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WHAT'S ON
INSIDE SCIENCE
CNIC & SOCIETY

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Dr. Valentín Fuster, General Director of Carlos III National Centre for Cardiovascular Research (CNIC)

THE RACE OF RESEARCH

After getting my degree at the University of Barcelona and following the advice of my first mentor, **Dr. Pedro Farreras Valentí**, author of the classic Spanish Internal Medicine textbook, I decided to spend every summer outside of Spain to learn basic science.

It was in Liverpool, where I went to study with a well-known pathologist, Professor **Harold Sheehan**, that I decided what I was going to do my thesis on. All because of a slide of a blood clot filled with platelets taken from the coronary artery of a patient who had died of a heart attack. When I asked why he had died **Sheehan** told me that no one knew, and at the same time, he suggested that I do my thesis on this topic. He wanted to know what a blood clot and platelets had to do with a heart attack. And that's exactly what I did; I went to the University of Edinburgh to do my PhD, which I later presented in Spain.

I know very well that to be a good student, as **Dr. Guillermo Oliver** rightly says in this issue of CNIC Pulse, one must be curious and passionate. And this is something you are born with; you either have it or you don't. Not everyone can be a researcher. Then, you need the environment and the tutoring, two aspects that are closely interconnected. The next step is very stressful: it's called a research career, and it comes with a lot of frustrations: experiments that don't work, projects that don't get accepted, grants that aren't obtained, etc. All this is a crucial test that helps define who will be a researcher and who will not. If this stress test is overcome, and one continues with resilience, it can probably be achieved.

But to be a researcher you have to have something more intuitive. When I gave up tennis, I had the intuition that I was not born to do that, I was not going to be the next Rafael Nadal. But if you really are born curious about research and have the right orientation, I think you can overcome these stress tests, frustrations and setbacks. And that means you were born to do it. These setbacks help to mature, and this is very positive because it indicates that you are on the right track.

CNIC PHD OFFICE, AT THE SERVICE OF STUDENTS

The CNIC's PhD Office aims to become a forum of support, guidance and scientific growth for all doctoral students enrolled in the CNIC Pre-Doctoral Program, regardless of their university affiliation or source of funding.

The office, coordinated by **Dr. Jorge Alegre**, head of the Molecular Mechanics of the Cardiovascular System Group, also has two permanent members: **Dr. Beatriz Ferreiro**, head of the CNIC's Office of Scientific Management, and **Dr. Ángel Ciprés**, member of the Research Office, as well as two doctoral students, a senior one and junior one. The representatives of the doctoral students in the office are elected annually through a vote where the candidates make a small electoral campaign, also helping the diffusion among the Predocs.

The office is thought of as an internal work group of the CNIC. It has a specific section on the intranet in the training

section, which has been presented to students. In addition, an open day has also been held.

At the same time, a welcome document for new PhD students promoted by the pre-doctoral office is being prepared too, with the aim of helping their integration into the CNIC, the PhD program and the rest of the pre-doctoral community.

The contribution of PhD students is fundamental to the CNIC's mission. "PhD students are an important part of the CNIC staff, with the particularity of being trainees," assure Inés Martínez and Ignacio Heras, the first students to join the office.

Up until now, the pre-doctoral community, on which a large part of the CNIC's research activity falls, did not have a body that would coordinate the specific scientific needs of the pre-doctoral researcher within the CNIC. For this reason, the current students in the Doctoral Office, Laura Lalaguna Díaz and Diego Calzada, assure that the office "can be of great help in the initial integration of Predoc students, giving support and promoting the creation of opportunities in their personal and professional development during this period and, in general, looking out for their interests."

Both Inés and Ignacio consider that this body is necessary because "it can handle two challenges that the Predoc group has at the CNIC: on the one hand, to improve integration into the institution and, on the other, to expand the training offer that the CNIC currently provides to PhD students."

For example, they say, many students have doubts about how to make use of the training money available to them, "either from different external sources of financing or from the CNIC training account, because the procedures and conditions are not very clear." In this sense, they point out, "the office is working to create simpler guidelines that make day-to-day life easier for students." **Dr. Jorge Alegre** adds that this simplification will have a positive impact on the operation of various CNIC departments.

MAIN REQUESTS

Inés and Ignacio point out that among the main requests received at the office, are the mentoring programs for senior scientists for students, apart from the thesis committee of the Predoctoral Program. In addition, "some students have proposed social or sports activities by and for students with the aim of promoting interaction."

That said, although a large-scale collection of proposals and/or needs of the pre-doctoral community is still pending, Laura and Diego acknowledge, "there are a series of common points on which the office should focus on." These are:

1. Open a channel of direct communication to collect all the proposals, aspects to improve or initiatives of the pre-doctoral community and safeguard their interests.
2. Provide professional development opportunities and activities.
3. Promote mental health and social relations among the Predoc community.
4. Assist and guide in the administrative processes of the Predoc activity (use of training funds, welcome guide...).

"One of the most advanced proposals is the creation of a welcome document for doctoral students who join the CNIC. In it we have collected information on the procedure of the predoctoral program and the organization of the center, advice from former CNIC Predoc students and other information and resources that we consider useful in this first stage," advances Laura Lalaguna. "Furthermore, we have begun to propose some informal activity with researchers aimed at motivating and bringing different scientific careers closer to the predocs," adds Diego Calzada.

In general, studying a PhD is a very enriching and rewarding experience, but no one can deny that it is also associated with a series of difficulties: some directly related to the scientific project and others that are more general.

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In regards to the first ones, the PhD is demanding and often frustrating (stalled projects, experiments that don't work out...), with the added-on stress caused by knowing that you have a limited time to complete your project successfully. Particularly, the CNIC also pursues scientific excellence that entails an increased complexity of the projects and with it an increased level of demand.

Doing a PhD requires developing skills in time management, critical thinking, writing, presentation, etc. "It is a constant learning process that is usually accompanied by frustration and stress," says Laura Lalaguna.

The academic career is very competitive. In a center of excellence like the CNIC, we work in a very demanding environment. The pressure to publish in high-impact magazines affects both group leaders and doctoral students, and this can affect our mental health, point out the members of the PhD Office.

Furthermore, they also add, "the doctoral students have obligations to the university they belong to, the organization from which they receive funding and the CNIC pre-doctoral program. These obligations are usually evaluation procedures, follow-up or registration procedures that must be kept in mind, which add to the multiple deadlines that add stress to the equation."

An opinion shared among the pre-doctoral group is the need to improve the training program better adapted to the students' needs, such as optional basic training courses in technical skills or transversal activities.

Inés Martínez and Ignacio Heras detail that among the actions that have been planned, one of the office's tasks has been to update the distribution list of CNIC pre-doctoral students. This has been done to facilitate the dissemination of information within the group, including, to as much extent as possible, pre-doctoral students who work at the CNIC and have an agreement with the CNIC, but are linked to other institutions

In addition, "this line of work includes increasing the participation of CNIC pre-doctoral students in the selection of seminars and guest scientists; as well as the launch of a line of seminars directly aimed at students, such as the one given by the researcher **Amelia Escolano**," points out Inés Martínez.

The office is currently organizing an active collection of proposals, although at the moment they have mostly received questions about administrative procedures and some proposals for complementary activities.

During the completion of their thesis, both Inés and Ignacio identified certain shortcomings and problems that affect a large part of the students. "Participating in the resolution of these problems will improve the experience of writing a doctoral thesis at the CNIC, and collaborating with this seems rewarding to us," they indicate.

"I think it will be an enriching experience," agree Laura Lalaguna and Diego Calzada. "In addition to exchanging ideas, listening to, and interacting with many members of the predoctoral community, it is comforting to know that we can take small steps to improve the predoctoral stage at the CNIC for ourselves and/or those who come after," they state.

The CNIC Predoctoral Program makes it possible for doctoral students to have a support and follow-up committee for their thesis. This committee is made up of the thesis director, another CNIC researcher and an expert from outside the Center. All predoctoral students complete the Frontiers in Cardiovascular Research course organized by the CNIC in collaboration with the UAM (Autónoma University of Madrid)

Functions of the **DOCTORAL OFFICE**

- Provide support and follow-up on the progress of CNIC doctoral students, particularly in relation to the actions described in the CNIC Pre-Doctoral Program (for example, organization and meetings of the thesis committee...).
- Facilitate the tutoring of CNIC doctoral students.
- Make proposals to other scientific and management bodies of the CNIC in scientific and training matters and activities that are relevant for doctoral students.
- Channel the proposals of CNIC doctoral students aimed at improving training at the CNIC.
- Ensure that the office is known by current and future doctoral students by maintaining a document on the CNIC intranet and website, which will include a scientific welcome to the CNIC, and the updated list of members of the office. With the same objective, the office will deliver an annual seminar for new and future doctoral students to present the office.
- Provide scientific mediation in the development of doctoral thesis projects.
- Advise the scientific direction of the CNIC on relevant issues for doctoral training and professional development of doctoral students.
- Provide other CNIC departments with information related to the CNIC Predoctoral Program.
- Promote the exchange of scientific experiences and career development between current and past doctoral students, and members of the CNIC Doctoral Office. ■

VISITING RESEARCHERS AT THE CNIC

SINCE 2013, THE JESÚS SERRA FOUNDATION AND THE CNIC, HAVE PARTICIPATED IN **A PROGRAM TO ATTRACT PRESTIGIOUS RESEARCHERS TO THE CNIC**

The international prestige that science has accomplished in Spain, together with the quality of its studies and initiatives and the results obtained, allows it to continue attracting the attention of important researchers, who visit the CNIC from the most diverse parts of the world.

Convinced of the importance of fostering interaction in the field of research to contribute to the advancement of science, the Jesús Serra Foundation collaborates with the CNIC - where many prestigious researchers come to visit, within the framework of the Jesús Serra Foundation Visiting Researchers program.

This program consists of bringing scientists of international prestige to carry out stays in Spanish research centers, with the objective that they can, on the one hand, deepen the scientific relationship of the host research group with that of the center of origin of the researcher, and, on the other, promote new lines of action based on new scientific interests.

In 2013, the Jesús Serra Foundation and the CNIC signed a collaboration agreement in the Visiting Researchers program. With this, the intention is to attract the presence of researchers of international prestige who are willing to stay between two to six months, and work on the projects the CNIC has up and running.

The Visiting Researchers program, which began its journey in 2008, is widely recognized in the area of scientific research, thanks to the work carried out by the Foundation and the support it offers to institutions and organizations to advance on projects that they work on. "We are aware of the current situation and we believe that thanks to programs such as Visiting Researchers we can ensure that many research projects can continue and do not have to be paralyzed due to lack of resources," says **Federico Halpern**, President of the Jesús Serra Foundation.

After the standstill caused by the COVID-19 pandemic, in 2022 the Jesús Serra Foundation and the CNIC resumed their collaboration and introduced the scientists participating in this program.

On this occasion, the conference included the intervention of the three visiting researchers, **Guillermo Oliver**, **Benedetta Izzi** and **Raffaele Strippoli**. Also participating, on behalf of the CNIC, were the scientific directors **Borja**

Ibáñez and **Vicente Andrés** and the managing director **Alberto Sanz**. And, participating on behalf of the Jesús Serra Foundation were **Laura Halpern**, vice president, **Ignacio Gallardo-Bravo**, general director, and **Susana Codina**, deputy director.

Until now, six scientists have already participated in this program. In addition to **Guillermo Oliver**, the researchers are **Benedetta Izzi** and **Raffaele Strippoli**, **Sandeep V. Pandit**, **Stuart Pocock** and **Gabriel Núñez**.

"At the CNIC we like to attract talent in the search for excellence in cardiovascular research. For this reason, the Visiting Researchers program of the Jesús Serra Foundation is especially attractive for the philosophy of the center that I manage. I am sure that great things will come out of this collaboration", underlines the General Director of the CNIC, **Dr. Valentín Fuster**.

SANDEEP PANDIT

Dr. Sandeep Pandit is an expert on arrhythmias from the University of Michigan (USA). **Dr. Pandit** was the first protagonist of the Visiting Researchers program. During his three-month stay at the CNIC, **Dr. Pandit** worked closely with **Dr. David Filgueiras**, head of the group of Advanced Development on Mechanisms and Therapies of Arrhythmias. There are two projects in which **Dr. Pandit** closely collaborated in: improving signal processing methods, as a way to improve the understanding of arrhythmias, and testing new drugs against the disease, especially in experimental models.

STUART POCOCK

Dr. Stuart Pocock, director of the Department of Medical Statistics at the London School of Medicine. Together with **Dr. Borja Ibáñez**, they directed the collaboration project "Statistics on CNIC research projects."

The collaboration focused on various clinical trials, observational studies, etc. He is a tutor for the interns of the CNIC Cardiojoven Training Program (in collaboration with the SEC- Spanish Society of Cardiology). The intern in 2019 was **Dr. Xavier Rosselló**.

GABRIEL NÚÑEZ

He is a professor in the Department of Pathology at the University of Michigan (USA) and is recognized as one of the leading experts in gastrointestinal and systemic inflammation, host-microbe interactions, and mucosal immunology. Together with **Dr. Andrés Hidalgo** he worked on the study of the role of neutrophils in bacterial infection and tissue damage, and with **Dr. José Antonio Enríquez** he carried out studies with genetic models of the role of mitochondrial metabolism in the antimicrobial function of neutrophils.

RAFFAELE STRIPPOLI

Dr. Raffaele Strippoli is an expert on molecular mechanisms of fibrosis, from the University of Rome Sapienza (Italy). **Dr. Strippoli** did his postdoctoral studies at the CNIC and has been actively collaborating with the CNIC for many years. During his stay at the CNIC as a researcher in the Visiting Researchers program, **Dr. Strippoli** is working closely with **Dr. Miguel Ángel del Pozo**, main researcher of the laboratory of Mechanoadaptation and Caveolae Biology. Specifically, **Dr. Strippoli** is collaborating in a research project that analyzes the role of a plasma membrane protein, caveolin, in determining changes in the plasticity of endothelial cells exposed to mechanical stimuli such as alterations in vascular flow, with implications in the genesis and progression of atherosclerosis.

BENEDETTA IZZI

Dr. Benedetta Izzi, from IRCCS Neuromed (Italy), is an expert on genomics and its relationship with environmental and lifestyle factors involved in cardiovascular disease. During her six-month stay at the CNIC, **Dr. Izzi** worked with **Dr. José Javier Fuster**'s team in the Hematovascular Physiopathology laboratory.

The projects in which she collaborated most actively covered two areas: first, the characterization of mutations associated with clonal hematopoiesis and their interaction with epigenetics; secondly, the validation at the CNIC of new markers of subclinical inflammation in humans, previously developed at IRCCS Neuromed. ■

FEINBERG CARDIOVASCULAR AND RENAL RESEARCH INSTITUTE
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CHICAGO (UNITED STATES)

Guillermo Oliver

"THE POSTDOC CAN BE THE BEST EXPERIENCE OF YOUR PROFESSIONAL LIFE"

Dr. Guillermo Oliver's Laboratory focuses on understanding how each type of cell and organ acquires all its specific and unique morphological and functional characteristics during embryogenesis. His goal is to dissect the different cellular and molecular processes that make each organ unique and perfect. Dr. Oliver has participated in the Visiting Researcher Program of the Jesús Serra Foundation at the CNIC.

