Capítulo IV Investigación en México sobre medicamentos biotecnológicos, ingeniería de tejidos y biosensores para diagnóstico

Chapter IV Research in Mexico regarding to biotechnological drugs, tissue engineering and biosensors for diagnostics

VALLEJO-CARDONA, Alba Adriana†*, OCHOA-RUIZ, Andrea Gabriela y CAMACHO-VILLEGAS, Tanya Amanda

Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco

ID 1st Author: *Alba Adriana, Vallejo-Cardona* / **ORC ID**: 0000-0002-4568-3787, **CVU CONACYT ID**: 50109

ID 1st Coauthor: *Andrea Gabriela, Ochoa-Ruiz* / **ORC ID**: 0000-0001-9873-6144, **CVU CONACYT ID**: 601997

ID 2nd Coautor: *Tanya Amanda, Camacho-Villegas* / **ORC ID** - 0000-0002-0540-0287 **CVU CONACYT ID**: 164427

DOI: 10.35429/H.2019.4.50.66

A. Vallejo, A. Ochoa y T. Camacho

avallejo@ciatej.mx

A. Marroquín, J. Olivares, P. Diaz, L. Cruz. (Dir.) La ciencia y las mujeres en Mexico. Handbooks-©ECORFAN-Mexico, Queretaro, 2019.

Abstract

Research groups who develop scientific advances in bioinformatics and biotechnological drugs, biomaterials for tissue engineering and diagnostics methods based in nanotechnology already exist in Mexico. This chapter presents basic and introductory aspects of the definitions and outreach of each discipline, as well as an extensive list of the research groups and institutions where pertinent studies are carried out to provide an update about the main focus of each investigation team. The information provided may be useful to create inter and multidisciplinary teams and thereby foster substantial improvements in these research areas. In addition, national regulations required on the field of biotechnological drugs, biomaterials for tissue engineering and diagnostics devices are presented with the objective that related and innovative projects could be taken to the market for the benefit of our society.

Bioinformatics, Biotechnological drugs, Tissue engineering, Diagnostic devices, Innovation, Research lines

1. Introduction

In the 60's and 70's, significant studies started to bloom and sparked new research areas that have now revolutionized the biomedical field, such as, genome sequencing studies which led to the development of biotechnological drugs (Maxson Jones, Ankeny, & Cook-Deegan, 2018); the study of stem cells for regenerative medicine (Anzaldúa Arce et al., 2007); and the research in nanotechnology which gave to biosensors (Qing et al., 2019).

The genome sequence of *C. elegans*, proposed in 1963 by the biologist Sydney Brenner from Cambridge University, began a new biotechnological era, which had another important inflexion point between 1990 and 2003 when the human genome was fully sequenced (Maxson Jones et al., 2018). The Human Genome Project began as a consortium, until 2000 when the Celera Genomics led by Dr. Craig Venter joined the cause (Martínez, 2010). Nevertheless, thanks to the "Bermuda Principles" from 1996 all this information is of public domain (Maxson Jones et al., 2018). Therefore even though Mexico did not participate in the project, important studies have been done in genomic medicine with the information provided by it (Martínez, 2010), for instance, the search for biomarkers for the diagnostic and treatment of multiple diseases (Manzanarez-Ozuna, Flores, Gutiérrez-López, Cervantes, & Juárez, 2018; Weissglas-Volkov et al., 2010).

The information derived from genome sequencing led to great advances in genetic and protein engineering. This gave rise to the development in 1975 of the first biotechnological drugs, which were human recombinant insulin produced in *E.coli* (Vecchio, Tornali, Bragazzi, & Martini, 2018). Biotechnological drugs are now available in the Mexican market, for example Cetuximab® also known as the commercial name Erbitux®. This drug consists of a monoclonal antibody used to treat diverse types of cancer, specially colon, rectum, head and neck (Peralta et al., 2018). There is already regulation for the proper manufacture of both biotechnological drugs (Arriola Peñalosa, 2012) and biocomparable ones (López Silva, 2012).

The design and development of biotechnological drugs have been accomplished as a result of the advance of new disciplines, such as bioinformatics, which has provided tools for both *in silico* analysis of sequencing information and the design of software that allows tridimensional protein analysis (Patel & Panchal, 2014). As for regenerative medicine, an important event occurred in 2006 when Takahashi and Yamanaka discovered that mouse fibroblast cells could return to a pluripotency state, also known as "undifferentiated", with the introduction of four transcription factors: Oct3/4, Sox2, c-Myc y Klf4 (Takahashi & Yamanaka, 2006). This discovery opened the possibility to create autologous tissues and avoid the rejection of allografts and transplants (Serrato Ochoa, Nieto Aguilar, & Aguilera Méndez, 2015).

Regenerative medicine is comprised of three disciplines: 1) cellular therapy, 2) *in situ* guided regeneration and 3) tissue engineering, which has had a more significant impact in recent years. Tissue engineering consists of the integration of stem cells, biomaterials and transcription factors in a system to mimic tissue and organ function based in similar structures generated *in vitro* (Kim, 2017; Serrato Ochoa et al., 2015).

The FDA has already approved artificial skin and cartilage; however, its application in the clinic is still scarce due to the high cost of treatments. At laboratory scale, arteries, skin grafts, cartilage, bladder and trachea have been implanted. However, more research is needed about the functionality and safety of the implantation of other organs created *in vitro*, such as heart, lung and liver (NIBIB, 2013), in order to fully replace organ donation.

Biosensors and devices to improve disease diagnostics have emerged due to the integration of nanotechnology, microfluidics and diverse signal transduction systems, which employ serum, saliva, blood, among other biological fluids. The main objective is to generate more accessible, sensitive and efficient diagnostic systems (Bhalla, Jolly, Formisano, & Estrela, 2016).

The advances in bioinformatics, tissue engineering and biosensors are gradually changing diagnostics as well as the treatment of diseases. Therefore, this chapter is focused on providing an insight of the most important research being conducted in our country in these fields. Moreover, regulation covering these fields is also discussed. This regulatory information should be considered when developing innovative products in the laboratory which could be translated to the market, thus generating a measurable and transcendental social impact.

2. Biotechnological Drugs

The Mexican General Health Law reformed in 2009 includes as the definition of a biotechnological drug: "any substance that has been produced by molecular biotechnology; which has therapeutic, preventive or rehabilitation effect; that it is presented as pharmaceutical and it is identified by its pharmacological and physical activities, as well as by its chemical and biological properties" (Ley General de Salud, 2018). In other words, a biotechnological drug refers to a drug that is manufactured by a biological culture or live organism, which has been previously manipulated or modified by genetic engineering and biotechnological tools. The most recognized drugs consist of proteins and monoclonal antibodies for diverse therapies, such as recombinant insulin to treat diabetes or antibodies for cancer treatment (Peralta et al., 2018; Vecchio et al., 2018).

Biotechnological drugs, when compared to synthetic drugs created by chemistry, not only differs in the production process, but also the molecules of biotechnological drugs are much bigger and complex (López Silva, 2012). Therefore, quality control of the biotechnological drug production process is extremely important as for instance, changes in the agitation and oxygen transfer could considerably affect the quality of the drug (López Silva, 2012). The general production process consist of: First

- Genetic modification, insertion, depletion and/or duplication of genes in the host cells which could be bacteria or mammalian. These transformed cells constitute the "working bank" and could be denominated as "transformed clones". Second,
- Obtaining a cell culture of the transformed clones for its growth and metabolite of interest expression derived from the genetic manipulation. The steps for the culture of the transformed clone include:

1. Fermentation: when the culture is transferred to bioreactors with selective media to preserve gene expression and the expression of the recombinant product. This step includes several upstream sub-steps, as the characterization of the culture in volumes of 1, 5, 10, 20, 200 or 1000 L.
2. Purification: segregation of the product of interest from the biomass (cells, culture media and residues). Depending on the product characteristics, different methods could be used, such as centrifugation, affinity chromatography, molecular exclusion and ultrafiltration, among others.
3. Formula development and packaging: refers to treat the product to obtain drug characteristics and can be commercialized, this includes pharmacological formula development, shelf life analysis, etc. (Dr. Ricardo Montenegro, n.d.).

