Alejo Rodríguez-Fraticelli: “The risk of cell therapies is not being able to do them fast enough in a scalable way”

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Alejo E. Rodríguez-Fraticelli was born in Argentina. In 2008, he moved to Madrid, where he studied biochemistry, and obtained his doctorate in developmental and cell biology from the Universidad Autónoma de Madrid in 2014. He subsequently moved to Boston (USA) to pursue work on cell fate determination in haematopoiesis at Harvard University and Boston Children's Hospital. During his post-doctoral fellowship, Alejo Rodríguez-Fraticelli worked on developing methods for single cell lineage tracing in the haematopoietic system. His research has enabled him to establish a revolutionary way of connecting cellular states with cellular fates through clonal analysis to determine how variations in cellular states contribute to cell phenotypic heterogeneity. Since 2021, Alejo Rodríguez-Fraticelli has been group leader at the Instituto de Investigación Biomédica (IRB Barcelona) where he heads the **Quantitative Stem Cell Dynamics laboratory.** The staff on his team represent a diverse group with different ethnic backgrounds and philosophical approaches who have a passion for sharing resources and knowledge.

- ***Where does your interest in science come from?***

I studied in Argentina. I moved to Spain to pursue my scientific career. Before I completed my thesis, I had already done a couple of internships in the United States, and eventually I spent seven years there working at the University of Harvard campus and in Boston Children's Hospital.

I worked in the Hospital's scientific area, which is internationally recognised for having started the treatment of paediatric cancer over 60 years ago. It is one of the best scientific environments to study something that seems fascinating to me, the origin of tumours and blood stem cells.

There are many cancers that originate in the blood cells but, when we began to study and understand the heterogeneity in haematopoietic cells, we realised that, in essence, this heterogeneity not only plays a role in cancer, but also has a part in all diseases: different types of immune and inflammatory diseases and even in cardiovascular diseases.

I believe that the work I did, which is what made it possible for me to set up my own research group, really highlights the fact that we need to understand biology from a new perspective: Instead of treating tissues, the cells of the tissues, as uniformly homogeneous populations that behave in a more or less uniform way, we have seen that this apparent uniformity is composed of a multiplicity of cellular behaviours that are highly defined and dominated by the origins of the cells themselves. This means that the cells that gave rise to these populations during their development have a great influence on their behaviour, response and, in many contexts, on disease.

This has opened our eyes, and now we are starting to understand this variation, which we all knew was there, but had put to one side. But now we have hit on one of the keys, which is that there is a highly intrinsic component to each of these cells, which is heritable and therefore propagates through cellular generations. When a cell divides, for instance, when we develop, and in the maintenance of our tissues, the daughter cells inherit characteristics that we have not fully determined, but which greatly define their functioning.

And although we have discovered it in blood, we believe this is probably valid for all of the cells in our organism, from the heart to the brain, liver, bones, etc. But due to the available tools, it is easier to apply to blood cells.

- ***So, the probability of having a disease is inherited through cell lineage?***

It is completely possible that the only reason that a cell of mutates and causes a cancer in you, whereas for me it does not, is due to cell lineage. Obviously, there is a very strong component of other factors: environmental, genetic, etc… We know that there are many processes, but we had never thought of this as a defining factor. I think this will help explain many things about biology that we haven't been able to explain so far. This is a growth field; at the moment there are 20 groups worldwide studying these things in this way, but there will be 100 of us by the end of the year, and thousands by the end of the decade.

In coming years, we will see therapies with modified immune cells to treat diseases from Alzheimer's to heart or kidney diseases. There will be an explosion of immunotherapies precisely because they are well tolerated by our body

- ***So, the €1.5 million of European Research Council (ERC) funding you were awarded is for research along these lines?***

We want to understand a very important process: ageing. Right now, we see ageing as something relatively stochastic, and we wonder whether there is something intrinsic in the process that defines which cells will age worst. If this is the case, we could eliminate them before, we could cut off the problem at the root and not wait until we get old to tackle ageing. This is very interesting for many reasons: first, because it should be a more or less specific therapy, not one aimed at all of the cells in the body, but only at those which are predetermined to age. And also, because -as we all know- prevention is always easier than a cure.
We want to study whether ageing is really something we can foresee at cellular level and, therefore, treat.

