiments of immunization and challenge against ticks using different mammalian hosts.

Patent

Patent (WO2012041260A1), granted in Cuba, published by the PCT) and granted in USA, China, Chile, Europe, Australia, South Africa and Rusia. and in progress in several countries where it was presented as Canada, Costa Rica, Colombia, Brazil, Dominican Rep., Perú, Mexico and Argentina.

Publications


• Rodríguez-Mallon A, Encinosa PE, Méndez-Pérez L, Bello Y, Rodríguez Fernández R, Garay H, et al. High efficacy of a 20 amino acid peptide of the acidic ribosomal protein P0 against the cattle tick, Rhipicephalus microplus. Ticks Tick Borne Dis. 2015.
Classical Swine Fever (Vaccine and Diagnostic) Project

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

*Area*: Veterinary.

*Goal*: Development of a sub-unit vaccine against the Classical Swine Fever Virus, as a complement of an integrated approach to the control and eradication of the disease.

*Business proposal*: Corporate partnership for out-licensing, co-development and commercialization.

**Description**

Classical swine fever virus (CSFV) elicits high mortality in infected herds during recurrent outbreaks. E2-viral envelope glycoprotein is responsible for the induction of neutralizing antibodies, which become this molecule in a prospective candidate to develop vaccines and diagnostic systems.

Previously, we have used E2 glycoprotein as a vaccine candidate, which induced full protection in immunized pigs after challenge with a highly pathogenic CSFV strain. However, this protein was not able to induce protection in the first 14 days post-vaccination. To overcome this issue, we fused E2 glycoprotein to the molecular adjuvant CD154 to increase immunogenicity. This is an applied research project, aimed to obtain a new product with Intellectual Property. These candidate vaccines have been produced by genetic engineering in cells CHO-DG44, CHO-K1 and HEK 293. The protective capacity of the E2CD glycoprotein was demonstrated in a challenge experiment using a biphasic immunization schedule with 50 and 25 μg/ml of the E2CD glycoprotein in pigs. The immunized animals developed neutralizing antibodies that were protective when the animals were faced to a challenge with 105 LD50 of the homologous CSFV “Margarita” strain administered by intramuscular injection. Consequently, no clinical signs of the disease were detected in the vaccinated pigs. Consequently, no clinical signs of the disease were detected in vaccinated pigs. Also, a preliminary study was carried out to evaluate cellular immune response after immunization with the vaccine candidates E2 and E2-
CD154 by measuring gamma interferon levels using porcine IFN-\(\gamma\) ELISA development kit. Results indicated that the induction of gamma interferon by E2-CD154 was higher than its counterpart E2. These results suggest that the vaccine candidate E2-CD154 may result immunologically superior for CSF prevention.

In parallel, we have developed a DIVA diagnostic system that allows distinguishing vaccinated animals from infected animals. Both tools allow establishing a program to assist in the eradication of Classical Swine Fever in our country.

The Main Achievements of this Project are

1. Cloning and characterization of E2 glycoprotein fused to CD154 molecule to swine.
2. Recombinant production of E2-CD154 protein in mammalian cells (CHO-DG44, CHO-K1 and HEK 293).
3. Demonstration of protective capacity of the E2CD glycoprotein was in a challenge experiment using a biphasic immunization schedule and a challenge with 105 LD50 of the homologous CSFV “Margarita”.
4. Demonstration of protective capacity after 7 days post vaccination of the E2CD glycoprotein using a one immunization and a challenge with 105 LD50 of the homologous CSFV “Margarita”.
5. Demonstration of inhibition to Transplacental transmission of CSFV.
6. Vaccination with CSF subunit marker vaccine E2CD154 able to distinguishing vaccinated animals from infected animals.

Patents

CHIMERIC VACCINE ANTIGENS AGAINST CLASSIC SWINE FEVER VIRUS. Antígenos vacunales quiméricos contra el virus de la peste porcina clásica (PPC) Patente PCT/CU 2006-052/ CU 23544.

Publications

Soybean Improvement with Biotechnology Tools

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

*Area:* Agriculture.

*Goal:* This is an applied research project aimed to develop molecular strategies to inhibit fungi diseases like asian rust in the commercial soybean genotypes come together with it resistance to herbicide glyphosate.

*Business Proposal:* Development and Evaluation Agreements to perform trials to validate the effectiveness of the methods. The results will lead to subsequent commercial agreements for specific territories and during a period of time.