2.1 Human genome data analysis to target new possible drugs

Bioinformatic tools allow proper analysis and design of biotechnological drugs. Due to the advances in human genome sequencing, it is now possible to design new and more specialized pharmaceuticals, including personalized drugs. Further, *in silico* analysis allows one to predict of the tridimensional structure of the new biotechnological drugs.

Genomic Medicine has its origins in human genome sequencing, and consists in the analysis of such information to improve diagnostics and treatments. Even though Mexico did not participate in this project, related studies began in 1994 at the National Autonomous University of Mexico (UNAM, "Universidad Nacional Autónoma de México") with a university health research program. Afterwards, in 2004, the National Institute of Genomic Medicine (INMEGEN, "Instituto Nacional de Medicina Genómica") was funded (Martínez, 2010). Nowadays INMEGEN has 20 research lines in genomics applied to different diseases such as cardiovascular, hepatic, metabolic, atopic, autoimmune, psychiatric, neurodegenerative, cancer, bone metabolism, and infectious, among others and even has research lines in nutrigenetics and nutrigenomics. All of these research lines can be seen on their website (www.inmegen.gob.mx).

The Project of Mexican Genomic Diversity carried out by INMEGEN, was the first study in Latin America to analyze the genomic diversity of the population (Silva-Zolezzi et al., 2009). Punctual changes in one nitrogen base in the DNA sequence were analyzed; each of these changes is better known as a single nucleotide polymorphism (SNP). Many SNPs present in a chromosome that are inherited together are called haplotypes. Therefore, the study of these haplotypes in projects, such as the HapMap has been important to correlate these mutational blocks with diseases. The first international HapMap project began by the end of 2002 with samples obtained from individuals in Nigeria, Japan, China and United States and financed by public and private sources from these countries (NIH, 2013). However, as the frequency of the appearance of these haplotypes is different between ethnic groups, it is necessary to know the specific map of the Mexican population (Martínez-levy, Vásquez-medina, & Cruz-fuentes, 2010).

Several research groups and laboratories are dedicated to the analysis of the Mexican genome. One of the most important is LAMPER from the Center for Research and Assistance in Technology and Design of the State of Jalisco, A.C. (CIATEJ, "Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco, A.C) and National Council for Science and Technology (CONACYT, "Consejo Nacional de Ciencia y Tecnología") (https://ciatej.mx/servicios-industria/medica-farmaceutica/lamper), founded in 2006 and dedicated to develop bioinformatics tools, such as the software, SNPClinic, which predicts SNP to develop more efficient pharmaceuticals (Prado Montes de Oca, n.d.). Flores Saiffe Farías and collaborators (2015), proposed an *in silico* method to detect SNPs in functional regulators of antimicrobial peptide genes applied to the analysis on genetic variants in patients with tuberculosis and HIV/AIDS in order to discover new drugs. Genomic data bases such as ENCODE, 1kGP, GXA, among others, were useful to develop an integral analysis and predict the impact of tuberculosis and HIV/AIDS infections in the presence of SNPs in regulators of the promoters of the genes DEFB1 and CAMP, which codify for antimicrobial peptides (Flores Saiffe Farías, Jaime Herrera López, Moreno Vázquez, Li, & Prado Montes De Oca, 2015).

2.2 Program design to analyze protein tridimensional structure

The most important data bases are GenBank from the United States, the European Molecular Biology Laboratory (EMBL) and the DNA Data Bank of Japan (DDBJ). In these data bases, information about genetic sequences can be found and homology, protein structure and prediction analysis can be performed. The Protein Data Bank (PDB) from the United States as well as UniProt from Europe are the most complete data bases for protein analysis, since sequences can be found and tridimensional structure simulation can be performed. Dr. Enrique Rudiño from the Biotechnology Institute (IBT) at UNAM has performed important contributions to these data bases with structural biochemistry studies of proteins and enzymes (UNAM, n.d.). Likewise, Dr. Eduardo Arturo Rodríguez Tello from the Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV, "Centro de Investigación y Estudios Avanzados del Instituto Politécnico Nacional") Unit Tamaulipas, uses modern metaheuristic algorithms for protein structural prediction based on the study of hydrophobic forces energy implicated in the folding process (Garza-Fabre, Rodriguez-Tello, & Toscano-Pulido, 2013; Garza-Fabre, Toscano-Pulido, & Rodriguez-Tello, 2015).

Table 3 mentions different research groups focused on bioinformatics applied to biotechnological drugs relating to human health. However, the main research line for these groups is developing identifying biomarkers for the diagnosis of diseases, for example, breast cancer (Manzanarez-Ozuna et al., 2018), diabetes (Mercader et al., 2017) and cardiovascular diseases (Weissglas-Volkov et al., 2010).

Once enough information has been gathered, it is expected that new pharmaceuticals could be designed based on the Mexican human genome. New research about these potential pharmaceuticals or complementing the existing research lines regarding biomarkers is of vital importance.

3. Tissue Engineering

While biotechnological drugs aim to bring molecules to the organism to treat a disease, tissue engineering and regenerative medicine go a step further in trying to replace a damaged tissue or organ to restore its normal function. That is, instead of providing insulin to patients with diabetes type I, nowadays the possibility of regenerating a whole pancreas with β- cells perfectly organized and functional is also explored, and thereby potentially eliminating the life-long administration of insulin to a patient or even decreasing organ donation. Tissue engineering is the next step in cellular culture evolution, as it is not only based in providing the correct culture media, but in integrating a scaffold and microenvironment to modulate a specific cellular response that allows restoration of tissue functionality or complete organs.

Table 4.1 depicts diverse types, sources, advantages and disadvantages of the cells that have been used for tissue engineering research, as the cells are the first basic aspect needed for this discipline. The term “somatic cells” refers to fully differentiated cells with a specific function and lineage; on the other hand “stem cells” refers to cells that have the capacity of regenerating themselves and give rise to different types of cells depending on the microenvironment. Among stem cells, depending on the differentiation capacity, they are distinguished between totipotent, pluripotent and multipotent cells, these last ones have the least differentiation capacity (Kim, 2017). It is worth noting that totipotent stem cells can give rise to a complete embryo or organism, but as they have limited auto renewal capacity and they have been found only at an embryonic stage (Anzaldúa Arce et al., 2007) its use in tissue engineering is limited.

Table 4.1 Types of cells used in Tissue Engineering

Type of cells	Source	Advantages	Disadvantages
Allogenic somatic cells	Donor source: different from receptor	Replace damaged cells from the receptor with healthy cells from the donor.	They can generate immune response, Immunosuppressive drugs are needed, Differentiated cells with low proliferating capacity, Disease transmission risk
Autologous somatic cells	Donor source: the same patient	Rejection is minimized, No need of immunosuppressive drugs	Differentiated cells with low proliferating capacity
Embryonic stem cells	Donor source: embryo	High capacity of regeneration and differentiation (pluripotent), *In vitro* differentiation into endodermal, ectodermal and mesodermal cells, Embryoids or tridimensional structures formation	Ethical concern associated to embryo destruction, Teratoma risk formation *in vivo*, Forbidden in many countries
Fetal stem cells	Donor source: amniotic fluid and placenta	Multipotent cells mixture that express embryonic stem cells and adult cells markers, Can be differentiated in many cell lineages, No teratoma risk formation *in vivo*	Less differentiation capacity than embryonic stem cells (multipotent)
Adult stem cells	Donor source: diverse tissues and organs (spine, adipose tissue, blood, heart, nerve tissue, muscle and urine)	Free of ethical concerns, Transplanted with no risk Easy to obtain as they self-renew during all organism life-spam, Differentiation into several type of tissues, Give rise to progenitor cells which are tissue-specific	Less differentiation capacity than embryonic stem cells (multipotent)
Induced Pluripotent Stem Cells (iPS)	Generated by the dedifferentiation process of adult somatic cells through the application of transcription factors	Obtained without embryos need, More differentiation capacity than adult stem cells (pluripotent)	Teratoma risk formation, Incomplete reprograming risk

Source: Anzaldúa Arce et al., 2007; Kim, 2017; Serrato Ochoa et al., 2015; Takahashi & Yamanaka, 2006

The second essential aspect of tissue engineering is the use of biomaterials as scaffolds for cell proliferation and differentiation. The characteristics of the ideal biomaterial consist of:

1. Ability to integrate to the host tissue without inducing an adverse inflammatory response.
2. Have a porous and tridimensional structure to facilitate cellular migration and induce vascularization.
3. Depending on the case, should be biodegradable to degrade at a controlled rate and induce new tissue formation.
4. Be biocompatible, sterilizable, safe and easy to produce under good manufacture practice.