- ***What treatment options would be possible?***

There are several possibilities. The first is to find routes, mechanisms that are present in these cells that age, which would allow us to minimise the impact of their impaired function so that, for instance, they don't spread. In the end, one of the great problems we face with ageing is that certain cell populations accumulate in our organism. We know that in haematopoiesis this type of maintaining populations that are not functional increases over time, and we want to see whether we can in fact identify the mechanisms that could avert this expansion.

And the other is with cell therapy, which means finding a way of modifying "aged" cells, maybe by extracting them from the organism and remodelling them, for instance, using gene or epigenetic therapy.

And, of course, the possibility also exists of not directly using haematopoietic cells but having cell therapy based on immunotherapy.

Immunotherapy has had great success in certain cancers; however, the main bottleneck when it comes to gaining approval for drugs is the risk that they may have for the patients who undergo treatment. The fact that so many cancer patients have been successfully treated with cell immunotherapy opens the door to applying these therapies as safe and tolerable for other types of disease. Many studies already exist, and in the coming years we will see therapies with modified immune cells to treat diseases from Alzheimer's to heart or kidney diseases. There will be an explosion of immunotherapies precisely because they are well tolerated by our body.

- ***But maybe what companies and governments see is the cost of treatment for each patient??***

That is the risk of cell therapies: not being able to achieve them fast enough in a scalable way. The main hurdle we need to overcome with cell therapies is that they are the patient's own cells. And that brings problems: it is a slow process and more costly. If we could, like any other product, make them universal, they would be more accessible.

- ***Public hospitals already exist, like Barcelona's Hospital Clínic, which have their own line of cell therapy. Can that make things easier?***

But the cells are still from the patients themselves. At the Hospital Clinic de Barcelona they realised that things can be done more quickly if they are all done in-house. That means they have the whole

pipeline centralised. And pharmaceutical companies know this, because before, they had a distributed assembly line, whereas now they are integrating them in a single production line. Universal cells are going to be the key, but that cell will be much stronger if it has more applications and will even be cheaper. We need to find the way to use cell therapies in a more ubiquitous way. And that day will come, especially due to their biosafety.

I'm certain that within the next decade or two there will be many developments in this field, and in the delivery of drugs to specific sites. We tend to think that it has to be lymphocytes, the immune cells, which perform this function, but we can also reach other cells to secrete drugs that are useful wherever they are necessary. A lot of attention is being paid to this field, but obviously there is still a lot of science to do.

- ***Your work as a scientist is very aimed at clinical practice…***

I have always like research more than the medical part. I have always been fascinated by the technological part, and when I was little, I was a fan of science fiction; I adored Isaac Asimov and Michael Crichton stories. I loved them! And I've always really liked that biotechnology aspect. I think that I'm a child of the genome generation; what I mean is that I'm from the generation that began to choose what course to do at the exact moment the genome was published and suddenly, biology changed forever. A discipline that was less objective than it is today changed radically with the advent of sequencing technologies. We went from an era, I think of it as the dark ages of biology, when nobody knew what there is and we were blindly stumbling around finding functions, mechanisms and genes based on mutations, and suddenly, the human genome was published. Everything is there to see, everything that makes us what we are. So, if everything is there, we must be able to decipher it.

And for many of us, who lived this revolution at a time when we had to decide what we wanted to do, this caused a great impact, and my decision was very clear to me: this is the next great challenge for humanity for the next 100 years..
We have to create a much stronger theoretical basis because the science being practised is increasingly multidisciplinary. You can't hope to reach a solution focusing exclusively on your microworld… things don't work that way

- ***Why biology?***

Like many other people, obviously, I had a couple of key moments, which were interactions with scientists that opened my eyes. In my case, from quite early on I began to be passionate about cell biology, the mechanisms related with development; I mean, how cells change their form or function. We go from being a single cell that has practically no identity to the diversity of trillions of cells that compose our organism. This has always fascinated me. At first, I was really attracted by the world of Drosophila (fruit flies). And I began to be fascinated by certain questions: development patterns, segmentation genes, and so on. Later, the most important question for me was knowing how these processes are regulated through the genome. And I knew that I wanted to do post-doctoral research to learn sequencing techniques, understand the functions and expression of genes, and work more closely in that field. I chose a laboratory to pursue my studies, collaborating with Fernando Camargo in the Children's Hospital of Boston, which at that time was starting to develop this new way of analysing cell histories, cell by cell, something that had not been technologically possible before. I really liked the idea of developing new technologies, of getting my teeth into topics of gene dynamics and expression.