**Description**

The widespread and sustainable exploitation of crops around the world is continuously challenged to pest control (Delgado, 2015) and particularly those come from fungi. The scale-up of crops is a factor that triggers the emergence of diseases that affect its yielding; such is the damage of Asian rust *Phakopsora pachyrhizi* associated with the extending of soybean around the world. Soybean rust is a severe foliar disease of soybean that occurs throughout most soybean producing regions of the world. Soybean rust causes significant yield loss to soybean crops in Asia, Africa, Australia, and nearly all tropical countries in the Eastern where soybeans are grown have reported its occurrence. Rust is considered to be a major threat to soybean production in the Western hemisphere. In Brazil, this disease was estimated to cost growers approximately $1.2 billion (USD) in 2003 alone. If *P. pachyrhizi* becomes established in the continental US, serious yield losses are likely to occur (Aragao, 2011; Enriquez et al., 2011). There are other fungal diseases associated with the cultivation of soybean that are of great interest because of their high frequency of incidence on the crop.

To solve the problem of diseases in cultivable plants, several interesting strategies have been approached (Borras et al., 2009; Portielles et al., 2010; Enriquez et al., 2011).

Thus, one of the researches carried out in the laboratory was to express the defensin NmDef02 in the Cuban soybean genotype in order to protect it against Asian rust produced by *P. pachyrhizi*. Several Incasoy36 and DT84 transgenic lines nmdfe02- and cp4epsps- expressing genes were obtained and challenged in two independent field trials. It demonstrated that some of these lines were able to protect against not only for asian rust but also to the most important fungi of soybean under field condition.

![Figure](image-url) **Figure.** Transgenic defensin-expressing soybean cv DT84 were tested for fungus in an in vitro growth assay.
Procedure for plant regeneration in Cuban soybean cv Incasoy36

Publications


Hebernem: Effective Biological Nematocide

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

*Area:* Agriculture.

*Goal:* To implement a previous evaluation and business joint ventures for the commercial exploitation of the bionematicide HeberNem.

*Business Proposal:* Development and Evaluation Agreements to perform clinical trials to validate the effectiveness of Hebernem as biopesticide and biofertilizer. Identifying appropriate partners to extend its use and application. The results will lead to subsequent commercial agreements for specific territories and during a period of time.

**Description**

At present, biological products for the control of pest and diseases are highly demanded worldwide. Their designs are oriented towards a friendly environmental nature compatible with organic agriculture and capable to strongly reduce or substitute the use of chemical pesticides. HeberNem is a biological nematicide, environmentally friendly, which has proven to be an efficient alternative, supplementing the action of chemical nematicides, under a system of integrated pest management. The product has been successfully tested in green houses dedicated to vegetable production in semi-protected crops and plantations of banana and guava. A nationwide mass marketing of bionematicide HeberNem is currently carried out by Permissions Nr. 001/2007 and 050/08 of National Pesticides Registry.

More than 17 years of toxicological and ecotoxicological studies (25 studies) have supported the product biosafety and bionematicide activity against several genera of plant parasitic nematodes. The product has proven to be environmentally friendly. Its mechanism of action has been elucidated. There are two formulations already registered: a liquid formulation (HeberNem-L) and solid (HeberNem-S).
Patents

The Project is supported by the following:

“Pesticides and antiparasitic compositions”. Cuba: CU2001-0004: PCT/CU01/00014 Granted in: Cuba, Europe, China, Vietnam, Israel, Mexico, Panama, United States, South Africa, Peru, Australia, Colombia, Russia, India, Canada, Brazil, Iran, Nigeria. Filed in Venezuela and Paraguay.


Hebernem treated greenhouse plantation free of plant nematodes
CIGB42 for Citrus Huanglongbing (HLB) Control

Center for Genetic Engineering and Biotechnology, Havana, Cuba.

**Area:** Agriculture.

**Goal:** To implement a previous evaluation and business joint ventures for the commercial exploitation of the CIGB42.

**Business Proposal:** Corporate partnership for out-licensing, co-development and commercialization.

The “Huanglongbing” (HLB) caused by the bacterium *Candidatus Liberibacter asiaticus* is the most destructive disease of citrus worldwide by the severity of symptoms, the rapidity with which it spreads and affects all commercial citrus species. The economic impact for the presence of HLB in citrus-producing countries has increased year by year, with losses estimated in about 30 to 100%, due to reduced yields and fruit quality. Until now, there is no region in the world where the HLB is adequately controlled and the disease does not exist, which contributes to increase its severity and incidence. CIGB is developing a product that contributes to solve the problem mentioned before, because offers an efficient alternative to activate the natural defense of citrus plants against the HLB. The applications of the product allow a significant reduction of the bacteria as causal agent of the disease.


Granted in Cuba, United States, Europe, China, Vietnam, Israel, Mexico, South Africa, Australia, India, Canada, Brazil.

