HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 4, e2060616 (3 pages)
https://doi.org/10.1080/21645515.2022.2060616

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Vaccine manufacturing is essential to ensure access

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As a child, I dreamed of being a biologist. However, my parents saw a biologist's career as difficult, especially in a country like Mexico, and proposed that I study engineering, which is where my scientific career started. I am a scientist in the soul and an engineer in my brain. That has marked my scientific career and has put ingenuity in the center, that has constantly been enriched by scientific discovery. I had the opportunity to go to graduate school abroad, but family issues required me to stay in Mexico, which I believe is the second strike of luck that marks my professional career. I entered the National University of Mexico (UNAM) as a graduate student, not knowing that it would define my path forward.

As a biochemical engineer, I wanted my research to be focused on bioprocess engineering. Pharmaceutical biotechnology was also very interesting and as a result, without much thought, I decided to perform my research with the process development of the insect cell-baculovirus expression vector system (BEVS). In the 90s, few people in Mexico were using the system, and most were only empirics, without any interest in process development. The work introduced me to the world of viruses, where I fell completely in love. Viruses are the most elegant and powerful beings, as they can take control of a cell and even a complete multicellular organism and convert them into virus factories. I decided to define myself a virotechnologist, someone that investigates the fantastic abilities of viral proteins and applies their capacities to develop new technologies beneficial for humans. Included, of course, were vaccines, which became the focus of my doctoral thesis. I ingenuously dreamed of creating a recombinant vaccine against rotavirus and to prevent diarrhea in children, a disease with a heavy burden on my country. As my research on bioprocess engineering and biophysics moved forward, aimed at designing a virus-like particle (VLP) vaccine, it became clear that developing a vaccine for children was out of my reach. Rotashield, the first rotavirus vaccine, was approved in 1998, only to be withdrawn from the market in 1999 because of its association with intussusception. Developing rotavirus vaccines would require hundreds of thousands of children in phase 3 clinical trials, which was impossible to achieve for a young researcher in Mexico.

After my doctoral studies, I began postdoctoral training with Mike Shuler at Cornell University. I had the opportunity to work with some of the protagonists of the development of the BEVS, such as Bob Granados, Pat Hughes, and Mike Shuler himself. In addition, I learned glycobiology, which also shaped my career.

When I returned to Mexico as an assistant professor at the Institute of Biotechnology of UNAM (IBt) in the group of Octavio Ramírez, I had unique expertise in protein assembly and the characterization of macromolecular assemblies, in particular VLPs. I had learned glycobiotechnology, an area that I have strengthened over the years, and was an expert in process development of BEVS. All these areas were relevant for vaccine development.

In the early 2000s, the veterinary industry manufactured vaccines in Mexico. Both Octavio and I advised on bioprocess engineering and scaling up. The importance of bioprocess engineering is especially relevant for the veterinary industry as processes must have very low costs that the veterinary industry can afford. Working with these companies further demonstrated the immense challenge of developing a vaccine. For humans and animals, vaccines are given to healthy individuals. Thus, the tolerance of adverse side effects and high prices is very low. Efficient manufacturing of vaccines is the only way to make these biologics commercially accessible.

After returning to Mexico, I was invited to lecture at a meeting where I met Dr. Manon Cox, then the Chief Operating Officer of Protein Sciences Corporation (PSC). She needed to characterize the glycosylation profile of their recombinant influenza vaccine and perform the characterization of the structure of macromolecular recombinant hemagglutinin protein assemblies. I had that expertise, and knowledge of process development and scale-up of BEVS. A professional relationship that has turned into a profound friendship started, first with a collaboration with my group at UNAM, and later with an invitation to become part of the Scientific Advisory Board of PSC. My research on physical virology, glycobiotechnology, and bioprocess engineering continued. Our collaboration with Mexican veterinary companies received recognition by Mexican scientific societies, and a recombinant avian influenza vaccine, manufactured with a process and analytical methods that received key support from our group at UNAM, was licensed in Mexico and abroad.

