
Papers

Biotechnology in Cuba: 20 years of scientific, social and economic progress

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Date Received (in revised form): 4th August, 2006

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Abstract

An analysis of the biotechnology development in Cuba for 20 years has been attempted in this paper. This paper deals with the evolution of the biotechnology sector from the 1980s, how it was structured and the most important scientific and technical results. Relevant discoveries, methodologies, technologies, and products developed at the Center for Genetic Engineering and Biotechnology are also presented as significant contributions to the advances of the life sciences. Data and evidences are shown in this document that demonstrates the feasibility of developing a new industry in a developing country under foreign economic pressures. Conclusions suggest new paradigms, and future discussions of the broadest interest on the Cuban approach followed for developing the biotechnology industry.

Journal of Commercial Biotechnology (2006) **13**, 1–11. doi:10.1057/palgrave.jcb.3050038

Keywords: Cuba, biotechnology, market, business, vaccines, therapeutics

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INTRODUCTION

In the 1980s, the gap between new knowledge and its subsequent application narrowed more than ever before in developed countries. Among major government concerns

was the use of recombinant DNA, human gene therapy, foetal biology, biosafety, and also in founding and funding new institutes for developing new technologies. Impressive advances in molecular biology generated a set of promising applications in the fields of health, agriculture, energy, industry, and environmental protection. But the majority of developing countries had little if any access to these new technologies, which would have helped to solve their economic and social problems. But this situation did and does not exist in all developing nations.

During the 1960s and 1970s, Cuba trained many scientists and engineers with about 1.8 researchers per 1,000 inhabitants, a figure well above the mean value of Latin America (0.4), and close to that of Europe (2.0).¹ This situation placed Cuba well outside the trend of correlation between the size of a countries scientific system compared with that of its economy, and subsequently these favourable conditions permitted a new development programme to be established.

The first attempts for developing the biotechnology industry in Cuba started with the foundation of the Biological Front in July 1980, a professional interdisciplinary forum working together with government authorities to explore potential applications of this emerging science. Outbreaks of meningitis, dengue fever, and conjunctivitis likely accelerated the decision-making process and Cuba subsequently established its first biotechnology institutions in the 1980s. Some

factors exclusively characterise the biotechnology sector in Cuba:

- i. the investor has been the Cuban government;
- ii. biotechnology is part of the health system, and for this reason the national needs are the first priority;
- iii. the research output is generated entirely by native rather migrant scientists and professionals;
- iv. operating capacity in a 'closed cycle' way from research to commercialisation by fully integrated institutions and profits from sales overseas;
- v. national collaboration instead of individual competition as the driven force;
- vi. spin-out companies derived from scientific and/or production institutions; and
- vii. improvement in the ability to access foreign markets, particularly in the developed world, based on quality (cGLP, cGMP, and cGCP), production volumes, cost, novelty, and joint ventures.²

Figure 1 shows a selection of publications which have described and analysed the Cuban biotechnology sector.

The development of a new industry required coordination of research and development (R&D) between institutions and mutual access to new discoveries through fair collaborations as the challenges being faced could not be overcome in a competitive environment, as is usual in developed countries, as resources are limited. The urgency for

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Some comments on the Cuban biotech industry:

- the three mains pillars of Cuban Society after the revolution were health, education and science
- the main driving force for the health biotechnology sector in Cuba has been to improve the health of Cubans, and the meningitis vaccine is a good example
- long-term governmental vision and policy coherence
- despite economic hardship, the government has continued to support health biotechnology
- promotion of domestic integration to spur innovation
- there are strong linkages between Cuba's health biotechnology research system and its health system capitalizing on international linkages

Figure 1: A selection of international publications reporting and analysing the Cuban biotech industry

immediate application of scientific results reinforced the need for expanding collaboration across all sectors, from health to agriculture. The new paradigm was then: how structure integration and collaboration?

