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# From Science to Hope: U.S.-Cuba Exchanges and Heberprot-P

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## Abstract

The evolution of scientific knowledge in the United States allowed Cuban researchers to have a significant amount of information at the time of the creation of institutions such as the Center for Genetic Engineering and Biotechnology. Subsequent exchanges between scientists from both countries were essential in the development of the only effective pharmacological treatment to date for severe diabetic foot ulcers. Policy revisions during the Barack Obama administration opened up opportunities to try to bring Heberprot-P to the U.S. market, which is closer to fruition with the Food and Drug Administration's approval of a Phase 3 clinical trial for this product.

***Keywords:*** *scientific exchange, Heberprot-P, biotechnology, diabetes*

## Introduction

On April 30, 2024, phase 3 clinical research for Heberprot-P was authorized in the United States. This fact is relevant since, in more than 25 years, no pharmacological treatment for the healing of complex ulcers has been approved by the regulatory agency of that country, the Food and Drug Administration (FDA)2 (Chen *et al*., 2023). However, beyond technical details, the announcement of that day stands out for being the most recent manifestation of how the evolution of scientific knowledge generated from Cuba and the United States has been able to translate into hope for hundreds of thousands of patients.

The purpose of the present article is to further elaborate this last statement. It is the first effort to record the main events and exchanges that led to the creation of the only option available in the world to date to treat the most severe stages of diabetic foot ulcer.[3]

This effort has combined both the skill and interest of researchers in both countries, as well as the action of various unofficial entities -some created for the purpose of registering the product- that found a space for their cooperative action in the context of the official exchange that took place between Cuban and U.S. health authorities in the period between 2015 and 2017.

These actions also have as a background the more than 150 years of permanent communications that have taken place between the respective academies of sciences and other research entities, which have constituted a unique link in the type of relationship that has been built between the two nations, even in those moments of greatest political tension.

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2 Federal agency of the U.S. government, subordinate to the Department of Health.

3 Diabetic foot is a syndrome manifested at the skin, nerve, circulatory and osteopathic levels. Ulceration is the preterminal stage, prior to amputation.

**Diabetes, lesions and cost**

According to the World Health Organization, diabetes is a chronic disease in which there is insufficient insulin production or response to insulin, resulting in a concentration of glucose in the bloodstream (World Health Organization, 2023). This condition can lead to serious health problems, including heart disease, loss of eyesight, kidney diseases and diabetic foot ulcers.

For decades, effective treatment for severe diabetic foot ulcers has been a major debit in the world of medicine. In the vast majority of cases, the solution to this ailment involves amputation of the affected limb, which starts a countdown that sets the survival of about 50% of patients for a period of no more than five years. Therefore, the search for a solution to diabetic foot ulcers involves a deeper debate than the patient's possibility of preserving a limb or not, or of suffering discrimination or psychological damage associated with his new condition. These realities, aside from being true, omit a greater repercussion: the action of amputating not only has the potential to minimize the patient's quality of life, but can ostensibly decrease his or her life expectancy.

Alarmingly, nearly half of the patients who suffer a lower limb amputation caused by a diabetic foot ulcer do not survive beyond five years. Among U.S. veterans, the prognosis is even grimmer, as survival beyond two years is uncommon in patients that develop gangrene. Of particular concern is the disproportionate impact in African-American communities, where Medicare beneficiaries are nearly twice as likely to suffer a lower limb amputation within one year of DFU diagnosis compared to their non-Hispanic white counterparts. Innovative therapeutic options for severe diabetic foot ulcers are not only needed, but long overdue for patients (Zelen, 2024).

Currently, this debt has been settled with the appearance of Heberprot-P, a product that allows the healing of severe lesions caused by diabetes. However, this has not eliminated amputation as a recurrent global response. One of the causes lies in the difficulties associated with the regulations that hinder the entry into national markets of a promising product, but made in a country subject to sanctions by the United States and isolated from the dynamics of the large pharmaceutical corporations of the first world.