Depending on the source, biomaterials are classified in synthetic or naturals. Among synthetic ones, the most used are polylactic acid (PLA), polyglycolic acid (PGA), poly (lactic-co-glycolic) acid (PLGA) and poly-caprolactone (PCL). The main advantage of these synthetic biomaterials is the ease of manufacture on a large scale with high reproducibility of their physical and chemical properties (Kim, 2017). Furthermore, their degradation rates can be controlled (Lerma et al., 2016). On the other hand, the degradation rate of natural biomaterials is difficult to control, and variations from batch to batch may exist. Nonetheless, because of its natural origin, these biomaterials, such as collagen, gelatin, alginate, fibrin, chitosan and hyaluronic acid, have more biocompatibility, (Kim, 2017; Serrato Ochoa et al., 2015).

Hydrogels are cross-linked structures designed by the mixture of different biomaterials, as for example, natural biomaterials and polyethylene glycol (PEG) which is synthetic. As they can absorb water, hydrogels can provide a microenvironment similar to native tissues. Still, their mechanical properties are weak and degrade at a faster rate (Kim, 2017). Chitosan hydrogels have been developed for diabetic foot treatment by researchers from the Autonomous Mexico State University (UAEM, “Universidad Autónoma del Estado de México”) (Narváez, 2018).

As for cell culture, differences between 3D and 2D cultures have been observed when modulating the cellular response in the presence of growth factors to guide cell differentiation. 3D cultures can create dynamic conditions with the advantage of facilitating industrial scale production, cellular adhesion and interconnection between cells, as compared with static 2D cell cultures with lower differentiation gene expression (Shekaran et al., 2015). To assess a biomaterial’s performance and to determine if it is suitable for tissue engineering, diverse techniques could be applied, as illustrated in table 4.2.

Table 4.2 Techniques to characterize biomaterials used in Tissue Engineering

Technique	Evaluation
Fourier- transformed infrared spectroscopy (FTIR)	Composition
Raman Spectroscopy	Composition
Nuclear Magnetic Resonance (NMR)	Composition
X-Ray Photoelectron Spectroscopy (XPS)	Composition
Gel Permeation Chromatography	Peso Molecular
Differential scanning calorimetry (DSC)	Thermic properties (fusion temperature, melting temperature)
X-ray Diffraction (XRD)	Microstructure and crystallinity
Scanning electron microscopy (SEM)	Microstructure
Dynamic mechanical analysis (DMA)	Mechanical properties (Young´s modulus, traction resistance)
Thermogravimetric analysis (TGA)	Degradation rate
Alkaline Phosphatase	Osteogenic differentiation
Alizarin Red	Mineralization or calcium deposits in osteogenic differentiation
Alamar Blue	Cell cytotoxicity

Source: Lerma et al., 2016; Zapata-Catzin et al., 2018

3.1 Tissue and organ modeling in Mexico

In 2016 the Mexican Network of Biomaterials and Tissue and Organ Engineering (Red Biot, A.C.) emerged to link pertinent researchers and to impulse the development of this innovative in our country. Dr. Miriam Verónica Flores Merino from the Health Science Research Department of UAEM is the president of Red Biot, A.C. (Narváez, 2018). Researchers from the Yucatan Scientific Research Center (CICY, “Centro de Investigación Científica de Yucatán”), who are part of Red Biot A.C., are developing is a research line focused on biomaterials for regenerative medicine and its application in bone and cardiovascular tissue engineering.

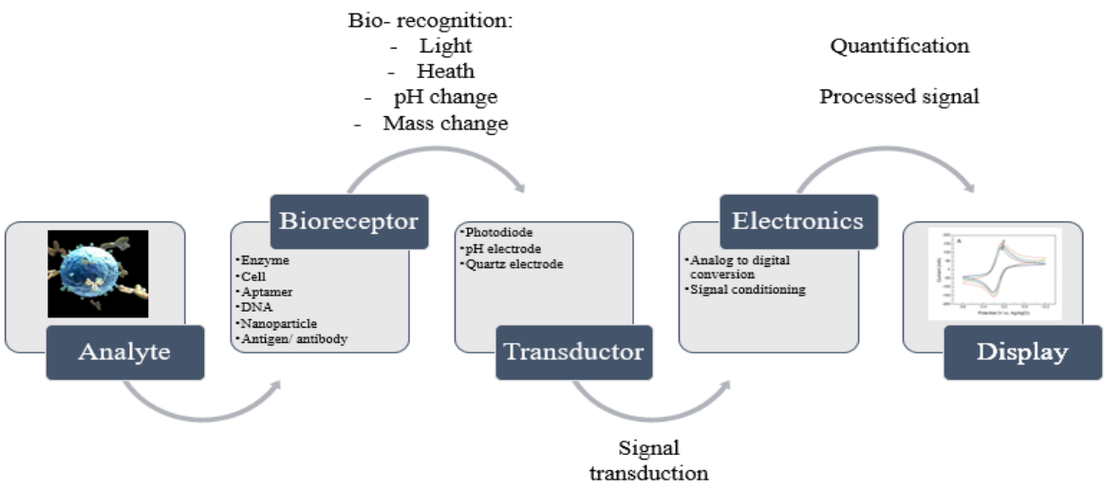
The CICY research group led by Dr. José Manuel Cervantes has developed a segmented polyurethane, which combined with β- glycerol phosphate promotes the adhesion, growth and osteogenic differentiation of human mesenchymal cells. This material is of great interest as the degradation rate can be controlled and has mechanical properties that enhance bone regeneration (Lerma et al., 2016). Another strategy used to minimize the rejection of allogenic transplant is the design of scaffolds with decellularized tissue, which refers to the removal of cellular components to preserve the extracellular matrix and feed it with the host cells. Dr. María Cristina Piña Barba from the Materials Research Institute at UNAM has worked on this strategy since 1996 (DGCS, 2016). Table 4.3 shows the main research lines for bone (Lerma et al., 2016), dental (Castro-Ceseña et al., 2016), cardiac (Zapata-Catzin et al., 2018) and skin tissues to promote wound healing (Rubio-Elizalde et al., 2019). At CIATEJ, a group led by Dr. Hugo Esquivel Solís are working on the research subline "Biomedical engineering of biotechnological drugs and tissue engineering" to develop *in vitro* kidney organoids. Additionally, biosensors and theranostic nanostructures are being developed by the research groups led by Dr. Alba Adriana Vallejo Cardona and Dr. Tanya Amanda Camacho Villegas (authors of this chapter). Also at Monterrey Institute of Technology and Higher Education (ITESM, "Instituto Tecnológico y de Estudios Superiores de Monterrey") there exists a research line specialized in corneal tissue engineering.

4. Biosensors

Biosensors are devices capable of transferring a biological event into a quantifiable signal (Zhu, 2017). Therefore, biosensors are formed by three parts. First, by a bioreceptor, which is a molecule that recognizes in a specific fashion the analyte of interest, for instance, the antibodies that target epitopes in a protein; second, by a transductor, which converts the energy of such a recognizing event into a measurable signal; and third, by an electronic component which presents the results to the user (Bhalla et al., 2016; Wongkaew, Simsek, Griesche, & Baeumner, 2018). The most used transducer methods are electrochemical, optical, piezoelectric and magnetic; however, the electrical, electrochemical and optical are faster, and therefore, preferred (Zhu, 2017). Advances in microfluidics have developed the design of "lab-on-a-chip" devices, capable of performing laboratory tasks in miniaturized versions and sometimes fully automated; furthermore, they consume less sample volume, are faster, easy to operate and allow multiple analyte analysis (Costantini et al., 2015). Also they can be more sensitive, selective and can perform real time measurements (Weng, Gaur, & Neethirajan, 2016).

Dr. Alfredo Márquez Lucero from Advanced Materials Research Center (CIMAV, "Centro de Investigación en Materiales Avanzados") has created electrical "nose" and "tongue" sensors to measure glucose in diabetic patients (CIMAV, n.d.; Santana-Jiménez, Márquez-Lucero, Osuna, Estrada-Moreno, & Dominguez, 2018). Listed on Table 4.3 are several carbon nanomaterial research groups in Mexico for biosensor development.

