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REVIEW ARTICLE

The dawn and the first twenty-five years of proteomics in Mexico: a personal chronicle



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Abstract This review does not aim to be an up-to-date of proteomics in Mexico; it simply tries to trace its development, exposing the story of the researchers, laboratories and some institutions that have contributed to the establishment and development of this science in Mexico.

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PALABRAS CLAVE

Proteómica;
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El nacimiento y los 25 primeros años de la proteómica en México: una crónica personal

Resumen Esta revisión no pretende cubrir el panorama actual de la proteómica en México, simplemente intenta describir su nacimiento y desarrollo, exponiendo la historia de algunos investigadores, laboratorios e Instituciones que han contribuido al establecimiento y crecimiento de esta ciencia en México.

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1. Introduction

The 21st century is the century of Biology, and the main reason is the development of the genomic sciences. Proteomics is one the more ancient disciplines in this field. In fact, the

“omics” term was used for the first time in 1993 by Marc Wilkins, who linked the genome products (proteins) to the “genome”, setting forth this new kind of terms and the new sciences. The terms “proteome” and “proteomics” were coined shortly after, also for Wilkins, in 1994.

Proteomics runs parallel to genomics in several ways. The starting point for genomics is a gene, and it makes inferences about its products the proteins. Proteomics begins with the functionally modified protein and turns backward to

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the gene responsible for its production. The first protein studies that can be called proteomics commenced in 1975 when three labs reported the two-dimensional gel electrophoresis technique.¹⁻³ With the discovering of this methodology, many proteins could be separated and visualized; however, they could not be identified.

2. Dawn of proteomics

In the early nineties (1992), I was working on the physiology of *Rhizobium etli*, a project led by Jaime Mora, who suggested that we should use the two-dimensional polyacrylamide gel electrophoresis (2D-PAGE), to analyze global patterns of protein expression to discover the metabolic differences occurring under aerobic and fermentative growth conditions. This visionary view was the origin of the proteomics field in México, even before the term was coined by Wilkins in Sienna, Italy, in 1994. Shortly after, Jaime Mora sent me for a short period to Fred Neidhardt's lab in Ann Arbor, Michigan, to learn proteomics-methodologies. That time was the raising of this new science in Mexico.

When two-dimensional electrophoresis was introduced, it became the most important and widely used technique to solve complex protein mixtures, allowing the start of proteomics sciences. However, the high-throughput analysis of proteomes challenged this pioneer methodology. Since the traditional 2D maps are labor-intensive to generate and run manually, and each spot from 2D maps has to be individually extracted, digested and analyzed by a time-consuming method. These shortcomings would encourage the growth of alternative methods; in the nineties, a new methodology, 2D chromatography, was launched, and the history changed. This technique was an entirely automated analysis through control by a central processing unit. Nevertheless, results were difficult to obtain because one could resort only to mini-sequences by Edman degradation for protein identification and, when available, with immunological techniques. In Mexico, Guillermo Mendoza, from Facultad de Medicina, Universidad Nacional Autónoma de México (UNAM)— in my view, the best Mexican mass spectrometry (MS) researcher that I have known in a long time— initiated protein characterization by Edman degradation in his laboratory. Mendoza had extraordinary skills in this field, and with his collaboration, we were able to identify some proteins in his lab and in laboratory facilities in the USA. We published the first proteomics papers produced in Mexico, with Jaime Mora as the group leader.

The Edman degradation technique was part of proteomics since the beginning and was the only option for protein identification. The great impulse came when MS became accessible for the analysis of proteins and sequencing peptides. For their contributions in this field (development of soft desorption ionization methods for mass spectrometric analyses of biological molecules), John Fenn and Koichi Tanaka shared the Nobel Prize in Chemistry in 2002.⁴ In our lab, Jaime Mora was able to obtain the resources to acquire the first MS equipment dedicated exclusively to protein identification in 2000. Later, Lourival Possani, at the former Centro de Investigación en Biotecnología, UNAM, currently Instituto de Biotecnología-UNAM, worked in protein and

peptide characterization related to proteomics and initiated the incursion into MS to characterize proteins.

