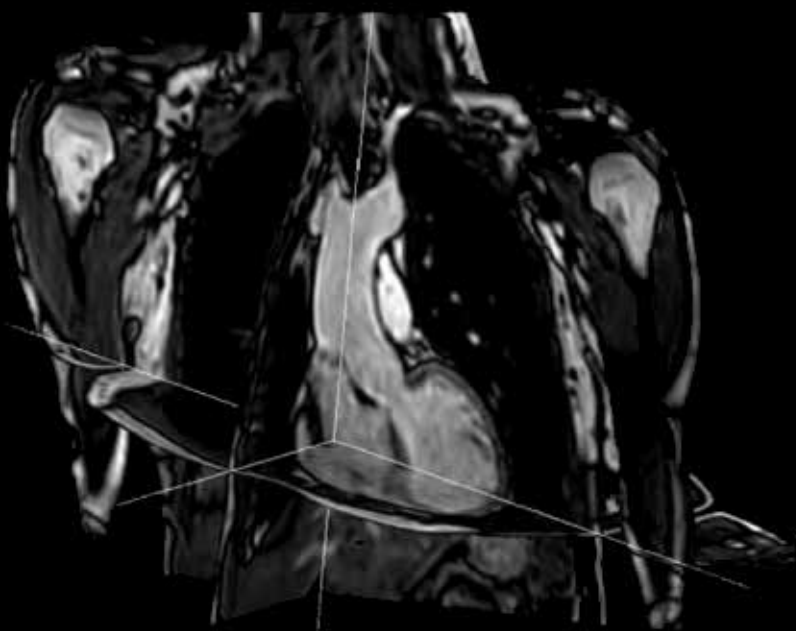
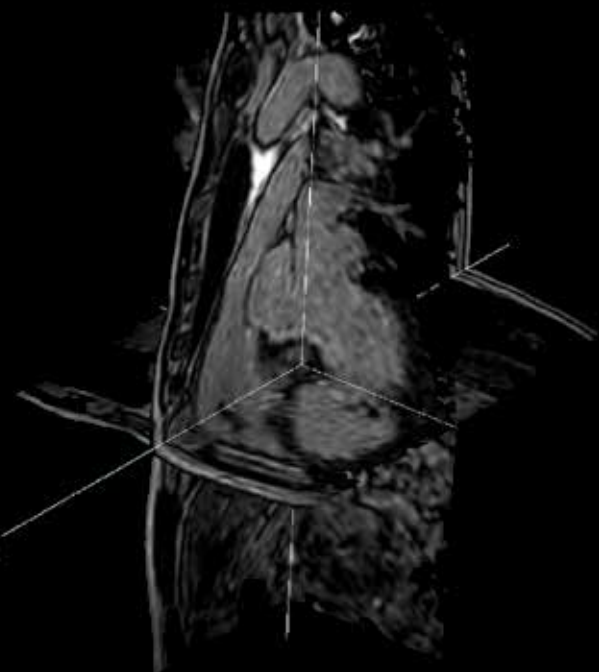


TRAIN2GAIN
WHAT'S ON
INSIDE SCIENCE
CNIC & SOCIETY

... *cnic*PULSE #12



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More than a year and a half after the appearance of Covid-19, society has realized that the only way to face a health crisis of these dimensions is to have robust health systems capable of providing a coordinated response and based on scientific evidence.

Health care systems, in addition to the availability of resources, are made up of professionals in the health field who have received the best possible training. And that is what we have been doing since 2008 at the CNIC with our global Training Plan, called CNIC-Joven, which covers all levels, from secondary education to the training of postdoctoral and young professionals.

This program is designed to bring biomedical research closer to young people and create a pool of future researchers and health professionals of excellence in the cardiovascular area.

SCIENCE CANNOT AND SHOULD NOT STOP

In 2020 and 2021, the CNIC Training Plan has continued, but adapting to the situation generated by Covid-19, and a total of 11 people have been trained in the field of biomedical research through two of the CNIC programs: CNIC-Acciona Master Scholarships and Carolina BBVA CNIC Foundation Master Scholarships.

Because science should not and cannot stop, says **Dr. Akiko Iwasaki**: "Once we have overcome this pandemic, we cannot stop." And not just basic research, to which she refers, but applied research that has a tangible benefit on the patient.

Two good examples of applied science that we do at the CNIC are detailed in this issue



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

of **CNIC Pulse**: RESILIENCE (REmote iSchemic conditioning in Lymphoma Patients REceiving ANthraCyclinEs) and the ERC-AdG "EU-Rythmy" project, coordinated, respectively, by **Dr. Borja Ibáñez** and **Dr. Silvia Pirori**.

RESILIENCE is an ambitious project specially designed to develop a new medical intervention aimed at reducing the prevalence of chronic heart failure in cancer survivors and tries to respond to two major unresolved clinical needs in relation to cardiotoxicity associated with the use of anthracyclines, a drug commonly used to treat cancer: the

lack of therapies capable of preventing or curing this condition and the absence of specific markers to identify the problem in its early stages.

ERC-AdG "EU-Rythmy" has, among others, the objective of developing a gene therapy strategy to prevent cardiac arrest in patients with arrhythmias of genetic origin, something that is extremely necessary because traditional treatments are not enough to address some of the worst diseases in the industrialized world.

These are just two examples of the work that we do daily at the CNIC and which endorses our commitment so that research can give back to society in terms of health.



PROFESSIONAL DEVELOPMENT & EDUCATION IN TIMES OF COVID-19: ACCIONA AND THE BBVA FUNDACIÓN CAROLINA

One of CNIC's primary objectives is professional development and education. That is why, in 2006, work began on CNIC-Joven, the comprehensive professional development and education plan covering all educational levels from secondary education to post-doctoral training and young professionals.

The plan is designed to bring biomedical research closer to young people and foster future generations of excellence among researchers in the cardiovascular field.

During 2020 and 2021, despite the pandemic, several CNIC professional development programmes continued, with the adaptations made necessary by Covid-19.

CNIC-ACCIONA MASTER'S GRANTS

One of these professional development programmes is the CNIC-Acciona Master's Grants, created in 2008 with the aim of contributing to the improvement of human potential in cardiovascular research.

These grants offer financial assistance for students to undertake an officially recognised master's course in biomedicine at a Spanish public university.

Each year, nine places are awarded, and despite this year's exceptional circumstances, all of the available places have been filled.

The participants in this programme research their Master's Final Project ("TFM" in Spanish) at a CNIC laboratory, where they have twelve months' access to continue the work begun for their master's and acquire further experience.

To date, 124 students have benefited from this programme, with 62% of beneficiaries staying on at CNIC to enrol in the predoctoral programme, and 42 who have already defended their doctoral thesis.

The majority of researchers who participated in the most recent round of these awards have a positive opinion both of their interaction with the CNIC groups they worked in, and of the programme itself, despite the enormous obstacles caused by the pandemic and measures to avoid transmission of Covid-19.

Carmen Morales Vidal considers that the programme "far surpassed" her expectations. "I was immersed in a group that isn't scared to start new, risky projects and that

comes up with brilliant ideas all the time. A truly enriching experience both personally and professionally."

Inés Bravo Ruiz, who signed up to the programme without a clear idea of a subject for her master's project, shares this opinion. "I was lucky enough to have the group leader, **José Javier Fuster**, as my tutor, and he guided me throughout the project and supervised all my work. The working environment is, without a doubt, unbeatable."

Speaking of his experience in the laboratory headed by **Rodrigo Fernández**, Jesús Martínez Gómez highlights the opportunity it gave him to work in a multidisciplinary team covering diverse areas of knowledge. "Thanks to this, I was able to see the whole process involved in a community-based clinical trial, from visits to the centres and sample collection, to data cleansing and analysis".

Carmen Morales, who will work on her thesis in the CNIC Genoxphos research group, expresses her gratitude for having learned to "...isolate mitochondria, work with cell cultures, use devices like the oxygraph and spectrophotometer, and design experiments, which has given me deeper knowledge of molecular techniques that will be useful in the future for my predoctoral work."

María Dolores Serrano Martín was also happy with her experience, although she mentions that potential improvements to the professional development programme could include "...interdisciplinary skills that are useful for sciences, such as how to give a good presentation, how to write scientific articles..."

For his part, Jorge Peña highlights having "...been able to consistently work in a laboratory, the opportunity to un-

dertake in-depth study into the essence of science and learn to organize and structure scientific work."

He is particularly grateful that "...from the word go, they listened to my opinion and my interests within the group's lines of research." He also points out that he was offered the opportunity to present his own data, problems and developments to the group, and discuss both his own ideas and those of others.

For Inés Bravo, one of the highlights was being able to work with rodents. "That was something I had never done in other laboratories, and I think it marks a considerable difference in the project's scope; and the experience I now have of handling animals will be very useful in the future."

AND HOW CAN THE PROGRAMME BE IMPROVED?

Carmen suggests using the university emails of all Spanish institutions to publicise the offer, helped by university lecturers who could provide information about the grants to all students who are in the final year of their degree.

Jesús indicates a substantial improvement in the programme would be a common training course for all interns or at least a structure to promote contact between them. "Being able to see and speak to people who are at the same stage as you is important," he adds. "In my case, I already knew many of the interns, but it is true that I haven't spoken to the rest, and have only seen them on two days."

He also mentions that a reception or events for interns to meet each other would have been beneficial.



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Marta Meireles da Silva Gil, who missed the personal contact prevented by the pandemic, highlights "...the opportunity to learn and practise many laboratory techniques with access to the highest level of services."

Depending on the results students obtain in their master's, and a positive evaluation of the group leader supported by the Centre's scientific management, participants in the programme may be offered an employment contract of up to two years for further professional development in their field.

CNIC BBVA FUNDACIÓN CAROLINA MASTER'S GRANTS

These grants are a result of collaboration between CNIC with BBVA and the Fundación Carolina, and their aim is to contribute to improving the knowledge of Portuguese and Latin American graduates in cardiovascular research. This grant programme, which began in 2017, has similar conditions to the CNIC-Acciona programme, but candidates for the BBVA Fundación Carolina master's grants must be nationals of a country in Latin America, a member of the Ibero-American Community of Nations or Portugal, and not be resident in Spain.

As it was not possible to complete the 2020 call, the grants not given in that year were awarded in 2021, and 10 students from Argentina, Colombia, Cuba, Ecuador, Guatemala, Honduras, Mexico and Nicaragua are soon to join the programme.

Sofía Vieto Fonseca and David Mendoza Cevallos are two students who have participated in the latest edition of the programme.

David worked on his project: "The role of lipodystrophy in cardiometabolic disorders associated with Hutchinson-Gilford syndrome progeria", supervised by **Vicente Andrés**, and considers that "...all of my expectations about professional development were met during the internship." David



also makes special mention of **Vicente Andrés** and **Carla Espinós** (one of the group's researchers and co-director of his master's dissertation) who were "always willing to help and clear up any doubts."

Sofía holds a similar opinion: "The CNIC course not only met, but exceeded my expectations. The area of biomedicine was completely new for me, and at CNIC, I received training in different techniques and in the use of equipment I was not familiar with. In all of the departments (the animal facility, cytometry, microscopy), I found people who were always willing to help me and teach me, and at **Andrés Hidalgo's** laboratory I received comprehensive scientific training that I feel privileged to have experienced."

Sofía, whose master's project is "Defining the role of phagocytosis in cardiac homeostasis", adds that, from the very first day, "All members of the laboratory were willing to teach me and help me at any time, and the help and mentoring that (the postdoc and second tutor for my project) **Ángel** gave was truly excellent. What's more, **Andrés** always paid attention to my work, and met with me to guide me throughout the course of my TFM project." Sofía is about to embark on a research fellowship at the Institute of Science and Technology Austria (IST Austria) thanks to a grant.

Since its inception, 18 students have completed their TFM at CNIC as beneficiaries of the CNIC BBVA Fundación Carolina Master's grants. And two of the participants, after returning to their countries of origin as stipulated in the award rules, have returned to complete their doctoral thesis at CNIC. ■



RESILIENCE, A PROJECT TO REDUCE THE PREVALENCE OF HEART FAILURE IN CANCER SURVIVORS

OVER ONE MILLION EUROPEAN CANCER PATIENTS
SUFFER FROM SIDE EFFECTS TO CHEMOTHERAPY



Cancer patients are a vulnerable population prone to develop cardiovascular complications. Among other factors, some anticancer therapies can induce adverse cardiovascular effects. Every year, more than 3 million Europeans receive anthracyclines alone or in combination with other anticancer agents. Anthracyclines are a frequently prescribed anticancer agent that can induce an irreversible toxic effect on the heart may lead to chronic heart failure in $\approx 5\%$ of the cases. It is estimated that in Europe the prevalence of chronic heart failure secondary to cancer therapy-related cardiotoxicity is ≈ 1 million people. The

trade-off between cancer and chronic heart failure is a massive psychological burden. For healthcare systems, the growing incidence of chronic heart failure has devastating consequences.

The two major unmet clinical needs related to anthracycline-induced cardiotoxicity are the lack of therapies to prevent or cure this condition, and the lack of markers to identify the problem in its early stages. RESILIENCE (RE-mote iSchemic conditioning in Lymphoma patients rEceiving aNthraCyclinEs) will tackle these challenges aiming to reduce the burden of cardiovascular disease in cancer survivors.

RESILIENCE is a multinational project funded by the European Commission through the H2020 "Health, Demographic Change and Wellbeing" programme. Eleven partners from six EU countries (Spain, France, The Netherlands, Portugal, Germany, Denmark) will work together under

the coordination of the Spanish National Centre for Cardiovascular Research (CNIC). RESILIENCE consortium is a multidisciplinary group, including experts in cardiology, haematology, cardio-oncology, and medical imaging. The consortium includes internationally renowned institutions and leaders with a history of participation in trials both in the field of haematology and cardiology. Different stakeholders caring for cancer patients are represented in the consortium: doctors, nurses, technologists, companies in the imaging industry, scientific societies and, importantly, patient associations.

The project received a six million EUR grant to perform a randomised clinical trial testing the role of “remote ischaemic preconditioning” as an intervention to prevent the development of anthracycline-induced cardiotoxicity.

To this aim, more than 600 patients recently diagnosed with Non-Hodgkin Lymphoma (NHL) scheduled to undergo chemotherapy with anthracyclines will be enrolled in 17 hospitals across the six EU countries. Patients will be randomly allocated to “remote ischaemic conditioning” (one weekly session during the four-month span of chemotherapy) or to a sham intervention (control). Cardiac function will be evaluated throughout the duration of the study.

