

Heberprot-P®: an idea turned into a product

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ABSTRACT

Diabetes mellitus has become a significant health problem throughout the world, where it constitutes the underlying cause for 84% of lower limb amputations due to recalcitrant ulcers. The Center for Genetic Engineering and Biotechnology (CIGB) at Havana, Cuba has designed an integrated strategy for preclinical testing, pharmaceutical development, production, clinical trials and business negotiations of an injectable drug for treating diabetic foot ulcers, denominated Heberprot-P®. This product, which uses epidermal growth factor as active ingredient and avoids these amputations, is the only registered drug of its type and has already had considerable medical, social and economic impact in Cuba and other nations, placing national science and the Cuban health system at the forefront of the fight against this disorder. Phase III trials are planned for 2013, pending approval of the Advisory Scientific Council of the European Medicines Agency (EMA), for examining its efficacy and safety in this continent. Research teams at CIGB continue to develop new Heberprot-P® versions, based on advanced controlled release systems employing micro and nanospheres, in order to continuously improve the product and extend its existing intellectual property coverage beyond the year 2030.

Keywords: Heberprot-P, pharmaceutical development, epidermal growth factor, infiltration, diabetes mellitus, diabetic foot ulcer, amputation

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RESUMEN

Heberprot-P®: una idea convertida en producto. La diabetes mellitus es un preocupante problema de salud que aporta el 84% de las amputaciones de los miembros inferiores por úlceras en el mundo. El Centro de Ingeniería Genética y Biotecnología (CIGB) de Cuba diseñó una estrategia de ensayos preclínicos, desarrollo farmacéutico, productivo, ensayos clínicos y negocios de un medicamento inyectable para el tratamiento de las úlceras del pie diabético. Heberprot-P® es el único fármaco registrado a escala mundial, cuyas propiedades terapéuticas, modo de aplicación y nicho de indicación han ejercido un extraordinario impacto médico, social y económico en Cuba y otros países. Su principio farmacéutico activo es el factor de crecimiento epidérmico. Está situando a la ciencia cubana y a su sistema de salud a la vanguardia internacional en el tratamiento de esa afección y evitar las amputaciones. En 2013, se prevén estudios clínicos fase III, luego del visto bueno del Comité Científico Asesor de la Agencia Europea de Medicamentos (EMA), para demostrar su eficacia y seguridad. Un equipo de investigadores del CIGB sigue trabajando en las nuevas generaciones de Heberprot-P®, basadas en novedosos sistemas para su liberación controlada en microesferas y nanoesferas, que permitan mejoras y optimización continuas, y prorroguen su patente más allá del año 2030.

Palabras clave: Heberprot-P, desarrollo farmacéutico, factor de crecimiento epidérmico, infiltración, diabetes mellitus, úlcera del pie diabético, amputación

Introduction

In 1992, Commander-in-Chief Fidel Castro Ruz, leader of our Revolution and driving force behind the birth and subsequent development of Cuban biotechnology, stated: “[...] from the time when we heard about interferon to the time we produced interferon [...] not even four months had gone by, and we were already producing interferon in Cuba in 1981” [1].

The unwavering dedication of our scientists combined with the political will of our government and massive investments into the biotechnological industry, together with a strategy based on closed-cycle institutions that take promising products with significant public health potential through the research and development stages to production and marketing, have characterized the rapid pace of Cuban biotechnological development. For over 26 years, the Center for Genetic Engineering and Biotechnology (CIGB) has operated as the flagship of a network of closely collaborating scientific centers that also works in coordination with the National Health System, meeting by and large the expectations of their founders, as

expressed by Commander in Chief Fidel Castro during the inaugural ceremony of one of its most genuine examples, the Center for Molecular Immunology, on December 5, 1994:

“[...] there are not many centers like this in the world. [...] and there is something I am sure nobody in the world can top, and that is the quality of the men and women who will work, or already work, in this center [...]. It is a matter of pride, right in the middle of this special period [economic crisis], to inaugurate this center. This is no luxury, but a promise of health and wellbeing for our people, a promise of future pay-offs for our economy, as it has [...] significant production capacities and can coordinate its work with other research institutions” [2].

