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Developmental Biology in México

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ABSTRACT Contemporary scientific endeavor in México emanates from two great public institutions: the Universidad Nacional Autónoma de México (UNAM) and the Instituto Politécnico Nacional (IPN), founded in 1929 and 1936, respectively. Here, the first research institutes and centers dedicated to various scientific areas were created. Thus, the origin of most laboratories of Developmental Biology in México was like that of other scientific fields. In this article, I have attempted to describe the establishment of a specialized community involved in the understanding of organism development during ontogeny. The use of chick embryos to study heart development was among the first experimental approaches developed in México. Then, a younger group employed chick embryos to study the mechanisms underlying limb development. Various laboratory animal models have been employed, including mouse, rat, rabbit, and recently the naked mole-rat, as well as some wild species, such as sea turtles and bats. Two classical invertebrates, *Drosophila melanogaster,* and *Caenorhadbitis elegans,* also form part of the multilayered complex models used by Mexican developmental biologists. My use of animals brought me closer to the pioneer developmental biologists who worked with animal models. Their academic trajectory was more detailed than that of investigators using plant models. However, the pioneering merit and bright contributions of the two groups are on a par, regardless of the biological model. As current scientific knowledge is the sum of individual contributions throughout human history, here I have attempted to describe my suitable experience as a witness to the birth of the fascinating field of developmental biology in my country.

KEY WORDS: *chick embryo, heart, limb, plant*

Introduction

The academical basis of modern Developmental Biology in México mostly originated in three greatest national institutions: the Secretaría de Salúd, the UNAM, and the IPN. These were created by the newly stabilized government, following a long period of social instability. These institutions established the first research laboratories initially involved in medical problems affecting Mexican society. Subsequently, in 1970 the Consejo Nacional de Ciencia y Tecnología (CONACyT) was created and then in 1984, the Sistema Nacional de Investigadores (SNI), provided comprehensive support through national and international fellowships, creating well-equipped laboratories that financed pair evaluated research projects. This new historical step fostered the development of the present Mexican scientific community. Young postdoctoral scientists, together with their students, founded laboratories involved in basic and applied science, including Developmental Biology.

I was kindly invited by former students to write a chapter about the history and present state of the Developmental Biology in México. Although, as a personal witness of the emergence of this field, this appeared relatively easy to me, I soon realized that well-documented history is also a research area. I asked each of the authors mentioned here, who used animal models to help me document her/his contribution to Developmental Biology in México. Thus, in a certain sense, this work can be considered a multi-author chapter.

Initiation

As classical descriptive and experimental embryology paved the way to modern developmental biology, the pioneer studies on cardiac embryology made by Professor Maria Victoria de la Cruz

Abbreviations used in this paper: IPN, Instituto Politécnico Nacional; UNAM, Universidad Nacional Autónoma de México.

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Fig. 1 (left). Mª. Victoria de la Cruz *was born in Cuba, graduated in Medicine from the University of Havana, and moved to Mexico City in 1945. She studied biology at the Instituto Politécnico Nacional and enter the National Institute of Cardiology. She founded the cardiac embryology department in 1951. Using fixed and living chick embryos, Professor de la Cruz explained the developmental processes involved in congenital heart anomalies.*

Fig. 2 (right). Horacio Merchant-Larios *trained as electron microscopist at the Institut de Recherches Sur le Cancer at Paris and graduated as SC.D. at the Facultad de Medicina, UNAM. in 1971. Returning to the Instituto de Investigaciones Biomédicas in Mexico, he found that male fetal testes, devoid of germ cells, underwent normal sexual differentiation. At the same time, infertile ovaries were severely affected, and the hypothalamus-pituitary-gonad axis is curtailed. Merchant-Larios' laboratory is involved in the cellular mechanisms underlying the temperature-dependent sex determination using the olive Ridley as an animal model.*

(Fig. 1) in México are of note, representing one of the world's foremost contributions. She was born in 1916 in Sancti-Spíritus, Cuba. She was self- educated and studied biology in her father's library, graduating in Medicine at the University of Havana in 1943. Two years later, her interest in basic science prompted her to transfer to México City to the National Institute of Cardiology, the first institution in the world to be entirely dedicated to cardiology. She studied biology at the Instituto Politécnico Nacional in México City and then, in 1949-50, visited the Universities of Michigan, Columbia, and the Carnegie Institute of Science, Department of Embryology. Baltimore, MD, USA, where she studied the best collections of human embryos and consolidated her vocation as a cardiac developmental biologist. Back in México, she founded the cardiac embryology department in 1951, acting as director until 1976, when she was invited to the Central University of Caracas and then to the Ramón y Cajal Hospital in Madrid. She returned to México City to establish the embryology laboratory at the Hospital Infantil, where she continued working until her death in 1999. Professor de la Cruz made distinguished contributions to explain complex congenital heart anomalies that resulted from developmental anomalies (De la Cruz and West, 1956). Using fixed and living chick embryos, she proposed the heart as the integration of independent individual segments with a specific developmental fate (De la Cruz *et al*., 1972); De la Cruz and Markwald, 1998).