![Figure 1](image1.png)
**Figure 1.** Quantification of C.I. in infected citrus plants treated with CIGB42 every 15 days during 6 months.

![Figure 2](image2.png)
**Figure 2.** Orange plants after 3 months of CIGB42 treatments.

**Publication**


2. More than 7 years of studies both at laboratory and plot scale have supported the product activity against citrus HLB.
Center of Molecular Immunology
CIMAvax-EGF®: New Therapeutic Vaccine for Advanced Non-Small Cell Lung Cancer

Center of Molecular Immunology, Havana, Cuba.

Goal: To benefit patients diagnosed of advanced Non-small cell lung cancer in term of improvement survival, quality of life, together with a very good safety profile by active immunotherapy against 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, chemotherapy 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.

Figure 2. Kaplan Meier curve in patients with high [EGF] at day 0.
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), with high EGF concentration at day 0. (Figure 3 and 4).

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.

CIMAvax-EGF® References


Family of Human IL2: Muteins with Therapeutic Potential for Cancer

Center of Molecular Immunology, Havana, Cuba.

Goal: To develop biopharmaceuticals with improved therapeutic ratio compared to high doses – IL2 for cancer patients by maximizing therapeutic effect together with a low toxicity profile (“do better than nature”).

Business proposal: Corporate partnership for product co-development, registration and marketing in selected territories according to signed licensing agreements with biotechnology or pharmaceutical companies. In particular, direct foreign investment is requested to create JVC in the Special Development Zone of Mariel (SDZM), Havana, Cuba.

Description

Interleukin 2 (IL2) or T Cell Growth Factor has a dual role in the regulation of the immune response activating both effector and regulatory T cells. Such multi-functional biological activity has limited the therapeutic application of native IL2. This cytokine exerts its biological effect on immune cells through a membrane receptor (IL2R). This membrane receptor is composed by 3 polypeptide chains (α, β and γ). The differential expression of such receptor chains on different immune cells determines the IL2 multi-functionality.

High doses (HD) – IL2 is oncology medical practice for the treatment of melanoma and renal cell carcinoma, with an impressive therapeutic effect in 15% of patients with good treatment adherence, but the clinical benefit is limited because of the reinforcement of immune checkpoints (expansion of Treg in treated patients) and the high toxicity mainly due to Capillary Leak Syndrome (CLS). Using bioinformatics two muteins were designed to split biological functions of native IL2. The first one unable to bind the receptor α chain and therefore it can’t induce receptor signaling. This “no – gamma IL2” mutein behaves as an IL2 antagonist preferentially for regulatory T cells (Treg) which over-express receptor α chain, reduces Treg in vivo and induces anti-tumor effect in mice. The second one behaves as a partial agonist, it can’t bind to receptor α chain and can’t activate Treg but it does activate memory CD8+ T cells and NK cells which only express a dimeric receptor (β and γ receptor chains). This “no – alpha IL2” mutein showed a higher anti-metastatic effect in mouse tumor models than native IL2 but with a lower toxicity profile.

IL2 muteins might have other potential therapeutic uses which are currently subject of clinical investigation with native IL2, for example Active Cell Therapy (ACT). Beside the two IL2 muteins obtained so far other mutation sets are being studied.
Patent Status

Two patent applications:

- WO 2011/063770 (US 8 759 486 B2) granted in 18 countries so far, including USA, Japan, China and other countries from South East Asia

- WO 2012/062228 (EP 2 639 241 B1) granted in 20 countries so far, including USA, Japan, China and other countries from South East Asia

Project Status

- “No – alpha IL2 partial agonist” is in pre – clinical evaluation to complete pharmacological and toxicological studies in experimental models. The production process is under development at Pilot Plant scale. IND application to Cuban regulatory agency is due to happen in 2016.

- “No – gamma IL2 antagonist” is in pre – clinical evaluation to enlarge the evidences of anti – tumor effects in mouse models. The production process is under research at bench scale.

Competitive advantages and milestones:

- “No – alpha IL2 partial agonist” produces an enhancement of anti – tumor immunity by activation of cytotoxic immune cells with a low toxicity profile, with an improved therapeutic ratio as compared to HD – IL2. It can be considered as a “best in class” product. Phase I clinical trial is due to start in 2017

- “No – gamma IL2 antagonist” produces an enhancement of anti – tumor immunity by inhibiting Treg (suppress immune check point). It can be considered as a “first in class” product.
**Bivalent Vaccine** **HER1+HER2**

**Center of Molecular Immunology, Havana, Cuba.**

**Goal**: Development of a vaccine formulation to induce humoral and cellular immune response against HER1 and HER2 oncogenes for patients with advanced tumors.