“Remote ischaemic conditioning has been shown to be extremely effective in preventing anthracycline-induced cardiotoxicity in large animal models of the disease, and this project is the translation of this therapy to patients at risk for developing cardiac complications,” says **Dr. Borja Ibáñez**, the Principal Investigator-Coordinator of RESILIENCE. The investigator explains that “the hypothesis behind this study is that remote ischaemic conditioning, an intervention consisting of repetitive brief episodes of arm ischaemia induced by inflating a blood pressure cuff for five minutes, followed by pressure relief, can diminish side effects. The substances released by the arm in response to this intervention reach different organs (the heart in this case) and make them more resistant to injuries, such as the exposure to anthracyclines.” Remote ischaemic conditioning has been tested in many trials before, although in different conditions, such as myocardial infarction or stroke. This is the first time that this intervention is tested in a large, randomised trial of cancer patients undergoing chemotherapy with anthracyclines.

Remote ischaemic conditioning will be tested as a non-invasive intervention to prevent cancer therapy-induced heart failure

Another unique aspect of the RESILIENCE project is the use of state-of-the art cardiac magnetic resonance (CMR) imaging provided by an industrial partner 1, to evaluate the impact of the intervention on cardiac function and composition. Patients enrolled in the trial will undergo three CMR studies before, halfway and after the four months of chemotherapy. By executing a comprehensive imaging study, the team will be able to validate a novel CMR-based marker of early cardiotoxicity, previously identified by some members of the consortium. The CMR protocol will also include another validation of a revolutionary CMR acquisition technique that can massively reduce the time of a CMR exam, from 45 minutes to less than one minute. This methodology will be tested for the first time in a multicentre international environment.

Cutting edge magnetic resonance imaging technology is key in the development of the project

Dissemination is a key aspect of the RESILIENCE project, which seeks to reach not only the medical and scientific communities, but also the public and patients. Besides its














presence in medical fora, the project will be active on social media to reach beyond classical boundaries. A dedicated Mobile App will be developed to increase patient engagement. Among other activities, the project includes multinational meetings bringing together consortium members, world leaders in the field of Cardio-Oncology, industry, specialised press and patients enrolled in the study. These meetings will take place at the European Society of Cardiology (ESC) headquarters in Sophia Antipolis. The ESC is a member of the consortium through the Council of Cardio-Oncology and will play a key role in the dissemination and communication activities of the project.

In RESILIENCE, patients will participate actively via direct contact with investigators, giving input on pre-defined measures of the study, and as full consortium members in meetings. **Natacha Bolaños**, European Manager of Lymphoma Coalition Europe (LCE) 2 says: “we will guarantee that the patient’s perspectives are always considered in any activity of this unique project.” ■

Remote ischaemic conditioning will be tested as a non-invasive intervention to prevent cancer therapy-induced heart failure

Cutting edge magnetic resonance imaging technology is key in the development of the RESILIENCE project



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12		Centro de Investigación Biomédica en Red (CIBER) PI: Pedro L. Sánchez	ES
13		Hospital da Luz Learning Health (GLSMED) PI: António Ferreira. Co-PI: António Almeida	PT

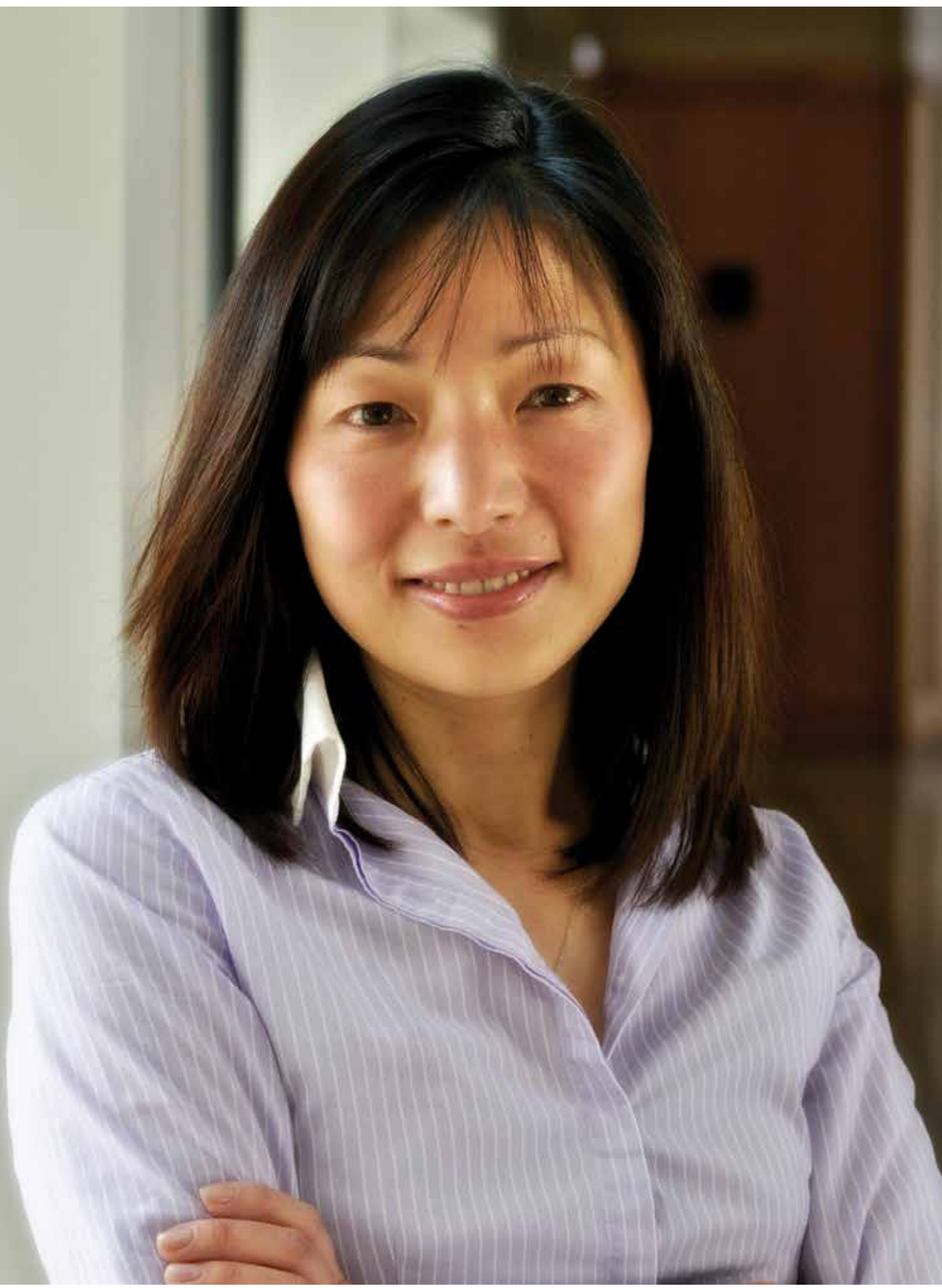


HOWARD HUGHES MEDICAL INSTITUTE
YALE UNIVERSITY SCHOOL OF MEDICINE
UNITED STATES

Akiko Iwasaki

"THERE NEEDS TO BE
MORE INVESTMENT
INTO BASIC SCIENCE
RESEARCH IF WE ARE TO BE
BETTER PREPARED
FOR THE NEXT PANDEMICS"

Akiko Iwasaki received her Ph.D. from the University of Toronto (Canada) in 1998. She joined Yale University (USA) as a faculty in 2000, and currently is an Investigator of the HHMI and Waldemar Von Zedtwitz Professor of Department of Immunobiology, and of Department of Molecular Cellular and Developmental Biology. Akiko Iwasaki's research focuses on the mechanisms of immune defense against viruses at the mucosal surfaces. Her laboratory works on a wide variety of topics, from mucosal immunology to viruses. She is the future president of the American Association of Immunologists. She also occasionally writes columns for *The New York Times* and is a Twitter celebrity. Together with some other scientists, she helped create a plan to stop Covid-19. She has also spoken out about the barrier's women face in the field of biology. Dr. Akiko Iwasaki held the seminar "Immune responses to SARS-CoV-2" at the CNIC, invited by Dr. Andrés Hidalgo.



How worried should we be about this new Covid-19 strains that has appeared all over the world?

There are now variants of concern that have higher transmission capability, evasion from antibodies and innate immune resistance mechanisms. To stop the spread of these variants, vaccines have to be given to as many people as possible, as soon as possible. We must also double down on mask wearing and physical distancing measures.

In this sense, is it normal that so many variants have appeared in this space of time?

It is a bit surprising that all these variants of concern and new variants of interest are arising in various parts of the world at the same time. This timing might reflect the duration needed to select for such variants amongst the population, particularly within immunocompromised patients who carry the virus for an extended time period.

What reinfection means for a pandemic? It seems like that this is now a bigger problem than what when the first cases appeared

Reinfection cases are rising as well. This may be because immunity acquired from the original infection is waning, and/or the rise of the variants that evade existing immunity. In addition, there are simply more people being exposed and reexposed to the virus around the world. Whether the reinfections are resulting in more or less severe disease, and what determines this outcome, is a key issue that still needs to be determined.

Your work analyzes people with long-term covid who can't shake symptoms like fatigue and brain fog. Could you give us any clue as to why these symptoms persist and if there is a definitive profile?

I think there are three possible ways in which long covid can happen. One is that the long term symptoms are caused by persisting viral infection that lingers. Second, is that these symptoms are caused by viral remnants that are persistent – not infectious virus but viral RNA and/or protein. Third, long covid is caused by autoimmune responses against self antigens. These are not mutually exclusive. Some long haulers have one while others all. It is important to understand which of these things are happening in which patient so we can provide appropriate therapy.

One of your works during the pandemic was to show that the amount of virus in the saliva can predict how severe the disease will be. How does it work?

In collaboration with **Dr. Aaron Ring's** laboratory at Yale, we found that saliva viral load much better predicts disease severity and outcome than nasopharyngeal viral load. We suspect this is because saliva pools virus from organs such as the lower respiratory tract, where the virus can cause much more damage than the upper respiratory tract (detected by the nasopharyngeal swab). Viruses in the lower respiratory tract can be propelled upwards through the airway mucociliary escalator, and end up in the oral cavity.

Autoimmune diseases are often more common in females than in males, but females perform better in Covid-19. Can you comment based on your last findings on auto-Ab?

"We found that saliva viral load much better predicts disease severity and outcome than nasopharyngeal viral load. We suspect this is because saliva pools virus from organs such as the lower respiratory tract, where the virus can cause much more damage"

"Given that long haulers are dominated by women of younger age than the severe acute Covid (men of older age), we suspect that long haulers might have distinct set of autoantibodies that contribute to their symptoms"

We found many autoantibodies in the patients suffering from acute Covid disease. These antibodies are capable of driving worse disease, because some of them attack the very immune molecules and immune cells that are fighting the virus infection. In long covid, we are now looking to see if autoantibodies are found and if so, what they target. Autoimmune diseases are generally more frequent in women than men. Given that long haulers are dominated by women of younger age than the severe acute Covid (men of older age), we suspect that long haulers might have distinct set of autoantibodies that contribute to their symptoms.

How science should prepare for the next pandemics. What have we learned from this one?

The great triumph of vaccines against Covid did not come about in a vacuum. It is enabled by decades of basic science research. There needs to be more investment into basic science research if we are to be better prepared for the next pandemics. ■

Dr. Akiko Iwasaki, Yale University (USA) held the seminar "Immune responses to SARS-CoV-2" at the CNIC, invited by Dr. Andrés Hidalgo.

Karina Yaniv

"KNOWLEDGE IS NEVER
LOST OR DISCARDED:
THE KEY TO THE QUESTION
IS KNOWING **WHEN**
AND **HOW** WE NEED
TO USE IT"



Dr. Karina Yaniv is renowned for her contributions in the field of vascular development. She is professor of Vascular Disease in the Department of Biological Regulation at the Weizman Institute of science, Rehovot, (Israel). Her laboratory focuses on understanding the mechanisms that control blood and lymphatic vessel formation during embryonic development and in disease. Among other awards, she has received the Israel Cancer Research Foundation Career Development Award, the Werner-Risau-Prize for outstanding research in vascular biology (2007) and the Susan G. Komen Young Investigator Scholarship from the Lymphatic Research Foundation. Dr. Yaniv participated in the CNIC Seminars with the lecture "Control of vascular growth and organ regeneration."

Your field of research is developmental biology of the cardiovascular system.

My career began in the area of developmental biology. That was the area of my doctoral thesis, and later, for my post-doctoral research, I focused more on the development of the cardiovascular system, using zebrafish as a model. And that is exactly what we do in the laboratory: try to understand how blood vessels, and specifically lymphatic vessels, develop in different organs and how, on the one hand, the vascular system controls each organ and on the other, they facilitate and promote functioning. That is

to say, the vascular system must have properties that are intrinsic to each organ to facilitate the function of each cell within each tissue.

In this respect, Spain has a great tradition in the area of research in developmental biology. Do you collaborate with any Spanish institutions?

I haven't had any formal collaboration, but I did my doctoral research into the neural crest and I remember, for instance, the articles published by **Ángela Nieto**, who at that time was starting her research into the transcription

factors related with the neural crest, which were the 'Bible'. Throughout my career, I have always had contact with researchers in various institutions in Spain. Here at CNIC, I have a relationship with **Rui Benedito**, as we have known each other for quite a while, since he was a postdoc. But I've never had a formal collaboration agreement like the one we are about to enter into with CNIC.

Is this your first visit to CNIC?

Yes, it has been my first visit to CNIC, but I have known about the centre for quite some time and, above all, about the research published. It is obviously a centre with a sterling reputation.

The challenges in developmental biology are not only to generate organs for transplant, but also organ regeneration. What is the current stage of research in this area?

The zebrafish study was a pioneer; the whole idea that the heart can be regenerated arose from the zebrafish research, with models that were first established by **Ken Poss** and later by **Nadia Mercader**, who developed an alternative model. These are the models that opened the idea that the heart can be regenerated. And everything that came later, in mice, for instance, was based on this idea that if the zebrafish does it, what have mammals or vertebrates lost that can be reactivated to achieve regeneration of the heart?

And from that moment on, there was an explosion of genetic and molecular data and about cellular mechanisms of how and what happens during the regeneration process, not only in the zebrafish but also in mice. I believe that this field of science has made meteoric advances in 20 years. Since publication of the first studies on zebrafish heart regeneration in 2002 or 2003, to the present day, when we already have some phase 2 or 3 clinical trials, the advances have come at breakneck speed. Hardly 20 years ago, there was no type of research and, in less than two decades, we already have clinical trials. It's incredible!

This rapid progression, is it the result of technological developments or of previously acquired knowledge?