Horacio Merchant Larios

Several years later, Horacio Merchant Larios (Fig. 2), born in 1940 at Tezoyo, Hidalgo, México, studied Biology as an undergraduate at the Facultad de Ciencias of the Universidad Nacional Autónoma de México (UNAM) in México City from 1959/1964. Throughout this period, he worked as a research assistant in the Instituto de Estudios Médicos y Biológicos (now Instituto de Investigaciones Biomédicas), UNAM. He then traveled to Paris to study with Dr. Wilhelm Bernard at the Institut de Recherches Sur le Cancer, where he trained as an electron microscopist. Back in México, Dr. Merchant received an Sc.D. degree in the Facultad de Medicina (UNAM) in 1971. Horacio became intrigued by the amazing ultrastructural cell diversification emerging from the fertilized egg. Subsequently, he spent two postdoctoral periods in the USA: The first, at the Worcester Foundation for Experimental

Fig. 3 (left). From left to right, M.C. Chang, a former mentor of Merchant-Larios; H. Merchant-Larios and his undergraduate student A. Alvarez-Buylla. *The photograph was taken at the Worcester Foundation for Experimental Biology in Shrewsbury, Mass, the USA, in 1983.*

Fig. 4 (right). Jesús Chimal and Diana Escalante as Dr. Merchant-Larios's undergraduate students. *Picture taken in 1989 in the garden of the Instituto de Investigaciones Biomédicas, UNAM.*

Biology, Massachusetts with Dr. M.C. Chang (Fig. 3). Then, with Dr. Luciano Zamboni at Harbor General Hospital, UCLA Here, he analyzed the ultrastructure of mouse fetal ovaries and became interested in germ-somatic cell interactions during early folliculogenesis. Returning to the Instituto de Investigaciones Biomédicas in México, Horacio complemented his descriptive ultrastructural studies with experimental approaches to gain insight into the role of germ cells in fetal gonadal development. Treating pregnant rats with Busulphan (a drug used to treat chronic leukemia in humans), he found that fetal gonads, devoid of germ cells, underwent sexual differentiation and that the postnatal consequences differed depending on sex. Whereas infertile males developed steroidogenic tissue and sexual behavior was normal, infertile females were severely affected. Lack of oocytes prevents the formation of ovarian follicles and, consequently, the differentiation of steroidogenic cells. Thus, the establishment of the hypothalamus-pituitary-gonad axis is curtailed (Merchant, 1975). With his research group including Diana Escalante and Jesús Chimal (Fig. 4), Horacio studied the somatic-cell interactions in developing gonads, applying ultrastructural and autoradiographic studies to a variety of vertebrate animal models (Merchant-Larios, 1976; Merchant-Larios and Coello, 1976; Merchant-Larios and Centeno, 1979; Merchant-Larios and Villalpando, 1981; Merchant-Larios *et al.,* 1984) and with the original contribution of his undergraduate student Arturo Alvarez-Buylla (Fig. 3), analyzed the process of primordial germ cell migration *in vivo* and *in vitro* (Merchant-Larios *et al.,* 1985; Alvarez-Buylla and Merchant-Larios, 1986). Subsequently, together with enthusiastic students such as Arturo Salame-Méndez, Leda Torres, Norma Moreno-Mendoza, Alejandro Marmolejo-Valencia, (Fig. 5 A,B) Verónica Díaz-Hernández (Fig. 6) and several others, he became very motivated to reveal the cellular mechanisms underlying the interesting process of temperature-dependent sex determination in developing gonads of the olive ridley sea turtle (Merchant-Larios *et al.,* 1989, 1997). His laboratory established the organotypic culture as an experimental technique for analyzing cell-cell interactions during gonadal sex determination and differentiation (Merchant-Larios and Villalpando, 1990; Moreno-Mendoza *et al.,* 1995; Merchant-Larios and Moreno Mendoza, 1998; Moreno-Mendoza *et al.*, 2001). Their contributions include the establishment of the temperature-sensitive stages, the role of estrogens, the spatiotemporal expression of key genes involved in sex determination, and the specification of gonadal cells in the urogenital ridge (Torres-Maldonado *et al.*, 2002; Díaz-Hernández *et al.,* 2012, 2015, 2019). At this time, Horacio Merchant-Larios and collaborators are interested in assessing the regulatory gene network involved in temperature sex determination and the extent to which results have been obtained under controlled laboratory conditions, compared to embryos developing in the beach nests. Hopefully, they will be able to design a practical strategy to relieve the increasingly unbalanced sex ratios of the olive ridley caused by current global warming. Several undergraduate and graduate students who worked in his laboratory are now independent developmental biologists. These include Susana Castro, Norma Moreno-Mendoza, Diana Escalante-Alcalde, Jesús Chimal-Monroy, and Verónica Díaz-Hernández. They founded new laboratories in México, where apart from their relevant research contributions, they also motivate young students to maintain their interest in the fascinating topic of developmental biology.

