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A brief personal account of a journey in science - an interview with Alejandro Sánchez Alvarado

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ABSTRACT Alejandro Sánchez Alvarado represents a younger generation of Latin American scientists that have achieved international scientific recognition. His work, together with that from other labs, has positioned the planaria *Schmidtea mediterranea* as a dynamic model system in which the cellular and molecular bases of regeneration in metazoans can be probed. During his professional career he has established strong ties with Latin America, hosting and training students and participating in seminars, workshops and courses throughout the region. In this interview he discusses his early scientific development and training, and his views on various issues related to the professional development of young scientists.

KEY WORDS: *Venezuela, planaria, regeneration, developmental biology*

Alejandro Sánchez Alvarado was born and raised in Caracas, Venezuela. He moved to the USA to complete his studies at Vanderbilt University (B.Sc.) and at the University of Cincinnati (Ph.D.). He has worked at the Carnegie Institution for Science (Baltimore), and The University of Utah School of Medicine. He is presently the Scientific Director at the Stowers Institute for Medical Research (Missouri) (Fig. 1). Among his many achievements, he is a Howard Hughes Medical Institute Investigator and a member of both the Latin American and the USA National Academies of Science.

Sánchez Alvarado trained as a molecular biologist using traditional models, but after completing his training he directed his interest toward the study of regeneration in the planarian flatworm *Schmidtea mediterranea*. Together with Philip Newmark, they developed molecular tools, particularly the use of double stranded RNA to disrupt gene expression in planarians (Sánchez Alvarado and Newmark 1998, 1999, Newmark *et al.,* 2003). This was a major breakthrough that helped firmly establish *S. mediterranea* as a powerful model to study regeneration (Sánchez Alvarado 2000, 2003). His work has helped characterize the role of stem cells (Newmark and Sánchez Alvarado 2000, Pellettieri *et al.,* 2007, Oviedo *et al.,* 2008, Zeng *et al.,* 2018, Kim *et al.,* 2019) and the genetic basis of regeneration (Reddien *et al.,* 2005, Robb *et al.,* 2015, Duncan *et al.,* 2019). Among his most recent works are studies showing the influence of the microbiota on regeneration (Arnold *et al.,* 2016) and the role of Wnt and TGF-β in regulating size-dependent behavior (Arnold *et al.,* 2019).

By way of introduction, please tell us a bit about your upbringing in Venezuela and how you became a biologist.

I was born in Caracas, Venezuela and received my elementary and high school education at the Colegio Emil Friedman (Fig. 2), where I was extremely fortunate to have had three particularly extraordinary teachers: professors María del Rosario Jiménez (literature), Rafael Benitez (literature) and Alberto López Maldonado (biology). From professors María del Rosario and Benítez I gained an appreciation for literature, *i.e.*, novels, poetry and theater that has served me well to this day. I spent many after-school hours with both of these teachers discussing language structure, etymology, the architecture of narrative in novels, plays and short stories and its evolution through time. In essence, we read a lot and discussed most major literary works of Spanish and other romance languages. I learned to analyze, interpret, and enjoy literature from these great teachers, who helped me develop a way of thinking akin to inductive inquiry. What I mean by that is that in our readings and discussions, professors María del Rosario and Benítez, each in their own way, taught me how to approach the unknown as an adventure into uncharted territories, unrestricted by preconceptions.

Yet, in retrospect, even though my literature teachers left an indelible intellectual mark, the one teacher that most profoundly

Abbreviations used in this paper: TGF, transforming growth factor.

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Fig. 1. Alejandro Sánchez Alvarado *is, at present, the Scientific Director of the Stowers Institute for Medical Research.*