How did you find out about the Visiting Researcher Program of the Jesús Serra Foundation?

Thanks to my friendship with **Miguel Torres**, which dates back to 1992. We were together at the Max Planck Institute (Germany) and we maintained our friendship throughout the years, which has led us to collaborate on several different projects of mutual interest. The original idea was to come in 2021, but due to COVID it had to be postponed to 2022.

It has been a wonderful experience. I have interacted with many people with varied scientific interests and, in particular, I highlight my conversations with students and my participation in various institutional seminars and groups. For me it has been most satisfying, and I think for them too. And not only because we have addressed scientific issues, but more importantly other aspects related to the scientific career, the future of science in Spain, etc. I have been able to meet very com-

mitted students, but also others who are very fearful of future job possibilities.
Furthermore, I'm positive that my interactions with various groups at the CNIC will make future collaborations possible in the near future.

How has your relationship been with the students at the CNIC?

I've realized that the current generation of students is completely different from mine. I come from a small country, Uruguay, and when I was a student there were very few opportunities to do science, and I knew that I had to leave my country in order to be able to advance in my scientific career. Unfortunately, from my interactions with the students at CNIC, I have noticed that they face a lot of uncertainty when it comes to work options in the scientific field. Many of them are amazed by the fact that we have been able to maintain the passion for science despite all the difficulties that we have faced. Although they share this passion, they want to be able to balance it better with other important things in life. Their priorities are different. Where is the formula? They have asked me. Many of them don't consider it a priority to leave Spain to do a Postdoc, because they think that if they go abroad, it will be very difficult, if not impossible, to get a stable job in the scientific field in Spain. And that worried me and made

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me sad. Undoubtedly, the CNIC has some of the best students in Spain. They are brilliant and I have been very impressed when speaking to them. But many of them have important doubts regarding the possibility of finding a job in Spain when they return, as well as the difficulties in obtaining funding.
Without a doubt, it is not easy to get a job in Spain, let's be realistic, but it isn't easy in any part of the world; the competition has been and will continue to be very hard. But what I tell them is to at least give themselves the chance, after 5 years of doing a PhD to do a Postdoc, if that's what they want they should go for it, so they don't regret it later. What I suggest is that they do a Postdoc and then decide. The Postdoc can be the best experience of their professional life. Some are hesitant and think about pursuing their career in the biotech and pharmaceutical industry. What industry? I tell them. In Spain it almost doesn't exist. Also, I get the impression that many have a very naive concept of what it is to work in the industry. Very few are going to be the CEOS, and the truth is that the majority are just going to be "using a pipette." And for that you don't need a PhD. With this I do not mean to say that all of them should be scientists, but then, why did they spend 5 years doing a PhD? I am proud that I have convinced at least two who were very doubtful at first and are now going to do a Postdoc abroad.

Which do you think are their main concerns?

There are many reasons: it is partly the country, partly the institution, and it is also the way the students themselves think about their future. Undoubtedly there is a cultural, economic issue, the fear of leaving family, friends, country since many still live with their parents. In Spain, as in my country, students don't have the habit of leaving home when they start University, like in the USA. What is more, I think it might also have to do with comfort; perhaps some decided to start a PhD because it offered a decent salary but the passion needed to be a scientist was not there from the beginning. It is possible that mine and **Miguel** [**Torres**'] generation were very naive and the only thing that we cared about was the scientific passion; the rest, that is, getting a job and a decent salary came from a lot of effort and dedication. I understand when young people today want to have a more balanced personal and family life but unfortunately science is very selfish in that sense.
My suggestion to the students: if you don't try, then you will always be in doubt. I am concerned about the fact that human capital as rich as that of the CNIC could be lost.
When **Miguel** [**Torres**] and I met, we both went with our families and we didn't speak German. It was tough, but I wouldn't change that experience for anything. I always say that the Postdoc experience is unique and it is the best moment of the academic period. As a student, you are a student; when you are a group leader, you have a lot of bureaucratic tasks, paperwork, which is horrible; but as a postdoc, it's the only time in your life that you get paid to do what you love and you don't have major responsibilities (sometimes a family). Furthermore, the future depends on you, on the effort, the hours that you dedicate to it is up to you, because it is for your future.
One problem that I have noticed at the CNIC is that there are very few foreign postdocs here, which surprises me, being it a first-class institution. I think that if the students were surrounded by foreign Postdoc students, they would have another vision. I can't find any other explanation than that they are afraid of speaking Spanish. A center like the CNIC, and in Madrid, should be more than attractive for a postdoc.
When a doctoral student decides to go do a Postdoc, they are convinced that they want to succeed and that enthusiasm and persistence is contagious. In contrast, when you only have students with many doubts and who are negative about the scientific future, a current of pessimistic feedback is generated.
Many students have told me that they are stressed. And I ask them, is there any job where this doesn't happen? Obviously, their vision of life is different, with an understandably greater balance between their personal and professional life; but if you have the passion to do science, you have to make an effort and find how to achieve that balance.
Coincidentally, during my stay, a group has been formed at CNIC to advise and interact with students.

Your group is a leader in embryonic development biology. In recent years there has been increasing talk of the possibility of regenerating the heart. How realistic is this line of work?

The dogma in the field of the heart is how to repair the heart after a heart attack. That is clearly the one-million-dollar question. We all know that the heart does not repair itself, in the sense that there is no proliferation of cardiomyocytes.

Many scientific groups are now working with stem cells as a way to generate new cardiomyocytes and induce proliferation. The problem with stem cells is that they can have unwanted side effects, as is well known.

Five or six years ago we began to have more knowledge about the lymphatic vasculature. It is known that, after a heart attack, the lymphatic vessels invade the affected region and their effect is that they protect the heart and improve cardiac function.

In 2020, we published in ***Nature*** magazine, a study that showed that lymphatic cells secrete factors, specifically in this case a protein called relin. This protein has a triple effect.

Firstly, during mouse embryonic development for the heart to grow to the normal size: when there is no relin, the heart is 1/3 smaller, which is an absolutely surprising result, because we never thought that the lymphatics could have that function.

> "My suggestion to the students: if you don't try, then you will always be in doubt. I am concerned about the fact that human capital as rich as that of the CNIC could be lost"

In addition, we saw that relin is also required for the regeneration and repair of the mouse heart. That is, it is important to help regeneration, very important for repair in adults after a heart attack. We have seen that if we put relin in the heart at the time of the heart attack, cardiac activity improves, and if we remove it, it worsens.

And, this occurs not because it improves the proliferation of cardiomyocytes, but because, in our case, what relin does is reduce cardiomyocyte death and decrease the infarcted area, and this consequently improved heart function. This does not mean that the lymphatics do not fulfill their traditional functions, like removing dead cells and circulating immune cells, but a very important function is to produce relin that reduces cell death and heart attacks. The question was - how are the new lymphatics formed? And that is what this new article that we recently published in ***The Journal of Clinical Investigation (JCI)*** explained, by showing that there is a protein, VEGFC, which is essential for stimulating the growth of the lymphatics, which is induced in macrophages when they trap cardiomyocytes, which are dying in the infarcted area. Those new lymphatics produce relin.

The important thing about this article was that it closed the circle. We now know that when there is heart damage, macrophages appear, which bring this VEGFC protein, and this protein causes the lymphatics to grow in the infarcted area, and these new lymphatics have a double function: to produce relin, which reduces cell death and the infarcted area, and on the other hand the classic immunological function that is to bring immune cells.

Additionally, we think that this occurs not only in the heart, but it is quite possible that this is a more generic function, because now there is more and more evidence that the lymphatic vessels have a beneficial or negative role in many heart diseases, in neurological diseases, Alzheimer's, Parkinson's or obesity.

Can this process be promoted? And if it is promoted, what effects will it have?

Yes, it can be promoted, although not in the way it has been done up to now, which is to use adenoviruses that are injected into the heart, since therapeutically it does not work and is risky. If there was a way to promote the growth of the lymphatics, it would have to be done with controls, due to the possible side effects. I don't think promoting a limited growth of lymphatics would be adverse, quite the contrary.

We are now trying to determine the effect on the lymphatics in producing relin. However, the problem with producing relin is that it is too large a protein, so it cannot be packaged into viruses.

We have a mouse model that produces relin and we are following this line of research and we eventually want to move on to another model, more similar to humans, such as the pig.

On the other hand, we also have data linking the role of the metabolic part of the lymphatics, which is very important in myocardial infarction.

We have shown with a mitochondrial mutant that if you alter the metabolism of the lymphatics, it also somehow impacts the role of the lymphatics in improving cardiac activity. This is another one of the areas that we are following: trying to understand relin, lymphatics and metabolism, to see how they correlate.

As soon as we identify relin through proteomics we have about 30 possible molecules that could do the same thing in the heart or in many other organs. We have proof that the same thing will surely occur in the lung, kidney and liver.

The idea that the lymphatics have a role in the development of an organ and its protection was completely unexpected. It was expected from the blood vessels, but not from the lymphatics.

How do you rate your experience at the CNIC?

It's been a crash course in cardiology in 3 months. During my stay at CNIC I have spoken with the 'holy cows' in the field of developmental biology and cardiology. In one way or another, they all work on the heart, but with different approaches: area of the immune system, more metabolic, more clinical. For me that has been very beneficial.

But on the other hand, it has generated many more doubts than I had before coming to Madrid. Now, I suddenly realize that I know a lot less than I thought.

"I always say that the Postdoc experience is unique and it is the best moment of the academic period"

My only frustration is not getting Postdoc students for my lab; I was sure I was going to convince someone to come to my lab in Chicago to help me with some of these projects.

Do you consider yourself to be a good mentor?

What I enjoy most about my career is being a mentor. I always say that it is like raising a child: if it goes badly, I suffer, if it goes well, I am happy. If you ask me what makes me proud, I would say it is when I am at a conference and the person presenting one of the talks has been a postdoc in my lab. I have a very good relationship with almost all the people who have passed through my laboratory for many years. We talk very often and we all learn from each other. And I realize that I am not the same today as I was 20 years ago.

In general, when I interview a person for a Postdoc, I am a bit obtuse. For me the key is why they want to come to my laboratory. It is essential that they come, not because they want a job, but because they chose my line of research and my laboratory.

And the second thing, is that they want to have their own group. If they tell me "Well, I don't know if I want to continue in the university or in the industry or do something else"..., it's not that I have anything against it because all the options are valid if one is satisfied with the choice, but to be a postdoc in my laboratory I prefer candidates who at least want to try to have their own research group, which will be a tremendous commitment on their part. Because the day I accept them, for 4 or 5 years I'm going to do everything possible for that person to do well, and I'm going to try my best to get them the best possible job. And that is a very serious commitment for me. I can't promise you that you're going to have your group, no, but I'm sure going to try.

My great pride is that 90% of the people who have passed through my laboratory today are successful team leaders around the world, and that is not a coincidence. I have tried to convince the CNIC students that they are going to come to a research area that is 'hot' and in which the chances of getting a job are very high, but I had no luck.

How would you assess the Visiting Researchers Program of the Jesús Serra Foundation?

The Jesús Serra Foundation scholarship has been exceptional. What I am most grateful for is for forcing me to make the decision to take a 3-month "break". And that is very valuable. It is the first time in my career of more than 30 years that I have done it. Although the reality is that I have not taken it as a sabbatical and I have continued working in my laboratory, remotely. There have been many days that I have slept 3 or 4 hours. That has been the most strenuous part of the situation.

But despite this, I recommend it to all my colleagues. Seeing things from a slightly more distant perspective has helped me to think and reflect more calmly, without the daily pressure of being in the office. ■

THE WISTAR INSTITUTE - VACCINE & IMMUNOTHERAPY CENTER
PHILADELPHIA (UNITED STATES)

Amelia Escolano

"CNIC IS LIKE AN OASIS FOR SCIENCE IN SPAIN"

Dr. Amelia Escolano was destined to be a scientist. Both of her parents were chemists, and research seemed to form part of her DNA. After completing her degree in biochemistry at the Universities of Oviedo and Turku (Finland), followed by a masters at the Centro de Biología Molecular Severo Ochoa in Madrid, she arrived at the Centro Nacional de Investigaciones Cardiovasculares (CNIC), where she obtained her PhD in biochemistry and molecular biology. After a placement at the Rockefeller University of New York to complete her post-doctoral training, she now leads her own research group in Philadelphia (USA), where she is assistant professor at the Vaccine and Immunotherapy Center of the Wistar Institute. With the goal of producing a universal vaccine against HIV, Escolano's group is working on a novel vaccination strategy called sequential vaccination, which consists of injecting a series of different versions of a viral component, in this case the HIV envelope protein, to induce an immune response giving broad protection against the AIDS virus. She also believes that SARS-CoV-2 and other viruses with the capacity to mutate can also be targeted with sequential immunisation.

Where does your interest in researching vaccines stem from?

During my pre-doctoral placement at CNIC, I studied the anti-inflammatory role of macrophages. But, on starting my postdoctorate in **Dr. Michel Nussenzweig**'s laboratory at the Rockefeller University in New York, I took a radically different route. **Dr. Nussenzweig**'s laboratory is internationally renowned for its research into HIV and B-cell biology, the cells that produce antibodies. That is where I began to work on the design of a universal vaccine to prevent infection by HIV, the virus that causes AIDS.

Now, I lead my independent laboratory at Philadelphia's Wistar Institute, where my research into vaccination continues. My group is working on the design of new vaccination strategies against HIV and on analysing the immune response induced by our vaccination regimes, in particular the response to B and T cells.

So, how important has the knowledge acquired from COVID vaccines been for application to other diseases?

In fact, the opposite is true: all of the efforts that the research community has made to understand HIV or the flu virus over the years are what has facilitated the development of a vaccine for SARS-CoV-2 so quickly. The same techniques, the same methods, the same studies have been used and applied to analyse infection from SARS-CoV-2 and to design treatments and vaccines.

Many researchers who were working on HIV, influenza, and so on, threw themselves into studying SARS-CoV-2, and have used all of their methodologies to study cellular and antibody response after infection or vaccination. It's been interesting to see how all of these efforts and prior research devoted to other viruses has facilitated and accelerated the design and production of a vaccine against SARS-CoV-2.

What's more, the success of mRNA vaccines and their validation in millions of people have promoted them being considered for other viruses, including HIV. It will be interesting to see the results of these trials in the near future.

Why is there still no vaccine for HIV?

HIV is very special. On the one hand, it is a virus that mutates very quickly, creating a wide diversity of different strains. This is the same problem we find with the flu virus, which is why we have to update the vaccine every year because the strain in circulation differs. We don't have a universal vaccine for the flu. An effective vaccine against HIV would have to induce production of a specific type of antibody that can neutralise a large number or the majority of HIV strains. These antibodies, called neutralising antibodies, cover a wide spectrum and attach to specific parts of the HIV virus that are conserved in all of the circulating HIV strains. To design a vaccine that can generate this type of antibody, we use the envelope protein of HIV, which is the equivalent of SARS-CoV-2's spike protein. When this protein is used as an immunogen, the antibodies that are produced generally attach to areas of the envelope protein that are variable and are not conserved between the different strains, so those proteins would not protect against wide viral diversity. This immunity could protect you against strain 1, but would not protect against strains 2, 3, 4, 5... This is one of the great challenges when designing a vaccine for HIV: it's very difficult to focus the antibody response to given areas of the envelope protein so that these antibodies can protect you against all of the existing strains.