In my opinion, of acquired knowledge. For instance, in the case of Covid, thanks to acquired knowledge a vaccine has been developed in a way that was unimaginable until now. And it has happened so fast because there have been years of basic research into this virus. This means that researchers in laboratories that were very small have been researching these viruses for years, and in truth, many people, even the researchers themselves, thought: what are we studying this for? What is the clinical relevance of this research?

And that's the beautiful thing about basic research. In the long term, we don't know when this knowledge will be useful, but the more we accumulate, the more we advance, as happened in the case of Covid.

The same thing happened in the field of developmental biology. For decades, the heart has been the subject of research. That is, the change from development to regeneration has a very, very solid knowledge base, which has made such rapid advances possible.

Do you think that, paradoxically, thanks to the Covid pandemic, society is realising the usefulness of basic research?

I hope so. Society now understands the benefits of basic research better. The problem isn't society, it is politicians. When science and politics meet, there is often a feeling that the objectives are not common, particularly in terms of time frames. Basic research requires more time than, for instance, applied science, which is usually much faster. But cases like this, the case of Covid, are proof that everything we have invested in learning has an application: knowledge is never lost or discarded. The key to the question is knowing when and how we need to use it.

Do you think we should not distinguish so much between basic and applied research?

I believe that the biggest problem lies in expecting one researcher to take on the whole process. Some researchers are highly focused on basic research, and that is their skill; others are very good at applied science, and excel at making this translation from basic research.

What I think is very good, what I have seen at CNIC, is this separation. What I mean is that I, with a heavy basic research focus, am sitting next to a colleague with a more clinical focus, and another who has a much more translational approach. So, if the three of us communicate with each other, it is much easier to move on in a project than if a single person is responsible for all of the different stages.

"Hardly 20 years ago, there was no type of research and, in less than two decades, we already have clinical trials. It's incredible!"

"In the long term, we don't know when this knowledge will be useful, but the more we accumulate, the more we advance, as happened in the case of Covid"

You have also researched the role of LDL cholesterol and cancer.

We know that cholesterol has highly beneficial functions for the organism that go beyond what happens when it accumulates in places where it shouldn't. Our laboratory discovered that there are other functions of the 'bad' cholesterol LDL molecule, which has other effects on the cells that form the blood vessels. And this result, for instance, may be very positive in the case of tumours, which is something we are studying in fish and mice. When mice have high cholesterol levels they have a lower tendency to develop aggressive tumours, because their blood vessels reproduce less. It is like a balance. The same molecule may



“One of the great problems is that we have very few female reference figures”

have very negative effects but also very positive ones. The idea is to try to understand the mechanism of action in this context versus the other scenario and see how they can be combined.

The zebrafish model gave us all the basic data to understand how the molecule functions, but we have reached the limits of what the fish can give us in this specific project, and we need to move on to the mouse model. The problem is that the whole lipid system of the mouse is a little different to that of humans, so the results we obtain for mice are not necessarily related with what occurs in humans. The idea, in this project, would be to go directly to large population studies such as, for instance, the CNIC's PESA study.

I am a great fan of basic research, but not for everything; you can't impose a model. You also have to know when to say 'this is as far as this project can go' and to progress, it needs to move on to another level of research.

How far are we from the possibility of regenerating hearts?

A lot closer than we imagined we would be when these studies began. I don't know if we can call it regeneration, because regeneration is too grand a term, but if we talk in terms of re-establishing function, or achieving what I won't call a cure, because I think the only cures in medicine are antibiotics or surgery, then we are much closer than we believe.

What does inclusive science mean to you?

It's a subject that has a much wider meaning than we think. It has many facets: a cultural one, the education we receive from when we are girls about what our role is as women, as mothers, as workers and also as scientists. On the other hand, the woman as a leader, a director, as the one who leads movement rather than one who follows. This is one of the most difficult hurdles for women to overcome. Many women reach at a time when they decide to lead, when they say "I want to be a leader". This takes us much more time than men, who seem to have been born with the capacity of wanting to lead.

And there is also the issue of support in our environment. How we can make women feel that society supports them to reach these roles is something that we are still very, very far away from.

My work alongside other female researchers at the Weizmann Institute covers many fronts. On the one hand, speaking to girls from an early age. One of the great problems is that we have very few female reference figures, women to look up to and say, "That person may be a scientist, a director, a mother, a wife, but she can have a life and enjoy herself". Because we mustn't forget that we also want to enjoy life, not just work.

I see that as my greatest challenge: if I can show by my example that it can be done, and if a young student says "if she can do it, so can I", I would feel fulfilled.

How can that work of creating awareness be achieved?

Several of the women at the Weizmann Institute have become ambassadors for Women in Science. Not just aimed at students, but also at men and group leaders. We are there to tell them 'when you write a letter of recommendation, be careful not to make a difference between a male and a female student'. We tend, for instance, when speaking about a man, to use adjectives like brilliant or hard-working, whereas if we talk about a woman, we say she is pleasant, helpful to everyone or that she teaches everyone. And maybe they don't notice, because nobody does it in bad faith. When a woman is assertive, she is automatically labelled aggressive. When she is pleasant, they think she is not serious enough. We should take great care with this sort of thing, and it's important that we continue to remind people, without being obsessive. It's painstaking work and I believe, in the long term, if we manage to make this topic part of the discussion, make people bear it in mind, that will be the start of change. ■

Dr. Karina Yaniv presented the seminar "Control of vascular growth and organ regeneration" at the invitation of Dr. Miguel Torres.

EXCELLENCE IN COMMUNICATION SCIENCE

LEADING JOURNALS PUBLISH CNIC SCIENCE

JACC

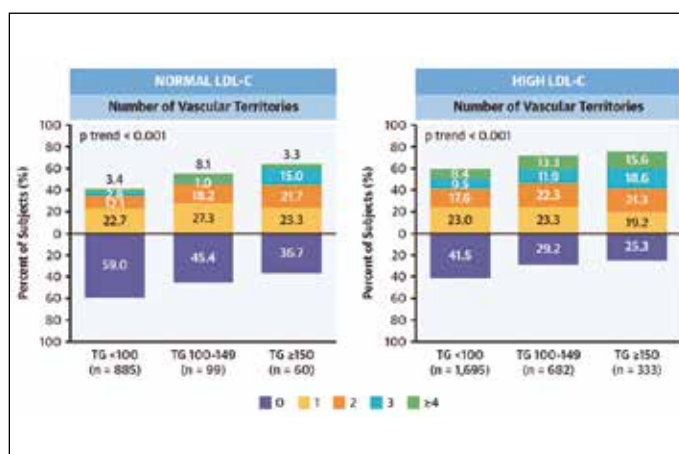
Spanish scientists provide the first demonstration that triglycerides are a primary risk factor in atherosclerosis

Triglycerides can be as important an indicator of cardiovascular risk as high cholesterol. A study conducted by researchers at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) shows for the first time that hypertriglyceridemia (excess circulating triglycerides) is associated with subclinical atherosclerosis (an accumulation of fats, cholesterol, and other substances within and on the surface of arteries, leading to restricted blood flow) and vascular inflammation in individuals with low-to-moderate cardiovascular risk, even if they have normal circulating concentrations of LDL-C, known as 'bad' cholesterol. The results are published in the *Journal of American College of Cardiology (JACC)*.

Until now, triglycerides have been considered a secondary factor in the origin of atherosclerosis, far less important than cholesterol, especially cholesterol bound to low-density lipoproteins (LDL). Indeed, "if LDL-C concentrations are normal, current cardiovascular prevention guidelines do not recommend treatment for high circulating triglyceride concentrations unless the patient has a high cardiovascular risk," said study first author **Dr. Sergio Raposeiras-Roubin**.

The new study provides the first demonstration that "in individuals with a low-to-moderate cardiovascular risk according to standard scores (the majority of the population), high circulating levels of triglycerides are associated with a greater risk of developing atherosclerosis, even among people with normal LDL-C."

The new study forms part of the PESA CNIC-Santander study (Progression and Early detection of Subclinical Atherosclerosis), a major long-term project run by the CNIC in partnership with Santander Bank. The PESA CNIC-Santander study examines the development of ath-



erosclerotic plaques in three arterial territories—the carotids, the abdominal aorta, and the iliofemoral arteries—in an asymptomatic population of Santander Bank employees between the ages of 40 and 54 years. The study, led by CNIC General Director **Dr. Valentín Fuster**, has demonstrated the high prevalence of subclinical atherosclerosis in the general population, establishing the importance of detecting the disease early in its silent phase.

Moreover, the new *JACC* article shows that triglyceride levels are associated not only with the presence of atherosclerosis, but also with vascular inflammation.

CNIC Clinical Research Director **Dr. Borja Ibáñez** explained that this result indicates a strong association between elevated circulating triglyceride levels and the early stages of atherosclerosis, a finding "with important implications for the design of preventive strategies."

The results indicate that clinical practice guidelines should be modified to emphasize the need to control not only LDL-cholesterol but also triglyceride levels. "The measurement of blood triglycerides is routine, and fortunately there are abundant effective medicines available to ensure appropriate levels," concluded **Dr. Fuster**.

The study received funding from the Carlos III Institute of Health and the European Regional Development Fund. **Dr. Ibáñez's** research is supported by the European Research Council through the MATRIX project (ERC-COG-2018-ID: 819775).

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doi: 10.1016/j.jacc.2021.04.059

ACS NANO

CNIC scientists describe a possible disease-causing mechanism in hypertrophic cardiomyopathy

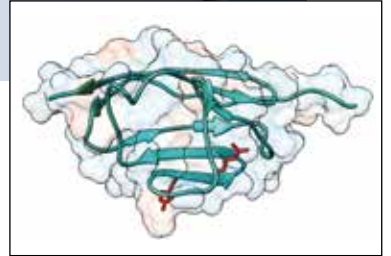
Scientists at the CNIC have described a potential disease-causing mechanism in hypertrophic cardiomyopathy (HCM), the most frequent hereditary disease of the heart. The study, published in the journal **ACS Nano**, provides the first description of an association between this disease and mechanical alterations to a component of the contractile machinery of the heart.

The heart muscle is under constant mechanical stress throughout life as it contracts to pump blood to the body. The laboratory led by **Dr. Jorge Alegre-Cebollada** investigates how the mechanical properties of the cardiac proteins determine the physiological behavior of this muscle and how alterations to these properties lead to the appearance of diseases like HCM. In this disease, the most frequent hereditary disease affecting the heart, the left ventricle becomes enlarged, and severe manifestations include heart failure and sudden death.

Scientists have known for more than 20 years that HCM is caused by mutations in proteins with a mechanical function in the heart. One of the challenges of cardiovascular genetics is to identify which among the genetic variants found in patients and their families cause disease. Knowing if a mutation is disease-causing or not is important because this information will determine the clinical follow-up of family members and, potentially, their treatment.

The new study, coordinated by **Dr. Jorge Alegre-Cebollada**, analyzed cardiac myosin-binding protein C (cMyBP-C), the most frequently mutated protein in HCM patients. "A high proportion of mutations in the cMyBP-C gene cause amino-acid changes in the protein; however, the mechanisms by which these mutations cause HCM are not precisely known."

Dr. Alegre-Cebollada's group, in close partnership with clinical and molecular researchers in Europe and the US, set up a database of cMyBP-C variants with a clear link to HCM in order to define the molecular defects underlying the disease.



Using bioinformatics and experimental approaches, the research team discovered that around half of these mutations affect the integrity of cMyBP-C messenger RNA (mRNA) or protein. These results have already been accepted for publication in the **Journal of Biological Chemistry** and have been the subject of a commentary article in the leading medical genetics journal **Genetics in Medicine**.

While alterations to mRNA or protein integrity could explain the pathogenicity of half the mutations analyzed in the earlier study, **Dr. Alegre** pointed out that the other half do not cause disease via this route.

Using advanced biophysical techniques based on atomic force microscopy, the team showed that some of the disease-causing mutations in cMyBP-C produce defects in the mechanical properties of the protein that can alter the contractile function of cardiomyocytes in HCM patients.

Identifying the molecular mechanisms underlying HCM is essential for determining which cMyBP-C mutations cause the disease. This knowledge is therefore also crucial for the clinical follow-up and possible treatment of patients and their families, say the authors.

The study was funded by the Ministerio de Ciencia e Innovación, the European Research Area Network on Cardiovascular Diseases (MINOTAUR consortium, through the Instituto de Salud Carlos III), the Comunidad de Madrid, the US National Institutes of Health, the government of the Basque region, the Italian Ministry of Education, Universities and Research, and postdoctoral fellowships from the School of Medicine and the Maternal and Child Health Institute at Stanford University. The research team also included scientists from the Cardiovascular Biomedical Research Network (CIBERCV).

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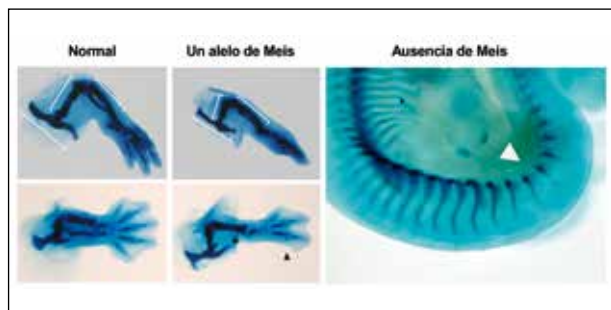
NATURE COMMUNICATIONS

CNIC scientists identify essential factors for limb formation

Scientists at the Centro Nacional de Investigaciones Cardiovasculares (CNIC), working in partnership with researchers at the Institut de Recherches Cliniques de Montréal (IRCM) in Canada, have identified Meis transcription factors as essential biomolecules for the formation and antero-posterior patterning of the limbs during embryonic development.

In the study, published in *Nature Communications*, the research team carried out an in-depth characterization of the Meis family of transcription factors. Genetic deletion of all four family members showed that these proteins are essential for the formation of the limbs during embryonic development. "An embryo that develops in the absence of Meis does not grow limbs," said study coordinator **Miguel Torres**, who leads the Genetic Control of Organ Development and Regeneration group at the CNIC.

Embryonic development is a highly complex process involving interactions among a large array of molecules to ensure the correct formation of a specific organ or tissue from a small initial number of cells. The limbs, explained first author **Irene Delgado**, "start to form as bulges on the flank of the embryo called limb buds. Growth of the limb bud eventually results in the formation of the skeletal components of the limb."



One of the factors that plays a crucial role in the developing limb is a group of transcription factors called Meis. "In a normal embryo, the Meis genes are expressed very early during the formation of the limb buds," the scientists explained.