affected me was my high school biology teacher, professor Alberto López Maldonado. Professor Maldonado had a fairly unorthodox way of teaching. I have told this story many times, but it is worth repeating to give you a flavor of all of the classes I had with him. On the first day of class, with all 30 of us students quietly sitting at our desks, professor Maldonado walked into the classroom, loudly placed his briefcase on his desk and proceeded to sit down. Without introducing himself and intently looking at us, he asked in a loud, yet unaggressive tone: "If you had to invent a language, what would be the minimum number of letters you'd need?". We all looked around at each other, puzzled and wondering whether we were in biology class or not. After what seemed a long time, with professor Maldonado sitting at his desk silently looking at us, a friend of mine who is now a psychiatrist, raised his hand, and after receiving tacit permission from Maldonado, my friend said: "One!". "Explíquese, bachiller", said Maldonado, which is the equivalent of saying, "explain yourself, young man". And my friend explained that if we were to take a single letter, say, the letter "a", one could make a language. He explained that the letter "a" would be one word, that "aa" would be another word, that "aaa" and "aaaa" would be yet other words and so on. Clearly not the most practical of languages, but a language nonetheless. After earnestly listening to my friend, professor Maldonado stood up and said: "Yes, that is correct, and nature has used the same logic, but instead of using one letter, it chose to use four letters: ACGT". And walking to the blackboard, professor Maldonado began to explain DNA to us and how these four letters were the alphabet used in nature to write the script that makes each and every life form populating our planet possible.

I want to share the following anecdote as well. After explaining the likely chemical origin of life, and how nucleotides may have arisen and come together to form a DNA double helix, professor Maldonado's gave us the following homework for the weekend: to imagine how that double helix could copy itself whenever a cell divided. We came back the following week armed with answers, all of them wrong. That day, and I still remember it vividly, he proceeded to explain to us the principles of centrifugation and how it worked to separate particles in solution according to their size, shape, density, medium viscosity and rotor speed. We did not know what centrifugation had to do with our homework and DNA replication, but that detailed explanation of centrifugation was professor Maldonado's way of introducing us to the work of Meselson and Stahl. It took me a while, but when I got it, when I saw how they resolved the problem of DNA replication via a semiconservative model, using heavy isotopes and centrifugation, I was astounded. Astounded because these two scientists were able to see and solve the invisible problem of how a complex molecule could replicate itself, using logic and relatively crude instruments (you can read a personal account of this experiment by Meselson himself here: https://explorebiology.org/collections/genetics/how-dna-replicates). From an early age, I had always admired the ability of ancient Greeks to solve complex problems in astronomy and physics using things like sticks and shadows, but I had not considered that similar approaches could be applied to biology. I think it was that day I wanted to become a molecular biologist.

As an aside, and now that you know this story, Matt Meselson and I met for lunch in 2014 at a local eatery in Woods Hole, Massachusetts to discuss aging and regeneration in rotifers and planarians (Fig. 3). From time to time, as we were discussing ideas, the thought would creep in: what would professor Maldonado make of this encounter? I kept in touch with professor Maldonado through the years, and even as recently as the early 2000's he used to share with me class plans he was developing for his students.

Fig. 2. A young Alejandro and his introduction to the natural wonders. *Taken in the Venezuelan plains (Llanos) where he spent many summers in his grandfather's cattle ranch.*

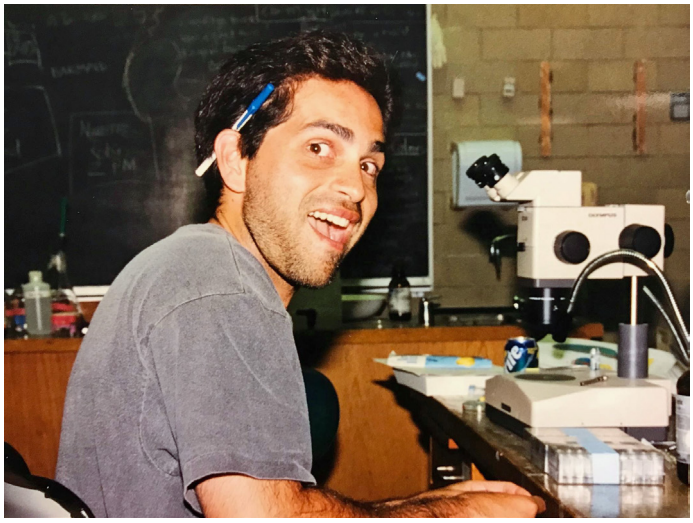

Fig. 3. Sánchez Alvarado participated in the Embryology course at the Marine Biology Laboratory in Woods Hole as a student *(shown here in 1995) and more recently as the course Director, together with Dr. Richard Behriger (Photo courtesy of Steve Gendreau).*

The last one we discussed was on genetic variegation, and as always, he did not fail to astound me! Sadly, his faculties declined in his last years and he passed away in 2015. I was never able to share with him my exchange with Matt Meselson.

