DESMOND BOYLAN FOR *NATURE*

Cuban science at a crossroads

When the United States eased restrictions on Cuba, some scientists there hoped for a research revolution. **They got evolution instead.**

BY SARA REARDON

The western edge of Havana hides a side of Cuban society that tourists rarely see. High fences and thick vegetation wall off the grand estates and embassies where the elites congregate. And amid these enclaves of privilege lies a cluster of concrete buildings belonging to the Polo Científico del Oeste — the 'scientific pole' of Cuba's capital city. Here, a cluster of biotechnology research institutions are protected from the chaos and poverty of a city in transition.

For a country whose entire gross domestic product (GDP) is just half of what the US government spends on research, Cuba punches above its weight in some areas of science. Fuelled by relatively generous government support, biomedical researchers have managed to excel at creating low-cost vaccines, developing cancer treatments and screening infants for disorders. Other areas of science get more meagre funding, but Cuba still boasts some bright spots. As the largest and most populous island in the Caribbean, it is a key node in international networks monitoring hurricanes and infectious-disease outbreaks. And because there is so little trade and tourism, the country has nearly pristine coral reefs and mangroves, which attract attention from researchers worldwide.

The productivity and quality of some research in Cuba surprises those from other countries. "We had the same thought about Cuban science as everyone else did: that it was stuck back in *I Love Lucy* days," says Kelvin Lee, invoking the 1950s TV show. Lee, an immunologist at Roswell Park Cancer Institute in Buffalo, New York, is organizing the first US clinical trial of a Cuban vaccine.

Yet the success stories don't outweigh the profound challenges facing scientists in Cuba. Research jobs pay poorly, and the number of students getting science doctorates has not risen in the past decade. Internet access is scarce, and those who have it find the service so sluggish that it can be next-to-impossible to e-mail a scientific paper. An energy shortage this summer forced government buildings to shut off their electricity for large portions of the week. During a temporary ban on air conditioning, scientists at the University of Havana sweltered over their laptops in 35 °C temperatures.

Another problem looms above all others: the US trade embargo. For the past half-century, the embargo has severely restricted the ability of Cuban researchers to buy scientific equipment, win international grants and travel in the United States.

Students collaborate on a physics experiment at the University of Havana.

But in December 2014, US President Barack Obama announced his intention to restore full relations between the two countries and began lifting travel restrictions. On 31 August 2016, a JetBlue Airways plane flew directly from Florida to Cuba — the first commercially scheduled flight between the two countries in five decades. This softening of relations has led to an era of evolution: it has opened up opportunities for researchers, such as easier travel to international meetings, and raises the prospect of many future benefits through collaborations and purchases. Yet the pace of progress has been much slower than many had hoped, and the future of US–Cuba relations remains uncertain. A decision to lift the embargo entirely requires action from a hostile Congress and lies in the hands of the next US president.

And in the meantime, Cuban researchers are stuck with many of the same problems as their counterparts in other developing nations: an exodus of young scientists, difficulty finding collaborators and an inability to afford increasingly specialized scientific equipment. This sets Cuba back years from where it could be, says Sergio Jorge Pastrana, executive director of the Academy of Sciences of Cuba. "The changes are coming but they change too slowly."

OLD SCHOOL

In the heart of Havana's Old Town, the academy is a cool, marble respite from the humidity. It is in the midst of remodelling: librarians sort century-old books of its proceedings, and Pastrana says that he plans to install solar panels. Outside, people pick their way along streets strewn with construction rubble while shops hawk Che Guevara shirts, cheap cigars and mass-produced paintings of cars.

> ***"You say embargo, we say blockade."***

Like the colourful, iron-railed buildings that surround it, the science academy is a grand institution, the first of its kind established outside Europe. In its 155 years, it has hosted greats such as Albert Einstein and one of Cuba's most famous scientists, epidemiologist Carlos Finlay, who discovered that mosquitoes transmit yellow fever in the late 1800s. Until the revolution, the Cuban academy shared close ties with the US National Academy of Sciences and with its European counterparts. Even under the embargo restrictions, the organization has forged ties with US scientists at institutions such as the American Museum of Natural History and the American Association for the Advancement of Science (AAAS).