Figure 4.1 Schematic representation of a biosensor



Source: Bhalla et al., 2016; Liu et al., 2012

An exhaustive research was done to construct Table 4.3, which is a list of institutions and investigation groups related to bioinformatics applied to the development of biotechnological drugs, tissue engineering and biomaterials, and biosensors in each state of Mexico. The majority listed are public research centers. Groups that work in different areas than the ones stated were excluded.

Table 4.3 Centers and research groups focused on Bioinformatics, Tissue Engineering and Biosensors in Mexico

State	University/ Research Center	Sub-Area	Researcher	Investigation Line	Web Page
Baja California	Ensenada Center for Scientific Research and Higher Education (CICESE, "Centro de Investigación Científica y de Educación Superior de Ensenada")	Experimental and Applied Biology Division / Department of Biomedical Innovation	Dr. Alexei Fedorovish Licea Navarro	Omics sciences applied to biomedical and biotechnological development; secondary metabolites and bioactive substances	https://www.cicese.edu.mx/investigacion/personal_academico/1746
			Dr. Ana Bertha Castro Ceseña	Composites materials developments for therapeutic applications in tissue engineering	https://www.cicese.edu.mx/investigacion/personal_academico/502239
			Dr. Gerard Jean Fournier Pierrick	Cancer research and treatment; bone pathologies	https://www.cicese.edu.mx/investigacion/personal_academico/3445
			Dr. Patricia Juárez Camacho	Cancer research and treatment; bone pathologies	https://www.cicese.edu.mx/investigacion/personal_academico/3444
			Dr. Aldo Moreno Ulloa	Clinic proteomic; biomarkers study for diagnosis and progression of chronic degenerative diseases	https://www.cicese.edu.mx/investigacion/personal_academico/3503
Coahuila	Center for Research in Applied Chemistry (CIQA, "Centro de Investigación en Química Aplicada")	Advanced Materials	Dr. Antonio Serguei Ledezma Pérez	Biosensors development; antimicrobial biomaterials with application in dentistry; bone tissue engineering	http://192.100.159.111:82/AntonioLedezma.aspx
			Dr. Ivana Moggio	Optic biosensor development for clinical corporal fluid diagnostic	http://192.100.159.111:82/IvanaMoggio.aspx
Chihuahua	Advanced Materials Research Center (CIMAV, "Centro de Investigación en Materiales Avanzados")	Department of Engineering and Materials Chemistry / Surface Chemistry Area	Dr. Alfredo Aguilar Eiguézabal	Nanostructured materials; carbon nanotubes, toxicity studies and biomedical applications, artificial photosynthesis	https://cimav.edu.mx/investigacion/ingenieria-y-quimica-de-materiales/quimica-superficies-nanotubos/
		Department of Materials Engineering and Chemistry /Polymers Area	Dr. Alfredo Márquez Lucero	Nanostructured polymeric sensors: electronic "nose" and "tongue" for glucose measurement in diabetic patients	https://cimav.edu.mx/investigacion/ingenieria-y-quimica-de-materiales/area-de-polimeros-sensores/
Mexico City (some of the research centers may have campus in Querétaro and Cuernavaca)	National Autonomous University of Mexico (UNAM, "Universidad Nacional Autónoma de México")	Center of Applied Physics and Advanced Technology (CFATA, "Centro de Física Aplicada y Tecnología Avanzada")	Dr. Josue David Mota Morales (Nanotechnology Department)	Macro porous polymers and nanocomposites for tissue engineering	http://www.fata.unam.mx/Academicos/DrJosueMota
			Dr. Domingo Rangel Miranda (Department of Molecular Materials Engineering)	Sensors and biosensors; medical devices innovation	http://www.fata.unam.mx/Academicos/DrDomingoRangel
			Dr. Eric Mauricio Rivera Muñoz (Nanotechnology Department)	Ceramic biomaterials for bone tissue engineering	http://www.fata.unam.mx/Academicos/DrEricRivera
		Biotechnology Institute (IBT, "Instituto de Biotecnología" Molecular Medicine and Bioprocesses	Dr. Baltazar Becerril	Antibodies genes synthesis, expression and characterization related to amyloidosis	http://www.ibt.unam.mx/server/PRG.base?tipo:doc,dir:PRG.grupo,par:Gbb,tit:Grupo_del__Dr._Baltazar_Becerri
			Dr. Martín Gustavo Pedraza	Molecular mechanisms studies which activate and regulate inflammatory processes in central nerve system	http://www.ibt.unam.mx/server/PRG.base?tipo:doc,dir:PRG.grupo,par:Ggp,tit:Grupo_del__Dr._Martin_Gustavo_Pedraza
			Dr. Leonor Pérez	Molecular mechanism which control neuronal differentiation	http://www.ibt.unam.mx/server/PRG.base?tipo:doc,dir:PRG.grupo,par:Glm,tit:Grupo_de_la__Dra._Leonor_Perez
			Dr. Enrique Rudiño	Structural biochemistry of proteins and enzymes. His research group have provided a great number of structures to Protein Data Bank (PDB)	http://www.ibt.unam.mx/server/PRG.base?tipo:doc,dir:PRG.grupo,par:Geu,tit:Grupo_del__Dr._Enrique_Rudi%F1o
		Biomedical Research Institute (IIB, "Instituto de Investigaciones Biomédicas" Molecular Biology and Biotechnology	Dr. Alejandro Manuel García Carrancá	Cervix organoids and oral cavity to study the interaction of VPH and stem cells	https://www.biomedicas.unam.mx/personal-academico/alejandro-manuel-garcia-carranca/
			Dr. Luis Antonio Mendoza Sierra	Modelling and simulation on regulatory networks of biological interest	https://www.biomedicas.unam.mx/personal-academico/luis-antonio-mendoza-sierra/
		IIB/ Genomic Medicine	Dr. Alejandro Mohar Betancourt	Breast cancer biomarkers	https://www.biomedicas.unam.mx/personal-academico/alejandro-mohar-betancourt/
			Dr. Alejandro Zentella Dehesa	Proteomics applied to the search of breast cancer biomarkers	https://www.biomedicas.unam.mx/personal-academico/alejandro-zentella-dehesa/
			Dr. María Eugenia Gonsebatt Bonaparte	Catechol route genes polymorphism involved in estrogen metabolism and it possible relationship with breast cancer	https://www.biomedicas.unam.mx/personal-academico/maria-eugenia-gonsebatt-bonaparte/