Diabetes is the eighth leading cause of death in the United States, and the number of adults diagnosed with diabetes is currently more than twice as high as it was two decades ago. It is also the leading cause of lower limb amputation, kidney failure, and blindness in adults (Centers for Disease Control and Prevention, 2024).

According to the Centers for Disease Control and Prevention, more than 38 million Americans of all ages have diabetes, 97 million adults have pre-diabetes - 1 in 3 adults - and there has been an increase in its incidence in children, both type 1 and type 2. According to the institution's statistics, in 2020 there were nearly 8 million hospital discharges associated with diabetes, of which 160 000 resulted in amputation of a lower limb, a figure similar to that of the previous year (Centers for Disease Control and Prevention, 2024).

The average annual expenditure for the treatment of diabetes is $12 022 per patient, so medical costs for people with diabetes are approximately 2.6 times higher than for people without the disease (Parker et al., 2024). The options available in the United States for patients with diabetic foot ulcers range from topical dressings and medications, from saline solutions to growth factors. However, the capacity for action of these resources is usually limited to less severe ulcers, i.e., those corresponding to grades 1 and 2 on the Wagner scale.[4] Therefore, patients with lesions corresponding to grades 3 and 4 see their options largely limited to amputation of the limb where the ulcer occurs.

The appearance of the article "Epidermal growth factor intralesional infiltrations can prevent amputation in patients with advanced diabetic foot wounds" (Berlanga Acosta et al., 2006) opened a new window in the global science for the treatment of severe diabetic foot ulcers. The text documents the results of a pilot study conducted on a heterogeneous group of 29 patients with grade 3 and 4 ulcers —severe and at high risk of amputation—,

4 A classification system widely accepted by the scientific community to evaluate diabetic foot ulcers. It covers 6 stages ranging from grade 0 —no skin damage— to grade 5 —extensive gangrene—.

with no additional therapeutic options. The treatment was applied between April 2001 and September 2002, with the aim of testing the effectiveness of this novel procedure in preventing amputation, and in the 17 cases that completed the 24 programmed sessions it was possible to prevent amputation. This was the first clinical evaluation of growth factor infiltration in critical and extensive diabetic lesions in the lower limbs.

The great contribution of Cuban science, as will be explained henceforth, was to observe the favorable effect of the topical use of the Epidermal Growth Factor in the healing process and to achieve greater effectiveness when administered in deeper layers of the wounds. Therefore, by injecting the Epidermal Growth Factor directly into the lesion, the active agent can penetrate into the desired areas, without the upper layers of the wound impeding its action (Berlanga Acosta *et al*., 2006).

**From EGF to Heberprot-P**

One of the strongest lines of research in the United States, fundamentally in basic science, is related to healing, tissue repair and regeneration of tissues and organs. To cite an outstanding example, the discovery and development of most of the growth factors5 has occurred in that country, which led among other milestones, to the Nobel Prize in Medicine or Physiology in 1986, shared between Stanley Cohen and Rita Levi-Montalcini for the discovery of Epidermal Growth Factor and Nerve Growth Factor, respectively.

Cohen and Levi-Montalcini had worked together under the tutelage of Professor Viktor Hamburger at the University of Washington. Hamburger was the first to somehow predict the existence of proteins that dictated to cells what their spatial distribution would be and what they should specialize in. Altogether, these scientists discovered a factor that made neurons grow in culture, which was associated with an ingredient present in saliva.

While researching this ingredient, Cohen had the idea of injecting a crude extract of salivary glands from adult mice into newborn mice, looking for nervous system development. The injected mice had an opening of the eyelids and a budding of the dentition 5 to 7 days earlier than the natural occurrence, so that the crude extract had triggered an accelerated maturation of epithelial structures. Consequently, the first name given to Epidermal Growth Factor was Eyelid-Tooth Factor.