In the new study, in-depth molecular characterization of developing mouse embryos revealed that Meis factors initiate a signaling cascade that is essential for limb bud development and involves contributions from Fgf10 and Lef1. "Our results identify roles for Meis transcription factors in the developing limb and reveal their participation in essential pathways for limb development. During early limb bud formation, Meis transcription factors are essential for inducing the expression of Fgf10 and Lef1."

An embryo that lacks Meis genes is unable to grow limbs, but the presence of just one of these four genes (a single allele) "is enough to initiate limb development and also re-

veals other functions of Meis, such as its importance for the formation of the proximal limb structures (pelvis and femur) and for antero-posterior limb patterning," said **Miguel Torres**.

Nevertheless, the pelvis and femur of embryos with a single Meis allele are smaller than those of a normal embryo. Moreover, added **Delgado**, "These embryos have defects in, or simply lack, posterior skeletal elements such as the fibula and posterior digits."

The authors further demonstrated that the molecular basis for these defects is failed initiation of the expression of the Sonic Hedgehog gene, which is essential for antero-posterior limb patterning.

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JACC

A blood sugar biomarker identifies patients with atherosclerosis and a risk of cardiovascular events

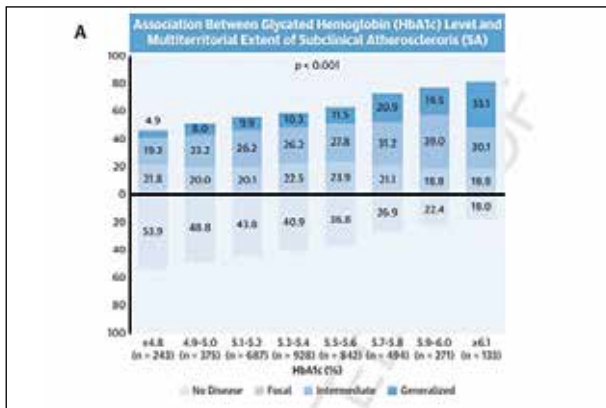
The routine use of the glycosylated hemoglobin test to track blood sugar levels in the general population can identify individuals with more advanced atherosclerotic disease. Currently used in the diagnosis and management of diabetes, glycosylated hemoglobin can provide a useful estimate of atherosclerotic disease, and therefore of cardiovascular risk, in individuals without diabetes with or without possible prediabetes.

The advance heralded by the CNIC study is the use of this blood-sugar measure in apparently healthy middle-aged individuals who do not have diabetes mellitus but with or without possible prediabetes.

When used in combination with traditional risk factors (hypertension, dyslipidemia, and smoking), the glycosylated hemoglobin test more accurately distinguishes between people at high and low risk of atherosclerotic disease.

The study, published in the *Journal of American College of Cardiology (JACC)*, proposes that, because glycosylated hemoglobin levels can easily be reduced through lifestyle changes, the test should be at the front line of risk reduction strategies.

The glycosylated hemoglobin diagnostic test is cheap, accessible, and widely used in daily clinical practice, explained **Dr. Xavier Rosselló**, CNIC scientist and cardiologist at Hospital Universitario Son Espases in Palma de Mallorca. The test can therefore be put to immediate use to calculate the degree of subclinical atherosclerosis in the general population.



The study forms part of the collaborative PESA-CNIC-Santander project, which is led by **Dr. Fuster**. Begun in 2010 and recently extended until 2030, the PESA-CNIC-Santander study is one of the most important cardiovascular prevention studies in the world.

Atherosclerosis is usually only detected at advanced stages, after it has already triggered a cardiovascular event such as a myocardial infarction or stroke. Events of this type severely worsen patient prognosis, and the early detection of atherosclerosis.

The new CNIC finding provides a simple way to increase the accuracy of cardiovascular risk ranking in individuals without diabetes with or without prediabetes

The authors conclude that “this study establishes glycosylated hemoglobin as a mass-use biomarker because its greatest benefit is in individuals at low cardiovascular risk, who form the immense majority of the general population and account for most cardiovascular deaths in absolute terms.”

The study was funded by the Instituto de Salud Carlos III (ISCIII, PI15/ 02019, PI17/00590, PI20/00819) and the European Regional Development Fund (ERDF) “A way to make Europe” and included scientists from the CIBER de Enfermedades CardioVasculares (CiberCV) research network.

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NEJM

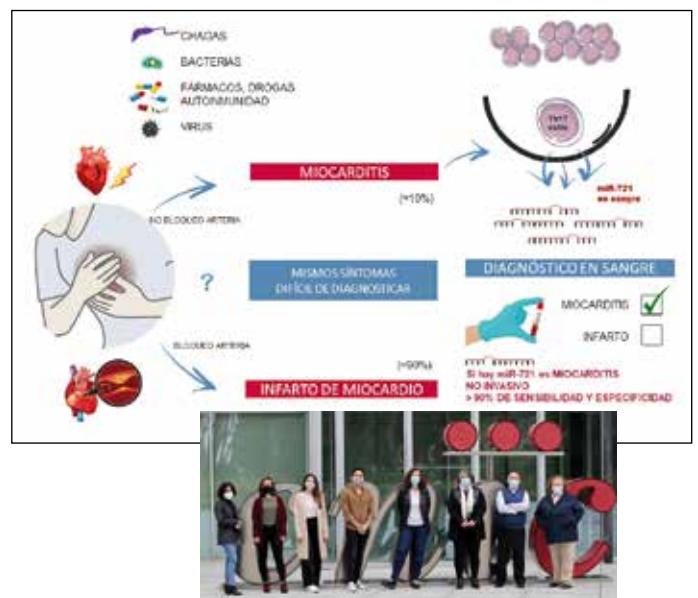
The first blood biomarker to distinguish between myocarditis and acute myocardial infarction

Scientists at the CNIC have identified the first blood biomarker for myocarditis, a cardiac disease that is often misdiagnosed as myocardial infarction. Nevertheless, the

diagnosis of myocarditis continues to be challenging in clinical practice.

The study, led by **Dr. Pilar Martín** and published in *The New England Journal of Medicine*, has detected the presence of the human homolog of micro RNA miR-721 in the blood of myocarditis patients.

CNIC General Director **Dr. Valentín Fuster** emphasizes that these results of paramount importance because they establish the first validated blood marker with high sensitivity and specificity (>90%) for myocarditis. This will allow clinicians to distinguish between this disease and other cardiomyopathies like acute myocardial infarction, myocardial infarction with nonobstructive coronary arteries (MINOCA), and other inflammatory diseases with an autoimmune origin.



“Our finding has great potential as a valuable clinical tool for the precise and noninvasive diagnosis of myocarditis from small drops of blood,” says **Dr. Martín**, whose project is funded by a Fundación BBVA Beca Leonardo award.

The diagnosis of myocarditis is challenging, and the availability of a sensitive and specific marker of acute myocardial inflammation could have a major clinical impact, improving the diagnosis of myocarditis both generally and particularly in its early phases.

Myocarditis is an inflammatory disease of the heart caused by infection, toxins, drugs, or autoimmune disorders. If untreated, myocarditis can progress to potentially fatal dilated cardiomyopathy, requiring heart transplant.

The prevalence of myocarditis remains uncertain because it is often difficult to achieve a confirmed diagnosis.

Myocarditis is usually diagnosed after coronary angiography or computed tomography scans have discarded coronary artery disease, followed by confirmation of the diagnosis by magnetic resonance imaging (MRI).

However, not all centers have access to MRI technology, and the current gold standard for myocarditis diagnosis is endomyocardial biopsy, an invasive procedure normally reserved for severe cases. There is thus a pressing clinical need for the development of reliable and accessible tools for the early diagnosis of acute myocarditis.

Moreover, myocarditis is a side effect that, although very rare, is potentially serious in cancer patients who are receiving treatment with immunotherapy drugs called “immune checkpoint inhibitors”.

There are currently no specific markers for the diagnosis of patients susceptible to developing myocarditis during cancer immunotherapy.

The researchers are currently designing studies to evaluate the potential of the biomarker as a predictor of short-term and long-term risk, the persistence of myocardial inflammation, and the risk of relapse, clinical progression, and adverse ventricular remodeling.

The CNIC is the sole owner of a patent related to the biomarker and its use for the diagnosis of myocarditis. The CNIC is now exploring licensing agreements with industrial partners to develop and commercialize this technology in order to make it available for clinical use.

The study received funding from the Ministerio de Ciencia e Innovación (MICINN) through the Instituto de Salud Carlos III (ISCIII)-Fondo de Investigación Sanitaria; the CIBERCV; the Comunidad de Madrid; a Fundación BBVA Beca Leonardo award; Fundació La Marató TV3; and European Research Council grants ERC-2011-AdG 294340-GENTRIS to F.S.-M. and ERC-2018-CoG 819775-MATRIX to B.I.

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JITC

CNIC scientists discover a new strategy to improve cancer immunotherapy

Scientists at the CNIC have designed a new strategy to potentiate immunotherapy, the treatment that has revolutionized cancer management. In the study, published in



the *Journal for Immunotherapy of Cancer*, the team led by **Dr. David Sancho** identifies a mechanism through which dead tumor cells stall the response of the immune system, reducing the antitumor capacity of immune cells that attack cancers.

The scientists improved the efficacy of cancer immunotherapy through an approach that combines blocking antibodies with cytokines or chemotherapy treatments that promote the development of dendritic cells. The team believe that this approach can be transferred to the clinic to optimize cancer immunotherapy.

Immunotherapy consists of reprogramming the immune system to recognize and eliminate tumor cells.

Unfortunately, not all patients benefit from this approach, because many cancers develop mechanisms to evade the immune system. One of these mechanisms consists of impeding the migration of immune cells to the tumor microenvironment. “The immune system has the ability to enter the tumor and eliminate it, thus improving patient prognosis. However, this does not always happen, and the aim of this project was to strengthen this capacity,” explained study coordinator **Dr. David Sancho**, who heads the Immunobiology laboratory at the CNIC.

The study shines a light on the mechanisms that promote correct infiltration of the tumor by antitumor immune cells and proposes a new strategy to potentiate this infiltration in antitumor immunotherapy.

The type of immune cells that enter the tumor has a major influence on cancer patient survival. Survival is higher after infiltration by CD8 T cells, which eliminate tumor cells, and by dendritic cell subtypes that attract and activate CD8 T cells. Scientists in the field have therefore focused their efforts on developing methods to increase the numbers of these cells in the tumor microenvironment.

Immune cells have an extensive repertoire of receptors through which they interact with their environment, allowing them to recognize pathogens and also detect tissue damage. **Dr. Sancho's** team recently showed that the detection of dead cells by the receptor DNGR-1, expressed on dendritic cells, prevents excessive inflammation. In cancer, this action can cause more harm than good. “High immune-cell infiltration of the tumor microenvironment will promote tumor elimination by the immune system,” said **Dr. Sancho**.

Dendritic cells form part of the innate immune system, the body's first line of defense. The presence dendritic cells in the tumor environment "goes a long way to ensuring an immune response against the tumor that will improve patient prognosis," said **Dr. Fresno**.

In the new study, the scientists found that the recognition of dead tumor cells through DNGR-1 expressed on dendritic cells prevents further infiltration of both dendritic cells and the tumor-eliminating CD8 T cells, thus preventing the immune system from attacking the tumor. The researchers managed to increase the efficiency of antitumor immunotherapy by using blocking antibodies in combination with cytokines or chemotherapy to promote dendritic cell development.

Immunotherapy is the reprogramming of the immune system to recognize and eliminate tumor cells; however, this approach does not work in all patients because many cancers develop mechanisms to evade the immune response

The research shows that the antitumor activity of dendritic cells can be promoted through targeted interventions. The first of these is the administration of the cytokine Flt3L, and the second is antibody blockade of DNGR-1. Flt3L acts as a 'stimulant', increasing the numbers of dendritic cells and promoting their entry into the tumor microenvironment. The team also found that circulating levels of Flt3L can be increased by stimulating the body's own production of the cytokine with specific chemotherapy treatments.

The new study shines a light on some of the mechanisms that promote correct tumor infiltration by antitumor immune cells and proposes a new strategy to potentiate this infiltration and antitumor immunotherapy. The study thus identifies a new tool for combating cancer by strengthening the body's own defense.

The study was funded by the Fundación "la Caixa", the Asociación Española contra el Cáncer (AECC), the National Institute for Health Research Manchester Biomedical Research Center, the European Research Council (ERC-2016-Consolidator Grant 725091), the European Commission (635122-PROCROP H2020), the Ministerio de Ciencia, the Agencia Estatal de Investigación (AEI), the European Regional Development Fund (ERDF) (SAF2016-79040-R), the IMMUNOTHERCAN de la Comunidad de Madrid, a FIS-Instituto de Salud Carlos III grant, the Fundación Acteria, Atresmedia (Constantes y Vitales), and Fundació La Marató de TV3.

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NATURE COMMUNICATIONS

Inhibition of proteins activated by nitric oxide reverses aortic aneurysm in Marfan syndrome

Scientists at the CNIC and Centro de Biología Molecular Severo Ochoa (CBM-CSIC-UAM) have discovered that the nitric oxide (NO) pathway is overactivated in the aortas of mice and patients with Marfan Syndrome and that the activity of this pathway causes the aortic aneurysms that characterize this disease.

The results of the study, published in **Nature Communications**, reveal the essential role played by NO in Marfan Syndrome aortic disease and identify new therapeutic targets and markers of NO pathway activation that could be used to monitor disease status and progression.

Aortic aneurysm (AA) is a progressive dilatation and weakening of the aortic wall. AA can be harmless, but in some patients can lead to dissection (rupture) of the aorta, resulting in death.

The study, funded by the Fundación "la Caixa", identifies new biomarkers associated with this syndrome that have the potential to improve the clinical treatment and prognosis of Marfan Syndrome patient's syndrome.

Marfan Syndrome is a hereditary disease that affects connective tissues, which are the fibrous structures that bind and anchor all the organs and tissues in the body. Marfan Syndrome principally affects the skeleton, the eyes, the heart, and the blood vessels. A particularly common disease manifestation is thoracic aortic aneurysm and dissection (TAAD). Aortic dissection accounts for more than 90% of deaths associated with Marfan Syndrome.

Current treatments for Marfan Syndrome are aimed at reducing blood pressure on the artery wall, but do not prevent its deterioration. The only effective intervention for the aortic disease in Marfan Syndrome is surgery.

The researchers therefore recognize "the urgent need to identify new targets for the development of pharmacological treatments for TAAD in Marfan Syndrome."

The researchers have demonstrated that silencing or inhibiting the activity of these proteins completely reverses the aortic disease in a mouse model of Marfan Syndrome

The study reveals the essential role played by NO in Marfan Syndrome aortic disease. "We previously detected high expression of a protein with a high capacity for NO production in the aortas of Marfan Syndrome patients and an

animal model of the disease, and we therefore undertook an in-depth investigation of the role of NO in the associated aortic disease," explained.