Products manufactured by the Center for Genetic Engineering and Biotechnology (CIGB) are used in the diagnosis, prevention and treatment of 26 separate diseases in Cuba. Some conspicuous examples are those of the recombinant vaccine against chronic hepatitis B virus infections, the conjugated vaccine

against type b *Haemophilus influenzae*, the pentavalent vaccine, recombinant alfa and gamma interferons, and recombinant streptokinase and granulocyte colony-stimulating factor.

Thanks to the introduction of the hepatitis B vaccine through the National Health System, there have been no cases of this disorder in our country among children younger than 5 years since 1999 and among children younger than 15 years since 2007, and the number of hepatitis B cases among adults has decreased by 95% since 1991. This vaccine, therefore, has played a pivotal role in controlling and eliminating the circulation of this virus in Cuba and reducing the number of deaths due to liver cancer, among other benefits.

However, important as it is to develop these products while securing intellectual property rights and publishing their results in high-impact scientific journals, these activities take a second seat to the goal of improving the health standards of people from Cuba and other countries.

Diabetes mellitus has become a formidable public health problem, due to the existence of complications for which existing therapeutic alternatives are not entirely satisfactory. According to current estimates, there are 300 million diabetic patients worldwide; and the incidence of diabetes is increasing at such a rate that this figure may well double within the next few years, ultimately surpassing the death toll of well-known killer diseases such as AIDS. Diabetes is the only non-infectious disease currently considered to be a global pandemic, and is the causal agent behind 84% of lower limb amputations throughout the world.

According to international reports, from 15 to 20% of diabetic patients will suffer a lower limb ulcer at some point in their lives, of which 10 to 25% will eventually endure an amputation. According to high-profile scientific journals such as *Diabetes Care*, a lower limb amputation caused by diabetes takes places every 30 seconds at some health institution in the world. Close to 50% of first-time amputees will suffer a second amputation in the contralateral limb within a period of 2 to 5 years, considerably deteriorating their quality of life and imposing a heavy financial burden on national health systems. To make matters worse, less than 50% of patients undergoing a major amputation survive the next 5 years, a situation that is not circumscribed to developing countries, as wealthy nations such as the United States have over 22 million diabetic patients of which from 80 000 to 120 000 suffer an amputation every year. The number of diabetic patients in Cuba is close to half a million, of which approximately 15 000 suffer diabetic foot ulcers (DFU). According to current estimates there are over a million diabetic patients in the Bolivarian Republic of Venezuela, although the number of patients with ulcers or disabilities caused by ulcers is larger.

From idea to product

During the decade of 1990, the scientific findings of a research group led by Dr. Jorge Berlanga at CIGB provided the foundation for a strategy designed and implemented by a multidisciplinary team of researchers, technicians and businessmen who combined pre-clinical testing, pharmaceutical development, clinical

trials and their business acumen to bring a new product to market: Heberprot-P®, code-named CIGB428 during its research and preclinical development stages and branded as Citoprot-P® during clinical trials. Developed and manufactured at CIGB together with specialists from the National Institute of Angiology and Vascular Surgery (INACV) and other Cuban medical institutions under the leadership of Dr. José Fernández Montequín, Heberprot-P® is an injectable drug for treating diabetic foot ulcers (DFU) of difficult cicatrization that are recalcitrant to conventional treatment options. Its active pharmaceutical ingredient is epidermal growth factor, formerly marketed elsewhere for the treatment of burns without much success.

The strategy for developing and later launching Heberprot-P® into national and international markets was designed by a multidisciplinary team directed from CIGB's General Management unit, and included negotiations for its registration, introduction and sale into traditional markets of the Heber Biotec S.A. company. It also comprised the parallel implementation of joint early stage business development agreements in developed countries, taking special care to ensure that short-term commercial deals did not hinder medium- and long-term global product development strategies.