From that time on, and for me when I set up my own laboratory, it was essential to understand the consequences of those processes. Now we have more information, the objective is to find new treatments.

- ***You talk about the clinical application of your research. Do you think it is important to have worked in a hospital to understand the idea of translating basic***

science?

For certain, because it didn't happen for me at university when I was doing my thesis in a much more academic environment. Working in a hospital, being in contact with patients, receiving funding from foundations, many of which are also formed of families or patients, changed my perspective on many things. For instance, I discovered that scientific enterprise is not only to do with scientists, rather it's a social undertaking of all the individuals in a society, who are the people that drive progress in a society. I was profoundly affected by the time I spent working at the Cystic Fibrosis Foundation on the development of the first therapies. There was practically no solution for patients with this disease, and there I saw how they, through the Foundation and with the creation of scientific projects funded by the Foundation, generated a billion dollar business, or financed a large part of it, and treated thousands of patients with cystic fibrosis all over the world. Having lived that, and seeing how supporting a scientific idea can create something so spectacular, profoundly changed my life.

Until that time, I saw things in isolation, as if they were not part of a whole; there was academic science, and then there was translational science, which were two distinct things. And that experience made me see that it wasn't like that; the patients were almost as involved as you, or even more so, in the molecular mechanisms, the biological bases, etc. and wanted to know exactly what was happening to their son, daughter, sister or mother. And that really opened my mind; there were not two different worlds, only a single continuum.

I think it is everybody's obligation, but we need to explain it well. For a person like me, who never had a biomedical vocation, having taken that decision helped me refine my message, to know how to explain things to patients and tell them how what we are doing may someday be a solution.

What's more, lots of these people don't seek solutions just for themselves or their families, they don't want it to happen to anyone else. At the end of the day, that is the hope behind everything we do.

- ***And does that in some way define the people that make up your group?***

There are people who have a very strong translational vocation complemented with a theoretical basis, but they are few. This, I think, reflects an educational problem that we have nowadays, which is too specialised and doesn't provide the strong theoretical basis that serves as an anchor, providing the academic knowledge necessary to face multidisciplinary problems. In the end, you are a specialist in a specific subject. This is a serious problem that we need to tackle from an educational point of view. We have to create a much stronger theoretical basis, because increasingly the science we practise is very multidisciplinary. One day you are a physicist, the next a mathematician or a physician. And you have to work on everything, you have to be able to, at least, integrate that knowledge. You can't hope to reach a solution to a problem focusing exclusively on your microworld of knowledge, because things don't work that way.

In my group, we try to compensate the disadvantages of the educational and academic system by contracting people from different disciplines to create a diverse, dynamic group. In my opinion, science is better that way, more productive in all aspects. And I'm not just talking about diversity of academic training, I mean different origins, cultures, nations and sexes. All of this generates a more diverse group that is more productive, has ideas that are more original and provides more exciting interactions that produce unexpected results.

- ***One of the aspects that some researchers who have visited CNIC mention is the very small number of foreign post-docs in Spain...***

We have a big problem in this country, which is that no system exists to recruit talent. We don't have a legal system that protects and promotes the attraction of talent. There should be a system of protection, as there is in other European countries, with mechanisms that are much more flexible for

recruiting talent.

We have an immense population crisis; in 20 or 30 years more than half of the population will practically be at retirement age. There is an absolutely terrible crisis and if we don’t bring in international talent we will pay dearly.

- ***Is the new Science Law any help?***

No, it is a terribly national law, and I understand that. There is a brain drain crisis that has to be mitigated and contained, because the dramatic truth is that the most talented people in the country are pursuing their careers abroad. But, in my opinion, the problem of attracting foreign talent is possibly even more serious. There are a great many jobs for talented people from abroad who want to come here, but they don’t come due to bureaucratic obstacles. It is senseless.

We need to bear in mind that before, science went more slowly. But now it is a race, a brutal race. Having, or not having, a patent worth multiple billions may entirely depend on whether that new machine on the market can be purchased next month or not until next year. This is what is completely changing the rules of the game. There is a lot of competition, and we need rules to be competitive.

Alejo Rodríguez-Fraticelli participated in the CNIC Seminar “Clonal determinants of blood stem cell heterogeneity,” at the invitation of Rui Benedito.