INTEGRATION AND COLLABORATION

New 'scientific poles' were set up in the 1990s to operate throughout Cuba and involved fully integrated research, higher education, and relevant health institutions, as well as enterprises as end users of the R&D results. These scientific poles have played a very important role, coordinating multi-institutional approaches and the introduction of results into the Cuban economy and society. From 1990 to 1996, the Cuban government invested around 1 billion US dollars in what is currently known as 'The Western Havana Bio-Cluster' (the first and most important) which comprises 52 major research, education, health, and economic institutions devoted to the biotechnology field.³⁻⁵ Ten of these institutions are at the core of the system as they supply economic support to the whole effort with their production capacities and exports. They are performing more than 100 research projects which have generated a product pipeline of more than 60 new products most of which are protected by intellectual property (IP), and more than 500 patents have been filed overseas.

Biotechnology had begun to add value to Cuba's economy even before the large investment as R&D projects had been yielding results with tangible applications from the 1980s, generating innovative products and technologies to satisfy unmet economic and social needs that supported the National Health System, as well as the R&D costs of the Cuban biotechnology industry. There are currently many projects in the pipeline and at various stages, from early stage to clinical trials. Maintaining a steady stream of new products in the pipeline has been possible through regular and systematic evaluation of product feasibility. There has been a global trend of increasing R&D costs (7.4 per cent annual increase of total capitalised costs) since

1980, as well as an increase in R&D expenditure per new drug (802 US millions/drug),⁶ and future predictions remain as formidable challenges.⁷ Therefore, it is not difficult to accept that huge resource allocation efforts will need to be initiated to keep the current growing trend of the biotechnology pipeline in Cuba, particularly as it faces significant foreign economic pressures.⁸

Several research institutions of the Havana Scientific Pole are held in very high esteem by the people of Cuba since they represent some of the most significant features of their national identity (humanity, solidarity, sacrifice, and toughness) and one of these institutions is the Center for Genetic Engineering and Biotechnology (CIGB).

THE CIGB'S PIPELINE

The CIGB has become one of the most important research-production facilities at the 'Western Havana Bio-Cluster' and conducts research in the fields of healthcare and agri/animal biotechnology. Research generated by the CIGB has developed a number of products, which are already having a significant impact to society.

One such product is CITOPROT-P[®] which was developed to treat diabetic foot ulcers which are the most common cause of non-traumatic lower extremity amputations in the industrialised world, let alone in developing countries. This product was the result of more than ten years of research and two subsequent clinical trials, which were performed in Cuba. The CIGB and the National Institute of Angiology and Vascular Surgery performed the first clinical trial with CITOPROT-P[®] in 29 type-II diabetic patients who had micro and/or macro angiopathy (disease of the blood vessels: arteries, veins, and capillaries) and as a result, 55 per cent of patients were saved from amputations. A second clinical trial was conducted with 41 patients and 80 per cent patients were saved from amputations.⁹ The novelty of CITOPROT-P[®] is in its application route. Rather than just applying it to the open wound it is injected into the healthy margins of the wound, thereby allowing the tissue to initiate the wound

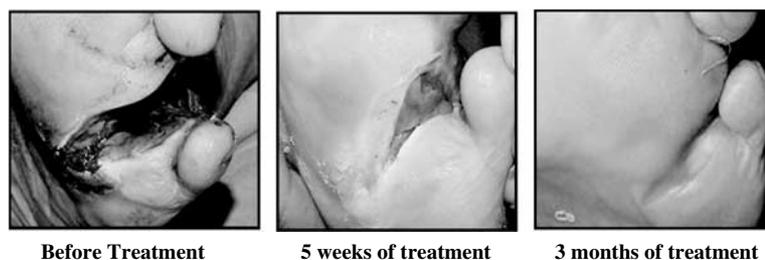


Figure 2: Treatment of diabetic foot ulcer with CITOPROT-P®

healing process before it is destroyed (see Figure 2).

In January 2006, the CIGB started the first clinical trial to assess the safety and performed a dose scale-up study with the trial drug CIGB-300 in patients with cervical intraepithelial neoplasia (CIN-II; the pre-invasive stage of cervical cancer) and carcinoma *in situ* (CIS; an early form of carcinoma defined by the absence of invasion of surrounding tissues) who have failed to respond to other available treatments. CIGB-300 is a proapoptotic cyclic peptide that works by blocking protein kinase 2 (CK2) phosphorylation and has been shown to exhibit antitumour effects *in vivo*.¹⁰

Other CIGB products include a *Haemophilus influenzae* type b vaccine (the only synthetic vaccine of its kind in the world) which was designed and synthesised at the Laboratory of Synthetic Antigens at the Havana University as well as a recombinant vaccine for Hepatitis-B, thrombolytic recombinant streptokinase, and human recombinant erythropoietin, granulocyte colony-stimulating factor, and alpha and gamma interferons. A therapeutic version of the anti-Hepatitis-B vaccine is in advanced evaluation stages and other innovative products include dengue fever, hepatitis C, and anticancer vaccines (Table 1). In addition, the CIGB is negotiating technology transfer operations with other countries for its vaccines and drugs.