We can assure that no lab can perform proteomics analysis without robust MS equipment. The instrumentation has to be carried out to an extremely sophisticated stage, and likewise, the software for information acquisition and analysis has been highly developed. Similar to the pioneer development of proteomics, there was a development of MS in Mexico.

3. The Mexican Proteomics Society

The Mexican Proteomics Society (SMP, from its Spanish initials) was established on June 1st, 2005, and it is the oldest Proteomics Society in Latin America. This Society was founded by a group of Mexican researchers led by Cesar Ferreira Batista and the author, Sergio Encarnación-Guevara. The aim of this group was to strengthen and promote the field in this country and to build a community among emerging national proteomics laboratories for the exchange of services, ideas and the training of students. It brought together a multi-disciplinary membership ranging from groups working on bacteria, human disease, and plant stress tolerance. Since its founding, the SMP has organized a biennial meeting as well as courses, and has invited researchers from different parts of the world to promote proteomics development in Mexico.

The first meeting of the SMP was held at Cocoyoc, Morelos, from the 19th to the 22nd of October 2005, entitled the 1st Mexican Symposium of Mass Spectrometry–Cellular and Molecular Proteomics. A parallel theoretical course on the Fundamental of Mass Spectroscopy Applied to Proteomics was also held, and these activities were organized by Cesar Ferreira Batista as President, Fernando Zamudio, Victoria Pando, Alicia Chagolla, Sandra Contreras, Magdalena Hernández and the author as Vice President. This first symposium was successful because was attended by near 200 participants mainly from Mexico, Latin America, and Europe. This group included 20 students who were enrolled thanks to Howard Hughes Medical Institute and the Instituto de Biotecnología-UNAM scholarships.

The second meeting was held in Guanajuato, Guanajuato in November, 2007, and again included a noteworthy list of international invited speakers. The organizing committee for the meeting was led by Alicia Chagolla in collaboration with the Executive Committee of the SMP. Alicia Chagolla is one of the trailblazers in the use of MS for protein identification in Mexico. She took part of this expertise in the Protein Research Group at the Southern Denmark University, where she was trained in protein MS by Peter Roepstorff.

The next encounter took place in November, 2009, in San Luis Potosí, San Luis Potosí and, as well as attracting internationally distinguished scientists, this meeting showcased a remarkable turn of Mexican scientists who are at present playing in the proteomics field. This event was organized by a local committee headed by Ana Paulina Barba and Luis Terán Juárez, with Anne-Claude Gavin, Richard Caprioli, and Sixue Chen as plenary speakers.

As mentioned above, the main aim of the SMP is to promote Proteomics teaching and technology to the next generation. For that reason, in the same year, from April

20 to 24, a theoretical and practical training was held in Cuernavaca, and the trainers were key members of the SMP. Scholars from all over Mexico attended the 5-day course including lectures. Students were given hands-on experience in 2D-PAGE and quantitative proteomics employing DIGE in addition to an introduction to MS.

The fourth symposium was held in Puebla, from November 8th to 11th, 2011, and organized by the Executive Committee (2010-2011) with Humberto Lanz as President, and Bronwyn Barkla, Victoria Pando, Rosario Vera Estrella. In addition, as part of their two-year plan for the Society, they also organized from May 2nd to 6th, 2011, an international course on Bioinformatics applied to Proteomics, provided by EBI/EMBL (European Bioinformatics Institute). Juan A Vizcaino, Joe Foster, Sandra Orchard, and David Ovelheiro from the European Molecular Biology Laboratory at the European Bioinformatics Institute were the trainers.

