INNOVATIVE BIOLOGICAL MEDICINES

BIOCUBAFARMA
CIENCIA PARA UNA VIDA SALUDABLE

Innovative medical approach for the management of COVID-19:

- Prevention and potentiation of the immunity of the patients with dysfunctional immune system caused by aging and/or comorbidities.
- Treatment of respiratory distress caused by cytokine storm on SARS-CoV-2 positive patients.

2020

Index

1 BIOCUBAFARMA

BIOCUBAFARMA, the Group of Biotechnology and Pharmaceutical Industries of Cuba is a company that research, develop, manufacture and commercialize biopharmaceuticals for prevention, diagnostic and treatment of infectious diseases, cardiovascular diseases, neurodegenerative diseases, autoimmune diseases and cancer, medical equipments, medical devices and other products for Cuban National Healthcare System as well as products for agricultural biotechnology and veterinary medicines.

BIOCUBAFARMA gather 32 enterprises in Cuba, 9 of them are commercial companies with import / export capabilities. It has 12 companies, 1 subsidiary company and 2 representation offices outside Cuba. Six (6) companies are joint venture companies (3 in China, 1 in Thailand, 1 in Singapore and 1 in Spain) and the other 6 are 100% wholly-owned companies by BIOCUBAFARMA (1 in Brazil, 1 in Ecuador, 2 in Mexico, 1 in Spain, and 1 in Venezuela).

At the end of 2019 BIOCUBAFARMA and its commercial enterprises had established a global network of international alliances, which include licensing and co-development agreements and representation, supply and distribution agreements in more than 60 countries in the world. BIOCUBAFARMA has more than 742 marketing approvals in 53 countries and export its products to more than 40 countries.

During the last 30 years BIOCUBAFARMA and its companies in collaboration with the Ministry of Health of Cuba have worked on the implementation of The National Health Programs which have resulted on a great impact on the health of the Cuban population.

The National Vaccination Program has dramatically reduced the incidence of several infectious diseases that were responsible for much suffering and deaths. In Cuba, childhood vaccination resulted in a substantial decrease in the incidence of numerous infectious diseases and associated mortality such as diphtheria, tetanus and polio, tuberculosis, pertussis, measles, mumps, and rubella.

The program for massive pre and neonatal screening and epidemiological surveillance, which includes among others, mother and child program, and program for blood certification. The epidemiological surveillance program was the first in Latin America who prevent the mother and child transmission of HIV and congenital syphilis.

The program for the comprehensive care of the diabetic patient that includes the management and treatment of patients who developed Diabetic Foot Ulcer (DFU) using the innovative drug Heberprot-P that had treated over 350,000 patients worldwide avoiding the amputation in 70% of them.

The program for prevention, diagnosis and treatment of cancer such as children gliomas, brain tumors in adult population, head and neck tumors and non-small cell lung cancers using innovative monoclonal antibodies (CIMAher®) and therapeutic cancer vaccines (CIMAvax-EGF®) that had shown to increase the life expectancy, survival benefit and quality of life of the patients.

It is estimated that current pipeline of commercial products and projects under development of BIOCUBAFARMA for (i) prevention and potentiation of the immunity of the patients with dysfunctional immune system caused by aging and/or comorbidities; (ii) Inhibition of viral replication and (iii) treatment of the respiratory distress caused by cytokine storm in SARS-CoV-2 positive patients could have a great potential to cause an impact on the management and treatment of COVID-19.

II The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a new emerging infection that as of June 5th, 2020 had been reported in 212 countries, causing over 6.761.109 cases infected with 394.971 deaths [1].

As an emerging virus, there is not a preventive vaccine or effective drug approved for the treatment of SARS-CoV-2 infection at the moment. Several countries following experience in Wuhan and WHO recommendations have introduced on their protocols of treatment combinations of antibiotics, antiviral drugs and new molecular entities [2, 3].

In a joined effort the Ministry of Health of Cuba and BIOCUBAFARMA have introduced several innovative research approaches and protocols for the prevention of the infections with SARS-CoV-2 in high-risk population and the treatments of patients severely and critically ill with COVID-19.