In non-human research, aquaculture has benefited from the development of the growth stimulator Acuabio-1 by the CIGB which improves both growth and survival of farmed fish and has been tested, in Cuba, in laboratory and pilot scale tests, and currently

being implemented in the National Aquaculture Program and is sponsored by the Fisheries Minister.

THE CIGB'S STRATEGIC APPROACH

The CIGB has more than 15 years of experience in the production of several recombinant biopharmaceutical molecules, which are already producing a positive impact on public health in Cuba and generate cash income from exports to more than 30 countries (Figures 3 and 4).

The CIGB strategy holds a high level of coherence with the global oriented commercial strategy of the Havana Scientific Pole, where the CIGB is one of the leading institutions. The CIGB develops scientific and production activities in close collaboration with other institutions of the Scientific Pole, and the National Health and Agriculture Ministries. Heber Biotec S.A. is the commercial arm that owns the exclusive rights for commercialisation of the CIGB and R&D projects. Heber Biotec S.A. closes the cycle from research to commercialisation of the CIGB results, and commercialises products from other seven Cuban biotechnology institutions. The commercial strategy involves the expansion of sales into new markets while maintaining current established positions. The CIGB and Heber Biotec S.A. are working together on the introduction of novel products in Europe and Canada, promoting early-stage associations for joint development of projects, and sharing commercial opportunities with partners. A critical mass of talent has had to be suitably managed to generate innovations from applied and basic research, and significant annual sale growth rates from the CIGB products and

Table 1: The CIGB's current R&D pipeline

Project	Discovery	Preclinical	Phase I	Phase II	Phase III	Approval
Hepatitis B without thiomersal	X	X	X	X	X	2001
G-CSF	X	X	X	X	X	2002
<i>H. influenzae</i> type b vaccine (Hib)	X	X	X	X	X	2003
IFN liquid without albumin	X	X	X	X	X	2003
IFN lyophilised without albumin	X	X	X	X	X	2003
IFN+ribavirina	X	X	X	X	X	2003
streptokinase without albumin	X	X	X	X	X	2003
DPT-HB	X	X	X	X	X	2004
Erythropoietin	X	X	X	X	X	2004
DPT-HB+Hib	X	X	X	X	X	2006
Citoprot-P	X	X	X	X	X	2006
Hepatitis A vaccine	X	X	X	X	X	2006
IFN colirium	X	X	X	X	X	2006
HB-Hib vaccine	X	X	X	X	X	2007
DPT-HB-Hib vaccine	X	X	X	X	X	2007
DPT+Hib vaccine	X	X	X	X	X	2007
Hebervis	X	X	X	X	X	2007
HA+HB vaccine	X	X	X	X	X	2007
IFN gel	X	X	X	X	X	2007
VEGF gene therapy	X	X	X	X	X	2007
Therapeutic HBV vaccine	X	X	X	X	X	2007
Therapeutic HBV/NASVAC	X	X	X	X	X	2007
CIGB-300	X	X	X	X	X	2007
CIGB-240	X	X	X	X	X	2007
Conjugate vaccine PS-C:P64k	X	X	X	X	X	2007
Prostate cancer vaccine	X	X	X	X	X	2007
Dengue vaccine	X	X	X	X	X	2007
AIDS vaccine CR3	X	X	X	X	X	2007
Meningitis vaccine	X	X	X	X	X	2007
HPV vaccine	X	X	X	X	X	2007
Therapeutic HCV	X	X	X	X	X	2007
CIGB-370	X	X	X	X	X	2007
CEA diabody fragment	X	X	X	X	X	2007
Antiangiogenic vaccine	X	X	X	X	X	2007
Vaccine IL-15 RA	X	X	X	X	X	2007
Autoimmunity AR	X	X	X	X	X	2007
Antivirals – dengue	X	X	X	X	X	2007
Post-EDL – HIV targets	X	X	X	X	X	2007
Antivirals – HIV	X	X	X	X	X	2007
Neuroregeneration	X	X	X	X	X	2007
Genomics	X	X	X	X	X	2007

