The Curious Case of Cuba's Biotech Revolution

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In late September 2018, the first US-Cuban biotech joint venture was established to trial CIMAVax-EFG, an innovative Cuban lung cancer immunotherapy treatment, with the intention of delivering it to patients in the United States. Innovative Immunotherapy Alliance SA was set up by Buffalo-based Roswell Park Comprehensive Cancer Center and Havana's Centre for Molecular Immunology (CIM); two institutions which benefited from the tentative rapprochement between the US and Cuba in mid-December 2014. The sheer fact that such an entity should exist is scientifically and politically ground-breaking for several reasons: First, it testifies to the extraordinary development of biotechnology in Cuba, a case largely overlooked in medical science and business history literature on the field.[1] Havana's Scientific Pole, a complex in Western Havana which hosts over 50 major integrated research, education, health, and commercial biotech institutions, is not included in references to 20 global biotech regions.[2] Lara Marks' masterful 2015 history of the development of monoclonal antibodies (MABs) omits Cuban advances that have placed the island at the forefront of MAB-based immunology therapies.[3]

Second, despite the fact that for nearly 60 years the United States blockade has obstructed Cuba's foreign trade, external financing, technology transfers and scientific exchange, including in the medical field, it is the Cubans who have contributed the innovative science to this joint venture; they have cracked a difficult nut - using immunology therapy to combat cancer. Third, while global biopharma is associated with speculative, mostly private, capital, the Cuban industry is entirely state-owned and financed. The emergence of the Scientific Pole for example, was the result of state planning, not market forces attracting private interests to a given location. Cárdenas points out that 'the State is focused not only on fast returns, but also on long term socioeconomic targets'.[4]

Finally, Cuban 'exceptionalism' does not lie in the mere fact of government support and/or public funding for the biotech industry; several analysts have pointed to this feature in the United States and elsewhere. The exceptionalism lies in the political economy context; Cuba is a small island nation that can boast 'developed-country health outcomes despite its developing-country economy'.[5] Arguably this has been possible because it has a centrally-planned, state-controlled economy, and a development strategy which has prioritised healthcare, education, and research into science and technology from the early 1960s. The universalisation of (free) education, beginning with the Literacy Campaign of 1961 and the University Reform of 1962, generated a 'critical mass' of scientists, many of whom initially were sent abroad to study. The Revolution also committed to provide free public health and pursued a policy of 'medical internationalism' from the outset. But the global pharmaceutical industry is dominated by the United States, the country imposing the comprehensive blockade of the island. Thus, the development of a domestic capacity to produce medical drugs and supplies was an imperative forced on Cuba, particularly after the loss of Cuba's socialist trade partners around 1990. Beyond the political economy framework, also important is the historical context of Cuban medical science, with its focus on parasitology and immunotherapy and the fact that the biotech sector was initiated with researchers came from biophysics and nuclear physics.[6] While Cuban scientists claim that their biotech revolution, 'demonstrates the feasibility of developing a new industry in a developing country under foreign economic pressures', the specific historical and political context within which the sector developed mean that the Cuban case is difficult to emulate.[7]

Biotechnology is the application of biological knowledge and techniques pertaining to molecular, cellular, and genetic processes to develop products and services.[8] Biological research into genomes and cells does not constitute biotechnology unless it involves industrial production. In that sense, Biotechnology is a manufacturing process, but the transformation of the raw material into a final product is done inside a living cell.[9] The world's first biotechnology enterprise was established in the United States in 1976. Just five years later, in 1981, the Biological Front was set up to develop the industry in Cuba. This was the first time in its economic history that Cuba had incorporated itself into an emerging industrial sector. While most developing countries had little access to the new technologies (recombinant DNA, human gene therapy, biosafety), Cuban biotechnology expanded and took on an increasingly strategic role in both the public health sector and the national economic development plan.[10] It did so despite the US blockade obstructing access to technologies, equipment, materials, and even knowledge exchange.

Among Cuba's biotech innovations are the world's first Meningitis B vaccine, treatment for diabetic foot ulcers, vaccines for Hepatitis B and dengue, and the world's first human vaccine with a synthetic antigen (a vaccine against Haemophilus influenza type b, or Hib).[11] Today, Cuba is among world leaders in oncology drugs. In 2012, CIM patented the first therapeutic lung cancer vaccine. In examining the curious case of Cuba's biotech revolution, this article starts with an overview of the industry in the advanced capitalist countries, particularly the United States, to better appreciate what makes the Cuban case so distinctive.

The rise of the biotechnology sector

California hosted the first and the largest biotech companies: Genetech was founded in San Francisco in 1976 by venture capitalist Robert A. Swanson and biochemist Herbert Boyer; and AMGen was set up in Los Angeles in 1980. Boston and San Francisco were leading biotech hubs early on and continue to be dominant. The location was no coincidence. These cities each have three of the nation's 20 top-ranked medical research institutions.[12] Biotech firms set up in close proximity to medical science research institutions (universities, hospitals, research centres) hosting the best scientists and facilities, 'and a globalising market where the best and the brightest from all over the world come to study'[13]. Those institutions receive government funding that runs into the billions of dollars annually. Studies have also shown the importance of access to local venture capital as a determinant of biotech firm location.[14]

In the early 20th century the US pharmaceutical industry developed in clusters between New York and Philadelphia, and these regions went on to develop substantial concentrations of biotech activity in the late 20th century.[15] San Diego, Seattle and Raleigh-Durham subsequently emerged as hubs. By 2002, these three cities had received 'an average of $500 million annually in National Institutes of Health (NIH) funding (in 2001 dollars) for more than a decade and $750 million new venture capital investment during the past six years, and each area also has one or more of the nation's 20 top ranked medical research universities'.[16] By the outset of the 21st century, the US biotech sector was concentrated in 9 of the country's 51 largest metropolitan areas.

Biotechnology took off in Europe in the 1990s, and subsequently in Japan, Singapore and China. By 2009, there were more biotech firms in Europe than in the US.[17] The character of the industries differed in that the US had twice as many publicly listed companies than Europe and more access to venture financing than the European industry. In 2008, three decades after the industry began, there were 1,754 biotech firms in the US, 371 of them publicly listed, and sector employment was hovering below 200,000.[18] But 'progress' was often evasive. Most small biotech firms were losing money. Half of US biotech firms formed since the 1970s had folded or were merged into other companies by 2000.[19] Internationally, the biotech sector did not achieve profits from product sales until 2009.