Pastrana says that science got lucky when Fidel Castro took over. Cuba could have ended up with "a very bad leader for science", he says. Instead, one of Castro's first acts was to create and enforce a universal-literacy requirement, and he prioritized knowledge building and discovery. "The future of our country has to be necessarily a future of men of science," Castro said in a 1960 speech. The now-famous quote is engraved in Spanish on the wall of the science academy's lecture hall.

The communist government also made health a top priority. Castro was unwilling to be left behind as other countries underwent a biotechnology revolution, especially as it became clear that the US embargo would cut the Cuban people off from modern treatments. In 1986, Cuba opened its Center for Genetic Engineering and Biotechnology (CIGB) in Havana's scientific pole. The CIGB now employs 1,600 people and has commercialized 21 products internationally, including cancer immunotherapies, a hepatitis B vaccine, pesticides and therapies for macular degeneration.

"I think they have accomplishments they can be quite proud of when adjusted to GDP and the size of the country," says Michael Clegg, a geneticist at the University of California, Irvine, and former foreign secretary of the US National Academy of Sciences. The investments in public health have paid off, as Cuba has logged impressive gains in recent decades. Cubans now live longer than Americans, on average, and infant mortality rates are comparable to those of the European Union and United States.

Castro's dedication to science was tested in 1991 following the break-up of the Soviet Union, which had heavily subsidized its communist ally. Scientists in some sectors suffered during the 'special period of economic depression' over the next decade.

Yet biotechnology continued to thrive through continued government support. In 1994, Cuba opened the Center of Molecular Immunology (CIM) in Havana to develop vaccines and other biologicals such as cancer immunotherapies. "In the middle of a big crunch of the national budget, money for science was respected," Pastrana says.

Unlike many of its Latin American peers, Cuba has had a stable government for decades, which has allowed the country to carry out long-term plans. And the country's isolation from foreign aid spurred innovation in ways that few other low-income nations can claim. An often-heard verb is *resolver* — to fix problems, often on your own. "Most Cuban scientists now didn't know Cuba before the blockade, and the fact you cannot get any device is so familiar," says Luis Montero Cabrera, a computational chemist at the University of Havana. There is something of a perverse pride: people who have spent their lives overcoming obstacles, he says, make the best scientists.

And they have had to scrape by with relatively little (see 'How Cuban science stacks up'). In the past 6 years, Cuba has spent between 0.3% and 0.6% of its GDP on research and development annually — one of the highest rates in Latin America, but far less than Brazil (1.2%) and the United States (2.7%). And the government has yet to honour repeated promises to create a competitive grant-funding agency akin to the US National Science Foundation.

The funding that is available can be strictly budgeted. Stem-cell biologist Porfirio Hernández Ramírez at the Institute of Hematology and Immunology in Havana has ready access to patients and to state-paid clinicians who can serve as researchers. Yet he says he has no grant money to publish papers in open-access journals that charge thousands of dollars, so he mostly publishes in small domestic journals. This can make it difficult for outside researchers to evaluate or replicate his work, and to form collaborations — a common problem for Cuban scientists.

TIGHT CONTROLS

Like their counterparts in biomedicine, physicists at the University of Havana yoke their research to Cuba's national interests — namely, energy and biotechnology. Several work with BioCubaFarma, the state-run biotechnology agency based in Havana, to develop computational models for new drugs and biologicals. Osvaldo de Melo Pereira has built his own furnace for growing cadmium sulfide particles into nanowires that could serve as semiconductors in solar panels. He shows off images of the tangle of tubes and wires — images made by collaborators in France who have access to more-powerful microscopes.