"We observed that treatment of healthy mice with supra-pharmacological doses of an NO donor induced TAAD similar to that seen in Marfan mice. The NO donor treatment also reproduced the degeneration of the aortic wall, an essential step in the development of TAAD," added **Dr. Redondo**. "Through these experiments, we showed that elevated production of NO is necessary and sufficient for the development of TAAD in Marfan Syndrome."

Given this important role of NO in the development of TAAD, the researchers decided to focus on the enzymes soluble guanylate cyclase (sGC) and type I cGMP-dependent protein kinase (PRKG1), two NO-regulated proteins. "Our analysis detected elevated activities of both sGC and PRKG1 in samples from mice and patients with Marfan Syndrome," said **Dr. Redondo**.

"We were able to completely reverse the aortic disease in Marfan mice by treating them with inhibitors of these two proteins or by genetically silencing the expression of Prkg1, demonstrating that the NO-sGC-PRKG1 pathway mediates the development of TAAD in Marfan Syndrome," added **Dr. Campanero**.

Given the need for new pharmacological treatments for Marfan Syndrome aortic disease, "the results of this study open the way to the use of sGC and PRKG1 inhibitors in preclinical and clinical trials for this syndrome and possibly other aortic diseases," said **Dr. Redondo**.

The research team also explored possible "footprints" left by high NO levels in the blood.

"This discovery has important implications for patients with this syndrome, because these molecules could be used as biomarkers for disease monitoring, and we are now studying their potential as prognostic indicators," explained **Dr. Redondo**.

The study was funded by the Fundación "la Caixa" through the CaixaResearch Call for Health Projects with 500.000 euros, the Ministerio de Ciencia, Investigación y Universidades, Comunidad de Madrid, el CSIC, la **Fundación Pro CNIC**, Marfan Foundation, the Fundación La Marató y the CIBER de cardiovascular (CIBER-CV) Instituto de Salud Carlos III.

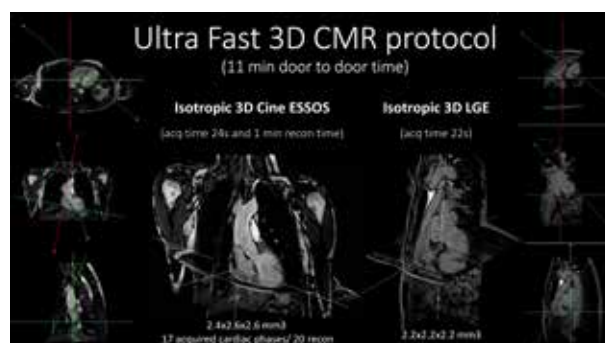
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JACC

CNIC and Philips develop ultrafast cardiac magnetic resonance technology that analyzes the heart in less than 1 minute

Scientists at the CNIC and Philips have developed a revolutionary technology that can perform cardiac magnetic resonance (CMR) scans in under a minute. ESSOS (Enhanced SENSE by Static Outer volume Subtraction) allows precise assessment of heart anatomy and function, as well as reducing healthcare costs and increasing patient comfort. The new methodology has been tested on more than 100 patients with diverse heart conditions. The results have just been published in **JACC: Cardiovascular Imaging**, the world-leading journal in the field of cardiac imaging.

CMR provides a noninvasive and radiation-free method for exploring the heart and is the ideal technique for studying heart anatomy, function, and even cell composition. Although most hospitals have magnetic resonance scanners, these are not often used for heart studies because a complete CMR study takes so long. Study first author **Dr. Sandra Gómez-Talavera**, a CNIC investigator and cardiologist at Fundación Jiménez Díaz University Hospital, explained that "a complete CMR study takes 45-60 minutes, and many patients don't go through with it because remaining in the scanner for this long is too uncomfortable."



In addition, hospital magnetic resonance scanners are needed for other studies, limiting their availability for long-duration cardiac studies.

To overcome these obstacles to CMR, CNIC scientists working in partnership with Philips have developed a technique for accelerated CMR acquisition. The technique, explained **Dr. Gómez-Talavera**, "allows the study of the anatomy and function (motility) of the heart muscle, as well as infarcted and fibrotic tissue. The method can be used to study the whole thoracic cavity in 3D, with algorithms used to focus exclusively on the heart and major vessels (the mobile elements), reducing the scan time."

The technique, called ESSOS (Enhanced SENSE by Static Outer volume Subtraction), has been tested on more than 100 patients with diverse heart conditions

"We have demonstrated in a large group of patients that CMR with this technology yields the same information as the standard technique, but for less than 10% of the pa-

tient scan time," said **Dr. Borja Ibáñez**, CNIC Clinical Research Director, a cardiologist at Fundación Jiménez Díaz University Hospital, and CIBERCV group leader. **Dr. Ibáñez** is one of the two lead authors on the study.

ESSOS is protected by a patent held jointly by the CNIC and Philips and is the fruit of almost 10 years' collaboration. The research team believe that this new technology will revolutionize cardiac imaging.

ESSOS allows images to be obtained 34 times faster than with the standard technology in current use. "All the information needed to understand heart form and function can be acquired in a little over 20 seconds," indicated **Sánchez-González**, adding that "a further 20-second acquisition is all that is needed to detect infarction or fibrosis. This brings the scan to an end, in less than 1 minute."

A key advantage of the technology is that it can be used with the magnetic resonance scanners already installed in hospital

The research was funded by the Instituto de Salud Carlos III through a FIS technology development grant, a Spanish Society of Cardiology Translational Research award, the European Research Council (ERC), and the Comunidad de Madrid (Red Madrileña de Nanomedicina en Imagen Molecular).

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JACC

CNIC researchers explain how high blood pressure, the most important cause of disease worldwide, accelerates atherosclerosis

High blood pressure, the most important cause of disease worldwide, accelerates atherosclerosis but the mechanism is unknown. Using gene modified minipigs, researchers from the Centro Nacional de Investigaciones Cardiovasculares (CNIC) and Aarhus University (Denmark), demonstrate that high blood pressure alters the structure of arteries leading to more accumulation of LDL cholesterol and faster development of atherosclerosis. The study has been published in the **Journal of the American College of Cardiology (JACC)**.

Blood pressure-lowering drugs are routinely used to prevent the development of atherosclerosis and heart disease, but the mechanism of this effect is still unknown. People suffering from high blood pressure (hypertension) often have accompanying changes in the hormones that



control blood pressure and it has been unclear whether the pressure itself or the hormonal changes are the driver of accelerated atherosclerosis.

To investigate this, researchers from the CNIC and Aarhus University analyzed the development of atherosclerosis in minipigs that were genetically engineered to have high blood cholesterol and develop atherosclerosis.

Minipigs have arteries that are very similar in structure to human arteries and like humans they develop atherosclerosis in the heart when exposed to high blood cholesterol, Dr. Jacob Fog Bentzon comments, coordinator of the study published in **JACC**. As is also the case in humans, the development of the early stages of the disease is asymptomatic and therefore experiments on atherosclerosis can be conducted in minipigs with high animal welfare.

By manipulating blood pressure in the pigs and by analyzing the effects on arteries in the heart, the researchers found that the direct forces of pressure on arteries leads to structural changes that facilitate the development of atherosclerosis. "Arteries become denser and allow less passage of molecules from the blood. This includes the LDL particles that carry blood cholesterol, which instead accumulate in the innermost layer of arteries, where they drive the development of atherosclerosis", **Dr. Jacob Fog Bentzon** explains.

This finding uncovers an intimate relationship between the most important risk factors for atherosclerosis, LDL cholesterol and high blood pressure. While it has been known for decades that accumulation of LDL particles in arteries lead to atherosclerosis, the new research shows that high blood pressure accelerates the accumulation of LDL. Therefore, high blood pressure aggravates the effect of having high LDL cholesterol in the blood.

The new insight supports the need to keep both LDL cholesterol and blood pressure low throughout life by healthy diet choices, weight control, exercise, and, when needed, by drug therapy. "It could also pave the way for the development of more effective therapies to offset the detrimental effects of hypertension on atherosclerosis", the researchers conclude.

The research was a collaboration among the Experimental Pathology of Atherosclerosis at CNIC, the Cardiovascular Proteomics groups at CNIC, CIBER de Enfermedades Cardiovasculares, and the Atherosclerosis Research Unit at Aarhus University in Denmark.

The work at CNIC was funded by the Ministerio de Economía, Industria y Competitividad with cofunding from the Fondo Europeo de Desarrollo Regional (SAF2016-75580-R and PGC2018- 097019-B-I00), the Instituto de Salud Carlos III-Fondo de Investigación Sanitaria (IPT17/0019-ISCIII-SGEFI/ERDF, ProteoRed), the Fundació la Marató de TV3 (grant 122/C/2015) and “la Caixa” Foundation (project code HR17-00247).

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doi: 10.1016/j.jacc.2020.11.059

JACC

CNIC scientists identify mutations acquired by blood cells that accelerate heart failure progression

A team of scientists at the CNIC and the Hospital Universitario Virgen de la Arrixaca in Murcia has discovered that clonal hematopoiesis increases the risk of rapidly progressing heart failure, one of the chief causes of death in the world.

The adult human body produces hundreds of billions of blood cells every day. This essential process unavoidably leads to the appearance of mutations in the DNA of the progenitor cells. These are known as somatic mutations because they are acquired, not inherited. While most of these mutations are innocuous, occasionally a mutation gives affected cells a competitive advantage that allows them to expand progressively, generating clonal populations of blood cells. This phenomenon is known as clonal hematopoiesis.

Clonal hematopoiesis is linked to aging, because over time there is an increasing chance that a culprit mutation will be produced, explained **Dr. José Javier Fuster**, coordinator of the study published in the *Journal of the American College of Cardiology (JACC)*.

“Recent studies showed that people with clonal hematopoiesis have a higher risk of developing hematological cancers and dying. Curiously, however, the death of these patients is often due not to the cancer, but to cardiovascular causes.”

“There is established evidence linking clonal hematopoiesis to an increased risk of atherosclerosis, the underlying

cause of most heart attacks and a high proportion of strokes,” commented **Dr. Domingo Pascual-Figal**, an external investigator at the CNIC and a cardiologist at the Hospital Universitario Virgen de la Arrixaca in Murcia.

The study shows that clonal hematopoiesis is an important pathological process that accelerates and aggravates the clinical progression of heart failure, independently of the presence of atherosclerosis.

In the new study, which included input from the CNIC Genomics and Bioinformatics Units and investigators at Hospital Universitari Germans Trias i Pujol in Badalona (Barcelona), the research team analyzed how the presence of mutations linked to clonal hematopoiesis affects the clinical progression of patients with ischemic or non-ischemic heart failure.

Commenting on the results, **Dr. Fuster** said that, independently of the origin of heart failure, “the presence of these mutant blood-cell clones aggravates disease progression and worsens prognosis.”

Dr. Pascual-Figal explained that the specific study finding was that “clones with mutations in 2 genes frequently linked to clonal hematopoiesis, TET2 and DNMT3A, were associated with a higher risk of heart-failure-related hospitalization and death.”

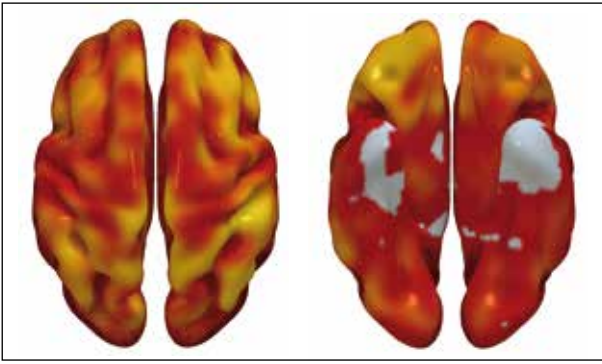
For the researchers, these findings “demonstrate the importance of clonal hematopoiesis as a pathogenic process that accelerates and aggravates heart failure progression, independently of the presence of atherosclerosis.”

The authors conclude that their study supports the emerging idea that “clonal hematopoiesis represents a new cardiovascular risk factor and an important link between aging and cardiovascular disease.” The results, moreover, “open the way to the development of personalized therapies for patients with these somatic mutations, with the aim of preventing heart failure progression.”

The study was funded by a Beca Leonardo para Investigadores y Creadores Culturales (2019) from the Fundación BBVA, the Carlos III Institute of Health, the Spanish Ministry of Science and Innovation, and the Fundación Séneca de Ciencia y Tecnología de la Región de Murcia. **José Javier Fuster** is a member of the Transatlantic Network on “Clonal hematopoiesis and atherosclerosis” funded by the Leducq Foundation.

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doi:10.1016/j.jacc.2021.02.028





JACC

Scientists uncover early links between cardiovascular risk and brain metabolism

The links between cardiovascular disease and cognitive impairment begin years before the appearance of the first clinical symptoms of either condition. In a study carried out at the CNIC in partnership with Santander Bank and neuroimaging experts at the Barcelonaβeta Brain Research Center (BBRC, the research center of the Fundación Pasqual Maragall), the investigators have identified a link between brain metabolism, cardiovascular risk, and atherosclerosis during middle age, years before the first appearance of symptoms.

The report, published in the *Journal of the American College of Cardiology (JACC)*, is important because it suggests that intervention in a modifiable condition (cardiovascular disease) could prevent the development of dementia, a disease for which there is currently no cure.

Dr. Valentín Fuster, CNIC and Mount Sinai Heart General Director, Physician-in-Chief of the Mount Sinai Hospital, and a lead author on the study, explained that “although everybody knows about the importance of caring for ourselves and controlling cardiovascular risk factors in order to avoid a heart attack, the association of these same risk factors with cognitive decline may increase awareness of the need to acquire healthy habits from the earliest stages of life.”

Moreover, the results provide yet more support for the importance of implementing primary cardiovascular prevention strategies in middle age as a valuable therapeutic approach to slowing or even halting brain alterations that could contribute to future cognitive decline.

The advanced stages of vascular disease and dementia often occur together, but until now this association has not been documented at earlier stages. The CNIC-coordinated study, led by **Dr. Marta Cortés Canteli**, shows that in middle age, years before any clinical signs appear, atherosclerosis and cardiovascular risk factors already show an association with low metabolism in brain regions implicated in the future development of dementia, especially Alzheimer disease.

Using advanced imaging by positron emission tomography (PET), the research team quantified brain metabolism in

more than 500 participants in the PESA-CNIC-Santander study. The participants had an average age of 50 years and no symptoms, but already had evidence of atherosclerosis in their arteries.

