Alejandro Sánchez Alvarado: "The real magic is to imagine the experiment and execute it"

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The researcher Alejandro Sánchez Alvarado is one of the greatest experts in the study of the mechanisms involved, cellular and biological, in regeneration in the planaria model

The replacement of differentiated cells is a major challenge for all organisms. Humans, for example, must replace approximately 10 billion cells every day. Despite the importance of regenerative processes for biology and human health, the molecular and cellular mechanisms that drive the restoration of body parts lost to physiological replacement and/or injury remain largely unexplored. This is paradoxical, especially considering that the regeneration of body parts raises important questions about the regulation of polarity, positional identity, and scale and proportion, all of which remain essentially unresolved. Therefore, "the objective of my laboratory is to discover the molecular and cellular mechanisms that support animal regeneration," explained Dr. Alejandro Sánchez Alvarado during his visit to the National Center for Cardiovascular Research to give a seminar. To address this problem, his group is working with the *Schmidtea mediterranea* model. “Planarias are recognized for their regenerative capacity, which is driven by a population of totipotent stem cells”, explains the Scientific Director of the Stowers Institute for Medical Research in Kansas City (USA), "

- ***Your work focuses on the regeneration mechanisms in animals? In which phase is the research right now?***

The problem in regeneration is that it is at a very basic research level because the mechanisms involved, cellular and biological, are almost entirely unknown. Twenty years ago we decided to investigate some animals that do preserve this regeneration process: the planarians. These are tlatworms whose regeneration mechanisms are highly activated: the animal can be amputated into many fragments and each one of them is capable of developing a new complete animal. In our laboratory we use this organism as a vehicle to try to elucidate and dissect the molecular and cellular processes of animal regeneration.

- ***What do these organisms have in common with bigger animals, such as mammals?***

We know that regeneration is widely distributed in the animal kingdom, but this distribution seems almost random. In other words, different organisms that are closely related phylogenetically do not have the same capacity to regenerate: one does and the other does not. The big mystery is why the regeneration capacities of animals are so unevenly distributed in the animal kingdom.

There are two possibilities. The first suggests that each animal 'invented' its own way of regenerating, therefore each species should be studied independently. The other is that it may be that the process of regeneration is ancestral and, in some way, the processes of adaptation or evolution have enhanced or eliminated these mechanisms in organisms.

This conservation allows us to investigate a process that interests us, such as regeneration, in animals that look nothing like us

When we began to observe regeneration in animals, it was not known to what extent these processes existed, for example, in the planaria, these could or could not be shared in more complex animals, such as vertebrates. And it turns out that today we still do not know for sure whether they are related or not, but we do know that the molecules that are executing the regeneration capacity of the planaria are highly conserved throughout the phylogenetic tree. That is to say, our genome has the genes used by the planarians to regenerate. These genes are not specific to these organisms, but rather are very well represented in the animal kingdom.

- ***So, if we have these genes, why don't we have this regeneration mechanism?***

This is what we are studying in these animals and we hope to find the answers and be able to manipulate this process to try to activate these processes in non-regenerative animals.

- ***In other words, we have the tools, but not the instructions on how to activate this mechanism?***

Our organism does have the capacity to regenerate in the sense that we have tissues that are constantly being reconstructed: the skin, hippocampal neurons, the epithelial tissue of the digestive system... We retain a regenerative capacity at the physiological level, but it is not sufficient to compensate for the level of damage from an extensive injury or degenerative disease. In other words, our body has a limited capacity to regenerate. In my opinion, this implies that we do have these processes, but somehow they have been lost in order to maintain our restorative capacity. Human beings can live about 80 years, while other organisms live shorter periods, so they do not require this type of tissue maintenance that is so important for our health. What we think is that there has been a kind of 'repression' in the evolution of our species that has mitigated our regenerative capacity compared to other animals.