This strategy is supported by a production system designed by CIGB and Heber Biotec S.A., which meets the high quality standards of modern Good Manufacturing Practice while ensuring that productive capacities meet the projected domestic and international product demand.

Patents for Heberprot-P® have been awarded in USA, Europe, Japan, Canada, Australia, Hong Kong, Singapore, South Korea, South Africa, Russia, China, India, Indonesia, Ukraine, Mexico, Malaysia, Argentina and Cuba, thanks to the discovery that this drug can be injected into the deep planes and the edges of diabetic foot ulcers. In addition, patent applications for this product are pending in Brazil, Thailand and Chile.

After over 15 years, Heberprot-P® remains the only registered drug worldwide providing an effective treatment to DFU. Its therapeutic properties, mode of application and indication offer a solution to a medical need that has remained unmet. This product places Cuban science and our health system on the forefront of therapy for this disorder.

Accolades earned by Heberprot-P® include the prize awarded by the World Intellectual Property Organization (WIPO) to Dr. Jorge Berlanga Acosta as Best Young Inventor, a gold medal from WIPO to the best invention, awarded for "Use of the pharmaceutical composition containing epidermal growth factor (EGF) for the prevention of diabetic foot amputations: Heberprot-P®", and the prize of the Cuban Intellectual Property Organization (OCPI) to creativity and technological innovation, both in 2011. These awards underscore the value of a product that is already registered in 17 countries and has spurred strategic negotiation and marketing actions to be conducted in over 50 countries until the year 2015.

During Havana's International Trade Fair of November 2010, Heberprot-P® was awarded the special prize to the innovating product of highest commercial dynamics. Heberprot-P® has become the flagship

product of Cuban biotechnology, and is expected to bring significant short, medium and long-term dividends to our economy.

The clinical efficacy of this product is supported by a large body of experimental data [3-10]. Product safety and efficacy has been proven not only by scientific experimentation, but by routine clinical use in over 85 000 patients.

Phase III clinical trials provide definitive evidence for product efficacy and safety, and are widely acknowledged to represent a major stumbling block during the development of pharmaceuticals. These trials are required to meet stringent international Good Clinical Practice standards and are usually performed in a triple-blinded fashion; that is, neither the subjects, the physicians, nor the sponsoring institution know which volunteer is receiving the test compound or the placebo until the last patient has been recruited and treated. Importantly, a new phase III trial for Heberprot-P® –currently in its preliminary stages– is planned for 2013 at the European Union. This trial, which represents an important milestone for the international marketing of this product, is currently waiting for approval from the Advisory Scientific Committee of the European Medicines Agency (EMA), and will involve close to 100 hospitals from 11 European countries, therefore becoming one of the largest trials ever performed for this medical indication, according to continental opinion leaders.

Worldwide awareness of the scientific results, clinical impact and international publications related to the development of Heberprot-P® has been gaining momentum. For instance, BioMedLib™, a search engine providing the most accurate records from millions of biomedical articles at the Medline® database of the National Library of Medicine [11], ranked the paper from Acosta JB *et al.* entitled “The pro-inflammatory environment in recalcitrant diabetic foot wounds” [6] at the tenth position in the specialized literature.

Another significant example was the designation as invited editors of Dr. Jorge Berlanga Acosta and Dr. Luis Herrera Martínez (CEO at CIGB) on May 18, 2012 by the peer-reviewed, open-access *Journal of Biomedicine and Biotechnology*, together with Drs. David G. Armstrong and Gregory Schultz, widely acknowledged leaders of this field.

The authorization granted on April, 2006 by the Cuban State Center for Drug Control for including Heberprot-P® among the basic set of medicines provided by the Ministry of Public Health (Minsap) prompted the implementation of an action plan for its introduction into the National Health System, on June 20, 2007. This plan included:

- Introducing the product into the integrated health care scheme for DFU patients in the angiology and vascular surgery services of all major Cuban hospitals (secondary health care), under the leadership of the respective heads of service.