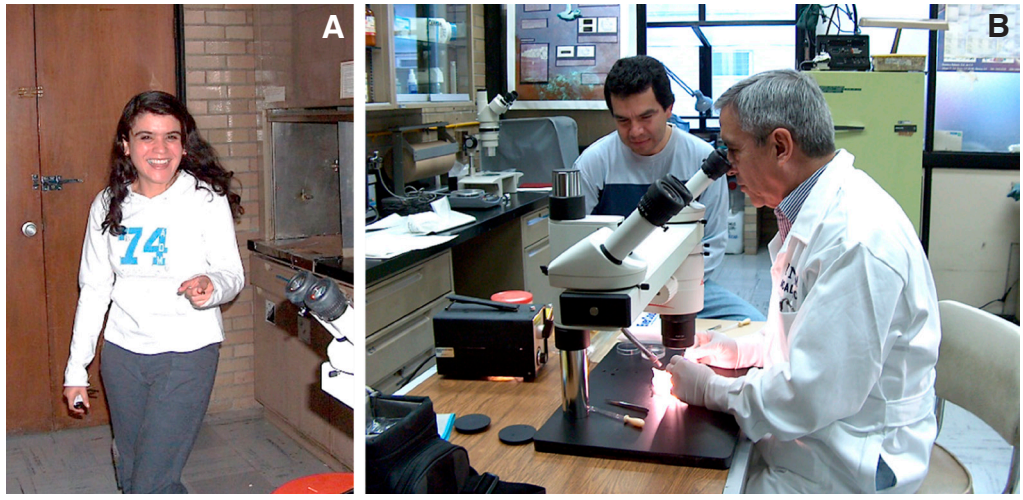

Fig. 5. Undergraduate students at Merchant-Larios' laboratory. (A) *Norma Moreno-Mendoza.* **(B)** *Alejandro Marmolejo-Valencia to the left of Horacio-Merchant-Larios. Photographs were taken in the late 1990s.*

Fig. 6. Verónica Díaz-Hernández and Alejandro Marmolejo-Valencia (2005). *Verónica was working on her D.Sci. thesis and Alejandro already had an associated position in the Merchant-Larios laboratory.*

Molecular Biology and Animal Developmental Biology

Investigators junior to Horacio, who first trained as molecular biologists in México, had the opportunity to undergo their postdoctoral training in well-established foreign developmental biology laboratories. They represent the progenitors of an expanding and diversified community of developmental biologists in México, who use various animals as system models.

Luis Covarrubias

Luis Covarrubias (Fig. 7) began his training on genetic engineering and the molecular biology of bacteria with Francisco Bolivar and then became interested in gene regulation in higher eukaryotes. In particular, he was curious about the origin of germ cells and how, after fertilization, these can reconstruct a genome with the potential to give rise to all cell types in an adult organism. He was attracted by the work of Beatrice Mintz. She at the beginning of the 1980s was recognized for her work with chimeric mice, the pluripotency of teratocarcinoma cells, and concerning the production of transgenic mice. In her laboratory, Luis Covarrubias participated in the characterization of several transgenic mouse lines and constructed a unique retroviral vector for the genetic modification of hematopoietic stem cells.

Luis's laboratory was established at the beginning of the 1990s, setting protocols for cell-type-specific immortalization of precursor cells, through the production of transgenic mice and with the promising incorporation of some enthusiastic students, who mention that their interest in developmental biology began during their stay in Horacio Merchant's laboratory. Luis said that this was not unexpected as Horacio was his main contact for discussions on developmental biology in México, after his fruitful work period with Beatriz Mintz. For the immortalization of primordial germ cells, they characterized the one for the tissue non-specific alkaline phosphatase (TNAP); this project was the opportunity for Diana Escalante to establish the technology for the production of transgenic mice by pronuclear microinjection (Escalante-Alcalde *et al.*, 1996). For the immortalization of neural stem cells, they generated neurosphere-like colonies from the embryonic mesencephalon (Santa-Olalla and Covarrubias, 1995), when there were very few articles reporting neurospheres, especially from embryonic tissues. With the participation of Susana Castro, they started to grow embryonic stem cells, initially to study neuronal differentiation, but later to study cell death in response to retinoic acid (Castro-Obregón and Covarrubias, 1996). This decision was influenced by the emerging interest in apoptosis in the early 1990s. Their findings were the basis of the project dedicated to determining the role of reactive oxygen species in the regulation of apoptosis during development (Hernández-García *et al.*, 2008; Salas-Vidal *et al.*, 1998; Schnabel *et al.*, 2006). With his group and particularly with David Hernández, Luis Covarrubias decided to establish gene targeting technology, and with the help of Ramiro Ramírez-Solís, knocked-out the gene encoding the antioxidant enzyme catalase; the phenotype was unexpected, but the efforts of Raúl Pérez defined very interesting characteristics in adult life (Pérez-Estrada *et al.*, 2019). Their interest in understanding the role of cell death during development was also the opportunity for Rodrigo Cuervo and Rocio Hernández to express new views on how cell death contributes to morphogenesis (Cuervo *et al.*, 2002; Cuervo and Covarrubias, 2004; Hernández-Martínez *et al.,* 2009). At the beginning of the new century, as the interest in stem cells was growing worldwide, José Manuel Baizabal was devising a strategy to test the differentiation potential of neural stem cells. The developed protocol was named "transplant-to-explant" and was key to establishing the differentiation potential of the embryoid body and neurosphere cells within an embryonic neurogenic environment (Baizabal and Covarrubias, 2009). Gilda Guerrero used this to study the differentiation potential of dopaminergic neural precursors (Guerrero-Flores *et al.,* 2017; Trujillo-Paredes *et al.,* 2016). Following the same basic idea, Magdalena Guerra and Omar Collazo, in collaboration with René Drucker's group, used embryoid body cells to detect neurogenic environments within the adult brain (Collazo-Navarrete *et al.,* 2019; Maya-Espinosa *et al.,* 2015; Rivero *et al.,* 2015) and later, these experiments showed Dulce María Arzate how to characterize evidence of transdifferentiation of astrocytes into neurons (Arzate *et al.,* 2019). Presently, metabolism, reprogramming, regeneration, and cancer are at the focus of Luis Covarrubias's research group.