There are currently many researchers working on how to modify this protein so that, for instance, certain areas (epitopes) are not immunogenic, or to make the epitopes of interest more immunogenic, which is very complicated.

How are you trying to solve this problem in your research?

What we are using is a type of vaccination called sequential vaccination. Unlike traditional vaccination systems, where the immunogen itself is administered several times, for instance, in the case of SARS-CoV-2, what we do is inject different versions of the immunogen, one after another, in order to target antibody response to the epitopes of interest and induce maturation of these antibodies so they acquire the capacity to neutralise HIV. We start by injecting a version of the HIV envelope that is highly modified and subsequently, instead of re-injecting the same one, we inoculate another that is a little less modified, more similar to the natural protein of the envelope. The envelope proteins are administered sequentially, with increasingly less modification until the final injection, which is the unmodified, natural type.

> "Sequential vaccination is being tested in the context of other viral infections like the flu or COVID. It is a type of vaccination that can be very useful to induce immunity against viruses that are highly variable"

We are currently designing different sequential vaccination protocols that we are testing on different animal models including murine and simian ones.

Is it used for other diseases apart from HIV?

Sequential vaccination is being tested in the context of other viral infections like the flu or COVID. It is a type of vaccination that can be very useful to induce immunity against viruses that are highly variable. In that way, we could get antibodies with the capacity to neutralise a wide spectrum of flu, SARS-CoV-2 or HIV viruses. What's more, sequential vaccination could be useful to induce immunity to bacteria and cancer, an area that we would like to explore in the near future.

Did your research at CNIC already focus on viruses?

At CNIC, I worked on macrophages and their anti-inflammatory role in different pathological contexts. What we saw was that in macrophages, when the phosphatase

calcineurin is inhibited or deleted, they acquire an anti-inflammatory phenotype that contributes to reducing different models of inflammation in mice. My thesis research project was in the field of immunology, but not related with virus, vaccines or B-cells, which is what I am currently studying in my Philadelphia laboratory. The step to post-doctoral work was a radical change as regards the focus of my research.

> "The first difference I noticed when I arrived in the USA was that society in general values and gives recognition to scientists. Spain still does not understand that science and innovation are pillar stones of the economy and progress"

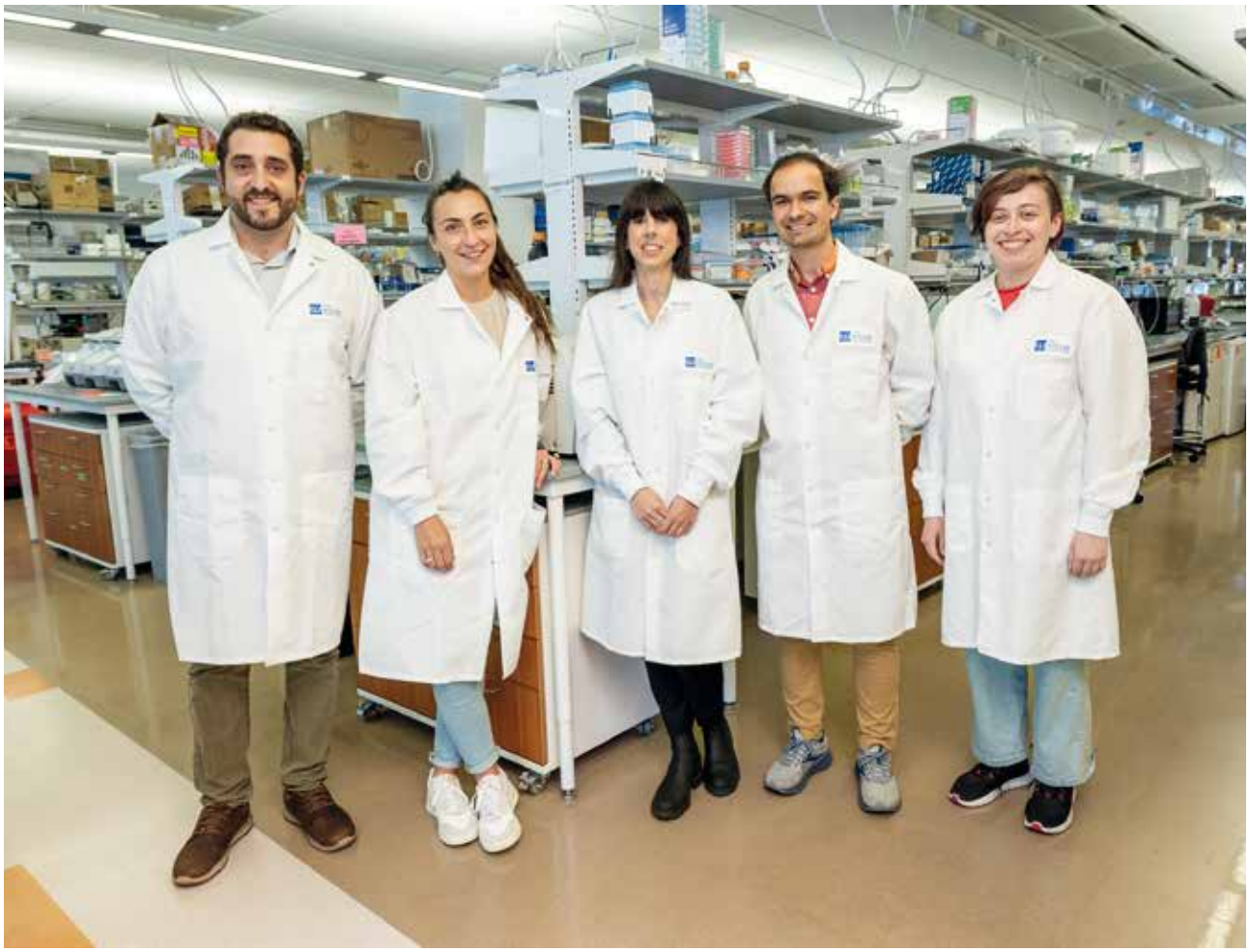
How did that change come about?

Towards the end of my thesis at the CNIC, I decided to do a pre-doctoral placement abroad with the idea of exploring laboratories for my post-doctoral research. Thanks to the recommendation of **Dr. Almudena Ramiro**, I decided to go to **Dr. Michel Nussenzweig**'s laboratory at the Rockefeller University in New York, where I did a three-month placement. After those three months, I returned to CNIC, defended my thesis, published my article and afterwards returned to the Rockefeller to do my post-doctoral work. During the first months I worked with macrophages and dendritic cells, helping a colleague to complete their studies, but I soon gravitated towards HIV and the design of vaccination protocols. At the time I arrived in New York, this was a hot topic and a completely new area for me, with all of the attendant difficulties, but I could never have imagined a better place to make that transition. My post-doctoral period was extremely productive and enriching. **Dr. Nussenzweig** was a fabulous mentor, and I received the first-class training that meant I could become an independent researcher in the USA.

What change did you notice between working at CNIC and in the United States?

The first difference I noticed when I arrived in the USA was that society in general values and gives recognition to scientists. Spain still does not understand that science and innovation are pillar stones of the economy and progress.

Rockefeller University is one of the top scientific institutions in the world. Its policy is to try to provide scientists with everything we need to do our job without having to



worry too much about other things. And, judging on the amount of recognition it receives, it seems to work.
My experience at CNIC was fantastic. My mentor, **Dr. Juan Miguel Redondo**, and my colleagues offered me everything I needed in my training as a scientist, and even today they continue to support and help me all they can, for which I am profoundly grateful. I don't think that my experience is representative of what doing a doctorate in Spain is like. I never felt that my work was limited by laboratory resources, but the CNIC is like an oasis for science in Spain. Colleagues of mine doing their theses in other Spanish institutions, and students that I have spoken to recently, have had to work on their thesis without receiving a salary. Their situation is precarious, and it is deplorable.

When you were studying at university or in CNIC, did you see going abroad as a necessary step?
From the very start of my degree, I knew that I would go abroad. In my case, it was not a forced decision. Going abroad is a way of developing, coming into contact with new stimuli and environments, meeting people and learning. Leaving Spain, or your comfort zone, is highly recommendable whenever possible. The last semester of my degree was spent in a laboratory at Turku University in Finland. That was my first experience abroad and it was one of the best of my life. It helped me gain a better understanding of myself, to know other cultures, other ways of seeing things, improve my English, and I had a great time. It was a very enriching experience. These experiences serve to put yourself to the test, discover your limits, and gain maturity and vision.

> "During my career I have worked with some extraordinary women, who have incredible strength, women who forged the path for those of us who have come later"

What were your professional decisions based on?
I now realise that when I finished my degree I did not have enough information to evaluate all of the options open to me, so my decisions were somewhat limited by a lack of information. My first decision was to stay in Oviedo and do the thesis. However, before starting the thesis, and almost unexpectedly, I received a grant from the Spanish National Research Council, the CSIC, for an introduction to research in Madrid. This period of time in Madrid made me rethink and reconsider my options. I changed my mind and decided to start my thesis in that laboratory in Madrid and a few months later I was recruited to Cincinnati. After a time in Cincinnati, I realised that it was not what I wanted and I returned to Spain to start a new thesis at CNIC, in **Dr. Redondo**'s laboratory, where I received an extraordinary training. When I made that decision, I did not even consider the option of staying in the USA, which could have been better or worse. Nowadays there is more information. It is important that students devote time to studying their own options and learning from the mistakes and successes of others so they can make informed decisions. The end of a degree and a thesis are stressful moments when we are expected to make decisions that can mark our future careers. In my case, it was not until the post-doctorate that I felt mature and informed enough to make my next decision, which was to establish myself as an independent researcher at the Wistar Institute in Philadelphia.

Did your predoctoral and post-doctoral experiences help when it came to forming your own group?
Both my thesis and my post doctorate were very long, six to seven years each, so I had time to mature and the training necessary to tackle the new stage. During my thesis I learned to design experiments, to analyse them and, to conclude, I learned a multitude of techniques, to work in a team, to present my work in public... My post-doc was also very complete and highly productive. It allowed me to specialise and gain a foothold in my area of research. When I finished my post-doc, and even before that, I felt that I was ready for independence. It has been a long journey, but each and every complication I have had to face in my career has helped me to become resilient, which is an indispensable quality in science.

What is your experience of being a woman in science?
The world of science, like many others, is still dominated by men, and the lack of female presence in some contexts is surprising. Little by little, women are carving out a niche in positions of greater responsibility, and conditions are becoming more equal. From my position, I would encourage all women not to let themselves be intimidated and to pursue their goals without fear. During my career I have worked with some extraordinary women, who have incredible strength, women who forged the path for those of us who have come later. I hope that my career also serves to forge a path for new generations of women in science.

You are now the mentor of the researchers in your group. How important is mentoring?
The role of mentor is indispensable, and one that we have to prepare for mainly during the post-doc. It is not a trivial thing; each student is different and needs to be treated differently. You have to know whether to give the help or independence that each person needs to develop in the most efficient way. You need to know how to give recognition and thanks, but also how to call things to order when necessary. My hope and aim are that all of the people who work with me enjoy their jobs. I have enjoyed myself enormously doing what I do, and I hope to be able to transmit my enthusiasm for science to my students. I also trust that my experience serves them when it comes to making their decisions. ■

Dr. Amelia Escolano participated in the 'Sequential vaccination to induce somatic hypermutation Seminar: From naïve PhD student to group leader.'

EXCELLENCE IN COMMUNICATION SCIENCE

LEADING JOURNALS PUBLISH CNIC SCIENCE

NATURE

CNIC scientists discover a cell behavior pattern that predicts cardiovascular disease

Scientists led by **Dr. Andrés Hidalgo** at the CNIC have discovered that circulating neutrophils—a type of immune cell—acquire different behavior patterns during inflammatory processes. The study, published in ***Nature***, identifies a harmful neutrophil behavior associated with cardiovascular disease.

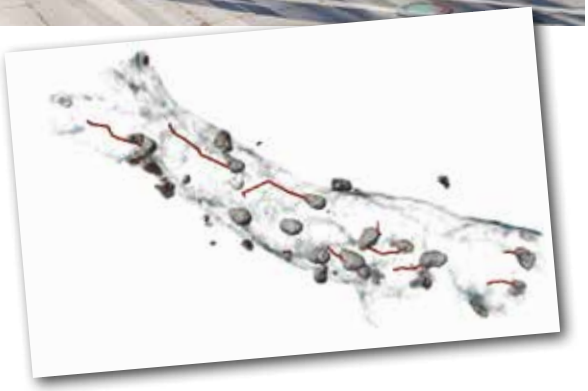
The study provides important information that could lead to new treatments to minimize the consequences of myocardial infarction.

Neutrophils are immune cells that form the first line of defense in the body but that can also damage healthy cells, including cells in the cardiovascular system.

The scientists designed a highly novel computational system that allowed them to analyze how cells behave in vessels through simple measures of changes in size, shape, and movement. This analysis identified three neutrophil behavior patterns during inflammatory processes but showed that only one of them, characterized by large size and proximity to the vessel wall, is linked to cardiovascular injury.

Combining this computational system with massive genetic analysis in animal models, the authors were able to identify the molecules responsible for the harmful neutrophil behavior.

The team found that the cause of this pathological behavior is a single molecule, Fgr. This discovery provides the key to selecting highly effective drugs able to prevent inflammation and cell death after a myocardial infarction. "The idea now is to continue with further tests and analysis needed to convert this into a clinical treatment for patients," said first author **Georgiana Crainiciuc**.



The scientists believe that the study signals a major advance not only toward improved treatment of cardiovascular disease, but also in the methodology for analyzing immune cells.

"Our model is unique because it allows the identification of cells not from their genetic profile but from their activity during a disease. This is a completely new approach to the study of immune processes that exploits the dynamism of

the disease state to generate new information," explained co-first author **Dr. Miguel Palomino-Segura**.

"The key to this approach is the ability of neutrophils to change their shape, activity, and capacity to migrate in a matter of seconds. These rapid changes can only be captured under the microscope," said **Dr. Hidalgo**.

The scientists made the discovery using high resolution intravital microscopy, which allows the visualization of cells within the blood capillaries of live animals

To extract the full potential of these images, the research team collaborated with engineers at Universidad Carlos III de Madrid, who developed new computer vision techniques for taking measurements in living tissues.

The authors hope that this new methodology will find application in other scientific arenas. "The idea now is to apply this technology in other settings, such as infection or cancer, in which immune cells also play a critical role in disease progression," said **Palomino-Segura**.

Collaborators on this project include researchers at Fundación Vithas, Universidad de Castilla-La Mancha, the Singapore Agency for Science, Technology and Research (A*STAR), and Harvard and Baylor Universities in the USA.

