

The Cuba-United States Collaboration in Biotechnology and Cancer: The Art of the Possible

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Abstract

Despite decades of political and economic hostility between the government of the United States of America and Cuba, scientific collaboration actions have occurred and continue to occur involving not only academic institutions but companies from both countries. It is a concrete experience that illustrates the uniqueness of scientific collaboration and knowledge-based industries and may contain clues on how to move forward in the future.

In this article we review the actions of scientific collaboration in cancer control, which led first to joint clinical trials with innovative Cuban products, with joint publications in scientific journals of international circulation, and then to the emergence of a joint venture, the first in the history of both countries. These actions take place in a context of respect and cordial and frank relations between Cuban and U.S. research teams.

The setting up for the first time ever of a business with shared ownership between U.S. and Cuban organizations represented a major challenge. Beyond the considerations expected in any venture with commercial purposes, and the high uncertainty associated with the development of biotechnological drugs, the creation of this company required the solution of important legal obstacles, especially because it is not a classic academic collaboration project, nor a conventional contract between companies, but a collaboration project precisely in that border zone where science becomes business development.

Despite the complexities, both the joint scientific research and the operation of the joint venture have been maintained for more than 5 years. The building of collaborative scientific relations between Cuba and the United States, after half a century of separate evolution, may be a unique historical opportunity.

American and Cuban scientists know each other and have always been enthusiastic about collaboration. In decades of political confrontation between the two countries there has always been closeness between the U.S. scientific community and Cuban scientists. Of course, this has been tempered or limited by the blockade and the hostility of U.S. policy towards Cuba. The "Art of the Possible" lies precisely in knowing how to manage this contradiction. The characteristic of the human activity that we do, Science, helps a lot in the approach. Science is not the

only intelligent activity of man, of course, but the essential characteristic of Science is its objectivity, its attachment to verifiable data.

The science and technology systems of both countries must now rebuild academic and business exchange relations. This exchange could be born, as is science itself in today's world, with a solid institutional framework, oriented to explicit objectives, integrated in programs that group several projects, and connected from the beginning to what we manage to build in terms of economic and cultural relations.

Keywords: *scientific collaboration, joint ventures, cancer, biotechnology*

Introduction

Historians do not agree on who is the author of the phrase "Politics is the art of the possible". They attribute it to Clausewitz, to Bismark, to Churchill, others to Machiavelli, or even to Aristotle.

Whoever the real author of the phrase is, the truth is that it serves us very well to describe the space of collaboration between Cuba and the United States in the field of Biotechnology and specifically its applications for the control of Cancer, in the more than 6 decades of hostility since the imposition of the economic, commercial and financial blockade on Cuba in 1960. It would be difficult to imagine more difficult conditions for scientific and even business collaboration between both countries, in a high technology field considered by many as "strategic". And yet, several collaborative actions have taken place, and are still taking place and can be projected further into the future.

Let us first review what has happened, and then try to explore what experiences we can gather and what connections this history has to the uniqueness of scientific collaboration and knowledge-based industries.

I. Scientific collaboration in cancer control

Academic collaboration between CIM and RPCCC

Scientific collaboration between the Center for Molecular Immunology (CIM) in Havana, Cuba and the Roswell Park Comprehensive Cancer Center in Buffalo (RPCCC), NY, began more than a decade ago, following the active participation of scientists from the institute in the meetings "Immunotherapy in the new century", which the CIM organizes every two years, practically since its inauguration.

Following the interest of the Roswell experts, a visit of CIM researchers to the institute took place which involved the presentation of pre-clinical and clinical results of innovative Cuban molecules, as well as discussions with the main experimental groups. As a result of these meetings, working stays of several young CIM scientists in Buffalo are organized. In 2015, the Roswell Park Center obtains a license from the Office of Foreign Assets Control (OFAC) to begin preclinical and clinical studies of products from the Center for Molecular Immunology in the United States. After hard work by the clinical and regulatory teams of both institutions, in 2017, the FDA authorizes the first clinical trial of a Cuban biotechnology product in the United States: the CIMAvax-EGF vaccine.

The CIMAvax-EGF vaccine involves a specific active immunotherapy designed to induce antibodies against an important tumor growth factor: Epidermal Growth Factor (EGF). The vaccine consists of recombinant human EGF conjugated to a recombinant protein derived from *Neisseriameningitidis* (P64k). The antibodies achieved after vaccination block the interaction of Epidermal Growth Factor Receptor (EGFR) with one of its most important ligands (EGF). At the time of OFAC licensing, the CIMAvax-EGF vaccine was registered in Cuba as a maintenance treatment for patients with advanced non-small cell lung cancer. A randomized Phase III study in patients with advanced lung cancer, where CIMAvax-EGF vaccine was used after first-line chemotherapy, demonstrated an overall survival advantage compared to best supportive care, particularly in patients with high baseline serum EGF levels. (Rodriguez PC, 2016).