This sequence of studies led to the discovery of a large family of growth factors, Platelet-derived growth factors (PDGF), discovered by a pathologist named Russell Ross. These PDGFs were found in conditioned media of transformed cells, i.e. malignant cells, because they constitute endocrine mechanisms of defense and, at the same time, of proliferation of malignant cells. In other words, these PDGFs, although they contribute to tissue repair, unfortunately also allow resistance to chemotherapy or radiotherapy.

When in the 1960s Cohen first noticed this effect on the skin, he prepared an eye drop with a saturate of mouse salivary glands, to which he added the aforementioned crude extract, to treat burns on the cornea of rabbits. As a result, he showed that these ulcers healed much faster, a conclusion that became the cornerstone of future research. The first clinical trial based on this discovery occurred in 1989, in burn patients, for which a semi-solid cream was prepared with the aim of accelerating the repair of the skin in the affected areas.

In the 1970s, intensive work began on smart dressings, first developed by Massachusetts General Hospital burn ward Principal, John Burke, from bovine collagen. This was probably the first dressing of biological origin to be used on burn patients. In addition, when the stem cell phenomenon was discovered, several institutes dedicated to regenerative medicine were created in the United States, where intensive work has been done on the reprogramming of these cells to achieve a prospective phenotype desired by the researcher for different structures of the organism, be they bone, adipose tissue, cartilage or other

This summary allows us to affirm that when the Center for Genetic Engineering and Biotechnology (CIGB) was created in Cuba in 1986 for research, development, production and commercialization of innovative products, there was an extraordinary amount of information from the United States on growth and healing factors, which

5 Growth factors set the guidelines for cellular and spatial repair of damaged peripheral or internal tissues in a given space and time.

allowed Cuba to become the second country in the world to obtain a recombinant human epidermal growth factor (rhEGF)6 in 1989.

After joining the CIGB in 1991, Professor Jorge Berlanga was entrusted with the study of Epidermal Growth Factor and scarring, at the request of Dr. Pedro Lopez-Saura, who was influenced by Irwin Kelman Cohen and Gregory "Greg" Schultz. Kelman Cohen was a reconstructive surgeon, founder of the American Wound Healing Society. Schultz was a biochemist, president of that institution, who anticipated that chronic wounds secrete chemicals -proteases- that degrade growth factors, both those produced by the organism and those applied exogenously. He was the person who first spoke of biofilm, a layer of bacteria and pathogens that create a symbiotic community among themselves and lead to the wound becoming chronic, which can lead to stagnation of healing.

A fortunate reaction to all this accumulation of knowledge that had been generated in the last decades was Dr. Berlanga's decision to establish contact, via manuscript messages, with several researchers based in the United States. An important impulse to this effort, which combines, without ignoring the institutional and the individual, was the scholarship granted to the Cuban researcher in the scarring laboratory attached to the Burn Unit of the University Hospital of Alberta, Canada, between 1994 and 1995. This experience brought him in contact with advanced research on the biochemistry of the skin and scar in a profound way. It also set the stage for his participation in the 57th North American Plastic Surgeons Meeting and increased his connections, with the valuable support of his mentor, Edward Tredget.

Tredget, in turn, was close to Anita Roberts, one of the discoverers of the Transforming Growth Factor-β (TGF-β) in the 1980s, who also actively sponsored the laboratory where the Cuban scientist fulfilled his scholarship.

Subsequently, with new knowledge and inputs, Cuban scientists initiated a series of experiments that led to the demonstration that controlled and sterile acute wound fluid was capable of degrading a chemical sequence analogous to Epidermal Growth Factor. In successive studies, a repeated finding was associated with the occurrence of topical adversities. To this was added an article published by the scientists of the University of Queensland, Sheree E. Cross and Michael S. Roberts, according to which, when applying a growth factor on the surface of a wound, the diffusion of the product in the deep parts of the wound is practically nil. In the eyes of the Cuban scientist, such conclusions weakened the prospects of achieving an effective topical treatment for deep lesions (Cross & Roberts, 1999).