The study received support from the following sources: Ministerio de Ciencia e Innovación; Fundación "la Caixa", Fundación Leducq, FET-OPEN European Commission, Federation of European Biochemical Societies and EMBO ALTF.

Crainiciuc, G., Palomino-Segura, M., Molina-Moreno, M. et al. *Behavioural immune landscapes of inflammation.* ***Nature*** (2022). https://doi.org/10.1038/s41586-021-04263-y

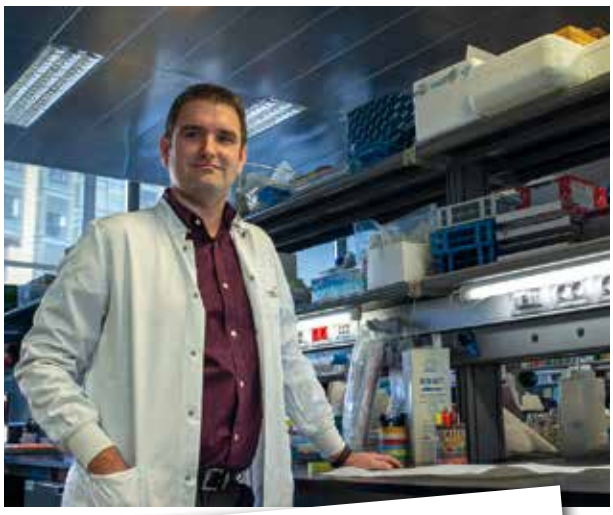
NATURE CARDIOVASCULAR RESEARCH

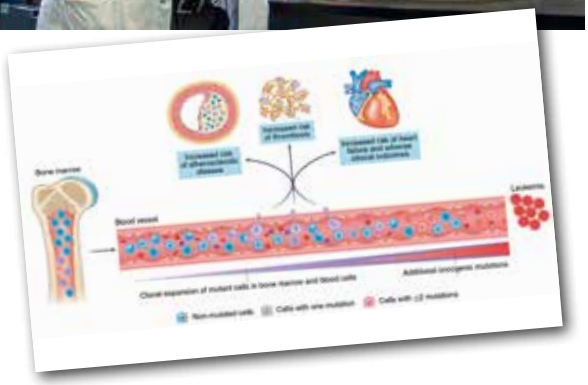
Mutations acquired by blood cells are an indicator of cardiovascular risk

Scientists at the CNIC and Columbia University, New York have published a review article in ***Nature Cardiovascular Research*** examining the role in cardiovascular disease of acquired mutations linked to clonal hematopoiesis.

In the article, CNIC scientist **José Javier Fuster** and **Dr. Alan Tall** of Columbia University review current knowledge on the role of clonal hematopoiesis in cardiovascular disease, highlighting areas where further research promises to transfer recent advances into tools for the prevention or treatment of cardiovascular disease.

Numerous clinical studies in recent years have demonstrated that acquired mutations linked to clonal hematopoiesis are associated with an elevated risk of multiple cardiovascular diseases, including myocardial infarction, stroke, and heart failure. In recent years, cardiovascular





researchers have debated the possibility that these mutations, which are also linked to a heightened risk of hematological cancer, contribute directly to the development of disease.

Work in several laboratories, including those led by **Drs. Fuster and Tall**, has shown that some mutations linked to clonal hematopoiesis accelerate the development of cardiovascular disease and aggravate inflammatory responses.

"A deeper understanding of these mechanisms could, in the future, lead to personalized strategies for cardiovascular prevention, aimed specifically at countering the proinflammatory effects of these mutations," said **José Javier Fuster**.

Despite the availability of effective treatments for traditional cardiovascular risk factors, cardiovascular disease continues to be the leading cause of death, explained **Dr. Fuster**.

Scientists have known for some years that inflammation is a central factor in cardiovascular disease, but this has not led to the general use of anti-inflammatory treatments for cardiovascular conditions.

These treatments should only be used in specific situations, since they can increase the risk of infectious disease.

The authors write that "the detection of acquired mutations linked to clonal hematopoiesis could help identify those people who could benefit most from anti-inflammatory treatment, when presenting with exacerbated in-

flammation, and inform which specific treatment could be especially effective".

Achieving this goal will, the authors conclude, require detailed research into the effects of different mutations associated with clonal hematopoiesis and, eventually, clinical trials of candidate treatments.

Drs. Fuster and Tall are members of the Clonal Hematopoiesis and Atherosclerosis Network, a Leducq Foundation-funded association of pioneering researchers in the field that also includes CNIC scientist **Andrés Hidalgo**.

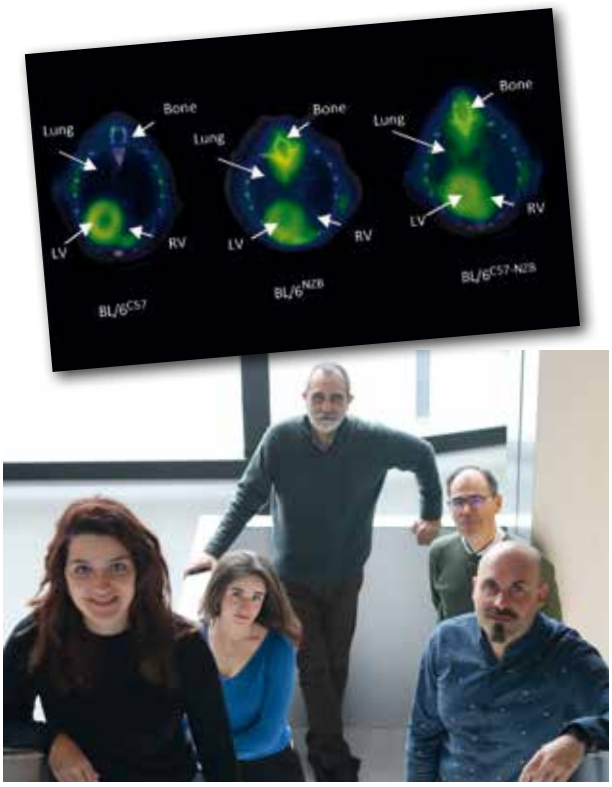
Tall, A.R. & Fuster, J.J. (2022). *Clonal hematopoiesis in cardiovascular disease and therapeutic implications.* ***Nature Cardiovascular Research***, 1(2), 116-124. https://doi.org/10.1038/s44161-021-00015-3

CIRCULATION

A CNIC study highlights the risks of mitochondrial therapeutic interventions

Research carried out at the CNIC has demonstrated that mixing mitochondrial DNAs (mtDNAs) of different origins can have damaging effects over the medium and long term. mtDNA is a component of the genetic material that is transmitted exclusively from mothers to their children.

The study, published in ***Circulation***, provides invaluable information about how to identify and avoid possible risks associated with mitochondrial therapeutic interventions. The most popular of these methods include the injection of mitochondria from a donor egg into the egg of a woman with fertility problems and mitochondrial replacement therapy aimed at preventing the transmission of disease-causing mutations to descendents, popularly known as "three-parent children." Mitochondrial replacement therapy has already been approved in the United Kingdom.



The new study shows that, while most cells do not tolerate the presence of two mitochondrial genetic variants and progressively eliminate one of the two mtDNAs, some major organs are unable to do this, including the heart, lungs, and skeletal muscle.

For lead researcher **Dr. José Antonio Enríquez**, who heads the Functional Genetics of the Oxidative Phosphorylation System (GENOXPHOS) group at the CNIC, the findings have major implications for treatments involving the transfer of donor mitochondria because they show that "animals generated through these procedures appear healthy early in life but go on to suffer in later life from heart failure, pulmonary hypertension, loss of muscle mass, frailty, and premature death."

In the body, most of the DNA is contained in the cell nuclei. In humans, this is where approximately 20,000 genes of the genome are located. However, another 37 genes are located outside the nucleus. "These genes are located in cellular compartments called mitochondria and constitute the mitochondrial DNA," explained **Dr. Enríquez**.

In contrast, mtDNA is inherited only from the mother because the sperm mitochondria are destroyed in the interior of the fertilized egg. Uniparental transmission of mtDNA is found in almost all organisms. In addition, mtDNA is present in multiple copies per cell, and these copies are all essentially identical, a phenomenon known as homoplasmy.

The presence of more than one mtDNA genetic variant in the cell is called heteroplasmy. Although very rare, heteroplasmy sometimes occurs naturally as a result of mtDNA mutations and can cause several diseases. New therapeutic approaches proposed in recent years and aimed at preventing disease or treating infertility can generate a new form of heteroplasmy in people.

"This new form of heteroplasmy, involving distinct non-mutated mtDNA variants, is produced when an individual's cells contain both the original recipient mtDNA and the donor mtDNA transferred during the intervention. In the GENOXPHOS group at the CNIC, we have been investigating whether this breaching of a natural biological barrier has detectable physiological effects," said **Dr. Enríquez**.

The researchers show that the selection between mtDNA variants coexisting in the same cell depends on their impact on cell metabolism and can be modulated by variations in gene function, drug actions, and dietary changes. "All of these factors help to determine the preference for one type of mitochondrial genome over another," they write.

"The question as to why mtDNA is transmitted to descendents from only one parent has yet to be answered, but until now the issue had no health implications," said first

author **Dr. Ana Victoria Lechuga-Vieco**. "The new medical therapies that breach this biological barrier can generate, intentionally or non-intentionally, mixtures of mtDNA from more than one individual in the same cell".

The study provides invaluable information for ensuring the safety of mitochondrial replacement therapies aimed at preventing the transmission of disease-causing mutations to descendents, popularly known as "three-parent children."

Before the publication of the new study, "we did not know what impact this mtDNA mixing had for the individual," said **Dr. Enríquez**.

To address this question, the GENOXPHOS group generated mice with a single nuclear genome but with all their cells simultaneously containing two distinct mtDNA variants. "This mouse strain was fertile, and young animals showed no related disease," explained **Dr. Lechuga-Vieco**.

"We observed that cells rejected the presence of two mitochondrial genomes, and most of them progressively eliminated one of the mtDNA variants. Surprisingly, however, major organs like the heart, lungs, and skeletal muscle were unable to do this," explained **Dr. Lechuga-Vieco**.

"Organs that could eliminate one of the mtDNA variants, like the liver, recovered their mitochondrial metabolism and cellular health, but those that could not progressively deteriorated as the animals aged," continued **Dr. Enríquez**.

Thus, the animals, which appeared healthy in their youth, in later life suffered from heart failure, pulmonary hypertension, loss of muscle mass, frailty, and premature death.

The researchers conclude that the dangerous effects of mitochondrial therapeutic interventions identified in the new study show the need for caution in the selection of the donor mtDNA genotype.

As the authors state in their article, the results of the ***Circulation*** study also imply that "even the most promising method, for the replacement of oocyte mitochondria carrying known pathological mtDNA mutations, may fail to achieve 100% replacement."

Any therapeutic strategy that involves mixing the healthy mtDNA of two individuals must ensure the genetic compatibility of the donor and recipient mitochondrial genomes.

The study shows that recipient cells have a high capacity to select and amplify the original, pre-existing mtDNA variant, which may have been undetectable before transfer of the donor mtDNA. The procedure thus has the potential to result in a mix of mtDNA from two individuals in descendent cells. "The same problem arises with oocyte rejuvenation by microinjection of donor cytoplasm," pointed out **Dr. Enríquez**.

Dr. Enríquez stressed that these risks do not mean that mitochondrial replacement therapy should be abandoned. In the same way as blood transfusions and organ transplants require careful control of compatibility between recipient and donor, **Dr. Enríquez** recommends that any therapeutic strategy that risks the mixing of healthy mtDNA variants from two individuals should "ensure full compatibility between the donor and recipient mitochondrial genomes."

The study was supported by the following funding bodies: CIBER de Enfermedades Respiratorias (CIBERES) and CIBER de Enfermedades Cardiovasculares (CIBERCV); Ministerio de Economía, Industria y Competitividad (MINECO); Ministerio de Asuntos Económicos y Transformación Digital (MEIC); Human Frontier Science Program; European Molecular Biology Organization; Programa Red Guipuzcoana de Ciencia, Tecnología e Información del Gobierno Vasco; and the ELKARTEK Program Department of Industry, Innovation, Commerce, and Tourism.

Lechuga-Vieco, A.V., Latorre-Pellicer, A., Calvo, E., Torroja, C., Pellico, J., Acín-Pérez, R., García-Gil, M.L., Santos, A., Bagwan, N., Bonzón-Kulichenko, E., Magni, R., Benito, M., Justo-Méndez, R., Simon, A.K., Sánchez-Cabo, F., Vázquez, J., Ruiz-Cabello, J., & Enríquez, J.A. (s.f.). *Heteroplasmy of Wild Type Mitochondrial DNA Variants in Mice Causes Metabolic Heart Disease With Pulmonary Hypertension and Frailty.* ***Circulation***. https://doi.org/10.1161/CIRCULATIONAHA.121.056286

NATURE COMMUNICATIONS

CNIC scientists identify a shuttle protein required for the nuclear import of proteins essential for organ growth and development

Organ growth and regeneration require the entry into the cell nucleus of proteins that activate essential genes for these processes. This process is the subject of a new study by CNIC scientists, led by **Dr. Miguel Ángel del Pozo Barriuso**, who heads the Mechanoadaptation and Caveolae Biology group, and group member **Dr. Asier Echarri Aguirre**. The scientists have identified the mechanism that controls the nuclear import of these proteins in re-

sponse to mechanical stimuli, such as the hemodynamic forces generated by arterial blood flow, tumor rigidity, or locomotory movements during routine activities like walking or sports. The results are published today in ***Nature Communications***.

Most biological processes require the nuclear entry of key regulatory factors. Processes such as fetal development, tissue regeneration after trauma or infarction, cardiovascular disease, and cancer generate mechanical signals that stimulate cell multiplication to regenerate the damaged tissue or remodel the surrounding tissue matrix.

These events require specific factors that are activated by mechanical signals and enter the nucleus, where they activate the expression of genes required to promote organ growth or regeneration.

"One of the most important of these factors is the protein YAP," explained **Dr. Del Pozo Barriuso**. "Its nuclear import is a highly regulated process, and only takes place when specifically required. Macromolecules like YAP enter the nucleus through nuclear pores by binding to a nuclear transport or shuttle protein."

What makes YAP especially interesting is that, in response to mechanical forces acting on the tissue, "it is activated and enters the nucleus, where it switches on several genes that determine the growth of the affected organ," explained **Dr. Echarri Aguirre**. "Moreover, YAP is mutated in many diseases, making it even more interesting," added study first author **María García**.

Nevertheless, although YAP has been studied extensively due to its roles in organ regeneration, cardiovascular disease, and cancer, its nuclear entry route and the nuclear shuttle protein it interacts with were unknown.

The CNIC scientists have now shown that the YAP shuttle protein partner is importin-7, which binds YAP and transports it to the nucleus, where it can induce cell and tissue growth.

The study have also demonstrated that YAP monopolizes importin-7, thereby restricting nuclear access by other factors. The study thus shows that YAP not only controls genes important for organ growth, but also regulates nuclear shuttle activity and the nuclear import of other factors.