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When the porcine influenza pandemic hit in 1999, we worked with PSC to get a pandemic influenza vaccine into Mexico. The manufacturing process was transferred to our laboratory at UNAM and prepared for transfer to Birmex, the Mexican state-owned company that manufactured vaccines. Unfortunately, when the pandemic faded, all this was forgotten by the Mexican government. But Octavio and I learned many lessons and developed a clear picture of the situation in Mexico regarding vaccine manufacturing and the situation at Birmex, with whom we had previously collaborated for several years, and in which I served in their Board of Directors for four years.

The situation in Mexico was similar to that of many other countries. While in the 1990s, Mexico was self-sufficient for manufacturing its vaccines and exporting to several other countries. In just a few years, Mexico became dependent on other countries to provide vaccines of general use. No vaccines had been developed in the country, and the existing facilities for manufacturing human vaccines were obsolete. In addition, Mexico has limited availability of vaccine development and manufacturing professionals and lacks expertise in modern vaccine analytical and clinical evaluation. In this scenario, Octavio and I made it our mission to create vaccine development and manufacturing strategies in Mexico, where scientific expertise does exist but technological and regulatory knowledge is limited. In the meantime, PSC got a significant grant from BARDA, USA, and was growing while preparing for Flublok's licensure. Then Manon and the PSC executive chairman invited me to join PSC during a Sabbatical leave. There I had the opportunity to work with Barry Buckland, who I had known for many years, but I had the chance to learn from him. When I returned to Mexico, I continued collaborating with PSC with a new set of abilities. Flublok was licensed in the USA in 2013. With Laboratorios Liomont, under the leadership of Sergio Valentinotti and Alfredo Rimoch, Flublok in its trivalent and quadrivalent formulations was licensed in Mexico. The collaboration with PSC continued until 2017, when Sanofi purchased PSC and terminated the collaboration.

Upon my return to Mexico, Octavio and I founded LAMMB in the IBt, a highly specialized analytical laboratory that provides specialized services for analyzing recombinant proteins and vaccines, including Flublok. The methods for Flublok release were transferred to LAMMB, and from there to COFEPRIS, the Mexican regulatory agency that releases vaccines. The first step in our larger dream was set with this laboratory. A key element for the development of vaccines in Mexico is the capability of manufacturing candidate vaccines for the clinical trials. For several years, we searched for collaborations that would fund the manufacturing of a cGMP plant for vaccine production. Finally, in 2021 we engineered a partnership between UNAM and the government of the Mexican state of Hidalgo. The manufacturing plant is under construction, and we hope it will be available next year for manufacturing and training professionals for vaccine manufacturing and development. LAMMB and the manufacturing plant will complete the route for vaccine manufacturing in Mexico will exist. We are thankful to UNAM and Hidalgo for their trust in this project that Octavio and I have pursued for years.

The COVID-19 pandemic, which has severely hit Mexico with one of the higher mortality rates, highlighted the lack of infrastructure in the country for vaccine development and production. Birmex started 2020 without producing vaccines, as the oral polio vaccine it produced was taken off the shelves by the WHO. Sanofi Pasteur manufactures an influenza vaccine in chicken embryos and sends the active pharmaceutical ingredient to France for fill and finish. Probiomed manufactures a recombinant hepatitis B vaccine since the 1990s. Other companies, especially from the veterinary sector, have the experience and adapted their facilities to produce human vaccines, such as Avimex, which is developing with support from the Mexican government the "Patria" vaccine. Several research groups, ours among them, with support from the Mexican Ministry of Foreign Affairs, had good ideas and were ready to test them. However, the lack of several links in the vaccine development chain became obvious. Therefore, we started a collaboration with the Institute of Biomedical Research, the Faculty of Chemistry (FQ), and the Faculty of Veterinary Medicine (FMVZ), UNAM, to establish a Biosafety level 3 laboratory with Good Laboratory Practices, recognized by OECD, that is needed for the evaluation of vaccines. Thanks to the support from the UNAM's Scientific Research Coordination and its coordinator, Dr. William Lee, and the Secretary of Education, Science, Technology, and Innovation (SECTEI) of Mexico City, Dr. Rosaura Ruiz, two laboratories BSL3 will be available shortly.

