PROFILE

Profile of Edward M. De Robertis

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Curiosity about the mysterious workings of embryos fuels the research of embryologist Edward M. De Robertis (also known as Eddy), who was elected to the National Academy of Sciences in 2013. His isolation of genes that control head-to-tail and back-to-belly patterning in early frog and mouse embryos led to the discovery that animal development is controlled by an ancient genetic toolkit. De Robertis dissected the process of embryonic induction, in which groups of cells called "organizers" control tissue differentiation. Earlier work by De Robertis and colleagues contributed to the beginning of the scientific discipline known as evo-devo, which takes an evolutionary perspective on development.

De Robertis, Norman Sprague Professor of Biological Chemistry at the University of California, Los Angeles (UCLA) and a Howard Hughes Medical Institute Investigator, is interested in how cells in the vertebrate embryo communicate with one another over long distances. Deciphering such cell signaling remains a fundamental problem in stem cell biology and cancer. De Robertis has been a member of the Jonsson Comprehensive Cancer Center at UCLA since 1985. He is also a member of the Pontifical Academy of Sciences and the Latin American Academy of Sciences, and is a Fellow of the American Academy of Arts and Sciences.

Childhood in Uruguay

De Robertis was born in 1947 in Boston, MA, while his neurobiologist father was a postdoctoral researcher at the Massachusetts Institute of Technology. The family moved to Montevideo, Uruguay, when he was three. His parents were Argentinians exiled by General Juan Perón. De Robertis describes Montevideo in the 1950s as an idyllic place to grow up. "These were peaceful, safe, and innocent times," he says. "I attended a primary and high school run by American Methodist Missionaries who provided a good education mostly in English."

During high school, his biology teacher, Mr. Lagomarsino, lent him the keys to the laboratory. At lunchtime, De Robertis would go to the laboratory to reproduce experiments he had read about in *Scientific American*, which, at the time, highlighted news about the emerging genetic code. "At that time, it was also customary to read inspiring science books such as *Microbe Hunters* by Paul de Kruif (1) and *The Life of the Bee* by Maurice Maeterlinck (2) as part of children's education," he says, mentioning his early interest in biology. His parents divorced when he was five. De Robertis stayed in Uruguay with his mother. His father returned to Argentina but visited regularly.

Introduction to Embryology

De Robertis' family assumed that he would follow in his father's footsteps. "Consequently, I did not have to invest any energy in choosing a career," he says. Students interested in biology were steered toward the field of medicine, so De Robertis went down that path. He earned a degree in medicine in 1971 from the University of Uruguay's School of Medicine. There he was an assistant to Roberto Narbaitz, who introduced him to embryology.

De Robertis married his childhood sweetheart, Ana Marazzi, the day after his final examination at the University of Uruguay. The newlyweds moved to Buenos Aires three days later, and De Robertis entered the Faculty of Sciences at the Instituto Leloir to start his doctorate of philosophy studies in chemistry. His advisor was biochemist, Héctor Torres, who taught De Robertis about enzyme kinetics. Another early mentor was the director, Nobel Laureate Luis Federico Leloir, who was in the adjoining laboratory. De Robertis has never forgotten Leloir's

Edward M. De Robertis. Image courtesy of Ana De Robertis.

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 20372.

disciplined schedule in which he conducted two experiments nearly every day: one in the morning and one in the afternoon.

A Fateful Meeting

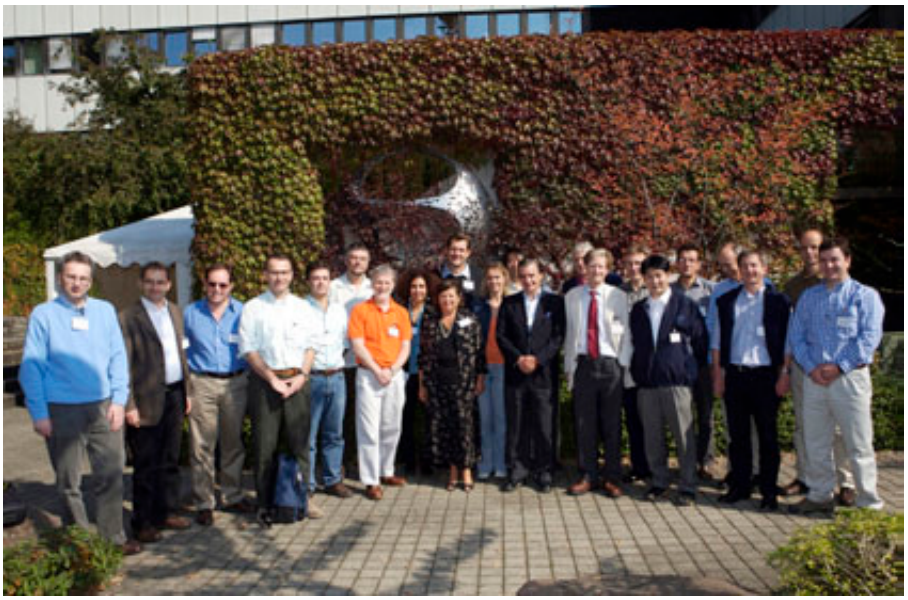
While on a tour of lectures in South America, renowned developmental biologist John Gurdon visited the Instituto Leloir. Gurdon was well known for his nuclear transplantation work as well as for synthesizing protein from mRNAs microinjected into frog oocytes. De Robertis introduced himself, and later spotted Gurdon leaving alone to brave the Buenos Aires rush hour. "Seeing that he was on foot," De Robertis says, "I went to my car, drove to the bus stop, and casually pretended to be surprised of seeing him there and gave him a ride to his hotel in the city center. This small gesture of politeness was to change my life."