In particularly, BIOCUBAFARMA provides biological products for (i) prevention and potentiation of the immunity of the patients with dysfunctional immune system caused by aging and/or comorbidities; (ii) Inhibition of viral replication and (iii) treatment of the respiratory distress caused by cytokine storm in SARS-CoV-2 positive patients.

III Potentiation of the Immune System with Biological Immunomodulators

In order to potentiate the immune system in people with gradual deterioration of the immune system caused by aging or in patients with comorbidities, BIOCUBAFARMA had introduced the following product as part of the protocol for prevention and also in the protocols for the treatment of SARS-CoV-2 positive patients.

BIOCEN
CENTRO NACIONAL DE BIOPREPARADOS

PRODUCT	**Biomodulina-T®**
	**Biomodulina-T®** is a natural biological drug extracted from bovine thymus (It is not a blood-derived product) approved for injection route. **Biomodulina-T®** is a diafiltrate extract of calf thymus containing specific fractions of thymus including polypeptides of low molecular weight and thymus hormones. Since the high homology of these polypeptides between different mammal species, these components are fully functional when administered to humans.
SCIENTIFIC RATIONALE	The thymus gland plays a vital role in the immune system by producing and secreting a set of polypeptides and hormones that act on the maturation and differentiation of T lymphocytes, ensuring normal development of the mechanisms of cellular and humoral thymus-dependent immunity. The innate immunity response is considered an essential factor in limiting the severity of COVID-19, particularly, the early type I interferon response. Once Biomodulina-T® is administered: • It acts as a primer of adaptive or acquired immune response by stimulation of T-lymphocyte maturation and differentiation (CD3 T-cells) • It restores immunosenescent CD4 and CD8 T-cells when administered to elderly patients. • It Increases CD4+/CD8+ ratio and improves the balance between pro-inflammatory and anti-inflammatory cytokines.

CLINICAL STUDIES	Phase IV on evaluation of the safety and efficacy of Biomodulina-T® for the preventions of infections including SARS-CoV-2 in elderly population in Cuba (ongoing).
Patient population	Observational study nationwide in elderly population (> 60 years old).
Administered dose	3 mg (1 vial) twice a week for 6 weeks.
Clinical results	As of May 25th, 2020 the drug had been administered to 9712 patients in nursing homes. Biomodulina-T® was administered in both as preventive setting in high risk elderly population, and patients with comorbidities as well as to patients positive to SARS-CoV-2.
Safety profile	No serious adverse reactions were reported after the use of Biomodulina-T® in more than 9712 patients. The most frequent Adverse Drug Reactions (ADR) were mild and moderate rash (40%), fever (35%), facial erythema (15%) and facial edema (10%).
Conclusions	Administration of Biomodulina-T® to elderly population (> 60 years old) had stimulated the immune system of this population of patients.
OTHER CLINICAL STUDIES (ongoing)	
Combination of Biomodulina-T® with intranasal administration of interferon alpha 2b.	Study that combined the administration of Biomodulina-T® (twice a week for 6 weeks) and intranasal interferon alpha 2b (two daily doses for 10 days) in 82 elderly patients at the nursing home with the purposes to enhance both innate and adaptive immune system on this population after some patients were tested positive to SARS-CoV-2 with the purposes to avoid the spread of infection.
Sequential administration of Biomodulina-T® with 1 dose of vaccine VA-MENGOC-BC.	Study to show synergistic effect of the sequential administration of two immunostimulating products, combining the use of Biomodulina-T® with one dose of the innate immune stimulating containing the outer membrane proteins of the Neisseria meningitides (VA-MENGOC-BC vaccine). It will be administered to 60 healthy volunteers aged > 60 years old.
PUBLICATION	Saavedra D. et al. (2019) Biomodulina-T® partially restores immunosenescent CD4 and CD8 T cell compartments in the elderly. Experimental Gereontology 124, pp. 110633. https://doi.org/10.1016/j.exger.2019.110633
REGULATORY STATUS	Marketing approval in Cuba.