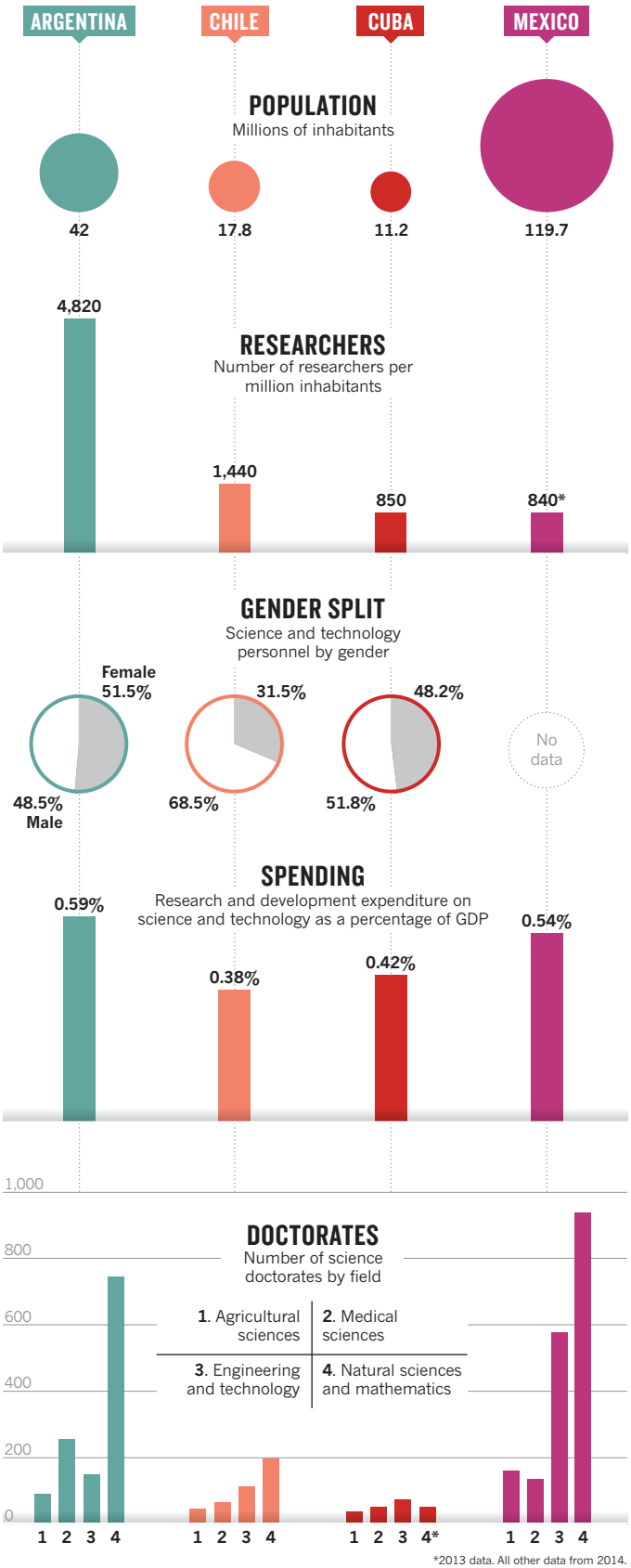
The research is still basic, de Melo Pereira admits, but he says that some of the particles show potential. The long-term goal of creating cheaper solar cells would be a boon for Cuba, which depends on its politically unstable Latin American trading partners for fossil fuels.

University of Havana physicist Alejandro Lage-Castellanos says the focus on national priorities makes sense for researchers. "It's rational to join those industries that already have some success." The overall lack of funding makes it difficult for young scientists who want to pursue other lines of research. "You have to survive or you have to emigrate," he says.

The government enforces such narrow pursuits. Graduate students, for instance, must defend their thesis not only to their department but also to a national tribunal that ensures the project will serve Cuba — a student would probably not be allowed to write a thesis on icebergs, for instance. To maximize scientific output, the tribunals also ensure that

HOW CUBAN SCIENCE STACKS UP

Despite its low gross domestic product (GDP), Cuba holds its own against some richer countries in Latin America in terms of several key science metrics.



*2013 data. All other data from 2014.

SOURCE: RICYT

no two students in the country are working on the same topic.

