Marcelo Nobrega: "Bioinformatics will be key in the future"

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Dr. Marcelo Nobrega works at his Laboratory of Human Genetics at the University of Chicago (USA) on the architecture and function of genes in their regulatory networks. For Nobrega, understanding these processes is crucial, because it is believed that the malfunction of the regulatory programs of the genes might be the cause of many human diseases, like obesity or diabetes. Dr. Nobrega's team identified what appears to be the real obesity gene, Irx3, which regulates the body mass and body composition. His study was published in *Natura*. His work also focuses on the regulation of genes that control cardiac development and congenital heart disease. Dr. Nobrega gave a seminar at the CNIC entitled "**Regulatory genetic variation and human diseases**", invited by Miguel Manzanares.

- What exactly is your field of research?

I have always been fascinated by the mechanisms and processes that underlie and trigger diseases. After finishing my degree in medicine, I started to train as a researcher and I realized how powerful genetics is in obtaining information about different mechanisms involved in pathologies. That's why I decided to focus my career on the field of genetics. The idea is that if we can compare different

groups of patients with different variations and genetic profiles, this will allow us to investigate the specific mutations of each one. In addition, time plays in our favour because technology is getting better each day; for example, thanks to the Human Genome Project we can analyse the genome of many individuals and obtain information on the genes and the mutations involved in several diseases, like the cardiovascular pathology. And now we know that the mutations are not in the genes but outside of them. 99% of the genome is stable, it doesn't suffer alterations; but in reality, we know very little about what occurs in this "grey area" of the genome. And it is precisely these mutations that make us more susceptible to a heart attack, cancer, diabetes, etc. This is where I develop my work. I work on the design of technologies to relate these mutations, already identified outside the genes, with the specific mechanisms of certain diseases.

- What type of mutations are they?

They are called non-coding mutations. The part of the genome that codifies the proteins involves merely 1% of the genome. The genome has three million letters, but only 30,000 of these letters produce proteins. So what does the rest of the genome do? It is possible that part of the answer to that question lies in its importance to regulate the expression of the genes. For example, each cell of our organism has the genetic information to produce insulin, but only some of the cells of the pancreas do it. Why do only the ones in the pancreas know how to activate this gene if all of our cells have the same genetic code and the same instructions? And the same occurs with the heart. It is fascinating. Somehow, these cells know how to use the different parts of the genome to develop their identity. And it is precisely in the part of the non-coding genome where this information is transmitted to the cells in order for them to activate a certain gene, and others not. We think that when there are mutations in these switches that activate or deactivate genes this balance is lost and that is how diseases are provoked.

- Do you know when, how or why these mutations are activated?

These switches are basically clusters of what is called transcription factor binding sites; they are DNA binding proteins that have the capacity to recruit other proteins to activate or deactivate genes. And what we believe is that these mutations have the capacity to alter or modify these transcription factor binding sites. We believe that when there is a mutation, the transcription factors do not bind to the DNA correctly, and therefore the target gene is neither activated nor repressed. And this has pathological consequences.

- And is this the cause of the origin of diseases, like in the example that was published on the obesity gene?

What we found at that time is a switch inside a gene that activated a gene which everyone thought was the obesity gene. No, in reality it is not the gene that causes obesity, but the switch. It's difficult to understand that it is the mutations of certain mechanisms the ones that activate and convert a good gene into a "bad" one. And, what we know is that the same that happened with the obesity gene is what occurs in many other diseases.

- Could these switches then be converted into pharmacological targets?

Not really, no. However, when we study the genetic causes that favour a greater predisposition to cardiovascular disease, we will definitely find the genes that are involved in such predisposition. And by studying the functions of these genes we will get information on the mechanisms that could become targets for future therapies. But under no circumstances could these be switches.

- What made you orient your professional life to research?

I studied my medical degree in Brazil. In fact, I was a very precocious student, as I began studying it when I was just 15 years old. It was my mother's fault, because she started taking me to school when I was just two years old, and that's why I was so advanced. But, in reality I did not want to study medicine, it was not my dream. I liked biology, physiology… That's why during the first two years of my degree I was very pleased, because everything is very basic. The problem started when we got to the clinic: it was boring. What I liked was knowing how things were produced, the

mechanisms involved and why it could go wrong. Fortunately, I got the opportunity to work in a research laboratory, first at my university in Brazil, and later on, in temporary stays in the USA. I loved what I saw in these laboratories and when I finished my medical degree, I applied for a research program in the USA. And that was 22 years ago. Since 11 years ago I have my own laboratory in Chicago, with a total of 9 researchers working there.