**Business proposal**: Corporative association for co-development, register and commercialization of the product, through license agreement with biotechnology or pharmaceutical enterprises.

- This project is contained in the negotiations with Roswell Park Institute of New York, USA. Clinical development in USA would increase the value of the project.
- This Project is currently in a negotiation process with the China National Biotec Group Company, which belongs to Sinopharma Enterprise. This the biggest pharmaceutical enterprise in China.

**Description**

HER1 or Epidermal Growth Factor Receptor (EGFR) and HER2 are considered tumor associated antigens due their role in tumor biology, and overexpression in several epithelial tumors, which has been associated with bad prognosis of the disease. HER1 oncogene participate in initiation and maintenance of tumorigenic process and its overexpression conduces to increased proliferation, angiogenesis, and invasive/metastatic capacity, whilst decrease apoptosis and tumor cells immunogenicity1. For all these reasons HER1 and HER2 are an attractive target for cancer immunotherapy and passive drugs targeting this oncogene are part of the medical Clinical practice in oncology2,3.

In this project have been used a novel strategy based on active specific immunotherapy (therapeutic vaccine) by using as antigens the extracellular domains of HER1 and HER2, and as adjuvant the VSSP (very small sized proteoliposomes), which have immune-potentiating properties. The rational of this vaccine, different to passive drugs, is to induce simultaneously both, humoral and cellular immune response. This activation of the immune system can be induced by using low doses of both antigens. The VSSP nanoparticles are composed of outer membrane proteins from Neisseria meningitides and NAcGM3 ganglioside. This nanoadjuvant is able to activate dendritic cells, induces TCD8+ cytotoxic response in leucopenia conditions, and inhibits the function of myeloid derived suppressor cells4,5.

The preclinical studies of this vaccine are demonstrating the capacity of the vaccine candidate HER1+HER2/VSSP, inoculated by subcutaneous way, to induce humoral immune response simultaneously against both receptors. This response was characterized for the generation of high polyclonal antibodies titers, specific for HER1 and HER2, which recognized a wide panel of human tumor cell
lines from diverse localizations and different HER1 and HER2 levels of expression. The induced antibodies inhibited the activation of both oncogenes but also inhibit the function of key proteins from MAPK, PI3K/Akt and STAT3 signaling cascades. Also, these antibodies showed cytotoxic capacity, inducing tumor cells death with apoptotic characteristic.

**Figure 1** IgG antibodies response against HER1 and HER2 induced by Bivalent Vaccine HER1+HER2 in mice, and in vitro effect of antibodies on the viability of treated human tumor cells

### Current status

The Bivalent Vaccine HER1+HER2 is at the momento in a phase of preclinical estudies. It is under evaluation its capacity to induce cellular immune response, antimetastatic effect, and the superior effect over the combination of monoclonal antibodies.

### Patent status

The Project has a patent WO 2015/0114327 A1 presented in Cuba and sended to 34 countries in 2016. This patent covers the Bivalent vaccine. It is under evaluation a new patent in 2017 from a new formulation of VSSP.

### Competitive advantages

The Bivalent Vaccine HER1+HER2 is unique because no other vaccine combine the oncogenes HER1 and HER2 in a formulation, neither use VSSP as platform. It has the advantage over passive drugs because can activate simultaneously humoral and cellular immune response against two oncogenes. Also, the induced immune response is polyclonal, generating antibodies against different epitopes of both oncogenes, which could potentially increment the effect respect to monoclonal drugs.

### References

4 Kong, AVC. Et al. (2008) PLoS ONE 3(8): 2881
5 Oliver, L. et al. (2012) Vaccine Apr 19;30(19):2963-72
Immunotherapy based on Antibodies Against Glycosaminoglycans and ApoB-containing Lipoproteins with Therapeutic Potential for Atherosclerosis

Center of Molecular Immunology, Havana, Cuba.

**Goal:** To develop antibodies useful for the treatment of atherosclerosis due their ability to avoid the retention in the artery wall of ApoB-containing lipoproteins and their subsequent modifications; or to bind specifically to modified proatherogenic low density lipoprotein.

**Business proposal:** 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.

**Description**

A murine monoclonal antibody (mAb) that recognizes sulfatides showed the unusual property of generating a strong anti-idiotype antibody (Ab2) response when administered in a syngenic animal model. The chimeric mouse/human IgG1 variant of P3 mAb (chP3) maintained the specificity and idiotypic immunogenicity of the murine antibody. Later, a chP3 mutant was obtained having an additional arginine in position 99 of H-CDR3 (chP3R99) displayed a higher reactivity to sulfatides and GAGs, mainly chondroitin sulfate (CS). This mAb blocked LDL–CS association and LDL oxidation in vitro and in vivo. In addition, chP3R99 mAb preferentially accumulates in rabbit and mice arterial atherosclerotic lesions.