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IV

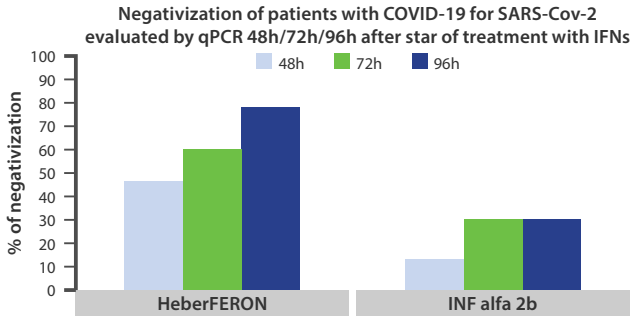
Anti-viral effect of HeberFERON® on the treatment of SARS-CoV-2 positive patients with some comorbidities and patients with SARS-CoV-2 viral persistence

Interferons can combat bacterial and parasitic infections, inhibit cell division, and promote or impede the differentiation of cells. Interferons also have immunoregulatory functions, they inhibit B-lymphocyte (B-cell) activation, enhance T-lymphocyte (T-cell) activity, and increase the cellular-destruction capability of natural killer cells.

These immunological properties of the interferons have been used as a rationale for combination of recombinant human interferon alpha 2b with recombinant human gamma interferon in a single vial and to study its potential use for the inhibition of viral replication in SARS-CoV-2 positive patients.

CIGB CENTRO DE INGENIERÍA GENÉTICA Y BIOTECNOLOGÍA

PRODUCT	**HeberFERON®**
	**HeberFERON®**: is a combination of recombinant human interferon alpha 2b with recombinant human gamma interferon in a single vial.
SCIENTIFIC RATIONALE	Interferons have the ability to increase the cytotoxic and phagocytic activity of macrophages, increase the development and differentiation of helper T cell (Th1), and also regulate the production of pro-inflammatory cytokines [7]. Due to its anti-viral nature interferons have been used against viral infections for which specific therapies are not available. The combination has shown to enhance biological activity and increase the anti-proliferative effect by 5 and 10 times more than each individual interferon with less adverse drug reactions.
CLINICAL STUDIES	EOpen-label randomized clinical study in patients positive to SARS-CoV-2 (ongoing).
Patient population	Patients positive to SARS-CoV-2 infection with some comorbidities and patients with SARS-CoV-2 viral persistence.

Administered doses	All patients received treatment according to the National Action Protocol for COVID-19 version 1.4 (MINSAP, Cuba). Kaletra (200 Lopinavir - 50 Ritonavir) 2 capsules every 12 h for 30 days, Chloroquine 1 pill every 12 h for 10 days and Interferon alpha 2b. Subsequently one group of patients received 3.5 M IU of HeberFERON® once a week for 2 consecutive weeks and the other group continued with the administration of interferon alpha 2b.
Clinical results	• The 77% of the patients were negative to SARS-CoV-2 at 4 days (96 hr) after the administration of the 1st dose of HeberFERON®. • When the product was used on another subset of patients with viral persistence (positive at day 15th by qPCR to SARS-CoV-2) the 75% of the patients were negative to SARS-CoV-2 after the treatment with HeberFERON®. 
Safety profile	No serious adverse reactions were reported after the use of HeberFERON® in more than 100 patients positive to SARS-CoV-2. The most frequent Adverse Drug Reactions (ADR) were mild and moderate fever, general discomfort, arthralgia and muscle pain.
Conclusions	• The potent antiviral activity of HeberFERON® was demonstrated in both subsets population of patients. • Administration of HeberFERON® allows to shorter the response windows against the viral infection.
PATENTS	CU 2005-0213: Patent number 23432 Stabilized pharmaceutical formulations that contain the interferons gamma and alpha in synergistic proportions (2005-11-02).
	US20090304628A1: "Stabilized pharmaceutical formulations that contain the interferons gamma and alpha in synergistic proportions" (2009).
	WO2007/051431A2: Formulaciones estabilizadas que contienen a los interferones gamma y alfa en proporciones potenciadoras (2007).
	CU 2020-0029 Pharmaceutical composition for the treatment of respiratory diseases from viral origin (2020-05-20).
PUBLICACIONES	Bello-Rivero I. et al. (2018) HeberFERON, a new formulation of IFNs with improved pharmacodynamics: Perspective for cancer treatment. Seminars in Oncology 45, pp. 27–33.
ESTADO REGULATORIO	Marketing approval in Cuba.