Mario Zurita

After a postdoctoral stay in the laboratory of Prof. Fotis C. Kafatos at Harvard, in 1994, Mario Zurita (Fig. 8) joined the Instituto de Biotecnología, UNAM, as a researcher. Upon his

Fig. 7 (left). Luis Covarrubias, *who trained in Mexico in the genetic engineering of bacteria. He had a fruitful stay in Beatriz Mintz' laboratory in which he participated in the characterization of transgenic mouse lines and constructed a retroviral vector for the genetic modification of hematopoietic stem cells. In the early 1990s, he returned to Mexico and established his laboratory in the Instituto de Biotecnología, UNAM. Luis is Mexico's pioneer in applying molecular biology methods to elucidate developmental mechanisms involved in mammalian germ cells and somatic stem cells, including the processes of apoptosis and neuronal differentiation. Several Mexican developmental biologists who are mentioned in the current article were trained in his laboratory.*

Fig. 8 (right). Mario Zurita *did a postdoctoral stage with professor F.C. Kafatos at Harvard, studying gene expression during oogenesis in* Drosophila melanogaster. *Upon his return to Mexico, he founded his laboratory at the IBT, UNAM, in 1994. Mario initially continued his previous line of research. Then, he kept using the fruit fly as a model to address various aspects of normal and pathological development, including cancer in humans. Mario's group is recognized for his contributions to elucidating HOX gene regulation and the ATRX homolog in* D. melanogaster. *Several of his graduated students are now successful independent researchers in Mexico and abroad.*

Fig. 9 (left). Jesús Chimal-Monroy. *After his graduation at the UNAM, Jesús went to Spain to join Professor Juan Hurle's group at the University of Cantabria in Santander. Back in Mexico, he returned to the Instituto de Investigaciones Biomédicas, UNAM. He kept his interest in the molecular mechanisms underlying the process of chondrogenesis during digit development. His laboratory began using the chick embryo as a model, and then, they also worked with the mouse. Moreover, the Mexican axolotl and* Xenopus laevis *are used to get insights into the process of limb regeneration. Several students who graduated under Jesus' guidance are now independent researchers.*

Fig. 10. Juan Riesgo-Escovar. *After he graduated from Yale University, Juan returned to Mexico and founded his laboratory in the Instituto de Neurobiología UNAM at Juriquilla, Queretaro. Using* Drosophila melanogaster *as a model system, Juan's research group mainly focuses on the genes underlying cell change processes and cell growth during embryonic development. Their outstanding contribution on the role played by the genes acal, piragua, aaquetzalli, and chem, are well recognized. Several students guided and graduated in Juan's laboratory became independent scientists.*

return, he began the first studies in Molecular Genetics of Development in *Drosophila melanogaster* in México. The first work Mario undertook on this subject was a continuation of his studies initiated at Harvard, on genes expressed preferentially during oogenesis in *Drosophila* (Reynaud *et al*., 1997). However, and given the high degree of conservation of different mechanisms during development between humans and *Drosophila*, he initiated a line of research that would focus on understanding the effects of mutations in transcription factors during embryonic development, affected by different pathologies in humans, including cancer, (Reynaud *et al*.,1999, Merino *et al*., 2002, Fregoso *et al*., 2007, Cruz *et al*., 2018). Cancer is one of his group's strongest lines of research. This finding has to provide insights into the defects during development caused by syndromes in humans. In parallel, in collaboration with Drs. Martha Vázquez and Viviana Valadez, his group, perform studies on the role of TRITHORAX genes that are involved in the regulation of HOX genes, as well as the role during the development of the ATRX homolog gene in *Drosophila* (Gutierrez *et al*., 2003, Valadez-Graham *et al*., 2012). Several graduates from his group are now independent researchers, including Dr. Enrique Reynaud (Institute of Biotechnology, UNAM) and Dr. Mariana Herrera (Autonomous University of Oaxaca), as well as others outside México, such as Dr. Mariana Fregoso at the University of McGill. The lines of research of the latter use *Drosophila* as the main experimental model.

Jesus Chimal-Monroy

For many years Jesus Chimal-Monroy (Figs. 4, 9) has focused his research on elucidating the mechanisms that control cell differentiation, morphogenesis, and patterning during embryonic digit formation and limb regeneration. Regarding cell differentiation, he focused on understanding the early mechanisms that control the cellular differentiation of cartilage and how these cells give rise to well-defined skeletal structures, such as digits (Marín-Llera *et al.,* 2019). His first experience with developmental biology began in the Merchant-Larios laboratory when he was studying for his undergraduate and master's degrees. He studied the process of ovarian folliculogenesis in the mouse embryo (Merchant-Larios and Chimal-Monroy, 1989). His doctorate studies continued in the Instituto de Investigaciones Biomédicas, where he became interested in the study of cartilage differentiation during limb development (Chimal-Monroy and Díaz de Leon 1997, 1999). His time with Dr. Juan Hurlé at the University of Cantabria in Santander, Spain, inspired Jesus Chimal-Monroy to study the molecular cascade of chondrogenesis, involved *in vivo* digit development (Chimal-Monroy *et al*., 2003).

Back in México, Chimal-Monroy focused on understanding the formation and positioning of the joints, showing that blocking a5β1 integrin in the embryonic limb of the mouse can generate an ectopic joint. In contrast, overexpression prevents the formation of joints in the limbs of chick embryos. Thus, the control of cartilage differentiation towards the maturation program or the joint program appears to be regulated by the interaction of cells and the extracellular matrix in the embryo (Garciadiego-Cazares *et al.,* 2004). His research group has also focused on determining the mechanisms by which retinoic acid regulates cell death and the boundaries between interdigital and chondrogenic tissue that give rise to the digits in chicken embryos (Abarca-Buis *et al.,* 2011, Díaz-Hernández *et al.,* 2013). Recently he has determined that mesenchymal cells from early limb buds in mouse embryos express cell markers associated with mesenchymal stromal cells (Marin-Llera and Chimal-Monroy, 2018).