			Dr. María Teresa Tusié Luna	Human genomics: genes search involved in diabetes development and other dyslipidemias related to cardiovascular risk in Mexican population	https://www.biomedicas.unam.mx/personal-academico/maria-teresa-tusie-luna/
		Materials Research Institute (IIM, "Instituto de Investigaciones en Materiales")	Dr. María Cristina Piña Barba	Biomaterials and tissue engineering	http://www.iim.unam.mx/index.php/investigacion/lineas-de-investigacion
	National Institute of Genomic Medicine (INMEGEN, "Instituto Nacional de Medicina Genómica")		Dr. Carmen Alaez Verson	Genómica del cáncer, diagnóstico de enfermedades hereditarias	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=3186
			Dr. Bárbara Patricia Antuna Puente	Cardiovascular diseases genomics, VIH genomics among other projects related to metabolic diseases	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=939
			Dr. Jaime Arellanes Robledo	Hepatic diseases genomic: alcoholic hepatic diseases and hepatocellular carcinoma	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=3428
			Dr. Selma Eréndira Avendaño Vazquez	Psychiatric and neurodegenerative diseases genomics	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=3423
			Dr. Samuel Canizales Quinteros	Metabolic diseases and intestinal microbiota genomics; native populations genomics	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=2147
			MSc. Karol Carrillo Sánchez	Hereditary diseases genomic diagnostic	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=9
			Dr. Gisela Ceballos Cancino	Functional genomics: signaling route characterization for he diagnostics, prognostics and/or treatment of cancer	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=216
			Dr. Cecilia Contreras Cubas	Autoimmune diseases genomics (systemic lupus erythematosus), metabolic diseases (diabetes type 2) and microbiome	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=2515
			Dr. Armando Cruz Rangel	Protein bio-physic-structural generation, production and characterization and its relevance in cancer, influenza, diabetes and autoimmune diseases	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=3082
			Dr. Mirelle Vanessa González Covarrubias	Mexican patients pharmacogenetics	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=2429
			Dr. Rafael Velázquez Cruz	Support tools in osteosarcoma and osteoporosis diagnostics	https://www.inmegen.gob.mx/investigacion/investigadores/curriculum-vitae/?perfil=36
Mexico City	National Institute of Rehabilitation (INR, "Instituto Nacional de Rehabilitación")	Tissue Engineering, Cell Therapy and Regenerative Medicine Unit	MSc.. Valentín Martínez López	Production of new musculoskeletal tissue and skin for reconstructive surgery, transplant of tissues and bio-compatible structures generated *in vitro*	https://www.inr.gob.mx/i20.html
Guanajuato	Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV, "Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional")	Irapuato Unit/ Genetic Engineering	Dr. Miguel Ángel Gómez Lim	Biopharmaceuticals production in plants	https://www.cinvestav.mx/Portals/0/sitedocs/investigacion/UnidadIrapuatoIngenieriaGenetica.pdf
Guerrero	Guerrero Scientific and Technological Research Center (CICTEG, "Centro de Investigación Científica y Tecnológica de Guerrero")	Red Biotechnology	Dr. Beatriz Mónica Pérez Ibarra	Genetic engineering to heal or prevent certain diseases through the introduction of genetic material into human cells	http://www.cicteg.org.mx/en/areas-de-investigacion/biotecnologia.html
Jalisco	Center for Research and Assistance in Technology and Design of the State of Jalisco (CIATEJ, "Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco A. C")	Medical and Pharmaceutical Biotechnology	Dr. Alba Adriana Vallejo Cardona	Biomedical engineering and biosensors, Surface modification with lipids and/or proteins through chemical and electrochemical reactions	https://ciatej.mx/investigacion/investigador/alba-adriana-vallejo-cardona-dra
			Dr. Emmanuel Díaz	Cellular reprograming mechanisms, stem cells and gene editing through CRISPR/Cas	https://ciatej.mx/investigacion/investigador/emmanuel-diaz-dr
			Dr. Hugo Esquivel Solís	Kidney human organoids development *in vitro*	https://ciatej.mx/investigacion/investigador/hugo-esquivel-solis-dr
			Dr. Pavel Hayl Lugo Fabres	Biomedical engineering of biotechnological drugs and tissue engineering	https://ciatej.mx/investigacion/investigador/pavel-hayl-lugo-fabres-dr
			Dr. Ernesto Prado Montes de Oca	National Laboratory of Personalized Medicine (LAMPER, "Laboratorio Nacional de Medicina Personalizada"); software development and preventive medicine	https://ciatej.mx/investigacion/investigador/ernesto-prado-montes-de-oca-dr

			Dr. Tanya Amanda Camacho Villegas	vNAR antibodies development and its application in POC biosensors	https://ciatej.mx/investigacion/investigador/tanya-amanda-camacho-villegas-dra
	Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV, "Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional")	Guadalajara Unit	Dr. Antonio Ramírez Treviño	Electro mechanic microsystems (MEMS) applied to glucometers and BioMems	https://www.cinvestav.mx/Portals/0/sitedocs/investigacion/UnidadGuadalajara.pdf
	Guadalajara University (UdG, "Universidad de Guadalajara")	University Center of Exact Sciences and Engineering (CUCEI, "Centro Universitario de Ciencias Exactas e Ingenierías")	Dr. Agustín Martínez Ruvalcaba	Biomaterials development	http://www.udg.mx/es/investigacion/directorio/agust-n-mart-nez-ruvalcaba
			Dr. Alejandro González Álvarez	Hydrogels synthesis and characterization	http://www.udg.mx/es/investigacion/directorio/alejandro-gonz-lez-lvarez
Morelos	Morelos Autonomous University (UAEM, "Universidad Autónoma del Estado de Morelos")	Biotechnology Research Center (CEIB, " Centro de Investigación en Biotecnología")	Dr. Elba Cristina Villegas Villarreal	Structure- function laboratory and protein engineering: bioinformatics, modelling and protein dynamics	https://www.uaem.mx/ceib/efipro.html
		Research Center in Cellular Dynamics (CIDC, "Centro de Investigación en Dinámica Celular")	Dr. Rodrigo Said Razo Hernández	Biophysics: in silico design of inhibitors for chronic degenerative diseases treatment	http://www.cidc.uaem.mx/rodrigo-said-razo-h/
Nuevo León	Autonomous University of Nuevo León (UANL, "Universidad Autónoma de Nuevo León")	Faculty of Dentistry	Dr. Casiano del Ángel Mosqueda	Tissue engineering with dental stem cells for disease treatment	https://www.uanl.mx/investigadores/casiano-del-angel-mosqueda/
		Faculty of Chemical Sciences	Dr. Isaías Balderas Rentería	Genetic polymorphism evaluation associated to hypertension, diabetes and obesity. Recombinant protein heterologous expression for biopharmaceuticals	https://www.uanl.mx/investigadores/isaias-balderas-renteria/
	Monterrey Institute of Technology and Higher Education (ITESM, "Instituto Tecnológico y de Estudios Superiores de Monterrey")	School of Medicine	Dr. Marco Antonio Rito Palomares	Bioengineering and regenerative medicine applied to: amyotrophic lateral sclerosis; Parkinson; metabolic syndrome; diabetes, sciatica; urinary tract disorders; lung fibrosis	https://tec.mx/es/investigacion/donde-se-realiza-la-investigacion/bioingenieria-y-medicina-regenerativa
			Dr. Arturo Santos García	Devices development for metabolic diseases treatment	https://tec.mx/es/investigacion/donde-se-realiza-la-investigacion/enfermedades-metabolicas
			Dr. Jorge Eugenio Valdez García	Tissue engineering applied to corneal tissue	https://tec.mx/es/investigacion/donde-se-realiza-la-investigacion/terapias-innovadoras-en-ciencias-visuales
		School of Engineering and Sciences	Dr. Mario Moisés Álvarez	Biomedical engineering: organ-on-a-chip systems and biomaterial engineering	https://tec.mx/es/investigacion/donde-se-realiza-la-investigacion/ingenieria-biomedica
			Dr. Sergio Omar Ramírez Chapa	Nano-sensors and devices: micro/nano carbon sensors	https://tec.mx/es/investigacion/donde-se-realiza-la-investigacion/sensores-y-dispositivos
Querétaro	Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV, "Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional")	Querétaro Unit	Dr. Gabriel Luna Bárcenas	Biomaterials for biomedical applications	https://www.cinvestav.mx/Portals/0/sitedocs/investigacion/UnidadQueretaro.pdf
San Luis Potosí	Potosine Institute of Scientific and Technological Research (IPICYT, "Instituto Potosino de Investigación Científica y Tecnológica A. C.")	Division of Molecular Biology / Cell Differentiation	Dr. Antonio de León Rodríguez	Production of therapeutic proteins in bioreactor and vaccines through synthetic genes. Tissue engineering.	https://www.ipicyt.edu.mx/curricular/AntonioDeLe%C3%B3nRodr%C3%ADguez
		Division of Molecular Biology / Therapeutic and prophylactic proteins encoded by synthetic genes	Dr. Samuel Lara González	Protein and enzymes structure-function characterization. For instance enzymes involved in the mobilization and storage of lipids in adipocytes	https://www.ipicyt.edu.mx/curricular/SamuelLaraGonz%C3%A1lez
Tamaulipas	Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV, "Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional")	Tamaulipas Unit	Dr. Eduardo Arturo Rodríguez Tello	Modern metaheuristic algorithms development for practical resolution of problems in bioinformatics	https://www.cinvestav.mx/Portals/0/sitedocs/investigacion/UnidadTamaulipas.pdf
Yucatán	Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV,	Mérida Unit/ Applied Physics	Dr. Juan José Alvarado Gil	Optic and photothermic spectroscopy, intelligent materials and nanomaterials in liquid, semisolid and solid matrices	https://www.cinvestav.mx/Portals/0/sitedocs/investigacion/UnidadMeridaFisicaAplicada.pdf