- What is, in your opinion, the one quality that a young researcher should have?

The truth is that the current situation in research has changed a lot. In some cases, for the worse, if we talk about financing, consequently, now you have to be very patient if you want to work in this field because things advance very slowly. For that reason, my principal advice is “don’t give up”. Then there are many other aspects that must be taken into account: we are talking about a very competitive field, so you have to work really hard. You have to give 100% of all your capacity and be very ambitious in your day to day. Ask and ask yourself questions every day and try to give answers. And if you fail, start over again. And another thing that I always insist on is that in the scientific careers there are many corners; not all scientists are going to run a laboratory, there are other options in science: assistant, scientific reporter, work in the industry. Something that I recommend is that in the last years of the doctorate you should decide exactly what you want to do.

The romantic idea of the “Eureka” moment does not exist

- You say that it is a complicated time for research, but also fascinating, right?

That’s right. If we put aside the economic financing, it’s a privilege to research at this moment that we find ourselves in. Right now we have tools and knowledge that just a few years ago was a chimera, especially in the field of genetics and genomics. In fact, we are in a time of transition, or almost revolution. Bioinformatics will be key in the future, and it is already almost now. You cannot be a competitive scientist in the future if you do not master this field. In fact, I do not master it myself, which is why I need to get enough money to attract those experts who do to my laboratory. The programs that do not approach “coding” as a fundamental science work will surely fail.

- Does that mean that in 10 years science as we know it today will be completely different?

We are going to continue using the same technologies that have been developed in the last 10 years but in a more sophisticated way. And precisely thanks to them, we are going to be able to polish the questions that we ask ourselves, which will be more and more complex. And so our research is going to focus on these complex mechanisms in order to redefine our ideas and hypothesis. There are more and more professional experts in bioinformatics analysis, while researchers, like myself, are very experienced, we do not have the training required to analyse those data bases in the right way. As I said before, I try to fill in that “gap” in my laboratory by hiring those professionals in data analysis and make them part of our laboratories. However, in the future, the good researchers will be those that combine these two areas: they will be the ones who will find the most interesting jobs, the ones who will develop innovative areas of knowledge… At least in the next 10 years. Further than that, it is hard to say.

- What is a normal day like in your laboratory?

I must admit that I hate administrative work. I am not very disciplined when it comes to organization, so I try to delegate these tasks. I know it’s a necessary part of my job in order for my laboratory to run well, but I have oriented my career in a way that the most part of my time is “protected”, so I can dedicate a lot of time to my lab. But as part of a community, I still have to devote some hours to administrative work. In my case, it is not more than 5 to 10 hours a week. But, that doesn’t mean that I spend the rest of the time researching, I actually spend most of it writing scientific articles, reading and acting as a mentor for my students

- Do you remember any particularly important or disappointing moment in your career?

The scientific field is full of failures. The day to day is monotonous, boring and sometimes frustrating. You have to be obsessed with what you're doing, but it has to be that way. It's the only way to go forward and solve problems, and little by little, continue progressing. The romantic idea of the "Eureka" moment, does not exist, at least I've never experienced it before. But there are little moments of intellectual satisfaction that make it possible, step by step, for all the pieces of research to come together. And I think people should be pleased with such a special job. The intellectual satisfaction comes from the possibility of solving problems of nature that nobody has succeeded in doing so until now. And, if you do not have that capacity, it will be difficult to make researching your career. Passion must be constant.

- **What is your opinion of CNIC?**

I had never been at CNIC, but I have always wanted to come. I have informally collaborated with my host Miguel Manzanares, many times before and from no won we are going to establish a formal collaboration between our laboratories. Nobody has the experience or knowledge necessary to do everything alone, and most certainly, Miguel's group is one with whom we will collaborate.

- ***Seminario "Regulatory genetic variation and human diseases", invited by Miguel Manzanares.***

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