He also focused on the study of limb regeneration in the Mexican axolotl (*Ambystoma mexicanum*) (Witchin *et al*., 2017) and the larva of *Xenopus laevis* (Cuervo and Chimal-Monroy, 2013*).* In this model, he determined that the chemical activation of WNT signaling leads to the prevention of limb regeneration, probably mediated by the inhibition of limb re-innervation. The chemical activation of the beta retinoic acid receptor in the *Xenopus* larva can produce homeotic transformations that lead to the formation of two limbs with bilateral symmetry joined by a pelvic girdle from the amputation site in the limb.

Juan Riesgo-Escovar

Juan Riesgo-Escobar (Fig. 10) has mainly focused on two topics in development: change in cell shape and cell growth in the *Drosophila melanogaster* model system. Control of change in cell shape during embryonic development, specifically during a process akin to wound healing, where two epithelial sheets change shape, stretching, and closing the embryo dorsally over an extraembryonic epithelium: the amnioserosa. This process is called dorsal closure. His laboratory focused on several genes, one of which, *acal*, codes for a long non-coding RNA. Mutations in *acal* are lethal: *acal* negatively regulates genes of the Jun

Fig. 11. Iván Velásco *became interested in neural and embryonic stem cells as a postdoctoral fellow at the National Institute of Health USA, in Dr. Ron McKay's laboratory. Back in Mexico, he established his laboratory at the Instituto de Fisiología Celular, UNAM, in 2004. With his research group, Ivan has made important contributions to elucidate the molecular mechanisms involved in developing embryonic stem cells into neurons. Their studies are relevant for getting molecular and developmental insights to understand the nervous system's human diseases, including Amyotrophic Lateral Sclerosis and Parkinson's disease.*

Fig. 12. Diana Escalante-Alcalde *was a postdoctoral fellow under Colin L. Stewart's supervision at the Cancer and Developmental Biology Laboratory, National Cancer Institute-NIH, in Frederick, Maryland, USA. In Mexico, she founded her laboratory at the Instituto de Fisiología Celular, UNAM, in 2003. Her group is a pioneer in studying the role of bioactive lipid metabolizing enzymes during neural development. They found that the enzyme LPP3 is important for extraembryonic vascular and cerebellum development. As the enzyme is involved in vascular permeability, their studies are relevant for understanding chronic pain and cardiac diseases.*

kinase pathway, which controls dorsal closure (Rios-Barrera *et al*., 2015; Rios-Barrera and Riesgo-Escovar, 2013). They have also studied *piragua*, which codes for a transcription factor that regulates timing during dorsal closure (Nazario-Yepiz and Riesgo-Escovar, 2017), and *aaquetzalli* and *chem*, which are involved in epithelial polarity (Mendoza-Ortiz *et al*., 2018; Zamudio-Arroyo and Riesgo-Escovar, 2016). His contribution to cell growth during development centers on the control exerted by the insulin pathway (Murillo-Maldonado and Riesgo-Escovar, 2017).

Ivan Velasco

Ivan Velasco (Fig. 11) was a postdoctoral fellow in the laboratory of Dr. Ron McKay at the National Institute of Health in the USA, where he began working with neural and embryonic stem cells. He joined the Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, forming his group in 2003. His laboratory has focused on neuronal differentiation to understand brain development or to produce specific neuronal subtypes, grafting these in animal models of neurodegenerative diseases, particularly, Amyotrophic Lateral Sclerosis and Parkinson's disease.

His group was the first to report the positive effects of histamine on proliferation and neuronal differentiation of neural stem/progenitor cells from the cerebral cortex (Molina-Hernández and Velasco, 2008). Interestingly, histamine had a different effect when introduced via ultrasound-guided injections in developing rat embryos: it prevented the differentiation of dopaminergic neurons in the midbrain (Escobedo-Avila *et al*., 2014), correlating with epigenetic changes *in vivo* (Vargas-Romero *et al.,* 2019).

They considered that spinal motor neurons differentiated from mouse embryonic stem cells might be used in cellular therapy to substitute the lost neurons in the ventral spinal cord in animals suffering from Amyotrophic Lateral Sclerosis. In 2009, his group reported that transplantation of motoneurons expressing GFP caused a transient recovery of motor function that was attributed to a trophic effect, as no axons left the spinal cord to reach the muscles (López-González *et al*., 2009). Later, mouse embryonic stem cells were engineered to express Glial cell line Derived Neurotrophic Factor (GDNF) and induced differentiation of motor neurons. Secreted GDNF induced a higher yield of motor neurons presenting electrophysiological signs of maturity (Cortes *et al*., 2016), which may be useful for survival after grafting.

Ivan Velasco's group focused on the differentiation of embryonic stem cells to dopaminergic neurons. The first report on the differentiation of this neuronal subtype in Latin America came from his laboratory (Díaz *et al*., 2007). With these differentiated neurons, studies of axonal guidance by class 3 Semaphorins were carried out: Semaphorin 3C had a dual effect, increasing the length of dopaminergic axons and attracting them to the source of Semaphorin 3C release (Tamariz *et al*., 2010; Carballo-Molina *et al*., 2016). A strategy to establish a new pathway containing cells that released Semaphorin 3C, between the substantia nigra and the striatum of parkinsonian rats, resulted in behavioral recovery and the establishment of monosynaptic contacts between the grafted neurons in the nigra and its axons in the striatum (Díaz-Martínez *et al*., 2013).