Subcutaneous administration of New Zealand White rabbits with chP3R99 mAb prevented Lipofundin-induced atherosclerosis (acute model). The atheroprotective effect was associated with the induction of anti-CS antibodies in chP3R99-immunized rabbits, capable of blocking CS-LDL binding and LDL oxidation. Then, the effect of chP3R99 administration was tested in hypercholesterolemic ApoE-deficient (ApoE-/-) mice. A striking (40%–43%) reduction (P<0.01) in total lesion areas was observed in 18-week-old mice immunized with chP3R99. The anti-atherosclerotic effect was associated with increased sera reactivity against sulfated GAGs.

All these results together contribute to broaden the potential use of this anti-GAG antibody-based immunotherapy as a novel approach to target atherosclerosis at different phases of progression.

On the other hand, natural antibodies bind to specific epitopes present on oxidized LDL (oxLDL) preventing the development of atherosclerotic lesions in mice and rabbits. In addition, epidemiologic clinical studies suggested the presence of IgM anti-oxLDL could be associated with atheroprotection. Murine mAbs with a high specificity to oxLDL have been obtained capable to inhibit the binding of these lipoproteins to macrophage scavenger receptors. In vivo pharmacological studies are ongoing to evaluate the anti-atherosclerotic effect of anti-oxLDL mAbs.
Properties of chimeric monoclonal antibody chP3R99

✓ Accumulates in atherosclerotic lesions of murine and rabbit models in vivo

Figure 1. Properties of monoclonal antibody chP3R99. Accumulates in atherosclerotic lesions of murine and rabbit models in vivo.

Brito et al. ATVB, 2012

Soto et al. Mabs, 2014

chP3R99-LALA immunization arrests atherosclerotic lesion progression

Figure 2. Therapeutic effect of monoclonal antibody chP3R99. Stopping the progression of atherosclerotic lesions

(Delgado L, Brito V. et al, FRBM 2015)
**Patent Status**

One patent application WO 2010/127642 A1 (US 8 470 322 B2) granted in 12 countries including USA, Japan and China, and requested in another 11 countries.

**Project Status**

- Anti-sulfated GAG antibody is in pre-clinical evaluation to complete pharmacological and toxicological studies in experimental models. The production process is under development at Pilot Plant scale. IND submission to Cuban Regulatory Agency to start clinical trial is expected by 2017.
- Anti-oxLDL murine mAbs have been obtained and characterized in vitro and in vivo experiments. Cloning and sequencing of such IgM mAbs are ongoing in order to obtain the corresponding recombinant antibodies. In vivo experiment to get Proof of Principle is expected to be completed by 2017.

**Competitive Advantages and Milestones**

- Anti-sulfated GAG antibody is the first product in development targeting the “Retention Hypothesis”, it could be considered a “first in class” product. This antibody inhibits the binding of LDL to the extracellular matrix, and consequently inhibits the LDL oxidation process and the inflammation in the artery wall. This new therapeutic concept induces a blockade of the atherogenic process through a mechanism different to hypocholesterolemic agents, as statins, and to drugs that inhibit the LDL-receptor degradation therefore it could benefit patients with advanced disease refractory to current treatments. Proof of Concept Clinical Trial is due to start by 2017.
- The discovery of natural IgM antibodies with very high specificity to oxLDL and ability to induce idiotypic cascades (“vaccinal effect”) provides the rationale for the development of “best in class” product. Such anti-oxLDL antibodies might potentiate the anti-atherosclerotic activity of anti-sulfated GAG antibody. A new patent application is expected by 2017.
Pharmaceutical Formulation (NeuroEPO) of Selected Glycoforms of Recombinant Human Erythropoietin with Therapeutic Potential for Several Brain Inflammatory Diseases

Center of Molecular Immunology, Havana, Cuba.

**Goal:** Develop a pharmaceutical formulation of recombinant human erythropoietin with low sialic acid content for nasal administration which allows pharmacological concentration inside the brain without systemic erythropoiesis, and a biological action similar to the erythropoietin produced in the brain, in such a way to maximize therapeutic effect and minimize adverse side effects. Such pharmaceutical formulation will be evaluated for the treatment of several brain inflammatory diseases, like stroke and neurodegenerative diseases.

**Business proposal:** 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.

**Description:** Erythropoietin (EPO) plays an important role in brain homeostasis. Both neurons and astrocytes express EPO-receptors at the cell membrane, and some EPO glycoforms are produced locally into the brain. 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. Clinical trials with rhEPO have been performed in several brain inflammatory diseases with encouraging results but no registration approval for medical use has been obtained so far.