PESA-CNIC-Santander, directed by **Dr. Valentín Fuster**, is a prospective study of more than 4000 asymptomatic middle-aged participants who have been exhaustively assessed for the presence and progression of subclinical atherosclerosis since 2010.

“We found that a higher cardiovascular risk in apparently healthy middle-aged individuals was associated with lower brain metabolism in parietotemporal regions involved in spatial and semantic memory and various types of learning,” said **Dr. Cortés Canteli**. **Dr. Juan Domingo Gisbert**, head of the Neuroimaging group at the BBRC, noted that “the brain areas showing low metabolism in participants with higher cardiovascular risk are the same areas affected in Alzheimer disease, suggesting that these individuals may have higher than normal vulnerability to this disease.”

The study is the largest of its type to date in a healthy middle-aged population and could signal a paradigm change in the understanding of the links between vascular and brain disease, say the authors.

Among the modifiable cardiovascular risk factors most closely associated with a reduction in brain metabolism, the investigators saw the biggest effect with hypertension. “We found that the same risk factors that damage the heart and the large arteries, and especially hypertension, are closely linked to the decline in brain metabolism years before the appearance of symptoms,” said **Dr. Fuster**.

The research team also found that a higher number of plaques in the carotid arteries, which carry blood to the brain, was associated with lower brain metabolism in areas of the limbic system and the parietal lobe, both of which are intimately linked to the development of Alzheimer disease.

“The next step will be to determine whether individuals with subclinical atherosclerosis in the carotid arteries and low brain metabolism at the age of 50 go on to experience cognitive decline 10 years later,” said **Dr. Cortés Canteli**.

These results will be a major stimulus for the implementation of early intervention strategies to reduce the incidence of cognitive decline in old age.

The PESA study is cofinanced equally by the CNIC and Santander Bank. PESA receives additional funding from the Instituto de Salud Carlos III, Madrid, Spain (ISCIII, PI15/O2019, PI17/O0590 & PI20/O0819), the European Regional Development Fund (ERDF - A Way to Build Europe), and the European Social Fund (ESF - Investing in Your Future). The CNIC is supported by the ISCIII, the MCIN and the Pro-CNIC Foundation. The BBRC is financed mainly

by the Fundación "la Caixa", the EU/EFPIA (European Federation of Pharmaceutical Industries and Associations) Innovative Medicines Initiative Joint Undertaking EPAD, and the Innovative Medicines Initiative 2 Joint Undertaking. This joint project was supported by the European Union Horizon 2020 research and innovation programme and the EFPIA.

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SCIENCE ADVANCES

Scientists identify a mechanism through which dendritic cells improve their antiviral and immune-activation abilities

Researchers at the CNIC led by **Professor Francisco Sánchez-Madrid** have found that dendritic cells, which initiate specific immune responses, can reprogram their genes to improve their immune response. The results of the study, funded by Fundación "la Caixa" and published in *Science Advances*, could have important applications in the development of new vaccination and immunotherapy strategies.



Dendritic cells are professional antigen-presenting cells that initiate adaptive or specific immune responses. As described by the research team, "dendritic cells capture possible pathogenic agents in different tissues and entry sites, process their components, and transport them to lymph nodes. Here, they establish communication with T lymphocytes through the formation of a specialized structure called the immune synapse. The immune synapse allows the dendritic cell to present processed components of the infectious agent to a T cell, so that they can be recognized and initiate a specific T cell immune response."

Until now, activation of T lymphocytes was thought to be dendritic cells' main function. However, **Prof. Francisco Sánchez-Madrid's** group, working together with the group led by **Dr. Almudena R. Ramiro**, have discovered that the dendritic cell also receives information from the T cell via the immune synapse. "The T cell sends instructions that induce a change in the dendritic cell's gene-expression program, promoting the expression of genes related to motility, antiviral responses, and secretion and thereby increasing the dendritic cell's capacity to generate protective anti-pathogen immune responses," explained **Sánchez-Madrid**.

"This study describes how gene-expression changes are accompanied by changes in epigenetic marks on DNA. These epigenetic marks in turn produce transient changes in specific genes that promote or hinder their expression," explained first authors **Irene Fernández Delgado** and **Diego Calzada Fraile**.

The research team found that, after participating in an immune synapse, dendritic cells migrate more efficiently to lymph nodes, where most processes involved in the activation of specific or adaptive immune responses take place.

The new study, carried out in close partnership with the CNIC Bioinformatics Unit (directed by **Fátima Sánchez-Cabo**) and Genomic Unit (**Ana Dopazo**), describes a new mechanism that explains how dendritic cells improve their antiviral and immune-activation abilities.

The researchers conclude that their study shows that dendritic cells, responsible for initiating specific immune responses, reprogram their genes through altered epigenetic DNA marks after interacting with a cognate T cell. "These changes improve their motility, so that they arrive sooner at immune response activation sites, representing a new mechanism for potentiating the immune response."

The results also have potential applications in the development of new vaccination and immune therapy strategies. For example, the described mechanism could be used to generate super-migratory post-synaptic dendritic cells able to induce stronger and more effective immune responses.

The study was supported by funding from Fundación "la Caixa" through Health Research Projects call HR17-00016 and an INPhINIT 'Retaining' doctoral project grant". ■

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CURING FATAL TACHYCARDIA

DR. SILVIA PRIORI'S RESEARCH GROUP BELIEVES THAT FINDING NEW THERAPIES TO COMBAT FATAL TACHYCARDIA WILL REDUCE THE SUDDEN DEATHS ASSOCIATED WITH THIS PATHOLOGY AND ALSO REDUCE ARRHYTHMIAS AMONG HEART FAILURE PATIENTS

During its life, the heart beats millions of times, most of which go completely unnoticed; irregular heartbeats, known as arrhythmias, can cause a heart to stop beating regardless of age.

For young people, the cause is usually due to inherited genetic defects that affect how the cardiac muscle works. Strenuous exercise and strong emotions can also trigger the onset of this type of arrhythmia. The heart begins to beat too fast, causing a loss of consciousness because not enough blood reaches the brain.

Beta blockers, which block cardiac cell adrenaline receptors, are one of the treatments used to prevent arrhythmias.

However, having to take medicine every day for your whole life represents a challenge for many patients.

Implantable defibrillators are another treatment option for these patients, but such devices may interfere with the daily life of adolescents.

The current research of **Professor Silvia Priori** of the Spanish National Centre for Cardiovascular Research (CNIC) Molecular Cardiology Laboratory and cardiologist of the Istituti Clinici Scientifici Maugeri de Pavia (Italy) seeks a solution to this condition.

Since traditional treatments are not sufficient to tackle some of the most serious diseases in the industrialised world, gene therapies could revolutionise modern medicine. **Professor Priori's** group holds an ERC advanced grant, "EU-rhythmy", one of the aims of which is to develop a gene therapy strategy to prevent cardiac arrest among patients with arrhythmias of genetic origin.

“Our preliminary data show that the absence of TRDN triggers the upregulation or downregulation of several proteins and leads to disorders to mitochondria in the heart”



As **Dr. Priori** explains, the aim of gene therapy is to cure the diseases that genetic mutations cause by correcting the effects the defective gene.

The therapy is based on introducing the correct version of a gene or modifying the expression of mutant genes; however, as there are millions of copies of these defective genes, it is no easy task to do this correctly.

Despite the challenges, **Professor Priori** and her team have developed a gene therapy to combat two causes of cardiac arrest: dominant catecholaminergic polymorphic ventricular tachycardia (CPVT) and Timothy syndrome.

This research, with European Research Council (ERC) funding, could constitute the step from treatment to cure of this kind of disease.

Another project led by **Dr. Priori**, Relation between triadin loss and cardiac proteostasis in catecholaminergic polymorphic ventricular tachycardia type 5, has been selected by the Fundación “La Caixa” in the fourth CaixaResearch Health Call and will receive funding of €496,100.

This project will study genetic variant five of CPVT (CPVT5), which causes a reduction in the expression of the protein TRDN as also occurs in heart failure, a disease that affects millions of patients. CPVT5 has a recessive inheritance pattern and is highly lethal in children; currently there is no effective therapy able to prevent premature death.

“Our project will advance knowledge about CPVT5, which is caused by mutations that induce the loss of triadin (TRDN), a sarcoplasmic reticulum junction (JSR) protein

that is a constituent of the macromolecular ryanodine receptor (RyR2)," says **Professor Priori**.

She also explains, "Our preliminary data show that the absence of TRDN triggers the upregulation or downregulation of several proteins and leads to disorders to mitochondria in the heart".

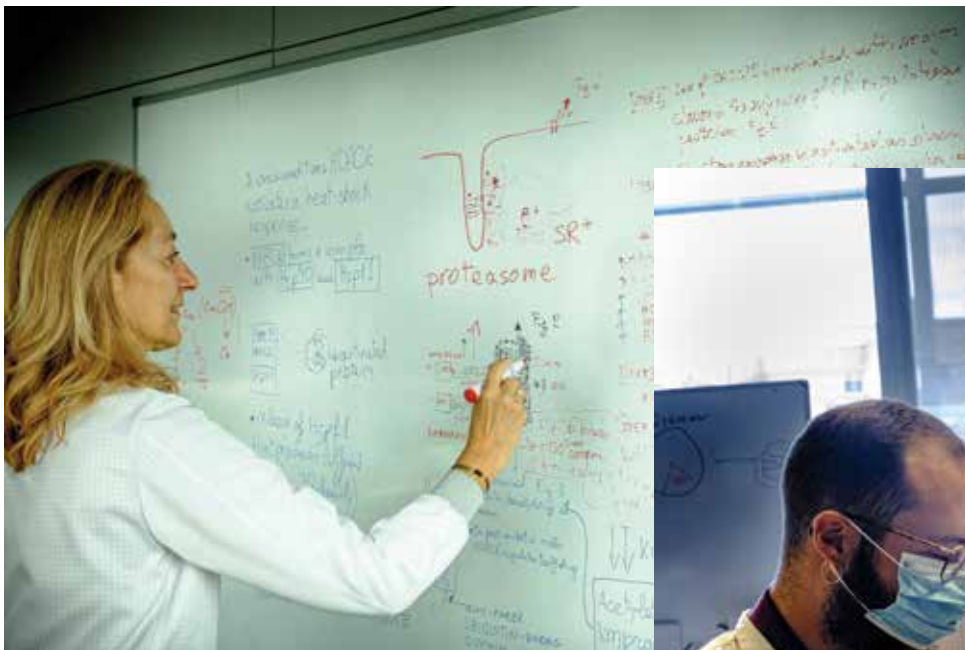
The hypothesis put forward by **Dr. Priori** is that "...arrhythmias are not simply the result of anomalous calcium handling, but arise from the dysregulation of other pathways that we are identifying."

The project seeks to identify new therapeutic targets and test whether their modulation is able to mitigate the effect of lethal arrhythmias.

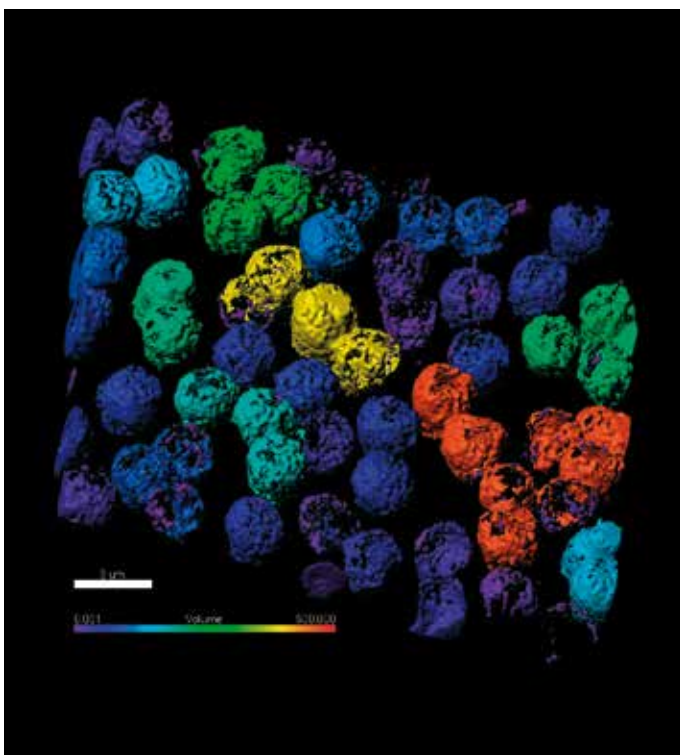
The investigator adds, "...by discovering new therapies, our research will reduce the mortality associated with CPVT5 and may also decrease arrhythmias among patients with heart failure."

In conclusion, the researchers believe that by investigating the model of CPVT5, "We will identify new disease mechanisms and relevant therapeutic approaches for patients with CPVT5 and for the general population affected by heart failure." ■

Since traditional treatments are not sufficient to tackle some of the most serious diseases in the industrialised world, gene therapies could revolutionise modern medicine



TRIMA: THE MOST COMPREHENSIVE SPANISH NANOSCOPY PLATFORM



On 23 April 2019, the then Ministry of Science, Innovation and Universities and CNIC, the Spanish National Centre for Cardiovascular Research, signed an agreement to expand the capacity of the TRIMA node of ReDIB, the medical images distribution network. On the point of completion, the update includes an increase in the capacity and super-resolution imaging services that the node offers.

ReDIB is a Unique Science and Technology Infrastructure (ICTS) for distribution comprised of CNIC's TRIMA (advanced translational imaging infrastructure), the CIC-bioMaGUNE's functional and molecular imaging platform, the La Fe University Hospital's Foundation for Research imaging platform and the Complutense University's bio-imaging Unit. This ICTS forms part of the current ICTS Map, approved by the Science, Technology and Research Policy Council (CPTI) on 6 November 2018.

Within the ReDIB Preclinical Imaging Section, the TRIMA node provides the Nanoscopy platform with set of equipment for the typification of biomolecules at an early stage and the ultrastructural analysis of subcellular organelles

using multicolour fluorescent markers. An investment plan was drawn up aimed at increasing the flexibility of this platform to update existing resolution capacities for super-resolution imaging. With this objective in mind, the current project increases the Nanoscopy Platform's flexibility and capacity, adapting it for ultra-rapid, multi-colour, in-vivo image capture.

The initial total budget for the project is €640,000, 50% of which will be co-funded by the European Regional Development Fund (FEDER) under the Pluri-Regional Operational Programme for Spain 2014 2020, assigned to the Ministry of Science and Innovation's General Secretariat for Research, with the objective of funding projects and actions related with infrastructure included in the current ICTS Map. CNIC will contribute the other 50% of funding.