Diana Escalante-Alcalde

Diana's (Figs. 4, 12) first experience of Developmental Biology occurred at the Merchant-Larios laboratory at the Instituto de Investigaciones Biomédicas, UNAM, while performing her undergraduate and MSc studies. During this period, she developed a passion for mammalian embryo and gonad development. Her interest in the field took her to study germ cell development during her Ph.D. studies under the supervision of Luis Covarrubias at the Instituto de Biotecnología, UNAM. She was a postdoctoral fellow under the supervision of Colin L. Stewart at the Cancer and Developmental Biology Laboratory, National Cancer Institute-NIH, in Frederick Maryland, USA. Back in México, she founded her laboratory at the Instituto de Fisiología Celular, UNAM, in 2003.

Her scientific contributions focused on understanding the role of bioactive lipid signaling during development and disease, with emphasis on neural development. Her group is a pioneer in studying the role of bioactive lipid metabolizing enzymes during development. Among her most notable contributions was the demonstration that LPP3 is essential for mammalian development, and that it plays a role in the establishment of the anterior-posterior polarity and extraembryonic vascular development (Escalante-Alcalde *et al*., 2003), as well as in neural differentiation (Sánchez-Sánchez *et al.,* 2012) and cerebellum development (López-Juárez *et al*., 2011), while also discovering its role in regulating dopaminergic neurotransmission (Gómez-López *et al*., 2016). The genetic tools that her group developed have been key to unveiling the role that the enzyme has in other biologi-

Fig. 13 (left). Norma Moreno-Mendoza. *Together with her group, Norma uses wildlife species as animal models. They study germ-somatic cell interactions in the gonads of phyllostomid bats. Their findings of neo-ovogenesis in adult ovaries and the mechanisms involved in gametogenesis and gonadal morphogenesis are recognized. Moreover, they are also working on the molecular mechanisms involved in the process of temperature sex determination and differentiation in the Mexican crocodile, Crocodylus moreletii.*

Fig. 14 (middle). Rosa Navarro-González *was trained under Dr. T. Keith Blackwell in the School of Medicine at Harvard, where she initiated her interest in the germline. Returned to Mexico, Rosa established her laboratory at the Instituto de Fisiología Celular, UNAM, using* **Caenorhabditis elegans** *as the animal model. Together with her group, they made relevant contributions to elucidate the differences between the mechanisms which regulate the physiological and stress-induced apoptosis in the germ cells.*

Fig. 15 (right). Susana Castro-Obregón *was at the Sanford Burnham Prebys Medical Discovery Institute in La Jolla, California as a postdoctoral fellow. Back in Mexico, Susana joined the Instituto de Fisiología Celular, UNAM. Susana's interest in aging and the diversity of the life span in mammalian species motivate her students to study the role of autophagy and cellular senescence in the neural system during development. Their findings that neuronal senescence is a consequence of autophagy dysfunction and that senescent neurons secrete factors which alter surrounding tissue are relevant to understanding age-related cognitive decline.*

cal processes such as vascular permeability and inflammation, lymphocyte egress from the thymus, regulation of lipids involved in the generation of pain (Nieto-Posadas *et al.,* 2012), cardiac function; as well as in understanding the mechanisms leading to greater risk for developing coronary artery disease found among individuals carrying particular *PLPP3* single nucleotide *p*olymorphisms, in collaboration with several groups worldwide.

Norma Angélica Moreno Mendoza

As an independent investigator, Norma A. Moreno-Mendoza (Figs. 5 and 13), together with her group, has used several wildlife species as animal models to study germ-somatic cell interactions in developing gonads. In phyllostomid bats, their main contributions are: (1) the presence of neo-ovogenesis in adult ovaries (Porras-Gomes *et al*., 2017a; Porras-Gomes *et al*., 2017b). (2) the mechanisms involved in gametogenesis and gonadal morphogenesis (Alvarez-Guerrero *et al*., 2014; Alvarez-Guerrero *et al*., 2016). Furthermore, they are interested in the molecular mechanisms involved in the process of temperature sex determination and differentiation in the Mexican crocodile, *Crocodylus moreletii* (Martínez-Juárez *et al*., 2018, 2019).

Rosa E. Navarro-González

Rosa Navarro (Fig. 14) founded the first laboratory in México, which used the nematode *Caenorhadbitis elegans* as its animal model. She trained with Dr. T. Keith Blackwell in the School of Medicine at Harvard, where she maintained her interest in the germline, including the mechanisms involved in apoptosis. With her students and collaborators, they made relevant contributions to the molecular differences among physiological apoptosis and stress-induced apoptosis during oogenesis (Salinas *et al.,* 2006; Láscarez-Lagunas *et al.,* 2014) and the role of TIAR-1 to protect female germ cells (Huelgas-Morales *et al.,* 2016). She motivated several graduate students, who are now involved in postdoctoral studies in the USA and South Korea.

