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GUEST EDITORIAL

Cuba: a different kind of role model for biotechnology

'What's happening in Cuba?', the good professor asked me. I realized that I was not the only one intrigued by what was happening in biotechnology in this little country. Much of the buzz about biotechnology has always emanated from the United States (US). And yet, important advances have been made in Cuba, a country that could not be more different from the US. Can we learn anything from its experience?

The revolution took place over a few years, ending by 1960. Fidel Castro, in power from 1961 to 2011, and followed by his brother Raul until 2018, emphasized the need for assuring all citizens a good education and good healthcare. In this he was successful, and today their life expectancy is as high as, and their infant mortality rate is lower than, that in the US (Stone, R., *Science*, 2015, **348**, 746–751). Castro also emphasized the need for developing indigenous science and technology (S&T), and he connected the S&T goals with the healthcare goals using biotechnology. In what turned out to be a seminal event, the former head of the M. D. Anderson Cancer Center in Texas, USA, R. Lee Clark, visited Cuba and had a meeting with Castro in 1980, convincing him that interferons would be magic bullet cures for cancer in the future (Kaiser, J., *Science*, 1998, **282**, 1626–1628). Castro sent some scientists to train at the Texan hospital, and these scientists also subsequently went to Finland for further training. Upon their return to Cuba, every possible resource was made available to them, despite the general poverty of the nation. It is reported that Castro took personal interest in the project, and used to frequently drop into the laboratories to see how things were coming along. Thus, in the mid-80s, the country was at par with Europe and the US in terms of trying to develop novel biomolecules that might be of use in the clinic.

The US had imposed economic sanctions on Cuba in 1960, and these grew tighter over the years. Thus, almost anything that the country attempted was despite the sanctions, and not due to any facilitation by the US. Instead, the country tilted towards the Soviet Union and received much support from it until 1991, when the Union collapsed. In fact, 1991 led to an economic crisis in a country that was not rich to start with, and yet the investment in biotechnology continued. Over US$ 1 billion was invested in this sector between 1990 and 1998 (Kaiser, J., *ibid*).

In this small country – whose population today only marginally exceeds that of Bengaluru – how was the biotechnology enterprise built up? After the revolution, the big emphasis on education ensured 100% literacy very soon. It also led to a manifold increase in the number of universities, and the development of a large scientific manpower. Then, starting from the return of the team sent to Finland, from 1986 onwards the first of many prominent institutes devoted to biotechnology started to come up. Overall, over 50 institutes were set up in what came to be known as the Western Havana Biocluster, with the better known ones being the Centre for Genetic Engineering and Biotechnology (CIGB), the Finlay Institute and the Centre for Molecular Immunology (CIM). Each institute has a particular specialization – molecular immunology, neurobiology, clinical trials, bioproduction and so on – and of particular note is that many, if not most, institutes have strong commercialization arms. The Government was clear that products should be developed, that these would boost the stature of the country internationally and develop goodwill, and that exports would boost the economy. Cuba's is a knowledge-based economy, and biotechnology has long been one of its biggest foreign exchange earners (https://www.forbes.com/forbes/2008/0324/044.html#3596f8c7863c).

What have been some of the biggest achievements of Cuba's industry? Even as far back as 2002, there were about two dozen locally produced products registered in Cuba. These included human recombinant erythropoietin, natural and recombinant interferons, recombinant streptokinase, recombinant hepatitis B vaccine, a tetanus vaccine, a DTPw vaccine and so on. Thus, several of their products are 'generics' of well-known products of the Western biotech industry. Most importantly however, Cuban scientists have developed first time ever, novel products. Amongst the earlier products, the anti-Haemophilus influenzae type B (Hib) vaccine, that helped prevent both pneumonia and meningitis was the most prominent. The production of this wholly synthetic, polysaccharide vi vaccine was reported in *Science* (Kaiser, J., *Science*, 2004, **305**, 460) and received much attention as it was the first polysaccharide-based vaccine in the world. A collaboration with a Quebec, Canada-based chemist had resulted in the reduction of the 16 steps of the synthesis pathway to a single step, thereby reducing the

enormous heterogeneity of the resultant polysaccharide, making it more amenable as a vaccine target. Subsequently, extensive collaborations amongst the various institutions in the Havana Biocluster enabled the testing and production of the vaccine. In parallel, and sanctions notwithstanding, the US Government permitted an American company to license some of the Cuban vaccines (Kaiser, J., *ibid*).