At the time of the clinical trial design in the United States, a major milestone in cancer research had been achieved: the registration of immune checkpoint inhibitory antibodies. In particular, anti-PD1 antibodies repre-

sented the new standard of treatment for patients with advanced lung cancer in progression. These therapies were not available in Cuba.

Despite being registered in Cuba, the first clinical trial of CIMAvax-EGF in the United States consisted of a Phase I trial, where the vaccine was combined with the anti-PD1 antibody nivolumab. The research was designed to primarily evaluate the safety and immunogenicity of the new combination (Evans R, 2022).

The study enrolled 13 patients with progressing lung cancer. The combination proved to be safe, while the immunogenicity of the vaccine was higher after co-administration with nivolumab. The median survival of subjects who completed the CIMAvax-EGF induction regimen was 18.3 months, which was higher than the expected survival for patients treated with nivolumab monotherapy (less than one year).

At the end of the research, a joint manuscript between RPCCC and CIM was published describing for the first time the treatment of patients in the United States with a molecule from Cuban biotechnology. (Evans R, 2022).

In 2018, the constitution of the joint venture between Cuba and the United States (Innovative Immunotherapy Alliance) was approved for the co-development of 4 new cancer therapies. Among the 4 molecules, there are 2 vaccines (CIMAvax-EGF and Glycovax) and 2 novel immune modulators (interleukin 2 mutein and VSSP), to reverse cancer-associated immune suppression. As of this year, all pre-clinical and clinical research at RPCC is conducted under the aegis of this first joint venture, incorporated in Cuba.

There are currently 3 clinical trials underway in the United States, with the CIMAvax-EGF vaccine.

The first trial, conducted in patients with advanced lung and head and neck cancer, is a Phase 2, open-label, non-randomized, multicenter study. The trial explores the combination of CIMAvax-EGF with an anti-PD1 antibody (pembrolizumab or nivolumab) in different treatment settings. The primary objective is to evaluate objective response rate, progression-free survival and overall survival. Exploratory objectives include characterization of anti-EGF antibody levels, serum EGF levels and other blood biomarkers in relation to clinical outcomes. Preliminary data from this investigation are favorable. Very encouraging survival data are obtained, particularly in patients who do not respond to anti-PD1 therapies, including those patients whose tumor has low PDL1 expression or who lack mutations in the KRAS oncogene (Frascati R, 2023).

The second study evaluates the safety and immunogenicity of the CIMAvax-EGF vaccine in patients with metastatic colorectal cancer, when administered in combination with standard therapies for advanced stage disease.

The last trial evaluates the effect of CIMAvax-EGF in preventing the occurrence of lung cancer in high-risk patients. It also includes patients who have undergone lung cancer surgery and are at risk of relapse. As part of the research, an in-depth pharmacodynamic characterization of the impact of the use of the vaccine on the lung epithelium will be performed.

In summary, after almost 15 years of relations with the Roswell Park Comprehensive Cancer Center, we can affirm that academic collaboration takes place in the context of deep respect and cordial and frank relations between the Cuban and U.S. research teams. Systematic virtual or face-to-face scientific discussions are held on the design and results of pre-clinical experiments and clinical trials. Experts from the Buffalo hospital have visited Cuba on numerous occasions, in order to hold exchanges with physicians and researchers, bring donations of equipment and consumables and organize joint training sessions on the procedures of research protocols. The work stays have not only been concentrated in Havana or in secondary or tertiary health care, but the Roswell doctors have been able to visit other provinces of the country and interact with specialists in primary health care, as well as with relatives and patients treated with CIM drugs.

Trials in the United States have allowed the evaluation of new Cuban drugs in the context of state-of-the-art cancer diagnosis and treatment, as well as access to advanced analytical technologies. As part of the collaboration, several samples from Cuban patients have been characterized at the Roswell Institute. Molecular and cellular studies have been transcendental in the elucidation of the mechanisms of action and in the identification of bio-

markers predictive of greater efficacy of the new therapies. The incorporation of new drugs to the joint venture's portfolio and the initiation of clinical trials with interleukin 2 mutein are anticipated.

II. The science-industry connection

Biotechnology applied to health is one of the branches of science where collaboration between Cuba and the United States can result in an important benefit for the populations of both countries, especially in fields such as the development of novel drugs for cancer and other chronic diseases that afflict our populations.