The study thus identifies a new target for the development of drugs targeting YAP nuclear import in diseases associated with an enormous societal and economic cost.

Scientists of the CIBER Cardiovascular Disease research network participated in this study. The study was supported by funding from the following bodies: Ministerio de Ciencia, Innovación y Universidades; Agencia Estatal de Investigación / European Regional Development Fund "A way to make Europe"; the Comunidad Autónoma de Madrid; Fundació La Marató de TV3; Fundación "la Caixa"; Asociación Española Contra el Cáncer; and the European Union's Horizon 2020 Research and Innovation Programme through a Marie Sklodowska-Curie award.

García-García, M., Sánchez-Perales, S., Jarabo, P., Calvo, E., Huyton, T., Fu, L., Ng, S.C., Sotodosos-Alonso, L., Vázquez, J., Casas-Tintó, S., Görlich, D., Echarri, A., & Del Pozo, M.A. (2022). *Mechanical control of nuclear import by Importin-7 is regulated by its dominant cargo YAP.* ***Nature Communications****,* 13(1), 1174. https://doi.org/10.1038/s41467-022-28693-y

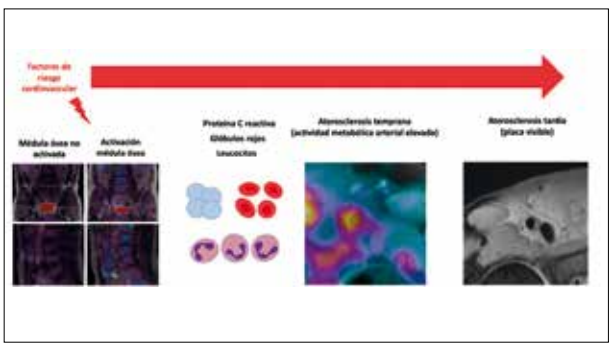
EHJ

Bone marrow contributes to the development of atherosclerosis

The activation of the bone marrow appears to play a key role in the origin and development of atherosclerosis, the pathological process underlying cardiovascular conditions such as myocardial infarction and stroke. A study carried out by scientists at the CNIC and led by cardiologists **Valentín Fuster** and **Borja Ibáñez** suggests that the bone marrow is activated in response to known cardiovascular risk factors. In the study, published in the ***European Heart Journal***, the researchers show that these risk factors lead to an increase in the number of circulating inflammatory cells, which go on to trigger the initiation and subsequent progression of atherosclerotic disease.

Atherosclerosis is a progressive deposition of fats and inflammatory cells in the arterial wall, resulting in the formation of atheroma plaques. Is the most frequent cause of death in the world and is considered a 'silent killer' because it develops quietly for years before producing symptoms. Identifying atherosclerosis in its initial phases, before symptoms appear, is a major goal of the PESA-CNIC-Santander (Progression of Early Subclinical Atherosclerosis) study. This study was launched in 2010 as a collaboration between the CNIC and Santander Bank and is led by **Dr. Valentín Fuster**, CNIC Director General and cardiologist and Medical Director at Mount Sinai Hospital in New York.

Cardiovascular risk factors that activate the bone marrow are those linked to metabolic syndrome: central obesity (the accumulation of abdominal fat), a high blood tri-



glycerides, low HDL cholesterol, elevated blood glucose, insulin resistance, and high blood pressure.

These factors trigger an increase in metabolic activity in the blood marrow that can be detected with the advanced image techniques available at the CNIC, such as hybrid positron emission tomography (PET)–magnetic resonance imaging (MRI). "The increased metabolic activity of the bone marrow unleashes an inflammatory process that activates atherosclerosis, from its earliest stages through to the appearance of established plaques," said **Borja Ibáñez**, CNIC clinical research director, cardiologist at Hospital Universitario Fundación Jiménez Díaz, and a group leader in the Spanish cardiovascular research network (CIBERCV), who directed the study together with **Fuster**.

PESA-CNIC-Santander is considered one of the most important cardiovascular prevention studies in the world. As **Dr. Valentín Fuster** explained, "PESA is the CNIC's flagship study, providing a focus for many of the center's pioneering research groups, each a leader in a defined area of cardiovascular disease. This joining together of basic and clinical researchers to investigate a large cohort like PESA is a unique venture in cardiovascular research.

Devesa, A., Lobo-González, M., Martínez-Milla, J., Oliva, B., García-Lunar, I., Mastrangelo, A., España, S., Sanz, J., Mendiguren, J.M., Bueno, H., Fuster, J.J., Andrés, V., Fernández-Ortiz, A., Sancho, D., Fernández-Friera, L., Sánchez-González, J., Rosselló, X., Ibáñez, B., Fuster. V. *Bone marrow activation in response to metabolic syndrome and early aterosclerosis.* ***European Heart Journal***, ehac102. https://doi.org/10.1093/eurheartj/ehac102

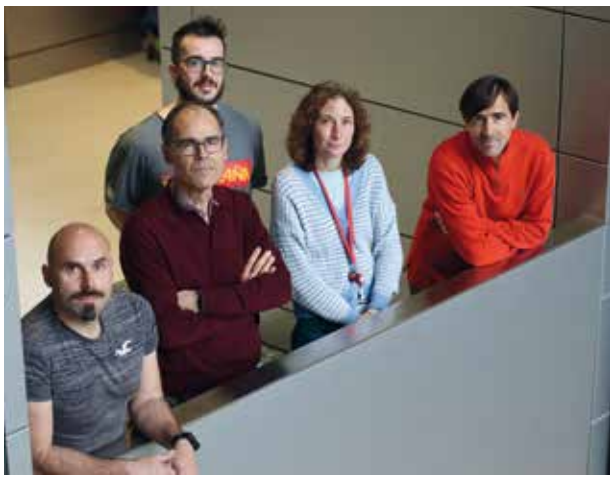
EBIOMEDICINE

Scientists discover a new method for the early detection of subclinical atherosclerosis

A study published in the journal ***eBiomedicine*** identifies new biomarkers that predict the presence of subclinical atherosclerosis. The study was carried out by scientists from the Spanish cardiovascular research network (CIBERCV) working at the CNIC and the Instituto de Investigación Sanitaria-Fundación Jiménez Díaz-Universidad Autónoma de Madrid (IIS-FJD-UAM), in partnership with other institutions.

"Atherosclerosis is a leading cause of cardiovascular disease, which is one of the major health problems in the world and places an enormous burden on health care systems. It is therefore a major goal to identify the disease in its earliest phases, so that interventions can halt its progression before it reaches an advanced stage," said study coordinator **Jesús Vázquez**, lead investigator of the CIBERCV and head of the Cardiovascular Proteomics laboratory at the CNIC.

Early prevention is the best approach to combatting the cardiovascular disease pandemic. Atherosclerosis has a long preclinical phase and is usually diagnosed only at



advanced stages, often after a cardiovascular event. The use of noninvasive imaging techniques to detect atherosclerosis allows a more precise stratification of risk than is possible with conventional methods, and current clinical guidelines recommend the use of imaging techniques to assess individual risk in combination with scales based on traditional risk factors, especially in individuals at low-to-moderate risk according to these scales.

Nevertheless, cardiovascular imaging techniques are not universally available, and the extent of atherosclerosis varies substantially between individuals in the same traditional risk category. There is therefore much interest in developing alternative rapid and noninvasive methods to estimate atherosclerosis burden.

Plasma biomarkers that track subclinical atherosclerosis, like the ones described in the ***eBiomedicine*** study, provide a way to sidestep the limitations of imaging approaches and to improve the prediction of cardiovascular risk

In the new study, the research team analyzed a collection of 880 blood plasma samples obtained from PESA CNIC-Santander study participants. The samples were examined by proteomic techniques with the aim of identifying circulating biomarkers of atherosclerosis in its early, asymptomatic phase.

From an initial panel of candidate biomarkers detected in this analysis, the team selected three proteins for validation in a collection of more than 3,000 plasma samples from the ILERVAS cohort. These samples were screened using rapid and widely available techniques through a partnership with The Binding Site and Hospital Quirónsalud Madrid.

Summarizing the findings, **José Luis Martín Ventura**, a CIBERCV scientist at the IIS-FJD-UAM and one of the study coordinators, said "the main contribution of this study is the development of a biomarker panel that can identify the presence of atherosclerosis in healthy, asymptomatic people, including individuals with none of the classical cardiovascular risk factors."

"The CNIC group has broad experience is the use of proteomic techniques for the massive analysis of samples

from patients with different cardiovascular conditions, and we have worked for several years with our colleagues at IIS-FJD on the identification and validation of cardiovascular biomarkers," explained **Jesús Vázquez**.

"Imaging techniques allow the efficient detection of atherosclerosis, but these methods are costly and require highly trained personnel and specialized apparatus, which are not available in some regions and countries," said **Vázquez**.

This is the largest study to date to explore the association between plasma protein concentrations and subclinical atherosclerosis using high-performance unbiased quantitative proteomics. The study demonstrates the potential of proteomics linked to mass-spectrometry for the discovery of human disease biomarkers.

The study received funding from the Ministerio de Ciencia, Innovación y Universidades through the Instituto Carlos III de Salud-Fondo de Investigación Sanitaria, CIBERCV y CIBERDEM, Fundació La Marató de TV3 and Fundación "la Caixa".

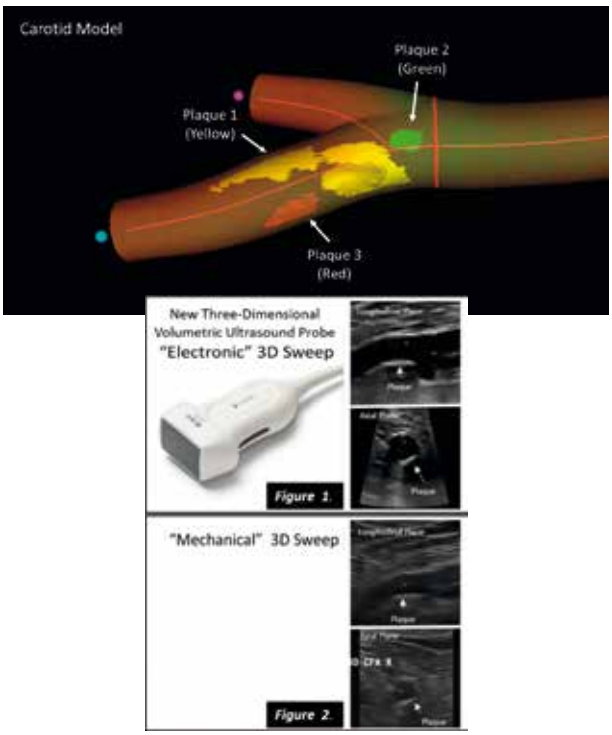
The PESA study is co-funded equally by the Centro Nacional de Investigaciones Cardiovasculares (CNIC) and Banco Santander. The ILERVAS study was funded by Lleida provincial council.

Núñez, E., Fuster, V., Gómez-Serrano, M., Valdivielso, J.M., Fernández-Alvira, J.M., Martínez-López, D., Rodríguez, J.M., Bonzón-Kulichenko, E., Calvo, E., Alfayate, A., Bermúdez-López, M., Escola-Gil, J.C., Fernández-Friera, L., Cerro-Pardo, I., Mendiguren, J.M., Sánchez-Cabo, F., Sanz, J., Ordovás, J.M., ... Martín-Ventura, J.L., Vázquez, J. (2022). *Unbiased plasma proteomics discovery of biomarkers for improved detection of subclinical atherosclerosis.* ***eBioMedicine****,* 76, 103874. https://doi.org/10.1016/j.ebiom.2022.103874

JACC
3D matrix ultrasound accurately identifies cardiovascular injury in healthy individuals

A new imaging technique for real 3D vascular ultrasound could become a key tool in strategies aimed at preventing cardiovascular disease in apparently healthy persons, complementing traditional risk parameters such as cholesterol and high blood pressure. The new results, published in ***JACC: Cardiovascular Imaging***, show that real 3D vascular ultrasound is reliable, accurate, and faster than previous methods for the assessment of plaque volume in the carotid and femoral arteries.

The new imaging method was first validated and implemented in a study of almost 200 healthy participants with an intermediate cardiovascular risk from the Athero Brain: Head-to-Heart study, led by **Dr. Valentín Fuster**, Director General of the Centro Nacional de Investigaciones Cardiovasculares (CNIC). The method has now been incorporated into the PESA-CNIC-Santander study, also led by **Dr. Fuster**, where it is being used to assess more than 4,000 healthy individuals over a 9-year follow-up.



The CNIC researchers partnered with Philips Ultrasound and Philips research Paris-Medisys to develop a new probe and software for real 3D ultrasound to facilitate exploration of the carotid and femoral arteries and speed up quantification of atherosclerotic plaque volume. As **Dr. Fuster** explained, "it is clear that traditional clinical evaluations based on measurements of cholesterol, blood pressure, blood glucose, and lifestyle habits cannot, on their own, accurately determine accumulated damage in the cardiovascular system, and without this crucial information we cannot take appropriate decisions to prevent acute events such as myocardial infarction or stroke."

The newly validated 3D vascular probe incorporates 3D matrix technology, which underpins the most advanced 3D ultrasound techniques. CNIC clinical research director **Dr. Borja Ibáñez** explained that the new technology allows simultaneous analysis by 2D and 3D ultrasound, includes all functionalities (color doppler, power-doppler, and contrast ultrasound), and is easily incorporated into daily clinical practice by technical and medical teams already experienced in ultrasound, emphasizing that "the integrated analysis software incorporates real 3D data processing."

In addition to demonstrating the accuracy of 3D matrix ultrasound, the study demonstrates that the new technique takes just half the time needed by previous methods to obtain all the information required for the definition of carotid and femoral plaque burden, essential information for correct patient management.

For patients, the outstanding feature of the new method is that the software generates a virtual 3D image of their own

arteries, allowing them to see the accumulated damage. "When patients see the state of their arteries, this impresses upon them the need to change their lifestyle, in graphic manner not achieved by reading a list of analytical data," said first author **Dr. Beatriz López Melgar**, a cardiologist at Hospital Universitario La Princesa and head of the 3D Cardioprevention Program at Hospital HM Montepríncipe in Madrid.

López Melgar concluded that, with the development of this technology, "we now have a tool that can be used on-the-fly in an initial consultation, speeding up decision making—an important consideration in cardiovascular prevention, where time is of the essence."

Collaborators on this project included scientists from the Spanish cardiovascular research network (CIBERCV), and financial support was provided by the Ministerio de Economía, Industria y Competitividad (MEIC) and the European Regional Development Fund.

López-Melgar, B., Mass, V., Nogales, P., et al. *New 3-Dimensional Volumetric Ultrasound Method for Accurate Quantification of Atherosclerotic Plaque Volume.* ***J Am Coll Cardiol Img***. 2022 Jun, 15 (6) 1124–1135. https://doi.org/10.1016/j.jcmg.2022.01.005

NATURE

International team led by BGI completes first whole-body cell atlas of a non-human primate

In a breakthrough that could lead to scientific advancement in the treatment of human diseases, researchers from BGI-Research, Jilin University and the Guangzhou Institutes of Biomedicine and Health (Chinese Academy of Sciences), together with scientific research teams from 35 international institutions including China, Germany, Italy, Singapore, Spain, Sweden and the UK, published the world's first non-human primate whole-body cell transcriptomic atlas in the scientific journal ***Nature***. The study, *Cell transcriptomic atlas of the non-human primate Macaca fascicularis,* obtained ethical clearance before it was conducted.