CEA=anti-carcinoembryonic antigen; CIGB=Center for Genetic Engineering and Biotechnology; DPT=diphtheria; G-CSF=granulocyte colony-stimulating factor; HA=hepatitis A; HB=hepatitis B; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IFN=interferon; IL=interleukin; HPV=human papilloma virus; NASVAC=a nasal vaccine candidate for chronic hepatitis B immunotherapy; VEGF=vascular endothelial growth factor.

technologies, under very narrow financial boundaries.

APPLIED RESEARCH

The production of the hepatitis B vaccine has allowed the Cuban Ministry of Health to comply, since 1992, with the recommendations of the World Health Organization (WHO) that all countries should introduce universal hepatitis B vaccination into their immunisation programmes.¹¹ After 12 years of worldwide clinical experience, this vaccine has shown to

be highly immunogenic, with excellent safety and efficacy profiles to protect against hepatitis B virus (HBV) infection. Other alternatives to hepatitis B vaccination are also currently under research at the CIGB. On the other hand, despite advances in antiviral therapies, there is still no effective treatment for hepatitis B infection and for this reason, the second strategy has been directed to the development of new drugs that could be used in the therapy of HBV-infected patients. Hepatitis C virus (HCV) is also a major worldwide health problem and a DNA

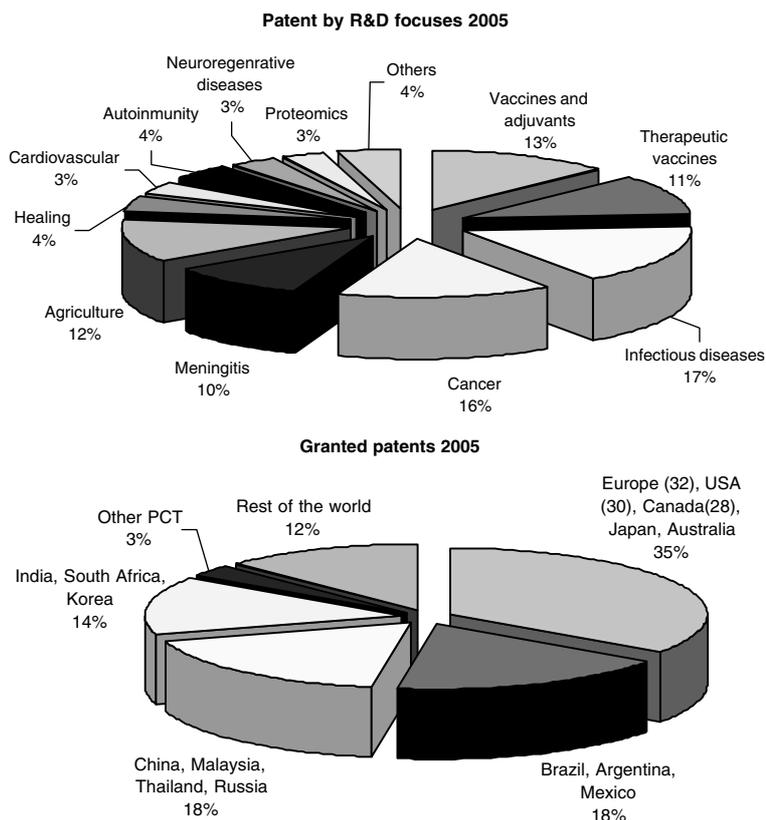


Figure 3: IP at the CIGB. One hundred and seventeen patents have been filed in Cuba and 74 in other countries with more than 470 patent applications in total. Values in parenthesis in lower figure are actual number of patents filed. PCT: Patent Cooperation Treaty