However, scientific collaboration without the business component does not allow the greatest benefits of this collaboration to be achieved. The development of drugs for use on a population scale involves very high costs, which in practice cannot be financed by the traditional mechanisms of scientific collaboration. This means that the development cycle of novel drugs must involve a business sector that can extract, from the expectations of future market profits, the substantial resources for the advanced phases of clinical research.

Business collaboration in the development of biotechnological medicines between Cuban companies and companies from other countries has been a reality for 30 years, with notable examples in countries such as China, India, Japan and others. Since the reestablishment of diplomatic relations in 2014, the possibility of collaboration with Cuban companies in the biotechnology sector began to be valued more seriously by companies in the pharmaceutical sector in the United States.

As of that date, executives of the main U.S. companies, responsible for evaluating opportunities for business alliances, began to visit Cuba to evaluate the portfolio of research projects of the Cuban biotechnological sector in search of new drugs to enrich their commercial offer to U.S. patients. Leading companies in this sector in the United States, such as Genentech and Biogen sent high-level delegations to Cuba to evaluate these opportunities, even in the midst of a panorama of legal uncertainty as to how the U.S. government blockade would regulate this potential collaboration. Cuban companies responded to this rapprochement by transparently showing their lines of research, and also their consolidated experience in establishing lasting alliances with companies from many countries in the joint development and exploitation of their intellectual property.

This period of business rapprochement reached a point of maximum activity when the Obama administration issued a general license authorizing any U.S. company to start collaborating with Cuban companies in the research of biomedical products, including their importation and commercialization in the U.S.

Unfortunately, this step, undoubtedly positive, occurred at the end of 2016, a few months before the election of Donald Trump president, which again generated a climate of legal uncertainty about the collaborations between the two countries.

The collaboration between the Roswell Park Comprehensive Cancer Center in Buffalo, New York, and the Center for Molecular Immunology in Havana, Cuba, stands out as an exception in this panorama of rapprochement between the biotechnological sectors of these countries. It began before 2014 as an academic collaboration motivated by the desire to offer American oncology patients other treatment alternatives to those already available in that country, especially in the emerging field of immunotherapy. When in 2015 the visits of delegations from the various states of the Union to Cuba began to take place, RPCCC and CIM already had a scientific collaboration consolidated by the scientific rigor of both parties and the shared vocation to benefit cancer patients in both countries.

The opportunity arose, therefore, with the relaxation of the aforementioned regulations of the U.S. administration, to transform this collaboration into a business alliance that would allow access to the necessary funds for the development in the United States of Cuban products for cancer immunotherapy.

The business modality chosen to make this opportunity come true was the creation of a joint venture between RPCCC and CIM, based on Cuban soil, but aimed at commercializing novel drugs in the United States and other countries. Which in fact turned the joint venture Innovative Immunotherapy Alliance (IIA), constituted in September 2018, into the first joint business venture between the two countries in the biomedical sector.

The setting up for the first time ever of a business with shared ownership between U.S. and Cuban organizations represented a major challenge. Beyond the commercial considerations expected in any commercial venture, and the high uncertainty associated with the development of biotechnology drugs, the creation of this company required the solution of important legal obstacles.

The first legal challenge, as was to be expected, was to find a way to deal with the possible consequences of the blockade on a business with operations in both countries, seeking not only the adequate defense of the parties against hostile actions by the U.S. government, but also thinking of the protection of patients, whose survival in the future could depend on a continuous supply of medicines.

Another no less important challenge was to familiarize the U.S. partner with the system of laws governing companies in Cuba, and to find within these the adequate protection of the investment and the autonomous operation of a mixed capital organization. The fact that the company is legally domiciled in Cuba, even though it implied the need for a more flexible position of the U.S. partner, turned out to be an undoubted advantage in the long run, since the legal regime in Cuba is much more stable than in the U.S., as demonstrated by the measures that were soon implemented by the Trump administration.

Paradoxically, the challenge of managing a joint business, the element that could be expected to be the most complicated, given the decades of isolation in the commercial relations between the two countries and the important differences in the business cultures between the two countries, has ended up working in an organic and natural way. For more than five years, the company has been strategically directed and operationally managed in a completely joint manner, with managers from both countries coordinating all activities on a daily basis. This shared operation did not stop either during the closure of the U.S. Embassy in Havana or during the COVID19 pandemic.