For his part, Kelman Cohen published in Plastic Reconstructive Surgery a clinical study he had performed on 17 healthy human volunteers, young people with two groin wounds, one of which was treated with silver sulfadiazine and the other with a combination of silver sulfadiazine and epidermal growth factor. The result was that there was no difference (Cohen *et al.*, 1995).

The concerns from Cuba about the topical application of epidermal growth factor and Kelman Cohen's discovery, which were relatively close in time, had important and disparate consequences for research on diabetic foot ulcer healing in both countries.

On the other hand, Cuban scientists accessed a study by researchers in England based on injections of Epidermal Growth Factor to patients with necrotizing enterocolitis (Sullivan *et al.*, 1991). This disease occurs in preterm newborns and manifests as necrosis of the intestine. To preserve the life of the infant in the most severe cases, an extensive portion of this organ may be removed. The risk of mortality is high for people with short bowel syndrome, as it is known in medicine, because they are deprived of the larger part of an organ that performs four functions at the same time and is characterized by a complex cellular specialization.

The article focused on the case of an eight-month-old infant with severe necrotizing enterocolitis, in whom a recombinant human epidermal growth factor was tested intravenously with parental consent. The procedure

6 The term recombinant refers to the fact that it is obtained in a laboratory by genetic engineering methods, and not by natural means, which allows the product to be developed on an industrial scale.

restored the patient's intestinal function and constituted a remarkable contribution to the application of epidermal growth factor, apart from topical, burn and healing applications.

Motivated by this discovery, Cuban scientists created a parenteral Epidermal Growth Factor[7] project in the then Division of Clinical and Preclinical Trials of the CIGB. This gave rise to the idea of replacing the topical application of Epidermal Growth Factor with an injectable variant.

While the English scientists had restricted their studies to the digestive tract, a series of experiments at CIGB focused on the sciatic nerve of rats demonstrated the protective anti-necrogenic effect of Epidermal Growth Factor injection outside the gastrointestinal system. The Cuban scientists had ventured for the first time into the peripheral soft tissues of a limb.

The experiments that followed this finding sought to prove whether the injection of Epidermal Growth Factor was really capable of preventing tissue death. Initially, they focused on ischemia in several organs and accumulated evidence. Subsequently, Dr. Berlanga was awarded a fellowship at what is now the Institute of Cancer Research in London, an experience that gave a definitive boost to the understanding of the biological potency of Epidermal Growth Factor injection and the fact that its pharmacological properties were much broader than when applied superficially.

Promising results led CIGB's director, Dr. Luis Herrera, to create a task force and begin clinical studies. In 2003, Stanley and Kelman Cohen were invited to Cuba to participate in the Cuban symposium on healing named Biotechnology Havana. Curiously, a letter of request had to be sent to U.S. President George W. Bush to authorize the scientists' participation in the event. On that occasion, the researchers were able to exchange on the particularities of Stanley Cohen's discovery, information that is not usually published and that appears in this article.

Two years later, in 2005, Dr. Berlanga was invited by Professors Kelman Cohen and Greg Schultz, at that time president of the American Healing Society, to present in the United States the first results of Cytoprot-P, the first name under which Heberprot-P was known. The conference was attended by Stanley Cohen and was introduced by Schultz, who praised the results achieved by Cuban scientists.

After the event, Dr. Berlanga went to Richmond, Virginia, where Professor Kelman Cohen resided. On that occasion he was able to meet Dr. Peter Sheehan, diabetes expert and director of New York Foot and Ankle Hospital, who unfortunately passed away unexpectedly in 2014 and important shared aspirations were cut short.

The first International Congress for the Control of Diabetes and its Complications was held in Cuba in 2010. It was attended by six U.S. scientists. Only six years later, the number had risen to 51, a sign of the interest in research in Cuba and the facilities resulting from the reestablishment of diplomatic relations between the two countries (Whitefield, 2018).