Nonetheless, billions of dollars poured into the industry. Lazonick and Tulum refer to this as the 'Pisano Puzzle', after Harvard Professor Gary Pisano's 2006 book questioned why money from venture capital and big pharma flowed into an industry in which profits are so hard to come by.[20] The answer is the role of financial mechanisms such as Initial Public Offerings (IPOs), Special Purpose Entities (SPEs), Special Purpose Corporations (SPCs), and patents licenses, in permitting profits to be made from a high-tech sector with low productivity. Start-up firms typically depend on venture capital investment to underwrite their initial costs. Cortright and Mayer explain that once some promising products are developed, venture capitalists and other early-stage investors seek to recoup their investment (or a portion of it) by having the firm issue stock to the public in an 'initial public offering' (IPO).[21] However, biotechnology products can take up to 20 years to commercialise, and many will never reach that point. By 2002, only about 100 biotech-related drugs had reached the market in 30 years, with the top ten accounting for nearly all of the sales.[22] In 2011, Lazonick and Tulum pointed out that virtually all biopharma companies that do IPOs are product-less: 'Rather than waiting 10-20 years to see whether a commercial drug will in fact be produced, the existence of a speculative stock market provides [venture capital and big pharma] with a mode of exit from their investments by mean of an IPO'.[23] Without such mechanisms, capital may never have been made available.

The 1971 establishment of the NASDAQ stock exchange, for financing risk-intrinsic high-tech businesses, and the rising power of financial capital since the early 1980s, shaped the emerging biotechnology sector. 'The stock exchange has become an instrument for subordinating corporations to the management norms and profitability standards requested by the shareholders…the evolution of the biotechnology industry clearly illustrates these findings', concludes Christian Zeller.[24] However, this relationship hides the vital role of US government policy in almost every stage of the biotech industry.

Public money for private profit?

Cortright and Mayer list the forms this take: the government heavily subsidises the training of medical researchers; US patent policy is set by Congress and administered by the US Patent and Trademark Office; the Food and Drug Agency (FDA) has to approve most biotech products and regulates conditions for manufacturing and advertising to consumers; decisions on healthcare and what drugs or therapies to include on national health care programmes like Medicare and Medicaid are decisive.[25] Lazonick and Tulum conclude: 'The biopharmaceutical industry has become big business because of big government [and] remains highly dependent on big government to sustain its commercial success.'[26]

The US government funds basic science through National Institutes of Health. Between 1978 and 2004, NIH spending on life sciences totalled $365 billion in 2004 dollars.[27] US institutions provide legislative support for the private biotech sector; the 1980 Bayh-Dolye Act gave universities and hospitals clear property rights to new knowledge that resulted from federally-funded research. Also in 1980, the Supreme Court decision in Diamond vs. Chakrabarty ruled that genetically engineered life forms are patentable. The Orphan Drug Act of 1983 provided generous tax credits for pharmaceutical companies that develop drugs for rare diseases. By 2008, orphan drugs accounted for 74% of total revenues and 75% of product revenues of the six leading companies.[28]

Lazonick and Tulum argue that these financial mechanisms and the wide scope of IP protection in biotechnology has become an obstacle to follow-on innovation, by limiting the new entrants who would compete to produce better and cheaper drugs, while financial speculation permits stock-market investors to reap huge rewards by trading biopharma stock, even in the absence of a commercial product. A similar view is strongly held by the Cuban medical scientists. Certainly, the absence of such financial mechanisms has contributed towards the distinctive character of their biotechnology industry. However, biopharma developments on the island also build upon a long history of infectious disease vaccinations. And that story begins in the nineteenth century.

The historical trajectory of Cuban medical science

Three private science institutes were set up in 19th century Cuba,[29] but the best known medical scientist of the century is Carlos Finlay who was born in colonial Cuba in 1833 to a Scottish father and a French mother. In 1881, Finlay presented a ground-breaking theory that the transmission vector, or carrier, of yellow fever was the mosquito. The following year, Finlay identified the *Aedas aegypti* mosquito as the culprit, and recommended controls to halt the spread of the disease. His finding was described as the greatest advance in medical science since the discovery of the smallpox vaccine in 1796.[30] Following Cuba's formal independence, between 1902 and 1909, Finlay served as Cuba's chief health officer.[31]

There were other outstanding individuals in the decades that followed, but the period between Cuban 'independence' in 1902 and the Revolution of 1959 were austere years for medical science. The country had only three universities; in Havana, Oriente (Santiago) and Villa Clara (set up in 1952), and they conducted little medical research. In 1937, Dr Pedro Kouri privately founded the Institute of Tropical Medicine, which did conduct investigations and earned a good international reputation among parasitologists and other specialists of Tropical Medicine.

Private medical clinics thrived, largely by offering US clients' services at lower cost than home, or services not available in the US.[32] There was a tradition of eminence in surgery. The big money spinner was cosmetic surgery which generated $5 million a year between 1948 and 1958. The main causes of childhood death on the island were parasitic infestation, gross malnutrition and enteric infections, leading to diarrhoea and dehydration. But the paediatrics department at the University of Havana Medical School barely addressed these ailments. Instead it specialised in hyperactivity and leukaemia.

There was also a medical focus on the diagnosis and treatment of cancer. Created in 1925, the League against Cancer in Cuba secured private funding to set up the hospital 'Calixto Garcia' where prestigious Cuban medics held private clinics. In 1929, the Institute of Cancer was set up, the first to treat malignant growths. Subsequently two more oncology centres were founded, mainly to treat patients in the advanced stages of cancer. Most of the doctors did not receive payment; this was philanthropic work. They did teach, however, and exchanged scientific information and experiences with oncology centres in developed countries.

The 1950 report by the Truslow Commission of the International Bank of Reconstruction and Development declared that 'the Mission could not find any suitable applied research laboratory, public or private, in Cuba'.[33] Three years later, the 1953 census recorded that 60% the population had between three years and no education.[34] Just over 1% of Cubans had university education, and of those only 1.7% were science students who mostly graduated without practical experience.

Revolutionary change from 1959

Speaking at the Cuban Academy of Sciences in mid-January 1960, one year after the Rebel Army took power, Fidel Castro declared: 'The future of Cuba will be a future of men of science.' This must have seemed like a pipe dream, given the backward state of Cuban scientific research and generally low level of education. The Revolution, declared Castro, was sowing opportunities for intelligence. It needed thinking men who would put their intelligence to 'good', on the side of 'justice', in the interests of the nation.