A few years later, De Robertis was looking for a postdoctoral position, and was referred to Gurdon. De Robertis wondered why Gurdon would even consider him. His professor informed De Robertis that, a few days after Gurdon's visit, the British Embassy sent someone to Leloir to say that if De Robertis ever wanted training in Britain, there would be a fellowship available for him. A few months later, in 1975, De Robertis and his family moved to Cambridge, England.

With Gurdon, De Robertis transplanted somatic kidney nuclei from *Xenopus* into the oocytes of a salamander and was able to show nuclear reprogramming using the then-new technique of 2D gels (3). De Robertis and a coworker also showed, for the first time, that a gene cloned using recombinant DNA could be translated into protein using the frog oocyte as a test tube (4). "What I did not know until arriving there was that the MRC Laboratory of Molecular Biology where Gurdon was working was the Mecca of molecular biology," De Robertis says. "Francis Crick, Max Perutz, Fred Sanger, Sydney Brenner, and Cesar Milstein were all working in a relatively small building. One learned so much simply listening to teatime conversations at the cafeteria. Cambridge was electrifying for a young molecular biologist."

Evo-Devo

After three years as a postdoctoral scholar and three years as a staff scientist working on nuclear transport of proteins, De Robertis moved to the Biozentrum at the University of Basel, Basel, Switzerland. There, at the age of 33, he became full professor of cell biology. It was a small department, and he and his colleagues had joint group meetings together with noted *Drosophila* geneticist, Walter Gehring. "In truth, I completed my education in developmental biology there," De Robertis says. "These were very exciting times, for Gehring's group had discovered a gene sequence conserved in several *Drosophila* genes, called 'homeotic genes,' which regulate anteroposterior cell differentiation. After one of these seminars, Walter and I had a brainstorm in his office and decided to search for similar sequences in vertebrate gene libraries."



De Robertis and colleagues at a 2007 EMBL symposium in Heidelberg, Germany. Image courtesy Iain Mattaj.

Although De Robertis' rationale for the experiment was wrong because he thought the genes would encode secreted neuropeptides, they nevertheless isolated the first Hox gene from a vertebrate (5). At the end of the paper's abstract, De Robertis boldly wrote: "This gene could perhaps represent the first development-controlling gene identified in vertebrates." It indeed was. Before the discovery, it was thought that development would be entirely different between *Drosophila* and *Xenopus*, but afterward came the realization that development is directed by a conserved genetic toolkit shared by all animals. This discovery marked the beginning of the new discipline of evo-devo.

Unraveling Cell Differentiation

In 1985, De Robertis accepted a position of Endowed Chair at the Department of Biological Chemistry at the UCLA School of Medicine. He and colleague Larry Zipursky started the weekly Embryology Club modeled around European seminars in Cambridge and Basel. "It is still running and has provided a wonderful forum for discussions," De Robertis says. In 1988, a book (6) by embryologist Viktor Hamburger, as well as one by embryologist Hans Spemann (7) who taught Hamburger, sparked discussion in the club about the possibility of isolating genes involved in embryonic induction.

In 1924, Spemann and a colleague had shown that a region of the amphibian embryo was able to induce the formation of Siamese twins after transplantation into another embryo (7). The cells from this region induced their neighbors to differentiate into tissues such as those for the central nervous system, muscles, or kidneys, so it was called the "organizer region." De Robertis and his team advanced those findings by isolating a homeobox transcription factor gene called *goosecoid*, which provided the first molecular marker for the organizer (8). They microinjected synthetic mRNA for *goosecoid*, inducing Siamese twins in *Xenopus* embryos. De Robertis recalls, "When my postdoc showed me these embryos, it was a great joy, so much so that I jumped on top of the bench! *Goosecoid* was a DNA-binding protein, so we reasoned it had to activate other genes that diffused to neighboring cells."

The team isolated many genes encoding secreted proteins enriched in Spemann's organizer and, surprisingly, most were

antagonists of known growth factors. They were hoping to find new signaling pathways, but discovered novel antagonists instead (9–11). One such antagonist was the protein Chordin, which the team showed works by binding to growth factors and blocking their signaling (12–15).

Spotlight on Chordin

Chordin is the focus of De Robertis' Inaugural Article in this issue of PNAS, in which he and his colleagues report that chordin diffuses in the embryo in a narrow layer of extracellular matrix that separates the ectoderm from the mesoderm (16). De Robertis explains, "These results are novel because they suggest a way in which embryonic induction of tissue types can take place coordinately in two different germ layers, even as cells undergo the extensive movements known as gastrulation." Tissue differentiation affecting both ectodermal and mesodermal cells may therefore happen simultaneously.

The work takes De Robertis a step closer to his goal of solving the long-standing mystery of embryonic self-organization. "Study of the cross-talk between cell-signaling pathways is taking us in unexpected directions. . .I want to understand how embryonic cells communicate with each other to form a perfect baby time after time."

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