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editors@medicc.org

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Aguilar-Guerra, Tania L; Gorry, Conner
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Magaz MS General Director, Molecular Immunology Center
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Monoclonal Antibodies vs COVID-19:

Eduardo Ojito-Magaz MS

General Director, Molecular Immunology Center

Tania L. Aguilar-Guerra MD MS and Conner Gorry MA

Cuba has five COVID-19 vaccines in clinical trials and is on track to receive emergency use authorization from the country's regulatory agency to begin mass vaccination with two of those candidates: Abdala and SOBERANA 02. Results from phase 1 and 2 trials of these vaccines, the first developed and produced in Latin America, have been encouraging, both in terms of safety and immunogenicity. The ongoing phase 3 trials will continue to look at safety, together with efficacy; parallel intervention studies involving over a million people in Havana will begin generating data on effectiveness. Coordination between Cuba's biotechnology sector and its public health system—particularly throughout the different levels of primary care—to control and treat COVID-19 is a cornerstone of the Cuban strategy and one that could serve as a blueprint for future pandemics.



Another Cuban product, itolizumab, is showing positive results mitigating cytokine release syndrome (CRS) in COVID-19 patients with moderate-to-severe acute respiratory distress syndrome (ARDS). Developed in collaboration with Biocon (India), itolizumab is administered under an expanded access program to treat vulnerable populations in Cuba. Marshaling complementary capacities of dozens of institutions belonging to BioCubaFarma—the country's biotech conglomerate—and developing therapies, vaccines and medical technologies together, is another cornerstone of Cuba's strategy to combat COVID-19 and improve population health.

The Molecular Immunology Center (CIM) is a key player in this strategy. Founded in 1992, CIM is a powerhouse in monoclonal antibody research and production, with 6 registered products and 22 in the pipeline. Known for several novel ther-

apeutic cancer treatments, CIM has over two decades' experience producing complex recombinant proteins in mammalian cells on an industrial scale. Once Cuba's Innovation Committee (convened in January 2020 as part of the National COVID-19 Prevention & Control Plan) determined Cuban researchers would pursue protein subunit vaccine candidates, they turned to CIM to produce the required receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, among other responsibilities.

CIM's General Director, Dr Eduardo Ojito-Magaz, is a chemical engineer and holds a master's degree in biotechnology. He spoke with **MEDICC Review** just days before 1.7 million Havana residents began participating in the country's largest intervention study with the COVID-19 vaccines his center helped make possible.

MEDICC Review: Cuba hopes to vaccinate its entire population this year with COVID-19 vaccines developed on the island. Can you tell us about CIM's role in producing the SOBERANA line?

Eduardo Ojito: CIM, together with the Genetic Engineering and Biotechnology Center (CIGB), are Cuba's leading institutions when it comes to immunology and cancer technologies. We're the brain trust so to speak—of all the research centers under the BioCubaFarma umbrella, CIM

and CIGB are the main repositories of knowledge about these technologies and immune response. Our institution has over 25 years' experience producing monoclonal antibodies (mAbs) and currently provides the national health system with several products using these proteins, including erythropoietin-stimulating agents, granulocyte colony-stimulating factor and human growth hormone. Recognizing this expertise, the Finlay Vaccine Institute (IFV) approached us to produce the proteins used in our country's first COVID-19 candidates, SOBERANA 01 and SOBERANA 02.

Our collaboration focused mainly on two areas: 1) developing the recombinant RBD and 2) producing enough recombinant RBD for the vaccine, using CIM technology based on mammalian cell cultures.

MEDICC Review: Most of the world has no idea about Cuba's history producing vaccines for use in its public health system, including a national regulatory authority that serves as a Regional Reference Authority for PAHO/WHO...

Eduardo Ojito: Cuba has over 30 years' vaccinology experience and proven safety profiles for the vaccines we produce, distribute and market abroad. This includes CIGB's pentavalent vaccine that protects children against pertussis, diphtheria, tetanus, hepatitis B and *Haemophilus influenzae* type b, and the VA-MENGOC-BC vaccine developed by IFV in 1989—the world's first safe, effective vaccine against serogroup B meningococcal disease. In addition to administering these through our own health system, Cuba exports these vaccines to dozens of other countries. In short, several million people around the world are immunized with Cuban vaccines.

Several million people around the world are immunized with Cuban vaccines

Such experience, coupled with a technological platform and evidence base spanning decades, allowed us to modify our processes quickly and confidently for a new vaccine—in this case, for COVID-19. It's no coincidence that SOBERANA 02 couples recombinant RBD with tetanus toxoid, which is used in all the vaccines in our national health system. Starting with a proven technology provides an added layer of confidence for our COVID-19 candidates.