Initiated the following January, the literacy campaign of 1961 reduced illiteracy from 24% to 4% in Cubans over-ten years old within one year. It was followed by the University Reform Law in January 1962, which removed their traditional autonomy and, by eliminating fees and facilitating access at all levels, opened the universities to the children of workers, peasants and non-white Cubans. Courses were introduced to train the specialists required for the Revolution's economic development plans. In 1962 the Cuban government created the National Commission for the Academy of Sciences of Cuba. New schools, colleges and universities were built, new teachers trained. Thousands of Cuban students studied in the socialist bloc countries, while others received scholarships from the west. Free, universal public healthcare provision was introduced.[35] From 1962 a national immunisation programme provided all Cubans with eight vaccinations free of charge. Infectious diseases were rapidly reduced, then eliminated, including polio (eliminated 1962); malaria (1968); diphtheria (1971); measles (1993); pertussis (1994); and rubella (1995).[36]

Guevara: revolutionary, medic, industrialist

In 1959, Cuba was dependent on US pharma for medicines. The market was dominated by two firms which made exorbitant profits. The industry was expropriated by revolutionary decree, putting production and distribution of medicines into government hands. It fell under the jurisdiction of Ernesto 'Che' Guevara as Minister of Industries. In his pre-revolutionary life, Guevara had graduated as a medic and researched allergies, asthma, leprosy and nutritive theory. As Minister, he set up nine research and development institutes, including, in 1963, the Institute for the Development of the Chemical Industry to foster the industrial application of human and animal anti-biotics.[37] While progress was limited, the institute established a research methodology which later became a distinctive feature of Cuban biotechnology. 'The idea was excellent', claims Tirso Saenz, then Guevara's Vice Minister of Science and Technology, 'to make an institution with what they call a complete cycle of innovation. The institute develops products at a scale where it can build pilot plants which, if successful, are turned into production plants.'[38]

Guevara commandeered an abandoned farm, to use for socio-productive and botanical experiments.[39] The personnel were students from the Rebel Army School, and they were joined by Chinese medical scientists, a Cuban post-doctoral researcher and three agronomy engineers. From the farm two dozen varieties of medicinal plants were supplied to scientists conducting laboratory experiments in the Hospital of Oncology in Havana. The fourth floor of the Hospital had 40 scientists working under Guevara's directives on laboratory experiments with plants, animals and raw materials.[40]

Guevara left Cuba in 1965 and the farm was transferred to the newly established National Centre for Scientific Research (CENIC), set up to initiate biological studies and a new scientific infrastructure. The directors in the post-1980 biotechnology institutes all began as students in CENIC.[41] Throughout the 1960s and 1970s, thousands of Cubans trained as scientists and engineers. Cuba achieved 1.8 researchers per 1,000 inhabitants, well above the Latin America mean (0.4) and close to that of Europe (2.0).[42] Among the many institutions created was the National Council of Science and Technology, in 1975, the same year that a new national scientific policy was approved at the First Congress of the Cuban Communist Party.

By the 1980s Cuba had the health profile of a highly developed country, having eliminated most infectious and poverty-related diseases, so that ailments like cancer, diabetes and heart disease became priorities, on a par with the developed capitalist world. These conditions are expensive to treat. Additionally, a new law passed by US President Reagan in 1982 prohibited foreign nations from exporting goods and equipment to Cuba if any part or process in its manufacture had been mediated by US companies or individuals. Cuban subscriptions to US science and technology journals could not be honoured.[43]

The curious origins of Cuban biotechnology

Cuba's biotechnology sector emerged independently from both the Soviet Union and the corporate capitalist model in the US and Europe.[44] Driven by public health demand, it has been characterised by the fast track from research and innovation to trials and application. This is illustrated by the story of how interferon was used to arrest a deadly outbreak of the dengue virus in 1981.[45]

Interferons are ‘signalling’ proteins produced and released by cells in response to infections (viruses, bacteria, parasites and tumour cells) which alert nearby cells to heighten their anti-viral defences. They were first identified in 1957 by Jean Lindenmann and Aleck Isaacs at the National Institute of Medical Research in London during their research into ‘viral interference’ - the process by which a cell that is infected by one virus can produce an immune response which protects it from another virus. Following this breakthrough, in the 1960s Ion Gresser, a US-researcher in Paris, showed that interferons stimulate lymphocytes that attack tumours in mice.

In 1970s, US oncologist Randolph Clark Lee, Director of a Cancer Hospital in Houston, Texas, took up this research. Catching the tail end of US President Carter’s improved relations with Cuba, Clark joined a delegation to visit the island’s health facilities. During the trip Clark met with Fidel Castro and convinced him that interferon was *the* wonder drug. Clark offered to host a Cuban researcher at his hospital. Castro persuaded him to take two. Shortly afterwards, a Cuban doctor and a haematologist spent time in Clark’s laboratory. He gave them the latest research about interferon and put them in contact with Kari Cantell, the researcher who, in the 1970s, had isolated interferon from human cells. Cantell’s commitment to global health led him to share his breakthrough without patenting his interferon procedure. In March 1981, six Cubans spent 12 days in Finland learning to produce large quantities of interferon. They were from the first generation of medical scientists entirely trained under the Revolution of 1959.

In April 1981, the day after returning from Finland, the Cubans moved into ‘House 149’, a former mansion converted into an interferon laboratory, which became the Centre for Biological Studies. Fidel Castro visited them frequently, securing them the resources they required. Within just 45 days the Cubans had produced their first Cuban batch of interferon. Safety and sterility tests were performed on mice before three of the scientists inoculated themselves. They experienced a slight rise in temperature, nothing worse. The laboratory in Finland confirmed the quality of their interferon.

Just in time, it turned out. Weeks later Cuba was struck by an epidemic of dengue, another disease transmitted by mosquitos. Notably, it was the first time this particularly virulent strand, which can trigger life-threatening dengue haemorrhagic fever, had appeared in the Americas. The epidemic affected 340,000 Cubans with 11,000 new cases diagnosed every day at its peak.[46] 180 people died, including 101 children. The Cubans suspected the CIA of releasing the virus. Castro announced: 'We share the people's convictions and strongly suspect that the plagues that have been punishing our country, especially the hemorrhagic [*sic*] dengue, could have been introduced into Cuba, into our country, by the CIA'.[47] The US State Department flatly denied it, although a recent Cuban investigation claims to provide evidence that the epidemic was introduced from the US.[48]

At the height of the epidemic, Cuba's Ministry of Public Health (MINSAP) authorised the scientists in House 149 to use interferon to halt it. This was done at great speed. They found that in advanced cases of dengue, interferon was not useful, but in recent infections in children, it cut short cases of haemorrhagic dengue shock. Mortality declined. In their historical account, Cuban scientists Caballero Torres and Lopez Matilla claim: 'It was the most extensive prevention and therapy event with interferon carried out in the world. Cuba began to hold regular symposia, which quickly drew international attention'.[49] The first international event in 1983 was prestigious; Cantell gave the keynote speech and Clark attended with Albert Bruce Sabin, the Polish American scientist who developed the oral polio vaccine that has helped to nearly eradicate the disease globally.