One of the root causes of some of the Cuban achievements has been the willingness to reach out to other countries, even the US. As mentioned above, a collaboration with a Canadian chemist helped in the development of the HiB vaccine. One of the latest stories of Cuba's outreach efforts (http://www.miamiherald.com/news/nation-world/world/americas/cuba/article155129444.html) relates to a Cuban scientist visiting her relatives in the US. From there she cold-called the Roswell Park Comprehensive Cancer Center in Buffalo, New York and talked about an anti-lung cancer vaccine, CIMAvax-EGF, which her group had developed. Invited to give a talk at Roswell Park, she quickly converted a skeptical audience to an enthusiastic one. After the American scientists attended an immunology conference in Havana, Cuba, they decided to seek the permission of the US Food and Drug Administration (FDA) to run a trial with this vaccine in the US. That has now happened, and American patients are now being dosed with the vaccine. This is the first time that a trial has been run in the US with a Cuban product. We also note that the vaccine, while available for free to locals, is priced at only US$ 12,000 for a year's treatment for visiting patients. This contrasts with a price of about US$ 12–15,000 per month in the US for the existing anti-lung cancer immunotherapy. Furthermore, as the vaccine stimulates the immune system to hit the epidermal growth factor (EGF), and because EGF is involved in various other cancers, the vaccine may have other uses as well.

The first foreign company which Cuba worked with was YM Biosciences in Canada, from 1994 onwards, for an anti-EGFR molecule (Lopez, E. *et al*., *J. Commer. Biotechnol.*, 2002, **9**, 1–5). In 2002, it started working with GlaxoSmithKline for a meningitis vaccine (Lopez, E., *ibid*). Local companies continue to enter into a wide range of agreements with foreign companies (Mola, E. L. *et al.*, *J. Commer. Biotechnol.*, 2003, **9**, 147–152). The foreign partner may pay for further development, including clinical development, regulatory filings abroad or patent maintenance fees in exchange for certain marketing rights. These rights would often be for the US, Europe and perhaps Japan, with Cuba retaining the commercialization rights for the rest of the world. However, local companies do not take on other companies' products for further development, since they do not have the financial wherewithal to do so.

Cuba has had its share of problems. Despite them, in some measure energized by it, the country has made enviable strides in getting products of biotechnology to patients around the world. It is unlikely that many observers would have given such efforts much of a chance, and in fact they were written off a long time ago (de la Fuente, J., *Nature Biotechnol.*, 2001, **19**, 905–907). And yet, from the very early years, foreign observers have been extremely impressed with Cuba's biotech-related science (Kaiser, J., *Science*, 1998, **282**, 1626–1628, Kaiser, J., *Ibid*). Today, the Roswell Park Center is working on a number of products developed in Havana (http://www.miamiherald.com/news/nation-world/world/americas/cuba/article155129444.html#storylink=cpy), and companies around the world are signing agreements with their companies. At least three Indian companies have done business with Cuban entities: Karnataka-based Biocon (with Cimab SA), and Punjab-based Panacea Biotech and Andhra Pradesh-based Transgene Biotek (both with Heber Biotec SA). At a higher level, countries too are entering into partnerships with Cuba. India signed such an agreement in December last, in the areas of pharma, medical devices, healthcare and so on (http://pib.nic.in/newsite/PrintRelease.aspx?relid=174648).

Before ending, and as an aside, I would like to briefly highlight two remarkable aspects of Cuba's medical enterprise. Fidel Castro believed in showing solidarity with the poor of the world. In due course Cuba had more medical doctors per person than any other country in the world, and he therefore sent many of these well-trained doctors to other countries, especially Africa and Latin America. In recent years many of these 'medical missions' have been to areas of conflict or disasters, such as Afghanistan, Nepal and Pakistan, and Cuban doctors have therefore developed strong expertise in emergency medicine. These doctors get a warm welcome, and by extension Cuba is perceived positively in these countries. Further, the Cuban government trains – for free – thousands of foreign students each year. It seeks good students from poor backgrounds, and hopes that they will return to serve their communities. These students come from over 100 countries, including the US.

Let us return to the biotech industry, and revisit the following statement: Over US$ 1 billion was invested in this sector between 1990 and 1998. It is often claimed that it takes more than US$ 1 billion to generate a new drug in the US today. Of course, this is accounting for failures. In Cuba too, they must have had their share of failures, and yet they have had resounding successes on what is a modest budget by comparison.

It is not essential that we model our own industry after that of the US, where the cost of biologic and other drugs is causing increasing distress. Of course we cannot fully model it after Cuba either. Nevertheless Cuba has demonstrated that drastically different ways of doing things can succeed, and at low cost. This should inspire us to find our own way.

Gayatri Saberwal

Institute of Bioinformatics and Applied Biotechnology,
Biotech Park, Electronics City,
Bengaluru 560 100, India
e-mail: gayatri@ibab.ac.in