When did you decide to continue your education in the USA? Why?

After high school, I was on track to become a physician in Venezuela. That was the expectation my family had for me at the time. But, medicine did not attract me as much as biology did, and by the time I graduated, I wanted to learn and practice molecular biology. As there was no way at the time (1981) to study this discipline in Venezuela, the only real option available to me was to consider studying abroad. After some pre-internet research consisting of many visits to many consulates and embassies in Caracas, I settled for the United States, and eventually Vanderbilt University to pursue my studies (Fig. 4).

Fig. 4. Adventurer and lover of nature. *Sánchez Alvarado is shown here collecting specimens in Australia's Great Barrier Reef with Bernie Degnan (not pictured).*

You came in late into the field of Developmental Biology. How did this happen? Do you see your previous work (and training) as an advantage to enter a new field with a different viewpoint or as a hindrance that you had to overcome?

Like many others today and before me, I came into developmental biology tangentially. I was getting my Ph.D. in the Department of Pharmacology and Cell Biophysics at the University of Cincinnati College of Medicine and Dr. Jeff Robbins offered me to join his lab. Jeff's lab was focused on understanding the functions of the alpha- and beta-myosin heavy chain (MHC) genes. After years of research using chickens, Jeff decided to transition his lab into mouse genetics at or about the time I joined because he wanted to mutagenize these MHC genes, and the plan was to delete/modify them using homologous recombination and observe the resulting cardiac deficiencies. I was introduced to mouse embryonic stem cells as a vector to generate mouse mutants, but as I began to read about these cells I became more and more interested in their origins as an experimental tool as well as their genesis and function during embryonic development. I learned to culture these cells and also to differentiate them *in vitro* into what we called back then beating embryoid bodies, that is, into spheroidal groupings of cells often containing tissue that was rhythmically contracting. I decided that my thesis would be to test whether these beating embryoid bodies were recapitulating cardiogenesis or not.

As I had never taken a class in developmental biology, I set out to learn about heart development and became smitten with the remarkable potency of stem cells and the temporal transformations these cells experience from a metastable undifferentiated state to stable differentiation states.

In several of your presentations and publications it is obvious that you have a profound interest in the historical aspects of biology and that you pursue this interest hand in hand with your ongoing research. Are there research questions or ideas that have sprung from the reading of the older historical literature? Can you share some of these with our readers?

I believe that when you love a discipline enough to dedicate your life to it, that the more you know about it, the better you become at understanding its potential and limitations. In fact, understanding the genesis of ideas gives one a perspective of the field and its associated disciplines that is quite hard to attain if one ignores their distant pasts. Kyle Gurley and Jochen Rink's paper on the generation of two-headed planarians after amputation is a good example (Gurley *et al.,* 2008). In this paper, we reported the role that Wnt/β-Catenin plays in allowing planarians to differentiate anterior from posterior. Our results were significantly more meaningful to us because of the work that T.H. Morgan (1866-1945) had published over 100 years ago on this topic. In fact, we acknowledged its influence in our thinking in the concluding remarks of our article, where we wrote: "More than 100 years ago, T. H. Morgan reported that fragments with closely spaced anterior and posterior amputation planes occasionally regenerate two-headed animals. He termed these animals 'Janus heads' and suggested that 'something in the

piece itself determines that a head shall develop at the anterior cut surface and a tail at the posterior cut surface' (Gurley *et al.,* 2008)." Our ability to generate "Janus heads" in planarians by abrogating β-Catenin function confirmed Morgan's conclusions, which he made as a young investigator before he received any of the accolades by which most of us know him by (*e.g.*, Nobel Prize). Reading his early, pre-*Drosophila* articles was like having access to a window into the mind of a brilliant young scientist looking for experimental vulnerabilities to tackle seemingly impenetrable problems, a mind that in just a few years, together with his graduate student Alfred H. Sturtevant (1891-1970) would gift the world with a method to map the relative location of a series of genes along the length of a chromosome, thus launching the modern era of genetics.