Convinced about the contribution and strategic importance of innovative medical science, the Cuban government set up the 'Biological Front' to develop the sector. In January 1982, the Centre for Biological Studies moved from House 149 into a newly built and better-equipped laboratory, with 80 researchers. Cuban scientists went abroad to study, many in western countries. Their research took on more innovative paths, as they experimented with cloning interferon. By the time Cantell returned to Cuba in 1986, the Cubans had developed a second generation interferon cloned in yeast.[50]

In 1982, the United Nations Industrial Development Organisation (UNIDO) launched a competition for an internationally-funded project to foster biotechnology in the 'Third World'. UNIDO's International Centre for Genetic Engineering and Biotechnology was to facilitate North-South knowledge transfer and cooperation in science. Reagan's 1982 measures tightening the US blockade gave Cuba an additional incentive to apply. In 1984, the fund was awarded to a joint application by

India and Italy. However, the Cubans, and most emphatically Fidel Castro, decided to proceed without support. Construction immediately began on Cuba's showpiece Centre for Genetic Engineering and Biotechnology (CIGB), to work in biology, chemical engineering and physics. It opened just two years later in 1986. By then Cuba was submerged in another health crisis, a serious outbreak of Meningitis B, which further spurred Cuba's biotechnology sector.

Cuba's Meningitis Miracle

In 1976, Cuba was struck by meningitis B and C outbreaks.[51] Since 1916 only a few isolated cases had been seen on the island. At that point, internationally, vaccines existed for Meningitis A and C, but not for B. Cuban health authorities secured a vaccine from a French pharmaceutical company to immunise the population against type C Meningitis. However, in the following years, cases of type B Meningitis began to rise. With infections and fatalities on the increase, in 1983 MINSAP established a team of specialists from different medical science centres, led by a woman biochemist, Concepción Campa, to work intensively on finding a vaccine. By 1984 Meningitis B had become the main health problem in Cuba. After six years of working around the clock, in 1988, Campa's team produced the world's first successful Meningitis B vaccine. Again, the scientists tested the vaccine on themselves, and their own children, before beginning clinical trials. Between 1987 and 1989, a randomised, double-blind controlled trial of the vaccine efficacy took place, with over 100,000 students aged 10 to 14 years. The results showed the vaccine to be 83% effective. Another member of Campa's team, Dr Gustavo Sierra recalled their joy: 'this was the moment when we could say it works, and it works in the worst conditions, under pressure of an epidemic and among people of the most vulnerable age.'[52]

MINSAP decided that more lives would be saved by starting nationwide vaccinations immediately with an 83% effective vaccine than delaying until a more effective one was produced (or not). During 1989 and 1990, three million Cubans, those most at risk (children and young people), were vaccinated. In the roll out, the efficacy ranged from 83% to 94% in difference provinces. No severe reactions occurred and another severe disease outbreak had been halted. Subsequently, 250,000 young people were vaccinated with the VA-MENGOC-BC vaccine, a combined Meningitis B and C vaccination. It recorded 95% efficacy overall, with 97% in the high-risk three months to six years age group. Cuba's Meningitis B vaccine was awarded a UN Gold Medal for global innovation. This was Cuba's meningitis miracle.[53]

‘I tell colleagues that one can work 30 years, 14 hours a day just to enjoy that graph for 10 minutes,’ says Agustin Lage, Director of the Centro for Molecular Immunology (CIM), referring to an illustration of the rise and sudden fall of Meningitis B cases in Cuba. ‘Biotechnology started for that. But then the possibilities of developing an export industry opened up, and today, Cuban biotechnology exports to 50 countries.’[54] This possibility came about after an outbreak of Meningitis B in Brazil a few years later. ‘The Brazilians bought the Cuban vaccine. It was a huge purchase and that money was invested in expanding the biotechnology industry here’, says Lage.

By 1986, Cuba had 39,000 scientific workers; one for every 282 people. 23,000 were involved in research. Thousands had been trained abroad, mainly in the socialist countries, but also in Western Europe. The revolutionary government’s investments in education and public health had created the ‘critical mass’ necessary for further progress in medical science. The Biological Front invested $1 billion to develop a biotechnology industry between 1981 and 1989, including establishing the Western Havana Scientific Pole, known as Science City, between 1986 and 1991.[55]

Science City

Science City is a cluster of biotechnology institutions that co-ordinate and integrate their work. Centre directors met monthly to discuss projects and exchange information in meetings attended by top government officials, including Fidel Castro. Thousands of housing units were constructed locally to enable the institution’s employees, working daily shifts of 14 hours, to walk to work. At the centre of Science City is the CIGB, which received the greatest investment in a Cuban science institution. Other institutions followed:

- 1987, the Centre for Immunoassay: to manufacture computerised and automated equipment for biochemical tests and screenings to detect pathologies.
- 1989, the National Centre for Meningococcal Vaccines: for research and production of the VA-MENGOC-BC vaccine and other human vaccines. It was renamed the Finlay Institute (to honour Carlos Finlay) in 1991.
- 1990, the Cuban Centre for Neuroscience: for the diagnosis and treatment of brain diseases.
- 1992, the Centre of Biopreparados: to produce Cuban biologicals.
- 1994, Centre of Molecular Immunology.

Along with the pace of these state investments, the astonishing fact is that they took place in the midst of Cuba's most acute economic crisis: the Special Period which began in autumn 1990, as the case of Cuba's Centre for Molecular Immunology shows.

Oncology meets biotechnology

In the 1980s, biotechnology and oncology began to converge globally. In Cuba's National Institute of Oncology and Radiobiology (which emerged from the Hospital of Oncology that Guevara had once commandeered), Lage was among a group of young scientists working on an experimental project into the role of immunology to fight cancer. In the early 1980s, INOR developed and trialled the first Cuban monoclonal antibodies (MABs) – clones of single antibody cells - with multiple medical uses. By the late 1980s, MABs were used for detecting malignant tumours and preventing organ rejection in Cuban transplant patients.[56] After a visit to INOR in 1989, Fidel Castro recommended expanding the institution, integrating it into the Scientific Pole, and providing it with industrial production capacity and authorisation to export. Construction began in 1991. In December 1991, when the USSR collapsed, only the prefabricated columns of the new Centre of Molecular Immunology (CIM) had been laid. Nonetheless, Fidel would not allow the project to be halted. Lage describes this as: 'a very audacious decision, when the country had no financial resources to say "this centre has to be completed". It was a Fidel's decision, a kind of offensive defence.'[57] The fact that the sector was entirely state-owned and controlled made that decision possible, and necessary, if CIM was to continue.

The Special Period - biotechnology exempt!