This operation is the most comprehensive Spanish nanoscopy platform, a unique facility that offers the most advanced technologies in the field of resolution imaging for biomedicine and life sciences, and will be accessible to a large number of academic and industrial professionals, in addition to students and researchers. All of which will increase the scientific and technological competitiveness of this ICTS, expanding its flexibility and potential uses, as well as providing pioneering imaging capacities for complex in-vivo studies. ■

The TRIMA node provides the Nanoscopy platform with set of equipment for the typification of biomolecules at an early stage and the ultrastructural analysis of subcellular organelles using multicolour fluorescent markers

CNIC AND PHILIPS DEVELOP A TECHNIQUE THAT ENABLES ASSESSMENT OF HEART ANATOMY BY MRI IN ONLY 15 SECONDS

THE DEVELOPMENT OF THIS **3D T1 MAPPING TECHNIQUE**,
CALLED "SACORA", COMES AS PART OF THE ONGOING
COLLABORATION BETWEEN CNIC AND PHILIPS

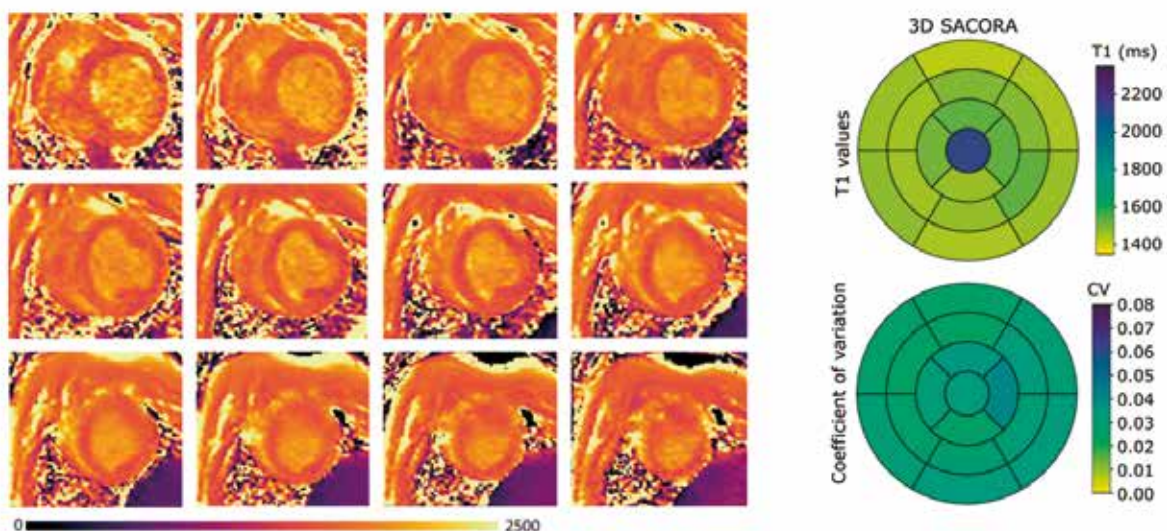
The Spanish National Centre for Cardiovascular Research (CNIC) and Philips, with support of the European project the 4D-Heart (Marie Skłodowska-Curie training programme N722427) coordinated by the CNIC, have developed a technique that makes it possible to obtain information about the composition of cardiac tissue (MRI mapping) in a single apnea, i.e., with the subject holding their breath for 15 seconds.

The new technique to assess the composition of cardiac tissue, called SACORA (SATuration recovery COMPresses SENSE Rapid Acquisition), has been validated in an animal model. The results were published in **MAGMA**, a specialist

journal for magnetic resonance imaging, and allow us "to obtain quantitative data about the composition of cardiac tissue of the whole heart in an acquisition time that is radically shorter than that required for standard T1 mapping", explains **Dr. Borja Ibáñez**, Director of the CNIC Clinical Research Department, cardiologist at the Fundación Jiménez Díaz and member of CIBERCV, the cardiovascular disease biomedical research centre.

Magnetic resonance imaging allows the anatomy (shape) and function (contractions) of the heart to be seen with great precision. Recently, additional magnetic resonance imaging techniques have appeared that allow us to study

In-vivo validation (entire 3D volume in 15s)



With this new method, developed by CNIC and Philips, it is no longer necessary to go “slice by slice” to obtain information about the whole heart, as the whole volume (3D) is acquired in one go

SACORA is the “combination of intelligent selection of the acquisition parameters based on the compressed sensing method of MRI acquisition that gives precise, independently reproducible T1 values independently of the patient’s heart rate”

not only the heart’s form and function, but also its composition. “These mapping sequences are the equivalent of a histological study, but are in vivo, and non-invasive”, indicates **Dr. Ibáñez**.

It has been shown that the composition of cardiac tissue plays an important role in the propensity to develop future heart problems. The ‘T1 mapping’ technique allows us to see the composition of the cardiac muscle and, therefore, its use is becoming routine in the study of heart diseases. These techniques provide what are known as T1 mapping that measure an intrinsic property of the tissue, called relaxation time, when exposed to the magnetic field.

The ‘T1 mapping’ technique allows us to see the composition of the cardiac muscle and, therefore, its use is becoming routine in the study of heart diseases

The presence of areas of microscopic fibrosis, which are not visible with classic methods, can be studied using these T1 mapping techniques. Such diffuse fibrosis is associated with the development of arrhythmias, heart failure and other malignant diseases. Until now, it has been necessary to sweep the heart, taking multiple stills in order to include the whole ventricle and complete T1 mapping of the whole heart, “like slices of bread”, explains **Ibáñez**. With this new method, it is no longer necessary to go “slice

by slice” to obtain information about the whole heart, as the whole volume (3D) is acquired in one go.

The development of this 3D T1 mapping technique, called “SACORA”, comes as part of the ongoing collaboration between CNIC and Philips. Using SACORA, in apnea (holding air in the lungs in a similar way to when swimming underwater) it is possible to obtain information about the whole of the heart. **Dr. Sánchez-González**, technical leader of the Clinical Science organization in Philips Iberia, points out that otherwise, if ten sections (slices) were needed, it would be necessary to do ten apneas, the study would take a lot longer and consequently the patient would become more tired during the course of the MRI study.

According to **Dr. Sánchez-González**, the last-named author of the paper, SACORA is the “combination of intelligent selection of the acquisition parameters based on the compressed sensing (CS) method of MRI acquisition that gives precise, independently reproducible T1 values independently of the patient’s heart rate”.

The combination of both advances, in addition to others they are currently working on, may result in full tissue mapping in a greatly reduced period of time, which would revolutionise heart MRI diagnosis

Dr. Borja Ibáñez, co-director of the study with **Dr. Sánchez-González**, moreover indicates that, unlike other options where information is obtained from a single heartbeat, SACORA acquires data from 15 beats, and the quality of the image is even better than classic 3D acquisitions where it is necessary to compensate for respiratory movement.

The same research group has developed and patented another revolutionary MRI technique to acquire anatomy and function in a single apnea, called “VF-3D-ESSOS”. The combination of both advances, in addition to others they are currently working on, may result in full tissue mapping in a greatly reduced period of time, which would revolutionise heart MRI diagnosis. ■

Using SACORA, in apnea (holding air in the lungs in a similar way to when swimming underwater) it is possible to obtain information about the whole of the heart

cnic AWARDS AND SCHOLARSHIPS

CNIC AWARDED SEVERO OCHOA CENTRE OF EXCELLENCE ACCREDITATION

The Spanish National Centre for Cardiovascular Research, (CNIC) has again received the Severo Ochoa Centre of Excellence accreditation of Spain's Ministry of Science and Innovation. The CNIC first received this award in 2011.

The aim of this accreditation is to provide funds for and acknowledge public research centres and units of any scientific field that have impact and give scientific leadership at international level, and which collaborate in their social and business environment. It is awarded to organizational structures that have highly competitive, ground-breaking programmes that are amongst the finest in the world in their respective fields of science.

Centres must meet a series of criteria in addition to being high-impact and competitive in their field of activ-

ity on the world scientific stage. Among other criteria, the research activities must undergo periodic scientific evaluation by external, independent scientific committees and be conducted within a strategic programme that generates ground-breaking knowledge. In addition, the institution must have activities that train, select and attract human resources at an international level, and actively maintain institutional collaboration agreements with other high-level research centres, in addition to strengthening the transfer and dissemination of knowledge to society.

The Severo Ochoa Centre of Excellence accreditation is valid for four years and brings one million euros funding per year, as well as allowing priority access to other research development initiatives.

THE ASSOCIATION OF CARDIOVASCULAR IMAGING OF THE SPANISH SOCIETY OF CARDIOLOGY (SEC) AWARDS ITS GOLD MEDAL TO DR. VALENTÍN FUSTER

Dr. Valentín Fuster, Director of the Spanish National Centre for Cardiovascular Research (CNIC) is to receive the Gold Medal of the Association of Cardiovascular Imaging of the Spanish Society of Cardiology (SEC) for his original and innovative scientific activity in cardiovascular imaging to reach new frontiers in cardiovascular health of the heart and brain.

Dr. Valentín Fuster receives the medal for his innovative research activities related to public health that highlight cardiovascular imaging. In the words of **Dr. Luis Jesús Jiménez Borreguero**, President of the SEC Association of Cardiovascular Imaging, "**Dr. Fuster** has promoted major studies in this field, such as the High-Risk Plaque Initiative or the Progression of Early Subclinical Atherosclerosis, an original, pioneering project in the use of non-invasive imaging techniques to improve the estimation of cardiovascular disease progression before the onset of symptoms".

Dr. Jiménez Borreguero adds, "**Dr. Fuster's** original, fresh perspective in promoting translational research is key for



many scientific projects. In this sense, his concept and the provision of an advanced multi-modal cardiovascular imaging system as an effective nexus between basic, pre-clinical and clinical research is already bearing its scientific fruits".

Dr. Jiménez Borreguero also highlighted **Fuster's**, "determined dedication to stimulating a scientific spirit among young people through his inspiring conferences, the CNIC programmes and grants, as well as his actions to promote cardiovascular health among the general public and, in particular, that of children and the least fortunate."

DR. BORJA IBÁÑEZ WINS THE FUNDACIÓN JESÚS SERRA RESEARCH AWARD FOR HIS WORK IN THE FIELDS OF NUTRITION AND FOOD SCIENCE

Dr. Borja Ibáñez, director of the Clinical Research Department of the Spanish National Centre for Cardiovascular Research (CNIC) and cardiologist at the Fundación Jiménez Díaz, is one of the winners of the third edition of the Fundación Jesús Serra Research Awards. This initiative of the Fundación Jesús Serra, part of the Catalana Occidente group, is aimed at scientists under the age of 45 who specialise in nutrition and food.

Dr. Borja Ibáñez was awarded this recognition for his clinical research career and, specifically, for his research work on "Nutritional approaches for the prevention of cardiotoxicity associated with cancer treatments", which focuses on the development of new therapeutic intervention aimed at reducing the prevalence of chronic heart failure in cancer survivors.

According to the General Director of CNIC, **Dr. Valentín Fuster**, "There are very few researchers in the world capable of understanding translational research as **Borja Ibáñez** does, and who are able to decipher the mechanisms of disease and treatment at this molecular level to apply them in clinical practice, testing the therapies in clinical trials". For **Dr. Borja Ibáñez**, receiving this award represents the "significant recognition of a study that we consider pioneer in Europe, and which will attract great interest in the cardiovascular and oncological fields, as well as among the general public. Moreover, it will enable us to increase the



resources devoted to this project so that we can meet the targets set."

The €35,000 awarded by the Fundación Jesús Serra Research Awards in each category are destined to incentivize research in the area of nutrition and food science, a field that has proved to be essential due to its connection with health. This connection has become so consolidated that many studies and research papers indicate that lifestyles and dietary habits can prevent and improve the clinical status of some diseases such as ischaemic heart disease, hypercholesterolemia, diabetes cancer or obesity, among others.

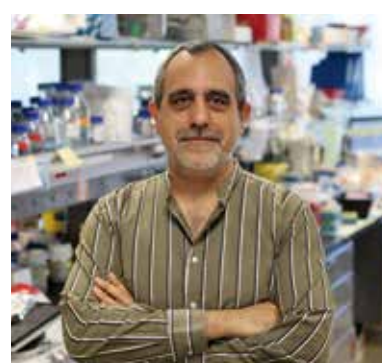
JOSÉ ANTONIO ENRÍQUEZ AND MIGUEL ÁNGEL DEL POZO, NEW MEMBERS OF EMBO

The researchers of the Spanish National Centre for Cardiovascular Research (CNIC) **José Antonio Enríquez** and **Miguel Ángel del Pozo** have been named members of the European Molecular Biology Organization (EMBO). EMBO announced the names of the 64 scientists accepted into the organization, whose members are over 1,800 of the finest researchers in Europe and the world; new members are nominated and voted for by current members. **Dr. Enríquez** and **Dr. Del Pozo** join their colleagues **Dr. Miguel Torres**, **Dr. Pura Muñoz** and **Dr. Francisco Sánchez Madrid**, bringing to five the number of CNIC researchers who are EMBO members.

"I am delighted to be able to welcome the new members to our organization and I hope to have

the opportunity to work with them", said **Maria Leptin**, Director of EMBO. "Membership of EMBO acknowledges the outstanding achievements in life sciences of the selected scientists. The new members will bring their experience to further strengthen EMBO and its initiatives".

EMBO members actively participate in the organization: They sit on the EMBO board, the various committees and the advisory editorial board of EMBO journals. They also evaluate the applications of EMBO calls for funding and act as mentors for scientists who are just setting out on their professional careers. The new members will be formally inducted at the annual meeting of EMBO members between 27 and 29 October 2021.



DR. GUADALUPE SABIO AWARDED THE BANCO SABADELL FOUNDATION PRIZE FOR BIOMEDICAL RESEARCH

The Banco Sabadell Foundation awarded the Spanish National Centre for Cardiovascular Research (CNIC) researcher, **Dr. Guadalupe Sabio Buzo**, the Prize for Biomedical Research for her contribution to understanding why obesity causes cardiometabolic diseases.



In order to foster research, excellence and innovation, the Banco Sabadell Foundation recognises the contributions of Spanish researchers in the fields of cardiometabolic diseases, sensory technology, political economy and economic development.

Dr. Guadalupe Sabio Buzo heads the research group on the role of stress-activated kinases in the development of cardiovascular disease, diabetes and cancer. The group's work focuses on understanding the factors that appear in obese individuals as an alteration of fat, deregulation of internal body clocks and cellular stress, which may be the causes of the onset of these diseases.