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). Such pharmaceutical formulation of rhEPOb (NeuroEPO) could have pharmacological effects into the brain without erythropoiesis activity.

Extensive pre-clinical evaluation of NeuroEPO has been performed in several experimental models of stroke and neurodegenerative disorder (including dementia), showing neuro-protective but also neuro-regenerative effects. Some preliminary data suggest astrocytes could be involved in the neuro-regenerative effect of NeuroEPO in several brain inflammatory diseases. Also clinical data have been gathered 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.

**Project Status**

- GMP production process at industrial scale has been set up.
- Phase I clinical trial in healthy people has been completed with positive results. Tolerance to
local administration was good. No serious AEs were reported. Vital signs, hematology and biochemistry values, including Hb, remained within normal levels.

- Phase II/III clinical trial in Ataxia Spinocerebellar type 2 has been 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 has been completed with positive results.

**Patent Status**

Two patent applications:

1. Rh-EPO Nasal Formulations with low sialic acid concentration for the treatment of diseases of the central nervous system (WO 2007/009404). Granted in: Mexico, MX/a/2008/000997; Cuba, CU 2758/2008; and Canada, 2,616,156.

2. Process for obtaining human recombinant erythropoietin and erythropoietin obtained (CU1998-0023). Granted in: Cuba, CU 22709 A1; Colombia, 27642; Argentina, AR013022B1; Malaysia, MY-122336; Russia, 2215748; Chile, 46618; Mexico, 241665; Vietnam, 4772; and Algeria, 2783.

**Competitive Advantages and Milestones**

- NeuroEPO has shown so far a better therapeutic ratio for the treatment of brain inflammatory diseases than usual rhEPO formulation for intravenous use, maximizing clinical benefit and minimizing thrombotic risk. NeuroEPO would act as a homeostatic regulator of neuron-astrocyte interaction improving neurological status but also cognitive functions. NeuroEPO could be considered a “best in class” product.
- Orphan drug registration approval by the Cuban Regulatory Agency for the treatment of Ataxia Spinocerebellar type 2 is expected by 2016
- Pivotal trial in Parkinson’s disease is due to start in 2016
- Phase I/II clinical trial in Alzheimer’s disease is due to start in 2016
- Completion of Phase II/III clinical trial in Stroke is expected by 2017
CIDEM 161: a New Chemical Entity (NCE) for the treatment of Cerebral Ischemia

CIDEM

Goals: Development, registration and marketing of a new neuroprotective drug for the treatment of cerebral ischemia.

Business proposal: Corporate partnership for joint development, and clinical trials (Phase I, II and III). The milestones are 1) concluding the development phase of a new drug, 2) to conduct Phase I, II and III clinical trials, 3) registration, and 4) market entry.

Description

Acute ischemic stroke is one of the major causes of permanent disability and the third largest cause of death worldwide. The American Heart Association states that every year an estimated 795,000 people are diagnosed with stroke in the US, a whopping 85.0% of which are identified as acute ischemic stroke. The cost of treating strokes in the country surpasses US$73 bn per year, thus the North America acute ischemic stroke diagnosis and treatment market is anticipated to retain its lead through 2020. Cerebral ischemia generated an expense of 183.13 billion in the United States in 2015. According to a recent study by the National Center for Health Statistics in the US, cerebral ischemia represented the fifth leading cause of death at national level. Therefore, the study concluded that this disease continues to constitute a major public health problem.

There is a limited choice of treatments that could improve the chances of recovering from a stroke. The currently available options, such as treatment with recombinant tissue plasminogen activator (rt-TPA), is only available for 10% of the population, due to its constraints (reduced therapeutic window and it is unusable in patients with hemorrhagic signs). Neuroprotective therapy has not been successful so far mostly because the compounds under development have been directed to a single therapeutic target. However, cerebral ischemia is a multifactorial disease, where mechanisms responsible for the damage, change over time.

CIDEM 161 is a first in class molecule composed by a 1,5-benzodiazepine fused to dihydropyridine moiety, which was designed and synthesized by researchers from the Faculty of Chemistry at the University of Havana. Evidences obtained through the relevant preclinical models that mimics the disease, has demonstrated that CIDEM-161 is a strong protective molecule acting through different, but disease-related, molecular pathways such as: antioxidant, anti-calcium, mitoprotective, antiapoptotic, antiinflammatory and anti-excitotoxic effects. CIDEM-161 was also effective in several in vivo experimental ischemia models, in which showed a strikingly wide therapeutic window (more than 8 hours). The protective mechanism has been proposed (for further details see related papers referenced below).