The collapse of the USSR and Eastern European socialism had a traumatic economic impact on Cuba. From having 85% of its trade conducted under planned agreements with socialist countries (unimpeded by the US blockade), Cuba was suddenly dependent on an international capitalist market dominated by the US, the country pursuing a merciless blockade on the island. One-third of world pharmaceutical production took place in the US. From where could Cuba get medical equipment and medicines?

In 1993, as Cuban socialism tottered on the edge of an abyss after GDP plummeted 35% in two years, Elsewhere there were drastic cuts, things fell apart, production and transport halted, belts tightened and scarcity appeared in almost every sector and space. In this context, the inherently high-risk nascent biotechnology sector was selected as one of three strategic economic sectors for investment, along with tourism and food production.

Between 1990 and 1996, another US $1 billion (1.5% of Cuba's GNP) was invested into the Scientific Pole. It functioned as an incubator of medical science enterprises which were protected directly by the President's office during the Special Period. When the institutions began to export, that money was reinvested into them; a 'closed economic cycle' was created. Thus it was in the most difficult economic period that Cuban biotechnology flourished. The motivation was domestic public health benefits, explains Lage. 'And because of the US blockade. We could not afford expensive drugs, sometimes we could not get them even if we had all the money in the world, because they would not sell them'.[58] Elsewhere in Latin America, neoliberal structural adjustment programmes saw public health provision privatised and rolled back in the 1990s, but the Cuban government held steadfast to its social-welfare orientated centrally-planned economy.[59]

Gradually the dust covering the country's pharmacy shelves was replaced by Cuban manufactured 'biosimilars' - copies of traditional and biotechnological medicines, as Cuba's medical science sector was channelled to meet this need. Copying biotech products involves high-level science; to synthesise genes and introduce them into cells to clone them. Cuba's interferon, erythropoietin, the vaccine against Hepatitis B have all been 'copy products'. Homeopathic alternatives also claimed shelf space. The need for cheap generic drugs was international, so Cuba increased its pharmaceutical exports. By the mid-1990s, they were earning $100 million a year.

Biotechnology with Cuban characteristics

The president of a multinational pharmaceutical company once told Lage that he was bound by his share-holders' interests. The director of CIM asked how many shareholders his company had. The answer was 300,000. Lage replied, 'well, I have 11 million. Our shareholders are all 11 million Cubans!'[60] Founded solely through state investment, with financing guaranteed through the state budget, the Cuban biopharma sector is state owned, with no private interests or speculative investments. Profit is not sought domestically, because the sector is completely integrated into the state-funded public health system. National health needs are prioritised. Medicines that Cuba cannot afford, or cannot get access to because of the US blockade have to be produced domestically. Today, 517 of the 800 or so medicines consumed in Cuba are produced domestically, close to 70%.

Cooperation prevails over competition as research and innovations are shared between institutions. Teams of scientists are established to take a project through from basic science, to product-oriented research, to manufacturing and marketing; activities that are carried out by different businesses in most countries. Dr Kelvin Lee is the Chair of Immunology in Roswell Park Comprehensive Cancer Centre in Buffalo, New York, and is currently leading clinical trials on CIM's CIMAVax-EFG, a therapeutic cancer vaccine for patients with advanced lung cancer.[61] He highlights these 'striking' and 'unique' characteristics of the Cuban biotech sector: 'They start with identifying a need, then figure out the science to develop that in the lab, manufacture their agent, test it in the Cuban medical system and then commercialise it and sell it overseas. Their system is particularly nimble in that ability.' The disadvantage the Cubans face, he adds, is that they can't pursue thousands of good ideas and write off those which don't work as sunk costs. 'They don't have the resources to do that'.[62] Their access to capital is extremely limited. So what, then, have been fruits of this distinctive Cuban system?

The Cuban cure

In 2015, the World Health Organisation announced that Cuba was first in the world to eliminate mother-to-child HIV transmission. Cuba has prevented an AIDS epidemic with domestically produced antiretroviral medicine that halts patient transmission, as if it were a vaccine. Cuba's mortality curve for AIDS continues to fall. The universal use of the CIGB's hepatitis B vaccine on new-borns means Cuba should be among the first countries free from Hepatitis B. This is one of the eight vaccines (out of 11 vaccines for 13 diseases) administered to Cuban children which are produced in Science City. Within ten years, 100 million doses of Cuba's Hep B vaccine were used around the world.

By 2017, CIGB employed 1,600 people and sold 21 products internationally. CIGB's portfolio of innovations with major public health implications includes Heberprot-P for diabetic foot ulcers, affecting some 422 million people worldwide, which reduces the need for amputations by 71%.[63] In ten years, 71,000 patients in Cuba have been treated with Heberprot-P plus 130,000 people in 26 other countries. The CIGB also has products for the agricultural and food production sectors.

Cuba was second in the Americas to achieve a complete congenital hypothyroidism screening programme, after Canada and before the United States. Cuba's Immunoassay Centre developed its own Ultramicroanalytic System (SUMA) equipment for prenatal diagnosis for congenital anomalies. Among other things, nearly 4 million babies have been tested for congenital hypothyroidism, which effects the production of thyroxine, a hormone needed for normal growth and development.[64] Treatment is easy and cheap. 'Since this system was introduced some children who would have had problems with mental development are in the universities' (Lage). In 2017, the Immunoassay Centre had 418 workers producing 57 million tests per year for 19 different conditions, including Hepatitis B and C, dengue fever, cystic fibrosis, Chagas disease, leprosy and HIV.

Cuba's Centre for Neuroscience is developing cognitive and biomarker tests for early screening of Alzheimer's disease. They have developed a hearing aid for children that costs just (US) $2, a fraction of the cost in the US and Europe, made to individual specification using a 3D printer.[65]

Cuban professionals have received ten gold medals from the World Intellectual Property Organisation (WIPO) over 26 years. The first was in 1989 for the Meningitis B vaccine; another was for the *Haemophilus influenza* type b (Hib) vaccine,[66] the result of a collaboration with the University of Ottawa; also for Heberprot-P; and Itolizumab for treating psoriasis.[67] By summer 2017, the Cuban biotech sector boasted 182 inventions with 543 patents granted in Cuba, 1816 patents abroad and 2336 patent applications.[68] Its products were marketed in 49 countries and it had partnerships with nine countries in the global south. Cuba's pharmaceutical industry has the capacity for large-scale production of Cuban and generic drugs for export cheaply to developing countries.

CIM's focus is on biotechnology of mammalian cells; monoclonal antibodies and cancer vaccines. Cancer is the biggest cause of death for under 65 year olds in Cuba, and second only to heart disease for over 65s. By summer 2017 CIM had 1,100 employees, 4 manufacturing facilities, 25 products in the pipeline, 6 registered products, exported to 30 countries, had 5 joint-venture companies abroad, 45 patented inventions, and 750 patents abroad. Over 90,000 Cubans had been treated by CIM products. Among CIM's most exciting innovations is CIMAvax: EFG, the lung cancer immunotherapy.

