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# Development of Cuban biotechnology

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#### **Abstract**

The emergence and expansion of biotechnology in Cuba as a new branch of the economy provide a good example of the challenges faced by a high-technology sector which deserves analysis. There are already clearly visible results in this sector such as investment in the research and production infrastructure, a qualified workforce, high-quality research and good product pipelines in the Cuban health system coupled with a growing export capacity, supporting a positive cash flow. These advances have been aided by the integration of research-production organisations, state funding, social ownership, export orientation and the comprehensive integration of the Cuban biotechnology multi-institutional system. In the forthcoming years, the future development of this sector in Cuba should produce a more evident impact on the economy and Cuban society.

#### INTRODUCTION

Cuba is a small country with limited resources, but it has an almost 100 per cent literacy rate. This green island is like a huge school with 2.3 million students in the whole educational system, 58 university centres, more than 12,000 scientists, 15 per cent of them PhDs, with more than 30,000 workers involved in research activities. Last year, Cuba reached impressive rates of infant mortality (6.2 per 1,000 live births) and life expectancy (75 years on average). Cuban biotechnology has played an important role in improving healthcare in this country.

## PREMISES FOR SCIENCE DEVELOPMENT IN CUBA

A national campaign against illiteracy took place just two years after the triumph of the Cuban Revolution and by 1965 the National Centre for Scientific Research was founded. This was the seed for all scientific institutions in Cuba today. The Biological Front was created by 1981 while similar movements were taking place in the USA and Japan.

The Centre for Genetic Engineering and Biotechnology (CIGB), flagship of

biotechnology in Cuba, was founded in 1986, and in the period 1990–1996 the Cuban Government invested around US\$1bn to give rise to what is currently known as 'The Western Havana Bio-Cluster', comprising 52 institutions.

## OUTLINE OF NINE OF THE WESTERN HAVANA BIO-CLUSTER INSTITUTIONS

The Centre for Genetic Engineering and Biotechnology (CIGB) and its commercial branch Heber Biotec SA work on vaccines, therapeutics, plant and animal biotechnology, bioinformatics and proteomics. Their leading products are the recombinant hepatitis B vaccine – (recently certified by the World Health Organization (WHO) which can now be sold to all UN agencies) recombinant interferon alpha and gamma, recombinant epidermal growth factor (EGF), streptokinase, and some veterinary products such as a recombinant vaccine for the cattle-tick *Boophilus microplus*.

The **Finlay Institute** and its commercial branch Vacunas Finlay SA work on human vaccines against several infectious diseases. Its leading product, the meningococcal vaccine against the serogroup B, unique in the world, was the

subject of an agreement with GlaxoSmithKline (GSK) for its distribution and marketing in Europe, the USA and in other markets. Its other licensed vaccines are trivalent leptospirosis, typhoid fever (purified polysaccharide Vi), DTPw, DT, dT and tetanus toxoid. (DTPw is a trivalent vaccine composed of difteria toxoid, tetanus toxoid and whole cells of *Bordetella pertussis*; DT and dT are bivalent vaccines for children and adults respectively of difteria toxoid and tetanus toxoid.)

The Centre for Molecular Immunology (CIM) and its commercial branch Cimab SA are devoted to the development of new products for the diagnosis and treatment of cancer, and other diseases related to the immune system. These include antibody engineering, glycobiology, computerassisted molecular modelling and idiotypic regulation of the immune response. CIM conducts clinical trials in diagnostic imaging and cancer therapy of varying origin, and other diseases of the immune system, in highly specialised hospitals.

The **National Centre for Scientific Research** (pioneer institution) and its commercial branch Laboratorios Dalmer SA are focused on natural products. Their leading products are a natural anticholesterolaemic drug known as PPG, medical equipments and biocompatible materials.

#### The National Centre for

**Neuroscience** and its commercial branch Neuronic SA work on the development of medical equipments and devices for the treatment of neurological damages. For instance, they have developed novel equipment for the detection of early auditive damages in children under 1 year old.