Development Stages Completed and Current Status

All preclinical studies (in vitro and in vivo models) related with cerebral ischemia were completed and the neuroprotective mechanisms of CIDEM 161 was proposed (See Figure 1). Genotoxicity studies and the physic-chemical characterization of the raw material are currently running. It is planned the performing of subchronic toxicity and pharmacokinetic studies, as well as the development of a drug formulation.
Figure 1. Simplified scheme showing the multitarget effect of CIDEM 161 for the treatment of cerebral ischemia.

Related Papers


Intellectual Property Status


Competitive Advantages

The product is directed to an unmet medical need for which there is a broad market, especially in developed countries. The product has shown a therapeutic window of more than 8 hours, which highlight it as a promising and attractive molecule for the development of a new drug for the treatment of cerebral ischemia.
CIDEM 162: a First in Class Molecule Promising for the Treatment of Dementia, Parkinson Disease and Neuropathic Pain

**CIDEM**

**Goals:** Development, registration and marketing of a new neuroprotective drug for the treatment of dementia, Parkinson disease and neuropathic pain.

**Business proposal:** Corporate partnership for joint development, and clinical trials (Phase I, II and III). The milestones are 1) conclude the development phase of a new drug (CIDEM 162), 2) conduct Phase I, II and III clinical trials, 3) registration, and 4) market entry and commercialization.

**Description:** CIDEM 162 is a novel molecule with demonstrated therapeutic potential in preclinical stage for the treatment of several neurodegenerative disorders. Its main pharmacological mechanism is related to the inhibition of excitotoxicity mediated by glutamate, antioxidant properties, inhibition of neuronal apoptosis, inhibition of neuroinflammation, and the protection of mitochondrial function. CIDEM 162 is a small molecular chemical entity, and the industrial synthesis of the API is not particularly troublesome.

In animal models related with vascular dementia (in vivo), CIDEM 162 showed a significant reduction in the cognitive impairment associated with the transient occlusion of the common carotid arteries, and preserved the viability of hippocampal neurons. In other models of dementia specifically related to the Alzheimer’s disease, CIDEM 162 inhibited the acetylcholinesterase activity (enhancing the cholinergic transmission). In preclinical models for the Parkinson’s disease, CIDEM 162 showed protection against the injury induced by 6-hydroxydopamine in several in vivo and in vitro models. Overall, these preclinical results strongly support the neuroprotective potential of CIDEM 162 in the treatment of different types of dementia and in the Parkinson’s disease. Other preclinical studies related with neuropathic pain have also shown promising results when combining CIDEM 162 with other known molecules related with this pathology.

The neurodegenerative diseases targeted by CIDEM 162 have a large prevalence in developed countries and all the world. According to WHO, 22% of people older than 60 years will suffer some kind of dementia by 2050. Currently, 10 millions of people suffer Parkinson disease, while 35.6 million suffer from Alzheimer.

**Development Stages Completed and Current Status**

Different preclinical studies (in vitro and in vivo models) related with dementia, Parkinson disease and neuropathic pain have been completed, and some neuroprotective mechanisms of CIDEM 162 were elucidated in relation with Parkinson disease and dementia (see Figures below). Other preclinical studies are required.
Related Papers


Intellectual Property Status


Competitive advantages

The product is directed to an unmet medical need for which there is a broad market especially in developed countries. CIDEM 162 has shown to be a promising candidate for the development of drugs for the treatment of dementia, Parkinson disease and neuropathic pain.
**Amylovis®**: New Molecules for Early Imaging Diagnosis of Alzheimer Disease

**Neurociences Center**

**Goal**: Converting new Beta Amyloid related molecules AMYLOVIS® into image contrasts for early diagnosis of Alzheimer’s Disease.

**Business proposal**: Corporate partnership are requested with companies able to finance and implement development actions (completion of pre-clinical trials and completion clinical of trials) with the necessary rigor for the sale of different contrast in markets of selected areas and BRICS. In exchange, these companies will receive licensing agreements for contrast in these markets.

**Description**

Alzheimer’s disease (AD) is the most common type of dementia and it is typically of elderly people. In 2015 only, 9.9 mill of people developed Alzheimer disease and 47 million are suffering from this disease worldwide. The forecast is that 75 million people will suffer AD in 2030, and 131.5 million in 2050. In all cases of dementia la AD corresponds between 50 and 75 %. It’s characterized pathologically by the presence of senile plaques (SP) and neurofibrillary tangles (NFT).

Early diagnosis of AD by neuroimaging methods have widened the horizons providing a mean for in vivo visualization of SP and NFT, showing the brain area and the magnitude in which they exist.