Through your work on Planaria, you have become a forceful voice for the study of "nonclassical" model organisms. What is it that you think we can learn from studies on species other than vertebrates, *Drosophila* or *C. elegans*?

Well, the way I see it, all organisms are a model organism for something, as they represent the distillation of millions of years of evolution of a deeply, evolutionarily conserved toolkit. Designating an animal as a model or non-model or non-classical model organism is an entirely sociological convenience, rather than a reflection on scientific logic. In 2018, I wrote the following in *Developmental Biology*:

"The time has come to dispose of the terms "model" and "non-model" systems and adopt instead the more accurate term "research organism". Our remarkable advances in genome editing, imaging, bioinformatics, high throughput assays and automation demands it. Adopting the term research organism allows us to bring our technological armamentarium to explore the wealth of Life on Earth and expand the boundaries of biological knowledge in the decades ahead. Organisms and entire ecosystems previously inaccessible to effective interrogation are no longer so, and the organisms inhabiting these, as of yet unexplored continents of knowledge may hold answers to some of the most vexing questions in biology." (Sánchez Alvarado 2018).

So yes, we have a lot to learn. A good place to start would be to study biological diversity to learn firsthand what is already possible before we start writing rules of what is or is not possible in biology. Specializing on the handful of extremely domesticated species inhabiting the brunt of life sciences laboratories in the US and the world has likely impeded our progress at best, and at worst, may be leading us astray from understanding fundamental biological principles.