#### The National Centre for

**Bioreagents** is a big production facility that along with the CIGB was recently certified by the WHO. Its leading products are the recombinant hepatitis B vaccine, microbiology cultures and antianaemics.

The 'Pedro Kouri' Tropical

Medicine Institute is a reference institution for the study of tropical diseases. It works in close collaboration with the WHO and the Pan-American Health Organization (PAHO) and has a vast experience in the conduction of clinical trials and diagnosis.

#### The National Centre for Laboratory Animals Production supplies laboratory animals for preclinical testing and production to the whole system in Cuba. This institution also researches in new animal models for basic

investigation and toxicology.

The **Centre for Immunoassays** and its commercial branch Tecnosuma SA are the key players of the Cuban national network for diagnosis. Its leading product is the ultra-micro-ELISA (enzyme-linked immunosorbent assay) for AIDS, hepatitis B and C, Dengue virus, Chagas, etc. This institution focuses its work on new ultra-micro-ELISA kits and new versions of SUMA instruments.

#### STRATEGY FOR BIOTECHNOLOGY IN CUBA

Some typical traits characterise this sector:

- the investor is the Cuban government;
- biotechnology is part of the health system and for this reason national needs are the first priority;
- the biotechnology success is totally supported by highly skilled Cuban scientists and professionals;
- operates in a 'closed cycle' way from research to commercialisation by fully integrated institutions and profits from sales in Cuba and in external markets;
- national collaboration instead of individual competition as the driving force of Cuban biotechnology;
- 'spin-off' companies derived from scientific or production institutions; and

Strategy for Cuban biotechnology

• improvement of the ability to access foreign markets, particularly the first world market in terms of: quality (GLPs, GMPs, GCPs – good laboratory, manufacturing medical and clinical practices), production volumes, costs, novelty and joint ventures.

#### PRODUCT PIPELINE

Cuban institutions have registered biotechnology products in over 55 countries mainly in Latin America, East Europe and Asia. National market priorities, technology assimilation and the attractiveness of the market opportunities in these areas were the driving forces of the development of the products we have today on the market (Table 1). Most of them are 'me too' products but there are successful examples of proprietary products among them, such as the meningococcal BC vaccine, the Ateromixol-PPG (anti-cholesterolaemic naturally derived drug), the hepatitis B vaccine (new formulations and manufacturing process) and the humanised anti-EGF-R monoclonal antibody for head and neck tumours.

## **Table 1:** Biological products and equipments registered in Cuba

Anti-CD3 monoclonal antibody Human recombinant erythropoietin Recombinant granulocyte colony-stimulating factor Humanised anti-EGF receptor monoclonal antibody Tumour-imaging monoclonal antibodies Natural and recombinant interferons Recombinant streptokinase Transfer factor Ateromixol-PPG Biomodulin-t Human chorionic gonadotrophin Recombinant epidermal growth factor Microbiological diagnostic system Audix: audiometry system Blood derivatives: albumin, normal IgG, antimeningococcal lg intalglobin (iv) Polysaccharide Vi vaccine against Salmonella typhi Leptospire trivalent vaccine Recombinant hepatitis B vaccine Tetanus vaccine DTPw vaccine Meningococcal BC vaccine Lotion Melagenina Plus

#### PROJECT PIPELINE

Today research and development is characterised by unique projects with a strong intellectual property position. Since 1995, Cuba has been signatory of the TRIPs agreements (trade-related aspects of intellectual property) and around 150 subjects of biotechnology's inventions and more than 500 patents have been filed or issued worldwide, most of them in northern markets. Research and development in human healthcare is mainly focused on the following areas:

- therapeutic and preventive vaccines;
- new adjuvants;
- new formulations;
- genomics and proteomics;
- bioinformatics;
- population genetics;
- transgenic plant products;
- cognitive neuroscience;
- nanotechnology.