After more than five years, the Innovative Immunotherapy Alliance exhibits significant results in business collaboration. In addition to the scientific and medical results outlined earlier in this paper, the company has been able to advance the development of its drug portfolio. Its intellectual property base has grown by 50% and significantly increased its value, which has been certified by international agencies specialized in this industry. The company has led to greater international visibility for both the Center for Molecular Immunology and Roswell Park, making it a benchmark example in any analysis of the practical possibility of long-term collaboration in the biomedical business sector.

The very existence of the joint venture, more than five years after its creation, ten years after the opening of diplomatic relations and after several very complex years in the health, economic and geopolitical panorama of the world, should lead us to reflect and draw lessons.

Without pretending to cover all of them, we highlight the following:

- Good science, particularly biomedicine, as a common interest between the scientific and business communities of both countries.
- The possibility of creating, and strengthening, a stable business environment in which innovation-oriented businesses can be developed with shared and protected intellectual property.
- The existence of a business work culture that is not very distant, and that can guarantee an environment of transparent administration, respect for legality and that turns the creativity of our two peoples into an engine for development.

These lessons and many others to be derived from this experience should lead us to imagine a future of new possibilities.

III. Possible futures

The previous sections illustrate a continuity (albeit intermittent and complex) of scientific collaboration actions whose reasons and roots we must try to understand. Both countries, obviously different in size and economic

possibilities, have for decades placed science at the center of their national projects. The first Cuban Academy of Sciences was founded in 1861, and the United States Academy of Sciences in 1863. They were the first two outside Europe.

Then, in the first half of the 20th century in Cuba, the dependent capitalism of the neocolonial republic hampered scientific development; but the Socialist Revolution accelerated it in the second half of the century and that take-off was supported in the 70's and 80's by an extensive scientific collaboration with the Soviet Union and the countries of the European socialist camp.

In the United States also, although for different reasons, an analogous dynamic was imposed: the economic depression of the 1930s affected investment in science; the military effort of the World War and the post-war American world economic leading role accelerated it in the second half of the century.

Simultaneously, in the second half of the 20th century, there were processes of direct connection of science with production and with the life of companies, which were evident in various sectors (chemistry, microelectronics, informatics) but especially in the nascent biotechnology industry. Parallels can also be found in this process between what was happening in the United States and in Cuba.

Very soon after recombinant DNA technology was established in the 1970s, the first biotech company (Genentech) was founded in California in 1976, the first recombinant product for broad medical use (rec insulin) was registered in the United States in 1982, followed by rec interferon in 1986 and the first therapeutic monoclonal antibody in 1997. Many new biotechnology companies were founded in the 80's until they became a high-tech industrial sector with more than 2500 companies. In Cuba, the first institution for the research and production of biotechnological products was founded in 1981, Interferon rec was registered in 1987 and the first therapeutic monoclonal antibody was obtained in 1982. New biotechnology companies also emerged in the 1980s and 1990s, which were grouped in the Scientific Hub in 1992 and in the business organization BioCubaFarma in 2012. BioCubaFarma today groups 47 companies, 13 of them abroad.

Both in Cuba and in the United States, the scientific and productive potential that was emerging in biotechnology was oriented in a privileged way to obtain products for cancer control.

In the field of Oncology, a framework of strengths and weaknesses with complementarities was being formed, making it a fertile ground for collaboration.

Malignant neoplasms are currently the second leading cause of death in both the United States and Cuba. Since the 1970s, both countries have implemented, with different approaches, comprehensive actions for the reduction of cancer mortality.

Cuba and the United States have a very special combination of differences and similarities, the comparative analysis of which can generate useful insights. The first difference is obviously the size of the economies and the volumes of resources that can be dedicated to cancer control. But in contrast to this enormous difference, the incidence and mortality patterns of both countries are close, characterized by long life expectancy, low infant mortality and a minimal fraction of mortality attributable to infectious diseases, with non-communicable chronic diseases prevailing as the leading cause of death, mainly heart disease and cancer.

In contrast, the organization of the Health System and the patterns of medical care, which fundamentally connect scientific developments with patients, differ greatly in both countries.

This polarization of similarities and differences does not occur to this extent with other North-South "country pairs". Its analysis may uncover very interesting facets of the process of transforming scientific research results into public health impact.

The prominence of science in society for more than 100 years, the intentional effort to connect science with the economy, the priority given to the biotechnology sector - and within it to products for cancer control - and the emergence of research and production companies created the objective bases for collaboration between the two countries, not only in science but also in the connection of science with industry.

That explains the stories of collaboration that we have described in the preceding sections of this article, and their resistance to the unfavorable context created by the climate of political hostility and its codification in U.S. laws.