Kelman Cohen had mentioned the virtues and potential of Cuban research to Dr. David Armstrong, a world leader in the treatment of diabetic foot ulcers. Armstrong visited Cuba in 2012 to participate in an event organized by the CIGB, as part of a delegation, which was a remarkable endorsement of the project. In Armstrong's own words:

> The cost of treating severe diabetic wounds is more expensive than that of the five major cancers in the United States. There is a huge disconnect between the public health need and the pharmacological approach in the United States. Our ability to partner with colleagues in Cuba and bring this drug into clinical trials in our country is potentially important in our ability to heal wounds and improve lives, worldwide (Ruiz-McGill, 2016).

The bases on which the success of Injectable Growth Factor to treat diabetic foot ulcers has been built are, firstly, to avoid degradation; secondly, to overcome the biofilm discovered by Schultz; and thirdly, to take the treatment to the wound planes where the responder cells are really located. In other words, the evolution of

7 Term that refers to that which is introduced into the organism by a route other than the digestive tract, such as intravenous, subcutaneous or intramuscular.

studies at a global level, but fundamentally in the United States and Cuba, added to the expertise of researchers on the Island, made it possible to delve deeper into the lesion until finding a greater density of receptors for the growth factor. This contribution has not been fortuitous and is extensively documented.

The novelty is not the product to be applied, since growth factors were already widespread in the global market. In the words of Kelman Cohen: "What the Cubans have done now is very clever. Instead of simply pouring it into the wound, they have injected it into the healthy margins of the wound, thus allowing it to initiate the healing of the wound before it is destroyed" (Murray, 2006), to which he added 'Cuba has very advanced ideas and we are not taking advantage of them', in reference to the impediment posed by political issues to the bilateral development of science.

A decade later, Professor Armstrong insisted on this topic, "It shatters me to know that there may be something out there that has the potential to save limbs and we don't have the opportunity to test it thoroughly because of political rather than public health issues" (Lenzer, 2016).

To mention an example, Cuban scientists face limitations to publish the results of their studies in specialized U.S. journals, which prevents their insertion in certain platforms that constitute global references for the study of diabetes. Fortunately, there are articles in which renowned Cuban and American scientists have jointly participated, such as "Glucose toxic effects on granulation tissue productive cells: the diabetics' impaired healing" (Berlanga-Acosta *et al*., 2013) and "Chronic Wounds with Emphasis in Diabetic Foot Ulcers", both in BioMed Research International (Berlanga-Acosta, *et al*., 2014); as well as "Expression of cell proliferation cycle negative regulators in fibroblasts of an ischemic diabetic foot ulcer. A clinical case report" (Berlanga-Acosta *et al*., 2012) and "Healing enhancement of diabetic wounds by locally infiltrated epidermal growth factor is associated with systemic oxidative stress reduction" (García Ojalvo *et al*., 2017), in the International Wound Journal.

**Heberprot-P in the United States**

For more than 60 almost uninterrupted years, the hostile nature of bilateral relations between the United States and Cuba has imposed limitations on cooperation in areas of common interest, from which the field of biotechnology has not been exempt. Nevertheless, there have been exceptions that continue to motivate the potential for collaboration between the two countries.

One of them was the signing of the Memorandum of Understanding between the Ministry of Public Health of Cuba and the Department of Health and Human Services of the United States in health matters, on June 13, 2016 (Minsap-HHS, 2016). The text declares the intention of both institutions, in line with the expressed will of then Presidents Raúl Castro and Barack Obama, to strengthen collaboration in scientific and health areas. Among these were listed non-communicable diseases such as diabetes, as well as biomedical research and development, clinical trials and regulation of medical products.

Related to this milestone, mention should also be made of the visit to Washington D.C. that same year of the then Cuban Minister of Public Health, Dr. Roberto Morales Ojeda, who headed a delegation of specialists in areas such as cancer, tropical diseases, neurology and cardiovascular diseases, who held productive conversations with senior executives of the U.S. National Institutes of Health. As part of the program, officials from the FDA and the Cuban counterpart CECMED initiated a dialogue that was to favor mutual knowledge of their respective work systems. On that occasion, Dr. Morales received recognition from the Pan American Health Organization as the first country on the continent capable of preventing mother-to-child transmission of HIV and syphilis.