- Organizing national workshops with the participation of heads of angiology and vascular surgery services together with the main specialists involved in Heberprot-P® development and clinical testing.

- Reaching a consensus on new treatment alternatives for DFU patients with this technology and updating accordingly the existing protocols for the

integrated attention and medical care of this patient population.

- Preparation, in close collaboration with the graduate education unit of Minsap, of training and educational activities on Heberprot-P® such as conferences, diplomas and both introductory and advanced courses, with the objective of facilitating the adoption of this product within the National Health System. Implementation of this program in other countries [12].

- Extension of the use of Heberprot-P® to the primary health care level, developing specific criteria for the identification of prospective patients (use of this drug type at the primary care level has never been attempted before in Cuba or elsewhere).

Introduction of Heberprot-P® at the primary care level was accomplished through integrated diabetic patient consultations at polyclinics, applying a preventive policy focused on controlling and reducing the originating disorder (diabetes) in order to decrease the incidence of DFU. This policy has enabled the implementation of an effective early, first-line therapeutic protocol that reduces the frequency of complex ulcers with a high risk of amputation, decreasing consequently the number of patients bearing these ulcers that are transferred to secondary health care institutions.

Five years after its introduction into the National Health System, over 15 000 Cuban DFU patients have benefitted from Heberprot-P®. The product has had a significant medical, social and economic impact, achieving a greater than 4.4-fold reduction in major amputations, reducing the recovery (granulation and cicatrization) period of complex DFU from 52 to 14 weeks and shortening hospital stays from 30 to 15 days in average, thereby contributing to the reincorporation of patients to productive life.

Under the direction of Minsap, Heberprot-P® is used today in Cuba by 43 hospitals, and plans exist to extend its use to at least one polyclinic for every municipality in the country.

The Cuban experience is also proving fruitful in the Bolivarian Republic of Venezuela, where a national health program, inspired by the humanitarian ideals championed by Commander President Hugo Rafael Chávez Frías and directed by the Ministry of People's Power for Health (MPPS) is currently being implemented. Development of this program was first agreed by both parties on May 2, 2008, and the first patient had already been treated by August of that same year.

According to Venezuelan experts, close to 70% of patients arriving to Venezuelan hospitals with complex diabetic foot ulcers would ultimately suffer major amputations before the implementation of this program. Currently, a total of over 70 000 Venezuelans from 15 states of this nation have received Heberprot-P® under the integrated program for the care of diabetic patients, and the available reports set the amputation rate at only 5% in this population. The product has, therefore, had an extraordinarily significant medical, social and economic impact in this nation as well.

Key elements behind the success of this program both in Cuba and Venezuela include:

- The political will of both governments, who spare no effort, economic or otherwise, to provide adequate health care for their citizens.

- The existence of national health systems, directed by Minsap and the MPSS in Cuba and Venezuela, respectively.

- The existence of specific national programs for this disorder structured into specialized units and services.

- The integration of Cuban angiology specialists and vascular surgeons, as well as specialists in nursery, podiatry and general medicine.

- The implementation of intensive training programs for secondary health care personnel, as well as their extension to primary health care practitioners.

- The recruitment of health promoters, known as *heberpropistas*, who have proven essential in the correct and timely organization, promotion and control of all program activities.

The considerable efforts devoted to ensuring that Heberprot-P® reaches every potential patient through

the implementation of integrated health programs organized into systems providing specialized care to DFU cases is, precisely, one of the most innovative aspects of this plan and one of its most challenging tasks. Currently, research teams from the Biomedical Research and the Product Development units of CIGB are working intensely on newer Heberprot-P® versions based on advanced controlled-release systems using micro and nanospheres, in order to continuously improve the product and extend its existing intellectual property coverage beyond the year 2030.

Not surprisingly, reluctance to change existing therapies upon the arrival of new technologies has become one of the most significant challenges during the introduction of Heberprot-P® in Cuba and abroad. In this scenario, Heberprot-P® has become, indeed, a paradigm-shifting milestone in the treatment and surgical approach to diabetic foot ulcers.

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