The term 'cancer' refers to a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Epidermal growth factor, or EFG, is a cellular protein that stimulates cell growth by binding to cells via epidermal growth factor receptors (EGFRs) on the cell surface. Back in 1984, Lage and the scientists at INOR were first in the world to describe the role of EGFRs in breast cancer: EGFRs were over-expressed in 60% of human breast tumours. They discovered that EGF was rapidly distributed, reached tumour cells and recognised specific cell membrane receptors. Lage reported: 'These results suggest that high doses of EGF could eventually be used for inhibition of the cell proliferation in some tumours.' Up until that point, EFG had been seen as part of the cancer problem; it nourishes tumours yet is natural to the body so it does not trigger the immune system. The Cubans were proposing to use human EFG as part of the solution: as an active agent that could be used to interfere with the normal, cancer-producing binding of EFG to its receptor – the EFGR.[69]

It is because the immune system struggles to recognise cancer as foreign to the body, that immunology therapy to combat cancer had proven so difficult. CIM wanted to use EFG to 'train' the body to respond to EFG and so produce cancer-specific antibodies. No other cancer researchers had managed it. This therapy would require one or two doses of a vaccine which would be cheap to develop and could be delivered through primary health care. This suits for the Cuban medical system. However, because it does not involve a lengthy course of expensive therapy in high-tech institutions, it is arguably antithetical to the profit-motivated interests of the global biopharma corporations. CIMAVax built on the Cuban therapeutic expertise of the vaccinologists at the Finlay Institute (Meningitis B) and the CIGB's work on recombinant protein from Neisseria meningitides bacteria P64 K. By using P64 K as a carrier protein with which to introduce EFG into patient's body, the researchers at CIM broke the body's tolerance to its own EFG.[70] The results are a vaccine that helps the body to help itself. Dr Kelvin Lee points out that the Cubans 'designed their lung cancer vaccine to actually be useful in things like colon cancer, head and neck cancer, breast cancer, pancreatic cancer. It has broad applicability.'[71] The Roswell Park/CIM joint venture, Innovative Immunotherapy Alliance, will be investigating some of these additional potentials.

These biotech achievements are accompanied by demographic ones. Most employees in Cuba's medical science centres are the children and grandchildren of workers and peasants, beneficiaries of Cuba's free education system. Today, 66% of Cuba's science and technology personnel are women.[72] The inordinate additional burdens imposed on the sector by the unrelenting and extensive US blockade has undoubtedly impoverished Cuba, denying the island access to resources, markets and knowledge transfers. But it has also fostered resilience and creativity in Cuban scientists.[73]

BioCubaFarma

In 2012, BioCubaFarma was created as a kind of 'holding company' for the pharmaceutical and biotechnology sectors. It integrated 38 companies, 60 manufacturing facilities and 22,000 workers, almost one-third of them scientists and engineers. By 2017, BioCubaFarma was exporting to nearly 50 countries with over 2,000 patents granted abroad. This reorganisation of Cuban medical science is integral to the broader restructuring of the Cuban economy under the 'guidelines for updating the economic and social model'. The economic reforms, which were initially introduced in 2011, confirm a key role for the biopharma sector in the national development plan. But only 1% of the nearly 3,000 Cuban state enterprises export innovative scientific products. How can this sector expand without the kind of speculative private investment and profit-motivated competition which characterises the capitalist biotech industry?

Lage conceptualises 'high-tech socialist state enterprises' in Cuba, requiring a distinct regulatory framework from the 'budgeted sector' (health, education and other social provisions funded entirely by state budget) and the state enterprise sector (state owned and expected to contribute towards the national coffers).[74] There is commitment to maintain biotechnology institutions under state control, with state investment for scientific research, with the sector increasingly contributing to economic growth through the export of high value-added products in a context of a state-monopoly over foreign trade. This requires strengthening of the integration between science and production, research institutions and universities and the promotion of the close-cycle of production.

Cuban biotech exports

Several global biopharma corporations have demonstrated interest in Cuban biotech products, but the US blockade, and the threat of receiving a huge fine, has largely proven an effective disincentive. Cuban collaborations with the global south have been more successful, in terms of exports and joint ventures. The knowledge economy in small countries has to be developed on the basis of exports, because domestic demand is insufficient. Between 2008 and 2013, Cuban biotech sales earned $2.5 billion USD.[75] By 2017, this had risen to $500,000 annually. The low cost of Cuba's biopharma exports is an incentive for governments in the global south to pursue deals. CIMAvax costs $1 per shot to manufacture, much cheaper than alternative lung cancer treatments.

The sector has also established joint ventures with foreign (state) companies. By 2017, the Cuban biotech sector had joint ventures operating in Brazil, China, Venezuela, Algeria, South Africa, Vietnam, India, Thailand and Iran. CIM alone has three joint ventures in China, manufacturing, variously, monoclonal antibodies and therapeutic cancer vaccines, recombinant proteins and biotech products for agriculture. Lage boasts that China - a country with 1 billion inhabitants, which produces aeroplanes and heavy industry - made its first monoclonal antibodies with Cuban technology.[76] The CIGB also has two joint ventures with China. A Cuba-China workgroup oversees the collaboration between the two countries. CIM also has two marketing joint-ventures, in Spain, for therapeutic cancer vaccines, and in Singapore for monoclonal antibodies. Another mixed enterprise is being set up in Russia.

The first Cuban patents are expiring, and the race is on to produce new innovative products. Globally, the average annual costs of research and development for new drugs is increasing. Between the 1980s and 2006 it increased 7.4%.[77] A 2014 report calculated the cost of developing a prescription drug that gains market approval at $2.6 billion, a 145% increase over their previous estimate in 2003.[78] Cuba is now bidding for substantial foreign investment in its biopharma industry.[79] However, there is no intention to relinquish state ownership of the sector, or to privatise it in any other form. The Cuban government does not want foreigners to fund innovations, thus claiming a stake in them. It wants investment in creating its industrial production capacity and it needs partners to help insert Cuban products into the global market, subverting the US blockade and increasing export earnings.

In the process of unravelling the US-Cuban rapprochement, on 8 November 2017, US President Trump's administration published a list of Cuban entities and sub-entities which US citizens and businesses are prohibited from engaging. This placed the breaks on new cooperation with the US, and because of the extraterritorial character of the blockade, with its European allies too. However, the insertion of a 'grandfather' clause meant that collaborations licensed under Obama, like the one between CIM and Roswell Park, can continue. There are ways and means around these regulations, even for US businesses, if they are determined. And given Cuban medical science breakthroughs on some key global health issues, such as cancer, HIV and AIDs, hepatitis and infectious diseases, it is likely they will find increasing incentives to do so.