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V Treatment of respiratory distress caused by cytokine storm in patients positive to SARS-CoV-2

Cytokine storm is a form of systemic inflammatory response featured by the release of a series of cytokines including TNFα, IL-1β, IL-2, IL-6, IFNα, IFNβ, IFNγ, and MCP-1. These cytokines induce immune cells to release a vast number of free radicals that cause hyper inflammation, high fever, excessive leakiness of blood vessels, blood clotting inside the body, extremely low blood pressure, lack of oxygen and excess acidity of the blood, and build-up of fluids in the lungs ("pleural effusion") [4].

White blood cells are misdirected to attack and inflame even healthy tissue, leading to failure of the lungs, heart, liver, intestines, kidneys, and genitals (Multiple Organ Dysfunction Syndrome, MODS) and this may worsen and shutdown the lungs (Acute Respiratory Distress Syndrome, ARDS) due to the formation of a so-called hyaline membrane, composed of debris of proteins and dead cells, lining the lungs, which makes absorption of oxygen difficult [4]. It had been described that most deaths due to COVID-19 are therefore due to respiratory failure.

Immunosuppression is essential in the treatment of cytokine storms, especially in severe and critically ill patients. Corticosteroids and tocilizumab, an anti-IL-6 monoclonal antibody, have been used to treat cytokine storm [5]. Other immunosuppression treatments for cytokine storm include the modulation of T cell-directed immune response; the blockade of IFN-γ, IL-1, and TNF; JAK inhibition [6].

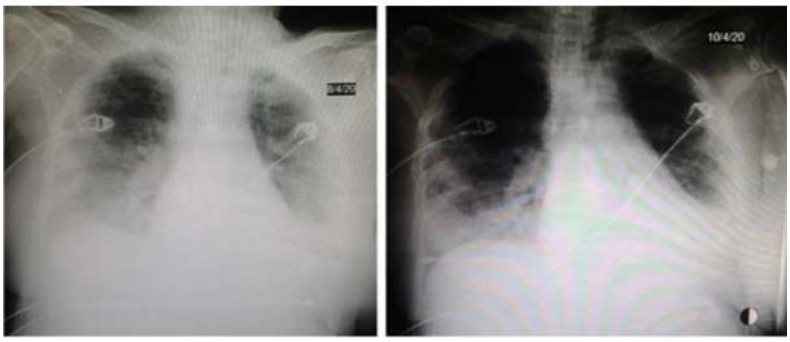
Several published articles report that between 80-90% of SARS-CoV-2 positive patients in severe and critical stages die due to respiratory distress caused by the cytokine storm. Only between 10-20% of patients positive to SARS-CoV-2 survive these stages.

Therefore, reducing the release or activity of pro-inflammatory mediators could prevent or reverse the cytokine storm syndrome, thereby improving the condition of patients. For these purposes two novel BioCubaFarma products were included in the protocols in Cuba for the treatment of respiratory distress caused by cytokine storm on patients positive to SARS-CoV-2.

5.1 Itolizumab (An anti-CD6 humanized monoclonal antibody) reduces circulating levels of IL-6 in severely ill and critically ill patients positive to SARS-CoV-2.