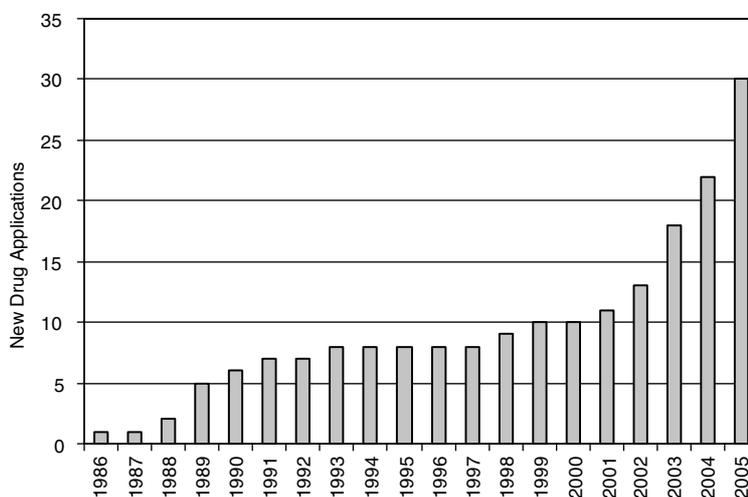


Figure 4: CIGB new production applications 1986–2005

vaccine formulation based on a construct comprising the genes for the three main structural antigens of the virus has been generated.

As a result of the collaboration between Havana University and the CIGB, a new

conjugated vaccine, for the active immunisation against invasive illnesses caused by the bacterium *Haemophilus influenzae* type b, has been developed. The vaccine differs from those already available in its composition, which is based on synthetic oligosaccharides

that mimic the natural capsular polysaccharide, conjugated with the tetanus toxoid carrier protein. The vaccine is immunogenic, safe, and very well tolerated, as demonstrated in several clinical trials with children.¹²

According to experts from the WHO, the current offer of combined vaccines in response to United Nations Organization (UNO) procurement is moving away from the projected demand;¹³ therefore, investments in new facilities must be amortised faster than is normal, which subsequently affects vaccine prices. The institution is working on a wide programme for developing combined vaccines. This includes bivalent HB-Hib, tetravalent DPT-HB, pentavalent DPT-HB + Hib, and other combinations. A clinical trial with the pentavalent DPT-HB + Hib vaccine is being performed, and in the next year a clinical trial with a liquid pentavalent vaccine will be started, in which all the antigens are mixed in a single vial. The application of these combined vaccines in Cuba will reduce the number of injections from 11 to five, and could also contribute to reduce the costs of WHO immunisation programmes.

The impact of the CIGB in the Cuban agriculture and food production has also been substantial, contributing to the propagation of new plant varieties which are resistant to pests and drought, providing advanced diagnostic systems for plant and animal diseases, creating and producing vaccines for cattle and poultry, and obtaining bioproducts for agriculture. Several projects apply biotechnology tools for improving the efficiency of plant and animal breeding. These include genomics, proteomics, and bioinformatics, besides advanced tissue culture techniques. Transgenic plants with resistance to biotic (pest and diseases) and abiotic (drought and salinity) stresses are also under development. Lastly, the use of plants and animals as bioreactors is the goal of several ongoing projects. Among these, are the expressions in plants of the antibodies CB. Hep-1 (anti-Hepatitis B) and TheraCIM[®] for cancer treatment.

BASIC RESEARCH

Applications of the science developed at the CIGB have been supported by the results of basic research with significant usefulness for

the world scientific community. The study of the pathogenic bacterium *Neisseria meningitidis* leads to the finding of the highly conserved *lpdA* gene codifying for P64k protein. This result was a valuable discovery to obtain a protein carrier useful for vaccine design. Appropriate carriers to activate the immune system against poorly immunogenic antigens are highly useful for developing vaccines. After characterising P64k, the CIGB researchers tested it as a protein carrier conjugated to weak immunogens. These results have born an exceptionally heavy burden of work. P64k protein has been used in experiments on the immune response against cyclic synthetic peptides and envelope fragments of the dengue-1 and dengue-2 viruses. This protein carrier has also been used in a cancer vaccine¹⁴ and a polysaccharide-protein conjugate vaccine.¹⁵ In addition, its safety profile has been evaluated in humans.¹⁶

The Laboratory of Molecular Oncology (LMO) has actively been searching for pathways of human oncogenesis inhibition. Starting with a relevant hypothesis and screening a random cyclic peptide phage display library, the LMO's research staff found a peptide (P15-Tat) with antitumour effect and this is now in Phase-I clinical trials. This research provided proof-of-concept that P15-Tat or other molecules that block protein kinase 2 (CK2) phosphorylation could be used in cancer therapy.¹⁰