With the leadership of the Undersecretary of Foreign Affairs, Martha Delgado, Dr. Esther Orozco, and the Ambassador of Mexico in Norway Ulises Canchola, UNAM (LAMMB IBt and UNIPREC, FQ, and FMVZ) presented a candidate to become part of the Centralized Laboratory Network of CEPI, becoming the first laboratory of Latin America to become part of the network. The leaderships of Isabel Gracia, Laura Cobos, and Octavio Ramírez were essential for this achievement. The Centralized Laboratory Network is a global initiative to harmonize the assessment of vaccines undergoing testing and will expand from the evaluation of COVID-19 vaccines to other infectious diseases. The collaboration of CEPI with Mexico was also strengthened by my appointment as a member of the CEPI's Scientific Advisory Committee.

During the last 21 years, I have served as a professional devoted to vaccine development in Chemistry, Manufacturing, and Control aspects of process development. On these topics, as I was appointed as an expert of the Subcommittee for the Evaluation of Biotechnological Products of COFEPRIS for 2013 to 2019, I had the opportunity to be part of the team that constructed the foundations for the evaluation of recombinant vaccines in Mexico.

The situation in Mexico remains precarious, but the COVID-19 pandemic has opened many opportunities. We have been filling gaps and contributing with the BSL3 laboratories, the CEPI Centralized Network Laboratory, and the cGMP plant in Hidalgo. Other Mexican groups are also proposing new strategies to fill gaps, such as the National Polytechnic Institute (IPN) graduate program in vaccinology and the collaboration between Laboratorios Liomont and Argentina to produce the ChAdOx AstraZeneca COVID-19 vaccine, which the WHO recently approved. Mexico will emerge stronger from the COVID-19 pandemic, but there are still many limitations. There is not enough personnel expert on vaccine manufacturing, analytics, and development, and many of them emigrate to other countries where there are also limitations. Also, the available infrastructure is not sufficient. Finally, more decisive support from the Mexican government in a strategic plan to nourish the environment for vaccine development and production in Mexico is required. Only when the critical mass for vaccine development exists in Mexico will we stop being totally dependent on others for basic vaccines.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

Notes on contributor

Laura A. Palomares is the Director of the Institute of Biotechnology of the National University of Mexico (UNAM). She is also a group leader and professor. Palomares is a biochemical engineer (ITESM, Mexico) with a doctorate in science from UNAM, and post-doctoral training at the School of Chemical Engineering at Cornell University (USA). Her research is based on physical virology, glycobio-technology, and bioprocess engineering. She studies viral proteins and glycoproteins that self-assemble into macrostructures with application as vaccines, gene therapy vectors, and as nanomaterials. She collaborated with Protein Sciences Corporation as a member of its Scientific Advisory Board, as Director of Process Development during a Sabbatical leave from UNAM, and in other projects that include the licensing of Flublok for Mexico, with Laboratorios Liomont. She has served as a member of the Board of Directors of Birmex, as an expert for the Biotechnology Committee of the Mexican Pharmacopoeia, as an expert of the Subcommittee for the Evaluation of Biotechnological Products for COFEPRIS, and as a member of the Scientific Advisory Committee for CEPI. She has also served as chair of several congresses and meetings in Mexico and abroad. Her former students are leaders in the vaccine and biotechnology industry in Mexico and abroad. Her work has been recognized with some of the most prestigious awards in Mexico, such as the Weizmann Award for the best doctoral thesis (Mexican Academy of Science), two times with the "Canifarma Veterinaria" Award, the Prize of the Mexican Academy of Science, the Interciencia Award for Life Sciences, the "Premio Universidad Nacional" (UNAM), and is a member of the SNI at the maximum level, a system that ranks researchers in Mexico. She has been named an Exceptional Mexican Innovator and one of the most powerful Mexican women.