It helps, too, that CIM's production technologies are certified by our national regulatory authority, the Center for State Control of Medicines and Medical Devices (CECMED), but also foreign authorities around the world. Any vaccine must be approved by the importing country's regulatory agency before it can be used in their health system. In Mexico, vaccines have to be approved by the Federal Committee for Protection from Sanitary Risks (COFEPRIS); the National Health Surveillance Agency, ANVISA, is the regulatory authority in Brazil; in Argentina, it's the National Administration of Drugs, Foods and Medical Devices (ANMAT); and so on. People trust our products because our vaccines have proven safe and effective according to independent regulatory authorities in individual countries for over 20 years.

MEDICC Review: It's clear Cuba has the brain power. But does it have the manufacturing power to produce enough doses of the COVID-19 vaccines?

Eduardo Ojito: Without a doubt we've shown our capacity for generating ideas—it's one of our strengths. Cuban science is intense; we generate knowledge at an incredible pace. What I mean by that is we are adept at identifying a scientific problem, generating a hypothesis to research that problem, and defining what scientific method is most appropriate for investigating it. The question is: how do you convert that knowledge, that scientific method, into a viable product? This has proven extraordinarily challenging with COVID-19 vaccines.

Organizationally, we've faced substantial hurdles. In just one year, we've had to conceive, develop and produce vaccine candidates, plus ramp up our technology, design and conduct clinical trials, and comply with all necessary requisites for any new pharmaceutical product like toxicology and stability studies. In order to achieve all this in such a short time, we innovated, by shifting our production capacity to the spike RBD for use in the SOBERANA candidates.

CIM's production capacity of monoclonal antibodies is on par with the biggest pharmaceutical manufacturers in Latin America and we have successfully produced enough doses for the ongoing phase 3 trials and intervention studies. To comply with our national vaccination plans, we will need 30–35 million vaccine doses to cover our entire population, meaning CIM has to produce 100 grams of spike RBD monthly. We have that capacity right now and will continue at this pace to be able to produce the 15 million doses needed over the next few months to begin vaccinating our population.

MEDICC Review: What implications has the push for a COVID-19 vaccine had for production of other therapies and treatments in CIM's portfolio?

Eduardo Ojito: To tell you the truth, this pandemic steamrolled us: initially, we thought our 500-liter bioreactor would be sufficient to produce the necessary quantities of antigen without affecting other products. But it quickly became clear that we had to speed up pharmaceutical and clinical development of our vaccine candidates, that time was of the essence and that CIM would have to switch over its entire production capacity to manufacture the proteins needed for COVID-19 vaccines. This represented a significant organizational and technological challenge for us.

As a result, we made the difficult decision to pause production of nimotuzumab, an anti-epidermal growth factor therapeutic monoclonal antibody used to treat head, neck and pancreatic cancers and astrocytoma tumors. We always maintain a three-month supply surplus to guarantee this treatment for our patients in case of any unforeseen event and are supplementing supplies with imported nimotuzumab. Cuba has joint venture production facilities in Bangkok and Beijing that manufacture our products for the Asian market; we're finalizing details now to receive nimotuzumab from our Beijing plant.

MEDICC Review: What about material resources? Has CIM faced problems acquiring the inputs it needs to produce the spike RBD?

Eduardo Ojito: We've had fewer challenges on this front because the same materials used to produce monoclonal antibodies for other vaccines in our portfolio are used in SOBERANA. For example, the inputs for erythropoietin—which we acquire from Latin America and Europe—are the same, so we didn't have to procure more materials; it was more a question of retooling our production lines and ramping up production. This was simpler than the organizational challenges, which were quite complex.

MEDICC Review: Shifting from vaccines, is CIM producing treatments for COVID-19 patients?

Eduardo Ojito: Yes. It's called itolizumab, and I'll admit it's one of my favorite products. Itolizumab was originally developed to treat cutaneous T-cell lymphoma and severe psoriasis; CIM founders tell

me it was the first mAb produced here. Researchers subsequently discovered that itolizumab moderated cytokines associated with inflammatory response in certain autoimmune diseases and could be used to treat rheumatoid arthritis, for example.

In March 2020, Dr Tania Crombet (Clinical Research Director, CIM; see *MEDICC Review's* Cuba's Women of Science Collection for an exclusive interview, Eds.) proposed using itolizumab to mitigate inflammatory response in COVID-19 patients. This was one of those 'aha! moments' provided by the pandemic: it forced us to look at science from a different perspective and take an innovative approach. From that moment, we began considering the possibility of repurposing itolizumab for COVID-19 treatment—a strategy that is gaining global traction as scientists repurpose existing drugs in an effort to find effective treatments. In the case of itolizumab, new findings were just published and oncologist researchers in the USA are investigating possible new applications of the drug. It's an amazing product; the evidence speaks for itself.