By using BGI's independently-developed DNBelab C4 single-cell library sequencing platform, the researchers completed the single-cell transcriptome of 45 tissues and organs from long-tailed macaque (cynomolgus) monkeys, obtaining a total of 1.14 million single-cell data and identifying 113 major cell types.

Non-human primates such as macaques are the species closest to humans in the evolutionary tree. By mapping the macaque transcriptome at the single-cell level, scientists now have a database, or single-cell library, that can be used for developing methods for disease diagnosis and treatment, assessment of clinical drug efficacy, analysis of cell evolution among species, and analysis of advanced cognitive functions of the brain.

Single-cell mapping allowed the team to identify the cell types that may contribute to human disease or make individuals more susceptible to the disease. For example, in COVID-19, the biggest manifestation is pneumonia because SARS-CoV-2 infects a small group of cells in the lung. However, the single-cell mapping of macaque also identified certain cells in other tissues that can become infected in primates. This can help doctors understand where to look for signs of COVID-19.

Single-cell mapping can also help identify which cells metabolize calories from fat, allowing researchers to comprehend underlying contributors to obesity. Likewise, this process could help identify which cells regulate neuronal circuits in the brain, leading to potential treatments for neurological diseases.

"Single-cell research is transforming our understanding of tissue and organ functions at a cellular level, which informs how diseases develop and how they can be treated" and "having a whole-body organ single-cell map of the adult macaque will significantly improve the ability to pinpoint how to develop potential treatments for human diseases with greater precision" said **Pura Muñoz-Cánoves**, one of the corresponding authors of the paper.

"By understanding cell types and their characteristics, scientists will be able to predict the impact of disease treatments on specific cell structures and thus develop more targeted approaches for monogenic or complex genetic diseases," said co-corresponding author **Dr. Xu Xun**, director of BGI-Research.

"This study fills the gap of the single-cell map of non-human primates and is a rich data resource that will serve as a very important reference for future species evolution, brain science, drug evaluation and screening, and preclinical research studies" said another co-corresponding author, **Dr. Miguel A. Esteban** from Jilin University and the Guangzhou Institutes of Biomedicine and Health (Chinese Academy of Science).

Han, L., Wei, X., Liu, C., Volpe, G., Zhuang, Z., Zou, X., Wang, Z., Pan, T., Yuan, Y., Zhang, X., Fan, P., Guo, P., Lai, Y., Lei, Y., Liu, X., Yu, F., Shangguan, S., Lai, G., Deng, Q., ... Liu, L. (2022). *Cell transcriptomic atlas of the non-human primate Macaca fascicularis.* ***Nature***, 1-9. https://doi.org/10.1038/s41586-022-04587-3

REDOX BIOLOGY

Discover a new mechanism involved in the modulation of heart muscle elasticity

Scientists at the CNIC, in collaboration with an international scientific team, have described a new mechanism of mod-

ulation of the mechanical properties of the heart, based on the oxidation of the protein titin, which is the main protein responsible for the passive elasticity of the heart muscle.

Titin is the largest protein in the human body and it is a key protein for the function of skeletal muscle and the heart. "Simplifying a lot, we can describe titin as a molecular spring that allows muscle cells to stretch and contract," explained **Dr. Jorge Alegre Cebollada**, who leads the Molecular Mechanics of the Cardiovascular System laboratory at the CNIC.

The study, published in ***Redox Biology***, builds on earlier observations showing that oxidation of the amino acid cysteine modulates the mechanical properties of titin in vitro. "We wondered whether these oxidations might be present in vivo and help to explain how the heart adapts mechanically to different situations and how it responds to disorders that alter the oxidative balance," explained **Dr. Alegre Cebollada**.

"We first found that titin contains a set of cysteines that are highly evolutionary conserved, suggesting that they play an important role in the function of the protein," commented **Dr. Elías Herrero Galán**, codirector of the study. This set of conserved cysteines are the ones observed to modulate the mechanical properties of titin in vitro. "Our experiments also showed that these amino acids are a target for oxidation in basal physiological conditions both in the mouse and the human heart", said **Dr. Herrero Galán**. This mechanism provides a possible explanation for alterations affecting the heart's oxidative state, such as myocardial infarction

Doctoral Student **Inés Martínez Martín** described how they identified the effects of these oxidations by running computer simulations based on mathematical models: "Depending on the type of oxidation, titin becomes more or less stiff, affecting the mechanics of the myocardium". "In general," she added, "these oxidations make titin more dynamic and malleable, allowing the heart to adapt to different metabolic and oxidative demands".

The authors propose that this mechanism might also explain the alterations that occur in the heart during pathological processes that affect its oxidative state, such as myocardial infarction.

The study was supported by funding from the Spanish Ministerio de Ciencia e Innovación, Madrid Regional Government, and Fundación "la Caixa". The study also received funding from the European Research Area Network on Cardiovascular Diseases through the MINOTAUR project.

Herrero-Galán, E., Martínez-Martín, I., Sánchez-González, C., Vicente, N., Bonzón-Kulichenko, E., Calvo, E., Suay-Corredera, C., Pricolo, M.R., Fernández-Trasancos, Á., Velázquez-Carreras, D., Careaga, C.B., Abdellatif, M., Sedej, S., Rainer, P.P., Giganti, D., Pérez-Jiménez, R., Vázquez, J., & Alegre-Cebollada, J. (2022). *Basal oxidation of conserved cysteines modulates cardiac titin stiffness and dynamics.* ***Redox Biology***, 52, 102306. https://doi.org/10.1016/j.redox.2022.102306

NATURE CARDIOVASCULAR RESEARCH

A CNIC team creates a dynamic 3D atlas of the formation of the embryonic heart

Scientists at the CNIC have used a collection of mouse tissue samples to create a 3D atlas of the formation of the heart during embryonic and fetal development. The 3D atlas has allowed the scientists to identify the first appearance of left–right asymmetry in the heart. The study, published in ***Nature Cardiovascular Research***, provides important information on the development of congenital heart malformations.

Study leader **Dr. Miguel Torres**, whose lab specializes in the Genetic Control of Organ Development and Regeneration, said that the new study "will be of immense help to researchers seeking to understand heart development."

During the early phases of cardiogenesis, no two embryonic hearts are alike, and the differences can be so great that it can be difficult to decide which is at a more advanced stage of development. Nevertheless, assured **Dr. Torres**, "the early, apparently divergent morphologies later converge to produce the well-formed, typical heart of the newborn animal."

The challenge is to gauge the average progression of cardiac geometry from the wide variability encountered in nature and to learn to discriminate between the various physiological morphologies and anomalous forms. Doing this requires access to a sufficiently large sample collection.

To get around the difficulties of obtaining live images, the CNIC team acquired a large collection of high-resolution images of embryonic mouse hearts at key developmental stages and at a high temporal density.

"We realized that we could not examine the morphogenesis of the heart in isolation from that of the adjoining tissues, because the formation of the heart tube can be likened to a geological fold, produced in a continuous layer of mesoderm (one of the cell layers in the early embryo) in the pericardiac cavity," said **Dr. Torres**. First author **Isaac Esteban**

described how the team therefore "captured images of all the tissues in the pericardiac cavity, as well as the endoderm of the underlying anterior intestine."

The investigators converted all the images into digital form and, using a morphometric staging system, ordered them into a temporal series, a superior approach to relying on the moment at which embryos were obtained, which does not necessarily correspond to the true timing of morphological development.

The CNIC scientists used a recently developed approach called mapping between surfaces. This technique generates corresponding surface point maps of similar structures at a high point density that allows reconstruction of the entire surface of the objects.

"This method allowed us to identify equivalent positions in groups of specimens from a similar developmental stage or at consecutive developmental stages," said **Esteban**. Using this approach, the team created a temporal 3D atlas that shows the trajectory of the formation of the heart tube and reveals local morphological variability at each stage.

The atlas reveals that the regions usually involved in heart malformations are also the regions that show high morphological heterogeneity or variability during development. "This observation suggests that this morphological variability could underlie the high incidence of congenital heart malformations, which affect 1% of live newborn babies," said **Esteban**.

The same approach used in this study can also be used to measure the morphogenesis of any organ or organoid (an in vitro model of a developing organ).

Dr Torres remarked that, while a picture may be worth a thousand words, "a movie provides much more information than a thousand individual images," and affirmed that "the dynamic 3D atlas and the morphometric staging system described in the study will be immensely useful and a source of inspiration for scientists interested in understanding the development of the heart."

The main limitation of the study is that it reconstructs a dynamic process from fixed images, and so does not reveal details of the cellular basis of tissue deformation. Nevertheless, the atlas will be indispensable for efforts to define these cellular interactions, and scientists are already working to incorporate cell data into the new dynamic atlas of heart development.

Esteban, I., Schmidt, P., Desgrange, A., Raiola, M., Temiño, S., Meilhac, S.M., Kobbelt, L., & Torres, M. (2022). *Pseudodynamic analysis of heart tube formation in the mouse reveals strong regional variability and early left–right asymmetry.* ***Nature Cardiovascular Research***, 1(5), 504-517.
https://doi.org/10.1038/s44161-022-00065-1

ELIFE

Study reveals how Duchenne muscular dystrophy causes heart rhythm problems

Abnormalities in the proteins responsible for transmitting electrical signals in the heart likely cause abnormal heart rhythms in patients with Duchenne muscular dystrophy (DMD), shows a study published in ***eLife***.

The results help explain why as many as 60% of patients with DMD have potentially life-threatening heart rhythm abnormalities. They may also suggest potential treatment strategies for heart problems in people with DMD.

Mutations in a gene that encodes a muscle-protecting protein called dystrophin cause DMD. The condition disproportionately affects males who inherit one copy of the abnormal gene from their mothers. Without functioning dystrophin proteins, patients develop progressive muscle loss. Women who often inherit one functional and one dysfunctional gene copy may have less severe muscle deterioration. But both men and women with DMD are at high risk of life-threatening heart rhythm abnormalities.

"No one knows why patients with DMD develop heart rhythm abnormalities," explained lead author **Eric Jiménez-Vázquez**, an assistant research scientist at the Center for Arrhythmia Research at the University of Michigan in Ann Arbor, Michigan USA. "We set out to determine the role of ion channels, which control electrical signals in the heart."

The study was a collaboration of physicians and scientists from four different laboratories in three different countries (the University of Michigan in the USA, the Centro Nacional de Enfermedades Cardiovasculares (CNIC) in Spain, and the Sheba Medical Center and the Technion Institute in Israel).

They collected skin biopsies of three people with DMD and two healthy volunteers without DMD. Two participants

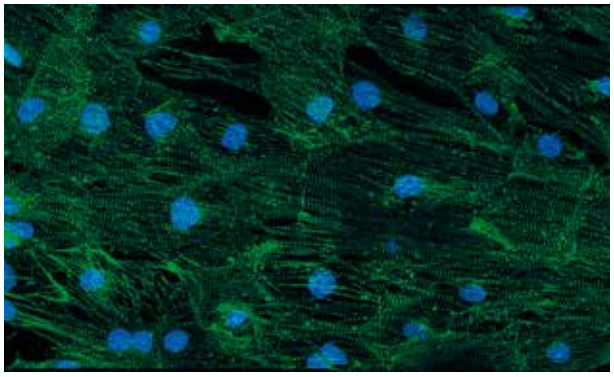
with DMD were males who inherited an abnormal copy of the gene for dystrophin, and one was a woman with one mutant copy and one normal copy of the gene. To determine why the patients developed arrhythmias, in the laboratory, they converted the biopsied cells into stem cells and then coaxed them to become heart muscle cells.

When they measured electrical activity in the newly formed heart cells, they found that cells from people with DMD had slower electrical signals, generated arrhythmias and were less able to contract than cells from people without the condition. Individuals with DMD also had less potassium and sodium ions flowing in their cell membranes, both essential for electrical signalling in the heart. They also found that heart muscle cells grown from the males with DMD had fewer sodium and potassium ion channels, which control the flow of sodium and potassium, than people without the condition.

But adding an essential partner protein of sodium and potassium channels called α1-syntrophin to the cells of one of the males with DMD corrected electrical activity in the cells and prevented abnormal rhythms.

The discoveries may help explain why both males and females with DMD may have life-threatening heart rhythm disturbances. In DMD, males are more often affected but females may be carriers because the dystrophin gene is located on the X chromosome. Since males have one X and one Y chromosome, if they inherit the DMD mutation from their mother's X chromosome, they do not have a way to make any active dystrophin protein. Thus, they have a high probability of developing the disease. Since females have two X chromosomes, they do not usually have disease symptoms because they can still make dystrophin from their good X chromosome. However, the pattern of distribution of the bad chromosome in the heart cells is random and may determine the severity of their symptoms. This inconsistent pattern may also explain why women with DMD are sometimes as prone to heart rhythms as their male counterparts.

"Our study helps explain why people with DMD develop severe heart rhythm abnormalities and may help scientists develop new treatments for this life-threatening complication," said senior author **José Jalife**, distinguished senior investigator at the CNIC and emeritus professor of Medicine and Molecular and Integrative Physiology at the University of Michigan.



The study was supported by National Institutes of Health; Fundación "la Caixa"; Fundación La Marató de TV3: Ayudas a la investigación en enfermedades raras 2020 (La Marató-2020); Instituto de Salud Carlos III/FEDER/FSE- Horizonte 2020 - Programa Marco de Investigación e Innovación - Research and Innovation Framework Programme; and Ministerio de Ciencia e Innovación (MCIN).