	"Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional")		Dr. José Antonio Azamar Barrios	Carbon nanomaterials synthess and characterization	https://www.cinvestav.mx/Portals/0/sitedocs/investigacion/UnidadMeridaFisicaAplicada.pdf
			Dr. José Pascual Bartolo Pérez	Solid materials characterization with electronic spectroscopies: AES, XPS, SEM y EDAX	https://www.cinvestav.mx/Portals/0/sitedocs/investigacion/UnidadMeridaFisicaAplicada.pdf
	Yucatan Scientific Research Center (CICY, "Centro de Investigación Científica de Yucatán A.C.")	Materials for Regenerative Medicine	Dr. Juan Valerio Cauich Rodríguez	Biomaterials for blood vessels regeneration	https://www.cicy.mx/unidad-de-materiales/investigador/juan-valerio-cauich-rodriguez
			Dr. José Manuel Cervantes UC	Peripheral nerve system tissue engineering	https://www.cicy.mx/unidad-de-materiales/investigador/jose-manuel-cervantes-uc
			Dr. Fernando Hernández Sánchez	Scaffolds for cardiac, skin and urethra tissue	https://www.cicy.mx/unidad-de-materiales/investigador/fernando-hernandez-sanchez
			Dr. Nayeli Rodríguez Fuentes	Mechanotransduction and its impact in tissue regeneration activated by biomaterials	https://www.cicy.mx/unidad-de-materiales/investigador/nayeli-rodriguez-fuentes

5. Regulatory Aspects

5.1 Biotechnological Drugs

The Health Secretary ("Secretaría de Salud") is the major authority that regulates all affairs related to drugs, treatments and health in Mexico. The General Health Law ("Ley General de Salud") was reformed in 2009 to include definition of "biotechnological drugs". The Mexican Official Emergency Norm NOM-EM-001-SSA1-2012 "Biotechnological drugs and biopharmaceuticals" establishes not only the guidelines for good manufacture practice, but also the technical and scientific characteristics that they have to fulfill in order to secure their safety, efficacy and quality. Furthermore, it also mentions aspects related to labeling, biocomparability and pharmacovigilance (Arriola Peñalosa, 2012).

Afterwards, in 2014 the Mexican Official Norm NOM-257-SSA1-2014 "Biotechnological drugs" was published to substitute the emergency norm of 2012 and the access to more advanced biotechnological drugs was reinforced when more rules were published in Federation Official Report (DOF).

Likewise, the Federal Commission for Protection Against Health Risks (COFEPRIS, "Comisión Federal para la Protección Contra Riesgos Sanitarios") through its state commissions, is the organization in charge of the sanitary regulations (legal dispositions), sanitary control (actions for sampling, inspections and sanctions) and sanitary promotion (continuous improvement) of the products, procedures, methods, establishments and services related to health supplies (Hernández Trejo, 2015).

To register and commercialize a new "biotechnological drug" a technical evaluation of both the Subcommittee for the Evaluation of Biotechnological Products (SEPB, "Subcomité de Evaluación de Productos Biotecnológicos") and the New Molecules Committee (CMN, "Comité de Moléculas Nuevas") must be conducted. The safety and efficacy have to be evaluated in pre-clinical and clinical studies, as well as quality assurance in the manufacture process. Additionally it is important to create a "Risk Management Plan" for pharmacovigilance and protect the industrial property (Hernández Trejo, 2015).

Among the legal framework it is important to distinguish between an "innovative biotechnological drug" and a "biocomparable biotechnological drug". To develop an "innovative biotechnological drug", a large investment of time and resources is necessary to bring it to market and therefore it is protected by a patent. Nonetheless, once the patent has expired, other enterprises different from the owners of the patent, can request permission to manufacture and commercialize such a drug under the denomination of "biocomparable". In the case of these "biocomparable biotechnological drugs" expenses in research and development are not likely necessary, thus, these drugs can be commercialized at a lower price. Furthermore, once these biocomparables are recognized as "bioequivalent", meaning that they have the same efficacy and safety level as the "reference innovative drugs", clinical trials may not be needed (López Silva, 2012).

Until 2012, approximately 180 biotechnological drugs were approved in Mexico (López Silva, 2012); Mentioned in Table 4.4 are some examples of biocomparable biotechnological drugs.

Table 4.4 Biocomparable Biotechnological Drugs approved by COFEPRIS at 2017

Generic Denomination	Distinctive Denomination	Sanitary Registry	Owner	Therapeutic Indication
Filgrastim	ZARZIO	395M2014 SSA	Sandoz, S.A. de C.V.	Neutropenia
Filgrastim	FILATIL	101M2001 SSA	Probiomed S.A. de C.V.	Neutropenia, myeloid leukemia
Alfa Folitropine	CORNEUMON	081M2017 SSA	Corne Laboratories, S.A. de C.V.	Ovary function stimulant
Infliximab	REMSIMA	398M2014 SSA	Celltrion Incorporated	Rheumatoid arthritis; ankylosing spondylitis; psoriasic arthritis; psoriasis; fistulizing Crohn's disease and ulcerative colitis
Interferon alfa 2b	URIFRON	458M97 SSA	Probiomed S.A. de C.V.	Antiviral
Interferon beta 1b	URIBETA	529M2001 SSA	Probiomed, S.A. de C.V.	Multiple sclerosis
Interferon beta 1b	ARABINEV	313M2017 SSA	Pisa Laboratories S.A. de C.V.	Multiple sclerosis
Insulin glargine	GALACTUS	091M2015 SSA	Pisa Laboratories S.A. de C.V	Diabetes Mellitus type 1 and type 2
Insulin glargine	ABASAGLAR	352M2015 SSA	Eli Lilly and Mexico Company S.A. de C.V.	Diabetes Mellitus type 1 and type 2
Insulin glargine	VALVEY	078M2017 SSA	Wockhardt Limited	Diabetes Mellitus type 1 and type 2
Rituximab	RIGETUXER	301M2017 SSA	Pisa Laboratories S.A. de C.V.	Low grade non-Hodgkin lymphoma, granulomatosis with Wegener polyangiitis, microscopic polyangiitis
Somatropin	OMNITROPE	084M2010 SSA	Sandoz, S.A. de C.V.	Disorder due to inadequate secretion of endogenous growth hormone. Deficient growth associated with chronic renal failure or with Turner syndrome.

Source: Comision de autorizacion sanitaria, 2018

5.2 Tissue Engineering

As tissue engineering research is still in the development phase, there is not specific regulation in Mexico related to this field; therefore the cellular components are regulated in one legislation and biomaterials in another. Cell therapy enterprises, who inject adult or fetal stem cells, are governed by the General Health Law of Transplants (SEGOB, 2014). On the other hand, biomaterials or hydrogels which are used for wound healing, are considered “medical devices” because they are in direct contact with the organism.

Prostheses, orthoses and functional aids are regulated by Mexican Official Norm NOM-241-SSA1-2012, “Good manufacture practices for the establishments dedicated to the production of medical devices”, where they are defined as “those devices destined to substitute or complement a function, organ or tissue in the human body”. However, these existing norms will need to be updated in the future to include, in a comprehensive way, tissue engineering developments with biomaterials, cells and transcription factors in the same device.

5.3 Biosensors

Medical devices are classified as: medical equipment; prostheses, orthoses and functional aids; diagnostic agents; dentistry supplies; surgical and healing materials; and hygienic products. Furthermore, they are classified according to risk (type I, II and III), for where it is determined what devices are considered low risk and may not need a Sanitary Registry (Ruiz Noria, 2017).

One should consult the stipulations and updates listed on COFEPRIS webpage (https://www.gob.mx/cofepris/acciones-y-programas/registro-de-dispositivos-medicos-nuevos), as well as the Health Supplies Regulation. However, the following four documents must be obtained according to an interview with COFEPRIS staff in ExpoDicLab in September 26, 2018:

1. Operating notice: is free and can be obtained immediately. There are two types of registry: commercialization registry (the one that requests the notice does not manufacture the product) or manufacture registry (the person that requests, manufactures and commercializes the product). It has to be determined the "sanitary responsible", as well as other aspects.