Centro de Inmunología Molecular

PRODUCT	**itolizumab**
	**itolizumab**: itolizumab: is an anti-CD6 humanized monoclonal antibody. CD6 is a membrane glycoprotein expressed primarily in mature, activated T cells. Ligand binding of CD6, increases events such as adhesion, activation, proliferation, differentiation and survival. In addition, CD6 mediates interaction between T cells and antigen-presenting cells, contributing to the maturation of immune synapses [8]. CD6-mediated co-stimulation contributes to the maturation of a Th1 pattern in human T cells and preferentially promotes a pro-inflammatory response characterized by the secretion of TNF-α, IL-6 and interferon [9]. Itolizumab modulates T-lymphocytes activation and proliferation induced by CD6-costimulation. The regulation of downstream pathways results in reduction of IFN-γ, TNFα and IL-6 both in vitro and in vivo.
SCIENTIFIC RATIONALE	Itolizumab effect is associated with the reduction of the production of pro-inflammatory cytokines including IL-6, IFN gamma and TNF alpha. Extremely high concentration of IL-6 is a driving force of cytokine storm, which may cause multiple organ dysfunctions in critically ill patients. Modulation of the cytokine release syndrome (CRS) and the severe inflammatory state in patients positive to SARS-CoV-2 is a very important strategy to limit the severity of the respiratory distress and systemic complications of the patients.
CLINICAL STUDIES (ongoing)	
Patient population	Moderately ill patients with very high risk of developing severe symptoms, severily ill and critical ill patients positive to SARS-CoV-2.
Administered dose	All patients received treatment according to the National Action Protocol for COVID-19 version 1.4 (MINSAP, Cuba). Kaletra (200 Lopinavir - 50 Ritonavir) 2 capsules every 12 h for 30 days, Chloroquine 1 pill every 12 h for 10 days and Interferon alpha 2b and when patients became moderately, severely or critically ill they received a 200 mg dose of itolizumab by i.v infusion every 3 days until improvement of respiratory condition.

Clinical results	When itolizumab was administered at 200 mg dose by i.v infusion every 3 days to more than 80 patients moderately ill, severely ill and critically ill positive to SARS-CoV-2 it had shown to reduce the production of the pro-inflammatory cytokine IL-6 and more than 60% of the patients survived from those stages. **BEFORE** **AFTER**  Infiltrado difuso intersticial-alveolar en ambos campos pulmonares, predominantemente en la base. Mejora radiológica con infiltrado difuso disminuido y radioopacidad en la parte superior de ambos pulmones.
Safety profile	Itolizumab was very safe and did not seem to exacerbate opportunistic secondary infections.
Conclusions	• Itolizumab reduces IL-6 levels in critically and severely ill patients and stabilizes the levels in moderate ill elderly patients. • Sixty (60) percent of the patients are recovered from these severely ill and critically ill stages.
PATENTS	Use of non-depleting anti-CD6 monoclonal antibodies on the treatment of cytokine storm. Application date: April 17th, 2020. Application number: CU 2020-0027.
PUBLICATIONS	Saavedra D. et al. (2020) An Anti-CD6 monoclonal antibody (itolizumab) reduces circulating il-6 in severe COVID-19 patients. Manuscript submitted for publication.
	Filgueira L.M. et al. (2020) Use of an anti-CD6 antibody (itolizumab) for the treatment of COVID-19 patients showing signs of cytokine storm. Manuscript submitted for publication.
REGULATORY STATUS	Marketing approval in Cuba and India.

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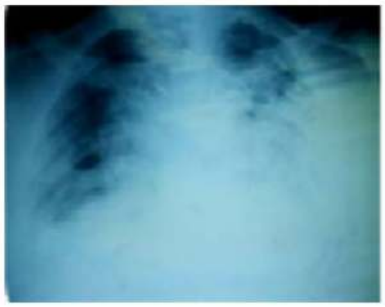
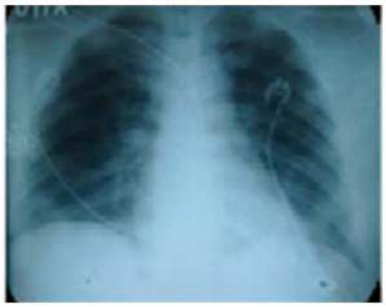
5.2 Jusvinza®: a HSP60-derived immunoregulatory peptide for the treatment of cytokine storms on patients positive to SARS-CoV-2.