Jiménez-Vázquez, E.N., Arad, M., Macías, Á., Vera-Pedrosa, M.L., Cruz, F.M., Gutiérrez, L.K., Cuttita, A.J., Monteiro da Rocha, A., Herron, T.J., Ponce-Balbuena, D., Guerrero-Serna, G., Binah, O., Michele, D.E., & Jalife, J. (2022). *SNTA1 gene rescues ion channel function and is antiarrhythmic in cardiomyocytes derived from induced pluripotent stem cells from muscular dystrophy patients.* ***eLife****,* 11, e76576.
https://doi.org/10.7554/eLife.76576

HEPATOLOGY

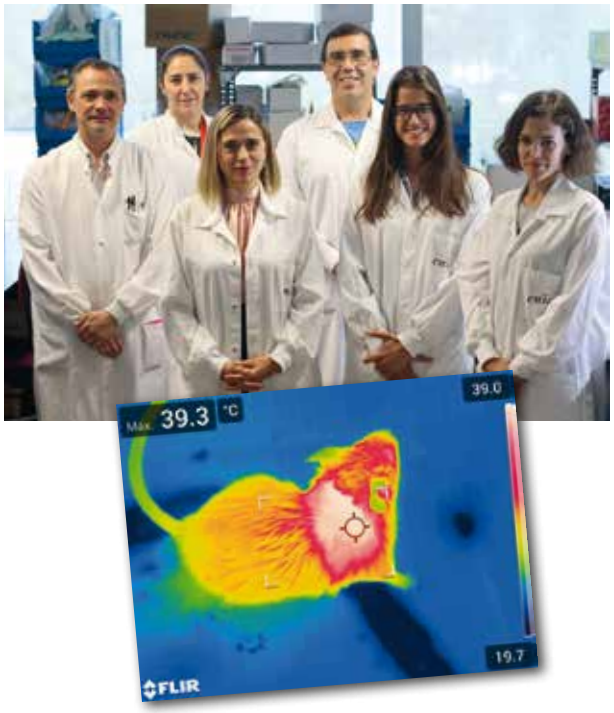
Immune cells in the liver regulate body temperature

A study published in ***Hepatology*** demonstrates that the activation of thermogenesis in the livers of obese mice contributes to weight loss and improves diabetes symptoms. Scientists at the CNIC have discovered a complex network of connections between tissues that allows the liver to regulate body temperature. The research team found that the secretion of a molecule called interleukin 12 (IL-12) by immune cells present in the liver reduces heat generation by brown fat.

The new study reveals that one of these molecules, the protein IL-12, blocks the production of another protein, FGF21, in the liver. The decline in FGF21 results in reduced generation of heat by brown fat. The Spanish scientists also discovered that the production of IL-12 by these immune cells is activated by the protein kinase p38, thus identifying a role for p38 in the regulation of liver endocrine function and whole-body metabolism. "We found that when we eliminated stress-kinase pathways in macrophages, these cells lost the capacity to adapt to a fatty diet and increased the production of IL-12, reducing the generation of heat," explained **María Crespo**, first author on the study.

The inflammatory component of obesity is very important because it contributes to the development of diabetes, fatty liver disease, and liver cancer. The study shows that IL-12 secreted by liver-infiltrating macrophages blocks the production of FGF21, a hormone produced in the liver that regulates body energy expenditure by promoting thermogenesis in brown fat. Although other groups have reported that thermogenesis is regulated by macrophages in fat tissue, this is the first study to demonstrate the regulation of thermogenesis by macrophages in another organ, and through a completely different mechanism.

The article also describes the link between IL-12 and the prognosis of patients with fatty liver disease. As study



leader **Dr. Guadalupe Sabio** explained, "we found that IL-12 is elevated in the livers of obese patients, and this is directly associated with worse liver damage. This result indicates that IL-12 contributes to the progression of steatosis and could be used as a new disease marker and as a target for the treatment of this disease."

The study highlights the importance of thermogenesis in the control of obesity, since activation of this process burns energy, promoting weight loss and ameliorating diabetes. As the authors point out, there are already drugs on the market that reduce the levels of IL-12, and these could in principle be used to treat patients with obesity or metabolic syndrome.

In addition to the CNIC group led by **Dr. Sabio**, the study also included contributions from scientists in the Spanish research network on the pathophysiology of obesity and nutrition (CIBERobn), the Universidad Rey Juan Carlos, and Hospital Universitario de Salamanca.

The study received funding from the following grant awarding bodies: Asociación Española Contra el Cáncer, EFSD, Lilly European Diabetes Research Programme; Ministerio de Ciencia, Innovación y Universidades; Comunidad de Madrid; Fundación BBVA; European Union 7th Framework Programme.

Crespo, M., Nikolic, I., Mora, A., Rodríguez, E., Leiva-Vega, L., Pintor-Chocano, A., Horillo, D., Hernández-Cosido, L., Torres, J.L., Novoa, E., Nogueiras, R., Medina-Gómez, G., Marcos, M., Leiva, M., & Sabio, G. (2022). *Myeloid p38 activation maintains macrophage-liver crosstalk and BAT thermogenesis through IL-12-FGF21 axis.* ***Hepatology*** (Baltimore, MD). https://doi.org/10.1002/hep.32581

SCIENCE ADVANCES

The genes that give the embryonic cells the maximum potential also control the process of their differentiation

The genes that make a cell pluripotent and have the capacity to become any other type of cell during the embryonic stage also influence the process by which cells choose their cellular identity and that of their descendants. This is demonstrated by a study conducted by the CNIC, in collaboration with the Severo Ochoa Center for Molecular Biology, a joint center of the Higher Council for Scientific Research (CSIC) and the Autónoma University of Madrid (UAM), whose results have been published in ***Science Advances***.

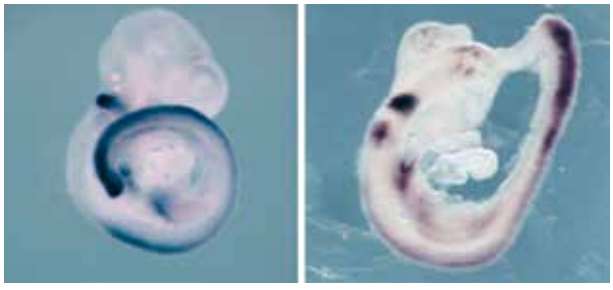
After fertilization, the zygote is generated, a single cell from which a complete organism will develop. In the first divisions, the cells are equivalent, they have a great capacity to proliferate and a plasticity that will allow them to develop cells as different as a neuron or a hepatocyte. However, this power is progressively lost throughout embryonic development, as the cells make lineage decisions and differentiate themselves.

Until now it was thought that these genes only made the pluripotent cell, but we have seen that they also influence the next process, that of differentiation. After implantation in the uterus, the embryo undergoes a process called gastrulation, in which the cells choose their fate within the body and at this point pluripotency as such ceases to exist. However, the expression of pluripotency factors continues a little longer in time and our goal has been to understand why these factors continue to be expressed and what their function is, beyond pluripotency," explains the researcher, **Miguel Manzanares**.

The ability to generate any type of cell is maintained in the embryo thanks to the action of the so-called pluripotency factors (OCT4, NANOG and SOX2, among others) that are only expressed in the early stages of development, while in an adult organism they are turned off.

The current research has focused mainly on OCT4, which is one of the four factors that in 2006 were overexpressed by **Shinya Yamanaka** to reprogram adult fibroblasts (cells that contribute to tissue formation) and convert them into induced stem cells. She was awarded the Nobel Prize in Physiology and Medicine in 2012 for this research.

To study this process in detail, the research team has characterized, both in vivo and in vitro, how the OCT4 factor



influences the regulation of Hox genes, which are responsible for attributing identity to the cells of the anteroposterior axis of the embryo.

"There are many projects on pluripotency, however very little is known about how this network is disassembled to allow determination of a specific cell lineage. Understanding pluripotency is the Rosetta stone for unraveling many important and complex processes such as tissue regeneration, rejuvenation or cancer", concludes **Manzanares**.

Tiana, M., López-Jiménez, E., Sainz de Aja, J., Barral, A., Victorino, J., Badía-Careaga, C., Rollán, I., Rouco, R., Santos, E., Sánchez-Iranzo, H., Acemel, R.D., Torroja, C., Adán, J., Andrés-León, E., Gómez-Skarmeta, J.L., Giovinazzo, G., Sánchez-Cabo, F., Manzanares, M. *Pluripotency factors regulate the onset of Hox cluster activation in the early embryo.* ***Science Advances***. DOI: 10.1126/sciadv.abo3583

EJHF

Spanish scientists combine genetic and imaging data to improve the treatment of dilated cardiomyopathy

Combining a person's genetic profile with imaging data obtained by cardiac magnetic resonance accurately predicts the prognosis of patients with dilated cardiomyopathy, the most frequent cause of heart failure.

This is the finding of a Spanish study published in the *European Journal of Heart Failure* and coordinated by **Dr. Pablo García-Pavía**, cardiologist at the CNIC and Hospital Puerta de Hierro Majadahonda in Madrid, and a member of the Spanish research network on cardiovascular disease (CIBERCV). The study is the largest in the world to correlate clinical outcomes with the genetic profiles and cardiac magnetic resonance data of dilated cardiomyopathy patients.

Dilated cardiomyopathy is the most frequent cause of heart disease in young people and the leading cause of heart transplantation in the world. The disease affects 1 person in every 250 of the general population and is characterized by an enlargement of the heart accompanied by a decline in its capacity to pump blood. Patients with this condition are at high risk of arrhythmias and sudden cardiac death.

The study examined genetic and cardiac magnetic resonance data collected from 600 patients in 20 Spanish hospitals between 2015 and 2020. The investigators demonstrated that a combination of specific genetic traits with the presence of fibrosis detected by cardiac magnetic resonance imaging accurately identifies those patients who will develop malignant arrhythmias or severe complications of heart failure.

The new study shows that classifying patients according to their genetic profile and the presence of fibrosis detected by cardiac magnetic resonance imaging "gives a much more accurate indication of patient risk than the extent of weakening of cardiac pumping capacity, the method used until now; the problem with the current method is that some patients with low-grade cardiac weakening develop complications, whereas others with extensive weakening are stable and don't develop problems over the long term," said **Dr. García-Pavía**.

The researchers found that patients lacking genetic alterations and showing no sign of fibrosis had a very good prognosis, with little risk of sudden death irrespective of the weakening of cardiac pumping capacity.

According to the authors, the study opens the way to a more personalized approach to dilated cardiomyopathy, with each patient receiving the most appropriate treatment based on a precise cardiological assessment. "The findings of this study allow dilated cardiomyopathy patients to be treated according to their specific characteristics and open the way to the application of personalized medicine in this area of cardiology," concluded **Dr. García-Pavía**.

The following centers participated in the study: Hospital Universitario Puerta de Hierro, IDIPHISA; CIBER Cardiovascular; Hospital General Universitario Gregorio Marañón; Instituto de Investigación Biomédica de Salamanca (IBSAL) - Complejo Asistencial Universitario de Salamanca; Universidad de Salamanca; Hospital Universitario Virgen de la Arrixaca de Murcia; Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona; Complejo Hospitalario de Navarra; Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña; Universidad de A Coruña; Complejo Hospitalario Universitario de Cáceres; Hospital Universitario Virgen de la Victoria IBIMA, Málaga; Instituto de Ciencias del Corazón (ICICOR); Hospital Clínico Universitario de Valladolid; Hospital General Universitario de Alicante, Instituto de Salud e Investigación Biomédica; Hospital Universitario 12 de Octubre, Instituto de Investigación i+12; Hospital Clínico, IDIBAPS, Universitat de Barcelona; Instituto de Investigación Sanitaria de Santiago; Complexo Hospitalario Universitario de Santiago; Hospital Universitario Virgen de las Nieves; Hospital Universitario Son Llàtzer & IdISBa; Hospital Universitario Virgen del Rocío; Hospital Univesitari Dr. Josep Trueta; Instituto del

Corazón & Hospital Universitario Germans Trias, and Universidad Francisco de Vitoria (UFV).

The study was funded by grants from the Instituto de Salud Carlos III with cofunding from the Euroean Regional Development Fund ("A Way to Build Europe") and the European Social Fund ("Investing in Your Future").

Mirelis, J.G., Escobar-López, L., García-Pavía, P., et al. (2022), *Combination of late gadolinium enhancement and genotype improves prediction of prognosis in non-ischaemic dilated cardiomyopathy.* ***Eur J Heart Fail****,* 24: 1183-1196.
https://doi.org/10.1002/ejhf.2514

EUROPEAN HEART JOURNAL
"One change a day makes 365 changes in a year"

Many cardiovascular disorders can be prevented by taking action to reduce risk factors. Making even small behavioral changes and sticking with them over the long term can help to preserve cardiovascular health. This is the conclusion of a study conducted at the CNIC and published in the ***European Heart Journal***. The study also demonstrates that the workplace is an ideal setting for programs promoting the adoption of heart-healthy habits and producing major health benefits.

A few years ago, CNIC General Director **Dr. Valentín Fuster** launched the TANSNIP project, an international initiative that includes partners in the United States (Icahn School of Medicine at Mount Sinai Hospital in New York and the Framingham study) and Europe (the CNIC and Amsterdam UMC). The goal of TANSNIP is to develop tools for lifestyle improvement based on the use of imaging techniques to detect the presence of atherosclerosis in its early stages, before the appearance of symptoms and events such as heart attack or stroke.

In 2015, the TANSNIP project launched a major intervention to promote a heart-healthy lifestyle in 1,000 individuals from the PESA-CNIC-Santander cohort in Madrid. The original goal of the PESA-CNIC-Santander study was to detect atherosclerosis long before the appearance of symptoms and thus to gain an understanding of the factors that trigger its development and progression.

"After months of work with our partners at Amsterdam UMC and with Banco Santander's medical services, we designed a lifestyle intervention for participants who are part of the PESA-CNIC-Santander cohort," explained **Dr. Inés García-Lunar**, a cardiologist at the CNIC and first author of the study.

The intervention consisted of a program of 12 motivational sessions distributed over three years in which an expert psychologist provided participants with the tools to introduce heart-healthy changes into their lifestyle. Participants also were given a physical activity bracelet to monitor the number of steps per day and a sit-stand desktop that allowed them to alternate sitting and standing during working hours, thus reducing sedentary time.

"More than 1,000 PESA-CNIC-Santander study participants at Banco Santander were randomly assigned to follow the intervention during their working hours or to continue with their normal routines," said **Borja Ibáñez**, CNIC scientific director and a cardiologist at Fundación Jiménez Díaz University Hospital.

"We found that individuals assigned to the intervention increased their level of physical activity, improved their diet, and reduced their sedentary time. And as a consequence of these behavioral changes, these participants' blood pressure and cholesterol also decreased," explained Dr. **José María Castellano**, a cardiologist at the CNIC and scientific director of the HM Hospitales Research Foundation.

"A very important result is that the effect of the intervention decreases over time, which suggests that programs of this type need even more frequent reinforcement to achieve sustained changes," noted **Dr. Inés García-Lunar**.

"The study represents a major finding, due to the complexity of implementing a program of these characteristics in a work environment, and this has been possible thanks to the hard work and commitment of all those involved, including the willing engagement of the participants," explained **Dr. Valentín Fuster**, who is the principal investigator on the study.

TANSNIP-PESA is funded by Fundación Centro Nacional de Investigaciones Cardiovasculares (CNIC) Carlos III through an Investigator-initiated Study grant to Icahn School of Medicine from AstraZeneca. The PESA study is cofunded by the CNIC and Banco Santander. The study also received funding from the Carlos III Institute of Health and the European Regional Development Fund. ■

García-Lunar, I., Van der Ploeg, H.P., Fernández Alvira, J.M., Van Nassau, F., Castellano Vázquez, J.M., Van der Beek, A.J., Rosselló, X., Fernández-Ortiz, A., Coffeng, J., Van Dongen, J.M., et al (2022). *Effects of a comprehensive lifestyle intervention on cardiovascular health: the TANSNIP-PESA trial.* ***European Heart Journal****.*
https://doi.org/10.1093/eurheartj/ehac378

THE BRIGHTFOCUS FOUNDATION AWARDS AN ALZHEIMER'S DISEASE RESEARCH STANDARD AWARD TO A CNIC PROJECT

THE ULTIMATE OBJECTIVE OF THE PROJECT IS TO GET FURTHER KNOWLEDGE ON **THE IMPACT THAT THE CARDIOVASCULAR RISK FACTORS HAVE ON THE BRAIN FUNCTION IN MIDDLE AGED PEOPLE**

The BrightFocus Foundation has awarded an Alzheimer's Disease Research Standard Award to the project *Understanding the impact of midlife cardiovascular risk factors & subclinical atherosclerosis on brain's health: a role on Alzheimer's pathology,* coordinated by **Dr. Marta Cortés Canteli**, researcher at the National Center for Cardiovascular Research (CNIC), together with **Dr. Valentín Fuster**, General Director of the CNIC, and **Dr. Juan Domingo Gispert**, from the CNIC and the Barcelonaβeta Brain Research Center.

