

# Alejandro Sánchez Alvarado

Alejandro Sánchez Alvarado is a Professor of Neurobiology and Anatomy at the University of Utah School of Medicine and is also a Howard Hughes Medical Institute Investigator. Born in Caracas, Venezuela, 24 February 1964, Sánchez Alvarado left his home to pursue education in the United States, where he received a Bachelor of Science in molecular biology and chemistry from Vanderbilt University in 1986 and a Doctorate in pharmacology and cell biophysics at the University of Cincinnati College of Medicine in 1992. During his PhD studies Sánchez Alvarado examined the *in vitro* differentiation of mouse embryonic stem cells. In 1994 he began a postdoctoral position at the Carnegie Institution of Washington's Department of Embryology, where he was appointed a staff associate in 1995. In 2002 he became an Associate Professor at the University of Utah School of Medicine in the Department of Neurobiology and Anatomy, and was promoted to Professor in 2005.

Sánchez Alvarado has often described regeneration as one of the long-standing problems of biology that still lacks a mechanistic understanding. The subject's rich history is something he has found very intriguing and motivating; indeed, he has lectured on the historical work of Abraham Trembley, Charles Bonnet, René-Antoine Ferchault de Réaumur, and Lazzaro Spallanzani. Sánchez Alvarado has often pointed to Thomas Hunt Morgan's work with planarians as a great inspiration.

During his postdoctoral years Sánchez Alvarado first became interested in exploring regenerative processes at the molecular level. He quickly noticed all of the standardized and sanctioned animal models such as the mouse, rat, fruit fly, and nematode worm distinctly lacked regenerative abilities. In many review articles Sánchez Alvarado has argued that this under-representation has stunted our understanding of regeneration, and therefore of development more generally. He has aimed to remedy this situation by promoting the incorporation of a wide range of organisms with regenerative capacities into regeneration studies; in particular he has developed molecular tools to study fresh water planarians. Undergirded by a synthetic perception of developmental biology, his research program strives to elucidate the evolutionary origins of regeneration and its relationship to embryogenesis. Motivated by the hopes of informing big questions in biology, including biomedicine, Sánchez Alvarado has suggested that planarians are an ideal model with which to investigate the basic mechanisms of regeneration and development.

To aid in studying the molecular biology of regeneration Sánchez Alvarado was determined to find an invertebrate organism that possessed regenerative abilities and was also amenable to genetic analysis and manipulation. These qualities led him to planarians: bilaterally symmetric metazoans, members of the phylum Platyhelminthes, and the suborder Triclada. Planarians are also classified with respect to their ecological habitat: freshwater, marine, or terrestrial. There are thousands of different planarian species but Alvarado's group focuses largely on the free-living, freshwater flatworm *Schmidtea mediterranea*, which was selected for a number of reasons. Unlike other planarians, *Schmidtea* has a stable diploid structure, a comparatively small genome size with nearly half the base pairs of many other species, and both sexual and asexual forms. Furthermore, *Schmidtea* survives well in the laboratory and can be manipulated by serial amputations to produce large clonal colonies, which have been successfully bred and maintained in the laboratory, thereby overcoming the earlier restriction posed by breeding difficulties. These six characteristics helped Sánchez Alvarado to select *Schmidtea mediterranea* from among the many planarian species. He had to be familiar with a diversity of organisms in order to make this selection.

Planarians regenerate missing parts by first assembling a specialized structure, the regeneration blastema. This form of regeneration is referred to as blastemal regeneration and involves the initial proliferation of a specialized cell population called the neoblasts, which were recently shown by

Sánchez Alvarado's group to be analogous to somatic stem cell populations. Sánchez Alvarado puts these definitions into historical context by referring back to Morgan's Regeneration where they were first introduced. Morgan's basic subdivision of regeneration into two general categories still holds today: epimorphosis, which involved cell proliferation, and morphallaxis, or the remodeling of existing cells without proliferation to restore missing or damaged structures. Epimorphosis was further subdivided by Sánchez Alvarado into non-blastemal and blastemal regeneration.

Non-blastemal based regeneration employs three general mechanisms: transdifferentiation of remaining tissue, such as lens regeneration in urodele amphibians; de-differentiation and proliferation of the surviving cells, as occurs during liver regeneration in humans; and proliferation and differentiation of stem cells already present in the damaged tissue, which occurs during bone regeneration in humans.

Blastemal regeneration requires the formation of the regeneration blastema, a specialized structure composed of two cell populations: an outer layer, the wound epidermis, which covers the wound surface after amputation; and an inner layer of mesenchymal cells. The basic structure of the blastema is similar in vertebrates and planarians, but the mechanism of formation differs. The wound epidermis in planarians forms by changes in cell shape rather than by cell proliferation, and the mesenchymal cells are derived from neoblasts, which are undifferentiated, pre-existing cells. The regeneration blastema may form within hours of amputation or may take up to a few days depending on the organism. Blastemal regeneration is a common mechanism observed in planarians, mollusks (gastropods and cephalopods), echinoderms, urochordates, and limb and tail regeneration in vertebrates.

Sánchez Alvarado asks why these different modes of regeneration are used in different cases. For example, why might regeneration occur via growth from a specialized blastema as opposed to the remodeling that occurs during morphallaxis? How do molecular pathways contribute to these different modes and also to the differences and similarities that exist between normal development and regeneration? He is also interested in studying the dynamics of the neoblast cell population, which makes up 25-35% of all planarian cells. Because these cells lack specific markers and have a rather uniform morphology, it is difficult to assess the heterogeneity of the population. His laboratory aims to detect the source of the neoblasts and to investigate the mechanisms underlying their ability to self-renew, dedifferentiate, and migrate.

Recently, Sanchez Alvarado used molecular tools to reanalyze one of Morgan's earlier observations, with rather interesting results. The paper " $\beta$ -Catenin defines head versus tail identity during planarian regeneration and homeostasis," investigated the molecular mechanisms that underlie polarity. It was published in *Science*, where it was selected as Editor's Choice, indicating the editors deemed the results to be widely relevant and exceptionally interesting. His results were also described in the news sections of *Nature Cell Biology* and *Nature Reviews Molecular Cell Biology*, which is further evidence of the relevance of his approach and the theoretical implications of his results.

Although Sánchez Alvarado's laboratory currently focuses on *Schmidtea mediterranea*, his approach to studying development incorporates knowledge of a diversity of organisms. Considering a diversity of organisms is important to Sánchez Alvarado because his work is driven by questions about regeneration's place in evolution. He hopes investigating the evolutionary origin of regeneration will ultimately shed light on much more than simply regenerative processes. His laboratory work has challenged accepted notions about developmental biology and demonstrated new ways to study regeneration in the context of both development and evolution.

## Sources

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