Susana Castro-Obregón

Susana Castro (Fig. 15) trained as a postdoctoral fellow at the Sanford Burnham Prebys Medical Discovery Institute in La Jolla, California, studying the molecular basis for neuronal vulnerability during neurodegeneration. She was then appointed staff research investigator at the Buck Institute for Research on Aging in Novato, California, USA, where she became interested in the biological reasons for the wide range of variation in lifespan and aging rates among mammals. Currently, she studies the role of autophagy and cellular senescence in nervous system development and aging, mentoring several Ph.D. students. Recently, the doctoral work of Daniel Moreno-Blas and Elisa Gorostieta-Salas described that during brain aging, neuronal senescence is a consequence of autophagy dysfunction, occurring before glial cell senescence and that senescent neurons secrete molecules that alter surrounding tissue, potentially contributing to age-related cognitive decline (Moreno-Blas *et al*., 2018; Moreno-Blas *et al*., 2019).

Under Horacio Merchant´s influence, a former mentor, Susana, developed a Comparative Biology approach to study the Biology of Aging. She is a pioneer in México, studying the naked mole-rat (*Heterocephalus glaber*), a mouse-sized eusocial rodent that exhibits neoteny and an exceptionally long lifespan with negligible aging. She established the first Naked Mole Rat Reproductive Unit in Latin America, aiming to promote the study of this emerging model in the region.

Fig. 16. First International Congress on Developmental Biology held in Hacienda de Chautla, Puebla, Mexico, in 2018. *The Mexican Society of Developmental Biology was founded in 1993 in Mexico City. Biannual national and international meetings bring together researchers and students with great success. The successful meetings strengthen international collaborations and the rising interest in developmental biology in Mexico among young scientists.*

Developmental Biology of Plants in México

In México, there are several leading laboratories interested in the developmental biology of plants (Table 1). At the UNAM, Dr. Judith Márquez-Guzmán in the Facultad de Ciencias is a precursor scientist in the Developmental biology of plants in México. She centered in *Lacandonia schismatica* as her main plant model making important contributions and inspiring young investigators (Valencia-Nieto *et al.,* 2018; Vázquez-Santana *et al.,* 1998). At the Instituto de Ecología, Dr. Elena Alvarez-Buylla, along with other researchers, focused on the mechanisms involved in the formation of roots in diverse models, including *Arabidopsis* (Alvarez-Buylla *et al.,* 2000; Alvarez-Buylla *et al.,* 2019). In her laboratory, they found the genetic networks involved in the morphogenesis of stem cell niches in the root of *Arabidopsis Thaliana* (García-Gómez *et al*., 2017). Similarly, at the Instituto de Biotecnología, UNAM, Dr. Lossif Dubrosky, and his group investigated the developing mechanisms in developing roots of Cactaceae among other plants (Torres-Martínez *et al*., 2019).

At the National Laboratory of Genomics for Biodiversity (LANGEBIO) of the Instituto Politécnico Nacional (IPN), doctors Jean Phillipe Vielle-Calzada, Stewart Gillmor, Stefan de Folter, Luis Alfredo Cruz Ramírez, Luis Herrera-Estrella made significant contributions to the biology of plant development, using *Arabidopsis* and Maize as their first model systems. They have continued working with several aspects of embryogenesis in plants, focused on stem cell, sexuality, and apomixis, as well as the development of flowers and fruits (López-Buceo *et al*., 2007; Del Toro-De León *et al.,* 2014; Herrera-Ubaldo *et al.,* 2019; Cervantes-Pérez *et al*., 2018). Finally, the important contribution

TABLE 1

SEVEN OF THE MOST IMPORTANT LABORATORIES WORKING ON THE DEVELOPMENTAL BIOLOGY OF PLANTS

Laboratories	Investigator	Address	Activities
Laboratorio de Desarrollo en Plantas	Judith Marquez-Guzman	Facultad de Ciencias, UNAM, Ciudad Universitaria, C.P. 04510. Ciudad de México	Reproductive and Developmental Biology of *Lacandonia schismatica*
Laboratorio de Genética Molecular, Epigenética, Desarrollo y Evolución de Plantas	Maria Elena Alvarez-Buylla Roces	Instituto de Ecologia, UNAM, Ciudad Universitaria, C.P. 04500. Ciudad de México	Systems biology focused on molecular genetic, epigenetics and evolutionary developmental ecology
Grupo de Desarrollo Reproductivo y Apomixis LANGEBIO	Jean-Philippe Vielle-Calzada	Cinvestav Irapuato C.P. 36821, Guanajuato, México	Genetic and epigenetic control of sexuality and apomixis in Arabidopsis
Regulación Genética e Ingeniería Metabólica LANGEBIO	Luis Rafael Herrera-Estrella	Cinvestav Irapuato C.P. 36821, Guanajuato, México	Regulation of root and shoot development in Arabidopsis
Laboratorio de Biología del Desarrollo de la Raíz	Joseph Dubrovsky	Instituto de Biotecnología, UNAM. Av. Universidad 2001, Chamilpa 62210. Cuernavaca, Morelos, México	Molecular and cellular mechanisms involved in root morphogenesis
Genómica Funcional del Desarrollo de Plantas LANGEBIO	Stefan de Folter	Cinvestav Irapuato C.P. 36821, Guanajuato, México	Gene regulatory networks involved in flower and fruit development
Complejidad Molecular y del Desarrollo LANGEBIO	Alfredo Cruz-Ramirez	Cinvestav Irapuato C.P. 36821, Guanajuato, México	Mechanisms involved in animal and plant regeneration

The investigator's name corresponds to the founder and head of the laboratory. The activities indicated are summarized and thus may be incomplete.