American and Cuban scientists know each other and have always been enthusiastic about collaboration. In decades of political confrontation between the two countries, there has always been closeness between the U.S. scientific community and Cuban scientists. That has not ceased to exist. Of course, it has been tampered with or limited by the blockade and the hostility of U.S. policy towards Cuba. For example, for the last 20 years, in our own Center of Molecular Immunology we have been organizing an international scientific event on cancer immunotherapy every two years. The foreign country that sends the most scientists to that event is the USA.

The characteristic of the human activity that we perform, Science, helps a lot in the approach. Science is not the only intelligent activity of man, of course, but the essential peculiarity of Science is objectivity, the attachment to verifiable data.

A scientist is very attached to the objective value of the data, to prove what he says. When you argue with people who are mentally trained to look for the facts and interpret them, many things are simplified. That scientist comes here and sees the facts in Cuba, the results of the achievements of the Revolution, also the problems we have, but he analyzes them, studies them, and that element of objectivity allows a dialogue between the scientific communities of different countries, with a common basis of connection. You can have scientists of different nationalities and different cultural roots in the same room, and you will find that they understand each other perfectly, because they speak the same language. In the early years of Cuban biotechnology, academic exchanges between Cuba and the United States, although severely limited by the blockade, had a certain level of activity. In the first venture of the nascent Cuban biotechnology, the production of interferon, those relations were present.

Also, in 1981 the organization NACSEX (US-Cuba Scientific Exchange) was created, which obtained authorizations for visits to Cuba by US scientists. In 1986 the U.S. Treasury Department ordered the suspension of the trips because it suspected "possible commercial implications". The Treasury letter to Dr. Halvorson stated that "... nothing of value will be provided to Cuba in return...". NACSEX ceased operations in 1993 but was able to contribute to more than 50 high-level scientists in molecular biology visiting Cuba and contributing to the Cuban effort.

In the field of neurosciences and since the 1970s, collaboration with American scientists had contributed to studies on brain electrical activity in Cuba and to the development of computing, including the manufacture of the first Cuban computers.

But for the most part (there are more than 1.5 million researchers in the United States), American scientists also saw "from afar" the development of science and biotechnology in Cuba and, although some individual academic visits in both directions and meetings in third countries continued to occur, there were no institutionalized actions of collaboration for several decades, neither in the academic field, much less in the business field. Many visa requests for Cuban scientists to participate in events in the United States were denied in those years.

Those were the same decades in which science was consolidated in the world as an institutionalized human activity, rather than as a sum of individual undertakings, and as a task of the States and, increasingly, of the companies.

Projecting these trends into the future, it becomes clear that it will not be possible to separate academic relations from economic relations. It was possible in the 19th century, but not in the 21st century. The future will not be an extrapolation of the past, but will contain discontinuities in trends. In which direction these trends will take us, we do not know. But we do know that it is something to be built consciously.

Such different historical roots will be projected into the future in many fields of social life. Also, in the field of scientific collaboration. At present and even in the context of the complexities of the relationship between the

two countries, multiple contacts are taking place in different sectors of science and projects are being discussed, several of which involve the access of patients in the United States to biotechnological products emerging from Cuban science, the evaluation and joint development of new products, and even the establishment of joint ventures, with research and production capabilities. We do not yet know how many and which ones will crystallize, and how many and which obstacles will have to be overcome, but the process is underway.

If we handle it poorly, the ideology of a science of elitist individualities could prevail, oriented towards the interests of those who already have today much more material resources, and amplifying national and social inequalities, and we will run the risks of the fragmentation of the Cuban scientific project into disconnected collaborative operations, the dismantling of integral programs (such as biotechnology and others), the theft of brains and finally the absorption of the capacities built by the “mass effect” of the much larger, more diverse and economically powerful North American institutional system.

But if we manage it well, the building of collaborative scientific relations between Cuba and the United States, after half a century of separate evolution, may be a unique historic opportunity. It will be decided in the next ten years, maybe less. That is “the art of the possible”.

In other countries of the South, incipient scientific development efforts in the second half of the 20th century could hardly mature, deformed by the influence of U.S. scientific and economic power, and interrupted by military coups and dictatorships. In Cuba, the scientific effort of the last 6 decades occurred in the context of a revolutionary project of national sovereignty and social justice, and matured as a “country program” integrated to the other components of the social project, and in certain sectors, such as biotechnology, connected to the productive and economic projects. In recent years, we scientists have been the protagonists of the heroic resistance of the Cuban people.

This is the science and technology system that must now rebuild academic exchange relations with the United States. This exchange could be born, as is science itself in today's world, with a solid institutional framework, oriented towards explicit objectives, integrated into programs that group together various projects, and connected from the beginning to what we manage to build in terms of economic and cultural relations.

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