Conclusion

With increasing frequency, Cuba's biotech breakthroughs are making global headlines. Cuba's biotechnology success can be understood in the context of the post-1959 commitment to high-standard, universal free public health and education, which created a 'critical mass' of medical scientists. It also reflects the political will of the country's leadership, particularly Fidel Castro, to develop science and technology as a means to socioeconomic development. It builds on a long history of infectious disease research and vaccinations. The US blockade also imposed the need to meet domestic demand for medical products with domestic production. The question of state control in a planned economy is also key. The flow between universities, research centres, medical science enterprises and the public health system is far more fluid than elsewhere, precisely because there is no proprietor-based conflicts of interest. The state controls production and distribution, equally of scientists and researchers as of medical products and innovations.

Research demonstrating the 'inseparability of the biotechnology industry and the state…in the US and elsewhere',[80] highlights that the curious case of Cuba's biotech revolution is about far more than government support for the sector. The US government supports the biopharma sector with public-research funding, legislation and patenting laws. It has also fostered the venture capital sector, on which biotech firms principally rely, through favourable monetary and fiscal policies and regulations. In the US, the danger is that the private interests of venture capitalists obstruct medical science innovations which would bring public health benefits globally. In Cuba, the challenges are accessing capital and navigating the US blockade which obstructs access to foreign biopharma partners, export markets, and patents and resources from around the world.

[1] Notable exceptions include work by historians of science Angelo Baracca and Rosella Franconi, for example, 'Cuba: the strategic choice of advanced scientific development, 1959-2014', *Sociology and Anthropology* 5, 4 (2017): 290-302; political geographer Simon M Reid-Henry, *The Cuban Cure: Reason and Resistance in Global Science*, (Chicago: The University of Chicago Press, 2010); and in the area of innovation theory, Andrés Cárdenas, *The Cuban Biotechnology*

Industry: Innovation and universal health care, 2009. https://pdfs.semanticscholar.org/df8b/95006fb835075a7b50a51cf3f61273b00304.pdf. Cuban medical scientists contribute to international journals, but these provide technical rather than historical accounts.

[2] For example, Christian Zeller, 'The Pharma-biotech Complex and Interconnected Regional Innovation Arenas', *Urban Studies* 47, 13 (2010): 2867–2894.

[3] Lara V Marks, *The Lock and Key of Medicine: Monoclonal Antibodies and the Transformation of Healthcare*, (New Haven and London: Yale University Press, 2015).

[4] Cárdenas, *Cuban Biotechnology*, 7.

[5] Cárdenas, *Cuban Biotechnology*, 1.

[6] I am grateful to the anonymous reviewer who highlighted this element as decisive.

[7] Ernesto Lopez Mola, Ricardo Silva, Boris Acevedo, José A Buxadó, Angel Aguilera, and Luis Herrera, 'Biotechnology in Cuba: 20 years of scientific, social and economic progress', *Journal of Commercial Biotechnology*, 13, 1 (2006), 1-11.

[8] Joseph Cortright and Heike Mayer, *Signs of Life: The Growth of Biotechnology Centres in the US*, (Massachusetts: The Brookings Institution Center on Urban and Metropolitan Policy, 2002): 6.

[9] Agustín Lage, Director of Cuba's Centre for Molecular Immunology, interview with the author in Havana, Cuba, 7 July 2017.

[10] The focus in this article is biotechnology for human healthcare, not animal healthcare or agriculture where Cuba also boasts some innovative developments.

[11] Halla Thorsteinsdóttir, Tirso Saenz, Uyen Quach, Abdullah S Daar and Peter A Singer, 'Cuba – innovation through synergy', *Nature Biotechnology*, 22, (2004): 21.

[12] Cortright and Mayer, *Signs of Life*, 14.

[13] Zeller, *Pharma-Biotech Complex*, 2889.

[14] Cortright and Mayer, *Signs of Life*, 3.

[15] Zeller, *Pharma-Biotech Complex*, 2883.

[16] Cortright and Mayer, *Signs of Life*, 33.

[17] Lazonick and Tulum, 'US biopharmaceutical finance and the sustainability of the biotech business model', *Research Policy* 40 (2011), 1182.

[18] Lazonick and Tulum, *US biopharmaceutical finance*, 1170.

[19] Cortright and Mayer, *Signs of Life*, 8.

[20] Lazonick and Tulum, *US biopharmaceutical finance*, 1170; Gary Pisano, *Science Business: The Promise, the Reality, and the Future of Biotech*, (Boston, MA: Harvard Business School Press, 2006).

[21] Cortright and Mayer, *Signs of Life*, 19.

[22] Cortright and Mayer, *Signs of Life*, 9.

[23] Lazonick and Tulum, *US biopharmaceutical finance*, 1172.

[24] Zeller, *Pharma-Biotech Complex*, 2870.

[25] Cortright and Mayer, *Signs of Life*, 9.

[26] Lazonick and Tulum, *US biopharmaceutical finance*, 1180.

[27] Lazonick and Tulum, *US biopharmaceutical finance*, 1176.

[28] Lazonick and Tulum, *US biopharmaceutical finance*, 1178.

[29] The Institute of Research in Chemistry (1848); the Observatory of Meteorology and Physics (1856); and the Royal Academy of Medical, Physics and Natural Sciences (1861), founded by the Spanish queen's decree. The word 'Royal' was dropped in 1902 following Cuban 'independence'.

[30] US President Obama acknowledged Finlay's contribution when he announced rapprochement between the US and Cuba, 17 December 2014. https://obamawhitehouse.archives.gov/the-press-office/2014/12/17/statement-president-cuba-policy-changes

[31] Many Cubans refer to this period as the 'Pseudo-Republic' as US domination of the island effectively turned it into a semi-colony or dependency.

[32] This and following information draws on Theodore MacDonald, *Hippocrates in Havana: Cuba's Health Care System* (Mexico: Bolivar Books, 1995), 15-79.

[33] International Bank for Reconstruction and Development (IBRD) in collaboration with the Government of Cuba, *Report of the Mission to Cuba* (Washington DC: Office of the President, 1951), 223.

[34] 31% of Cubans over six years old had no schooling; another 29.4% had three years' schooling or less. In rural Cuba, 41.7% of over-ten year olds were illiterate.

[35] C. William Keck and Gail A. Reed, 'The Curious Case of Cuba', *American Journal of Public Health* 102, 8 (2012).

[36] Baracca and Franconi, *Cuba: strategic choice*, 9; MacDonald, *Hippocrates in Havana*, 28.

[37] See Yaffe, *Che Guevara: the Economics of Revolution* (London: Palgrave Macmillan, 2009), 163-198.