CIGB CENTRO DE INGENIERÍA GENÉTICA Y BIOTECNOLOGÍA

PRODUCT	**Jusvinza®**
	**Jusvinza®** (CIGB-258) increases the frequency of regulatory T-cells (Treg) and their suppressive capacity against the antigen responding effector CD4+T cells. Furthermore, this peptide induced a reduction of pro-inflammatory cytokines: TNFα, IL-17 and IFN alpha in preclinical studies.
SCIENTIFIC RATIONALE	HSP60 protein increases its concentration during viral infections and inflammation. Peptides derived from HSP60 may constitute a danger signal that can produce inflammatory physiological responses. However, peptides also derived from HSP60 can induce T cells with regulatory function [10]. Therefore, researchers have assigned to HSP60 a role in regulating the immune response.
CLINICAL STUDIES	Phase I/II LIVE study: Effect and safety of CIGB-258 peptide in the treatment of severely or critically ill COVID-19 patients (ongoing).
General objective	To assess the effect and safety of CIGB-258 peptide administration compared against standard therapy in the treatment of severely or critically ill COVID-19 patients..
Trial design	Open-label, controlled, randomized 2:1.
Patient population	Fifty four (54) patients SARS-CoV-2 positive, 26 patients severely ill and 28 patients critically ill.
Administered dose	All patients received treatment according to the National Action Protocol for COVID-19 version 1.4 (MINSAP, Cuba). Kaletra (200 Lopinavir - 50 Ritonavir) 2 capsules every 12 h for 30 days, Chloroquine 1 pill every 12 h for 10 days and Interferon alpha 2b and when they became severely or critically ill they received Jusvinza® (CIGB-258) at 1 mg i.v injection every 12 hours until improvement of the respiratory condition
Clinical results	The product had been administered to 54 severely ill and critically ill patients positive to SARS-CoV-2. The results had shown that on severely ill patients 92.3% and on critically ill patients 78% improved the respiratory conditions and survived these stages.

Clinical results	**BEFORE**  **Radiografía de tórax antes de la ventilación:** opacidad de ambos hemitórax. **Hemitórax derecho:** aspecto heterogéneo. **Hemitórax izquierdo:** infiltrado perihilar bilateral. **AFTER**  **Radiografía de tórax 48 hr después del tratamiento con Jusvinza:** se aumentó la trama broncovascular. **Relación cardiotorácica (CTR)** en el límite superior normal.
Safety profile	No serious adverse events associated with Jusvinza® (CIGB-258) were reported during therapy or the follow up stage. Before patients were discharged from the hospital they underwent a CT-scan and no lesions associated with fibrotic events were found in their lungs.
Conclusions	• Improvement of the respiratory condition of the patients correlates with a decrease of C-reactive protein (CRP) and interleukin-6 (IL-6) levels. • Ninety two (92) percent of severely ill patients and 78% of critically ill patients recovered from the respiratory distress condition caused by the cytokine syndrome and survived.
PATENT POSITION	Peptides and their derived type -APL of the HSP60 and pharmaceutical compositions. PCT/CU2005/000008.
	Use of an APL peptide for the treatment of inflammatory bowel disease and type 1 diabetes. PCT/CU2009/000009.
	Pharmaceutical composition comprising peptide type APL. PCT/CU2018/050007, WO/2019/129315.
	Péptido para el tratamiento del síndrome de la tormenta de citosinas. Application Date: April 13, 2020. Patent application number: CU 2020-0026.
PUBLICATION	Venegas-Rodríguez R. et al. (2020) CIGB-258 immunomodulatory peptide: a novel promising treatment for critical and severe COVID-19 patients. https://doi.org/10.1101/2020.05.27.20110601.
ESTADO REGULATORIO	Use during conditions of COVID-19 pandemic.

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