The project pipeline includes products in the discovery, early and late stages of development. In the discovery stage there are more than 60 projects under development in the research areas described above of which one eloquent example is the target identification in population-associated gene-related diseases (Table 2). Cuba, owing to its

**Table 2:** Target identification in population-associated gene-related diseases

Disease	Population
Hypertension, lupus, prostate cancer	More frequent in Africans
Alzheimer, dyslipidaemia	More frequent in Europeans
Dengue	Less frequent in Africans

### Lotion Melageni

**Product and project** 

pipeline

**Business models** 

unique population mixture, is ideal for this type of target identification study.

In early stage development there are a large number of products in preclinics for diverse applications including a wide range of vaccines for infectious diseases such as Dengue, AIDS, hepatitis C, meningitis produced by *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups A, B, C, Y and W<sub>135</sub>, and cholera, among others, as well as cancer vaccines and monoclonal antibodies for immunotherapy of cancer and autoimmune diseases (Table 3).

Table 3: Early stage development products and patent status

Project	Patent
Recombinant Dengue vaccine	Filed Patent Cooperation Treaty (PCT)
Preventive and therapeutic AIDS vaccine	Filed PCT
Therapeutic hepatitis C vaccine	Filed PCT
New anti-endotoxin agents	Granted: USA
Meningococcal C conjugate vaccine	Filed Cuba
DT-polyscaccharide Vi of Salmonella typhi vaccine	Filed: Cuba
Cholera-inactivated vaccine	_
Monoclonal antibodies (Mabs) for cancer immunotherapy	Filed: PCT
Therapeutic hu-Mabs for autoimmunne diseases	Granted: Cuba, Australia, Colombia, South Africa, Venezuela
Hepatitis B nasal formulation	Filed Patent Cooperation Treaty (PCT) Granted: South Africa

Source: Cuban biotechnology project portfolio. Internal Report, January 2002.

Table 4: Late stage development products and patent status

Project	Development	Patent
Recombinant P64k, vaccine carrier Recombinant EGF, new therapeutic applications	Phase II Phase II	Granted: Europe, USA Filed PCT
Ganglioside-based anti-idiotype Mab cancer vaccine	Phase I/II	Granted: Europe, USA
Ganglioside cancer vaccine	Phase II	Granted: Canada, Europe, Japan, USA
Cholera attenuated vaccine	Phase I/II	Filed PCT
DPT-HB vaccine	Phase III	_
Combined vaccines	Phase I-III	_
TheraCIM h-R3	Phase II/III	Granted: Europe, USA, Canada, China
EGF cancer vaccine	Phase II	Granted: Canada, Europe, Japan, USA
Brain and heart tomography	Field trial	Granted: USA
New Haemophilus influenzae type b vaccine	Phase II	Filed: PCT

Source: Cuban biotechnology project portfolio. Internal Report, January 2002.

Late stage development products can be found in clinical trials from Phase I to III. As an example, in some key areas such as cancer, there are clinical trials ongoing in Cuba, Canada, the UK, Argentina, South Africa and other countries for the treatment of major cancer localisations such as breast, lung, colon, head and neck and melanoma (Table 4).

#### BIOTECHNOLOGY BUSINESS MODEL

Businesses in the field of biotechnology in Cuba operate by a combination of small and big pharma needs. Institutions involved in this area are looking for external capital, regulatory experiences, intellectual property defence, improvement of commercial capabilities, novelty of products, greater scientific productivity, and the reduction of ongoing costs.

The strategy of the Cuban biotech business model is to look for partners to develop specific projects and products in the Cuban pipeline. The investment could include the acquisition of new technology platforms. General alliances to develop projects from other companies' pipelines are not sought by Cuban biotech companies because scientific resources are fully invested in existing projects. However, alliances to assist with Cuban R&D projects are welcomed from North America and Europe. Negotiation agreements are approved 'case by case' by the Board of Directors.