The life cycle of the HCV has been extensively studied by the CIGB's researchers to explain host-viral interactions. The lack of appropriate protocols to determine subcellular location of HCV in hepatocytes gave rise to investigations of the HCV core protein and nucleocapsid-like particles by electron microscopy. For the first time, the HCV core protein and nucleocapsid-like particles were localised in the nuclei of hepatocytes which is important to understand functions of the viral proteins during HCV infection and to find targets for drug design. Further studies on the localisation of HCV components in extrahepatic cells gave some important evidence that will contribute to explain the mechanism of HCV pathogenesis.¹⁷

Discovery activity at the CIGB has been driven by the researchers' interest to get a

deeper understanding of disease mechanisms and in turn to find useful therapeutic and prophylactic drugs. Useful techniques for the study of biological systems and their molecules have been developed for decades at the institution. The development of a methodology to evaluate modelling software is one of the most relevant. The scientific community has reported in more than 60 papers, since 1998, the application of the method for homology modelling, quality evaluation, and protein models evaluation. Such methods have been an essential tool for research projects that involve determining protein structure when experimental procedures cannot be applied, contributing to reduce the difference between the number of known gene sequences and the number of solved protein structures.¹⁸

Life sciences scientists usually work with complex biological samples to isolate a few molecules by using validated protocols, and trying to keep the integrity of the separated entities. The development of a technique for intact protein isolation is certainly a most promising direction in proteomics. A procedure for the isolation of proteins by reverse staining was developed by the CIGB's scientists. The result was a protocol with sensitivity higher than the Coomassie blue acrylamide gel staining method and was faster and adequate for the handling of proteins at low concentrations. The method was improved during ten years at the Laboratory of Physical Chemistry and optimised procedures for the detection and analysis of proteins were published. This method does not compromise the integrity and activity of unmodified proteins, which is of high significance for analysis and applications of the isolated molecule. These studies have also contributed to a better understanding of the separation mechanism and its applications in proteomics.¹⁹

Antibody generation is another important field of investigation for the CIGB researchers. A novel method to create antibody libraries developed at the institution, in collaboration with the Lund University (Sweden), has been cited in more than 40 papers.²⁰ The procedure consists of linking antigen recognition and phage replication to mimic

the immune response in a phage display system. Such a methodology represented a relevant step towards implementing a faster protocol with higher specific enrichment factors.

Cuban discoveries and methodologies available in the published literature are just piece of evidence which shows that Cuban contributions are firmly rooted in current research methods (the CIGB has published 680 peer-reviewed papers in scientific journals, from 1986 to 2006). It is also worth noting that the CIGB's papers have been cited in more than 3,000 papers.²¹ These figures demonstrate that the CIGB's results have been useful for the worldwide scientific community. This paper does not suggest that basic research is the first priority of the CIGB, but the results reported in the literature suggest no current cause for concern on the future of the discovery activities at the institution. The rationale for exclusively performing pure basic science in a Cuban institution, at present is not clear, because the major factor driving the economic and social development of a developing country is the access to new cutting-edge technologies coming from both, basic and applied research.

THE CIGB'S HEALTH IMPACT

Health impact is considerable at the population level in many fields, for example hepatitis-B has disappeared in the infant population (Figure 5). Cuba does not only hope to eradicate this infectious disease in a few years, but also to eliminate the virus circulation. Additional relevant facts supply a picture of the CIGB health impact:

- i. The hepatitis B vaccine manufactured at the CIGB has reduced the incidence of this infectious disease in Cuba from 376 cases in 1991 to eradication in 2000, it has been on the WHO's list of vaccines purchased by UNO from 2001. \$220m worth of vaccine were sold in ten years and 100 million doses have been used.
- ii. In clinical trials with the recombinant streptokinase manufactured at the CIGB, 86 per cent efficacy was obtained for the treatment of prosthetic heart valve thrombosis and