Four months later, on October 17, the Presidential Policy Directive on Relations with Cuba (DPP-43) went into effect. This document authorized, on the basis of a general license from the Office of Foreign Assets Control (OFAC)8, joint commercial and non-commercial medical research between individuals and entities of both countries, as well as research, clinical trials, marketing and distribution of Cuban biopharmaceutical products,

8 Unit of the U.S. Department of the Treasury. It is in charge of the Cuban Assets Control Regulations (CACR).

which were previously approved by the FDA. Additionally, the Treasury Department granted licenses for clinical trials of specific Cuban drugs (González Gómez, 2023).

Thus, in addition to the interest in exchanging knowledge that existed within the scientific community in Cuba and the United States, there was also the political will of the government to channel it.

After three years of negotiations, in 2018 the Cuban company Heber Biotec, belonging to BioCubaFarma, and the U.S. company Mercurio Biotec agreed to work together to introduce Heberprot-P in the U.S. market (Alcalde & Barsotti, n.d.). Likewise, OFAC authorized Mercurio Biotec to enter into agreements with CIGB to secure the necessary procedures to import Heberprot-P for the purpose of conducting clinical trials (Granma, 2018).

This effort was cut short, but was an important precedent to what is now CIGB's agreement with U.S.-based Discovery Therapeutics Caribe (DTC), based in Cleveland, Ohio. In early 2024, DTC submitted an Investigational New Drug (IND) application to the FDA, which included a Phase 3 protocol for a randomized, double-blind, placebo-controlled trial of Heberprot-P for Wagner scale grade 3 and 4 diabetic foot ulcers. On April 10, the company received a clearance letter from the FDA to proceed with the proposal. This would be the first time that the Cuban product will be studied for use in U.S. patients with diabetic foot ulcers. According to David Armstrong: "This trial represents an encouraging potential to change the current paradigm and provide new hope to those who desperately need it" (Armstrong, 2024).

With this step, hope has resurfaced among scientists, patients, relatives and specialists on both sides of the Straits of Florida, that new avenues will open up to achieve the goal that we should all be striving for: the improvement of the quality of life of human beings. It remains in the hands of officials and politicians the possibility of turning the project into reality.

**Conclusions**

The experience of the long road travelled between the discovery of Epidermal Growth Factor and the authorization for clinical trials of Heberprot-P in the United States reinforces the need to promote and preserve scientific exchanges between the two countries regardless of the dynamics associated with bilateral political relations.

It is not possible to write the history of Heberprot-P without mentioning the remarkable contributions of scientists in the United States and the exchanges between researchers based in both countries, as well as the fluent personal and institutional communication that has been maintained over the years, expressed in visits, participation in events and joint publications.

The existing connections between the scientific communities of both countries for the treatment of diabetic foot ulcers got a remarkable boost with the policy revisions that occurred in the last years of the Barack Obama administration. Without them, efforts such as those of Mercurio Biotec and Discovery Therapeutics Caribe would not have been possible.

The commercial vision associated with the biopharmaceutical industry in the United States was a brake on the development of effective products for the treatment of advanced diabetic foot ulcers. This reality, added to the high and growing rates of diabetes in that country, creates a propitious space for bilateral collaboration, which would be greatly favored with the lifting of restrictions that affect the free exchange of knowledge. In this sense, the approval of the Phase 3 clinical trial for Heberprot-P shortens the gap that currently exists between serious patients and their hopes of not resorting to amputation.

The present text may be useful for the purpose of transmitting accurate information that will enable both specialists and decision-makers to have the most appropriate alternatives available, both for dealing with this disease and for establishing more stable exchange mechanisms that will make joint progress possible in the fight against other diseases. The analysis of the potential impact that this possible bilateral cooperation would have in relation to third countries, which are not even in a position to propose the appropriation of this knowledge, remains the objective of another publication.

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