- ***In exchange for the capacity to live longer?***

That's one possibility. But there's another, which is that we lost it because it encouraged tumor formation. Regeneration requires cell superproliferation, and when this is abnormal, tumors are generated. It's like a switch: do you want to regenerate or do you want to die? Furthermore, it does not happen in all mammals as it does in man; for example, there are mice, called 'spiny mouse', originating from Africa, that as an adaptation process, when they are attacked by a bird of prey, they are able to detach themselves from their skin to avoid being captured and, subsequently, they regenerate all their skin in just a few weeks. That is something that human beings cannot do. This is an example of a mammal capable of maintaining its capacity to regenerate and also an example of the irregularity in the distribution of these processes. The question is, if mammals share this ancestral genome, why can some do it and others can’t? The difficulty nowadays is to understand why such irregularities in the capacity to regenerate occur.

- ***How does your model serve this purpose?***

The model of the planarias allows us to clarify how cellular potentiality is regulated. All of our cells have essentially the same genetic information. Each cell performs a specific task. But they all have the same DNA, which means that they have a fairly specific capacity for differentiation. Stem cells are undifferentiated cells that can be uni, multi or pluripotent. Most species have stem cells that are pluripotent and possibly totipotent, meaning that a specific cell is capable of producing all the cell types that make up the anatomy of the animal.

The planarias have an abundance of that type of cells, they are at the surface of the skin. They are not hidden, which allows us to benefit from that abundance of stem cells to try to understand how they are able to regulate their potentiality.

Think that if we have a cell that is capable of producing all the tissues, **it allows us to know how the chromatin, the chromosomes**, and even the genes within those chromosomes are being regulated to activate a choreography of genetic expression that allows it to produce specific lineages of particular cells. That is, that a cell is capable of producing the muscle line, the nerve line, the epithelial line, or the digestive system, etc. These are decisions that are made at the molecular level and that we do not yet understand.

We know which transcriptional factors are capable of activating these processes, but it is completely unknown how they are coordinated so that a tumor is not generated, but rather that the appropriate number and type of cells are produced to maintain the form depending on the animal, not only in planarians, but in practically all the organisms that we have studied up until now.

- ***Do these totipotent cells have other organisms?***

Yes, they do, but at more specialized levels. We can obtain multipotential cells capable of producing a large number of cell types, but not all of them. We also have very abundant and very important unipotential cells, such as germ line cells that only produce gametes, the cells that are going to perpetuate the species through fertilization.

Planarias allow us to dissect these processes of regulation of cellular potentiality in a relatively efficient way. This model system allows us to advance a little more than we would have been able to if we had not studied these little animals.

- ***Can a planaria be created from one of these totipotent cells?***

Yes, it is necessary to have a context in which to introduce the cell, but such a cell is capable of restoring the viability and regenerative capacity of the animal. What we have done in the laboratory is to identify technologies that allow us to purify these cells and, by purifying them, we can introduce them into an animal in which all the stem cells have been eliminated, and which are destined to die in two or three weeks because they are not capable of maintaining their tissue.

If we inject one of these cells into this animal, that cell begins to proliferate and produce lineages that will generate all the animal's tissues and, in approximately 60 days, the viability and regenerative capacity of the animal is restored.

This is the kind of exaggeration that we, as biologists, love to research, because it allows us to attack the problem directly; we don't have to separate layers of complexity to reach the center of the problem, but rather, the nucleus is exposed at the surface of the skin, and that is one of the great advantages of being able to do research on organisms that exacerbate these processes.

That is the beauty of being able to study this simpler organism; it allows us to clarify very complex problems

And one of the most profound things that biology has taught us over the last 20, 30 years is the immense genetic and evolutionary conservation that we humans share with all the organisms on the planet.

Dozens of genomes have already been sequenced and all of those genomes are highly conserved. In the sense that you can go to the genome of a planaria, which has lived for millions of years, and when you extract the genome and sequence it, you realize that the order of the genes on the chromosomes is preserved in the same way as the order of genes on the human chromosomes.

We're talking about an evolutionary distance of 700 million years. **Such deep conservation implies that the scope or space that the genome can occupy to produce phenotypes is limited.** Each animal could have evolved with completely different genes or different structures, but no, it turns out that all this genomic sequencing indicates that there was an ancestral organism from which all the organisms that inhabit the planet today supposedly originate.

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It is not difficult to imagine a situation in which one can do this dissection, organize all the parts, put everything back together and, with that process, think about what is happening in other animals as well. It's much easier to look at a limited number of genes, than at the 20,000 genes that exist in the human genome, and see how they are relating to each other.