The project has a duration of 3 years and will count with an annual financing of $100,000. **Dr. Borja Ibáñez** and **Dr. Fátima Sánchez Cabo**, from the CNIC, will participate in this project, along with the world leaders in plasma biomarker determination, **Dr. Kaj Blennow** and **Dr. Henrik Zetterberg**, from the University of Gothenburg (Sweden), who will participate as external collaborators, among others.

The project focuses on the longitudinal determination of specific plasma biomarkers of neuronal damage, neuroinflammation and Alzheimer's disease of the people participating in the PESA-CNIC-Santander study whose brain images have been obtained.

The BrightFocus Foundation is a nonprofit organization that supports research and provides public education on brain and eye diseases, including Alzheimer's disease, macular degeneration, and glaucoma.

The Progression of Early Subclinical Atherosclerosis (PESA-CNIC-Santander) is a prospective study that began two decades ago in more than 4,000 asymptomatic middle-aged people that aims to identify the presence of atherosclerosis and associated disorders from the early stages until the transition to symptomatic phases.

It is known that the relationship between cardiovascular disease and the factors of cognitive impairment occurs many years before the first clinical symptoms of either pathology appear. In 2021, a CNIC study, in collaboration with the Bank of Santander and neuroimaging experts from the Barcelonaβeta Brain Research Center, proved that there is an association between brain metabolism, cardiovascular risk and atherosclerosis during middle age, years before the first symptoms appear.

The information, which was published in the ***Journal of the American College of Cardiology (JACC)***, is highly relevant because, as **Dr. Valentín Fuster** – General Director of the CNIC, and one of the main authors of this study assures, it opens up the possibility of intervening on a modifiable disorder, such as cardiovascular diseases, to prevent the evolution of a pathology for which there is no treatment, such as dementia.

Furthermore, the Director of the CNIC also underlines that, "despite the fact that we all know the importance of taking care of ourselves and controlling cardiovascular risk factors to avoid a heart attack, the fact that they are related to a deterioration in cognitive status can lead to greater awareness of the need to acquire healthy habits in the younger phases of life."

The project focuses on the longitudinal determination of specific plasma biomarkers of neuronal damage, neuroinflammation and Alzheimer's disease of the people participating in the PESA-CNIC-Santander study whose brain images have been obtained

In addition, the data obtained in this study further support the importance of implementing primary cardiovascular prevention strategies in midlife as a valuable therapeutic approach to delay or even stop brain alterations that may contribute to future cognitive decline.

The project now financed by the BrightFocus Foundation will analyze whether these already identified biomarkers are related to the presence of cardiovascular risk factors and subclinical cardiovascular disease, among other variables, in order to determine if there is an association between cardiovascular and brain disease on a subclinical level and thereby understand what the mediators and the possible mechanisms causing this association are.

The results of this study, already published in different scientific magazines, indicate that subclinical atherosclerosis is very frequent in this healthy middle-aged cohort. And, furthermore, **Dr. Cortés Canteli** points out that it has been shown "that in those individuals in the PESA study with subclinical atherosclerosis, cardiovascular risk and subclinical cardiovascular disease are associated with cerebral hypometabolism in brain regions known to be hypometabolic in the Alzheimer disease."

The next step, she says, thanks to funding from BrightFocus, is to "further advance these analyses and determine to what extent this cerebral hypometabolism is due to neuronal injury and whether neuroinflammation and/or Alzheimer's pathology is also involved."

This study, she adds, "would be an important step forward in our knowledge to develop preventive interventions to reduce the incidence of Alzheimer's dementia in old age."

"We are proud and excited to fund **Dr. Cortés Canteli**'s project, which will provide priceless information on how cardiovascular risk contributes to cognitive decline and the onset of dementia," said **Sharyn Rossi**, director of Scientific Programs, Neuroscience at BrightFocus. ■

The BrightFocus Foundation is a nonprofit organization that supports research and provides public education on brain and eye diseases, including Alzheimer's disease, macular degeneration, and glaucoma

In those individuals in the PESA study with subclinical atherosclerosis, cardiovascular risk and subclinical cardiovascular disease are associated with cerebral hypometabolism in brain regions known to be hypometabolic in the Alzheimer disease

cnic AWARDS AND SCHOLARSHIPS

AWARDS

DOCTOR FUSTER RECEIVES THE PRESTIGIOUS MAHIDOL AWARD IN THE FIELD OF MEDICINE

Her Royal Highness Princess **Maha Chakri Sirindhorn** bestowed the Prince Mahidol Award, in the field of Medicine to **Dr. Valentín Fuster**, Director of the CNIC. It was awarded to him in 2020, but due to the COVID-19 pandemic, he could not pick it up in person.

This prestigious recognition granted by the Prince Mahidol Foundation acknowledges the international leadership of **Dr. Fuster** carried out during the last four decades by his innovative contributions to cardiovascular medicine, both in the field of research and from the clinic care, and more recently as an advocate for the promotion of global cardiovascular health throughout the world.

GUADALUPE SABIO BUZO, AWARDED WITH THE MEDAL OF EXTREMADURA

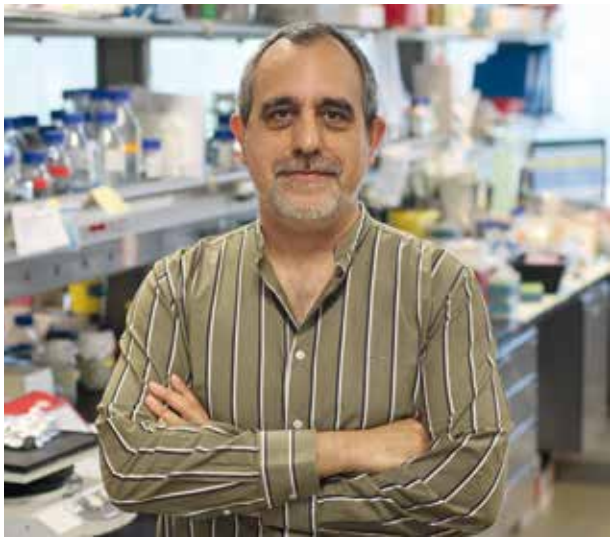
Guadalupe Sabio Buzo, who directs the group 'The role of the stress-activated kinases in the development of cardiovascular diseases, diabetes and cancer', received the Medal of Extremadura. The President of the Regional Government of Extremadura, Guillermo Fernández Vara, highlighted her work for "bringing science to society, to both adults and children." The Medals of Extremadura are awarded according to the proposals of citizens, entities and municipalities.

Dr. Sabio's work focuses on understanding factors that appear in obese people, such as the alteration of fat, dysregulation of internal clocks and cellular stress, which could be the cause of the occurrence of these diseases. In addition, her research shows that the fact that men have higher probabilities in developing cancer than women could be due to the differences in the production of hormones by the fatty tissue.

DR. VALENTÍN FUSTER, AWARDED FOR HIS SOCIAL COMMITMENT AS A DISSEMINATOR AND PROMOTER OF HEALTY HABITS AMONG THE POPULATION

Dr. Valentín Fuster received the CEU Ángel Herrera award in the Ethics and Values category, from the San Pablo CEU University Foundation. The Foundation hands him this award for his social commitment as a disseminator, attending to the need of promoting healthy habits with the aim of improving the overall health of the population.

The jury has also highlighted his relevant contributions to cardiovascular medicine throughout his extensive scientific career, which have made him the most cited Spanish researcher in history.



THE FRANCISCO COBOS FOUNDATION GRANTS THE 16TH SCIENTIFIC CAREER AWARD TO JOSÉ ANTONIO ENRÍQUEZ

The Francisco Cobos Foundation granted its 16th Scientific Career Award to the CNIC researcher **José Antonio Enríquez Domínguez**. The prize, endowed with €50,000, has been awarded for his contributions to the study of mitochondrial biogenesis in the functioning of the mitochondrial respiratory chain and understanding of the mitochondrial pathophysiology and aging.

THE AMERICAN COLLEGE OF CARDIOLOGY CREATES THE VALENTÍN FUSTER AWARD FOR INNOVATION IN SCIENCE

The American College of Cardiology (ACC) has instituted a new award in honor of **Dr. Valentín Fuster**, General Director of the CNIC, which will bear the name Valentín Fuster Award for Innovation in Science.

The award has been established in recognition of the significant contributions to cardiovascular medicine **Dr. Fuster** has made, and continues to make today, which have made him a world leader in scientific research in this field.

In addition, with this award we want to underline his innovative vision in the promotion of science through transforming mechanisms. The ACC points out that, this award serves to recognize **Dr. Fuster**'s international leadership in promoting scientific research applied to health with the aim of improving the care of cardiovascular patients and promote heart health.

The award will be given, each year, to just one doctor during the next 15 years.

ANDRÉS HIDALGO OBTAINS THE 18TH ANNUAL HEALTH SCIENCES AWARD FROM THE CAJA RURAL GRANADA FOUNDATION

The project *Mapping the immune behaviors of inflammation,* from the CNIC research group led by **Andrés Hidalgo**, received the 18th Annual Health Sciences Award from the Caja Rural Granada Foundation.

The research, published in the prestigious ***Nature*** magazine, has discovered "a new way of describing the immune cells during the process of inflammation in living organisms." This is a milestone that is of great scientific importance taking into account that, as explained by **Andrés Hidalgo**, "inflammation as a protective response of the organism in situations of damage or stress has both advantages and disadvantages."

The Caja Rural Granada Foundation co-organizes this award with the Andalusian Public Foundation Technological Park of Health, with the collaboration of the Regional Government of Andalusia, the University of Granada and the Colleges of Physicians and Pharmacists of Granada.

DOCTOR ANDRÉS HIDALGO, NEW MEMBER OF EMBO

The CNIC researcher **Andrés Hidalgo** has been named member of the European Molecular Biology Organization – EMBO. With the incorporation of **Dr. Hidalgo**, there are now six members of the CNIC in the EMBO. **Dr. Andrés Hidalgo** will join Dr. **José Antonio Enríquez**, **Dr. Miguel Ángel del Pozo**, **Dr. Miguel Torres**, **Dr. Pura Muñoz** and **Dr. Francisco Sánchez Madrid**.

The EMBO members participate actively in the organization. The different committees intervene in the EMBO Council and the advisory editorial boards of the EMBO press reviews. In addition, they evaluate the applications for calls for EMBO funding and act as mentors to scientists at the start of their careers. The new members will be welcomed formally at the EMBO annual members meeting, between October 26th and 28th 2022.

SCHOLARSHIPS

THE ALEXANDRA PERAUT PROGERIA ASSOCIATION MAKES A DONATION TO THE CNIC FOR THE RESEARCH OF THIS DISEASE

The Alexandra Peraut Progeria Association made a donation of €6,500 to the Molecular and Genetic Cardiovascular Physiopathology Laboratory, directed by **Dr. Vicente Andrés** at the CNIC, so that it can invest in the research of Hutchinson-Gilford progeria syndrome. The donation comes from the benefits of the book *A girl in twenty million,* which tells the story of Alexandra, with the aim of making progeria visible and promoting the normalization of minority diseases.

At the CNIC laboratory, also a part of CIBER for Cardiovascular Diseases (CIBERCV), **Dr. Andrés**' group has been working on this disease for years and has recently created the HGPSrev mouse - the first animal model that can suppress the appearance of progerin in a temporally and spatially controlled fashion. This new preclinical model, has made it possible to demonstrate that it is never too late to treat the disease and that therapies directed exclusively at the cardiovascular system can create very significant therapeutic benefits.

WORKING WOMEN'S DAY: 'WE DO RESEARCH AT THE CNIC'

On the occasion of Working Women's Day, the CNIC organized a round table with the title 'We do research at the CNIC', led by **Dr. Pilar Martín**, head of the group Regulatory Molecules of Inflammatory Processes, in which an attempt was made to give a complete vision of the research that is done at the CNIC from different female points of view.

In order to cover all possible aspects of the research, the colloquium counted with the participation of Lorena Esteban, Juan de la Cierva Postdoctoral researcher from the Genetic Control of the Development and Regeneration of Organs group; Irene Fernández, laboratory technician from the Cardiovascular Imaging and Population Studies group; Mercedes Grima, FPU Predoctoral researcher in the Tissue Regeneration group; Laura Lalaguna, FPI SO Predoctoral researcher in the Molecular Regulation of the Heart Failure group; and Beatriz López, IPF Predoctoral researcher in the Hematovascular Physiopathology group.

All of them explained why they decided to dedicate themselves to science, what attracts them to scientific work, projects that they are involved in and how they think their work contributes to society.

The CNIC has internship programs so that people who are interested can do training stays. You can find all the information at https://www.cnic.es/es/formarse-cnic

THE CNIC PARTICIPATES IN THE 2022 OPEN ADMINISTRATION WEEK

The CNIC participated in the 2022 Open Administration Week. Three researchers from the center, **Gonzalo Pizarro**, **Manuel Desco** and **Valeria Caiolfa**, gave informative scientific talks within the framework of the Distributed Biomedical Imaging Network (ReDIB), which is part of the Scientific and Singular Techniques Infrastructure (ICTS) of the Ministry of Science and Innovation.

The CNIC is part of ReDIB with the Advanced Infrastructure for Translational Imaging (TRIMA).

The Open Administration Week is an initiative promoted globally by the Open Government Partnership (Open Gov Week). Its main objective is to bring the Public Administrations closer to citizens, based on the principles of Open Government: transparency, accountability, citizen participation, public integrity and collaboration.

During the seminar, the capabilities and infrastructures available for application in medical imaging research, were explained to the participants. The event took place in the CNIC auditorium and it was also possible to attend online.

VISIT FROM DR. PIETER MUNTENDAM

Dr. Pieter Muntendam, founder and President/CEO of SQ Innovation; founder of G3 Pharmaceuticals and lead co-researcher of the BioImage-2 study to test a new method of carotid ultrasound, visited the facilities of the CNIC, in the company of **Dr. Borja Ibáñez**, **Dr. Vicente Andrés** and **Antonio Quesada**.

VISIT FROM THE STUDENTS AT NEBRIJA UNIVERSITY

Students from the Master in Journalism in Television, of the University of Nebrija, visited the CNIC. ■

TRAIN2GAIN
WHAT'S ON
INSIDE SCIENCE
CNIC & SOCIETY

cnicPULSE #14