The government's tight control on science has actually provided some freedom in the biotech sector, where companies are run by the state and researchers don't worry about profitability. "Instead of focusing on the market, we can focus on problems," says Eulogio Pimentel Vázquez, director-general of the CIGB. These can include particular genetic disorders that are common in Cuba, or problems associated with ageing — a growing concern, because 18% of the population is over the age of 60. The neurosciences centre CNEURO, for instance, is developing cognitive and biomarker tests that would allow earlier screening for Alzheimer's disease.

And Cuban researchers say that the top-down approach allows for a more efficient process. At the CIGB, the structure of the suburban campus mirrors the research and development process, with basic research taking place on the top floor, research and engineering to scale up the operations downstairs, and production in nearby buildings. And the research process there is relatively inexpensive: labour on the island is cheap, and Cuban scientists, who are accustomed to frugality in their daily lives, carefully choose experiments and recycle items such as pipette tips that a wealthier laboratory would discard.

Cuban researchers take pride in their creative approaches. In 1970, for example, scientists at CNEURO decided that they wanted a primate research lab but had no money to buy the animals. So director Mitchell Valdés-Sosa says he joined the crew of a cement steamer as the ship's doctor to get a free ride to St Kitts, where he picked up 25 vervet monkeys — which are regarded as an agricultural pest on the island. One monkey escaped when the ship docked near Santiago, and Valdés-Sosa jumped overboard to rescue it. Now CNEURO has a colony of 50 monkeys that its scientists use for cognitive research.

Valdés-Sosa runs the centre along with his twin brother Pedro, who serves as vice-director. At CNEURO, they have made cheap translation of basic research a priority. Pedro is working on ways to obtain brain mapping from quantitative electroencephalography (qEEG) — a non-invasive measurement of brain activity that is much cheaper than magnetic resonance imaging (MRI) and many other scanning techniques. The centre has also developed a hearing aid for children that costs just US$2, a fraction of the cost in the United States or Europe. Physicians send scans of children's ears to CNEURO, where technicians create a structure for the implant using a 3D printer. The device can be inexpensively reprinted as the child's ear grows.

A TESTED COUNTRY

Cuba is an enthusiastic user of medical testing, especially for newborns. In 2015, the World Health Organization declared Cuba the first country in the world to eliminate mother-to-child transmission of HIV — an achievement reached through the use of intensive screening and drugs for HIV-positive mothers.

The Center for Immunoassays (CIE) manufactures much of the medical equipment used in the country, some of which is also used for research. Miguel Angel Garcia, director of science policy at the CIE, says the centre produces a total of 57 million tests per year for 19 different diseases, including HIV and Chagas disease. The facility saves money by doing everything in-house. Upstairs, researchers working in old fume hoods are developing better fluorescent markers for tests for Chagas disease. Next door, a machine shop grinds out metal sheets for spectrophotometers that will read the tests and spit out results. "The circumstances force us to integrate all that technology," Garcia says. The system also lowers the price: a glucose-monitoring system that costs only $0.40 may sell for 100 times more in the United States.

Although medical care is free for Cubans, the immunoassays centre and other branches of BioCubaFarma have been able to make a profit through exports. According to the Cuban government, international biotech sales netted the country $2.5 billion between 2008 and 2013 — a figure that the agency expects to double by 2018.

Cuban scientists blame much of their difficulty in breaking into global science on the US economic sanctions. They are quick to correct foreigners who mention the embargo. "You say embargo, we say

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Inside a laboratory at the Center for Genetic Engineering and Biotechnology in Havana.

blockade," says Ileana Morales, director of science and technology at Cuba's public-health ministry. "You might say it's a play on words but it's a major impact." Cuba, in her opinion, is under a debilitating siege.

The sanctions are legally complex, and include a prohibition on selling products to Cuba without the appropriate licence if more than 10% of the components are made in the United States — a cut-off raised to 25% in 2015. But the rules are so complex that many companies with US branches tend to play it safe by not selling to Cuba.

The embargo creates constant problems for researchers, who complain about how long it takes to obtain reagents. Getting an enzyme from Europe, for instance, can take weeks. And some products aren't available at all. Researchers at BioCubaFarma want to buy a line of mice that are genetically engineered to lack three genes involved in Alzheimer's disease, but the animals are sold only by a US firm.