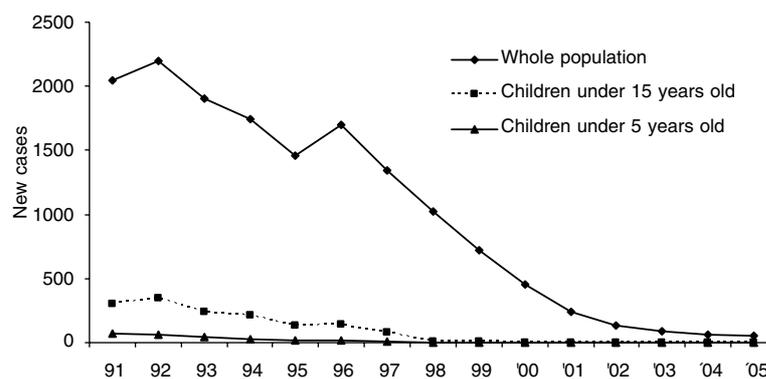


Figure 5: Incidence of acute hepatitis B in Cuba 1991 to 2005

- in acute myocardial infarction, the rate of thrombolysis was around 50 per cent and even 70 per cent in some medical units.²²
- iii. Large-scale production of the first world-wide synthetic vaccine was made possible by the CIGB's staff, a few months after the vaccine discovery. In clinical trials, 99.7 per cent of the test infants reached antibody titres above those considered appropriate for long-lived protection against *Haemophilus influenzae* type b.²³
 - iv. The recombinant humanised antibody against the epidermal growth factor receptor, now in clinical trials for cancer therapy in Cuba and other countries, was transiently expressed in tobacco leaves, correctly assembled and retaining its biological activity.²⁴
 - v. The Finlay Institute, the CIGB, and the Centre for Bioreagents have overcome the huge challenge of supplying a safe tetravalent vaccine to the Cuban Immunization Program. The new combined vaccine Trivac-HB[®] will protect children from four lethal infectious diseases: diphtheria, tetanus, whooping cough, and hepatitis B.
 - vi. The new product CITOPROT-P[®], with 85 per cent efficacy for preventing amputation in patients with end-stage diabetic foot ulcers, is in the market and the Cuban Health System has started its application.⁹

CONCLUSIONS

Overall, it must be concluded that the results from developing biotechnology in Cuba have been rewarding. A new industry has been

created in a developing country, which is supplying cutting-edge technology products to its people, and is generating significant profits from overseas sales in spite of severe financial constraints. Certainly, there is no evidence showing that a similar scientific, social, and economic phenomenon has taken place in any other country. Similarly, the possibility of a continuous development of this sector of the Cuban economy suggests a promising future for the solution of ongoing national problems. The decision of implementing integration and collaboration between research institutions was right; otherwise, the results would have to be disappointing. Two decades is enough time to make relevant conclusions from a study case: the CIGB. First, universal access to education is the most important factor that set up optimal conditions to start the development of a high technology industry. Secondly, when several research institutions work in close collaboration for the development of its country, the results are impressive, a vast amount of economic and social problems are solved, and the nation can be proud of its achievements. Thirdly, suitable IP policy, projects planning and evaluation, and rational resource allocation allowed the building of a balanced and growing product pipeline that begins to generate new products with market potentiality when commercialised by a global oriented enterprise. Fourth, when such a pool of expert researchers is created they can turn their attention to major problems affecting people on a global scale such as disease pandemics, hunger, and environmental deterioration. Fifth, the amount and relevance

of contributions to basic and applied research that can generate integration and collaboration between national research institutions is unpredictable, since mutual access to novel approaches and results opens new alternative pathways in the course of each project, increasing its probability of success in a shorter time and with lower R&D costs.

Lastly, and turning to the rationale of the idea, it can be concluded that the concept has been proven, since the new industry has a good health after 20 years. But new paradigms have been born: should all developing countries follow exactly the same pathway? Is the Cuban's approach feasible for other emerging industries? What should be the starting point in each case? Here, an attempt has been made to draw a route to develop a new industry in a developing country, which has given rise to challenging questions, with the hope of contributing to the solution of the most urgent worldwide problems. Therefore, it is predictable that future discussions on this issue could be of the broadest interest.

Acknowledgments

The authors would like to acknowledge the encouraging discussions with Marta Dueñas Porto, PhD and Glay Chinae Santiago, PhD. We also acknowledge valuable critical readings of Eduardo Martínez Díaz, PhD, and Professor José Luis Fernández Sierra.

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