The fifth symposium was held in Cancun, Mexico; the Executive Committee was composed by Victoria Pando-Robles as President, Arturo Guevara, Sandra Contreras, Ángeles Cancino, Luis de Luna, and Alicia Chagolla. One of the main achievements of this enthusiastic Committee was the recovery of a respectable number of participants to our biannual event, which had been losing attendance in the previous symposiums. This success was certainly helped by the organization of the traditional Pre-symposium courses entitled "Mass Spectrometry Based Proteomics" and "Informatics for Proteomics", as well as the participation of an extraordinary group of experts in proteomics, including Catherine Costello, former President of the HUPO, Alma Burlingame, Juan Calvete (editor in chief of Journal of Proteomics), Andrej Shevchenko, and Donald Hunt, among others.

The last symposium was held in Puerto Vallarta, Jalisco, with Ana Paulina Barba, Sergio Encarnación-Guevara, Alicia Chagolla, Silvia Valdes, Rossana Arroyo and José Angel Huerta as members of the organizing committee. The goal of this symposium was to provide a forum to exchange experiences in different MS fields including, for the first time, experts in metabolomics, lipidomics and other omics technologies, such as Pier Giorgio Righetti, Fernando Corrales, Concha Gil, Oliver Fiehn, Luca Bini and Scott Peck. On the other hand, going along with our long-proven pre-symposium courses, we offered "Skyline", with Michael MacCoss and Brendan MacLean from the Department of Genome Sciences at the University of Washington, and "Introduction to PANTHER: a library of protein families and subfamilies indexed by function", with Pascale Gaudet, from the Swiss Institute of Bioinformatics.

4. Enlargement of Proteomics in Mexico

Since the creation of the SMP, in my view, its history has been strongly linked to the progress of Proteomics development in Mexico. Since its foundation, different proteomics laboratories and unit services have been created in different parts of Mexico, starting with the Proteomics Lab at the Center for Genomic Sciences, which produced the first papers in this area fully developed in Mexico. Later, in 2005, the Proteomics Unit at the Instituto de Biotecnología-UNAM was created as the first facility in our country that

serves to research groups at UNAM and other Mexican institutions. This Unit is led by Cesar Ferreira Batista, one of the most important driving forces of proteomics in Mexico. Likewise, in this Institute, using 2D-DIGE and quantitative proteomics, Bronwyn Barkla, Rosario Vera Estrella, Omar Pantoja and Arturo Guevara have developed different proteomics projects in plants, with special focus in *Arabidopsis thaliana*, *Thellungiella iflodonea*, and *Ettlia oleoabundans*, a non-sequenced oleaginous green microalga. In the same research center, the group led by Gerardo Corzo had developed proteomics projects in *Triatoma pallidipes*, specifically identifying and characterizing proteins from saliva, some of them belong to the anti-hemostatic protein families.

At the Center for Infectious Diseases of the National Institute of Public Health, a Proteomics Unit (UNIPRO) was created in 2004, headed by Rosa Victoria Pando Robles, which operates a MALDI-TOF/TOF 4800 Plus Proteomics Analyzer, ABI. Also in this Institute Humberto Lanz, a former President of the SMP, head a research group involved in proteomics experiments with *Anopheles albimanus* mosquitoes as a model to understand the regulation of the neuroendocrine-immune system in this insect during parasite infection.

In CINVESTAV Irapuato, different researchers are involved in proteomics projects, as Luis Eugenio González de la Vara, at the Laboratory for Bioenergetics and Biomembranes, who is characterizing proteins through MS, analyzing the transduction of signals from the plasmatic membrane of vegetal cells. Silvia Edith Valdés Rodríguez at the Laboratory for Biochemistry and Molecular Biology of Proteins is analyzing the differential response of the plants to hydric stress. Alejandro Blanco Labra is analyzing proteins involved in plant defense mechanisms, including the quaternary structure of the polyphenol oxidase of grape. He is also working on the isolation, biochemical and molecular characterization of different enzyme inhibitors and their effects on the growth and development of certain insects and its effects in the metastasis of certain types of cancer, and Robert Winkler is the principal investigator of the Laboratory of Biochemical and Instrumental Analysis. His research topics include novel MS techniques, such as low-temperature plasma ionization and covalent protein staining, new approaches in the high-throughput metabolomics profiling of plants, computational MS, and proteomics.