In general business models used in Cuba can be classified into three groups:

- R&D contract for developing potential new products;
- technology transfer;
- non-exclusive intellectual property licences.

Contracts for the development of new products are implemented in Cuba through the traditional business model. YM Biosciences<sup>1</sup> (Toronto: YM pb.TO)

and the Centre for Molecular Immunology (CIM)<sup>2</sup> signed a pioneer agreement between investors from the first world and the Cuban biotechnology sector. The agreement is based on the development of a humanised recombinant antibody that recognises the EGF receptor (TheraCIM h-R3).

For this purpose, YMB is financing the R&D of this project, clinical trials in Cuba and abroad, and the maintenance fee of the patent while CIM retains global production and manufacture rights and royalties from YMB sales of this product. YMB acquired exclusive commercial rights in North America, Europe and Japan. Any commercial association with third parties for the aforementioned territories would be operated in joint venture with YMB and CIM. At the same time, CIM retained the commercial rights for the rest of the world.

TheraCIM h-R3 is under Phase II clinical trials in Cuba and Canada. TheraCIM h-R3, designed to identify tumours over-expressing EGF-r, was the first of these products to be approved by Health Canada to enter clinical trials in Canada. Cuban authorities accepted conditional registration for the treatment of head and neck tumours in 2002.

A further example is the agreement signed between GlaxoSmithKline plc (GSK) (former SmithKline Beecham plc (SK)) and Vacunas Finlay SA (Havana) to commercialise a Neisseria meningitidis serogroup B preventive vaccine in the world under a Cuban technology patent granted in several countries. GSK will finance the joint development and new clinical trials to register the vaccine in the new markets while Vacunas Finlay retains the production rights, except for the US market where an eventual full technology transfer to GSK will be needed to manufacture this vaccine. The Cuban vaccine is the only one with efficacy demonstrated against N. meningitidis serogroup B, one of the epidemic causal agents of fatal disease by meningitis in infants.

An agreement between the Centre for Genetic Engineering and Biotechnology (CIGB)<sup>3,4</sup> and a European company for the joint research and development of IL-15 inhibitors to treat the rheumatoid arthritis was signed last year.<sup>5</sup> The European company will partly finance this project at risk 'step by step' and, hence, will obtain commercial rights in European countries by strategic alliances with the CIGB and third parties, while the CIGB will retain patent commercialisation rights for the rest of the world.

Technology transfer agreements constitute other business models under successful exploration by Cuban biotechnology institutions. The Cuban meningoccocal B vaccine is a good example of this kind of technology transfer. Transfer technologies from Cuba to southern countries include the technology to produce the hepatitis B vaccine and recombinant streptokinase. These products are transferred from Cuban institutions under special agreements to satisfy the local demand with some local manufacturing producers. In fact, more than 38 business operations are in progress or under negotiation between Cuba and 14 countries at present (Algeria, Brazil, Canada, China, Egypt, India, Iran, Mexico, Malaysia, Russia, South Africa, Tunisia, the UK and Venezuela).

Patent licence is the other business model applied by Cuban institutions. A non-exclusive out-licence agreement to transfer technology know-how for the production of the Dextranase enzyme was carried out between the CIGB and an Indian company. Also, a patent for a humanising antibodies method was granted to the CIM, and under a non-exclusive licence, two European companies were given the rights to exploit the principles of the method.

#### CONCLUSION

Cuba developed its highly skilled human resources throughout the Revolution and as a result holds a strong position today in the fields of life sciences and modern

**Agreements** 

industrial biotechnology. Despite its small size, Cuba has made improving the standard of health within the country a priority and has developed biotechnology to achieve this aim, being successful not just in the area of human health, but also in the areas of agro-industrial and animal health. With a number of ongoing initiatives well underway, Cuban biotechnology should be able to sustain these positive results, in both the

economic and social sense, and is ready to make a significant contribution to the international biotechnology arena.

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