In addition, an article by **Dr. Sabio's** group receives the Antoni Esteve Foundation Research Award. The study, published in *Nature* in 2019, revealed relevant data about the involvement of the protein p38gamma in the development of the main type of primary liver cancer, which affects over a million people a year worldwide.



In 2019, the Spanish National Centre for Cardiovascular Research (CNIC) group led by **Dr. Guadalupe Sabio** published data in the journal, *Nature*, about the involvement of protein p38-gamma in the development of the main type of primary liver cancer.

The international jury, which awards the Antoni Esteve Foundation Research Award every two years, considers this scientific article to be the most important pharmacological publication by a Spanish author between 2019 and 2020.

As first author of the paper, **Antonia Tomás Loba** received the award on behalf of the whole team in an awards ceremony.

This is the seventeenth edition of the Antoni Esteve Foundation Research Awards, which grant €18,000 to the best work of pharmacological research of any kind (design, synthesis, galenic development, clinical or laboratory evaluation, etc.) published by a Spanish author in the last two years.

ALMUDENA RAMIRO, CAJA RURAL DE GRANADA FOUNDATION, HEALTH SCIENCES AWARD

Dr. Almudena Ramiro of the Spanish National Centre for Cardiovascular Research (CNIC) received the XVII Caja Rural de Granada Health Sciences Award for her research into the treatment of atherosclerosis.



Vascular diseases are the main cause of death in the Western world. Heart attacks and strokes are the consequence of thrombus that form and obstruct arteries, causing destruction of the tissue affected by the lack of blood flow. The creation of the thrombus is, in turn, the consequence of a process that remains asymptomatic for a long period, and is known as atherosclerosis. For years, we have known that immune response plays a major role in atherosclerosis, but the implications of this response in the development of atherosclerotic disease are not known in detail.

Dr. Ramiro and her team have approached this problem using highly innovative technology to study the genes of B lymphocyte antibodies in mice with atherosclerosis. This research has been able to catalogue 18 antibodies that

identify atherosclerotic plaque. Closer analysis revealed that one of them (known as A12) targets ALDH4A1, a molecule of the organism itself.

The importance of this finding was confirmed when it was discovered that production values of this molecule increase during atherosclerosis. Apart from the value of this biomarker in the development of the disease, a particularly important finding was the fact that use of the A12 antibody as a blocker was able to notably reduce free cholesterol levels and the formation of atherosclerotic plaque.

The award jury valued the quality of results as well as their originality and clinical significance since, apart from identifying a target structure for altered immune response, the A12 antibody may constitute a completely new strategy of great relevance for the future treatment of patients with vascular diseases. This work was published in *Nature*, one of the highest-impact medical journals in the world.

DR. JORGE ALEGRE, NAMED MEMBER OF THE ACADEMIA JOVEN DE ESPAÑA

The CNIC researcher, **Dr. Jorge Alegre Cebollada** has been voted one of the ten new members of the Academia Joven de España, a Spanish organization established as a scientific public corporation whose main aim is to represent young scientists and give them greater visibility. This organisation is linked to the Global Young Academy and the Instituto de España (the umbrella organization for Spanish Royal Academies and Institutes).

Dr. Alegre received leads the CNIC Molecular Mechanics of the Cardiovascular System research group that investigates how mechanical forces determine muscle function at molecular, cellular, tissue and organism levels.

In 2020, the project “ProtMechanics-Live: Uncovering Protein Mechanics in Physiology and Disease”, led by **Dr. Alegre**, was selected for one of the European Commission’s ERC-consolidator grants. The project will receive 2 million euros over the next five years.

One of the distinguishing characteristics of the Academia Joven de España is precisely that it allows young Spanish researchers who work abroad to become full members. This new measure was introduced in order to foster collaboration among young Spanish researchers, and to connect those of them who are working outside the country with academic institutions in Spain.



DR. MIGUEL TORRES APPOINTED ASSOCIATE EDITOR OF SCIENCE ADVANCES

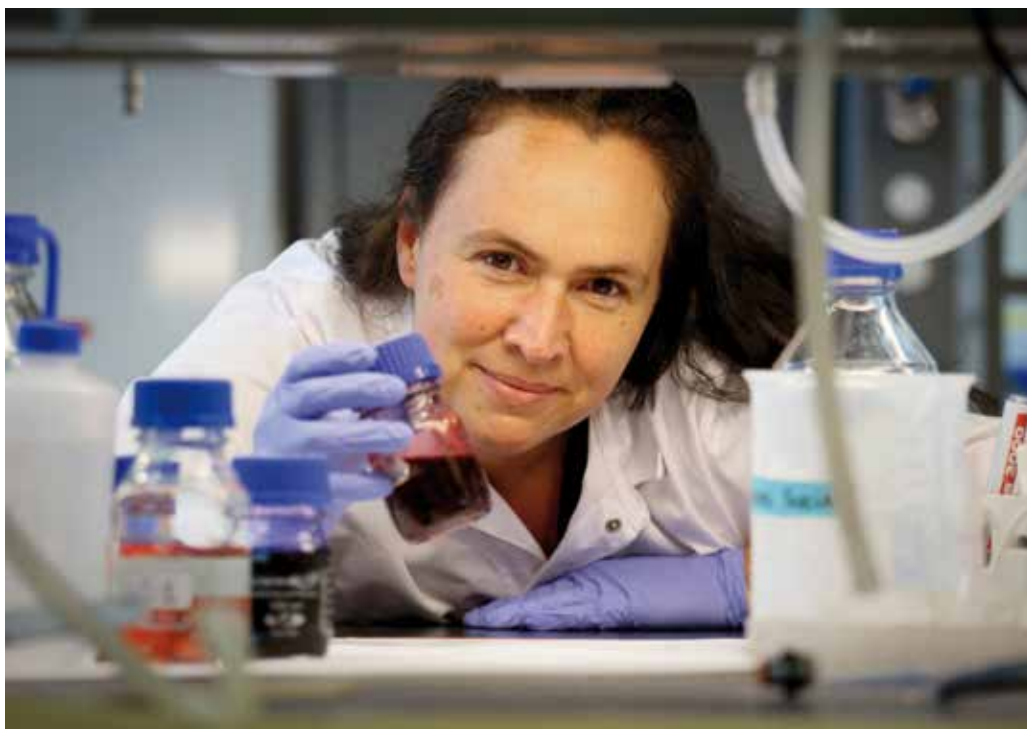
The researcher at the National Center for Cardiovascular Research (CNIC), **Dr. Miguel Torres**, has been appointed Associate Editor of the prestigious scientific journal **Science Advances**.

Science Advances is a peer-reviewed, open access, multidisciplinary scientific journal created in early 2015 and published by the American Association for the Advancement of Science (AAA).

Dr. Torres is a member of the European Molecular Biology Organization (EMBO). **Dr. Miguel Torres**’s scientific research focuses on the regulation of embryonic development and the formation and regeneration of organs. His major contributions include the understanding of how gene activities regulate regionalization processes in the developing embryo and the discovery of mechanisms involved in quality control and organ regeneration.



Dr. Miguel Torres’s scientific research focuses on the regulation of embryonic development and the formation and regeneration of organs



MARTA CORTÉS CANTELI RECIPIENT OF A 2021 LEONARDO GRANT

Marta Cortés Canteli's research project on the "Preclinical connection between cardiovascular disease and Alzheimer's disease", has obtained one of the BBVA Foundation's 2021 Leonardo Grants for Researchers and Cultural Creators.

Her project, which will receive a gross 40,000 euros, aims to determine the levels in blood of the plasma biomarkers for Alzheimer's, in particular of the phosphorylated tau-181 protein, among asymptomatic middle-aged individu-

als with cerebral hypometabolism and subclinical atherosclerosis disease to ascertain whether they were already in the initial stages of Alzheimer's disease (AD).

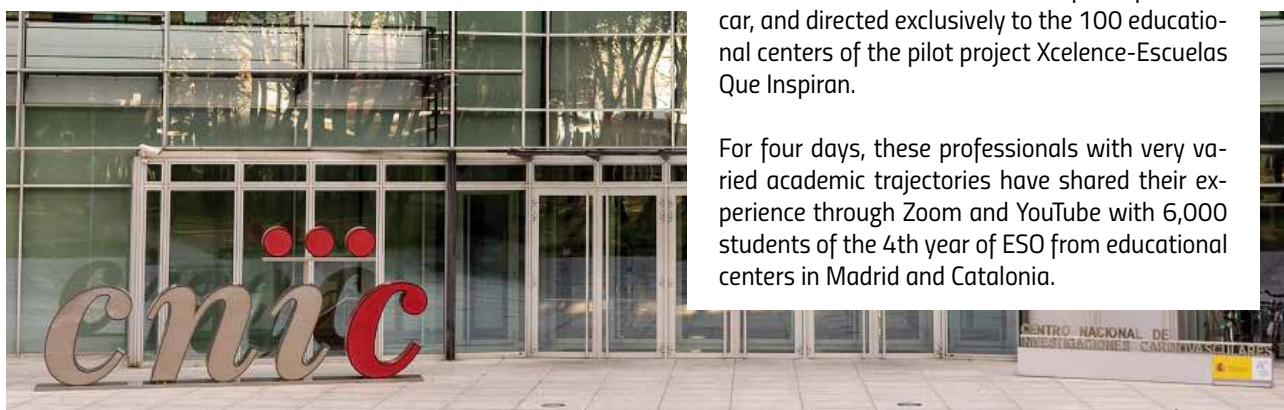
The PESA-CNIC-Santander Progression of Early Subclinical Atherosclerosis study, led by **Dr. Valentín Fuster**, is a prospective study that includes over 4000 asymptomatic middle-aged subjects among whom the presence and progression of subclinical atherosclerosis has been exhaustively evaluated since 2010.

For four days, these professionals with very varied academic trajectories have shared their experience with 6,000 students from educational centers in Madrid and Catalonia

THE CNIC PARTICIPATES IN THE 'MEETINGS INSPIRATIONAL WITH PROFESSIONALS'

The CNIC researcher **Marta Cortés Canteli** was one of 36 professionals from different areas that participated in the 'Encuentros inspiring among professionals and students', promoted by the Bertelsmann Foundation and Empieza por Educar, and directed exclusively to the 100 educational centers of the pilot project Xcelence-Escuelas Que Inspiran.

For four days, these professionals with very varied academic trajectories have shared their experience through Zoom and YouTube with 6,000 students of the 4th year of ESO from educational centers in Madrid and Catalonia.





**FRANCISCO SÁNCHEZ MADRID RECEIVED
THE SANTIAGO RAMÓN Y CAJAL NATIONAL PRIZE
IN THE AREA OF BIOLOGY**

Francisco Sánchez Madrid received the Santiago Ramón y Cajal National Prize in the area of Biology. **Dr. Sánchez Madrid** leads the research group at the Spanish National Centre for Cardiovascular Research (CNIC), is Professor of Immunology at the Universidad Autónoma of Madrid (AUM), Spain, and Chief of the Immunology Service at La Princesa University Hospital, Spain.

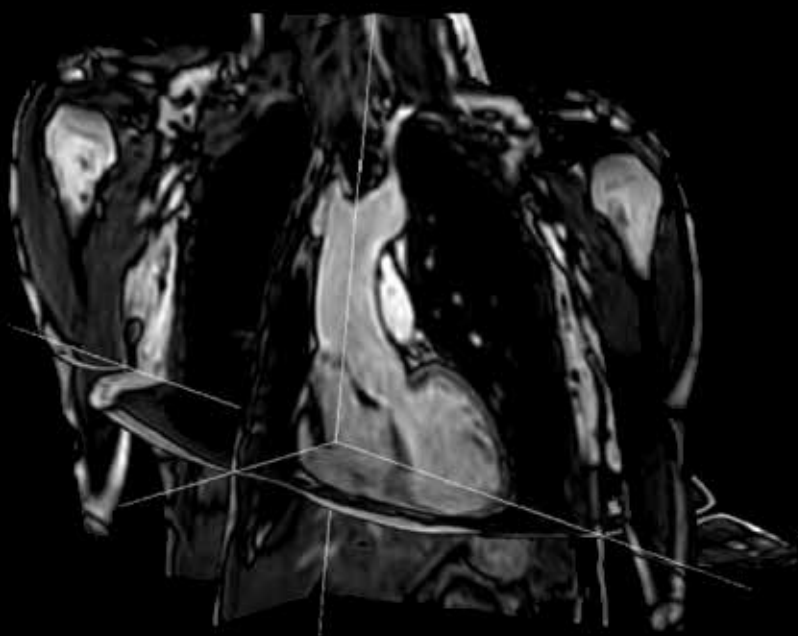
The jury awarded him this prize, which he received from the King, in November 2020 for his contributions to biomedical investigation in the area of inter-cellular communication, adhesion, migration and activation of leukocytes, and for the impact that this has had on the study of chronic inflammatory diseases. The award was earned not only for these achievements, but also for the international repercussion of his scientific career, in addition to the relevance of his work in teaching, training and tutoring young Spanish scientists.

The juries highlighted the extraordinary quality of all candidates. In order to select the winner, the juries evaluated the merit of each candidacy on a competitive basis and applied the principles of publicity, transparency, equality and non-discrimination. ■

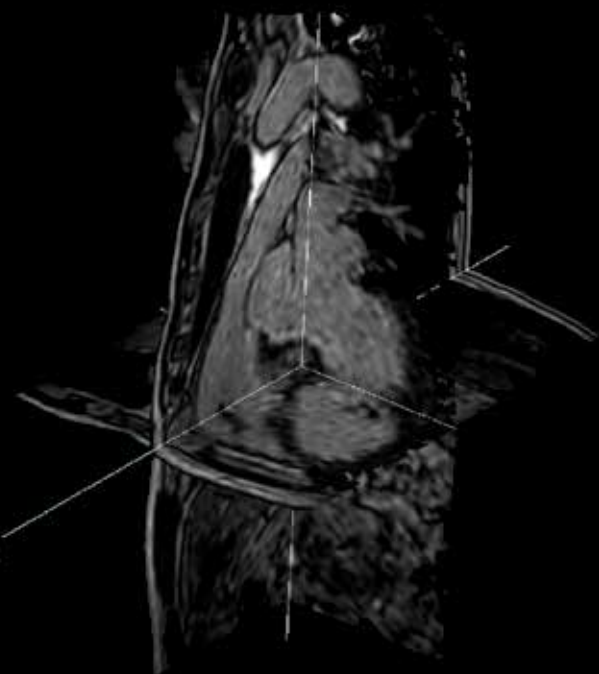
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TRAIN2GAIN
WHAT'S ON
INSIDE SCIENCE
CNIC & SOCIETY

... *cnic*PULSE #12



3D Cine ESSOS



3D LGE