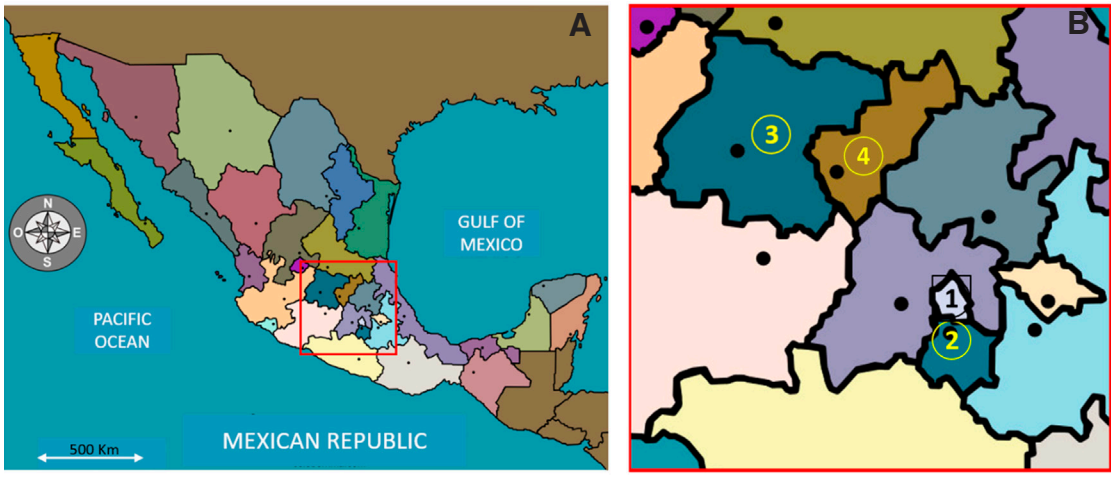

Fig. 17. Geographical location of the research laboratories involved in Developmental Biology in Mexico. (A) *The Mexican Republic consists of 31 States and Mexico City.* **(B)** *This picture is a magnification of the red square in (A). All laboratories are located at the center of the country.* **(1)** *Mexico City: Instituto de Investigaciones Biomédicas, Instituto de Biología Celular, Instituto de Ecología, and Facultad de Ciencias; all at the UNAM.* **(2)** *Morelos State: Instituto de Biotecnología, UNAM.* **(3)** *Guanajuato State: LANGEBIO IPN.* **(4)** *Queretaro State: Instituto de Neurobiología, UNAM.*

of Alfredo Herrera-Estrella working founder of the laboratory of Gene Expression and Development in Hongos completes the models in the three kingdoms of Developmental Biology (Medina-Castellanos *et al.,* 2018).

The Mexican Society for Developmental Biology

The Mexican Society of Developmental Biology (MSDB), founded by 15 members, organized its first meeting in México City in 1993. Oscar Ramirez Toledano, José Luis Reyes, and Carlos Arguello were members on the first board. Since then, the MSDB has steadily expanded thanks to the enthusiastic participation of the former Presidents, including Juan Riesgo Escovar (2001), Mario Zurita (2003), Diana Escalante-Alcalde (2005) and more recently, Alfredo Varela 2009, Iván Velasco 2011, Adriana Garay (2013), Jesús Chimal-Monroy (2015) and the current president Daniel Ortuño 2018.

The biannual meeting of the MSDB is a strong tradition, and up until now, 13 meetings have been organized. Throughout this period, the MSDB participated with other Developmental Biology Societies. Diana Escalante-Alcalde and Mario Zurita, together with the Latin-American Society of Developmental Biology (LASDB) and the Society of Developmental Biology (US), organized the Pan-American meeting held in 2007 at Cancún, México. In 2013, the MSDB, together with the International Society of Developmental Biologists (ISDB), LASD and SDB, organized the 12th International Congress of Developmental Biology in Cancún, México. Recently, Jesús Chimal-Monroy, Jessica Cristina Marín-Llera, Diana Escalante-Alcalde, Susana Castro-Obregón and Daniel Ortuño of the MSDB, organized the First International Congress in Hacienda de Chautla, Puebla, México in 2018 (Fig. 16). This meeting brought together 35 developmental biology experts, 16 nationals, and 19 internationals, and the talks were divided into eight keynote and 27 short talks. Speakers came from Argentina, Brazil, Chile, Germany, Israel, Spain, the United States, the United Kingdom, and Portugal. This meeting, as others organized by the MSDB in México, was an academic success. Invited speakers, young scientists, and students share ideas in a stimulating and friendly environment.

Conclusions

Developmental biology, as an integrative biological area, is relatively recent in México (Fig. 17). The historical complexity of Latin American countries delayed the expansion of academic activities; funding was limited, and scientific vocations were rather scarce. However, the enthusiasm of several professors, some of them republican Spanish migrants from the civil war, hired mainly at the Universidad Nacional Autonóma de México (UNAM) and the Instituto Politécnico Nacional (IPN), promoted scientific vocations among young students. The first research laboratories were at the Medicine School and the Biology Institute, both at the UNAM. Biomedical investigations were generally categorized as morphological, physiological, biochemical, or genetic; later, the expansion of cellular and molecular biology led to the integration of these four classical fields.

Modern technologies produced new research fields. Genomics, epigenomics, transcriptomics, proteomics, etc. applied to several species, provide a huge amount of data to strengthen theoretical biology, along with corroborating evidence. Developmental Biology was thus capacitated to discover new mechanisms faster than ever. The precise understanding of the developmental processes enlightens most other fields of biology, including evolution, ecology, and Medicine. Fortunately, México now maintains an enthusiastic community of developmental biologists. They, together with international scientists, contribute to the knowledge required to mitigate the global damage to nature caused by human activity.

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