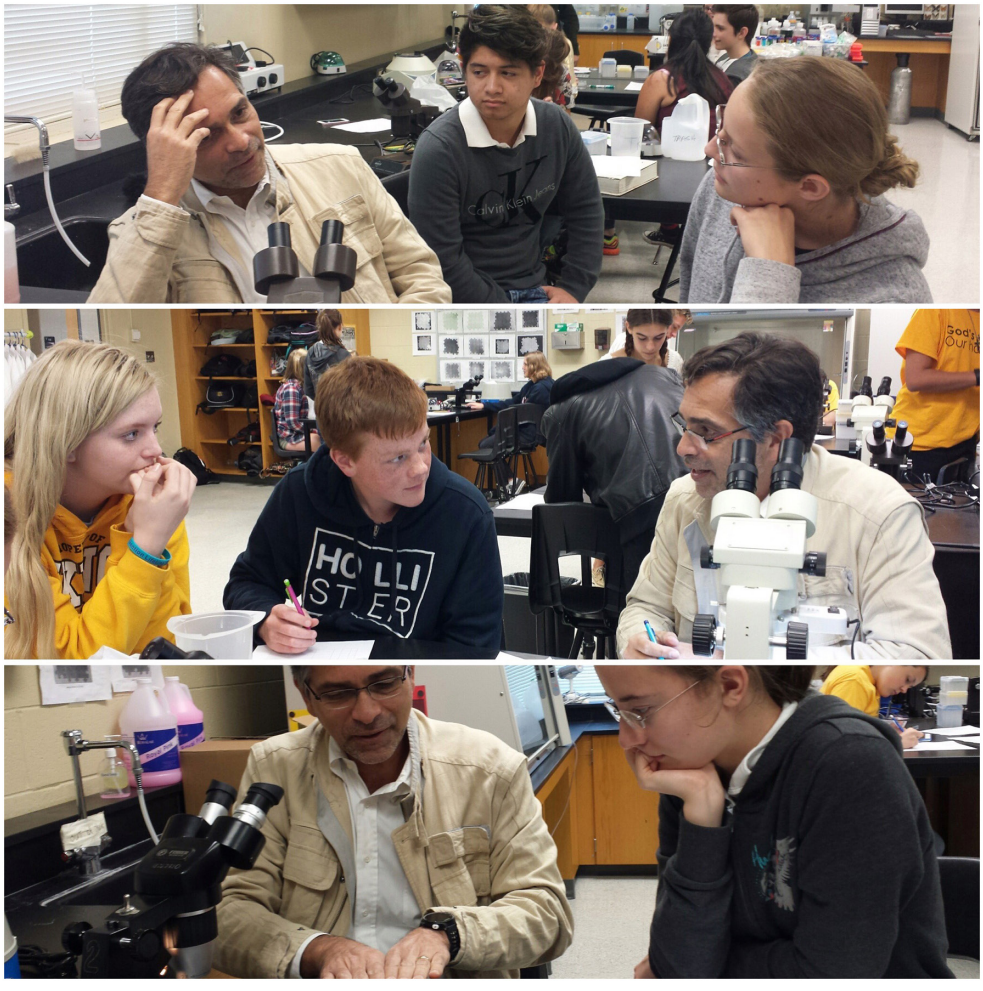

Fig. 5. Sánchez Alvarado is committed to scientific education and outreach. *He is shown here running a planarian lab with local high school students in Kansas City.*

You belong to a younger generation of scientists from Latin America whose work has achieved international recognition. What do you consider helped you in attaining this distinction? Discipline, hard work, focus, luck, other?

I think luck and preparation go hand in hand. I have been very lucky to have had phenomenal mentors who have challenged me and helped me along each step of my intellectual and scientific development. And yes, discipline and hard work have helped me a great deal, but in my particular case, a healthy appetite for both adventure and intellectual exploration have been key motivators for me.

Recently, you accepted a position as Scientific Director of the Stowers Institute. Do you view this as a big change in your career? What is your scientific goal for the institution?

I often say that you can chart the arc of my career by the times I have declined administrative responsibilities. So holding a position like Scientific Director is not something I immensely desired. But finding intellectual ecosystems in which the practice of science can be carried out rigorously and with minimal distractions is difficult. Such ecosystems are

Fig. 6. Discussing planarian embryology with students at the International Developmental Biology course in Quintay, Chile. *(Photo courtesy of Alfonso Martínez Arias).*

rare, and helping to preserve, cultivate and grow them becomes more and more important as we grow older and gain perspective on what it takes to do science. I believe the Stowers to be such a place and as such, the Institute is uniquely positioned to become a fountainhead of biomedical research innovation, a place where fundamental problems of biology can be systematically and rigorously dissected, a place where scientists can follow ideas of great substance, whether they are fashionable or not. The Stowers is relatively young, barely 20 years, and what it has accomplished thus far is nothing short of extraordinary. I envision the Institute's research efforts will not only continue to grow in depth and complexity in the years ahead, but also that such efforts will extend into novel areas of inquiry where few would dare to go, while creating new models of how to carry out great science. I consider myself fortunate that in my career I will have a chance to contribute to this unique, collective effort to advance human knowledge (Fig. 5).

As a recognized scientist, you travel to many institutions all around the world. From this advantage viewpoint, how do you see the development of science, and in particular of Developmental Biology, in Latin America?

I see talent overflowing from its scientists at all levels: from students to faculty (Fig. 6). I also see the many difficulties in bridging the obvious gap that exists when it comes to being able to acquire and maintain the new and rapidly evolving technologies necessary for the practice of modern life sciences, including developmental biology. These are, unfortunately, global structural problems of commerce and trade that scientists and institutions of higher learning alone cannot solve. The best we can do, in my opinion, is to create opportunities that permit talented Latin American scientists at all career stages to pursue ideas and generate new knowledge, be it at their home countries or abroad.

What would be your advice to a student in Latin America that is interested in the Developmental Biology field?

Read broadly and with abandon. Identify a problem that robs you of your sleep. Think of ways in which you could address that problem. Think it over again. Run the thought experiments. Visualize what it would take to solve it. Do it again to see if there are any loose ends you did not consider earlier. Read some more. Think some more. Once your knowledge about the problem you have chosen is as complete as it can get and your ideas to tackle it have crystalized, identify a place where you can try to carry out your ideas. Write e-mails, send direct messages, get in touch with those labs. Be persistent, for you are an unknown and not everyone may see the value of your approach. Get used to being told no and/or to be ignored. Persist. You will get through, and once you get through, be convincing with your arguments without being overbearing. And most importantly: be prepared and bring your very best for when you finally get a "yes, we'd like you to join us".

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