[38] Tirso Sáenz, interview with the author in Havana, 20 February 2006.

[39] The farm was called Ciro Redondo after a fallen Rebel Army captain from Guevara's column.

[40] Yaffe, *Che Guevara*, 188-190.

[41] José Luis Rodríguez, former Minister of the Economy, interview with author in Havana, 20 December 2016.
[42] Lopez Mola, *Biotechnology in Cuba*, 2.
[43] MacDonald, *Hippocrates in Havana*, 143.
[44] Reid-Henry, *Cuban Cure*, 26. Biological sciences stagnated in the USSR from the 1920s to the mid-1960s, under the influence of Trofim Lysenko. In 1948, the study of genetics was outlawed. See Reid-Henry, *Cuban Cure*, 26.
[45] Information from Baracca & Franconi, *Cuba: Strategic Choice*; Idania Caballero Torres and Lien Lopez Matilla, *La historia del CIM contada por sus trabajadores*', unpublished paper, 2017. Lage, *interview*; and Reid-Henry, *Cuban Cure*.
[46] New York Times, 'Epidemic in Cuba sets off dispute with US', 6 September, 1981. www.nytimes.com/1981/09/06/world/epidemic-in-cuba-sets-off-dispute-with-us.html (last accessed 29/11/18)
[47] Fidel Castro, 26 July 1981, cited by New York Times, *Epidemic in Cuba*.
[48] Marieta Cabrera, 'La ciencia desnuda un crimen contra Cuba', *Bohemia*, 29 January 2016. http://bohemia.cu/ciencia/2016/01/la-ciencia-desnuda-un-crimen-de-ee-uu-contra-cuba-en-1981/. The study states: 'Cuban researchers were able to amplify and sequence the full genome of the original strains obtained in different moments of the epidemic in 1981, using bioinformatic tools…'
[49] Caballero Torres y Lopez Matilla, *Historia del CIM*, 10
[50] Reid-Henry, *Cuban Cure*, 47.
[51] Meningococcal disease is one of a group of bacteria responsible for the life-threatening infections meningococcal meningitis and meningococcal septicaemia. Untreated, these conditions can kill within 24 hours. 10% of survivors suffer serious, long-term disabilities, including brain damage. Meningococcal disease is among the top ten global causes of death due to infection. There are 13 different forms of the disease but serogroups A, B and C are by far the most common. According to the World Health Organisation there are up to 25,000 meningococcal deaths every year in Africa.
[52] Dr Gustavo Sierra cited in 'Meningitis B – Cuba', documentary posted by Journeyman Pictures, posted 25 Janurary 2008 www.youtube.com/watch?v=rgQZhTg04IM
[53] Despite this, Cuba's achievement has been ignored or censored in Britain. In September 2015 when the NHS introduced a new Meningitis B vaccine for babies it claimed the vaccine: 'makes England [sic] the first country in the world to offer a national, routine and publicly funded MenB vaccination programme' (NHS Choices https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/448820/PHE_9402_VU230_June_2015_12_web.pdf). The then-British Health Secretary Jeremy Hunt repeated the claim. Until 2014, only Cuba had developed a safe and effective Meningitis B vaccine and millions of people in Cuba and around the world had benefited.
[54] Agustin Lage, *Interview*, 2017.
[55] This occurred during a period in Cuba known as Rectification from the mid-to-late 1980s, during which Fidel Castro pulled Cuba away from the Soviet economic management model, fostering innovative science and technologies instead of the heavy industries the Soviet's recommended.
[56] The first monoclonal antibody registered for cancer treatment in the US was 1997.
[57] Lage, *Interview*, 2017.
[58] Lage, *Interview*, 2017.
[59] Helen Yaffe, 'Cuban Development: Inspiration to the ALBA-TCP' in Thomas Muhr (ed.), *Counter- Globalization and Socialism in the 21st Century: the Bolivarian Alliance for the Peoples of Our America* (London: Routledge), 101-118.
[60] Lage, *Interview*, 2017.
[61] Roswell Park received a US government licence to pursue collaboration with Cuba and trials were authorised in the brief period of improved relations towards the end of Obama's presidency.
[62] Dr Kelvin Lee, Chair of Immunology in Roswell Park Comprehensive Cancer Centre in Buffalo, New York, Interview with the author via Skype, 3 October 2017.
[63] Given this ratio, 52,000 amputations which take place annually in the US due to diabetic foot ulcers could be prevented.
[64] Orfilio Peláez, 'The jewel that Fidel conceived', *Granma*, 7 September 2017, http://en.granma.cu/cuba/2017-09-07/the-jewel-that-fidel-conceived.
[65] Sara Reardon, 'Can Cuban Science go Global?' in *Nature*, 29 September 2016. www.scientificamerican.com/article/can-cuban-science-go-global/
[66] *Haemophilus influenza* type b (Hib) is a bacteria responsible for severe pneumonia, meningitis and other invasive diseases almost exclusively in children aged less than 5 years.
[67] Similarly to Heberprot-P, over 100,000 patients worldwide have benefited from using Itolizumab.
[68] This pales into insignificance in comparison to the US, however, where some 5,500 patents are awarded annually according to Cortright and Mayer, *Signs of Life*, 9

[69] Reid-Henry, *Cuban Cure*, 99-100.
[70] Subsequently, they sought a more efficient carrier for EFG.
[71] Dr Lee, *Interview*.
[72] In Britain women make up only 12.8% in science, technology, engineering and maths workforce. See www.theguardian.com/news/datablog/2015/jun/13/how-well-are-women-represented-in-uk-science
[73] This, and low salaries in Cuba, have prompted many Cuban medical scientists to seek employment overseas. However, there is no evidence that the 'brain drain' from Cuba is greater than in other developing countries.
[74] Agustín Lage Dávila, *La Economia del Conocimiento y el Socialismo: Preguntas y Respuestas* (La Habana: Editorial Academia, 2015).
[75] Reardon, *Cuban Science*.
[76] Lage, Interview, 2017.
[77] Lopez Mola, *Biotechnology in Cuba*, 3.
[78] Rick Mullin, Tufts Study Finds Big Rise In Cost Of Drug Development, Tufts Center for the Study of Drug Development, November 20, 2014, https://cen.acs.org/articles/92/web/2014/11/Tufts-Study-Finds-Big-Rise.html.
[79] Total biopharma investments sought in 2017/8 were at least $850 million, nearly one-tenth of the $9 billion sought in the annual portfolio.
[80] Sharmistha Bagchi-Sen, Helen Lawton Smith and Linda Hall, 'The US biotechnology industry: industry dynamics and policy', *Environment and Planning C: Government and Policy*, 22 (2004): 199.