International companies have reason to worry about the embargo. In 2009, the United States slapped a $130,000 fine on the domestic branch of Philips Electronics for selling medical equipment to Cuba, including half of the MRI machines at CNEURO. That caused the company to stop servicing its machines in Cuba, which meant the centre could not use those scanners. The problem didn't affect CNEURO's other machines, which came from Siemens, based in Munich, Germany. The US government says that the situation has since been resolved.

THE BIG THAW

With the improved relations between the United States and Cuba, there are signs that some issues are getting easier for scientists. Later this year, researchers in the United States plan to begin the first clinical trials in the country of a Cuban therapy: a cancer vaccine called CimaVax that the CIM has been developing for two decades. Lee, the New York immunologist collaborating on the project, says he was initially surprised that the CIM had a lung-cancer vaccine, especially one that seems so effective — a 400-person study suggests that the vaccine can increase survival in people with lung cancer by a year (P. C. Rodriguez *et al. Clin. Cancer Res.* **22,** 3782–3790; 2016).

CimaVax is approved in four Latin American countries, and approval is pending in several others, so Lee hopes that the US government approval process will move quickly. So far, it has been arduous. "We're sailing in uncharted waters," he says. But he has been surprised at how open the US government has been to the idea of working with Cuba.

A few scientific fields have been doing this for some time. US and Cuban government agencies have been collaborating on hurricane forecasting since the 1950s. Because of the intense risk to the island, the government has provided strong support for weather radar systems, says Juan Carlos Antuña-Marrero, an atmospheric scientist at the Meteorological Center of Camagüey. Antuña-Marrero works with the University of Valladolid in Spain, which provides equipment for his group to measure atmospheric aerosols. And in 2014, US researchers were able to donate and install a Global Positioning System instrument in Camagüey as part of a Caribbean earthquake-monitoring network called CoCoNet. In addition to geodetic information, the device records meteorological data such as water vapour. "Our team's research philosophy is to get as much as possible from the instrument," Antuña-Marrero says.

International researchers are flocking to Cuba to study its coral reefs and mangroves before hordes of US tourists arrive. These ecosystems are among the best preserved in the world, and the Cuban government has been proactive about creating protected areas, says Luis Solórzano, executive director of the Nature Conservancy's Caribbean programme, based in Coral Gables, Florida. But the influx of tourists could threaten coastal regions.

Foreign researchers who visit the island to study those ecosystems find that many Cuban scientists are happy to show off the areas they've been studying for so long. One of those looking forward to more international contacts is Alieny González Alfonzo, a graduate student working in an ornithology lab at the University of Havana. On the last day of classes before the summer break, she is one of the few people in her building as she finishes up some work.

After nine years in the lab, she is getting ready to leave for the United States on an exchange programme later this year. But González Alfonzo plans to return to Cuba to finish her degree. Once she graduates, she will be one of only seven ornithologists in the country with a PhD. "I want to contribute here," she says. "This is the best job in Cuba with birds."

González Alfonzo is in a minority — more and more students seem to leave each year, says Montero Cabrera. According to data from the Network for Science and Technology Indicators — Ibero-American and Inter-American (RICYT), the number of science PhDs awarded annually has generally remained flat for the past decade. Montero Cabrera says that, in 2015 alone, 22 of the approximately 70 faculty members with PhDs in the University of Havana's chemistry department left the country for jobs overseas. Cuba is simply not an attractive market. With the exception of BioCubaFarma, science jobs at government institutions pay a fraction of labourers' and engineers' salaries. Few, if any, jobs in Cuba's small private sector make use of a science degree.

Several US science associations, including the AAAS and the American Physical Society, have recently set up exchange programmes that will bring Cuban students to the United States for training. Europe already has many such programmes. And the relaxed US travel restrictions are already making it easier for Cuban scientists to attend international meetings.

But unless Cuba's economy picks up, thawed relations may not be enough to boost Cuban science to world recognition, however good its scientists. "Now young PhDs from Cuba have the opportunity to change everything here," Montero Cabrera says. "But they must find the resources." ■

Sara Reardon *reports for* Nature *from Washington DC.*