2. Good manufacture practices: this certification is free if the factory is inside the Federal District, if not, traveling expenses of the reviewing official to the factory must be covered. It can be obtained in 20 labor days (week days, not including holidays) and certifies the factory where the product is manufacture. It has to satisfy Mexican Official Norm NOM-241-SSA1-2012, "Good manufacture practices for establishments dedicated to the production of medical devices". COFEPRIS verifies the facilities and procedures. A complete production run has to be shown.

3. Sanitary Registry: has a cost of $10,000 to $25,000 and it expires within 5 years, as long as no changes are done to the brand or type of registry (manufacture or commerce). At least 150 days before its renewal, a Technovigilance report has to be presented. To apply for this registry the applicant must show the following:

a) Specify the type of device
b) Specify the category and classification
c) Demonstrate its safety and efficacy.

4. Technovigilance: is free and can be obtained in 60 labor days. The responsible individual of the factory has to be defined (the person in charge of answering to adverse incidents) and where the factory is located.

6. Conclusions

Research in bioinformatics applied to biotechnological drugs, tissue engineering and biosensors is being carried out in Mexico, however, economic resources are needed in order to continue it innovation and perform preclinical and clinical trials. Moreover, updated and specific regulation is needed to achieve commercial applications.

Programs that encourage industry with scientific research relationship would be a way to impulse new developments as well as propel existing developments to clinical trials. The creation of collaborations with international institutions to foment the interchange of knowledge, as for example the ones created by the Higher Council of Scientific Research (CSIC, "Consejo Superior de Investigación Científica") in Spain, can drive scientific progress in developing countries. At CSIC, there are grants for clinical trials as for example, the one given to the Institute of Sanitary Research in La Fe in Valencia (https://www.iislafe.es/es/investigacion/convocatorias/12/convocatoria-de-ayudas-economicas-para-el-desarrollo-de-ensayos-clinicos). Another example is the Higher Council for Science and Technology (HCST) in Jordan offers a grant inviting industry to invest in science and technology projects with the objective of increasing their competiveness (http://www.hcst.gov.jo/en/node/154). In Mexico exists a great opportunity to guarantee the support and success of both, research projects and scientific innovations, that can bring together government, industry, biotechnological companies and community.

While constructing Table 4.3, it was found the diversity and large amount of areas that converge for biotechnological drugs, tissue engineering and biosensors development. We have listed on table 4.3 examples of research groups and departments that are focused on applying the mentioned disciplines solely in the medical area. As every day novel techniques and applications are described in these areas, it is needed to reinforce the inter and multidisciplinary work between these fields and medical research, thus, capitalizing the sum of efforts, capacities, abilities, knowledge, innovation and infrastructure, which would generate greater success of products developed in Mexican research laboratories in our country and in the world. Furthermore, the legal framework for biotechnological drugs in Mexico is at the forefront compared with other countries in Latin America. Yet it is necessary to continue updating the norms to correspond to scientific discoveries and developments.

The most important capital that a country can have is human resources. In 2016, the reported number of researchers in Mexico by the National System of Researchers (SNI) was 25,072 (Rodríguez, 2016); if it is considered that in 2016 there were 127.5 million people in our country, this number barely represents 0.02% of the population. This shows that high quality human capital exists in Mexico and we should continue to focus not only on increasing these percentage, but to promote international knowledge exchange and collaboration among researchers. Therefore, it is necessary to provide the economic and infrastructure support to keep our research at the international leading edge, and most importantly, allowing the opportunity of these developments to have a positive impact on the health and well-being of our community.

7. Acknowledgment

Special thanks to Ean Hundley of the U.S. Peace Corps for his special contribution in editing this work.

8. References

Anzaldúa Arce, S. R., Juárez Mosqueda, M. de L., Villaseñor Gaona, H., Ríos Mas, M. C., Cornejo Cortés, M. Á., & Meraz Ríos, M. A. (2007). ¿Qué son las células troncales o "células madre"? Veterinaria Mexico, 38(1), 81–104.

Arriola Peñalosa, M. A. Medicamentos biotecnológicos y sus biofármacos (2012). México. Retrieved from https://www.dof.gob.mx/nota_detalle_popup.php?codigo=5269530

Bhalla, N., Jolly, P., Formisano, N., & Estrela, P. (2016). Introduction to Biosensors. Essays in Biochemistry, (June), 1–8. https://doi.org/10.1042/EBC20150001

Castro-Ceseña, A. B., Camacho-Villegas, T. A., Lugo-Fabres, P. H., Novitskaya, E. E., McKittrick, J., & Licea-Navarro, A. (2016). Effect of starch on the mechanical and in vitro properties of collagen-hydroxyapatite sponges for applications in dentistry. Carbohydrate Polymers, 148, 78–85. https://doi.org/10.1016/j.carbpol.2016.04.056

CIMAV. (n.d.). Sensores Poliméricos Nanoestructurados. Retrieved from https://cimav.edu.mx/investigacion/ingenieria-y-quimica-de-materiales/area-de-polimeros-sensores/

Comision de autorizacion sanitaria. (2018). Listado de medicamentos biotecnológicos biocomparables, 2017–2018.

Costantini, F., Sberna, C., Petrucci, G., Manetti, C., de Cesare, G., Nascetti, A., & Caputo, D. (2015). Lab-on-chip system combining a microfluidic-ELISA with an array of amorphous silicon photosensors for the detection of celiac disease epitopes. Sensing and Bio-Sensing Research, 6, 51–58. https://doi.org/10.1016/j.sbsr.2015.11.003

DGCS. (2016). Descelularizan en la UNAM tejidos y órganos vitales. Retrieved from http://www.dgcs.unam.mx/boletin/bdboletin/2016_576.html

Dr. Ricardo Montenegro. (n.d.). Innovación para el futuro ¿Qué es un medicamento biotecnológico? Comunicado de Prensa Roche. Retrieved from http://www.roche-cac.com/content/dam/roche_cac/es_CR/documents/Medicamentos Biotecnológicos.pdf

Flores Saiffe Farías, A., Jaime Herrera López, E., Moreno Vázquez, C. J., Li, W., & Prado Montes De Oca, E. (2015). Predicting functional regulatory SNPs in the human antimicrobial peptide genes DEFB1 and CAMP in tuberculosis and HIV/AIDS. Computational Biology and Chemistry, 59, 117–125. https://doi.org/10.1016/j.compbiolchem.2015.09.002

Garza-Fabre, M., Rodriguez-Tello, E., & Toscano-Pulido, G. (2013). Comparative analysis of different evaluation functions for protein structure prediction under the HP model. Journal of Computer Science and Technology, 28(5), 868–889. https://doi.org/10.1007/s11390-013-1384-7

Garza-Fabre, M., Toscano-Pulido, G., & Rodriguez-Tello, E. (2015). Multi-objectivization, fitness landscape transformation and search performance: A case of study on the hp model for protein structure prediction. European Journal of Operational Research, 243(2), 405–422. https://doi.org/10.1016/j.ejor.2014.06.009

Hernández Trejo, A. (2015). Regulación de Medicamentos Biotecnológicos en México. COFEPRIS.
Kim, B. W. (2017). Clinical regenerative medicine in urology. Clinical Regenerative Medicine in Urology. https://doi.org/10.1007/978-981-10-2723-9

Lerma, C.-C., Taylor, K., Amy, C., Rossana, V.-C., Maricela, R.-S., José, C.-U., … Juan, C.-R. (2016). Human mesenchymal stem cell behavior on segmented polyurethanes prepared with dexamethasone and beta-glycerol phosphate. Frontiers in Bioengineering and Biotechnology, 4(2), 1–22. https://doi.org/10.3389/conf.fbioe.2016.01.02437

Ley General de Salud (2018). Estados Unidos Mexicanos. Retrieved from http://www.diputados.gob.mx/LeyesBiblio/pdf/142_241218.pdf

Liu, Y., Liu, Y., Feng, H., Wu, Y., Joshi, L., Zeng, X., & Li, J. (2012). Layer-by-layer assembly of chemical reduced graphene and carbon nanotubes for sensitive electrochemical immunoassay. Biosensors and Bioelectronics, 35(1), 63–68. https://doi.org/10.1016/j.bios.2012.02.007

López Silva, C. (2012). México retoma un liderazgo regulatorio sobre medicamentos biotecnológicos y biocomparables Salud y derecho correspondencia. Gaceta Médica de México, 148, 83–90. Retrieved from https://www.anmm.org.mx/GMM/2012/n1/GMM_148_2012_1_083-090.pdf

Manzanarez-Ozuna, E., Flores, D. L., Gutiérrez-López, E., Cervantes, D., & Juárez, P. (2018). Model based on GA and DNN for prediction of mRNA-Smad7 expression regulated by miRNAs in breast cancer. Theoretical Biology and Medical Modelling, 15(1), 1–12. https://doi.org/10.1186/s12976-018-0095-8

Martínez-levy, G. A., Vásquez-medina, J. A., & Cruz-fuentes, C. S. (2010). Implicaciones y perspectivas para la investigación en psiquiatría genética en México. Salud Mental, 33(3), 273–280.