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- ***Why is basic research so important?***

Producing knowledge has its own merit. This type of research brings us a little closer to technologies that we have not yet invented, to therapeutic options that we have not interpreted, because it is very difficult to invent without knowing; one can invent on the basis of what one knows, but since we do not know to what extent we have understood the biological processes at the most fundamental level, we have problems in generating technologies that may not have side effects or that are effective enough to cure, or eliminate, any type of pathology.

Normally, a large part of our methodologies for attacking diseases, such as cancer, are approaches that have not succeeded in eradicating this type of damage that we humans experience. And the reason is because we do not know, at a very fundamental level, what is the specific and ancestral function of the genes and the genetic processes that keep those tissues viable for so long.

I think that basic research is absolutely necessary to get us a little closer to therapeutic applications. We need to work very hard to be able to elucidate that.

- ***Have you always wanted to be a researcher?***

Since high school. I had an excellent, excellent biology teacher: **Mr. Maldonado**. I thought I was going to be a physicist or study music, but I had this biology teacher who, although I didn't know it at the time, created a very big impact on the way I saw the world.

He taught in a very unorthodox way, instead of forcing things to be memorized, he started the classes with a question. In the first class we had with him, he asked us the following question: "If you had to invent a language, what would be the minimum number of letters you would need?" This is biology, how can it be, I thought. A colleague, who is now a psychiatrist, raised his hand and said: "One, Mr. Maldonado". "Good job", the professor said, "explain that." My colleague explained it and Mr. Maldonado said "ok, all right, you are right, but nature uses 4 letters". That's how he introduced us to DNA. I was very impressed that there was such a powerful capacity for synthesis that it allows you to make a metaphor like that.

When one looks around and observes what surrounds us, which is very little, but at the same time really impressive, -imagine in Venezuela, in the tropics, where there are birds and plants of all kinds-, and one thinks that this diversity that one can see is all based on 4 letters... well, it knocked me down! Then one begins to think that 95 percent of all living beings on the planet are microscopic, and that what we are seeing is just the tip of the iceberg and that all this biological activity is based on 4 nucleotides?... "it really fascinated me."

All the classes were like that; once he explained to us what the structure of DNA was like, the task was to invent a way for DNA to copy itself. This was before the age of the Internet, so you couldn't go to Google and look it up.

So then he explained the Meselson and Stahl experiments [Matthew Meselson and Franklin Stahl explained semiconservative DNA replication], but he did it in a very systematic way. We did the experiment practically on the blackboard and I still haven't forgotten it, so that says it all.

Imagine, being in a marine laboratory [Woods Hole Marine Biological Laboratory] in the United States where I go every summer, and realizing that one of the scientists who was walking in the center was Meselson! To me, it's the most beautiful experiment in the history of biology. I didn't know who he was and we started talking, and then I wondered – is he the same person I studied in high school? He and Stahl came up with the experiment, in that same center, under a tree. He showed me how it was all done and I realized that one of the powers of modern **Evolutionary Biology** is that you can use reasoning to design experiments that take advantage of the experimental vulnerabilities of very complex problems in order to dissect them. That is the power of Evolutionary Biology, of Molecular Biology, which allows us to interpret extremely complex things that, to a certain extent, can be considered magic; but real magic is to imagine the experiment and execute it to demonstrate whether its notions are correct or not. It's marvelous, I was fascinated.

- ***Do you also do that type of teaching work?***

I try to, but it's very difficult to copy Mr. Maldonado. In the summers I teach a biology course and get together with 24 students. I also do it at my institute, I teach PhD students. I try to instill in them the notion of reasoning, get them to think that science is not really about discovering the truth, but rather making things a little less false, because our interpretation is always incomplete.

- ***It's your first visit to the CNIC, what do you think of the center?***

I feel very privileged to be at the CNIC, a center where researchers who are trying to advance in the knowledge of the regeneration process are researching. Of course, it has a very direct association with the capacity of our species to generate therapies and develop processes through which we can mitigate human suffering produced by diseases that we have not yet been able to tame.

Alejandro Sánchez Alvarado gave the Seminar "Understanding the source of regenerative ability in

animals" held at the CNIC invited by Dr. Miguel Torres.