The Cuban Neurosciences Center (CNEURO) has developed and been granted the patents for a set of compounds called AMYLOVIS® that binds to SP. These statements are supported by in silico, in vitro and in vivo studies.

The AMYLOVIS® molecules have the advantage of being versatile in radiolabeling. Therefore, could be adapted to the equipment possibilities (PET, SPECT and MRI) in a health center.

Different in vivo clinical trials have corroborated that AMYLOVIS® can be labeled independently with different types of radionuclide, both gamma ray emitters (99mTc, 123I or 131I) for SPECT, and with positron emitters (18F and 11C) for PET, as shown in figures 1 and 3.

**Figure 2.** Scintigraphy image of SPECT (A) and activity curve in head (B), in a Wistar healthy rat, after being induced 131I-AMYLOVIS®, via i.v.

**Figure 2B.** shows that 131I-AMYLOVIS® passed the blood-brain barriers (BBB), bi-directionally. This characteristic is decisive for a compound that pretends act over the brain temporarily.
AMYLOVIS® Facts

1. Pass through the blood brain barrier (BBB)
2. Bind to the βAmyloid plaques that characterize Alzheimer’s disease
3. Have shown no toxicity in animals
4. Are labeled as contrasts for PET, SPECT and MRI

AMYLOVIS® for PET is under radiopharmacological evaluation in experimental animal models.

AMYLOVIS® for SPECT is under radiopharmacological evaluation in experimental animal models. The precursors for radiolabeling phase are in the production stage at bench scale, and the definition of product critical attributes.

AMYLOVIS® for MRI will start in silico, in vitro and in vivo phases and definition of product critical attributes.

Therapeutic AMYLOVIS® is under pharmacological evaluation in experimental animal models. Therapeutic AMYLOVIS® is in the production stage at bench scale, and the definition of product critical attributes is being done.

Patent Situation


Spect y Rmn

There are no contrasts approved in the detection of amyloid plaques using SPCT or RMI.
**AMYLOVIS®: New Molecules for the Treatment of Alzheimer Disease**

Neurociences Center

*Goal:* Develop Amylovis® compound as a drug able to interact with the \( \beta \)-Amyloid in cerebellum, for the treatment of Alzheimer disease (AD)

*Business proposal:* Requested corporate partnership with companies able to finance and implement development of actions (completion of pre-clinical trials and testing) with the necessary rigor for the sale of Tera-Amylovis in selected markets and BRICS. In exchange, these companies will receive licenses for the sale of these contrasts in selected territories.

## Description

Alzheimer’s disease (AD) is the most common type of dementia and it is typically of elderly people. In 2015 only, 9.9 mill of people developed Alzheimer disease and 47 million are suffering from this disease worldwide. The forecast is that 75 million people will suffer AD in 2030, and 131.5 million in 2050. In all cases of dementia la AD corresponds between 50 and 75 %. It’s characterized pathologically by the presence of senile plaques (SP) and neurofibrillar tangles (NFT).

The Neuroscience Center of Cuba has developed and patented a set of compounds called AMYLOVIS®, that perfectly match to the SP, and have a disaggregating effect in the formed plaques and a cytoprotective activity in cultures of cerebellum granule cell exposed to cytotoxic stimuli, evidenced by tests.

![PROTEIN BEFORE AND AFTER TREATMENT](image)

In silicus study evidenced that AMYLOVIS® compounds interact with monoacids that participate in the formation of fibers by means of hydrophobic and Van der Waals forces, interfering in the formation \( \beta \) Amyloid (Figure 1).
Summary, this group of molecules derivate from naphthalene:

- Pass through the blood-brain barrier (BBB)
- They bind perfectly to β Amyloid that characterize Alzheimer disease (AD)
- Non-toxicity demonstrated in animals.
- They have a cytoprotective activity in cultures of cerebellum granule cell exposed to cytotoxic stimuli.

**Development Phases Concluded Actual State**

Tera-AMYLOVIS® is being radiopharmaceutical evaluated in animal experimental models and in the production phase in laboratory scale and in defining the critical attributes of products.

**Timetable to Completion**

<table>
<thead>
<tr>
<th>AMYLOVIS® Stage</th>
<th>PRE-CLINICAL Test</th>
<th>CLINICAL tests</th>
<th>REGULATORY APPROVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMYLOVIS® Medication</td>
<td>2017</td>
<td>2018</td>
<td>2020</td>
</tr>
<tr>
<td>PHASE I</td>
<td>PHASE II</td>
<td>PHASE III</td>
<td></td>
</tr>
</tbody>
</table>

**Patents Status**