Close to this research center, also in Irapuato, the Laboratorio Nacional de Genómica para la Biodiversidad (LANGEBIO) opened the MS services Unit, which offers access to a range of chromatography and MS techniques. This Unit is led by José Ordaz Ortiz and features a very qualified team with proven ability in the field of MS, which is available to corporate customers and external academic institutes. In my opinion, one of the most important advantages is the possibility that they offer training and consultancy services.

One of the most recently created proteomics laboratories is the Laboratory for Immunology and Proteomics Research, which was founded at Hospital Infantil de México Federico Gómez, and is led by Genaro Patiño López. This new lab is standardizing different quantitative proteomics techniques, and they also are starting analysis about post-translational modifications, such as phosphorylation.

Increasingly, other several institutions in Mexico are contributing to the training and dissemination of proteomics and its applications. Cesar López Camarillo, at UNAM, is looking for new biomarkers in breast and lung cancers. In CINVESTAV-Zacatenco, Patricia Talamas, from the Departamento de Infectómica y Patogénesis Molecular, leads a group focused on using proteomics analysis to monitor changes in the expression profiles of the proteins with clinical relevance associated with the processes of invasive ovarian cancer. They are also characterizing proteins that constitute the ascites, to understand the molecular mechanisms that determine the growth and progression of a tumor. Eventually, they aim to the identification of molecules useful for the design of new diagnostic methods to detect early stages of ovarian cancer. In the same department, Rossana Arroyo Verástegui is involved in studying the molecular pathogenesis of trichomoniasis, with focus on the analysis of cysteine peptidase of *Trichomonas vaginalis* which has a relevant role in trichomonal pathogenicity, cytoadherence, hemolysis, cytotoxicity and immune evasion. Eliel Ruiz May, at the Instituto de Ecología (INECOL), is working in proteomics in plants focused on posttranslational modifications. José Ángel Huerta Ocampo at the Laboratorio de Bioquímica de Proteínas y Glicanos, in Hermosillo, Sonora, in food proteomics. Ana Paulina Barba de la Rosa, a former President of the MPS, is working at the Laboratorio de Proteómica y Expresión Génica at the Instituto Potosino de Investigación Científica y Tecnológica A.C. The main research line is proteomics in plants with a focus on amaranth, nopal and bean, and also on microorganisms such as *Bifidobacterium longum*, and *Ustilago maydis*. On the other hand, in the National Institute of Genomic Medicine (INMEGEN), different groups are also involved in proteomics research, for example, Juan Pablo Reyes Grajeda is looking biomarkers for diagnosis of different diseases, and Claudia Rangel Escareño is analyzing the proteomics expression in different isolates of *Leishmania mexicana*.

Because of the relevance of proteomics in the New Biology, these are some examples of researchers and groups now involved in proteomics in our country. Some groups are building up projects in biochemistry related to proteomics techniques. Some are occupied with proteomics projects, but only preparing samples or running 2D gels; samples for protein identification are sent to MS facilities. In my opinion, one very valuable gain that proteomics fostered in

Mexico and that should prevail is collaboration. In my case, it is core to our laboratory. This special issue was carried out after 25 years of proteomics research in Mexico.

5. Are we closer?

Despite some advances in technology and scale of proteomics, we are still just in the starting line. Our growth in proteomics in comparison with other countries in the world, including some countries in Latin America like Brazil, has been too slow. In other countries, different Centers or even Institutes for proteomics research have been created with millions of dollars to purchase equipment. In Mexico, the research councils like CONACyT, continuously is shortening the number and amount of budgets destined to support research projects, including scholarships for degree studies. Scientists in our nation need to fight, not only to compete at international research levels but also against the ignorance of our authorities.

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Conflict of interest

The author declares no conflicts of interest of any nature.

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