MEDICC Review: How is Cuba contributing to that evidence base?

Eduardo Ojito: Clinical trials evaluating the safety and efficacy of itolizumab in COVID-19 patients with acute respiratory distress syndrome (ARDS) are currently underway at the Manuel Piti Fajardo Military Hospital in the central city of Santa Clara. Trial protocols and design are registered with the Cuban Public Registry of Clinical Trials (<https://rpcec.sld.cu>). More than a dozen clinical sites in the central and western part of the country are participating in the trial but it is coordinated at the Santa Clara hospital because they have the most clinical experience applying itolizumab in patients with severe SARS-CoV-2 pneumonia, including appropriate administration for ICU patients and evaluating adverse reactions. The professionals at the Manuel Fajardo Hospital are in the forefront of this initiative and are researching applications of itolizumab to treat other acute respiratory infections, as well; treatment protocols for these additional applications are being designed now.

MEDICC Review: Our readers may recall another CIM product making headlines prior to COVID-19. Can you update us on the CIMAvax clinical trials being conducted at Roswell Park in the United States?

Eduardo Ojito: In 2018, Cuba and Roswell Park Comprehensive Cancer Center entered into a research and development partnership to produce innovative cancer therapies. CIMAvax, a CIM therapy for non-small cell lung cancer approved for Cuba's Basic Drug List in 2012, is currently in clinical trials at the Roswell Park campus in Buffalo, New York. This is a strategic, but also historic alliance: receiving FDA approval for trials using a Cuban product is groundbreaking and the joint venture agreement to produce CIMAvax in Cuba for the US market is *sui generis*.

Three dozen patients—well shy of the 100 required—are currently enrolled in the CIMAvax trials being conducted at Roswell Park. Ultimately, the goal is to complete phase 3 trials in the United States, gain FDA approval for the treatment and make it available to US patients.

The trials recently incorporated off-campus cancer patients from the surrounding community. This is extraordinarily important in my view. Here in Cuba, CIMAvax is administered to patients at the primary

care level, not in oncology hospitals or other tertiary institutions. That Cuba's community-based approach is being adapted to a US context, using a Cuban-produced therapy, is an endorsement of our biopharmaceutical products, but also our organizational know-how, and Cuban science in general.

MEDICC Review: A Cuban biopharmaceutical product with FDA approval...that is groundbreaking. Were there hurdles?

Eduardo Ojito: As you know, any pharmaceutical product has to adhere to regulatory standards, best practices and other parameters set by the country where it will be used. The FDA has approved CIMAvax for phase 1/2 use and we've had no problems to date. The plan to produce CIMAvax for the US market at a manufacturing plant in Cuba's Mariel Economic Development Zone is more challenging. Regulatory standards for phase 3 and commercial use in the US are very high. Ours are too, but compliance for the US market implies making certain upgrades, technological updates, and auxiliary-system improvements. So the plan is on hold for now—at least until the required number of candidates for the clinical trials at Roswell Park is reached and that depends on the epidemiological situation created by COVID-19.


MEDICC Review: Are other monoclonal antibodies in production or in the pipeline at CIM?

Eduardo Ojito: The only mAb commercially available at the moment is nimotuzumab. Meanwhile, itolizumab, another monoclonal antibody, has received conditional registration from CECMED for treating COVID-19 patients and is currently in clinical trials, as I mentioned. Another product we have in the pipeline and which has already received Cuban registration is Ac CD20, used to treat B-cell malignancies. We had to pause production temporarily on this product due to limited manufacturing capacity. Other mAbs in different stages of development include the PD-L1 molecule for certain cancerous cells and the 14F7 molecule, used to treat solid tumors. The latter is in clinical trials here in Cuba.

We're taking advantage of evolving technology to complement our mAb products with others, especially antibody-cytokine fusion proteins known as immunocytokines. One molecule showing great promise in clinical development is interleukin-2 (IL-2) mutein, as well as another fusion protein, IL-2 Fc.

We're also working with bispecific antibodies (bsAbs), molecules that can bind to two different antigens simultaneously. We acquired this technology overseas and are positioning CIM to remain on the cutting edge of science and technology moving forward.

MEDICC Review: How does it feel to have your entire country watching your work and awaiting results while the pandemic rages? It must be an anxious mix of stress, pride, and accomplishment.

Eduardo Ojito: I'm 49 years old, born, raised and inculcated with the ideals of the Revolution—ethical, humble, unpretentious. I honestly don't feel as if I'm doing anything special. I'm just trying to make good on our commitment to our citizens, our country, to have a safe, effective vaccine that can cover our entire population by year's end. 

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