Martínez, L. M. (2010). Proyecto Genoma Humano y medicina genómica en México: su efecto en instituciones y organismos, en lo político y en la sociedad. Revista Casa Del Tiempo, 11(35), 29–33.

Maxson Jones, K., Ankeny, R. A., & Cook-Deegan, R. (2018). The Bermuda Triangle: The Pragmatics, Policies, and Principles for Data Sharing in the History of the Human Genome Project. Journal of the History of Biology, 51(4), 693–805. https://doi.org/10.1007/s10739-018-9538-7

Mercader, J. M., Liao, R. G., Bell, A. D., Dymek, Z., Estrada, K., Tukiainen, T., … Florez, J. C. (2017). A Loss-of-Function Splice Acceptor Variant in IGF2 Is Protective for Type 2 Diabetes. Diabetes, 66(11), 2903–2914. https://doi.org/10.2337/db17-0187

Narváez, M. (2018). Red Biot, Ingeniería de Tejidos y órganos. Retrieved from http://cienciamx.com/index.php/tecnologia/materiales/24769-red-biot-organos-tejidos

NIBIB. (2013). Ingeniería de Tejidos y Medicina Regenerativa. Instituto Nacional de Bioingeniería e Imágenes Biomédicas. Retrieved from https://www.nibib.nih.gov/sites/default/files/Ingeniería de Tejidos y Medicina Regenerativa_0.pdf

NIH. (2013). 2002: The International HapMap Project is announced. Retrieved from https://www.genome.gov/25520489/online-education-kit-2002-the-international-hapmap-project-is-announced

Patel, P., & Panchal, H. (2014). In silico structure modeling and comparative analysis of characterization properties of protein polymers useful for protein-based nano particulate drug delivery systems (NPDDS): A bioinformatics approach. International Journal of Peptide Research and Therapeutics, 20(1), 103–108. https://doi.org/10.1007/s10989-013-9369-5

Peralta, R., Garcia, P., Valdivia, A., Lopez, A., Apresa, T., Hernandez, D. M., … Salcedo, M. (2018). HPV Could be a Potential Factor of Survival in Laryngeal Cancer: a Preliminary Study in Mexican Patients. Asian Pacific Journal of Cancer Prevention : APJCP, 19(6), 1711–1716. https://doi.org/10.22034/APJCP.2018.19.6.1711

Prado Montes de Oca, E. (n.d.). Lamper. Retrieved from https://ciatej.mx/servicios-industria/medica-farmaceutica/lamper

Qing, Z., Bai, A., Xing, S., Zou, Z., He, X., & Wang, K. (2019). Biosensors and Bioelectronics Progress in biosensor based on DNA-templated copper nanoparticles. Biosensors and Bioelectronic, 137(May), 96–109. https://doi.org/10.1016/j.bios.2019.05.014

Rodríguez, C. E. (2016). El Sistema Nacional de Investigadores en números, 32. Retrieved from http://www.foroconsultivo.org.mx/FCCyT/sites/default/files/SNI_en_numeros.pdf

Rubio-Elizalde, I., Bernáldez-Sarabia, J., Moreno-Ulloa, A., Vilanova, C., Juárez, P., Licea-Navarro, A., & Castro-Ceseña, A. B. (2019). Scaffolds based on alginate-PEG methyl ether methacrylate-Moringa oleifera-Aloe vera for wound healing applications. Carbohydrate Polymers, 206(3918), 455–467. https://doi.org/10.1016/j.carbpol.2018.11.027

Ruiz Noria, K. L. (2017). Marco regulatorio para el desarrollo de dispositivos médicos. COFEPRIS.
Santana-Jiménez, L. A., Márquez-Lucero, A., Osuna, V., Estrada-Moreno, I., & Dominguez, R. B. (2018). Naked-eye detection of glucose in saliva with bienzymatic paper-based sensor. Sensors (Switzerland), 18(4), 1–12. https://doi.org/10.3390/s18041071

SEGOB. Reglamento de la Ley General de Salud en Materia de Trasplantes (2014). México. Retrieved from http://www.dof.gob.mx/nota_detalle.php?codigo=5338349&fecha=26/03/2014

Serrato Ochoa, D., Nieto Aguilar, R., & Aguilera Méndez, A. (2015). Ingeniería de Tejidos. Una nueva disciplina en medicina regenerativa. Investigación y Ciencia de La Universidad Autónoma de Aguascalientes, (64), 61–69.

Shekaran, A., Sim, E., Tan, K. Y., Chan, J. K. Y., Choolani, M., Reuveny, S., & Oh, S. (2015). Enhanced in vitro osteogenic differentiation of human fetal MSCs attached to 3D microcarriers versus harvested from 2D monolayers. BMC Biotechnology, 15(1), 1–13. https://doi.org/10.1186/s12896-015-0219-8

Silva-Zolezzi, I., Hidalgo-Miranda, A., Estrada-Gil, J., Fernandez-Lopez, J. C., Uribe-Figueroa, L., Contreras, A., … Jimenez-Sanchez, G. (2009). Analysis of genomic diversity in Mexican Mestizo populations to develop genomic medicine in Mexico. Proceedings of the National Academy of Sciences, 106(21), 8611–8616. https://doi.org/10.1073/pnas.0903045106

Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell, 126(4), 663–676. https://doi.org/10.1016/j.cell.2006.07.024

UNAM. (n.d.). Grupo del Dr. Enrique Rudiño. Retrieved from http://www.ibt.unam.mx/server/PRG.base?tipo:doc,dir:PRG.grupo,par:Geu,tit:Grupo_del__Dr._Enrique_Rudi%F1o

Vecchio, I., Tornali, C., Bragazzi, N. L., & Martini, M. (2018). The discovery of insulin: An important milestone in the history of medicine. Frontiers in Endocrinology, 9(October), 1–8. https://doi.org/10.3389/fendo.2018.00613

Weissglas-Volkov, D., Plaisier, C. L., Huertas-Vazquez, A., Cruz-Bautista, I., Riaño-Barros, D., Herrera-Hernandez, M., … Pajukanta, P. (2010). Identification of two common variants contributing to serum apolipoprotein B levels in Mexicans. Arterioscler Thromb Vasc Biol, 30(2), 353–359. https://doi.org/10.1016/ATVBAHA.109.196402

Weng, X., Gaur, G., & Neethirajan, S. (2016). Rapid detection of food allergens by microfluidics ELISA-based optical sensor. Biosensors, 6(2), 1–10. https://doi.org/10.3390/bios6020024

Wongkaew, N., Simsek, M., Griesche, C., & Baeumner, A. J. (2018). Functional Nanomaterials and Nanostructures Enhancing Electrochemical Biosensors and Lab-on-a-Chip Performances: Recent Progress, Applications, and Future Perspective. Chemical Reviews. review-article. https://doi.org/10.1021/acs.chemrev.8b00172

Zapata-Catzin, G. A., Bonilla-Hernández, M., Vargas-Coronado, R. F., Cervantes-Uc, J. M., Vázquez-Torres, H., Hernandez-Baltazar, E., … Cauich-Rodríguez, J. V. (2018). Effect of the rigid segment content on the properties of segmented polyurethanes conjugated with atorvastatin as chain extender. Journal of Materials Science: Materials in Medicine, 29(11). https://doi.org/10.1007/s10856-018-6165-y

Zhu, Z. (2017). An Overview of Carbon Nanotubes and Graphene for Biosensing Applications. Nano-Micro Letters, 9(3), 1–24. https://doi.org/10.1007/s40820-017-0128-6